SUPPLEMENTARY APPENDIX 3: Evidence Report

2022 American College of Rheumatology Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases: Evidence Report

Prepared for: American College of Rheumatology

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Introduction

This report evaluates outcomes of vaccinations among patients with the following rheumatic and musculoskeletal diseases (RMD): inflammatory arthropathies, connective tissue diseases, vasculitides, and inflammatory disorders.

Critical outcomes

- Each table reports the summary of findings from randomized trials and/or observational studies reporting the critical outcomes. The critical outcomes, as chosen by the Core Team, varied among different PICO questions. Immunogenicity and/or reactogenicity were critical outcomes for several PICO questions, as were vaccine-preventable infections. Disease flare or change in disease activity were critical outcomes for a few PICO questions. For PICO 2, adverse outcomes from vaccine-preventable diseases (including all markers of severity, e.g., hospitalization, death, morbidity) were the critical outcomes.
- Note that serious adverse events are rare, and thus it is quite difficult to achieve a statistically significant difference between groups for this outcome in randomized trials powered for efficacy outcomes that occur much more often.
- Not every study identified examined all critical outcomes. Each outcome was analyzed separately.

Interventions

The following vaccines were within the scope of this guideline:

- Protein/Subunit/Recombinant/Inactivated organism
    - Seasonal influenza (inactivated or recombinant, injectable) (Standard dose, High dose, Adjuvanted)
    - Tetanus toxoid/Td/Tdap
    - Hepatitis B
    - Human Papilloma Virus (HPV)
    - Hepatitis A
    - Herpes zoster (recombinant Shingrix)
    - Meningococcus B (recombinant MenB--Bexsero, Trumenba)
    - Inactivated polio (IPV)
- Polysaccharide
    - Pneumococcus (PPSV23, Pneumovax)
    - Typhoid (Vi-PS, injectable)
- Conjugate
    - Pneumococcus (PCV13, Prevnar)
    - Meningococcus ACWY (conjugate—MenACWY, Menactra, Menveo)
    - H. influenza b (Hib)
- mRNA and others

    - SARS-COV 2
- Live attenuated vaccines
    - MMR
    - Yellow fever
    - Zoster (live attenuated, Zostavax)
    - Rotavirus
    - Varicella
    - Influenza (live attenuated, nasal spray)
    - Typhoid (live attenuated, oral Ty21a)
- T-cell dependent Neo-antigens
    - Bacteriophage □X174
    - Keyhole limpet haemocynan (KLH)

The following immunosuppressive and immunomodulating medications were within the scope of this guideline:

- Glucocorticoids: prednisone, prednisolone, methylprednisolone, dexamethasone
- Immunosuppressive/immunomodulating medications
    - Mycophenolate mofetil/mycophenolic acid
    - Azathioprine
    - Calcineurin inhibitors (Cyclosporine, Tacrolimus, Voclosporin)
    - Apremilast
    - Intravenous immunoglobulin (IVIg)
    - Cyclophosphamide
    - Colchicine
    - NSAIDS
    - Acetaminophen
- csDMARDs (conventional synthetic disease-modifying anti-rheumatic drugs)
    - Methotrexate
    - Leflunomide
    - Sulfasalazine
    - Hydroxychloroquine
- bDMARDS (biologic DMARDs) including biosimilars
    - Tumor necrosis factor inhibitors (TNFi) (Etanercept, Infliximab, Adalimumab, Golimumab, Certolizumab pegol)
    - B-cell depleting agents (Rituximab, Ocrelizumab, Obinutuzumab)
    - T-cell co-stimulation blockers (Abatacept)
    - IL-I inhibitors (Anakinra, Canakinumab, Rilonacept)

    - IL-6 inhibitors (Tocilizumab, Sarilumab)
    - IL-17 inhibitors (Secukinumab, Ixekizumab)
    - IL-12/IL-23 inhibitors (Ustekinumab)
    - IL-23 inhibitors (Guselkumab, Tildrakizumab, Risankizumab)
    - BLyS/Baff inhibitors (Belimumab, Tabalumab)
    - Interferon alpha blockers (Anifrolumab)
    - RANKL inhibitors (Denosumab)
- tsDMARDs (targeted synthetic DMARDs)
    - JAK inhibitors (Tofacitinib, Baricitinib, Upadacitinib, Filgotinib, Ruxolitinib)

Systematic Literature Review

- Randomized controlled trials (RCTs) and observational studies that directly or indirectly addressed PICO questions were included. Case reports and case series with fewer than 10 patients were excluded.

Quality Assessment

- Quality assessment was performed separately for each outcome using the GRADE system, which results in one of four possible evidence grades that reflect level of confidence in the effect estimate: high, moderate, low, and very low.
- Study design is the starting point for quality assessment: randomized controlled trials (RCTs) start at high quality and observational studies start at low quality.
- Five factors can lower the quality of evidence grade: risk of bias, inconsistency, indirectness, imprecision, and publication bias.
- Risk of bias refers to limitations in study design or execution (e.g. lack of allocation concealment or blinding).
- Inconsistency refers to unexplained heterogeneity in results of studies evaluating the same outcome.
- Indirectness refers to lack of direct comparisons of interventions of interest (e.g. studies comparing drug A vs. placebo and drug B vs. placebo when the comparison of interest is drug A vs. drug B), lack of applicability in the interventions or populations being evaluated, or use of indirect (surrogate) outcome measures.
- Imprecision refers to uncertainty in the estimate of effect due to very low numbers of patients or events and/or wide 95% confidence intervals that cross a clinical decision threshold (i.e. between recommending and not recommending treatment).
- Publication bias refers to selective publication of studies that show greater treatment effects (i.e. negative studies are suppressed).
- Quality of evidence can vary from outcome to outcome. The final quality assessment for the PICO question is based on the critical outcome with the lowest quality assessment.
- The level of evidence listed in this report for either an individual paper or a group of papers is not meant to be an absolute statement about the quality of the study (or studies) under consideration. Rather, the intention is to rate the paper(s) *in relation to the question being asked in this guideline*. Because of this, a very well conducted study might actually be rated down in this evidence report, possible reasons including that the population or intervention being studied does not completely match the population or intervention being examined by the PICO question in this guideline (in other words, downgrading for indirectness). The level of evidence may also be downgraded due to imprecision in the effect estimate (wide

confidence intervals that cross the line of no effect, or a low number of patients or events). A combination of these factors may result in quality of evidence from a well-conducted study being rated as low.

Presentation of effects

- The treatment effects from binary (yes or no) outcomes are presented as relative effects and absolute effects.
- Relative effects capture the difference between intervention and control in relative terms. For example, a 10% event rate in controls and a 5% event rate in the intervention represents a 50% relative risk reduction (10% - 5%/ 10%)
- The same difference represents a 5% absolute risk reduction (10% - 5% = 5%). In general, for patients, the absolute effect is the most important.
- Relative effects for dichotomous outcomes in the tables are expressed as relative risk (RR) or odds ratio (OR). RR is the default effect size because it is more easily interpretable, but under some circumstances RRs can lead to impossible numbers when calculating absolute risk differences. In such instances ORs were used instead of RRs.
- In the tables, when RR or OR is specified, the first intervention (vaccine or drug) (e.g. tocilizumab vs methotrexate, or methotrexate vs placebo) is the reference intervention.

Evidence Summaries including Summary of Findings (= Tables under each PICO question, except some PICO questions for which no evidence was available)

- Direct comparisons are situations where trials directly compare intervention A to intervention B within one of the patient subgroups covered in this guideline.
- Indirect comparisons: Some studies do not include a direct comparison of drugs or interventions specified in a given PICO question. An example of this is trials that compare drug A to placebo, or an observational study where all patients received vaccine A and a pre-post comparison is made.

Interpreting the evidence

- It is important to take into account the information presented specifically as it relates to the question of interest. For example, when the only evidence for a given PICO question is indirect due to the comparison or patient population, it appropriately gets downgraded for indirectness as shown under the column labeled “indirectness.” Also, if the 95% confidence interval around an effect size is wide and crosses the line of no difference between treatments, the evidence for that outcome is downgraded due to imprecision. Study design and risk of bias also may result in downgrades in the quality of evidence. The overall quality of evidence takes all these factors into account, and is appropriately rated as high, moderate, low or very low. This quality of evidence is key to your decisions.

Moving from evidence to recommendations

- In GRADE, recommendations can be either strong or conditional. Generally, strong recommendations are restricted to high or moderate quality evidence. Low quality evidence almost invariably mandates a weak recommendation.
- There are, however, situations in which low quality evidence can lead to strong recommendations. For instance, if there is low quality evidence favoring an intervention but high quality evidence of important harm then a strong recommendation against the intervention may be appropriate.

Bibliography of included studies

- Separate reference lists of studies included for each PICO question with an evidence base appear at the end of the summaries for each question. For two questions with a very large evidence base (PICO 3 and 8), we have placed reference lists after specific subsections rather than a single overall reference list for each question.

Results

PICO Question 3: In patients with [RMD Disease X], what is the effect of [Drug Y/Drug Class] on immunization responses to [Vaccine Z, Vaccine Type] in comparison with [General population, or Drug Y']?

Due to the large amount of literature addressing this question, we have prepared separate summary sections for each type of vaccine.

Influenza vaccines

Summary:

The literature search identified 88 studies that addressed this PICO question comparing influenza vaccine response in rheumatic disease patients and that in healthy controls or rheumatic disease patients taking or not taking a particular medication. Below the results are summarized according to rheumatic disease.

Lupus:

The following studies showed lower responses among SLE patients vs. healthy controls (or SLE not on "Drug Y"). A study compared SLE patients to controls receiving influenza vaccine with outcomes were slightly in favor of the healthy controls, but the result is imprecise [1]. Another study found SLE patients have lower seroprotection and seroconversion rates in response to influenza vaccine compared to healthy controls [2]. Among SLE patients, those on DMARDs had significantly LOWER seroprotection response to influenza vaccine compared to those on no medications. When broken down by medication, patients on azathioprine, methotrexate, and MMF all showed lower seroprotection responses, but these individual differences were not statistically significant. Chloroquine was not associated with a difference in seroprotection response, regardless of whether used as monotherapy or in combination with a DMARD. SLE pts on prednisone >20 mg/day did not have a different seroprotection response to influenza vaccine [2]. Another study compared SLE patients to healthy controls 4 weeks post influenza vaccine and reported that outcomes (seroconversion, seroprotection) were favorable to healthy controls compared to SLE patients [3]. Two observational studies comparing SLE patients on any medications to healthy controls show that outcomes for vaccine efficacy, seroprotection, seroconversion and GMT increase in favor of healthy controls [4, 5]. One observational study compared SLE patients on MTX to SLE patients not on MTX showed outcomes in favor of SLE patients not on MTX, but the results are very imprecise [4]. One study comparing SLE patients on prednisone to those not on prednisone showed outcomes are no different for vaccine efficacy and seroprotection [4], while another study showed the levels of influenza antibody titers in favor of patients not on prednisone with the results very imprecise for H1N1 and H3N2 and high precision for B-Malaysia strain, but the sample size was very small [5]. A study of influenza vaccinated SLE patients compared to healthy controls reported outcomes were in favor of healthy controls [6].

The following studies showed similar responses among SLE patients vs. healthy controls (or SLE not taking Drug "Y"). A study compared influenza vaccine response among SLE patients on prednisone compared to no medications and reported that SLE patients on prednisone had similar seroconversion and seroprotection responses to influenza vaccine to SLE patients not on prednisone ("vaccine efficacy" = seroconversion and/or seroprotection) [4]. This study also reported that SLE patients on hydroxychloroquine had similar seroconversion and seroprotection responses to influenza vaccine to SLE patients not on hydroxychloroquine [4].

The following studies showed inconsistent responses among SLE Patients vs. healthy controls (or SLE not taking "Drug Y"). A study compared SLE patients taking azathioprine compared to no medications and reported SLE patients on azathioprine had similar seroconversion and seroprotection responses to influenza vaccine to SLE patients not on azathioprine ("vaccine efficacy" = seroconversion and/or seroprotection), but they had lower seroprotection to 1 out of 3 antigens [4]. Another study comparing SLE patients to healthy controls reported higher GMT in the SLE group at 30 days post-vaccination; seroprotection and seroconversion did not differ significantly between groups but the direction of effect favored the SLE group (which had a higher baseline GMT than the control group) [9980]. This same study compared vaccine responses in SLE patients on medications (including hydroxychloroquine, glucorticoids, and immunosuppressive agents) to SLE patients off medications; none of the outcomes showed a significant between-group difference, but this may have been due to study being underpowered to detect such differences [9980].

RA:

The following studies showed lower responses among RA patients vs. healthy controls (or RA not taking "Drug Y"):

Two studies combining data of RA patients on rituximab vs. healthy controls found the outcomes are more favorable to healthy controls [7, 8]. Among patients with RA treated with RTX compared to RA patients on csDMARDs who receive the influenza vaccine outcomes are more favorable to patients on csDMARD's than to patients on RTX [7, 8]. A study of RA patients on tofacitinib found lower responses (baseline seroprotection, seroprotection, seroconversion) to influenza vaccine compared to RA patients not on tofacitinib (with or without background methotrexate) [9]; RA patients on tofacitinib + MTX who received influenza vaccine had lower baseline seroprotection, lower seroprotection response, and lower seroconversion response than RA patients on MTX alone [9]; and RA patients on tofacitinib+MTX had lower seroprotection and seroconversion compared to RA patients on no DMARD therapy [9]. :In an open-label trial with RA patients and healthy controls, the immune response to influenza 7 days after immunization was in favor of healthy controls but the results are imprecise [10]. A study compared RA patients on MTX compared to MTX + RTX, and found that RA patients treated with MTX have slightly better outcomes for 4-fold and 2-fold titer increase at 4 weeks after immunization, but the results are imprecise [11]. A study found RA patients had lower response to influenza vaccine compared to healthy controls [12]; RA pts have mostly lower responses to influenza vaccine compared to age-matched controls [12]; RA patients on MTX had lower response to influenza vaccine compared to healthy controls [12]; RA patients on chloroquine had lower responses to influenza vaccine compared to healthy controls [12]; RA patients on steroids had lower responses to influenza vaccine compared to healthy controls [12]; RA-MTX compared to RA-no MTX: RA patients on MTX had lower responses to influenza vaccine compared to RA patients not on MTX [12]; RA-steroids compared to RA-no steroids: RA patients on steroid had lower seroprotection response to influenza compared to RA

patients not on steroid [12]. In another study of Influenza response in RA on biologics compared to no biologics or HCs, at 6 weeks, the outcomes were in favor of healthy controls but the results are imprecise [13].

The following studies showed similar responses among RA patients vs. healthy controls (or RA not taking Drug "Y"):

A study of RA patients on infliximab who received influenza vaccine (3 weeks later) compared to Healthy Controls receiving influenza vaccine response found no significant difference in seroconversion or GMT in RA pts on infliximab compared to healthy controls (vaccine 3 weeks after infliximab) [14]. RA patients on infliximab-receiving influenza vaccine (given same day) compared to Healthy Controls for influenza vaccine response showed no significant difference in seroconversion or GMT in RA pts on infliximab (vaccine given same day as infliximab) compared to healthy controls [14]. There was also no significant difference in influenza vaccine seroconversion or GMT in RA pts on infliximab compared to RA patients not on infliximab (vaccine given same day as infliximab) [14]. Another study of RA patients on tofacitinib monotherapy had similar influenza vaccine responses to RA patients not on DMARDs [9]; RA patients on MTX monotherapy had similar response to influenza vaccine as compared to RA patients on no DMARDs [9]; and RA patients on tofacitinib monotherapy had SIMILAR responses to influenza vaccine compared to RA pts on MTX monotherapy [9]. Another study of RA patients on tocilizumab had similar seroconversion and seroprotection response to influenza vaccine compared to RA patients on conventional DMARDs [15]; RA patients on tocilizumab had SIMILAR seroconversion response to influenza vaccine as RA patients on TNFi [15]. Another study found that RA pts treated with adalimumab had SIMILAR seroconversion response to influenza vaccine compared to those treated with placebo [16]. In a study of RA on biologics compared to RA not on biologics for influenza vaccine response, RA patients on biologics had SIMILAR response to influenza vaccine compared to RA patients not on biologics (biologics included both TNFi and tocilizumab) [13]. Another study found RA patients on TNFi had SIMILAR responses to influenza vaccine compared to RA not on TNFi. Response defined as seropositive OR seroconversion at 4-6 weeks [17]. A study of RA patients compared to Healthy controls for influenza vaccine response found that RA patients had similar responses to influenza vaccine as compared to healthy controls, regardless of specific medication [18]. A study of Influenza within 0-3 days compared to 4-7 days of last MTX for RA patients with influenza vaccine on MTX found that comparing influenza vaccine administered within 0-3 days compared to 4-7 days of last MTX dose for RA patients the outcomes were not different between groups [19]. In a study comparing RA patients to healthy controls, the outcomes were not different or statistically significant except for Seroprotection rate - Brisbane/H1N1, 6 months, which was statistically significant in favor of healthy controls [20]. In a study of RA on biologics compared to RA not on biologics for influenza vaccine response: RA patients on biologics had similar response to influenza vaccine compared to RA patients not on biologics (biologics included both TNFi and tocilizumab) [13].

The following studies showed inconsistent or more favorable responses among RA Patients vs. healthy controls (or RA not taking "Drug Y"):

There are four studies that compared effect of influenza vaccine in RMD patients on csDMARD's vs healthy population. The results show that vaccine response was slightly in favor of RMD patients with high imprecision, but seroprotection and GMT more favorable for healthy population [4, 5, 7, 8]. One study compared RA patients treated with DMARD's vs healthy controls and DMARD-naïve RA patients to healthy controls [21]. In both RA patients on DMARD's and DMARD-naïve patients the outcomes were better than in healthy controls, but better in DMARD-naïve patients than in RA+DMARD patients. Another study compared RA patients on tofacitinib+MTX vs. tofacitinib monotherapy and found that those on combination tofacitinib/MTX treatment had similar baseline seroprotection and vaccine response to RA patients on tofacitinib monotherapy,

but lower responses (seroprotection, seroconversion) to influenza vaccine compared to RA pts on tofacitinib monotherapy [9]. A study compared RA on anti-TNFa vs. healthy controls receiving influenza vaccine and found outcomes differ by each strain, but no largely different between groups with high imprecision for each outcome [22]. One study found that RA patients on TNFi had similar or HIGHER responses to influenza vaccine compared to healthy controls. Response defined as seropositive OR seroconversion at 4-6 weeks [17]. Another study made the following comparisons: RA-MTX vs HC, RA-RTX vs HC, RA-RTX vs RA-MTX (H1N1/H3N2-IgG1/IgG3, IgG4) response to influenza vaccine: This study examined the outcomes for H1N1 and H3N2-specific IgG1/IgG3, and IgG4. The IgG levels were slightly better or equal in healthy controls compared to patients in RA-MTX group, significantly better than in patients in RA-MTX group, and the outcomes in RA-MTX group were better than in patients RA-RTX group, however due to the low number of patients the results are imprecise [23]. Another study compared Certolizumab vs Placebo for influenza vaccine response and found that RA patients on certolizumab had similar overall response to influenza vaccine as compared to RA patients who received placebo, but lower response to H3N2 antigen [24].

JIA: The following studies were included that compared JIA to healthy controls with respect to influenza vaccine response: In one study, seroconversion in response to influenza vaccine was lower in JIA patients compared to healthy controls, was similar in JIA patients on MTX vs not on MTX; and was similar in JIA patients on TNFi vs not on TNFi [25]. Another study reported that JIA pts on MTX, TNFi, or both had similar seroprotection responses to influenza vaccine compared to healthy controls [26]. Another study evaluating patients with systemic JIA on tocilizumab compared to healthy control for influenza vaccine response and reported that SJIA patients on tocilizumab, as compared to healthy controls, had higher GMT to 1/3 influenza antigens, lower GMT to 2/3 influenza antigens, and similar seroprotection and seroconversion rates [27]. Additionally, among SJIA patients on tocilizumab, patients also taking prednisolone doses <0.2 mg/kg/d had higher GMT response to influenza vaccine that patients with prednisolone doses >0.2 mg/kg/d [27]. Another study of patients with JIA patients on biologics (TNFi, IL-6 inhibitors) had similar seroprotection response compared to JIA patients not on biologics [28]. Another study of influenza vaccine immunogenicity among individuals with JIA on various meds, at 1 and 6 months, were similar to healthy controls [29].

Non-RMD population: There were four studies included in this data summary that assessed response to influenza vaccine among individuals without rheumatic disease on a drug of interest. One study compared immunogenicity in response to influenza vaccine in renal patients (of varying causes) on immunosuppression versus healthy controls and showed favorable results for renal patients, but the results are imprecise [30]. In another study of individuals with lymphoproliferative diseases, influenza vaccine response was compared for those taking rituximab vs. not taking rituximab and found that seroconversion and seroprotection were not statistically significantly lower among rituximab users [31]. Seroprotection after influenza vaccine among individuals with inflammatory bowel disease on TNFi compared to not on TNFi was evaluated in another study that found no difference between outcomes in both groups, except for A/Switz/H3N2 titer which was more favorable for group with no TNFi treatment [32]. Lastly, Influenza vaccine response for individuals with cancer receiving rituximab compared to no rituximab was compared, the outcomes favored patients not receiving rituximab [33].

Mixed Rheumatic Diseases: Several studies compared influenza vaccine response among individuals with mixed rheumatic diseases.

The following studies showed similar responses to influenza vaccine among individuals with mixed rheumatic diseases compared to controls. One study compared response to seasonal influenza vaccine at 3-5 weeks among individuals with rheumatic diseases (RD) compared to controls

and showed that response was similar [34]. Another study found that (1) Mixed RMD patients on conventional DMARDs had similar response to influenza vaccine as compared to healthy controls. ("seropositivity" not clearly defined) [35], (2) Mixed RMD patients on biological DMARDs had similar response to influenza vaccine as compared to healthy controls ("seropositivity" not clearly defined) [35], and (3) Mixed RMD patients on conventional DMARDs had similar response to influenza vaccine as compared to RMD patients on biological DMARDs ("seropositivity" not clearly defined) [35]. Another study compared response to influenza A/H1N1 2009 vaccine (JDM compared to pediatric healthy controls), 3 weeks and showed no noticeable difference in outcomes between RMD patients and healthy controls [36]. Another study found that response to seasonal influenza at 3-5 weeks in patients with rheumatic disease and controls was similar and there was little benefit of a second dose of the influenza vaccine at 3-5 weeks [34].

The following studies found diminished responses to influenza vaccine in patients with mixed RMD vs. healthy controls: One study showed RMD patients on rituximab had LOWER seroconversion rates in response to influenza vaccine as compared to healthy controls. Pre-vaccination antibody titers to influenza antigens were SIMILAR, and post-vaccination titers were LOWER in the rituximab group [37]. Another study evaluated RMD patients on mixed treatments and healthy controls measured at 3 weeks, 3 months, 6 months and reported outcomes were in favor of healthy controls [38]. Another study evaluated post influenza vaccine-dose 1 responses in mixed RMD compared to healthy controls, and at 3-4 weeks f/u reported healthy controls had more favorable outcomes in comparison to post-dose 1 than post-dose 2 [39]. Pooled estimates were calculated for rheumatic disease patients on mixed therapies compared to Healthy Controls at day 21. There were five studies with different RD patients on mixed treatments that measured seroprotection and seroconversion against influenza at day 21. The pooled estimates showed that RD patients have on average 15%, and 25% at most and 5% at least, less probability of developing seroprotection and seroconversion compared to healthy controls [38, 40-44].

The following studies found inconsistent outcomes between RMD patients and healthy controls: One study compared seroconversion among pediatric rheumatic disease patients compared to healthy controls for Influenza and reported inconsistent outcomes across titers, favoring healthy controls for H1N1 titer, and RD patients for H3N2 and B titers, but the results are very imprecise [45]. One study found that individuals who were not taking immunosuppressive treatment had similar outcomes as patients taking immunosuppressive treatments [46]; however, individuals on immunosuppressants (corticosteroids >=10mg/day, cytotoxic agents) had more favorable outcomes than patients on biologics (rituximab, adalimumab, etanercept or infliximab). The study results are imprecise. One study evaluated seroconversion after influenza vaccine among pediatric rheumatic disease patients compared to controls and reported outcomes for H1N1 were more favorable to healthy controls than to pediatric RMD patients, while outcomes for H3N2 and B strains are more favorable to pediatric RMD patients, but the results are very imprecise [45]. Another study compared bDMARDs monotherapy vs. controls for influenza vaccine response in mixed rheumatic disease and found that mixed RMD patients on biological monotherapy had lower GMT responses; SIMILAR seroprotection to 3/3 antigens, and SIMILAR seroconversion to 2/3 antigens as compared to healthy controls [47]. This study also compared BDMARDs+DMARDs compared to controls for influenza vaccine response in mixed rheumatic disease and found that mixed RMD patients on combination therapy (biological plus conventional DMARDs) had lower GMT responses; SIMILAR seroprotection to 3/3 antigens, and similar seroconversion to 2/3 antigens as compared to healthy controls [47]. Further, Rituximab was compared to controls for influenza vaccine response in mixed rheumatic disease: Mixed RMD patients on

rituximab had LOWER GMT responses but SIMILAR seroprotection and SIMILAR seroconversion to influenza vaccine as compared to healthy controls [47].

Myositis: One study evaluated patients with juvenile dermatomyositis compared to pediatric healthy controls and found no significant difference between groups with respect to response to influenza A/H1N1 2009 vaccine at 3 weeks [36].

Vasculitis: Three studies evaluated individuals with vasculitis who received the influenza vaccine. In one study, compared to AAV patients, healthy controls had more favorable responses to influenza vaccine with statistical significance for factor increase GMT [48]. In an open-label randomized studies of individuals with GPA (WG), patients had similar outcomes as healthy controls, but the results are imprecise [49]. Another study compared influenza seroprotection and seroconversion anti-HA among individuals with GPA compared to healthy controls and reported that seroprotection for H1N1, H3N2 and B strains was in favor of healthy controls with statistical significance only for B strain. Seroprotection for H1N1, H3N2 and B strains was in favor of healthy controls but the results were imprecise [50].

Seronegative Spondyloarthropathy: Two studies compared influenza vaccine response for individuals with seronegative spondyloarthropathy. One study compared AS/PsA patients on secukinumab compared to healthy controls for influenza vaccine response and found that AS/PsA patients on secukinumab had similar responses to influenza vaccine as compared to healthy controls (seroconversion) [51]. A second study compared SpA patients to healthy controls for influenza vaccine response and found that among SpA patients, those patients on TNFi had lower responses as compared to healthy controls, and SpA pts on conventional DMARDs had similar or higher responses as compared to SpA pts on TNFi [18].

Sjogren's Syndrome: One study compared the immunogenicity of 2009 H1N1 vaccine in Primary Sjogren's patients compared to controls at 21 days follow up and noted that the outcomes were in favor of Primary Sjogren's disease patients [52].

Summary of other observational studies: The majority of studies had mixed populations or/and mixed treatments. The outcomes measured and reported were vaccine response, cellular response, seroconversion, seroprotection, 4-fold increase in titers, increase in geometric mean titers (GMT) of H1N1, H3N2, B strains. Control groups represented either healthy controls or patients with no medications of interest as opposed to patients on medications. The vaccine response and GMT titer increase were slightly better in healthy controls or patients not on immunosuppressive meds than in patients on csDMARD's [[7, 53]]. In other study, the DMARD group had lower rates of positive immune response compared to healthy controls only for H3N2 strain [21]. The proportion of responders were similar across patients with different rheumatic diseases but was significantly higher for the healthy controls [54]. SLE patients on scDMARD's and glucocorticoids, whether used separately or combined, had similar rates of seroconversion, seroprotection and GMT [55]. But in one study [2516], the RA patients, regardless of timing of taking infliximab, as well RA patients on csDMARD's and healthy controls had similar results in humoral response and equally high GMT titers. RA patients taking RTX had lower vaccine response, fold increase and seroconversion than healthy controls or patients on DMARD's [[7, 8, 37]], and had no significant increase in IgG or IgM levels post-vaccine for all titers [[23, 56]], even cellular response didn't differ among those patients [[7]] or was lower in RTX group [56]. Patients on TNFi had higher antibody response than patients taking either MTX, Abatacept,

or RTX [38], with lowest antibody response in RTX patients [38], but patients taking TNFi had lower GMT, seroconversion than patients not taking TNFi or healthy controls and equal seroprotection rate [[57, 58]]. In a study with patients taking TOFA, MTX, TOFA+MTX or no DMARD, the highest GMFR responses for H1N1 & H3N2 were in No DMARD group; lower but similar responses in the MTX alone, TOFA alone, and TOFA+MTX groups [9]. One pediatric study of children with mixed RMD found lower vaccine responses among RMD children on bDMARDs or a combination of bDMARDs plus csDMARDs compared to healthy controls [10244].

Quality of evidence across all critical outcomes: Very low for most comparisons, Moderate for a few (see individual tables for ratings for specific comparisons).

Table 1: Immunogenicity in response to influenza vaccine in renal patients on immunosuppression versus healthy controls showed favorable results for renal patients, but the results are imprecise [30].

Level of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal patients on immunosuppression	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
GMT titers in renal pts on immunosuppressants v healthy controls												
1	Observational study	serious[a]	not serious	not serious	serious[b]	none	30	46	-	MD **28.7 higher** (10.81 lower to 68.21 higher)	⊕◯◯◯ Very low	
Seroconversion rate in renal pts on immunosuppressants v healthy controls												
1	Observational study	serious[a]	not serious	not serious	serious[b]	none	30	46	-	MD **25.7 higher** (8.21 lower to 59.61 higher)	⊕◯◯◯ Very low	
Geometric fold rise in												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Renal patients on immunosuppression	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	Observational study	serious[a]	not serious	not serious	serious[b]	none	30	46	-	MD **5.3 higher** (1.52 lower to 12.12 higher)	⊕◯◯◯ Very low	

Seroprotection rates in renal pts on immunosuppressants v healthy controls

1	Observational study	serious[a]	not serious	not serious	serious[b]	none	30	46	-	MD **31.4 higher** (13.81 lower to 76.61 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 2: SLE patients compared to controls receiving influenza vaccine - The outcomes were slightly in favor of the healthy controls but the result is imprecise [1].

Level of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	controls	Relative (95% CI)	Absolute (95% CI)		
Fourfold increase in titers, 4 weeks follow up												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	14/29 (48.3%)	18/29 (62.1%)	**RR 0.78** (0.49 to 1.25)	**137 fewer per 1,000** (from 317 fewer to 155 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 3. Response to H3N2 vaccine at 30 days in SLE patients vs healthy controls [9980]

Level of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
GMT in SLE compared to HC D0 (pre-vaccination)												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	81	81	-	MD **74.3 higher** (47.85 higher to 100.75 higher)	⨁◯◯◯ Very low	Favors SLE
GMT in SLE vs Healthy Controls D30 post vaccination												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	81	81	-	MD **145.4 higher** (91.28 higher to 199.52 higher)	⨁◯◯◯ Very low	Favors SLE
Seroprotection D0 between SLE and HC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	72/81 (88.9%)	62/81 (76.5%)	**OR 2.45** (1.03 to 5.81)	**123 more per 1,000** (from 5 more to 184 more)	⨁◯◯◯ Very low	Favors SLE

Seroprotection D30 between SLE and HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	77/81 (95.1%)	74/81 (91.4%)	**OR 1.82** (0.51 to 6.48)	**37 more per 1,000** (from 70 fewer to 72 more)	⨁◯◯◯ Very low	

Seroconversion D30 between SLE and HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/81 (16.0%)	9/81 (11.1%)	**OR 1.53** (0.61 to 3.81)	**49 more per 1,000** (from 40 fewer to 211 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. observational study

b. small sample

Table 4. Response to H3N2 vaccine at 30 days in SLE patients on medications vs SLE patients off medications [9980]

Level of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on med	off med	Relative (95% CI)	Absolute (95% CI)		
SC rate in SLE pt on or off HCQ D30												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/51 (15.7%)	5/30 (16.7%)	**OR 0.93** (0.27 to 3.15)	**10 fewer per 1,000** (from 115 fewer to 220 more)	⊕◯◯◯ Very low	
SC SLE on or off GC D30												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on med	off med	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/41 (19.5%)	5/40 (12.5%)	**OR 1.70** (0.50 to 5.72)	**70 more per 1,000** (from 58 fewer to 325 more)	⨁◯◯◯ Very low	

SC SLE on or off IS agents D30

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/50 (12.0%)	7/31 (22.6%)	**OR 0.47** (0.14 to 1.55)	**105 fewer per 1,000** (from 187 fewer to 86 more)	⨁◯◯◯ Very low	

SC SLE with active (sledai 2K>=4) or not disease D30

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on med	off med	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/57 (12.3%)	6/24 (25.0%)	**OR 0.42** (0.12 to 1.42)	**127 fewer per 1,000** (from 212 fewer to 71 more)	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. observational study

b. small sample size

Table 5: RA patients on csDMARDs compared to healthy controls receiving influenza vaccine. There are four studies that addressed this PICO question comparing effect of influenza vaccine in RMD patients on csDMARD's vs healthy population. The results show that vaccine response was slightly in favor of RMD patients with high imprecision, but seroprotection and GMT were more favorable for the healthy population [4, 5, 7, 8].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-csDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/17 (58.8%)	7/16 (43.8%)	**RR 1.34** (0.68 to 2.66)	**149 more per 1,000** (from 140 fewer to 726 more)	⊕◯◯◯ Very low	
Vaccine response - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11/17 (64.7%)	7/16 (43.8%)	**RR 1.48** (0.77 to 2.85)	**210 more per 1,000** (from 101 fewer to 809 more)	⊕◯◯◯ Very low	
Vaccine response - B influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-csDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	13/17 (76.5%)	6/16 (37.5%)	**RR 2.04** (1.03 to 4.05)	**390 more per 1,000** (from 11 more to 1,000 more)	⨁◯◯◯ Very low	Favors RMD patients

Post-vaccine seroprotection - H1N1

4	observational studies	serious[a]	not serious	not serious	not serious	none	111/140 (79.3%)	79/89 (88.8%)	**RR 0.88** (0.79 to 0.97)	**107 fewer per 1,000** (from 186 fewer to 27 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Post-vaccine seroprotection - H3N2

4	observational studies	serious[a]	not serious	not serious	not serious	none	109/140 (77.9%)	80/89 (89.9%)	**RR 0.88** (0.78 to 1.00)	**108 fewer per 1,000** (from 198 fewer to 0 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Post-vaccine seroprotection - B influenza

4	observational studies	serious[a]	not serious	not serious	serious[b]	none	92/140 (65.7%)	65/89 (73.0%)	**RR 0.87** (0.65 to 1.16)	**95 fewer per 1,000** (from 256 fewer to 117 more)	⊕◯◯◯ Very low	

Post-vaccine GMT - H1N1

1	observational studies	serious[a]	not serious	not serious	not serious	none	23	29	-	MD **55.1 lower** (56.46 lower to 53.74 lower)	⊕◯◯◯ Very low	Favors healthy controls

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	not serious	none	23	29	-	MD **30.1 lower** (31.4 lower to 28.8 lower)	⊕◯◯◯ Very low	Favors healthy controls

Post-vaccine GMT – B

1	observational studies	serious[a]	not serious	not serious	not serious	none	23	29	-	MD **18.8 lower** (20.14 lower to 17.46 lower)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational studies

b. wide CI crosses significant effect and no-effect lines

Table 6: Patients with RA on rituximab compared to healthy controls. There are three observational studies that address this part of PICO question. Compared to RTX patients, the outcomes are more favorable to healthy controls [7, 8].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/29 (24.1%)	7/16 (43.8%)	**RR 0.55** (0.24 to 1.29)	**197 fewer per 1,000** (from 333 fewer to 127 more)	⊕◯◯◯ Very low	
Vaccine response - H3N2												
1	observational studies	serious[a]	not serious	not serious	not serious	none	4/29 (13.8%)	7/16 (43.8%)	**RR 0.32** (0.11 to 0.92)	**298 fewer per 1,000** (from 389 fewer to 35 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Vaccine response - B influenza												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/29 (34.5%)	6/16 (37.5%)	**RR 0.92** (0.41 to 2.06)	**30 fewer per 1,000** (from 221 fewer to 398 more)	⊕◯◯◯ Very low	
Post-vaccine seroprotection - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	serious[a]	not serious	not serious	serious[b]	none	25/52 (48.1%)	39/45 (86.7%)	**RR 0.49** (0.17 to 1.46)	**442 fewer per 1,000** (from 719 fewer to 399 more)	⨁◯◯◯ Very low	

Post-vaccine seroprotection - H3N2

2	observational studies	serious[a]	not serious	not serious	serious[b]	none	23/52 (44.2%)	40/45 (88.9%)	**RR 0.46** (0.19 to 1.07)	**480 fewer per 1,000** (from 720 fewer to 62 more)	⨁◯◯◯ Very low	

Post-vaccine seroprotection - B influenza

2	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/52 (61.5%)	30/45 (66.7%)	**RR 0.61** (0.06 to 6.04)	**260 fewer per 1,000** (from 627 fewer to 1,000 more)	⨁◯◯◯ Very low	

Post-vaccine GMT - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	23	29	-	MD **55.1 lower** (56.46 lower to 53.74 lower)	⊕◯◯◯ Very low	Favors healthy controls

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	not serious	none	23	29	-	MD **30.1 lower** (31.4 lower to 28.8 lower)	⊕◯◯◯ Very low	Favors healthy controls

Post-vaccine GMT – B

1	observational studies	serious[a]	not serious	not serious	not serious	none	23	29	-	MD **18.8 lower** (20.14 lower to 17.46 lower)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational studies

b. Wide CI crosses no-effect line

Table 7: Among patients with RA treated with RTX compared to RA patients on csDMARDs who receive the influenza vaccine outcomes are more favorable to patients on csDMARD's than to patients on RTX. [7, 8]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	RA-csDMARDs	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - H1N1												
1	observational studies	serious[a]	not serious	not serious	not serious	none	7/29 (24.1%)	10/17 (58.8%)	**RR 0.41** (0.19 to 0.88)	**347 fewer per 1,000** (from 476 fewer to 71 fewer)	⊕◯◯◯ Very low	Favors RA patients on csDMARD's
Vaccine response - H3N2												
1	observational studies	serious[a]	not serious	not serious	not serious	none	4/29 (13.8%)	11/17 (64.7%)	**RR 0.21** (0.08 to 0.57)	**511 fewer per 1,000** (from 595 fewer to 278 fewer)	⊕◯◯◯ Very low	Favors RA patients on csDMARD's
Vaccine response - B influenza												
1	observational studies	serious[a]	not serious	not serious	not serious	none	10/29 (34.5%)	13/17 (76.5%)	**RR 0.45** (0.26 to 0.79)	**421 fewer per 1,000** (from 566 fewer to 161 fewer)	⊕◯◯◯ Very low	Favors RA patients on csDMARD's
Post-vaccine seroprotection - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	RA-csDMARDs	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	serious[a]	not serious	not serious	serious[b]	none	25/52 (48.1%)	28/37 (75.7%)	**RR 0.59** (0.30 to 1.16)	**310 fewer per 1,000** (from 530 fewer to 121 more)	⊕◯◯◯ Very low	

Post-vaccine seroprotection - H3N2

2	observational studies	serious[a]	not serious	not serious	not serious	none	23/52 (44.2%)	29/37 (78.4%)	**RR 0.56** (0.36 to 0.85)	**345 fewer per 1,000** (from 502 fewer to 118 fewer)	⊕◯◯◯ Very low	

Post-vaccine seroprotection - B-influenza

2	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/52 (61.5%)	22/37 (59.5%)	**RR 0.94** (0.63 to 1.41)	**36 fewer per 1,000** (from 220 fewer to 244 more)	⊕◯◯◯ Very low	

Post-vaccine GMT - H1N1

1	observational studies	serious[a]	not serious	not serious	not serious	none	23	20	-	MD **29.1 lower** (30.75 lower to 27.45 lower)	⊕◯◯◯ Very low	Favors RA patients on csDMARD's

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	RA-csDMARDs	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine GMT - H3N2												
1	observational studies	serious[a]	not serious	not serious	not serious	none	23	20	-	MD **19.8 lower** (21.12 lower to 18.48 lower)	⨁◯◯◯ Very low	Favors RA patients on csDMARD's
Post-vaccine GMT – B												
1	observational studies	serious[a]	not serious	not serious	not serious	none	23	20	-	MD **2.5 lower** (3.97 lower to 1.03 lower)	⨁◯◯◯ Very low	Favors RA patients on csDMARD's

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational studies

b. Wide CI crosses no-effect line

Table 8. RA-DMARD patients vs. RA-DMARD-naïve patients receiving influenza vaccine. One study compared RA patients treated with DMARD's vs healthy controls and DMARD-naïve RA patients to healthy controls [21]. In both RA patients on DMARD's and DMARD-naïve patients the outcomes were better than in healthy controls, but better in DMARD-naïve patients than in RA+DMARD patients [21].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
Geometric Mean titer H1N1 strain RA+DMARD vs HC												
1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **154.73 lower** (250.99 lower to 58.47 lower)	⊕◯◯◯ Very low	Favors healthy controls
Geometric Mean Titer H1N1 strain RA DMARD Naïve vs HC												
1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **72.64 lower** (167.58 lower to 22.3 higher)	⊕◯◯◯ Very low	
GMT H3N2 strains RA+DMARD vs HC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **83.43 lower** (174.28 lower to 7.42 higher)	⊕◯◯◯ Very low	

GMT H3N2 strain RA DMARD Naïve vs HC

1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **83.43 lower** (174.28 lower to 7.42 higher)	⊕◯◯◯ Very low	

GMT Yamagata strain RA+DMARD vs HC

1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **106.82 higher** (98.71 lower to 312.35 higher)	⊕◯◯◯ Very low	

GMT Yamagata strain RA DMARD Naïve vs HC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **192.26 higher** (106.21 higher to 278.31 higher)	⊕◯◯◯ Very low	Favors RA DMARD-naïve patients

Mean Fold increase in GMT H1N1 strain, RA+DMARD vs HC

1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **0.51 lower** (5.49 lower to 4.47 higher)	⊕◯◯◯ Very low	

Mean Fold increase in GMT H1N1 strain RA DMARD Naïve vs HC

1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **1.89 higher** (5.69 lower to 9.47 higher)	⊕◯◯◯ Very low	

Mean Fold increase in GMT H3N2 strain, RA+DMARD vs HC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **0.99 lower** (3.9 lower to 1.92 higher)	⊕◯◯◯ Very low	

Mean Fold increase in GMT Yamagata strain, RA+DMARD vs HC

1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **2.74 lower** (8.35 lower to 2.87 higher)	⊕◯◯◯ Very low	

Mean Fold increase in GMT Yamagata strain RA DMARD Naïve vs HC

1	observational studies	serious[a]	not serious	not serious	not serious	none	51	45	-	MD **1.14 lower** (8.53 lower to 6.25 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. Observational study

Table 9: RA patients on infliximab who received influenza vaccine (3 wks later) compared to Healthy Controls receiving influenza vaccine; no significant difference in seroconversion or GMT in RA pts on infliximab compared to healthy controls (vaccine 3 weeks after infliximab) [14].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
Humoral response - H1N1												
1	observational studies	serious[a]	not serious	not serious	not serious	none	7/16 (43.8%)	8/17 (47.1%)	**RR 0.93** (0.44 to 1.97)	**33 fewer per 1,000** (from 264 fewer to 456 more)	⊕◯◯◯ Very low	
Humoral response - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	8/16 (50.0%)	10/17 (58.8%)	**RR 0.85** (0.45 to 1.60)	**88 fewer per 1,000** (from 324 fewer to 353 more)	⊕◯◯◯ Very low	

Humoral response - B

1	observational studies	serious[a]	not serious	not serious	not serious	none	8/16 (50.0%)	5/17 (29.4%)	**RR 1.70** (0.70 to 4.12)	**206 more per 1,000** (from 88 fewer to 918 more)	⊕◯◯◯ Very low	

Post-vaccine GMT - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	16	16	-	MD **0.4 lower** (1.57 lower to 0.77 higher)	⊕◯◯◯ Very low	

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	not serious	none	16	16	-	MD **0.6 lower** (1.74 lower to 0.54 higher)	⊕◯◯◯ Very low	

Post-vaccine GMT - B

1	observational studies	serious[a]	not serious	not serious	not serious	none	16	16	-	MD **1.8 lower** (2.94 lower to 0.66 lower)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. No randomization

Table 10: IFX-(vax given 3 wks later) compared to RA-Controls for influenza vaccine response - no significant difference in seroconversion or GMT in RA pts on infliximab compared to RA patients not on infliximab (vaccine 3 wks after infliximab) [14].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
Humoral response - H1N1												
1	observational studies	serious[a]	not serious	not serious	not serious	none	7/16 (43.8%)	11/23 (47.8%)	**RR 0.91** (0.45 to 1.84)	**43 fewer per 1,000** (from 263 fewer to 402 more)	⊕◯◯◯ Very low	
Humoral response - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	8/16 (50.0%)	16/23 (69.6%)	**RR 0.72** (0.41 to 1.26)	**195 fewer per 1,000** (from 410 fewer to 181 more)	⊕◯◯◯ Very low	

Humoral response - B

1	observational studies	serious[a]	not serious	not serious	not serious	none	8/16 (50.0%)	10/23 (43.5%)	**RR 1.15** (0.58 to 2.26)	**65 more per 1,000** (from 183 fewer to 548 more)	⊕◯◯◯ Very low	

Post-vaccine GMT - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	16	23	-	MD **0.3 lower** (1.41 lower to 0.81 higher)	⨁◯◯◯ Very low	

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	not serious	none	16	23	-	MD **0.7 lower** (1.9 lower to 0.5 higher)	⨁◯◯◯ Very low	

Post-vaccine GMT - B

1	observational studies	serious[a]	not serious	not serious	not serious	none	16	23	-	MD **0.8 lower** (2.16 lower to 0.56 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. No randomization

Table 11: RA patients on infliximab-receiving influenza vaccine (given same day) compared to Healthy Controls for influenza vaccine response showed no significant difference in seroconversion but a lower GMT in RA pts on infliximab (vaccine given same day as infliximab) compared to healthy controls [14].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
Humoral response - H1N1												
1	observational studies	serious[a]	not serious	not serious	not serious	none	10/22 (45.5%)	8/17 (47.1%)	**RR 0.97** (0.49 to 1.91)	**14 fewer per 1,000** (from 240 fewer to 428 more)	⊕◯◯◯ Very low	
Humoral response - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	not serious	none	14/22 (63.6%)	10/17 (58.8%)	**RR 1.08** (0.65 to 1.80)	**47 more per 1,000** (from 206 fewer to 471 more)	⨁⨁◯◯ Low	

Humoral response - B

1	observational studies	serious[a]	not serious	not serious	not serious	none	9/22 (40.9%)	5/17 (29.4%)	**RR 1.39** (0.57 to 3.39)	**115 more per 1,000** (from 126 fewer to 703 more)	⨁◯◯◯ Very low	

Post-vaccine GMT - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	22	16	-	MD **0.7 lower** (1.69 lower to 0.29 higher)	⊕◯◯◯ Very low	

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	not serious	none	22	16	-	MD **0.9 lower** (1.79 lower to 0.01 lower)	⊕◯◯◯ Very low	Favors healthy controls

Post-vaccine GMT - B

1	observational studies	serious[a]	not serious	not serious	not serious	none	22	16	-	MD **2.2 lower** (3.29 lower to 1.11 lower)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. No randomization

Table 12: No significant difference in influenza vaccine seroconversion or GMT in RA pts on infliximab compared to RA patients not on infliximab (vaccine given same day as infliximab) [14].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
Humoral response - H1N1												
1	observational studies	serious[a]	not serious	not serious	not serious	none	10/22 (45.5%)	11/23 (47.8%)	**RR 0.95** (0.51 to 1.78)	**24 fewer per 1,000** (from 234 fewer to 373 more)	⊕◯◯◯ Very low	
Humoral response - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	14/22 (63.6%)	16/23 (69.6%)	**RR 0.91** (0.60 to 1.39)	**63 fewer per 1,000** (from 278 fewer to 271 more)	⊕◯◯◯ Very low	

Humoral response - B

1	observational studies	serious[a]	not serious	not serious	not serious	none	9/22 (40.9%)	10/23 (43.5%)	**RR 0.94** (0.47 to 1.87)	**26 fewer per 1,000** (from 230 fewer to 378 more)	⊕◯◯◯ Very low	

Post-vaccine GMT - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	22	23	-	MD **0.6 lower** (1.52 lower to 0.32 higher)	⊕◯◯◯ Very low	

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	not serious	none	22	23	-	MD **1 lower** (1.96 lower to 0.04 lower)	⊕◯◯◯ Very low	Favors RA controls

Post-vaccine GMT - B

1	observational studies	serious[a]	not serious	not serious	not serious	none	22	23	-	MD **1.2 lower** (2.51 lower to 0.11 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. No randomization

Table 13: RA patients on tofacitinib had lower responses (baseline seroprotection, seroprotection, seroconversion) to influenza vaccine compared to RA patients not on tofacitinib (with or without background methotrexate) [9].

"Vaccine response" = seroconversion (>4-fold increase in titer in at least 2/3 antigens). "Seroconversion" = proportion of patients lacking baseline seroprotection that meet the above criteria for seroprotection at 35 days post-vaccination.

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA	PLACEBO (+/- background MTX)	Relative (95% CI)	Absolute (95% CI)		
Vaccine response – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/102 (56.9%)	61/98 (62.2%)	**RR 0.91** (0.73 to 1.15)	**56 fewer per 1,000** (from 168 fewer to 93 more)	⊕⊕⊕◯ Moderate	
Baseline seroprotection – Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA	PLACEBO (+/- background MTX)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	20/102 (19.6%)	32/98 (32.7%)	**RR 0.60** (0.37 to 0.98)	**131 fewer per 1,000** (from 206 fewer to 7 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on tofacitinib

Seroprotection – Influenza

1	randomised trials	not serious	not serious	not serious	serious[a]	none	78/102 (76.5%)	90/98 (91.8%)	**RR 0.83** (0.74 to 0.94)	**156 fewer per 1,000** (from 239 fewer to 55 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on tofacitinib

Seroconversion – Influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA	PLACEBO (+/- background MTX)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/82 (70.7%)	58/66 (87.9%)	**RR 0.80** (0.68 to 0.95)	**176 fewer per 1,000** (from 281 fewer to 44 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on tofacitinib

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide confidence interval and/or small sample size

Table 14: RA patients on tofacitinib monotherapy had similar influenza vaccine responses to RA patients not on DMARDs [9].

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA monotherapy	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
Vaccine response – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	29/45 (64.4%)	29/43 (67.4%)	**RR 0.96** (0.71 to 1.29)	**27 fewer per 1,000** (from 196 fewer to 196 more)	⊕⊕⊕◯ Moderate	
Baseline seroprotection – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	10/45 (22.2%)	13/43 (30.2%)	**RR 0.74** (0.36 to 1.50)	**79 fewer per 1,000** (from 193 fewer to 151 more)	⊕⊕⊕◯ Moderate	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA monotherapy	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
Seroprotection – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	41/45 (91.1%)	39/43 (90.7%)	**RR 1.00** (0.88 to 1.15)	**0 fewer per 1,000** (from 109 fewer to 136 more)	⊕⊕⊕◯ Moderate	No difference
Seroconversion – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	31/35 (88.6%)	26/30 (86.7%)	**RR 1.02** (0.85 to 1.23)	**17 more per 1,000** (from 130 fewer to 199 more)	⊕⊕⊕◯ Moderate	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide confidence interval and/or small sample size

Table 15: RA patients on MTX monotherapy had similar response to influenza vaccine as compared to RA patients on no DMARDs [9].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
Vaccine response – Influenza												
1	observational studies	serious [a]	not serious	not serious	not serious	none	32/55 (58.2%)	29/43 (67.4%)	**RR 0.86** (0.64 to 1.17)	**94 fewer per 1,000** (from 243 fewer to 115 more)	⊕◯◯◯ Very low	
Baseline seroprotection – Influenza												
1	observational studies	serious [a]	not serious	not serious	not serious	none	19/55 (34.5%)	13/43 (30.2%)	**RR 1.14** (0.64 to 2.04)	**42 more per 1,000** (from 109 fewer to 314 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
Seroprotection – Influenza												
1	observational studies	serious [a]	not serious	not serious	not serious	none	51/55 (92.7%)	39/43 (90.7%)	**RR 1.02** (0.91 to 1.15)	**18 more per 1,000** (from 82 fewer to 136 more)	⊕◯◯◯ Very low	No difference
Seroconversion – Influenza												
1	observational studies	serious [a]	not serious	not serious	not serious	none	32/36 (88.9%)	26/30 (86.7%)	**RR 1.03** (0.86 to 1.23)	**26 more per 1,000** (from 121 fewer to 199 more)	⊕◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

b. Not randomized

Table 16: RA patients on tofacitinib monotherapy had SIMILAR responses to influenza vaccine compared to RA pts on MTX monotherapy [9]**.**

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA monotherapy	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Vaccine response – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	29/45 (64.4%)	32/55 (58.2%)	**RR 1.11** (0.81 to 1.51)	**64 more per 1,000** (from 111 fewer to 297 more)	⊕⊕⊕◯ Moderate	
Baseline seroprotection – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	10/45 (22.2%)	19/55 (34.5%)	**RR 0.64** (0.33 to 1.24)	**124 fewer per 1,000** (from 231 fewer to 83 more)	⊕⊕⊕◯ Moderate	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA monotherapy	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Seroprotection – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	41/45 (91.1%)	51/55 (92.7%)	**RR 0.98** (0.87 to 1.11)	**19 fewer per 1,000** (from 121 fewer to 102 more)	⊕⊕⊕◯ Moderate	No difference
Seroconversion – Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	31/35 (88.6%)	32/36 (88.9%)	**RR 1.00** (0.84 to 1.18)	**0 fewer per 1,000** (from 142 fewer to 160 more)	⊕⊕⊕◯ Moderate	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide confidence interval and/or small sample size

Table 17: RA patients on tofacitinib + MTX who received influenza vaccine had lower baseline seroprotection, lower seroprotection response, and lower seroconversion response than RA patients on MTX alone [9].

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	29/57 (50.9%)	32/55 (58.2%)	**RR 0.87** (0.62 to 1.23)	**76 fewer per 1,000** (from 221 fewer to 134 more)	⊕⊕⊕◯ Moderate	
Seroprotection – Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	37/57 (64.9%)	51/55 (92.7%)	**RR 0.70** (0.57 to 0.86)	**278 fewer per 1,000** (from 399 fewer to 130 fewer)	⨁⨁⨁◯ Moderate	Favors patients on MTX

Seroconversion – Influenza

1	randomised trials	not serious	not serious	not serious	serious[a]	none	27/47 (57.4%)	32/36 (88.9%)	**RR 0.65** (0.49 to 0.85)	**311 fewer per 1,000** (from 453 fewer to 133 fewer)	⨁⨁⨁◯ Moderate	Favors patients on MTX

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide confidence interval and/or small sample size

Table 18: TOFA+MTX compared to TOFA monotherapy for influenza response: RA patients on tofacitinib+MTX had similar baseline seroprotection and vaccine response to RA patients on tofacitinib monotherapy, but lower responses (seroprotection, seroconversion) to influenza vaccine compared to RA pts on tofacitinib monotherapy [9]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	TOFA monotherapy	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - Influenza												
1	observational studies	serious [a]	not serious	not serious	not serious	none	29/57 (50.9%)	29/45 (64.4%)	**RR 0.79** (0.56 to 1.10)	**135 fewer per 1,000** (from 284 fewer to 64 more)	⊕◯◯◯ Very low	
Baseline seroprotection - Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	TOFA monotherapy	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	10/57 (17.5%)	10/45 (22.2%)	**RR 0.79** (0.36 to 1.73)	**47 fewer per 1,000** (from 142 fewer to 162 more)	⨁◯◯◯ Very low	

Seroprotection - Influenza

1	observational studies	serious [a]	not serious	not serious	not serious	none	37/57 (64.9%)	41/45 (91.1%)	**RR 0.71** (0.58 to 0.88)	**264 fewer per 1,000** (from 383 fewer to 109 fewer)	⨁◯◯◯ Very low	Favors patients on TOFA monotherapy

Seroconversion - Influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	TOFA monotherapy	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	27/47 (57.4%)	31/35 (88.6%)	**RR 0.65** (0.49 to 0.85)	**310 fewer per 1,000** (from 452 fewer to 133 fewer)	⨁◯◯◯ Very low	Favors patients on TOFA monotherapy

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

Table 19: TOFA+MTX compared to No DMARDs for influenza response: RA patients on tofacitinib+MTX had lower seroprotection and seroconversion compared to RA patients on no DMARD therapy [9]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
Vaccine response – Influenza												
1	observational studies	serious [a]	not serious	not serious	not serious	none	29/57 (50.9%)	29/43 (67.4%)	**RR 0.75** (0.54 to 1.05)	**169 fewer per 1,000** (from 310 fewer to 34 more)	⊕◯◯◯ Very low	
Seroprotection – Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	37/57 (64.9%)	39/43 (90.7%)	**RR 0.72** (0.58 to 0.89)	**254 fewer per 1,000** (from 381 fewer to 100 fewer)	⨁◯◯◯ Very low	

Seroconversion – Influenza

1	observational studies	serious [a]	not serious	not serious	not serious	none	37/57 (64.9%)	39/43 (90.7%)	**RR 0.72** (0.58 to 0.89)	**254 fewer per 1,000** (from 381 fewer to 100 fewer)	⨁◯◯◯ Very low	Favors patients not on DMARD's

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

Table 20: Seroconversion in response to influenza vaccine was lower in JIA patients vs healthy controls; similar in JIA patients on MTX vs not on MTX; and similar in JIA patients on TNFi vs not on TNFi. [25]

Level of Evidence: Very Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Drug	No drug	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, total												
1	observational studies	serious[a]	not serious	not serious	not serious	none	79/95 (83.2%)	87/91 (95.6%)	**RR 0.87** (0.79 to 0.96)	**124 fewer per 1,000** (from 201 fewer to 38 fewer)	⊕◯◯◯ Very low	Favors patients not on drugs
Seroconversion, JIA patients on MTX vs not on MTX												
1	observational studies	serious[a]	not serious	not serious	not serious	none	39/47 (83.0%)	40/48 (83.3%)	**RR 1.00** (0.83 to 1.19)	**0 fewer per 1,000** (from 142 fewer to 158 more)	⊕◯◯◯ Very low	No difference

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Drug	No drug	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, JIA pts on TNFi vs not on TNFi												
1	observational studies	serious[a]	not serious	not serious	not serious	none	15/16 (93.8%)	64/79 (81.0%)	**RR 1.16** (0.98 to 1.37)	**130 more per 1,000** (from 16 fewer to 300 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

Table 21: Rituximab compared to No rituximab for Influenza in patients with lymphoproliferative disease: Seroconversion and seroprotection were clinically, but not statistically, lower in lymphoproliferative disease patients on rituximab compared to patients not on rituximab [31]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	No rituximab	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, Rituximab vs no rituximab												
1	observational studies	serious [b]	not serious	serious[b]	not serious	none	2/14 (14.3%)	10/26 (38.5%)	**RR 0.37** (0.09 to 1.46)	**242 fewer per 1,000** (from 350 fewer to 177 more)	⊕◯◯◯ Very low	
Seroprotection, rituximab vs no rituximab												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	No rituximab	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	serious[b]	not serious	none	3/14 (21.4%)	12/26 (46.2%)	**RR 0.46** (0.16 to 1.37)	**249 fewer per 1,000** (from 388 fewer to 171 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. No randomization

b. Non-RMD population

Table 22: Immune response RA compared to healthy controls 7 days after immunization: In an open-label trial with RA patients and healthy controls, the immune response was in favor of healthy controls but the results are imprecise [10].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immune response RA	HC	Relative (95% CI)	Absolute (95% CI)		
Immune response, RA vs HC												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	15/25 (60.0%)	14/19 (73.7%)	**OR 0.54** (0.15 to 1.96)	**135 fewer per 1,000** (from 441 fewer to 109 more)	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. Open-label trial

b. Wide CI crosses significant effect and no-effect lines

Table 23: JIA pts on MTX, TNFi, or both had similar seroprotection responses to influenza vaccine compared to healthy controls [26].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/solomon Islands H1N1												
1	observational studies	serious[a]	not serious	not serious	not serious	none	26/31 (83.9%)	5/10 (50.0%)	**RR 1.68** (0.89 to 3.18)	**340 more per 1,000** (from 55 fewer to 1,000 more)	⊕◯◯◯ Very low	
Seroprotection, A/Wisconsin H3N2												
1	observational studies	serious[a]	not serious	not serious	not serious	none	27/31 (87.1%)	9/10 (90.0%)	**RR 0.97** (0.76 to 1.24)	**27 fewer per 1,000** (from 216 fewer to 216 more)	⊕◯◯◯ Very low	
Seroprotection, B/Malaysia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	27/31 (87.1%)	9/10 (90.0%)	**RR 0.97** (0.76 to 1.24)	**27 fewer per 1,000** (from 216 fewer to 216 more)	⨁◯◯◯ Very low	

Seroprotection, A/Brisbane H1N1

1	observational studies	serious[a]	not serious	not serious	not serious	none	13/15 (86.7%)	6/6 (100.0%)	**RR 0.91** (0.68 to 1.22)	**90 fewer per 1,000** (from 320 fewer to 220 more)	⨁◯◯◯ Very low	

Seroprotection, A/Brisbane H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	10/15 (66.7%)	4/6 (66.7%)	**RR 1.00** (0.51 to 1.95)	**0 fewer per 1,000** (from 327 fewer to 633 more)	⊕◯◯◯ Very low	

Seroprotection, B/Florida

1	observational studies	serious[a]	not serious	not serious	not serious	none	9/15 (60.0%)	4/6 (66.7%)	**RR 0.90** (0.45 to 1.81)	**67 fewer per 1,000** (from 367 fewer to 540 more)	⊕◯◯◯ Very low	

Seroconversion, A/solomon Islands H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	7/12 (58.3%)	4/5 (80.0%)	**RR 0.73** (0.38 to 1.39)	**216 fewer per 1,000** (from 496 fewer to 312 more)	⨁◯◯◯ Very low	

Seroconversion, A/Wisconsin H3N2

1	observational studies	serious[a]	not serious	not serious	not serious	none	6/13 (46.2%)	6/8 (75.0%)	**RR 0.62** (0.30 to 1.25)	**285 fewer per 1,000** (from 525 fewer to 188 more)	⨁◯◯◯ Very low	

Seroconversion, B/Malaysia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	8/14 (57.1%)	2/4 (50.0%)	**RR 1.14** (0.39 to 3.36)	**70 more per 1,000** (from 305 fewer to 1,000 more)	⨁◯◯◯ Very low	

Seroconversion, A/Brisbane H1N1

1	observational studies	serious[a]	not serious	not serious	not serious	none	4/6 (66.7%)	1/1 (100.0%)	**RR 0.86** (0.32 to 2.27)	**140 fewer per 1,000** (from 680 fewer to 1,000 more)	⨁◯◯◯ Very low	

Seroconversion, A/Brisbane H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	4/9 (44.4%)	3/5 (60.0%)	**RR 0.74** (0.27 to 2.06)	**156 fewer per 1,000** (from 438 fewer to 636 more)	⨁◯◯◯ Very low	

Seroconversion, B/Florida

1	observational studies	serious[a]	not serious	not serious	not serious	none	6/12 (50.0%)	2/3 (66.7%)	**RR 0.75** (0.28 to 2.00)	**167 fewer per 1,000** (from 480 fewer to 667 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

Table 24: RA patients on tocilizumab had similar seroconversion and seroprotection response to influenza vaccine compared to RA patients on conventional DMARDs [15]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on Tocilizumab	RA pts on DMARD	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A(NC) Toci vs DMARD												
1	observational studies	serious[a]	not serious	not serious	not serious	none	17/38 (44.7%)	18/24 (75.0 %)	**RR 0.60** (0.39 to 0.91)	**300 fewer per 1,000** (from 458 fewer to 67 fewer)	⊕◯◯◯ Very low	Favors patients on csDMARD's
Seroconversion, A(HIR) Toci vs DMARD												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on Tocilizumab	RA pts on DMARD	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	18/38 (47.4%)	13/24 (54.2%)	**RR 0.87** (0.53 to 1.44)	**70 fewer per 1,000** (from 255 fewer to 238 more)	⊕◯◯◯ Very low	

Seroconversion, B(MAL) Toci vs DMARD

1	observational studies	serious[a]	not serious	not serious	not serious	none	24/38 (63.2%)	19/24 (79.2%)	**RR 0.80** (0.58 to 1.10)	**158 fewer per 1,000** (from 333 fewer to 79 more)	⊕◯◯◯ Very low	

Seroprotection, A(NC) Toci vs DMARD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on Tocilizumab	RA pts on DMARD	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	36/38 (94.7%)	22/24 (91.7%)	**RR 1.03** (0.90 to 1.19)	**28 more per 1,000** (from 92 fewer to 174 more)	⊕◯◯◯ Very low	No difference

Seroprotection, A(HIR) Toci vs DMARD

1	observational studies	serious[a]	not serious	not serious	not serious	none	35/38 (92.1%)	23/24 (95.8%)	**RR 0.96** (0.85 to 1.09)	**38 fewer per 1,000** (from 144 fewer to 86 more)	⊕◯◯◯ Very low	No difference

Seroprotection, B(MAL) Toci vs DMARD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on Tocilizumab	RA pts on DMARD	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	32/38 (84.2%)	21/24 (87.5%)	**RR 0.96** (0.78 to 1.18)	**35 fewer per 1,000** (from 192 fewer to 157 more)	⨁◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

Table 25: RA patients on tocilizumab had SIMILAR seroconversion response to influenza vaccine as RA patients on TNFi [15].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on TNFi	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A(NC) Toci vs TNFi												
1	observational studies	serious[a]	not serious	not serious	not serious	none	17/38 (44.7%)	6/15 (40.0%)	**RR 1.12** (0.55 to 2.28)	**48 more per 1,000** (from 180 fewer to 512 more)	⊕◯◯◯ Very low	
Seroconversion, A(HIR) Toci vs TNFi												
1	observational studies	serious[a]	not serious	not serious	not serious	none	18/38 (47.4%)	8/15 (53.3%)	**RR 0.89** (0.50 to 1.59)	**59 fewer per 1,000** (from 267 fewer to 315 more)	⊕◯◯◯ Very low	
Seroconversion, B(MAL) Toci vs TNFi												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	24/38 (63.2%)	4/15 (26.7%)	**RR 2.37** (0.99 to 5.67)	**365 more per 1,000** (from 3 fewer to 1,000 more)	⊕◯◯◯ Very low	

Seroprotection, A(NC) Toci vs TNFi

1	observational studies	serious[a]	not serious	not serious	not serious	none	36/38 (94.7%)	11/15 (73.3%)	**RR 1.29** (0.94 to 1.77)	**213 more per 1,000** (from 44 fewer to 565 more)	⊕◯◯◯ Very low	

Seroprotection, A(HIR) Toci vs TNFi

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	35/36 (97.2%)	12/15 (80.0%)	**RR 1.22** (0.94 to 1.57)	**176 more per 1,000** (from 48 fewer to 456 more)	⊕◯◯◯ Very low	

Seroprotection, B(MAL) Toci vs TNFi

1	observational studies	serious[a]	not serious	not serious	not serious	none	32/38 (84.2%)	8/15 (53.3%)	**RR 1.58** (0.96 to 2.59)	**309 more per 1,000** (from 21 fewer to 848 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

Table 26: RA pts treated with adalimumab had SIMILAR seroconversion response to influenza vaccine compared to those treated with placebo [16]

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adalimumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, influenza, >=2 out of 3 antigens												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	51/99 (51.5%)	69/109 (63.3%)	**RR 0.81** (0.64 to 1.03)	**120 fewer per 1,000** (from 228 fewer to 19 more)	⊕⊕⊕◯ Moderate	
Seroconversion, influenza, H1N1												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	50/99 (50.5%)	61/109 (56.0%)	**RR 0.90** (0.70 to 1.17)	**56 fewer per 1,000** (from 168 fewer to 95 more)	⊕⊕⊕◯ Moderate	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adalimumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, influenza, H3N2												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/99 (58.6%)	74/109 (67.9%)	**RR 0.86** (0.70 to 1.06)	**95 fewer per 1,000** (from 204 fewer to 41 more)	⊕⊕⊕◯ Moderate	
Seroconversion, influenza, B (Hong Kong)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	48/99 (48.5%)	66/109 (60.6%)	**RR 0.80** (0.62 to 1.03)	**121 fewer per 1,000** (from 230 fewer to 18 more)	⊕⊕⊕◯ Moderate	
Seroprotection, influenza, >=2 out of 3 antigens												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adalimumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	97/99 (98.0%)	103/109 (94.5%)	**RR 1.04** (0.98 to 1.09)	**38 more per 1,000** (from 19 fewer to 85 more)	⨁⨁⨁⨁ High	No difference

CI: confidence interval; **RR:** risk ratio

Explanation

a – Wide CI crosses significant effect and no-effect lines

Table 27: MTX compared to MTX + RTX for health problem or population: RA patients treated with MTX have slightly better outcomes for 4-fold and 2-fold titer increase at 4 weeks after immunization, but the results are imprecise [11].

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	MTX + RTX	Relative (95% CI)	Absolute (95% CI)		
Patients with 4-fold titer increase 4 weeks												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	11/26 (42.3%)	25/64 (39.1%)	**RR 1.08** (0.63 to 1.86)	**31 more per 1,000** (from 145 fewer to 336 more)	⊕⊕⊕◯ Moderate	
Patients with 2-fold titer increase 4 weeks												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	16/26 (61.5%)	34/64 (53.1%)	**RR 1.16** (0.79 to 1.70)	**85 more per 1,000** (from 112 fewer to 372 more)	⊕⊕⊕◯ Moderate	
GMT 4 weeks after vaccine												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	26	64	-	MD **1.3 higher** (1.74 lower to 4.34 higher)	⊕⊕⊕◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide CI crosses significant effect and no-effect lines

Table 28: JIA patients on biologics (TNFi, IL-6 inhibitors) had similar seroprotection response compared to JIA patients not on biologics [28].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biological	no biological	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/H1N1, bio vs no bio												
1	observational studies	serious [a]	not serious	not serious	not serious	none	24/25 (96.0%)	10/10 (100.0%)	**RR 0.99** (0.84 to 1.16)	**10 fewer per 1,000** (from 160 fewer to 160 more)	⊕◯◯◯ Very low	No difference
Seroprotection, A/H3N2, bio vs no bio												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biological	no biological	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	24/25 (96.0%)	10/10 (100.0%)	**RR 0.99** (0.84 to 1.16)	**10 fewer per 1,000** (from 160 fewer to 160 more)	⨁◯◯◯ Very low	No difference

Seroprotection, B, bio vs no bio

1	observational studies	serious [a]	not serious	not serious	not serious	none	22/25 (88.0%)	9/10 (90.0%)	**RR 0.98** (0.76 to 1.26)	**18 fewer per 1,000** (from 216 fewer to 234 more)	⨁◯◯◯ Very low	

Seroconversion, A/H1N1, bio vs no bio

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biological	no biological	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	15/25 (60.0%)	8/10 (80.0%)	**RR 0.75** (0.48 to 1.17)	**200 fewer per 1,000** (from 416 fewer to 136 more)	⨁◯◯◯ Very low	

Seroconversion, A/H3N2, bio vs no bio

1	observational studies	serious [a]	not serious	not serious	not serious	none	15/25 (60.0%)	7/10 (70.0%)	**RR 0.86** (0.51 to 1.44)	**98 fewer per 1,000** (from 343 fewer to 308 more)	⨁◯◯◯ Very low	

Seroconversion, B, bio vs no bio

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biological	no biological	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	9/25 (36.0%)	8/10 (80.0%)	**RR 0.45** (0.25 to 0.83)	**440 fewer per 1,000** (from 600 fewer to 136 fewer)	⨁◯◯◯ Very low	Favors patients not on biologics

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

Table 29: Patients with mixed rheumatic diseases who were not on immunosuppressive treatment had similar outcomes as patients on immunosuppressive treatment [46].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IS	no IS	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, seasonal												
1	observational studies	serious[a]	not serious	not serious	not serious	none	75/94 (79.8%)	65/75 (86.7%)	**RR 0.92** (0.80 to 1.05)	**69 fewer per 1,000** (from 173 fewer to 43 more)	⊕◯◯◯ Very low	No difference
Seroprotection, pandemic												
1	observational studies	serious[a]	not serious	not serious	not serious	none	68/108 (63.0%)	59/86 (68.6%)	**RR 0.92** (0.75 to 1.12)	**55 fewer per 1,000** (from 172 fewer to 82 more)	⊕◯◯◯ Very low	
Seroconversion, seasonal												
1	observational studies	serious[a]	not serious	not serious	not serious	none	30/94 (31.9%)	31/75 (41.3%)	**RR 0.77** (0.52 to 1.15)	**95 fewer per 1,000** (from 198 fewer to 62 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IS	no IS	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, pandemic												
1	observational studies	serious[a]	not serious	not serious	not serious	none	47/108 (43.5%)	42/86 (48.8%)	**RR 0.89** (0.66 to 1.21)	**54 fewer per 1,000** (from 166 fewer to 103 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

Table 30: Patients on immunosuppressants (corticosteroids >=10mg/day, cytotoxic agents) had more favorable outcomes than patients on biologics (rituximab, adalimumab, etanercept or infliximab). Results are imprecise. **[46]**.

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IS	Biotherapy	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, seasonal												
1	observational studies	serious[a]	not serious	not serious	not serious	none	75/94 (79.8%)	9/15 (60.0%)	**RR 1.33** (0.87 to 2.04)	**198 more per 1,000** (from 78 fewer to 624 more)	⊕◯◯◯ Very low	
Seroprotection, pandemic												
1	observational studies	serious[a]	not serious	not serious	not serious	none	68/108 (63.0%)	5/16 (31.3%)	**RR 2.01** (0.96 to 4.23)	**316 more per 1,000** (from 13 fewer to 1,000 more)	⊕◯◯◯ Very low	
Seroconversion, seasonal												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IS	Biotherapy	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	30/94 (31.9%)	1/15 (6.7%)	**RR 4.79** (0.70 to 32.54)	**253 more per 1,000** (from 20 fewer to 1,000 more)	⨁◯◯◯ Very low	

Seroconversion, pandemic

1	observational studies	serious[a]	not serious	not serious	not serious	none	18/108 (16.7%)	0/16 (0.0%)	**RR 5.77** (0.36 to 91.37)	**30 more per 1,000** (from 4 fewer to 565 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

Table 31: Seroconversion after influenza vaccine among pediatric rheumatic disease patients compared to controls.

Summary: This study has controversial results showing outcomes for H1N1 more favorable to healthy controls than to pediatric RMD patients, while outcomes for H3N2 and B strains are more favorable to pediatric RMD patients, but the results are very imprecise [45].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion, peds rheum dis	control	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A/H1N1, peds RD vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	21/49 (42.9%)	19/36 (52.8%)	**RR 0.81** (0.52 to 1.27)	**100 fewer per 1,000** (from 253 fewer to 143 more)	⊕◯◯◯ Very low	
Seroconversion, A/H3N2, peds RD vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25/49 (51.0%)	13/36 (36.1%)	**RR 1.41** (0.85 to 2.36)	**148 more per 1,000** (from 54 fewer to 491 more)	⊕◯◯◯ Very low	
Seroconversion, B, peds RD vs control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion, peds rheum dis	control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	22/49 (44.9%)	13/36 (36.1%)	**RR 1.24** (0.73 to 2.12)	**87 more per 1,000** (from 98 fewer to 404 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 32: Seroprotection after influenza vaccine among individuals with inflammatory bowel disease on TNFi compared to not on TNFi

Summary: In this study there was no difference between outcomes in both groups except for A/Switz/H3N2 titer which was more favorable for group with no TNFi treatment **[32].**

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroprotection, TNFi	No TNFi	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/Cal/H1N1, TNFi vs No TNFi												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16/27 (59.3%)	67/101 (66.3%)	**RR 0.89** (0.63 to 1.26)	**73 fewer per 1,000** (from 245 fewer to 172 more)	⊕◯◯◯ Very low	
Seroprotection, A/Switz/H3N2, TNFi vs No TNFi												
1	observational studies	serious[a]	not serious	not serious	not serious	none	14/27 (51.9%)	86/101 (85.1%)	**RR 0.61** (0.42 to 0.88)	**332 fewer per 1,000** (from 494 fewer to 102 fewer)	⊕◯◯◯ Very low	Favors no TNFi
Seroprotection, B/Phuket, TNFi vs No TNFi												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroprotection, TNFi	No TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	23/27 (85.2%)	82/101 (81.2%)	**RR 1.05** (0.87 to 1.26)	**41 more per 1,000** (from 106 fewer to 211 more)	⨁◯◯◯ Very low	No difference

Seroprotection, B/Texas, TNFi vs No TNFi

1	observational studies	serious[a]	not serious	not serious	not serious	none	22/27 (81.5%)	85/101 (84.2%)	**RR 0.97** (0.79 to 1.18)	**25 fewer per 1,000** (from 177 fewer to 151 more)	⨁◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 33: Response to seasonal influenza vaccine at 3-5 weeks among individuals with rheumatic diseases (RD) compared to controls [34].

Level of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
Seasonal flu, ELISA A IgG, RD vs Control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	137	54	-	MD **4 lower** (7.6 lower to 0.4 lower)	⊕◯◯◯ Very low	Favors controls
Seasonal flu, ELISA A IgA, RD vs Control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	137	54	-	MD **3.3 higher** (0.17 higher to 6.43 higher)	⊕◯◯◯ Very low	Favors RD
Seasonal flu, ELISA B IgG, RD vs Control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	137	54	-	MD **7.1 lower** (11.1 lower to 3.1 lower)	⊕◯◯◯ Very low	Favors control

Seasonal flu, ELISA B IgA, RD vs Control

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	137	54	-	MD **2.3 higher** (0.56 lower to 5.16 higher)	⊕◯◯◯ Very low	

Seasonal flu, H1N1 GMT, RD vs Control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	137	54	-	MD **48.7 higher** (3.7 lower to 101.1 higher)	⊕◯◯◯ Very low	

Seasonal flu, H3N2 GMT, RD vs Control

1	observational studies	serious [a]	not serious	not serious	not serious	none	137	54	-	MD **753 lower** (1036.41 lower to 469.59 lower)	⊕◯◯◯ Very low	Favors control

Seasonal flu, Flu B GMT, RD vs Control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	137	54	-	MD **8.8 higher** (65.65 lower to 83.25 higher)	⊕◯◯◯ Very low	

Seasonal flu, H1N1 seroprotection, RD vs control

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	122/137 (89.1%)	50/54 (92.6%)	**RR 0.96** (0.87 to 1.06)	**37 fewer per 1,000** (from 120 fewer to 56 more)	⊕◯◯◯ Very low	

Seasonal flu, H3N2 seroprotection, RD vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	133/137 (97.1%)	54/54 (100.0 %)	**RR 0.98** (0.94 to 1.02)	**20 fewer per 1,000** (from 60 fewer to 20 more)	⊕◯◯◯ Very low	

Seasonal flu, Flu B seroprotection, RD vs control

1	observational studies	serious [a]	not serious	not serious	not serious	none	134/137 (97.8%)	54/54 (100.0 %)	**RR 0.98** (0.95 to 1.02)	**20 fewer per 1,000** (from 50 fewer to 20 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
Seasonal flu, H1N1 seroresponse, RD vs control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	67/133 (50.4%)	13/54 (24.1%)	**RR 2.09** (1.27 to 3.46)	**262 more per 1,000** (from 65 more to 592 more)	⊕◯◯◯ Very low	Favors RD
Seasonal flu, H3N2 seroresponse, RD vs control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	38/134 (28.4%)	8/17 (47.1%)	**RR 0.60** (0.34 to 1.07)	**188 fewer per 1,000** (from 311 fewer to 33 more)	⊕◯◯◯ Very low	

Seasonal flu, Flu B seroresponse, RD vs control

1	observational studies	serious [a]	not serious	not serious	not serious	none	43/129 (33.3%)	17/50 (34.0%)	**RR 0.98** (0.62 to 1.55)	**7 fewer per 1,000** (from 129 fewer to 187 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 34: Response to influenza A/H1N1 2009 vaccine (JDM compared to pediatric healthy controls), at 3 weeks was not significantly different between RMD patients and healthy controls [36]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to influenza A/H1N1 2009 vaccine (JDM	pediatric healthy controls), 3 weeks	Relative (95% CI)	Absolute (95% CI)		
Seroprotection at 21 days - after immunization												
1	observational studies	serious[a]	not serious	not serious	not serious	none	27/30 (90.0%)	79/81 (97.5%)	**RR 0.92** (0.81 to 1.04)	**78 fewer per 1,000** (from 185 fewer to 39 more)	⊕◯◯◯ Very low	
Seroconversion (at 21 days post vaccine)												
1	observational studies	serious[a]	not serious	not serious	not serious	none	26/30 (86.7%)	79/81 (97.5%)	**RR 0.89** (0.77 to 1.03)	**107 fewer per 1,000** (from 224 fewer to 29 more)	⊕◯◯◯ Very low	
GMT at 21 days - after immunization												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to influenza A/H1N1 2009 vaccine (JDM	pediatric healthy controls), 3 weeks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	30	81	-	MD **0.7 lower** (115.04 lower to 113.64 higher)	⨁◯◯◯ Very low	

Fold increase in GMT (21 days post immunization)

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	30	81	-	MD **1.2 lower** (9.72 lower to 7.32 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 35: SLE patients have lower seroprotection and seroconversion rates in response to influenza vaccine compared to healthy controls [2].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	HC	Relative (95% CI)	Absolute (95% CI)		
Seroprotection at 21 days												
1	observational studies	serious [a]	not serious	not serious	not serious	none	359/555 (64.7%)	143/170 (84.1%)	**RR 0.77** (0.70 to 0.84)	**193 fewer per 1,000** (from 252 fewer to 135 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroconversion at day 21												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	HC	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	337/555 (60.7%)	136/170 (80.0%)	**RR 0.76** (0.69 to 0.84)	**192 fewer per 1,000** (from 248 fewer to 128 fewer)	⨁◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

Table 36: Meds compared to no meds in seroprotection, seroconversion response to influenza vaccine in SLE patients

Summary: Among SLE patients, those on DMARDs had significantly LOWER seroprotection response to influenza vaccine compared to those on no medications. When broken down by medication, patients on azathioprine, methotrexate, and MMF all showed lower seroprotection responses, but these individual differences were not statistically significant. Chloroquine was not associated with a difference in seroprotection response, regardless of whether used as monotherapy or in combination with a DMARD. SLE pts on pred >20 mg/day did not have a different seroprotection response to influenza vaccine [2].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meds	no meds	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - SLE on chloroquine monotherapy vs no medications												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	82/105 (78.1%)	56/75 (74.7%)	**RR 1.05** (0.89 to 1.24)	**37 more per 1,000** (from 82 fewer to 179 more)	⊕◯◯◯ Very low	No difference
Seroprotection: SLE on DMARD vs no medications												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meds	no meds	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	49/95 (51.6%)	56/75 (74.7%)	**RR 0.69** (0.55 to 0.87)	**231 fewer per 1,000** (from 336 fewer to 97 fewer)	⊕◯◯◯ Very low	Favors patients not on DMARD

Seroprotection: SLE on DMARD vs no medications - On aza

1	observational studies	serious [a]	not serious	not serious	serious[b]	none	21/38 (55.3%)	19/25 (76.0%)	**RR 0.73** (0.51 to 1.04)	**205 fewer per 1,000** (from 372 fewer to 30 more)	⊕◯◯◯ Very low	

Seroprotection: SLE on DMARD vs no medications - On mtx

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meds	no meds	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	14/27 (51.9%)	19/25 (76.0%)	**RR 0.68** (0.45 to 1.04)	**243 fewer per 1,000** (from 418 fewer to 30 more)	⨁◯◯◯ Very low	

Seroprotection: SLE on DMARD vs no medications - On mmf

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	14/30 (46.7%)	18/25 (72.0%)	**RR 0.65** (0.41 to 1.02)	**252 fewer per 1,000** (from 425 fewer to 14 more)	⨁◯◯◯ Very low	

Seroprotection: SLE on DMARD vs DMARD + chloroquine

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meds	no meds	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	56/95 (58.9%)	31/46 (67.4%)	**RR 0.87** (0.67 to 1.14)	**88 fewer per 1,000** (from 222 fewer to 94 more)	⨁◯◯◯ Very low	

Seroprotection: SLE on pred >/=20mg/day with and without DMARD

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	47/76 (61.8%)	48/76 (63.2%)	**RR 0.98** (0.77 to 1.25)	**13 fewer per 1,000** (from 145 fewer to 158 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 37: RA on anti-TNFa compared to health controls receiving influenza vaccine found outcomes differ by each strain, but no substantial difference between groups with high imprecision for each outcome [22].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on anti-TNFa	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion 30 days 2005/2006 H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/22 (45.5%)	5/10 (50.0%)	**RR 0.91** (0.42 to 1.96)	**45 fewer per 1,000** (from 290 fewer to 480 more)	⊕◯◯◯ Very low	
Seroconversion 30 days 2005/2006 H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/22 (36.4%)	6/10 (60.0%)	**RR 0.61** (0.29 to 1.28)	**234 fewer per 1,000** (from 426 fewer to 168 more)	⊕◯◯◯ Very low	
Seroconversion 30 days 2005/2006 B												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on anti-TNFa	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/22 (13.6%)	2/10 (20.0%)	**RR 0.68** (0.13 to 3.46)	**64 fewer per 1,000** (from 174 fewer to 492 more)	⊕◯◯◯ Very low	

Seroprotection 30 days 2005/2006 H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	15/22 (68.2%)	9/10 (90.0%)	**RR 0.76** (0.53 to 1.08)	**216 fewer per 1,000** (from 423 fewer to 72 more)	⊕◯◯◯ Very low	

Seroprotection 30 days 2005/2006 H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/22 (77.3%)	8/10 (80.0%)	**RR 0.97** (0.66 to 1.42)	**24 fewer per 1,000** (from 272 fewer to 336 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on anti-TNFa	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection 30 days 2005/2006 B												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	11/22 (50.0%)	4/10 (40.0%)	**RR 1.25** (0.53 to 2.97)	**100 more per 1,000** (from 188 fewer to 788 more)	⊕◯◯◯ Very low	
Seroconversion 30 days 2006/2007 H1N1												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	8/22 (36.4%)	3/8 (37.5%)	**RR 0.97** (0.34 to 2.78)	**11 fewer per 1,000** (from 247 fewer to 668 more)	⊕◯◯◯ Very low	
Seroconversion 30 days 2006/2007 H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on anti-TNFa	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	1/22 (4.5%)	0/10 (0.0%)	**RR 1.43** (0.06 to 32.46)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	

Seroconversion 30 days 2006/2007 B

1	observational studies	serious[a]	not serious	not serious	serious[a]	none	1/22 (4.5%)	0/8 (0.0%)	**RR 1.17** (0.05 to 26.23)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	

Seroprotection 30 days 2006/2007 H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16/22 (72.7%)	8/8 (100.0%)	**RR 0.76** (0.56 to 1.03)	**240 fewer per 1,000** (from 440 fewer to 30 more)	⊕◯◯◯ Very low	

Seroprotection 30 days 2006/2007 H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on anti-TNFa	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	18/22 (81.8%)	8/8 (100.0%)	**RR 0.85** (0.66 to 1.10)	**150 fewer per 1,000** (from 340 fewer to 100 more)	⊕◯◯◯ Very low	

Seroprotection 30 days 2007/2008 B

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/22 (59.1%)	7/8 (87.5%)	**RR 0.68** (0.44 to 1.04)	**280 fewer per 1,000** (from 490 fewer to 35 more)	⊕◯◯◯ Very low	

Seroconversion 30 days 2007/2008 H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/20 (40.0%)	3/7 (42.9%)	**RR 0.93** (0.34 to 2.56)	**30 fewer per 1,000** (from 283 fewer to 669 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on anti-TNFa	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion 30 days 2007/2008 H3N2												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	3/20 (15.0%)	2/7 (28.6%)	**RR 0.53** (0.11 to 2.52)	**134 fewer per 1,000** (from 254 fewer to 434 more)	⊕◯◯◯ Very low	
Seroconversion 30 days 2007/2008 B												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	3/20 (15.0%)	2/7 (28.6%)	**RR 0.53** (0.11 to 2.52)	**134 fewer per 1,000** (from 254 fewer to 434 more)	⊕◯◯◯ Very low	
Seroprotection 30 days 2007/2008 H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on anti-TNFa	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16/20 (80.0%)	7/7 (100.0%)	**RR 0.84** (0.63 to 1.12)	**160 fewer per 1,000** (from 370 fewer to 120 more)	⊕◯◯◯ Very low	

Seroprotection 30 days 2007/2008 H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/20 (85.0%)	5/7 (71.4%)	**RR 1.19** (0.72 to 1.97)	**136 more per 1,000** (from 200 fewer to 693 more)	⊕◯◯◯ Very low	

Seroprotection 30 days 2007/2008 B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on anti-TNFa	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/20 (85.0%)	5/7 (71.4%)	**RR 1.19** (0.72 to 1.97)	**136 more per 1,000** (from 200 fewer to 693 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 38: PICO 3 SLE compared to Healthy controls, week 4 post influenza vaccine, outcomes (seroconversion, seroprotection) were favorable to healthy controls compared to SLE patients [3]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 3 SLE	Healthy controls, week 4	Relative (95% CI)	Absolute (95% CI)		
Seroconversion week 4 H1N1												
1	observational studies	serious [a]	not serious	not serious	not serious	none	33/62 (53.2%)	39/47 (83.0%)	**RR 0.64** (0.49 to 0.84)	**299 fewer per 1,000** (from 423 fewer to 133 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroconversion week 4 H3N2												
1	observational studies	serious [a]	not serious	not serious	not serious	none	34/62 (54.8%)	40/47 (85.1%)	**RR 0.64** (0.50 to 0.83)	**306 fewer per 1,000** (from 426 fewer to 145 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroconversion week 4 Type B												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 3 SLE	Healthy controls, week 4	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	35/62 (56.5%)	34/47 (72.3%)	**RR 0.78** (0.59 to 1.03)	**159 fewer per 1,000** (from 297 fewer to 22 more)	⨁◯◯◯ Very low	

Seroprotection week 4 H1N1

1	observational studies	serious [a]	not serious	not serious	not serious	none	38/62 (61.3%)	46/47 (97.9%)	**RR 0.63** (0.51 to 0.77)	**362 fewer per 1,000** (from 480 fewer to 225 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroprotection week 4 H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 3 SLE	Healthy controls, week 4	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	41/62 (66.1%)	44/47 (93.6%)	**RR 0.71** (0.58 to 0.86)	**271 fewer per 1,000** (from 393 fewer to 131 fewer)	⊕◯◯◯ Very low	Favors healthy controls

Seroprotection week 4 Type B

1	observational studies	serious [a]	not serious	not serious	not serious	none	45/62 (72.6%)	42/47 (89.4%)	**RR 0.81** (0.68 to 0.97)	**170 fewer per 1,000** (from 286 fewer to 27 fewer)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

Table 39: RA on biologics compared to RA not on biologics for influenza vaccine response: RA patients on biologics had SIMILAR response to influenza vaccine compared to RA patients not on biologics (biologics included both TNFi and tocilizumab) [13].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on biologics	RA not on biologics	Relative (95% CI)	Absolute (95% CI)		
RA on biologics vs RA not on biologics - seroprotecton												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/36 (47.2%)	32/53 (60.4%)	**RR 0.78** (0.52 to 1.18)	**133 fewer per 1,000** (from 290 fewer to 109 more)	⊕◯◯◯ Very low	
RA on biologics vs RA not on biologics - seroresponse												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on biologics	RA not on biologics	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	14/36 (38.9%)	31/53 (58.5%)	**RR 0.66** (0.42 to 1.06)	**199 fewer per 1,000** (from 339 fewer to 35 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small numbers

Table 40: RA patients on TNFi had similar or HIGHER responses to influenza vaccine compared to healthy controls. Response defined as seropositive OR seroconversion at 4-6 weeks [17].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on TNFi	HC	Relative (95% CI)	Absolute (95% CI)		
Response, A/H1N1/New Caledonia												
1	observational studies	serious [a]	not serious	not serious	not serious	none	12/27 (44.4%)	9/52 (17.3%)	**RR 2.57** (1.24 to 5.32)	**272 more per 1,000** (from 42 more to 748 more)	⊕◯◯◯ Very low	Favors patients on TNFi
Response, A/H3N2/Hiroshima												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on TNFi	HC	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	12/27 (44.4%)	13/52 (25.0%)	**RR 1.78** (0.94 to 3.34)	**195 more per 1,000** (from 15 fewer to 585 more)	⊕◯◯◯ Very low	

Response, B/Malaysia

1	observational studies	serious [a]	not serious	not serious	not serious	none	8/27 (29.6%)	5/52 (9.6%)	**RR 3.08** (1.12 to 8.51)	**200 more per 1,000** (from 12 more to 722 more)	⊕◯◯◯ Very low	Favors patients on TNFi

CI: confidence interval; **RR:** risk ratio

Explanations

a. No randomization

Table 41: RA patients on TNFi had SIMILAR responses to influenza vaccine compared to RA not on TNFi. Response defined as seropositive OR seroconversion at 4-6 weeks. [17].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on TNFi	RA not on TNFi	Relative (95% CI)	Absolute (95% CI)		
Response, A/H1N1/New Caledonia												
1	observational studies	serious [a]	not serious	not serious	not serious	none	12/27 (44.4%)	8/36 (22.2%)	**RR 2.00** (0.95 to 4.20)	**222 more per 1,000** (from 11 fewer to 711 more)	⊕◯◯◯ Very low	Favors patients on TNFi
Response, A/H3N2/Hiroshima												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on TNFi	RA not on TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	12/27 (44.4%)	12/36 (33.3%)	**RR 1.33** (0.71 to 2.49)	**110 more per 1,000** (from 97 fewer to 497 more)	⊕◯◯◯ Very low	

Response, B/Malaysia

1	observational studies	serious [a]	not serious	not serious	not serious	none	8/27 (29.6%)	8/36 (22.2%)	**RR 1.33** (0.57 to 3.10)	**73 more per 1,000** (from 96 fewer to 467 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. No randomization

Table 42: Compared to AAV patients, healthy controls had more favorable responses to influenza vaccine with statistical significance for factor increase GMT [48]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated AAV	vaccinated healthy individuals	Relative (95% CI)	Absolute (95% CI)		
Factor increase GMT - H1N1												
1	observational studies	serious [a]	not serious	not serious	not serious	none	24	53	-	MD **7.2 lower** (11.22 lower to 3.18 lower)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT - H3N2												
1	observational studies	serious [a]	not serious	not serious	not serious	none	24	53	-	MD **9.44 lower** (15.48 lower to 3.4 lower)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT - B-Malay												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated AAV	vaccinated healthy individuals	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	24	53	-	MD **2.09 lower** (3.61 lower to 0.57 lower)	⊕◯◯◯ Very low	Favors healthy controls

Seroconversion - H1N1

1	observational studies	serious	not serious	not serious	serious [b]	none	13/24 (54.2%)	34/53 (64.2%)	**RR 0.84** (0.56 to 1.28)	**103 fewer per 1,000** (from 282 fewer to 180 more)	⊕◯◯◯ Very low	

Seroconversion - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated AAV	vaccinated healthy individuals	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious	not serious	not serious	not serious	none	12/24 (50.0%)	43/53 (81.1%)	**RR 0.62** (0.40 to 0.94)	**308 fewer per 1,000** (from 487 fewer to 49 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroconversion - B-Malay

1	observational studies	serious	not serious	not serious	serious[b]	none	8/24 (33.3%)	24/53 (45.3%)	**RR 0.74** (0.39 to 1.39)	**118 fewer per 1,000** (from 276 fewer to 177 more)	⨁◯◯◯ Very low	

Seroprotection - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated AAV	vaccinated healthy individuals	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious	not serious	not serious	not serious	none	17/24 (70.8%)	48/53 (90.6%)	**RR 0.78** (0.60 to 1.03)	**199 fewer per 1,000** (from 362 fewer to 27 more)	⨁◯◯◯ Very low	

Seroprotection - H3N2

1	observational studies	serious	not serious	not serious	not serious	none	17/24 (70.8%)	51/53 (96.2%)	**RR 0.74** (0.57 to 0.96)	**250 fewer per 1,000** (from 414 fewer to 38 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroprotection - B-Malay

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated AAV	vaccinated healthy individuals	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious	not serious	not serious	serious	none	10/24 (41.7%)	30/53 (56.6%)	**RR 0.74** (0.43 to 1.25)	**147 fewer per 1,000** (from 323 fewer to 142 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 43: RA patients had lower response to influenza vaccine compared to healthy controls. [12]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - pH1N1												
1	observational studies	serious [a]	not serious	not serious	not serious	none	204/340 (60.0%)	194/234 (82.9%)	**RR 0.72** (0.65 to 0.80)	**232 fewer per 1,000** (from 290 fewer to 166 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT - pH1N1												
1	observational studies	serious [a]	not serious	not serious	not serious	none	340	234	-	MD **6 lower** (8.36 lower to 3.64 lower)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion - pH1N1												
1	observational studies	serious [a]	not serious	not serious	not serious	none	181/340 (53.2%)	180/234 (76.9%)	**RR 0.69** (0.61 to 0.78)	**238 fewer per 1,000** (from 300 fewer to 169 fewer)	⨁◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

Table 44: RA pts have mostly lower responses to influenza vaccine compared to age-matched controls [12].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA	age-matched controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - pH1N1												
1	observational studies	serious [a]	not serious	not serious	not serious	none	59/88 (67.0%)	153/184 (83.2%)	**RR 0.81** (0.69 to 0.95)	**158 fewer per 1,000** (from 258 fewer to 42 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT - pH1N1												
1	observational studies	serious [a]	not serious	not serious	not serious	none	88	184	-	MD **2.8 lower** (6.31 lower to 0.71 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA	age-matched controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion												
1	observational studies	serious [a]	not serious	not serious	not serious	none	56/88 (63.6%)	140/184 (76.1%)	**RR 0.84** (0.70 to 1.00)	**122 fewer per 1,000** (from 228 fewer to 0 fewer)	⨁◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

Table 45: RA patients on MTX had lower response to influenza vaccine compared to healthy controls [12].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious [a]	not serious	not serious	not serious	none	114/215 (53.0%)	194/234 (82.9%)	**RR 0.64** (0.56 to 0.73)	**298 fewer per 1,000** (from 365 fewer to 224 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT												
1	observational studies	serious [a]	not serious	not serious	not serious	none	215	234	-	MD **7.7 lower** (9.97 lower to 5.43 lower)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion												
1	observational studies	serious [a]	not serious	not serious	not serious	none	100/215 (46.5%)	180/234 (76.9%)	**RR 0.60** (0.52 to 0.71)	**308 fewer per 1,000** (from 369 fewer to 223 fewer)	⨁◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

Table 46: RA patients on chloroquine had lower responses to influenza vaccine compared to healthy control [12].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-CQ	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious [a]	not serious	not serious	not serious	none	73/124 (58.9%)	194/234 (82.9%)	**RR 0.71** (0.61 to 0.83)	**240 fewer per 1,000** (from 323 fewer to 141 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT												
1	observational studies	serious [a]	not serious	not serious	not serious	none	124	234	-	MD **6.6 lower** (9.16 lower to 4.04 lower)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-CQ	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion												
1	observational studies	serious [a]	not serious	not serious	not serious	none	62/124 (50.0%)	180/234 (76.9%)	**RR 0.65** (0.54 to 0.79)	**269 fewer per 1,000** (from 354 fewer to 162 fewer)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

Table 47: RA patients on steroids had lower responses to influenza vaccine compared to healthy controls [12].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious [a]	not serious	not serious	not serious	none	146/247 (59.1%)	194/234 (82.9%)	**RR 0.71** (0.63 to 0.80)	**240 fewer per 1,000** (from 307 fewer to 166 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT												
1	observational studies	serious [a]	not serious	not serious	not serious	none	247	234	-	MD **6.8 lower** (9.49 lower to 4.11 lower)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion												
1	observational studies	serious [a]	not serious	not serious	not serious	none	122/247 (49.4%)	180/234 (76.9%)	**RR 0.64** (0.56 to 0.74)	**277 fewer per 1,000** (from 338 fewer to 200 fewer)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

Table 48: RA-MTX compared to RA-no MTX: RA patients on MTX had lower responses to influenza vaccine compared to RA patients not on MTX [12].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	RA-no MTX	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious [a]	not serious	not serious	not serious	none	114/215 (53.0%)	90/125 (72.0%)	**RR 0.74** (0.62 to 0.87)	**187 fewer per 1,000** (from 274 fewer to 94 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT												
1	observational studies	serious [a]	not serious	not serious	not serious	none	215	125	-	MD **5.9 lower** (9 lower to 2.8 lower)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	RA-no MTX	Relative (95% CI)	Absolute (95% CI)		
Seroconversion												
1	observational studies	serious [a]	not serious	not serious	not serious	none	100/215 (46.5%)	82/125 (65.6%)	**RR 0.71** (0.59 to 0.86)	**190 fewer per 1,000** (from 269 fewer to 92 fewer)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

Table 49: RA-steroids compared to RA-no steroids: RA patients on steroid had similar seroprotection response to influenza compared to RA patients not on steroid [12].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	RA-no steroids	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious [a]	not serious	not serious	not serious	none	146/247 (59.1%)	56/93 (60.2%)	**RR 0.98** (0.81 to 1.19)	**12 fewer per 1,000** (from 114 fewer to 114 more)	⊕◯◯◯ Very low	No difference
Factor increase GMT												
1	observational studies	serious [a]	not serious	not serious	not serious	none	247	93	-	MD **1.1 lower** (3.22 lower to 1.02 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	RA-no steroids	Relative (95% CI)	Absolute (95% CI)		
Seroconversion												
1	observational studies	serious [a]	not serious	not serious	not serious	none	122/247 (49.4%)	51/93 (54.8%)	**RR 0.90** (0.72 to 1.13)	**55 fewer per 1,000** (from 154 fewer to 71 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

Table 50: bDMARDs monotherapy compared to controls for influenza vaccine response in mixed rheumatic disease: Mixed RMD patients on biological monotherapy had lower GMT responses; SIMILAR seroprotection to 3/3 antigens, and SIMILAR seroconversion to 2/3 antigens as compared to healthy controls [47]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Cal H1N1 bDMARDs mono vs controls												
1	observational studies	serious[a,b]	not serious	not serious	serious[b]	none	80	15	-	MD **145.1 lower** (247.78 lower to 42.42 lower)	⨁◯◯◯ Very low	Favors healthy controls
GMT, A/Swi H3N2 bDMARDs mono vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	80	15	-	MD **89 lower** (137.22 lower to 40.78 lower)	⨁◯◯◯ Very low	Favors healthy controls
GMT, B/Phu Yamagata bDMARDs mono vs controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[b]	not serious	not serious	serious[b]	none	80	15	-	MD **35.1 lower** (67.35 lower to 2.85 lower)	⨁◯◯◯ Very low	Favors healthy controls

Seroprotection, A/Cal H1N1 bDMARDs mono vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66/66 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	

Seroprotection, A/Swi H3N2 bDMARDs mono vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	65/66 (98.5%)	13/13 (100.0%)	**RR 1.01** (0.91 to 1.13)	**10 more per 1,000** (from 90 fewer to 130 more)	⨁◯◯◯ Very low	

Seroprotection, B/Phu Yamagata bDMARDs mono vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66/66 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	

Seroconversion, A/Cal H1N1 bDMARDs mono vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/58 (13.8%)	3/9 (33.3%)	**RR 0.41** (0.13 to 1.28)	**197 fewer per 1,000** (from 290 fewer to 93 more)	⨁◯◯◯ Very low	

Seroconversion, A/Swi H3N2 bDMARDs mono vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/58 (15.5%)	6/9 (66.7%)	**RR 0.23** (0.11 to 0.50)	**513 fewer per 1,000** (from 593 fewer to 333 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroconversion, B/Phu Yamagata bDMARDs mono vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/58 (5.2%)	2/9 (22.2%)	**RR 0.23** (0.04 to 1.21)	**171 fewer per 1,000** (from 213 fewer to 47 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 51: BDMARDs+DMARDs compared to controls for influenza vaccine response in mixed rheumatic disease

Summary: Mixed RMD patients on combination therapy (biological plus conventional DMARDs) had lower GMT responses; SIMILAR seroprotection to 3/3 antigens, and similar seroconversion to 2/3 antigens as compared to healthy controls [47]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs + DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Cal H1N1 bDMARDs+DMARDs vs controls												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	110	15	-	MD **133.6 lower** (235.89 lower to 31.31 lower)	⨁◯◯◯ Very low	Favors healthy controls
GMT, A/Swi H3N2 bDMARDs+DMARDs vs controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs + DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	110	15	-	MD **104.7 lower** (151.45 lower to 57.95 lower)	⨁◯◯◯ Very low	Favors healthy controls

GMT, B/Phu Yamagata bDMARDs+DMARDs vs controls

1	observational studies	serious [a]	not serious	not serious	serious[b]	none	110	15	-	MD **36.6 lower** (68.43 lower to 4.77 lower)	⨁◯◯◯ Very low	Favors healthy controls

Seroprotection, A/Cal H1N1 bDMARDs+DMARDs vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs + DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	98/99 (99.0%)	13/13 (100.0 %)	**RR 1.02** (0.92 to 1.13)	**20 more per 1,000** (from 80 fewer to 130 more)	⊕◯◯◯ Very low	No difference

Seroprotection, A/Swi H3N2 bDMARDs+DMARDs vs controls

1	observational studies	serious [a]	not serious	not serious	serious[b]	none	96/99 (97.0%)	13/13 (100.0 %)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⊕◯◯◯ Very low	No difference

Seroprotection, B/Phu Yamagata bDMARDs+DMARDs vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs + DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	99/99 (100.0%)	13/13 (100.0 %)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	No difference

Seroconversion, A/Cal H1N1 bDMARDs+DMARDs vs controls

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	24/86 (27.9%)	3/9 (33.3%)	**RR 0.84** (0.31 to 2.24)	**53 fewer per 1,000** (from 230 fewer to 413 more)	⨁◯◯◯ Very low	

Seroconversion, A/Swi H3N2 bDMARDs+DMARDs vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs + DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/86 (19.8%)	6/9 (66.7%)	**RR 0.30** (0.16 to 0.56)	**467 fewer per 1,000** (from 560 fewer to 293 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroconversion, B/Phu Yamagata bDMARDs+DMARDs vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/86 (5.8%)	2/9 (22.2%)	**RR 0.26** (0.06 to 1.16)	**164 fewer per 1,000** (from 209 fewer to 36 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 52: Rituximab compared to controls for influenza vaccine response in mixed rheumatic disease: Mixed RMD patients on rituximab had LOWER GMT responses but SIMILAR seroprotection and SIMILAR seroconversion to influenza vaccine as compared to healthy controls [47].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Cal H1N1 rituximab vs controls												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	5	15	-	MD **182 lower** (285.83 lower to 78.17 lower)	⊕◯◯◯ Very low	Favors healthy controls
GMT, A/Swi H3N2 rituximab vs controls												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	5	15	-	MD **44.3 lower** (137.79 lower to 49.19 higher)	⊕◯◯◯ Very low	
GMT, B/Phu Yamagata rituximab vs controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	5	15	-	MD **4.3 higher** (61.98 lower to 70.58 higher)	⨁◯◯◯ Very low	

Seroprotection, A/Cal H1N1 rituximab vs controls

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	5/5 (100.0%)	13/13 (100.0 %)	**RR 1.00** (0.77 to 1.30)	**0 fewer per 1,000** (from 230 fewer to 300 more)	⨁◯◯◯ Very low	

Seroprotection, A/Swi H3N2 rituximab vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [b]	not serious	not serious	serious[b]	none	5/5 (100.0%)	13/13 (100.0 %)	**RR 1.00** (0.77 to 1.30)	**0 fewer per 1,000** (from 230 fewer to 300 more)	⨁◯◯◯ Very low	

Seroprotection, B/Phu Yamagata rituximab vs controls

1	observational studies	serious [a]	not serious	not serious	serious[b]	none	5/5 (100.0%)	13/13 (100.0 %)	**RR 1.00** (0.77 to 1.30)	**0 fewer per 1,000** (from 230 fewer to 300 more)	⨁◯◯◯ Very low	

Seroconversion, A/Cal H1N1 rituximab vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	0/4 (0.0%)	3/9 (33.3%)	**RR 0.29** (0.02 to 4.52)	**237 fewer per 1,000** (from 327 fewer to 1,000 more)	⨁◯◯◯ Very low	

Seroconversion, A/Swi H3N2 rituximab vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	1/4 (25.0%)	6/9 (66.7%)	**RR 0.38** (0.06 to 2.18)	**413 fewer per 1,000** (from 627 fewer to 787 more)	⨁◯◯◯ Very low	

Seroconversion, B/Phu Yamagata rituximab vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	2/4 (50.0%)	2/9 (22.2%)	**RR 2.25** (0.47 to 10.78)	**278 more per 1,000** (from 118 fewer to 1,000 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 53: RA-MTX vs HC, RA-RTX vs HC, RA-RTX vs RA-MTX (H1N1/H3N2-IgG1/IgG3, IgG4) response to influenza vaccine

Summary: This study examined the outcomes for H1N1 and H3N2-specific IgG1/IgG3, and IgG4. The IgG levels were slightly better or equal in healthy controls compared to patients in RA-MTX group, significantly better than in patients in RA-MTX group, and the outcomes in RA-MTX group were better than in patients RA-RTX group, however due to the low number of patients the results are imprecise [23].

Level of Evidence: Very low.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Group	Control Group	Relative (95% CI)	Absolute (95% CI)		
H1N1-specific IgG1 for RA-MTX vs HC												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	20	28	-	MD **14.23 lower** (68.43 lower to 39.97 higher)	⊕◯◯◯ Very low	
H3N2-specific IgG1 for RA-MTX vs HC												
1	observational studies	serious[a]	not serious	not serious	not serious	none	20	28	-	MD **1.21 higher** (85.74 lower to 88.16 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Group	Control Group	Relative (95% CI)	Absolute (95% CI)		
H1N1-specific IgG3 for RA-MTX vs HC												
1	observational studies	serious [a]	not serious	not serious	not serious	none	20	28	-	MD **0.84 lower** (1.65 lower to 0.02 lower)	⊕◯◯◯ Very low	Favors healthy controls
H3N2-specific IgG3 for RA-MTX vs HC												
1	observational studies	serious [a]	not serious	not serious	not serious	none	20	28	-	MD **0.46 lower** (1.23 lower to 0.3 higher)	⊕◯◯◯ Very low	
H1N1-specific IgG4 for RA-MTX vs HC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Group	Control Group	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	20	28	-	MD **0.01 lower** (0.24 lower to 0.21 higher)	⊕◯◯◯ Very low	

H3N2-specific IgG4 for RA-MTX vs HC

1	observational studies	serious [a]	not serious	not serious	not serious	none	20	28	-	MD **0.32 lower** (0.95 lower to 0.3 higher)	⊕◯◯◯ Very low	

H1N1-specific IgG1 for RA-RTX vs HC

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	23	28	-	MD **37.36 lower** (85.39 lower to 10.67 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Group	Control Group	Relative (95% CI)	Absolute (95% CI)		
H3N2-specific IgG1 for RA-RTX vs HC												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	23	28	-	MD **59.69 lower** (108.45 lower to 10.93 lower)	⊕◯◯◯ Very low	Favors healthy controls
H1N1-specific IgG3 for RA-RTX vs HC												
1	observational studies	serious [a]	not serious	not serious	not serious	none	23	28	-	MD **0.87 lower** (1.73 lower to 0)	⊕◯◯◯ Very low	Favors healthy controls
H3N2-specific IgG3 for RA-RTX vs HC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Group	Control Group	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[a]	none	23	28	-	MD **0.65 lower** (1.42 lower to 0.11 higher)	⨁◯◯◯ Very low	

H1N1-specific IgG4 for RA-RTX vs HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	28	-	MD **0.16 lower** (0.39 lower to 0.07 higher)	⨁◯◯◯ Very low	

H3N2-specific IgG4 for RA-RTX vs HC

1	observational studies	serious[a]	not serious	not serious	not serious	none	23	28	-	MD **0.49 lower** (1.09 lower to 0.1 higher)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Group	Control Group	Relative (95% CI)	Absolute (95% CI)		
H1N1-specific IgG1 for RA-RTX vs RA-MTX												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	20	-	MD **23.13 lower** (74.9 lower to 28.64 higher)	⊕◯◯◯ Very low	
H3N2-specific IgG1 for RA-RTX vs RA-MTX												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	20	-	MD **60.9 lower** (137.24 lower to 15.44 higher)	⊕◯◯◯ Very low	
H1N1-specific IgG3 for RA-RTX vs RA-MTX												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Group	Control Group	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	23	20	-	MD **0.03 lower** (0.42 lower to 0.37 higher)	⊕◯◯◯ Very low	

H3N2-specific IgG3 for RA-RTX vs RA-MTX

1	observational studies	serious [a]	not serious	not serious	not serious	none	23	20	-	MD **0.19 lower** (0.57 lower to 0.2 higher)	⊕◯◯◯ Very low	

H1N1-specific IgG4 for RA-RTX vs RA-MTX

1	observational studies	serious [a]	not serious	not serious	not serious	none	23	20	-	MD **0.15 lower** (0.21 lower to 0.08 lower)	⊕◯◯◯ Very low	Favors RA-MTX patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention Group	Control Group	Relative (95% CI)	Absolute (95% CI)		
H3N2-specific IgG4 for RA-RTX vs RA-MTX												
1	observational studies	serious [a]	not serious	not serious	not serious	none	23	20	-	MD **0.17 lower** (0.4 lower to 0.05 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. Observational studies

b. Wide CI interval crosses significant effect and no-effect line

Table 54: RMD-RTX compared to Healthy controls, for influenza vaccine response

Summary: RMD patients on rituximab had LOWER seroconversion rates in response to influenza vaccine as compared to healthy controls. Pre-vaccination antibody titers to influenza antigens were SIMILAR; post-vaccination titers were LOWER in the rituximab group [37].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD-RTX	Healthy controls,	Relative (95% CI)	Absolute (95% CI)		
Seroconversion (1+/3 antigens)												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	2/12 (16.7%)	10/15 (66.7%)	**RR 0.25** (0.07 to 0.93)	**500 fewer per 1,000** (from 620 fewer to 47 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Mean pre-vaccine Ab titer - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD-RTX	Healthy controls,	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **38.33 lower** (80.86 lower to 4.2 higher)	⊕◯◯◯ Very low	

Mean pre-vaccine Ab titer - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **13.33 lower** (31.6 lower to 4.93 higher)	⊕◯◯◯ Very low	

Mean pre-vaccine Ab titer – B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD-RTX	Healthy controls,	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious	none	12	15	-	MD **55 lower** (97.88 lower to 12.12 lower)	⨁◯◯◯ Very low	Favors healthy controls

Mean post-vaccine Ab titer - H1N1

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	12	15	-	MD **60 lower** (115.5 lower to 4.5 lower)	⨁◯◯◯ Very low	Favors healthy controls

Mean post-vaccine Ab titer - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD-RTX	Healthy controls,	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **103.33 lower** (191.77 lower to 14.89 lower)	⊕◯◯◯ Very low	Favors healthy controls

Mean post-vaccine Ab titer - B

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **178.33 lower** (277.95 lower to 78.71 lower)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 55: Immunogenicity of JIA compared to control, on various meds, at 1 and 6 months were similar to healthy controls [29].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on different meds	Healthy Control	Relative (95% CI)	Absolute (95% CI)		
Seroprotection 1 month after seasonal flu vaccine in JIA vs HC												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	21/31 (67.7%)	11/14 (78.6%)	**RR 0.86** (0.60 to 1.24)	**110 fewer per 1,000** (from 314 fewer to 189 more)	⊕◯◯◯ Very low	
Seroprotection at 6 months												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	24/31 (77.4%)	11/14 (78.6%)	**RR 0.99** (0.71 to 1.37)	**8 fewer per 1,000** (from 228 fewer to 291 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational studies

b. Wide CI crosses significant effect and no-effect lines

Table 56: Influenza vaccine response among SLE patients prednisone compared to no medications: SLE patients on prednisone had similar seroconversion and seroprotection responses to influenza vaccine to SLE patients not on prednisone. ("vaccine efficacy" = seroconversion and/or seroprotection) [4]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⊕◯◯◯ Very low	
Vaccine efficacy - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⨁◯◯◯ Very low	

Vaccine efficacy - B-influenza

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/14 (35.7%)	7/12 (58.3%)	**RR 0.61** (0.26 to 1.43)	**228 fewer per 1,000** (from 432 fewer to 251 more)	⨁◯◯◯ Very low	

Seroprotection - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/14 (92.9%)	11/12 (91.7%)	**RR 1.01** (0.81 to 1.27)	**9 more per 1,000** (from 174 fewer to 248 more)	⊕◯◯◯ Very low	

Seroprotection - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/14 (85.7%)	12/12 (100.0%)	**RR 0.87** (0.67 to 1.11)	**130 fewer per 1,000** (from 330 fewer to 110 more)	⊕◯◯◯ Very low	

Seroprotection - B-influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/14 (57.1%)	11/12 (91.7%)	**RR 0.62** (0.38 to 1.01)	**348 fewer per 1,000** (from 568 fewer to 9 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 57: Influenza vaccine response among SLE patients: AZA compared to No medications: SLE patients on azathioprine had similar seroconversion and seroprotection responses to influenza vaccine to SLE patients not on azathioprine. ("vaccine efficacy" = seroconversion and/or seroprotection). They had lower seroprotection to 1 out of 3 antigens [4].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: AZA	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/13 (30.8%)	7/12 (58.3%)	**RR 0.53** (0.20 to 1.36)	**274 fewer per 1,000** (from 467 fewer to 210 more)	⊕◯◯◯ Very low	
Vaccine efficacy - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	1/13 (7.7%)	7/12 (58.3%)	**RR 0.13** (0.02 to 0.92)	**508 fewer per 1,000** (from 572 fewer to 47 fewer)	⊕◯◯◯ Very low	Favors SLE patients not on AZA

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: AZA	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - B-influenza												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/13 (23.1%)	7/12 (58.3%)	**RR 0.40** (0.13 to 1.19)	**350 fewer per 1,000** (from 508 fewer to 111 more)	⊕◯◯◯ Very low	
Seroprotection - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/13 (69.2%)	11/12 (91.7%)	**RR 0.76** (0.51 to 1.13)	**220 fewer per 1,000** (from 449 fewer to 119 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: AZA	No medications	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/13 (61.5%)	12/12 (100.0%)	**RR 0.63** (0.41 to 0.98)	**370 fewer per 1,000** (from 590 fewer to 20 fewer)	⊕◯◯◯ Very low	Favors SLE patients not on AZA
Seroprotection - B-influenza												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/13 (61.5%)	11/12 (91.7%)	**RR 0.67** (0.42 to 1.07)	**302 fewer per 1,000** (from 532 fewer to 64 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 58: SLE patients on hydroxychloroquine had similar seroconversion and seroprotection responses to influenza vaccine to SLE patients not on hydroxychloroquine [4]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/17 (41.2%)	7/12 (58.3%)	**RR 0.71** (0.34 to 1.48)	**169 fewer per 1,000** (from 385 fewer to 280 more)	⊕◯◯◯ Very low	
Vaccine efficacy - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/17 (47.1%)	7/12 (58.3%)	**RR 0.81** (0.40 to 1.62)	**111 fewer per 1,000** (from 350 fewer to 362 more)	⨁◯◯◯ Very low	

Vaccine efficacy - B-influenza

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/17 (47.1%)	7/12 (58.3%)	**RR 0.81** (0.40 to 1.62)	**111 fewer per 1,000** (from 350 fewer to 362 more)	⨁◯◯◯ Very low	

Seroprotection - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	14/17 (82.4%)	11/12 (91.7%)	**RR 0.90** (0.68 to 1.19)	**92 fewer per 1,000** (from 293 fewer to 174 more)	⨁◯◯◯ Very low	

Seroprotection - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16/17 (94.1%)	12/12 (100.0%)	**RR 0.95** (0.80 to 1.14)	**50 fewer per 1,000** (from 200 fewer to 140 more)	⨁◯◯◯ Very low	No difference

Seroprotection - B-influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/17 (70.6%)	11/12 (91.7%)	**RR 0.77** (0.54 to 1.09)	**211 fewer per 1,000** (from 422 fewer to 83 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 59: Influenza vaccine response in SLE patients compared to healthy controls

Summary: Two observational studies comparing SLE patients on any medications to healthy controls show that outcomes for vaccine efficacy, seroprotection, seroconversion and GMT increase in favor of healthy controls [4, 5].

Level of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												
1	observational studies	serious [a]	not serious	not serious	not serious	none	24/56 (42.9%)	16/17 (94.1%)	**RR 0.46** (0.33 to 0.63)	**508 fewer per 1,000** (from 631 fewer to 348 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Vaccine efficacy - H3N2												
1	observational studies	serious [a]	not serious	not serious	not serious	none	22/56 (39.3%)	15/17 (88.2%)	**RR 0.45** (0.31 to 0.64)	**485 fewer per 1,000** (from 609 fewer to 318 fewer)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - B-influenza												
1	observational studies	serious [a]	not serious	not serious	not serious	none	23/56 (41.1%)	12/17 (70.6%)	**RR 0.58** (0.38 to 0.90)	**296 fewer per 1,000** (from 438 fewer to 71 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroprotection - H1N1												
2	observational studies	serious [a]	not serious	not serious	not serious	none	83/103 (80.6%)	40/44 (90.9%)	**RR 0.87** (0.77 to 0.98)	**118 fewer per 1,000** (from 209 fewer to 18 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroprotection - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	serious[a]	not serious	not serious	not serious	none	80/103 (77.7%)	40/44 (90.9%)	**RR 0.86** (0.76 to 0.97)	**127 fewer per 1,000** (from 218 fewer to 27 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroprotection - B influenza

2	observational studies	serious[a]	not serious	not serious	serious[b]	none	70/103 (68.0%)	35/44 (79.5%)	**RR 0.85** (0.67 to 1.07)	**119 fewer per 1,000** (from 262 fewer to 56 more)	⨁◯◯◯ Very low	

Seroconversion - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27/47 (57.4%)	22/27 (81.5%)	**RR 0.71** (0.52 to 0.96)	**236 fewer per 1,000** (from 391 fewer to 33 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion - H3N2												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	29/47 (61.7%)	22/27 (81.5%)	**RR 0.76** (0.57 to 1.01)	**196 fewer per 1,000** (from 350 fewer to 8 more)	⊕◯◯◯ Very low	
Seroconversion - B-Malaysia												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	24/47 (51.1%)	17/27 (63.0%)	**RR 0.81** (0.54 to 1.21)	**120 fewer per 1,000** (from 290 fewer to 132 more)	⊕◯◯◯ Very low	
Post-vaccine GMT - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	47	27	-	MD **1138 lower** (1611.96 lower to 664.04 lower)	⊕◯◯◯ Very low	

Post-vaccine GMT - H3N2

1	observational studies	serious [a]	not serious	not serious	not serious	none	47	27	-	MD **988 lower** (1488.58 lower to 487.42 lower)	⊕◯◯◯ Very low	

Post-vaccine GMT - B-Malaysia

1	observational studies	serious [a]	not serious	not serious	not serious	none	47	27	-	MD **874.1 lower** (1318.61 lower to 429.59 lower)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational studies

b. Wide CI crosses significant effect and no-effect lines.

Tale 60: SLE on MTX compared to SLE not on MTX for influenza vaccine response

Summary: One observational study compared SLE patients on MTX to SLE patients not on MTX showed outcomes in favor of SLE patients not on MTX, but the results are very imprecise [4].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on MTX	SLE not on MTX	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine antibody titer - H1N1												
1	observational studies	serious[a]	not serious	not serious	not serious	none	8	39	-	MD **467.9 lower** (1103.61 lower to 167.81 higher)	⨁◯◯◯ Very low	
Post-vaccine antibody titer - H3N2												
1	observational studies	serious[a]	not serious	not serious	not serious	none	8	39	-	MD **376.9 lower** (1079.28 lower to 325.48 higher)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on MTX	SLE not on MTX	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine antibody titer - B-Malay												
1	observational studies	serious[a]	not serious	not serious	not serious	none	8	39	-	MD **339.2 lower** (631.41 lower to 46.99 lower)	⨁◯◯◯ Very low	Favors SLE not on MTX

CI: confidence interval; **MD:** mean difference

Explanations

a. Observational studies

Table 61. SLE patients: Prednisone compared to no medications

Summary: One study comparing SLE patients on prednisone to those not on prednisone showed outcomes are no different for vaccine efficacy and seroprotection [4]. Another study showed the levels of influenza antibody titers in favor of patients not on prednisone with the results very imprecise for H1N1 and H3N2 and high precision for B-Malaysia strain, but the sample size was very small [5]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⨁◯◯◯ Very low	
Vaccine efficacy - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⨁◯◯◯ Very low	

Vaccine efficacy - B-influenza

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/14 (35.7%)	7/12 (58.3%)	**RR 0.61** (0.26 to 1.43)	**228 fewer per 1,000** (from 432 fewer to 251 more)	⨁◯◯◯ Very low	

Seroprotection - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	13/14 (92.9%)	11/12 (91.7%)	**RR 1.01** (0.81 to 1.27)	**9 more per 1,000** (from 174 fewer to 248 more)	⨁◯◯◯ Very low	

Seroprotection - H3N2

1	observational studies	serious[a]	not serious	not serious	not serious	none	12/14 (85.7%)	12/12 (100.0%)	**RR 0.87** (0.67 to 1.11)	**130 fewer per 1,000** (from 330 fewer to 110 more)	⨁◯◯◯ Very low	

Seroprotection - B-influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/14 (57.1%)	11/12 (91.7%)	**RR 0.62** (0.38 to 1.01)	**348 fewer per 1,000** (from 568 fewer to 9 more)	⨁◯◯◯ Very low	

Post-vaccine antibody titer - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	24	-	MD **320 lower** (895.03 lower to 255.03 higher)	⨁◯◯◯ Very low	

Post-vaccine antibody titer - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	24	-	MD **182.6 lower** (765.01 lower to 399.81 higher)	⨁◯◯◯ Very low	

Post-vaccine antibody titer - B-Malay

1	observational studies	serious[a]	not serious	not serious	not serious	none	23	24	-	MD **536.9 lower** (892.88 lower to 180.92 lower)	⨁◯◯◯ Very low	Favors no medications

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational studies

b. Wide CI crosses no-effect line

Table 62: systemic JIA on tocilizumab compared to healthy control for influenza vaccine response: SJIA patients on tocilizumab, as compared to healthy controls, had higher GMT to 1/3 influenza antigens, lower GMT to 2/3 influenza antigens, and similar seroprotection and seroconversion rates [27]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
GMT, A/H1N1, SJIA/toci vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27	17	-	MD **18.5 higher** (15.42 higher to 21.58 higher)	⊕◯◯◯ Very low	Favors sJIA on tocilizumab
GMT, A/H3N2, SJIA/toci vs control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27	17	-	MD **133.4 lower** (135.64 lower to 131.16 lower)	⊕◯◯◯ Very low	Favors healthy control

GMT, B, SJIA/toci vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27	17	-	MD **10.2 lower** (13.16 lower to 7.24 lower)	⊕◯◯◯ Very low	Favors healthy control

Seroprotection, A/H1N1, SJIA/toci vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/27 (88.9%)	13/17 (76.5%)	**RR 1.16** (0.87 to 1.56)	**122 more per 1,000** (from 99 fewer to 428 more)	⊕◯◯◯ Very low	

Seroprotection, A/H3N2, SJIA/toci vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23/27 (85.2%)	17/17 (100.0 %)	**RR 0.86** (0.72 to 1.03)	**140 fewer per 1,000** (from 280 fewer to 30 more)	⊕◯◯◯ Very low	

Seroprotection, B, SJIA/toci vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11/27 (40.7%)	6/17 (35.3%)	**RR 1.15** (0.52 to 2.54)	**53 more per 1,000** (from 169 fewer to 544 more)	⊕◯◯◯ Very low	

Seroconversion, A/H1N1, SJIA/toci vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/27 (48.1%)	8/17 (47.1%)	**RR 1.02** (0.54 to 1.94)	**9 more per 1,000** (from 216 fewer to 442 more)	⊕◯◯◯ Very low	

Seroconversion A/H3N2, SJIA/toci vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/27 (37.0%)	9/17 (52.9%)	**RR 0.70** (0.36 to 1.36)	**159 fewer per 1,000** (from 339 fewer to 191 more)	⨁◯◯◯ Very low	

Seroconversion, B, SJIA/toci vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/27 (14.8%)	2/17 (11.8%)	**RR 1.26** (0.26 to 6.15)	**31 more per 1,000** (from 87 fewer to 606 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 63: Prednisolone <0.2 mg/kg/d compared to Prednisolone >0.2 mg/kg/d for Influenza in SJIA patients on tocilizumab: In SJIA patients on tocilizumab, patients with prednisolone doses <0.2 mg/kg/d had higher GMT response to influenza vaccine than patients with prednisolone doses >0.2 mg/kgd [27]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importan
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisolone <0.2 mg/kg/d	Prednisolone >0.2 mg/kg/d	Relative (95% CI)	Absolute (95% CI)		
GMT, A/H1N1 Pred <0.2 vs Pred >0.2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **24.7 higher** (21.43 higher to 27.97 higher)	⨁◯◯◯ Very low	Favors prednison dose <0.2 mg/kg/d
GMT, A/H3N2 Pred <0.2 vs Pred >0.2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **223.2 higher** (219.83 higher to 226.57 higher)	⨁◯◯◯ Very low	Favors prednison dose <0.2 mg/kg/d
GMT, B Pred <0.2 vs Pred >0.2												

Certainty assessment							№ of patients		Effect		Certainty	Importan
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisolone <0.2 mg/kg/d	Prednisolone >0.2 mg/kg/d	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **7 higher** (4.88 higher to 9.12 higher)	⨁◯◯◯ Very low	Favors prednisor dose <0.2 mg/kg/d

CI: confidence interval; **MD:** mean difference

Explanations

a. Not randomized

b. Small sample size

Table 64: AS/PsA patients on secukinumab compared to healthy controls for influenza vaccine response: AS/PsA patients on secukinumab had SIMILAR response to influenza vaccine as compared to healthy controls (seroconversion) [51].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AS/PsA patients on secukinumab	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Vaccine Response - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/17 (58.8%)	7/13 (53.8%)	**RR 1.09** (0.58 to 2.07)	**48 more per 1,000** (from 226 fewer to 576 more)	⨁◯◯◯ Very low	
Vaccine Response - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AS/PsA patients on secukinumab	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	2/17 (11.8%)	1/13 (7.7%)	**RR 1.53** (0.15 to 15.09)	**41 more per 1,000** (from 65 fewer to 1,000 more)	⨁◯◯◯ Very low	

Vaccine Response - B-Brisbane

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/17 (35.3%)	6/13 (46.2%)	**RR 0.76** (0.32 to 1.83)	**111 fewer per 1,000** (from 314 fewer to 383 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 65: csDMARDs compared to Healthy controls for seropositivity influenza vaccine: Mixed RMD patients on conventional DMARDs had similar response to influenza vaccine as compared to healthy controls. ("seropositivity" not clearly defined) [35].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - Ag A - Adjusted												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	38/46 (82.6%)	44/48 (91.7%)	**RR 0.90** (0.77 to 1.06)	**92 fewer per 1,000** (from 211 fewer to 55 more)	⊕◯◯◯ Very low	
Seroprotection - Ag B - Adjusted												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	28/46 (60.9%)	36/48 (75.0%)	**RR 0.81** (0.61 to 1.08)	**142 fewer per 1,000** (from 293 fewer to 60 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 66: bDMARDs compared to Healthy controls for seropositivity influenza vaccine: Mixed RMD patients on biological DMARDs had similar response to influenza vaccine as compared to healthy controls. ("seropositivity" not clearly defined) [35].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - Ag A - Adjusted												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	63/68 (92.6%)	44/48 (91.7%)	**RR 1.01** (0.91 to 1.13)	**9 more per 1,000** (from 82 fewer to 119 more)	⊕◯◯◯ Very low	No difference
Seroprotection - Ag B - Adjusted												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	44/68 (64.7%)	36/48 (75.0%)	**RR 0.86** (0.68 to 1.10)	**105 fewer per 1,000** (from 240 fewer to 75 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. small sample size

Table 67: bDMARDs compared to csDMARDs for seropositivity influenza vaccine: Mixed RMD patients on conventional DMARDs had similar response to influenza vaccine as compared to RMD patients on biological DMARDs. ("seropositivity" not clearly defined) [35]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs	csDMARDs	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - Ag A - Adjusted												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	63/68 (92.6%)	38/46 (82.6%)	**RR 1.12** (0.97 to 1.30)	**99 more per 1,000** (from 25 fewer to 248 more)	⨁◯◯◯ Very low	
Seroprotection - Ag B - Adjusted												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	44/68 (64.7%)	28/46 (60.9%)	**RR 1.06** (0.79 to 1.42)	**37 more per 1,000** (from 128 fewer to 256 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small sample size

Table 68: RA patients compared to Healthy controls for influenza vaccine response: RA patients had similar responses to influenza vaccine as compared to healthy controls, regardless of specific medication [18]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Factor increase in GMT, RA DMARD vs healthy controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	41	117	-	MD **3.5 lower** (7.25 lower to 0.25 higher)	⊕◯◯◯ Very low	
Factor increase in GMT, RA MTX vs healthy controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	117	-	MD **5.4 lower** (8.9 lower to 1.9 lower)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase in GMT, RA TNFi vs healthy controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	41	117	-	MD **2.8 lower** (6.69 lower to 1.09 higher)	⨁◯◯◯ Very low	

Factor increase in GMT, RA Etanercept vs healthy controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11	117	-	MD **3.8 lower** (7.68 lower to 0.08 higher)	⨁◯◯◯ Very low	

Factor increase in GMT, RA DMARD vs RA TNFi

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	41	41	-	MD **0.7 lower** (4.82 lower to 3.42 higher)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Factor increase in GMT, RA MTX vs RA Etanercept												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	11	-	MD **1.6 lower** (5.48 lower to 2.28 higher)	⊕◯◯◯ Very low	
Seroconversion RA patients on DMARD vs Healthy controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	41	117	-	MD **12.4 lower** (28.66 lower to 3.86 higher)	⊕◯◯◯ Very low	
Seroconversion RA patients on MTX vs Healthy controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	25	117	-	MD **18.3 lower** (38.4 lower to 1.8 higher)	⨁◯◯◯ Very low	

Seroconversion RA patients on TNFi vs Healthy controls

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	41	117	-	MD **8.4 lower** (24.57 lower to 7.77 higher)	⨁◯◯◯ Very low	

Seroconversion RA patients on Etanercept vs Healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	11	117	-	MD **10.7 lower** (36.88 lower to 15.48 higher)	⨁◯◯◯ Very low	

Seroconversion RA patients on DMARD vs RA patients on TNFi

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	41	41	-	MD **4 lower** (24.09 lower to 16.09 higher)	⨁◯◯◯ Very low	

Seroconversion RA pts on MTX vs RA pts on Etanercept

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	25	11	-	MD **7.6 lower** (38.7 lower to 23.5 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. Not randomized

b. Small sample size

Table 69: SpA patients compared to Healthy controls for influenza vaccine response: In SpA patients, patients on TNFi had lower responses as compared to healthy controls; SpA pts on conventional DMARDs had similar or higher responses as compared to SpA pts on TNFi [18].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SpA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Factor increase in GMT, SpA DMARD vs healthy controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	75	117	-	MD **2.4 higher** (2.33 lower to 7.13 higher)	⊕◯◯◯ Very low	
Factor increase in GMT, SpA MTX vs healthy controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	35	117	-	MD **9.7 higher** (0.58 higher to 18.82 higher)	⊕◯◯◯ Very low	Favors SpA patients on MTX
Factor increase in GMT, SpA TNFi vs healthy controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SpA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	79	117	-	MD **5.6 lower** (8.53 lower to 2.67 lower)	⨁◯◯◯ Very low	Favors healthy controls

Factor increase in GMT, SpA Etanercept vs healthy controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	15	117	-	MD **2.2 lower** (5.69 lower to 1.29 higher)	⨁◯◯◯ Very low	

Factor increase in GMT, SpA DMARD vs TNFi

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	75	79	-	MD **8 higher** (3.67 higher to 12.33 higher)	⨁◯◯◯ Very low	Favors SpA patients on DMARD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SpA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Factor increase in GMT, SpA MTX vs ETN												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	35	15	-	MD **11.9 higher** (2.78 higher to 21.02 higher)	⊕◯◯◯ Very low	Favors SpA patients on DMARD
Seroconversion SpA patients on DMARD vs Healthy controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	75	117	-	MD **0.4 higher** (12.09 lower to 12.89 higher)	⊕◯◯◯ Very low	
Seroconversion SpA patients on MTX vs Healthy controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SpA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	35	117	-	MD **5.7 higher** (9.32 lower to 20.72 higher)	⊕◯◯◯ Very low	

Seroconversion SpA patients on TNFi vs Healthy controls

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	79	117	-	MD **16.1 lower** (29.38 lower to 2.82 lower)	⊕◯◯◯ Very low	Favors healthy controls

Seroconversion SpA patients on ETN vs Healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SpA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	15	117	-	MD **12.4 higher** (5.65 lower to 30.45 higher)	⨁◯◯◯ Very low	

Seroconversion SpA patients on DMARD vs TNFi

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	75	79	-	MD **16.5 higher** (2.01 higher to 30.99 higher)	⨁◯◯◯ Very low	Favors SpA patients on DMARD

Seroconversion SpA patients on MTX vs ETN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SpA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	35	15	-	MD **6.7 lower** (27.42 lower to 14.02 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. Not randomized

b. Small sample size

Table 70: Certolizumab compared to Placebo for influenza vaccine response: RA patients on certolizumab had similar response to influenza vaccine as compared to RA patients who received placebo, lower response to H3N2 antigen [24].

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	certolizumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Satisfactory humoral response to Influenza vaccine, week 6												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	54/107 (50.5%)	59/109 (54.1%)	**RR 0.93** (0.72 to 1.20)	**38 fewer per 1,000** (from 152 fewer to 108 more)	⊕⊕⊕◯ Moderate	
Antibody titer change, Influenza antigen H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	certolizumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	86	83	-	MD **139.8 lower** (285.44 lower to 5.84 higher)	⨁⨁⨁◯ Moderate	

Antibody titer change, Influenza antigen H3N2

1	randomised trials	not serious	not serious	not serious	serious[a]	none	86	83	-	MD **355.6 lower** (648.15 lower to 63.05 lower)	⨁⨁⨁◯ Moderate	

Antibody titer change, Influenza antigen B, Brisbane

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	certolizumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	86	83	-	MD **28.5 lower** (144.17 lower to 87.17 higher)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Small sample size

Table 71. Wegener's granulomatosis (WG) patients (on IS and not on IS) compared to Healthy Controls receiving influenza vaccine

Summary: In this open-label RCT WG patients had similar outcomes as healthy controls, but the results are imprecise [49].

Level of Evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WG patients (on IS and not on IS)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A/H1N1												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/29 (51.7%)	40/49 (81.6%)	**RR 0.63** (0.44 to 0.92)	**302 fewer per 1,000** (from 457 fewer to 65 fewer)	⊕⊕◯◯ Low	Favors healthy controls
Seroconversion, A/H3N2												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22/29 (75.9%)	38/49 (77.6%)	**RR 0.98** (0.76 to 1.26)	**16 fewer per 1,000** (from 186 fewer to 202 more)	⊕⊕◯◯ Low	
Seroconversion, B												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WG patients (on IS and not on IS)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17/29 (58.6%)	27/49 (55.1%)	**RR 1.06** (0.72 to 1.58)	**33 more per 1,000** (from 154 fewer to 320 more)	⊕⊕◯◯ Low	

Seroprotection, A/H1N1, improvement from 0 to 1 month

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/29 (55.2%)	38/49 (77.6%)	**RR 0.71** (0.50 to 1.02)	**225 fewer per 1,000** (from 388 fewer to 16 more)	⊕⊕◯◯ Low	

Seroprotection, A/H1N2, improvement from 0 to 3-4 months

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	10/29 (34.5%)	28/49 (57.1%)	**RR 0.60** (0.35 to 1.05)	**229 fewer per 1,000** (from 371 fewer to 29 more)	⊕⊕◯◯ Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WG patients (on IS and not on IS)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/H3N2, improvement from 0 to 1 month												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	19/29 (65.5%)	38/49 (77.6%)	**RR 0.84** (0.62 to 1.14)	**124 fewer per 1,000** (from 295 fewer to 109 more)	⊕⊕◯◯ Low	
Seroprotection, A/H3N2, improvement from 0 to 3-4 months												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	18/29 (62.1%)	33/49 (67.3%)	**RR 0.92** (0.65 to 1.30)	**54 fewer per 1,000** (from 236 fewer to 202 more)	⊕⊕◯◯ Low	
Seroprotection, B, improvement from 0 to 1 month												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WG patients (on IS and not on IS)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17/29 (58.6%)	29/49 (59.2%)	**RR 0.99** (0.67 to 1.45)	**6 fewer per 1,000** (from 195 fewer to 266 more)	⨁⨁◯◯ Low	

Seroprotection, B, improvement from 0 to 3-4 month

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12/29 (41.4%)	21/49 (42.9%)	**RR 0.97** (0.56 to 1.66)	**13 fewer per 1,000** (from 189 fewer to 283 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Open-label

b. Wide CI crosses significant effect and no-effect lines

Table 72: RMD patients compared to Healthy Controls receiving influenza vaccine: Seroprotection and seroconversion rates between RMD patients on mixed treatments and healthy controls measured at 3 weeks, 3 months, 6 months were in favor of healthy controls [38]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection rate - 3 weeks												
1	observational studies	serious [a]	not serious	not serious	not serious	none	101/149 (67.8%)	39/40 (97.5%)	**RR 0.70** (0.62 to 0.78)	**293 fewer per 1,000** (from 371 fewer to 214 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroprotection rate - 6 weeks												
1	observational studies	serious [a]	not serious	not serious	not serious	none	88/149 (59.1%)	38/40 (95.0%)	**RR 0.62** (0.53 to 0.72)	**361 fewer per 1,000** (from 446 fewer to 266 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroprotection rate - 6 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	40/149 (26.8%)	30/40 (75.0%)	**RR 0.36** (0.26 to 0.49)	**480 fewer per 1,000** (from 555 fewer to 383 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroconversion rate - 3 weeks

1	observational studies	serious [a]	not serious	not serious	not serious	none	95/149 (63.8%)	34/40 (85.0%)	**RR 0.75** (0.63 to 0.90)	**213 fewer per 1,000** (from 315 fewer to 85 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroconversion rate - 6 weeks

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	80/149 (53.7%)	32/40 (80.0%)	**RR 0.67** (0.54 to 0.83)	**264 fewer per 1,000** (from 368 fewer to 136 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroconversion rate - 6 months

1	observational studies	serious [a]	not serious	not serious	not serious	none	49/149 (32.9%)	26/40 (65.0%)	**RR 0.51** (0.37 to 0.70)	**319 fewer per 1,000** (from 410 fewer to 195 fewer)	⨁◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

Table 73: Post influenza vaccine-dose 1: Mixed RMD compared to healthy controls, 3-4 weeks f/u in RMD (and controls), impact of meds (1 and 2 doses)

Summary: Healthy controls had more favorable outcomes in comparison to post-dose 1 than post-dose 2 [39].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-dose: Mixed RMD	healthy controls, 3-4 weeks f/u	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, Post-dose 1: Mixed RMD compared to healthy controls												
1	observational studies	serious [a]	not serious	not serious	not serious	none	103/138 (74.6%)	114/131 (87.0%)	**RR 0.86** (0.76 to 0.96)	**122 fewer per 1,000** (from 209 fewer to 35 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroconversion, Post-dose 1: Mixed RMD compared to healthy controls												
1	observational studies	serious [a]	not serious	not serious	not serious	none	97/138 (70.3%)	106/131 (80.9%)	**RR 0.87** (0.76 to 1.00)	**105 fewer per 1,000** (from 194 fewer to 0 fewer)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-dose: Mixed RMD	healthy controls, 3-4 weeks f/u	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, RMD post-dose 2 compared to controls post-dose 1 in RMD (and controls)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	126/148 (85.1%)	114/131 (87.0%)	**RR 0.98** (0.89 to 1.08)	**17 fewer per 1,000** (from 96 fewer to 70 more)	⊕◯◯◯ Very low	No difference
Seroconversion, RMD post-dose 2 compared to controls post-dose 1 in RMD (and controls)												
1	observational studies	serious [a]	not serious	not serious	not serious	none	119/148 (80.4%)	106/131 (80.9%)	**RR 0.99** (0.89 to 1.11)	**8 fewer per 1,000** (from 89 fewer to 89 more)	⊕◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

Table 74: **Responses to influenza vaccine among RD on Mixed Therapies compared to Healthy Controls at day 21**: There were five studies with different RD patients on mixed treatments that measured seroprotection and seroconversion against influenza at day 21. The pooled estimates showed that RD patients have on average 15%, and 25% at most and 5% at least, less probability of developing seroprotection and seroconversion compared to healthy controls [38, 40-44].

Level of Evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RD	controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection at 21 days												
6	observational studies	serious[a]	serious[b]	not serious	not serious	none	1480/2123 (69.7%)	507/595 (85.2%)	**RR 0.85** (0.75 to 0.96)	**128 fewer per 1,000** (from 213 fewer to 34 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroconversion at 21 days												
6	observational studies	serious[a]	serious[c]	not serious	not serious	none	1370/2123 (64.5%)	475/595 (79.8%)	**RR 0.84** (0.75 to 0.94)	**128 fewer per 1,000** (from 200 fewer to 48 fewer)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational studies

b. I-squared 81%

c. I-squared 67%

Table 75: Seroconversion, peds with rheumatic disease compared to healthy controls for Influenza in pediatric rheumatic disease

Summary: This study had inconsistent outcomes across titers, favoring healthy controls for H1N1 titer, and RD patients for H3N2 and B titers, but the results are very imprecise [45].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion, peds rheumdis	control	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A/H1N1, peds RD vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	21/49 (42.9%)	19/36 (52.8%)	**RR 0.81** (0.52 to 1.27)	**100 fewer per 1,000** (from 253 fewer to 143 more)	⊕◯◯◯ Very low	
Seroconversion, A/H3N2, peds RD vs control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion, peds rheum dis	control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25/49 (51.0%)	13/36 (36.1%)	**RR 1.41** (0.85 to 2.36)	**148 more per 1,000** (from 54 fewer to 491 more)	⨁◯◯◯ Very low	

Seroconversion, B, peds RD vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	22/49 (44.9%)	13/36 (36.1%)	**RR 1.24** (0.73 to 2.12)	**87 more per 1,000** (from 98 fewer to 404 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 76: Seroprotection and seroconversion anti-HA, GPA compared to healthy controls for Influenza in GPA patients

Summary: Seroprotection for H1N1, H3N2 and B strains was in favor of healthy controls with statistical significance only for B strain. Seroprotection for H1N1, H3N2 and B strains was in favor of healthy controls but the results were imprecise [50].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroprotection anti-HA, GPA	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/H1N1												
1	observational studies	serious [a]	not serious	not serious	serious[b]	None	26/35 (74.3%)	31/35 (88.6%)	**RR 0.84** (0.67 to 1.05)	**142 fewer per 1,000** (from 292 fewer to 44 more)	⨁◯◯◯ Very low	
Seroprotection, A/H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroprotection anti-HA, GPA	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	None	18/35 (51.4%)	23/35 (65.7%)	**RR 0.78** (0.52 to 1.17)	**145 fewer per 1,000** (from 315 fewer to 112 more)	⨁◯◯◯ Very low	

Seroprotection, B

1	observational studies	serious [a]	not serious	not serious	not serious	None	19/35 (54.3%)	33/35 (94.3%)	**RR 0.58** (0.42 to 0.79)	**396 fewer per 1,000** (from 547 fewer to 198 fewer)	⨁◯◯◯ Very low	Favors healthy controls

Seroconversion, A/H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroprotection anti-HA, GPA	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	26/35 (74.3%)	31/35 (88.6%)	**RR 0.84** (0.67 to 1.05)	**142 fewer per 1,000** (from 292 fewer to 44 more)	⊕◯◯◯ Very low	

Seroconversion, A/H3N2

1	observational studies	serious [a]	not serious	not serious	serious[b]	none	21/35 (60.0%)	25/35 (71.4%)	**RR 0.84** (0.60 to 1.18)	**114 fewer per 1,000** (from 286 fewer to 129 more)	⊕◯◯◯ Very low	

Seroconversion, B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroprotection anti-HA, GPA	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	25/35 (71.4%)	30/35 (85.7%)	**RR 0.83** (0.65 to 1.07)	**146 fewer per 1,000** (from 300 fewer to 60 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study
b. Wide CI crosses significant effect and no-effect lines

Table 77: Longitudinal seasonal flu response, RD compared to controls for Influenza in patients with rheumatic disease

Summary: Among 137 individuals with autoimmune inflammatory rheumatic disease, seroprotection, seroresponse, and change in geometric mean titers (GMT) in AIRD patients was not compromised compared to healthy controls [34]. However, response to H1N1 favored RD for some outcomes, and response to H3N2 favored controls for some outcomes.

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
18-90 days, GMT, H1N1, RD vs control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	109	24	-	MD **65.6 higher** (3.56 higher to 127.64 higher)	⊕◯◯◯ Very low	Favors RD
18-90 days, GMT, H3N2, RD vs control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	109	24	-	MD **1558.5 lower** (1824.62 lower to 1292.38 lower)	⊕◯◯◯ Very low	Favors controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
18-90 days, GMT, Flu B, RD vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	109	24	-	MD **88.7 lower** (209.81 lower to 32.41 higher)	⊕◯◯◯ Very low	
>180 days, GMT, H1N1, RD vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	109	24	-	MD **2.5 higher** (28.8 lower to 33.8 higher)	⊕◯◯◯ Very low	
>180 days, GMT, H3N2, RD vs control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	109	24	-	MD **1375.8 lower** (1650.24 lower to 1101.36 lower)	⨁◯◯◯ Very low	Favors controls

>180 days, GMT, Flu B, RD vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	109	24	-	MD **85.1 lower** (175.48 lower to 5.28 higher)	⨁◯◯◯ Very low	

18-90 days seroprotection, H1N1, RD vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	98/109 (89.9%)	23/24 (95.8%)	**RR 0.94** (0.85 to 1.04)	**58 fewer per 1,000** (from 144 fewer to 38 more)	⨁◯◯◯ Very low	

18-90 days seroprotection, H3N2, RD vs control

1	observational studies	serious[a]	not serious	not serious	not serious	none	109/109 (100.0%)	24/24 (100.0%)	**RR 1.00** (0.94 to 1.06)	**0 fewer per 1,000** (from 60 fewer to 60 more)	⨁◯◯◯ Very low	

18-90 days seroprotection, Flu B, RD vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	107/109 (98.2%)	24/24 (100.0%)	**RR 1.00** (0.94 to 1.06)	**0 fewer per 1,000** (from 60 fewer to 60 more)	⨁◯◯◯ Very low	

>180 days seroprotection, H1N1, RD vs control

1	observational studies	serious [a]	not serious	not serious	not serious	none	79/109 (72.5%)	21/24 (87.5%)	**RR 0.83** (0.68 to 1.00)	**149 fewer per 1,000** (from 280 fewer to 0 fewer)	⨁◯◯◯ Very low	Favors controls

>180 days seroprotection, H3N2, RD vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	108/109 (99.1%)	24/24 (100.0%)	**RR 1.01** (0.95 to 1.07)	**10 more per 1,000** (from 50 fewer to 70 more)	⨁◯◯◯ Very low	No difference

>180 days seroprotection, Flu B, RD vs control

1	observational studies	serious [a]	not serious	not serious	not serious	none	103/109 (94.5%)	24/24 (100.0%)	**RR 0.96** (0.89 to 1.03)	**40 fewer per 1,000** (from 110 fewer to 30 more)	⨁◯◯◯ Very low	No difference

18-90 days seroresponse, H1N1, RD vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	60/107 (56.1%)	5/24 (20.8%)	**RR 2.69** (1.21 to 5.98)	**352 more per 1,000** (from 44 more to 1,000 more)	⨁◯◯◯ Very low	Favors RD

18-90 days seroresponse, H3N2, RD vs control

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	33/106 (31.1%)	1/2 (50.0%)	**RR 0.62** (0.15 to 2.56)	**190 fewer per 1,000** (from 425 fewer to 780 more)	⨁◯◯◯ Very low	

18-90 days seroresponse, Flu B, RD vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	35/101 (34.7%)	5/20 (25.0%)	**RR 1.39** (0.62 to 3.10)	**97 more per 1,000** (from 95 fewer to 525 more)	⨁◯◯◯ Very low	

>180 days seroresponse, H1N1, RD vs control

1	observational studies	serious[a]	not serious	not serious	serious[a]	none	23/107 (21.5%)	4/24 (16.7%)	**RR 1.29** (0.49 to 3.39)	**48 more per 1,000** (from 85 fewer to 398 more)	⨁◯◯◯ Very low	

>180 days seroresponse, H3N2, RD vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Longitudinal seasonal flu response, RD	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/106 (12.3%)	1/2 (50.0%)	**RR 0.25** (0.06 to 1.07)	**375 fewer per 1,000** (from 470 fewer to 35 more)	⨁◯◯◯ Very low	

>180 days seroresponse, Flu B, RD vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/101 (7.9%)	3/20 (15.0%)	**RR 0.53** (0.15 to 1.82)	**71 fewer per 1,000** (from 128 fewer to 123 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 78: Vaccinated SLE patients compared to Healthy controls, influenza vaccine response.

Summary: Comparing SLE patients to healthy controls, outcomes tended to favor healthy controls [6].

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion rate - H1N1, 28 days												
1	observational studies	serious[a]	not serious	not serious	not serious	none	24/54 (44.4%)	42/54 (77.8%)	**RR 0.57** (0.41 to 0.80)	**334 fewer per 1,000** (from 459 fewer to 156 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroconversion rate - H3N2, 28 days												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	37/54 (68.5%)	41/54 (75.9%)	**RR 0.90** (0.71 to 1.14)	**76 fewer per 1,000** (from 220 fewer to 106 more)	⊕◯◯◯ Very low	
Seroprotection - Day 28 - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	44/54 (81.5%)	48/54 (88.9%)	**RR 0.92** (0.78 to 1.07)	**71 fewer per 1,000** (from 196 fewer to 62 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - Day 28 - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	41/54 (75.9%)	50/54 (92.6%)	**RR 0.82** (0.69 to 0.97)	**167 fewer per 1,000** (from 287 fewer to 28 fewer)	⨁◯◯◯ Very low	Favors healthy controls
Seroprotection - 3-4 mths - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	36/54 (66.7%)	39/54 (72.2%)	**RR 0.92** (0.72 to 1.19)	**58 fewer per 1,000** (from 202 fewer to 137 more)	⨁◯◯◯ Very low	
Seroprotection - 3-4 mths - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	37/54 (68.5%)	45/54 (83.3%)	**RR 0.82** (0.66 to 1.02)	**150 fewer per 1,000** (from 283 fewer to 17 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 79: Influenza within 0-3 days compared to 4-7 days of last MTX for RA patients with influenza vaccine on MTX

Summary: Comparing influenza vaccine administered within 0-3 days compared to 4-7 days of last MTX dose for RA patients the outcomes were not different between groups [19].

Quality of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza within 0-3 days	4-7 days of last MTX	Relative (95% CI)	Absolute (95% CI)		
Satisfactory positive response/seroconversion												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	30/65 (46.2%)	43/95 (45.3%)	**RR 1.02** (0.72 to 1.44)	**9 more per 1,000** (from 127 fewer to 199 more)	⊕⊕⊕◯ Moderate	
Seroprotection rate, H1N1												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	53/65 (81.5%)	85/95 (89.5%)	**RR 0.91** (0.80 to 1.04)	**81 fewer per 1,000** (from 179 fewer to 36 more)	⊕⊕⊕◯ Moderate	No difference
Seroprotection rate, H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza within 0-3 days	4-7 days of last MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	49/65 (75.4%)	76/95 (80.0%)	**RR 0.94** (0.79 to 1.12)	**48 fewer per 1,000** (from 168 fewer to 96 more)	⊕⊕⊕◯ Moderate	No difference

Seroprotection rate, Yagamata

1	randomised trials	not serious	not serious	not serious	serious[a]	none	55/65 (84.6%)	86/95 (90.5%)	**RR 0.93** (0.83 to 1.06)	**63 fewer per 1,000** (from 154 fewer to 54 more)	⊕⊕⊕◯ Moderate	No difference

Seroprotection rate, Victoria

1	randomised trials	not serious	not serious	not serious	not serious	none	49/65 (75.4%)	72/95 (75.8%)	**RR 0.99** (0.83 to 1.19)	**8 fewer per 1,000** (from 129 fewer to 144 more)	⊕⊕⊕⊕ High	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide CI crosses significant effect and no-effect lines

Table 80: Response to seasonal influenza vaccine, RD compared to controls, second dose at 3-5 wks for Influenza in patients with rheumatic disease [34]. Vaccine response was similar among individuals with RD and controls (although certain outcomes favored RD and others favored controls) and there was little benefit of a second dose of the influenza vaccine at 3-5 weeks.

Level of evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
Seasonal flu, ELISA A IgG, RD vs Control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	137	54	-	MD **4 lower** (7.6 lower to 0.4 lower)	⊕◯◯◯ Very low	Favors controls
Seasonal flu, ELISA A IgA, RD vs Control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	137	54	-	MD **3.3 higher** (0.17 higher to 6.43 higher)	⊕◯◯◯ Very low	Favors RD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
Seasonal flu, ELISA B IgG, RD vs Control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	137	54	-	MD **7.1 lower** (11.1 lower to 3.1 lower)	⊕◯◯◯ Very low	Favors controls
Seasonal flu, ELISA B IgA, RD vs Control												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	137	54	-	MD **2.3 higher** (0.56 lower to 5.16 higher)	⊕◯◯◯ Very low	
Seasonal flu, H1N1 GMT, RD vs Control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	137	54	-	MD **48.7 higher** (3.7 lower to 101.1 higher)	⊕◯◯◯ Very low	

Seasonal flu, H3N2 GMT, RD vs Control

1	observational studies	serious [a]	not serious	not serious	not serious	none	137	54	-	MD **753 lower** (1036.41 lower to 469.59 lower)	⊕◯◯◯ Very low	Favors controls

Seasonal flu, Flu B GMT, RD vs Control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	137	54	-	MD **8.8 higher** (65.65 lower to 83.25 higher)	⊕◯◯◯ Very low	

Seasonal flu, H1N1 seroprotection, RD vs control

1	observational studies	serious [a]	not serious	not serious	serious[b]	none	122/137 (89.1%)	50/54 (92.6%)	**RR 0.96** (0.87 to 1.06)	**37 fewer per 1,000** (from 120 fewer to 56 more)	⊕◯◯◯ Very low	No difference

Seasonal flu, H3N2 seroprotection, RD vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	133/137 (97.1%)	54/54 (100.0 %)	**RR 0.98** (0.94 to 1.02)	**20 fewer per 1,000** (from 60 fewer to 20 more)	⊕◯◯◯ Very low	No difference

Seasonal flu, Flu B seroprotection, RD vs control

1	observational studies	serious [a]	not serious	not serious	not serious	none	134/137 (97.8%)	54/54 (100.0 %)	**RR 0.98** (0.95 to 1.02)	**20 fewer per 1,000** (from 50 fewer to 20 more)	⊕◯◯◯ Very low	No difference

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
Seasonal flu, H1N1 seroresponse, RD vs control												
1	observational studies	serious [a]	not serious	not serious	not serious	none	67/133 (50.4%)	13/54 (24.1%)	**RR 2.09** (1.27 to 3.46)	**262 more per 1,000** (from 65 more to 592 more)	⊕◯◯◯ Very low	Favors RD
Seasonal flu, H3N2 seroresponse, RD vs control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to seasonal influenza vaccine, RD	controls, 3-5 wks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	38/134 (28.4%)	8/17 (47.1%)	**RR 0.60** (0.34 to 1.07)	**188 fewer per 1,000** (from 311 fewer to 33 more)	⊕◯◯◯ Very low	

Seasonal flu, Flu B seroresponse, RD vs control

1	observational studies	serious [a]	not serious	not serious	not serious	none	43/129 (33.3%)	17/50 (34.0%)	**RR 0.98** (0.62 to 1.55)	**7 fewer per 1,000** (from 129 fewer to 187 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 81: RA on biologics compared to RA not on biologics for influenza vaccine response: RA patients on biologics had similar response to influenza vaccine compared to RA patients not on biologics (biologics included both TNFi and tocilizumab) [13].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on biologics	RA not on biologics	Relative (95% CI)	Absolute (95% CI)		
RA on biologics vs RA not on biologics - seroprotection												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/36 (47.2%)	32/53 (60.4%)	**RR 0.78** (0.52 to 1.18)	**133 fewer per 1,000** (from 290 fewer to 109 more)	⊕◯◯◯ Very low	
RA on biologics vs RA not on biologics - seroresponse												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	14/36 (38.9%)	31/53 (58.5%)	**RR 0.66** (0.42 to 1.06)	**199 fewer per 1,000** (from 339 fewer to 35 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized

b. Small numbers

Table 82: Influenza vaccine response for individuals with cancer receiving RTX compared to no RTX.

Summary: In this study comparing cancer patients on rituximab vs not on rituximab, the outcomes were in favor of patients not on rituximab. [33]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	no RTX	Relative (95% CI)	Absolute (95% CI)		
GMT after first dose of pandemic influenza vaccine												
1	observational studies	serious[a]	not serious	not serious	not serious	strong association	13	78	-	MD **306.02 lower** (422.6 lower to 189.45 lower)	⨁⨁◯◯ Low	Favors no RTX
GMT after second dose of pandemic influenza vaccine												
1	observational studies	serious[a]	not serious	not serious	not serious	strong association	13	75	-	MD **329.21 lower** (500.09 lower to 158.33 lower)	⨁⨁◯◯ Low	Favors no RTX
Seroconversion after first dose of pandemic influenza vaccine												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	no RTX	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	strong association	0/13 (0.0%)	48/78 (61.5%)	**RR 0.06** (0.00 to 0.89)	**578 fewer per 1,000** (from 68 fewer to --)	⨁⨁◯◯ Low	Favors no RTX

Seroconversion after second dose of pandemic influenza vaccine

1	observational studies	serious[a]	not serious	not serious	not serious	strong association	0/13 (0.0%)	63/75 (84.0%)	**RR 0.04** (0.00 to 0.65)	**806 fewer per 1,000** (from 294 fewer to --)	⨁⨁◯◯ Low	Favors no RTX

Seroprotection after first dose of pandemic influenza vaccine

1	observational studies	serious[a]	not serious	not serious	not serious	strong association	0/13 (0.0%)	49/78 (62.8%)	**RR 0.06** (0.00 to 0.87)	**591 fewer per 1,000** (from 82 fewer to --)	⨁⨁◯◯ Low	Favors no RTX

Seroprotection after second dose of pandemic influenza vaccine

1	observational studies	serious[a]	not serious	not serious	not serious	strong association	1/13 (7.7%)	65/75 (86.7%)	**RR 0.09** (0.01 to 0.58)	**789 fewer per 1,000** (from 858 fewer to 364 fewer)	⨁⨁◯◯ Low	Favors no RTX

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	no RTX	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine seroprotection rate A/Brisbane/59/2007(H1N1)												
1	observational studies	serious[a]	not serious	not serious	not serious	strong association	1/12 (8.3%)	46/66 (69.7%)	**RR 0.12** (0.02 to 0.79)	**613 fewer per 1,000** (from 683 fewer to 146 fewer)	⊕⊕◯◯ Low	Favors no RTX
Post-vaccine seroprotection rate A/Uruguay/10/2007(H3N2)												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/12 (25.0%)	39/66 (59.1%)	**RR 0.42** (0.16 to 1.15)	**343 fewer per 1,000** (from 496 fewer to 89 more)	⊕◯◯◯ Very low	
Post-vaccine seroconversion rate A/Brisbane/59/2007(H1N1)												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	0/12 (0.0%)	28/66 (42.4%)	**RR 0.09** (0.01 to 1.39)	**386 fewer per 1,000** (from 420 fewer to 165 more)	⊕◯◯◯ Very low	
Post-vaccine seroconversion rate A/Uruguay/10/2007(H3N2)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	no RTX	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	0/12 (0.0%)	33/66 (50.0%)	**RR 0.08** (0.01 to 1.18)	**460 fewer per 1,000** (from 495 fewer to 90 more)	⨁◯◯◯ Very low	

Post-vaccination GMT A/Brisbane/59/2007(H1N1)

1	observational studies	serious[a]	not serious	not serious	not serious	strong association	12	66	-	MD **128.64 lower** (194.42 lower to 62.87 lower)	⨁⨁◯◯ Low	Favors no RTX

Post-vaccination GMT A/Uruguay/10/2007(H3N2)

1	observational studies	serious[a]	not serious	not serious	not serious	strong association	12	66	-	MD **563.48 lower** (935.43 lower to 191.52 lower)	⨁⨁◯◯ Low	Favors no RTX

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 83. Immunogenicity of 2009 H1N1 vaccine in Primary Sjogren's, 21 days f/u compared to placebo for PICOs 3 and 8 -seasonal flu vaccine, primary Sjogren's Syndrome/controls: In this study comparing immunogenicity of 2009 H1N1 vaccine in Primary Sjogren's versus healthy control at 21 days, the outcomes were slightly in favor of Primary Sjogren's disease patients but these findings were imprecise [52].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primary Sjogren's patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection 21 days after H1N1 vaccination												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	30/36 (83.3%)	26/36 (72.2%)	**RR 1.15** (0.90 to 1.48)	**108 more per 1,000** (from 72 fewer to 347 more)	⊕◯◯◯ Very low	
Seroconversion 21 days after vaccination												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	28/36 (77.8%)	25/36 (69.4%)	**RR 1.12** (0.85 to 1.48)	**83 more per 1,000** (from 104 fewer to 333 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 84: RA patients compared to Healthy controls receiving influenza vaccine.

Summary: In a study comparing RA patients to healthy controls, the outcomes were not different or statistically significant except for Seroprotection rate - Brisbane/H1N1, 6 months, which was statistically significant in favor of healthy controls [20].

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion rate - Brisbane/pH1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	20/30 (66.7%)	7/13 (53.8%)	**RR 1.24** (0.70 to 2.17)	**129 more per 1,000** (from 162 fewer to 630 more)	⊕◯◯◯ Very low	
Seroconversion rate - Brisbane/H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	20/30 (66.7%)	8/13 (61.5%)	**RR 1.08** (0.66 to 1.78)	**49 more per 1,000** (from 209 fewer to 480 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion rate - B influenza												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	20/30 (66.7%)	7/13 (53.8%)	**RR 1.24** (0.70 to 2.17)	**129 more per 1,000** (from 162 fewer to 630 more)	⊕◯◯◯ Very low	
Seroconversion rate - California H1N1												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	25/30 (83.3%)	7/13 (53.8%)	**RR 1.55** (0.91 to 2.62)	**296 more per 1,000** (from 48 fewer to 872 more)	⊕◯◯◯ Very low	
Seroprotection rate - Brisbane/pH1N1, 1 month												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	24/30 (80.0%)	13/13 (100.0%)	**RR 0.82** (0.67 to 1.01)	**180 fewer per 1,000** (from 330 fewer to 10 more)	⨁◯◯◯ Very low	

Seroprotection rate - Brisbane/H3N2, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	26/30 (86.7%)	11/13 (84.6%)	**RR 1.02** (0.78 to 1.34)	**17 more per 1,000** (from 186 fewer to 288 more)	⨁◯◯◯ Very low	

Seroprotection rate - B, 1 month

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	30/30 (100.0%)	12/13 (92.3%)	**RR 1.10** (0.91 to 1.33)	**92 more per 1,000** (from 83 fewer to 305 more)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection rate - California/H1N1, 1 month												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	25/30 (83.3%)	9/13 (69.2%)	**RR 1.20** (0.81 to 1.79)	**138 more per 1,000** (from 132 fewer to 547 more)	⊕◯◯◯ Very low	
Seroprotection rate - Brisbane/H1N1, 6 months												
1	observational studies	serious [a]	not serious	not serious	not serious	none	14/30 (46.7%)	12/13 (92.3%)	**RR 0.51** (0.33 to 0.76)	**452 fewer per 1,000** (from 618 fewer to 222 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroprotection rate - Brisbane/H3N2, 6 months												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	21/30 (70.0%)	9/13 (69.2%)	**RR 1.01** (0.66 to 1.56)	**7 more per 1,000** (from 235 fewer to 388 more)	⊕◯◯◯ Very low	

Seroprotection rate - B, 6 months

1	observational studies	serious [a]	not serious	not serious	not serious	none	29/30 (96.7%)	13/13 (100.0%)	**RR 0.99** (0.87 to 1.12)	**10 fewer per 1,000** (from 130 fewer to 120 more)	⊕◯◯◯ Very low	

Seroprotection rate - California/H1N1, 6 months

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	14/30 (46.7%)	5/13 (38.5%)	**RR 1.21** (0.55 to 2.67)	**81 more per 1,000** (from 173 fewer to 642 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosse significant effect and no-effect lines

Table 85: Influenza response in RA on biologics compared to no biologics or HCs, 6 weeks: The outcomes were in favor of healthy controls but the results are imprecise. [13]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
RA (total) compared to HC for seroprotection												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	49/89 (55.1%)	10/14 (71.4%)	**RR 0.77** (0.53 to 1.13)	**164 fewer per 1,000** (from 336 fewer to 93 more)	⊕◯◯◯ Very low	
RA (total) compared to HC for seroresponse												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	45/89 (50.6%)	9/14 (64.3%)	**RR 0.79** (0.51 to 1.22)	**135 fewer per 1,000** (from 315 fewer to 141 more)	⊕◯◯◯ Very low	

RA on biologics vs RA not on biologics – seroprotecton

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/36 (47.2%)	32/53 (60.4%)	**RR 0.78** (0.52 to 1.18)	**133 fewer per 1,000** (from 290 fewer to 109 more)	⊕◯◯◯ Very low	

RA on biologics vs RA not on biologics – seroresponse

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	14/36 (38.9%)	31/53 (58.5%)	**RR 0.66** (0.42 to 1.06)	**199 fewer per 1,000** (from 339 fewer to 35 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 86: Response to influenza A/H1N1 2009 vaccine (JDM compared to pediatric healthy controls), 3 weeks.

Summary: This study showed no noticeable difference in outcomes between RMD patients and healthy controls.[36]

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to influenza A/H1N1 2009 vaccine (JDM	pediatric healthy controls), 3 weeks	Relative (95% CI)	Absolute (95% CI)		
Seroprotection at 21 days - after immunization												
1	observational studies	serious [a]	not serious	not serious	not serious	none	27/30 (90.0%)	79/81 (97.5%)	**RR 0.92** (0.81 to 1.04)	**78 fewer per 1,000** (from 185 fewer to 39 more)	⊕◯◯◯ Very low	No difference
Seroconversion (at 21 days post vaccine)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to influenza A/H1N1 2009 vaccine (JDM	pediatric healthy controls), 3 weeks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	26/30 (86.7%)	79/81 (97.5%)	**RR 0.89** (0.77 to 1.03)	**107 fewer per 1,000** (from 224 fewer to 29 more)	⨁◯◯◯ Very low	

GMT at 21 days - after immunization

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	30	81	-	MD **0.7 lower** (115.04 lower to 113.64 higher)	⨁◯◯◯ Very low	

Fold increase in GMT (21 days post immunization)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Response to influenza A/H1N1 2009 vaccine (JDM	pediatric healthy controls), 3 weeks	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	30	81	-	MD **1.2 lower** (9.72 lower to 7.32 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 87: Vaccinated (influenza) SLE patients compared to Healthy controls:

Summary: Comparing SLE patients to healthy controls, outcomes (seroconversion, seroprotection) were in favor of healthy controls.[6]

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion rate - H1N1, 28 days												
1	observational studies	serious [a]	not serious	not serious	not serious	none	24/54 (44.4%)	42/54 (77.8%)	**RR 0.57** (0.41 to 0.80)	**334 fewer per 1,000** (from 459 fewer to 156 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Seroconversion rate - H3N2, 28 days												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	37/54 (68.5%)	41/54 (75.9%)	**RR 0.90** (0.71 to 1.14)	**76 fewer per 1,000** (from 220 fewer to 106 more)	⨁◯◯◯ Very low	

Seroprotection - Day 28 - H1N1

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	44/54 (81.5%)	48/54 (88.9%)	**RR 0.92** (0.78 to 1.07)	**71 fewer per 1,000** (from 196 fewer to 62 more)	⨁◯◯◯ Very low	

Seroprotection - Day 28 - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	41/54 (75.9%)	50/54 (92.6%)	**RR 0.82** (0.69 to 0.97)	**167 fewer per 1,000** (from 287 fewer to 28 fewer)	⊕◯◯◯ Very low	Favors healthy controls

Seroprotection - 3-4mths - H1N1

1	observational studies	serious [a]	not serious	not serious	serious [b]	none	36/54 (66.7%)	39/54 (72.2%)	**RR 0.92** (0.72 to 1.19)	**58 fewer per 1,000** (from 202 fewer to 137 more)	⊕◯◯◯ Very low	

Seroprotection - 3-4 mths - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	37/54 (68.5%)	45/54 (83.3%)	**RR 0.82** (0.66 to 1.02)	**150 fewer per 1,000** (from 283 fewer to 17 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 88: bDMARD in Children with RMD versus Healthy Controls[10244]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD monotherapy	Controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Cal H1N1pdm09												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66	13	-	MD **145.1 lower** (246.25 lower to 43.95 lower)	⊕◯◯◯ Very low	Favors controls
GMT, A/Swi H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66	13	-	MD **89 lower** (136.53 lower to 41.47 lower)	⊕◯◯◯ Very low	Favors controls
GMT, B/Phu Yamagata												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66	13	-	MD **35.1 lower** (66.88 lower to 3.32 lower)	⊕◯◯◯ Very low	Favors controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD monotherapy	Controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/Cal H1N1pdm09												
1	observational studies	serious[a]	not serious	not serious	not serious	none	66/66 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	
Seroconversion, A/Cal H1N1pdm09												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/58 (13.8%)	3/9 (33.3%)	**RR 0.41** (0.13 to 1.28)	**197 fewer per 1,000** (from 290 fewer to 93 more)	⨁◯◯◯ Very low	
Seroprotection, A/Swi H3N2												
1	observational studies	serious[a]	not serious	not serious	not serious	none	65/66 (98.5%)	13/13 (100.0%)	**RR 1.01** (0.91 to 1.13)	**10 more per 1,000** (from 90 fewer to 130 more)	⨁◯◯◯ Very low	
Seroconversion, A/Swi H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD monotherapy	Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/58 (15.5%)	6/9 (66.7%)	**RR 0.23** (0.11 to 0.50)	**513 fewer per 1,000** (from 593 fewer to 333 fewer)	⨁◯◯◯ Very low	Favors controls

Seroprotection, B/Phu Yamagata

1	observational studies	serious[a]	not serious	not serious	not serious	none	66/66 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	No difference

Seroconversion, B/Phu Yamagata

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/58 (5.2%)	2/9 (22.2%)	**RR 0.23** (0.04 to 1.21)	**171 fewer per 1,000** (from 213 fewer to 47 more)	⨁◯◯◯ Very low	

Percentage increase in antibody titers 28 days post vaccination, A/Cal H1N1pdm09

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD monotherapy	Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66	13	-	MD **29.3 lower** (96.29 lower to 37.69 higher)	⊕◯◯◯ Very low	

Percentage increase in antibody titers 28 days post vaccination, A/Swi H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66	13	-	MD **103.3 lower** (197.73 lower to 8.87 lower)	⊕◯◯◯ Very low	Favors controls

Percentage increase in antibody titers 28 days post vaccination, B/Phu Yamagata

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66	13	-	MD **48.8 lower** (149.99 lower to 52.39 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

b. Less than 200 patients per arm and wide CI crosses significant effect and no-effect lines

Table 89: bDMARD+DMARD in Children with RMD versus Healthy Controls[10244]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD + DMARD	Controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Cal H1N1pdm09												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	99	13	-	MD **133.6 lower** (225.6 lower to 41.6 lower)	⨁◯◯◯ Very low	Favors controls
GMT, A/Swi H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	99	13	-	MD **104.7 lower** (150.44 lower to 58.96 lower)	⨁◯◯◯ Very low	Favors controls
GMT, B/Phu Yamagata												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD + DMARD	Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	99	13	-	MD **36.6 lower** (67.67 lower to 5.53 lower)	⨁◯◯◯ Very low	Favors controls

Seroprotection, A/Cal H1N1pdm09

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	98/99 (99.0%)	13/13 (100.0%)	**RR 1.02** (0.92 to 1.13)	**20 more per 1,000** (from 80 fewer to 130 more)	⨁◯◯◯ Very low	

Seroconversion, A/Cal H1N1pdm09

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/86 (27.9%)	3/9 (33.3%)	**RR 0.84** (0.31 to 2.24)	**53 fewer per 1,000** (from 230 fewer to 413 more)	⨁◯◯◯ Very low	

Seroprotection, A/Swi H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD + DMARD	Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	96/99 (97.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	

Seroconversion, A/Swi H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/86 (19.8%)	6/9 (66.7%)	**RR 0.30** (0.16 to 0.56)	**467 fewer per 1,000** (from 560 fewer to 293 fewer)	⨁◯◯◯ Very low	Favors controls

Seroprotection, B/Phu Yamagata

1	observational studies	serious[a]	not serious	not serious	not serious	none	99/99 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	No difference

Seroconversion, B/Phu Yamagata

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD + DMARD	Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/86 (5.8%)	2/9 (22.2%)	**RR 0.26** (0.06 to 1.16)	**164 fewer per 1,000** (from 209 fewer to 36 more)	⨁◯◯◯ Very low	

Percentage increase in antibody titers 28 days post vaccination, A/Cal H1N1pdm09

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	99	13	-	MD **8 higher** (59.92 lower to 75.92 higher)	⨁◯◯◯ Very low	

Percentage increase in antibody titers 28 days post vaccination, A/Swi H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	99	13	-	MD **128.9 lower** (219.98 lower to 37.82 lower)	⨁◯◯◯ Very low	Favors controls

Percentage increase in antibody titers 28 days post vaccination, B/Phu Yamagata

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARD + DMARD	Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	97	13	-	MD **47.2 lower** (151.34 lower to 56.94 higher)	⨁◯◯◯ Very low	

Explanations

a. Observational study

b. Less than 200 patients per arm and wide CI crosses significant effect and no-effect lines

Table 90: Observational studies (Data not suited for RevMan)

Summary: These studies report immunization responses to influenza vaccines. The majority of studies had mixed populations or/and mixed treatments. The outcomes measured and reported were vaccine response, cellular response, seroconversion, seroprotection, 4-fold increase in titers, increase in geometric mean titers (GMT) of H1N1, H3N2, B strains. Control groups represented either healthy controls or patients with no medications of interest as opposed to patients on medications. The vaccine response and GMT titer increase were slightly better in healthy controls or patients not on immunosuppressive meds than in patients on csDMARD's [[7, 53]]. In another study, the DMARD group had lower rates of positive immune response compared to healthy controls only for H3N2 strain [21]. The proportion of responders were similar across patients with different rheumatic diseases but was significantly higher for the healthy controls [54]. SLE patients on scDMARD's and glucocorticoids, whether used separately or combined, had similar rates of seroconvertion, seroprotection and GMT [55]. But in one study [2516], the RA patients, regardless of timing of taking infliximab, as well RA patients on csDMARD's and healthy controls had similar results in humoral response and equally high GMT titers. RA patients taking RTX had lower vaccine response, fold increase and seroconversion than healthy controls or patients on DMARD's [[7, 8, 37]], and had no significant increase in IgG or IgM levels post-vaccine for all titers [[23, 56]], even cellular response didn't differ among those patients [[7]] or was lower in RTX group [56]. Patients on TNFi had higher antibody response than patients taking either MTX, Abatacept, or RTX [38], with lowest antibody response in RTX patients [38], but patients taking TNFi had lower GMT, seroconversion than patients not taking TNFi or healthy controls and equal seroprotection rate [[57, 58]]. In a study with patients taking TOFA, MTX, TOFA+MTX or no DMARD, the highest GMFR responses for H1N1 & H3N2 were in No DMARD group; lower but similar responses in the MTX alone, TOFA alone, and TOFA+MTX groups [9].

Quality of evidence across all critical outcomes: Very low

Ref ID, Author, year	Study type	Duration	Population Description	Intervention	Results
1177 Arad (2011) [7]	Prospective cohort study	Follow-up to 4-6 weeks post-vaccine	**29 RA patients on RTX** (Mean age 61.8 years, 79.2% female, median RA duration 9.5 years, mean DAS28 4.5) **17 RA patients on csDMARDs**	All participants received one dose of trivalent seasonal influenza vaccine (inactivated, standard dose). **RTX group (n=29):** Each patient received 1000 mg	**Cellular response** **Percentage of influenza-specific CD4+ cells:** Healthy controls: Pre vaccine: Median 0.6% Post-vaccine: Median 0.3% RA-csDMARD: Pre vaccine: Median 0.1% Post-vaccine: Median 0.2% RA-RTX: Pre vaccine: Median 0.1% Post-vaccine: Median 0.3%

			(Mean age 61.2 yrs, 70.6% female, median RA duration 9 yrs, mean DAS28 4.1) **16 healthy individuals** (Mean age 44.5 years, 87.5% female). Rate of influenza vaccination in previous year significantly lower in HC group (3/16; 18.6%) vs. csDMARD group (8/17; 47.1%) and RTX group (15/29; 51.7%)	IV infusion x 2 doses; 41% on concomitant MTX (mean dose 14.5 mg weekly); 34% on prednisone (mean dose 13.2 mg daily). 16/29 vaccinated within 5 months of last RTX infusion, 13/29 vaccinated >5 months after last RTX. 25/29 (86.2%) of RTX patients had <1% CD19+ B cells at time of vaccination. In remaining 4 patients, interval from last RTX to vaccine ranged from 5.5-9 months post-RTX. **csDMARD group (n=17):** 69% MTX (mean dose 15 mg weekly); 77% prednisone (mean dose 8.2 mg daily). Significantly higher rate of prednisone use in csDMARD group vs. RTX group.	No significant differences between groups. No correlation of cellular response with age, prior influenza vaccine, use or dose of MTX or prednisone, or baseline DAS28. **Geometric mean titers (GMT):** No significant differences between groups in pre-vaccine GMTs for the 3 antigens Significant increase in GMT between pre- and post-vaccine for all antigens in healthy control & RA-csDMARD groups: In RA-RTX group, significant increase in GMT for B antigen only. Average percentage of vaccine responders across three antigens: Healthy controls: 41.7% RA-csDMARDs: 68.4% RA-RTX: 26.4%

				Healthy individuals (n=16): No IS drugs.	
1351_Louii [59]	Case control	3 months	11 SLE pts, age 18-56 years, 10 women 8 controls, age 27-40 years, 5 women	Influenza whole bivalent A /New Jersey/76 (Hsw1N1) and A/Victoria/75 (H3N2)	8/11 (73%) patients had 4-fold increase in AB titer to A/NJ/76 w/in 4 weeks 5/11 (45%) showed a significant IgM AB response In control group, 7/8 (87%) had a 4-fold increase of AB titer w 4 showing significant IgM AB response Adequate levels of total AB to A/Victoria/75 were elicited in 7/11 SLE patients and in 2 a significant response was noted. 5/8 control subjects also developed significant AB titers, in one subject primary IgM response occurred Geometric mean AB responses to both A/NJ/76 and A/Vitoria/75 were no different in SLE vs control group at any time during the 3 months observation period
1671 Launay 2013 [60]	Case-series	30 days	27 SLE SLEDAI = 0 5 SLEDAI 1-4 = 17 SLEDAI >4 = 5	2009–2010 seasonal trivalent inactivated influenza vaccine: A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2) and B/Brisbane/60/2008	GMT at Day 0: H1N1 45 + 55; H3N2 41 + 20; Influenza B 79 + 87 GMT at Day 7: H1N1 118 + 141 (p=0.012); H3N2 + 52 + 21 (p=0.009); Influenza B 145 + 152 (p=0.012) GMT at Day 30: H1N1 265 + 233 (p=4.3x10-5); H3N2 + 60 + 38 (p=0.005; Influenza B 200 + 187 (p=0.001) Seroconversion: 15/27 H1N1, 5/27 H3N2, 15/27 Influenza B
2045 Kobie, 2011 [57]	Prospective cohort study	6 months	261 subjects—164 RA and 97 healthy controls at the University of Rochester from 2006-2010.	Seasonal inactivated trivalent influenza vaccine (TIV)	At one month following vaccination, RA patients treated with anti-TNF had on average throughout all the study years 50%, 65%, and 30% lower H1, H3, and B GMT, respectively, compared with HC.

2503_Jain_2017 [21]	Cohort, case control, prospective	Feb-March 2014	DMARD group: 51 patients w RA on MTX ≥ 15mg/wk x 3 months or more (concurrent SSZ, HCQ and/or prednisolone ≤ 7.5mg/day were continued); vs DMARD-naïve group: 51 RA patients DMARD naïve (tx NSAIDS & IA or low dose PO steroids; 45 Healthy controls	Inactivated seasonal trivalent influenza vaccine (containing A/California/7/2009-H1N1 and A/Vicotria/361/2011- H3N2 and one B strain – B Massachusetts/2/2012)	In all groups, post-vaccination seroprotection rates were >90 % for all the three strains except for Yamagata strain (84.4%). There was a significant difference in post-vaccination seroprotection for Yamagata strain in all the groups (100 vs. 94.11 vs. 84.44%; P=0.001) The maximum immune response (70.58%) was seen for H1N1 strain and the least immune response for Yamagata strain (35.29%) in DMARD-naïve patients. Significant difference in immune response seen only for the Yamagata strain (56.85 vs. 35.29 vs. 57.78%; P<0.05). The DMARD group had lower rates of positive immune response compared to healthy controls only for H3N2 strain [37.25 vs. 57.78% for H3N2 (P<0.05, odds ratio (OR) – 0.43, 95% CI: 0.19-0.98)]
2516 Elkayam (2010) [14]	Prospective, single-center, cohort study	4-6 weeks post-vaccine	43 patients with RA, 18 patients with AS, and 17 healthy controls matched for age and gender to the RA group 20/43 RA patients and all 18 AS patients treated with infliximab 3	All participants received one standard dose of trivalent inactivated seasonal influenza vaccine (H1N1/H3N2/B). RA & AS patients: 22 patients vaccinated on the day of IFX (IFX-T1) vs 16 patients vaccinated 3 weeks	Significant increases in GMT titers for all 3 antigens were observed in all groups (IFX-T1, IFX-T2, RA controls, healthy controls) at 4-6 weeks post-vaccine compared to pre-vaccine. Proportion of participants with humoral response to each of the 3 influenza antigens was similar in IFX-T1, IFX-T2, RA controls, and healthy controls. Predictors of response: No association with humoral response for the following predictor variables: age, sex, RA duration, SJC, TJC, ESR, CRP, use or dose of prednisone, use or dose of MTX.

			mg/kg IV q6-8 weeks for >6 months. 23 RA "control" patients were on csDMARDs. All patients on stable drug treatment for 3+ months pre-vaccine.	after infliximab infusion (IFX-T2). RA+IFX (n=20): 17/20 (85%) MTX; 12/20 (60%) prednisone; 5/20 (25%) on HCQ. AS+IFX (n=18): 8/18 (44%) MTX; 3/18 (16%) prednisone, 1/18 (5%) on SSZ. RA controls (n=23): 19/23 (82%) MTX; 8/23 (35%) prednisone; 6/23 (26%) on HCQ, 2/23 (8%) on SSZ.	
2526 Park (2017) [61]	Prospective single-center randomized single-blind parallel-group intervention study	20 weeks (4 weeks pre-vaccine, 16 weeks postvaccine)	277 patients with RA aged 18 years or older and on a stable dose of MTX for 6 weeks or longer	All participants received one dose of inactivated seasonal trivalent influenza vaccine (H1N1/H3N2/B-Yamagata). Randomized 1:1:1:1 to: Group 1 (n=69) continue MTX; Group 2 (n=68) suspend MTX for 4 weeks before vaccination; Group	Primary analysis performed on per-protocol population (n=199): Group 1 (n=54), Group 2 (n=44), Group 3 (n=49), Group 4 (n=52). **<u>Noncomparative data:</u>** Group 1 (n=54) RA patients receiving influenza vaccine while continuing MTX. 46.3% on GC (mean dose 2.2 mg daily), mean MTX dose (12.7 mg weekly), 9.3% SZZ, 18.5% HCQ, 25.9% LEF, 9.3% TNFi. **Vaccine response** at 4 weeks post-vaccine (4-fold or greater increase in HI antibody titer): 1+ antigens: 42/54 (77.8%) 2+ antigens: 29/54 (53.7%) 3 antigens: 17/54 (31.5%) H1N1: 28/54 (51.9%) H3N2: 39/54 (72.2%)

				3 (n=71) suspend MTX for 2 weeks before & 2 weeks after vaccination; Group 4 (n=69) suspend MTX for 4 weeks after vaccination.	B-Yamagata: 21/54 (38.9%) **Fold increase in GMT (mean, 95% CI):** H1N1: 5.1 (3.4-7.8) H3N2: 5.9 (4.3-8.1) B- Yamagata: 2.9 (2.2-3.8) **Seroconversion at 4 weeks post-vaccine:** H1N1: 22/36 (61.1%) H3N2: 15/15 (100%) B-Yamagata: 18/33 (54.5%)
2545 Winthrop (2016) [9]	Randomized, double-blind, placebo-controlled, phase II study	64 days (35 days post-vaccination)	200 tofacitinib-naive adult patients with RA Participants received tofacitinib 10 mg BID (n=102) vs. placebo (n=98), stratified by background MTX use. 4 exposure groups: No DMARDs (n=43), MTX monotherapy (n=55), TOFA monotherapy (n=45), MTX+TOFA (n=57)	Background MTX in 57/102 (55.9%) of TOFA group, 55/98 (56.1%) placebo group. All participants received one dose of PPSV-23 and one dose of 2011-2012 seasonal trivalent influenza vaccine (H1N1/H3N2/B-Brisbane) at 4 weeks after initiation of study treatment.	**GMFR - Fold increase in geometric mean titer (GMT) from pre- to 35 days post-vaccine** For influenza vaccination, lowest GMFR responses consistently observed for influenza B antigen, with similar GMFR across 4 groups. More robust GMFR responses to H1N1 and H3N2 antigens in all groups. Highest GMFR responses for H1N1 & H3N2 in No DMARD group; lower & similar responses in the MTX alone, TOFA alone, and TOFA+MTX groups.

2613_Elkayam_2011 [54]	Cohort, case control	Nov 2009-Jan 2010	41 RA patients (age 52.6 +/- 14.5); MTX 25 (61%), prednisone 19 (46.3%), TNF 13 (31.7%), HCQ 6 (14.6%) 21 SLE; MTX 3 (14.3%), prednisone 15 (71.4%), TNF none, HCQ 15 (71.4%) 17 PsA; MTX 7 (41.2%), prednisone 3(17.6%), TNF 14 (82.4%), HCQ none 15 AS: MTX 1 (6.7%), prednisone none, TNF 12 (80%), HCQ none 25 healthy controls age and sex matched	adjuvanted H1N1v monovalent influenza vaccine	Four weeks s/p vaccination: all RA, SLE, AS, and PsA patients and healthy participants displayed significant increases in their geometric mean titers of the HI antibody against A/California/ 7/2009 (H1N1v): RA: From 5.72 to 64.29 (*P* <0.0001) SLE: from 6.91 to 70.93 (*P*< 0.0001) PsA: from 5.6 to 55.5 (*P* <0.001) AS: from 2.33 to 57.04 (*P* <0.0001) Healthy control: from 4.3 to 127 (*P*< 0.0001) Seroprotection: Proportion of responders was similar for the patients with RA (56%), SLE (67%), PsA (59%), and AS (53%), but was significantly higher for the healthy controls (84%; *P* 0.04 compared to the RA group) % of patients achieved seroprotective level s/p vaccination was high: 92% for the controls, 71% for the RA patients, 76% each for the SLE and PsA patients, and 60% for the AS patients.
2479_Holvast_2009 [53]	Controlled clinical trial, not randomized,	Oct-Dec 2007	52 SLE patients w quiescent disease; mean age 45.2 +/- 10 yrs; 17.3% males	Trivalent subunit influenza vaccine s/p 4 weeks only SLE patients received a second	PRED/AZA group (28 pts) had lower AB response to influenza vaccination vs with NO-imm/HCQ pts (17), reflexted by lower GMT against A/H1N1 and A/H3N2 following first vaccination and a lower seroconversion rate against A/H1N1. Second vaccination had slight additional effect for A/H1N1 within Pred/AZA pts

	open prospective		Most used immunosuppressives especially prednisone (31 pts), HCQ (25 pts) , and AZA (15 pts); 5 not on meds 7 on other immunosuppressive drugs: 4 on MTX, 2 MMF, 1 cyclosporin vs 28 Healthy control age and sex matched Subanalysis for PICO 3: 28 pts on prednisone and/or AZA vs 17 pts using no immunosuppressives or HCQ only. 7 pts using other immunosuppressive drugs then prednisone, AZA and HCQ (excluded)	booster dose of vaccination	**Pred/AZA t=4 wks s/p vacc** **Seroprotection rate** H1N1 23 (82.1%) H3N2 19 (67.9%) B 17 (60.7%) **GMT** H1N1 72.5 H3N2 39 B 36.7 **Seroconversion rate** H1N1 4 (14.3%) H3N2 5 (17.9%) B 3 (10.7%) Pred/AZA t=8 wks s/p vacc **Seroprotection rate** H1N1 25 (89.3%) H3N2 19 (67.9%) B 17 (60.7%) **GMT** H1N1 92.8 H3N2 41 B 40 **Seroconversion rate** H1N1 3(10.7%) H3N2 0 B 0 **No immunosupp/HCQ t=4 wks s/p vacc** **Seroprotection rate** H1N1 16(94.1%)

					H3N2 16 (94.1%) B 11 (64.7%) **GMT** H1N1 130.5 H3N2 78.4 B 40.8 **Seroconversion rate** H1N1 11 (64.7%) H3N2 5 (29.4%) B 5 (29.4%) **No immunosupp/HCQ t=4 wks s/p vacc** **Seroprotection rate** H1N1 16 (94.1%) H3N2 16 (94.1%) B 10 (58.8%) **GMT** H1N1 130.5 H3N2 83.3 B 43.4 **Seroconversion rate** H1N1 1 (5.9%) H3N2 0 B 0
3062 Setti 2009 [62]	Open-label, cohort study	12 months	46 scleroderma 20 controls age- and gender-matched	Trivalent seasonal influenza vaccine: 15 ug of hemagglutinin (HA) for A/Wisconsin/67/2005 (H3N2); A/New	PICO 3 Mean GMT increase at 1 month -H3N2: 2.09 scleroderma, 3.0 control Seroconversion at 1 month - H3N2: 41/46 (90%) scleroderma, no data for control Seroprotection at 1month

				Caledonia/20/99 (H1N1); B/Malaysia/2506/2004	- H3N2: 31/46 (67%) scleroderma, 20/20 (100%) control
3341 Trollmo 1994 [10]	Open labeled, controlled intervention study	7-10 days	Experiment 1: (oral) 25 patients with RA, 9 patients with AS, 19 health controls Experiment 2: (IV): 14 patients with RA, 9 patients with AS, 10 health controls	Oral influenza (Experiment 1) Parenteral influenza vaccine (Experiment 2)	**<u>Oral Influenza Vaccine:</u>** 1. RA, AS and HC groups all had similar patterns (shown only visually): No influenza-specific SFCs (spot forming cells) at day 0, a few at day 4, peak response at day 7, and decreasing number of SFCs at day 10 . 2. Immune response = >5 antigen specific SFC/16 PBMC detected at 7 days: **see RevMan file.** - RA: 15/25 (60%) - AS: 7/9 (78%) - HC: 14/19 (74%) 3. "No difference in B cell response in patients with RA treated with cytotoxic drugs [MTX, cyclosporin, podophyllotoxinum] vs. other pharmacotherapies" (steroids, sulphasalzin, auranofin, natrium-aurothiomalas) (data not shown). **<u>Parenteral Influenza Vaccine:</u>** 1. 7 days after vaccine, SFC were seen in: - 13 of 14 patients with RA - 9 of 9 patients with AS - 10 of 10 HC 2. number of SFCs was lower in RA vs controls ($p<0.01$) and patients with AS ($p<0.05$). Similar but not stat signnifcant trend was seen for IgA-specific B cell responses. IgM responses similar in all groups. 3. No differences in antigen specific B cell response in aptients with RA treated with cytotoxic drugs [MTX, cyclosporin, podophyllotoxinum] vs. other pharmacotherapies" (steroids, sulphasalzin, auranofin, natrium-aurothiomalas) (data not shown).
3345_Lu_ 2011 [55]	Controlled clinical	6 months s/p	21 SLE; age 34.3 +/- 11.8, all taking one or	Split-virion inactivated monovalent	SLE (n=21) vs controls (n=15) GMT T= 0 day 28.28 vs 28.28

	trial, not randomized	vaccination	more immunosuppressives- prednisolone (17), HCQ (15), disease-modifying antirheumatic drugs ,or cytotoxic agents i.e AZA (18), CYC vs 15 healthy controls; sex, age matched	A/H1N1 vaccination between Dec 2009-Jan 2010	T = 21 days 148.74 vs 116.19 T= 6 months 60.14 vs 44.50 Seroprotection rate T= 0 day 9.5% (2/21) vs 6.7% (1/15) T = 21 days 76.2% (16/21) vs 80.0% (12/15) T= 6 months 66.7% (14/21) vs 60.0% (9/15) Seroconversion rate 21 days 76.2% (16/21) vs 80.0% (12/15) 6 months 52.4% (11/21) vs 53.3% (8/15) Prednisolone (n=17), AZA (n=18), HCQ (n=15) GMT T=0 days 30.31 vs 30.31 vs 25.20 T= 21 days 127.0 vs 113.1 vs 58.10 T = 6 months 55.08 vs 53.84 vs 58.10 Seroprotection rate T= 0 days 5.9% (1) vs 5.6 % (1) vs 0 T= 21 days 70.6% (12) vs 72.2% (13) vs 80.0% (12) T= 6 months 64.7% (11) vs 61.1% (11) vs 73.3% (11) Seroconversion rate T=21 days 70.6% (12) vs 72.2% (13) vs 80.0% (12) T= 6 months 47.1% (8) vs 55.6% (10) vs 66.7% (10) No difference was found in the GMT, the percentages of seroprotection and seroconversion rate among these three groups Prednisolone & AZA (n=15) GMT T= 0 33.6 T=21 days 99.0 T=6 months 48.3 Seroprotection rates T= 0 5.9% (1) T=21 days 70.6% (12) T= 6 months 60% (9)

					Seroconversion rates T=21 days 66.7% (10) T = 6 months 40.0% (6) AZA & HCQ (n=12) GMT T= 0 28.3 T=21 days 109.6 T=6 months 49.2 Seroprotection rates T= 0 5.6% (1) T=21 days 75.0% (9) (<0.0001) T= 6 months 66.6% (8) (<.0001) Seroconversion rates T=21 days 75.0% (9) T = 6 months 58.3% (7) HCQ & Prednisolone (n=13) GMT T= 0 28.3 T=21 days 134.5 T=6 months 51.51 Seroprotection rates T= 0 0 T=21 days 76.9% (10) (<0.0001) T= 6 months 69.2% (9) (<.0001) Seroconversion rates T=21 days 76.9% (10) T = 6 months 61.5% (8) Evaluation of GMT, the percentages of seroprotection and seroconversion rate among these three groups revealed no specific differences
3731 vanAssen (2010) [8]	Prospective cohort study	28 days post-vaccine	**23 adult patients with RA on RTX** 12/23 (52%) influenza vaccine in	All participants received one standard dose of trivalent inactivated	**Fold increase in titers at 28 days post-vaccine compared to baseline – median (range):** <u>Healthy controls (n=29):</u> H3N2: 1.4 (-1.4 to 16) H1N1: 2 (-1.4 to 128) B strain: 1.4 (-1.4 to 32)

			preceding year, median RA duration 13.8 years) **20 patients with RA on MTX** 10/20 (50%) influenza vaccine in preceding year, median RA duration 8.7 years) **29 healthy volunteers** 21/29 (72%) influenza vaccine in preceding year) Baseline CD19+ cells significantly higher in healthy controls & RA-MTX group compared to RA-RTX group	seasonal influenza vaccination. **RA-RTX group (n=23):** RTX 1000 mg IV x 2 doses, 2 weeks apart, except 375 mg/m2 IV wekly x 4 doses. First RTX cycle in 11/23 (48%), second cycle in 5/23 (22%). Median MTX dose 17.5 mg weekly, median prednisone dose 8.75mg OD Vaccination 4-8 wks post-RTX in 11 patients (Early) vs. 6-10 months post-RTX in 12 patients (Late). Baseline CD19+ B cell numbers similar in both subgroups. **RA-MTX (n=20):** Median MTX dose 16.3 mg weekly, no corticosteroids	<u>RA-MTX (n=20):</u> H3N2: 2 (1 to 11.3) H1N1: 4 (1 to 16) B strain: 1 (-1.4 to 16) <u>RA-RTX (n=23):</u> H3N2: 1 (-2 to 2) H1N1: 1 (-2 to 8) B strain: 1 (-2 to 5.7) Compared to RA-RTX group, significantly higher fold increase in Ab titers in HC group for H1N1 and B strain; in RA-MTX group for H3N2 & H1N1 (all $p < 0.05$). **Seroconversion:** (Fourfold or greater increase from baseline in Ab titer to at least 1:40 post-vaccine): Higher rate of seroconversion in RA-MTX group vs. RA-RTX group for H3N2 (p=0.011) & H1N1 (p=0.020). Seroconversion to any of the 3 influenza strains occurred in only 3 RA-RTX patients, all in the <u>Late</u> vaccine subgroup.
405 Allen 2016 [63]	Observational	28 days	191 RA patients from the ACQUIRE study	2011–2012 trivalent seasonal influenza vaccine;	Patients achieving protective antibody levels (antibody titer ≥1:40 for influenza antigens):

			received influenza vaccine	abatacept and DMARDs	Influenza (≥2 of 3 antigens): 151/184 (82.1%, 95% CI: 76.5 to 87.6)
4082, Saad, 2011 [40]	Cohort study	21 days post vaccination	Adults w mixed RMD n = 1668, healthy controls n = 234;	single IM dose (0.5 ml) H1N1 A/California/7/2009-like virus (A/California/7/2009/Butantan Institute/Sanofi Pasteur)	Factor increase in GMT was significantly lower with RMD population vs. controls (8.9, 95% CI: 8.3 to 9.6 RD population vs. 13.2, 95% CI: 11.1 to 15.8 controls; p<0.0001).
409 Richi 2019 [64]	Cohort study Multicenter	6 months	253 mixed autoimmune inflammatory rheumatic diseases (AIIRD)	Seasonal influenza vaccination	PICO 3 Seropositivity (IgG $\geq$ 11.5 AU) RA: Influenza A 69/90 pre- vs 64/90 post- p=0.648; Influenza B 37/90 pre- vs 50/90 post- **p=0.031** SpA: Influenza A 67/87 pre- vs 72/87 post- p=0.267; Influenza B 40/87 pre- vs 45/87 post- p=0.486 PsA: Influenza A 34/42 pre- vs 33/42 post- p=1.00; Influenza B 22/42 pre- vs 22/42 post- p=1.00 CTD: Influenza A 4/7 pre- vs 4/7 post- p=1.00; Influenza B 3/7 pre- vs 2/7 post- p=1.00 RA: Influenza A 4/6 pre- vs 4/6 post- p=1.00; Influenza B 1/6 pre- vs 2/6 post- p=1.00
4092, Aikawa, 2013 [42]	Prospective cohort	21 days	38 juvenile ARD vs healthy controls n = 11	2 IM doses (0.5 ml) of a non-adjuvanted vaccine against influenza A H1N1/2009 administered 21 days apart	No significant difference in fold increase in GMT (16.7, 95% CI: 10.7 to 26.1 RD vs. 36.3, 95% CI: 12.3 to 106 control; p=0.23) and GMT (151.5 RD vs. 282.1 control, p=0.26).
4113, Miossi, 2013 [65]	Prospective cohort	21 days	MCTD n = 69, healthy controls n = 69	single IM dose (0.5 ml) H1N1 A/California/7/2009-like virus (A/	Post vaccination seroprotection rate (75.4% vs. 71%, p = 0.70), seroconversion rate (68.1% vs. 65.2%, p = 1.0) and factor increase in GMT (10.0 vs. 8.0, p = 0.40) remained similar in both groups

				California/7/2009/ Butantan Institute/Sanofi Pasteur)	MCTD pts post-vaccination with and without therapy revealed comparable seroprotection (p = 1.0), seroconversion (p = 1.0) and FI GMT (p = 0.61). Seroconversion rates were alike in pts w and w/o the following therapies: glucocorticoids (p = 0.80), chloroquine (p = 0.79), azathioprine (p = 0.26), methotrexate (p = 1.0) and leflunomide (p = 0.68). Pts w and w/o immunosuppressive agents also had a similar post-vaccination seroprotection rate (75.6%; 95% CI, 62.3-88.9% vs. 75%; 95% CI, 59-91%; p = 1.0), FI GMT (13.5; 95% CI, 8.2-22.1 vs. 6.4; 95% CI, 4.3-9.5; p = 0.06) and seroconversion rate (73.2%; 95% CI, 59.4-86.9 vs. 57.1; 95% CI, 38.5-76%; p = 0.2)
4114 deBruyn (2016) [66]	Parallel group, prospective, randomized, open-label study	3-5 weeks post-vaccine	132 patients with IBD on maintenance infliximab therapy and between 9-60 years of age. 51.8% male, 16% pediatric, 84% CD, 70.8% inactive disease.	All participants received one standard dose of the seasonal 2012/2013 trivalent influenza vaccine (H1N1/H3N2/Influenza B) Participants randomized 1:1 to either receive vaccine at Time 0 (Day 0-4 after IFX infusion; n=69) vs. Time 1 (Day 21-28 after IFX infusion; n=68).	Some analyses excluded patients missing baseline titers (n=2 in Time 0 group; n=8 in Time 1 group), missing FU titers (n=2 in Time 0 group) 137 IBD patients receiving influenza vaccine while on maintenance IFX. **Seroprotection at 3-5 weeks post-vaccine:** H1N1: 89/135 (65.9%) H3N2: 62/135 (45.9%) B-Influenza: 100/135 (73.0%) **Immunologic response (3-5 weeks post-vaccine)** H1N1: 40/125 (32%) H3N2: 32/125 (25.6%) B-Influenza: 46/125 (36.8%)
4351 Gabay 2011 [39]	Prospective cohort study	3-4 weeks	82 with RA, 45 with SpA, 46 with other IR diseases and 138 controls on DMARDs (73 MTX, 41 SSZ or	Controls received 1 dose of adjuvanted influenza A/09/H1N1 vaccine, and patients received 2	<u>Post-dose 1, mixed RMD vs. healthy controls</u>: Significantly lower HIA-GMTs in mixed RMD vs patients (146 mixed RMD, 340 healthy controls; p<0.001). <u>Post-dose 2 mixed RMD vs post-dose 1 healthy controls</u>: Results indicated similar HIA-GMTs (287 mixed RMD vs. 340 healthy controls).

			HCQ, 23 LEF, 28 AZA or CYC or MMF, 3 other) 22 on RTX, 67 on oral steroids (46 on <10 mg/day, 21 on ≥10 mg/day)	doses of the vaccine. Post-dose 1: 138 patients, 131 healthy controls Post-dose 2: 148 patients	Multivariate regression analysis indicated after 2 doses of H1N1 vaccine, use of TNFIs (-0.02. (SE 0.15); p=0.91) and some DMARDS (MTX, LEF, AZA, MMF, CYC) was significantly associated with lower antibody response. Use of HCQ and SSZ (0.11 (SE 0.14); p=0.45) was not significantly associated with lower antibody response.
4428 Turner-Stokes 1988 [67]	Prospective cohort	4 weeks	28 pts with SLE 10 with RA 4 MCTD 2 RA/SLE crossover	Influenza vaccine Anti-influenza antibody assay levels conducted at 7 day intervals up to 28 days	No significant association with disease activity or immunosuppressive therapy
45 Ribeiro, 2013 [68]	Subanalysis of a prospective study	Blood samples were col-lected before and 21 days after the vaccination	RA-ABA (abatacept) n=11; RA+MTX, n=33; Healthy controls, n=55	Sanofi Pasteur Influenza A/H1N1, was a nonadjuvanted monovalent pandemic 2009 influenza A/H1N1 killed virus vaccine (A/California/7/2009/Butantan Institute/Sanofi Pasteur, Sa˜o Paulo, Brazil) containing 15g hemagglutinin from an influenza A/California/07/2009(H1N1) virus-like strain (NYMCx-179A) per 0.5-ml dose	Prevaccination GMTs were very low and similar in all groups. Seroconversion was not obtained in any of the RA-ABA patients, and only 1 subject (9%) achieved seroprotection. These trends were significantly different from those observed in other groups (P < 0.001 for seroconversion and P =0.001 for seroprotection). Despite a significant and slight increase in GMT (6.0 [95% confidence interval (95% CI) 4.6 –7.9] to 10.7 [95% CI 7.2–15.7]; P 0.008) after vaccination, FI-GMT (P < 0.001) and postvaccination GMT (P < 0.001) were severely reduced in the RA-ABA group compared to the other groups. RA-MTX patients and controls had more significant increases in GMT after vaccination (6.0 [95% CI 5.3– 6.9] to 52.6 [95% CI 31.5– 87.7]; P < 0.001 and 6.6 [95% CI 5.8 –7.5] to 76.1 [95% CI 52.9 –109.3]; P < 0.001, respectively). In all parameters analyzed, RA-MTX patients exhibited lower responses than controls, but these differences did not reach statistical significance. No correlation was observed between any of the end points and the duration of treatment with ABA or time since the last dose (P > 0.05).

4721 Mercado 2004 [69]	Single-arm intervention	8 weeks	18 SLE patients; 17 patients on pred (mean dose of 14mg/day, range of 2.5-50mg/day); mean Mex-SLEDAI of 5.5	2001-2002 Fluarix trivalent inactivated seasonal influenza vaccine	SLE patients had HAI antibody titers of >1:40 more often 4 weeks post-vaccination compared to pre-vaccination (A/Moscow 28% vs 67%; A/New Caledonia 22% vs 72%; B/Sichuan 17 vs 61%), but less than healthy controls (77%, 94%, and 94% respectively).
4728 Crowe 2011 [70]	Single-arm intervention	12 weeks	72 SLE patients (and 72 healthy controls) in Oklahoma	2005-2006 or 2007-2008 trivalent subunit seasonal influenza vaccines	Amongst the 36 of patients classified as "low responders," an increased rate of "lupus disease flare" (SELENA SLEDAIs reportedly scored, but no scores given) was noted 6 weeks following the vaccine, in comparison to "high responders." At 6 weeks, 7 low responders (20%) were reported to have mild/moderate flare (compared to 3 of the high responders), and another 3 (8%) were reported to have a severe flare (compared to 1 of the high responders). This difference was not noted at 12 weeks following the vaccine, when the two groups were equal with 8 (22%) mild/moderate flares in each group, and 1-2 (3-6%) severe flares in each group.
489 Wiesik-Szewczyk 2010 [3]	Case control	12 weeks	62 SLE on medications vs 47 healthy control	Inactivated Influenza vaccine 15ug HA each of A/H1N1, A/H3N2, and B	GMT at 4 weeks (SLE, controls) H1N1: 39.06, 104.32; p<0.0011 H3N2: 42.97, 91.36; p=0.001 Type B: 50.80, 81.19; p=0.05 GMT at 12 weeks (SLE, controls) H1N1: 24.21, 69.03; p<0.001 H3N2: 25.71, 60.45; p=0.0001 Type B: 28.28, 52.16; p=0.0008 Mean fold increase at 4 weeks (SLE, controls) H1N1: 6.23, 16.48; p=0.000002 H3N2: 6.61, 14.23; p<0.0001 Type B: 7.02, 11.9; p=0.0002

					Mean fold increase at 12 weeks (SLE, controls) H1N1: 3.86, 10.91; p=0.000005 H3N2: 3.96, 9.42; p=0.0001 Type B: 3.91, 7.65; p=0.000086
4918 Kogure 2014 [71]	Single-arm intervention	4 weeks	57 RA patients	2011-2012 trivalent subunit seasonal influenza vaccine	Seroprotection at 4 weeks was achieved for H1N1 in 63% of patients, for H3N2 in 81% of patients, and for B in 26% of patients. GMT and fold-change data also provided.
6154 Shingo 2012 [44]	Cohort	21 days	dermatomyositis (DM, n=37) and polymyositis (PM, n=21), age-and gender-matched healthy controls (n=116)	Sanofi Pasteur 2009 influenza A (H1N1) was a novel monovalent adjuvant-free vaccine (A/California/7/2009/Butantan Institute/Sanofi Pasteur)	No significant difference in GMT and factor increase in GMT post-vaccination with DM/PM vs. controls. GMT: 119.0 (75.3-188.1) DM/PM vs. 102.8 (82.8-127.8) controls; p=0.573 Factor increase in GMT: 13.6 (9.1-20.3) DM/PM vs. 11.6 (9.3-14.4) controls; p=0.496
647 Morgan 2016 [72]	Cohort-case control	Median FU post vaccination 4.6 years, total patient FU was 363 patient-years (none lost to FU)	92 patients with EGPA, GPA, MPAnor classical PAN in stable remission > 6 months had not received RTX within 6 months, on <10mg of prednisone per day, currently on no more than 1 IS + prednisolone,	Multiple vaccines incuding Haemophilus influenzae type b (Hib)	Median AB titers for all the vaccine components increased at 4 weeks postvaccination 4 weeks postvaccination, significant improvement in the percentage of patients who had AB titers above the threshold, although there was variability in the response between antigens (antibody response above the protective threshold for each antigen median of 46% [IQR 39–58%]) Serotype PreVacc Post Vacc P Hib 26 68 0.001

			9 patients on RTX, 35 on AZA, 35 on MMF		
7029 Jeffs (2015) [48]	Open, single-center, prospective cohort study	28 days post-vaccine	31 AAV (20 GPA & 11 MPA) patients median age 62 in clinical remission for 3+ months (BVAS <2) on different meds 67 healthy individuals, median age 23	AAV patients randomized 3:1 to receive trivalent (H1N1/H3N2/B influenza) seasonal influenza vaccine (n=24) versus no vaccination (n=7). Healthy individuals also randomized 3:1 to receive vaccine (n=53) versus no vaccine (n=14).	Vaccinated AAV patient group satisfies European CPMP guidelines for effective responses to all three influenza vaccine antigens (at least one of: seroprotection rate >70%, seroconversion rate >40%, seroconversion factor >2.5). Post hoc: No significant difference in number of immunosuppressive medications and post-vaccine GMT for either of the influenza A antigens. Patients on no immunosuppressives had higher post-vaccine GMT for B-Malaysia compared to patients on 2 or 3 drugs ($p<0.05$).
7034 Evision 2009 [73]	Randomized double blind trial	4-6 weeks	304 total: 131 HIV, 47 mixed RMD (28 RA, 13 AS, 3 SLE, 2 Sarcoidosis, 1 vasculitis), 74 renal transplant, 47 hemodialysis, 5 nephrologic disease	Trivalent seasonal 2005-2006 influenza subunit vaccine vs the virosomal vaccine: 15 mg of A/California/20/99 (H3N2), A/New Caledonia/20/99 (H1N1), B/Shanghai/361/2002	Seroconversion for mixed RMD - 20/28 (71%) subunit vaccine - 18/19 (95%) virosomal vaccine Seroprotection for mixed RMD - 18/28 (64%) subunit vaccine - 16/19 (84%) virosomal vaccine
7194	Prospective	Follow-up to 3-5	26 patients with NMO	All participants received one	At T1, 3 (18.8%) patients in the rituximab group showed seropositivity, while 6 (37.5%) patients in the rituximab group seroconverted. Mean fold increase was 3.3±4.1.

Kim (2013) [74]	cohort study	weeks post-vaccine	spectrum disorders (NMOSD), 9 with MS, and 8 healthy controls aged 18-65 years. RTX group (n=16 NMOSD patients): Mean age 38.8 years, 81.25% female	standard dose of a monovalent adjuvant H1N1 influenza vaccine (2009 pandemic).	
7199 Ribeiro (2011) [12]	Prospective single-center cohort study	21 days post-vaccine	340 patients with RA mean DAS28-ESR 3.66, aged 18 years or older on stable RA medications vs. 234 healthy controls.	All participants received a single dose of pH1N1 vaccine.	Multivariable analysis for seroconversion: age, RA (vs. controls), and MTX use associated with impaired seroconversion ($p<0.05$). MTX use (vs. no MTX): OR 0.51; 95% CI 0.32-0.82 for seroconversion post-vaccine.
7496 Westra (2014) [23]	Prospective cohort study	28 days post-vaccine	43 patients with RA aged 18 years or older, 20 on MTX, 23 on RTX. Mean (SD) age 55.5 (7.6) years in RA-RTX, 57.1 (6.7) years in RA-MTX. 28 healthy controls (HC).	All participants received one standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B-Malaysia). RA-RTX group (n=23): 11/23 (48%) vaccinated early - 4-8 weeks after RTX, 12/23 (52%) vaccinated	Significant increase in anti-influenza specific IgG and IgM antibody levels (for both H1N1 & H3N2) at 28 days post-vaccination compared to baseline for healthy controls & RA-MTX. No significant increase in IgG or IgM levels post-vaccine for either influenza strain in the RA-RTX group.

			Mean (SD) age 45.2 (11.3) years. Previous influenza vaccination in 52% of RA-RTX, 50% RA-MTX, 71.4% HC.	late - 6-10 months post-RTX. <u>RA-MTX group (n=20):</u> Median dose 16.3 mg weekly, , no corticosteroids.	
7510 Eisenberg 2013 [37]	Prospective single-center cohort study	Follow-up to 6 months post-vaccine in RMD patients; follow-up to 8 weeks post-vaccine in controls	25 patients on active RTX therapy for autoimmune disease enrolled, 17/25 (68%) completed the study. Type of RMD: 8/17 (47%) RA, 6/17 (35%) pSS, 2/17 (12%) SLE, 2/17 (12%) PM, 1/17 (6%) GPA. A subset of 12/17 patients (70.6%) with synchronized studies were used to assess vaccine response. 15 adult, age-matched	All participants received one standard dose of trivalent inactivated seasonal influenza vaccine (four different vaccines used over four different influenza seasons: 2006-2007, 2007-2008, 2008-2009, 2009-2010). All RMD patients vaccinated between 7-9 months post-RTX treatment. All RMD patients were on concomitant immunosuppressive therapy, including low-dose prednisone (n=4), HCQ (n=4), LEF	**Overall B cell numbers:** All patients had complete B-cell depletion at 4 weeks post-RTX, defined as an absolute B cell count <=5 cells/uL. Variable B-cell recovery at 7-9 months post-RTX, with reconstitution in a few patients. **B-cell subsets:** Significantly fewer IgM memory cells & switched memory cells in RMD-RTX patients vs. controls at baseline ($p<0.001$ for both). At 7-9 months post-RTX, switched memory B cells & non-switched memory B cells remained depleted at <10% starting values. **T-cell subsets:** The number of naïve CD4+ cells ($p=0.05$), naïve CD8+ cells ($p=0.01$), effector CD4+ cells ($p<0.01$), and effector CD8+ cells ($p<0.01$) were all significantly lower in RMD-RTX patients vs. controls at baseline. **T cell response to influenza:** At baseline, T cell response was similar between RMD-RTX patients & healthy controls No increase in T cell response observed post-vaccination in the RMD-RTX group (data not shown). **T cell repertoire among RMD-RTX patients:** No changes in T cell repertoire observed between baseline, 4 weeks post-RTX, 7-9 months post-RTX (vaccination), 2-months post-vaccine, and 6-months post vaccination. **Seroconversion (fourfold or greater increase in titer post-vaccination for at least 1/3 strains):**

			controls: 8/15 (53% female), 11/15 (73%) Caucasian.	(n=2), AZA (n=1), MTX (n=1).	2/12 RMD-RTX patients (one strain each) vs. 10/15 controls (multiple strains in most cases); p=0.009. **Pre-existing aggregate HI titers (defined as sum of titers to 3 serotypes):** For individual RMD-RTX patients, aggregate HI titers varied little over the course of the study, from baseline to 6-months post-vaccination, suggesting pre-existing titers were retained post-RTX treatment.
7615 Holvast (2006) [4]	Prospective, single center, cohort study	Follow-up to 30 days post-vaccine	56 adult patients (89.3% female) with SLE and quiescent disease (SLEDAI 5 or less) VS. 18 age- and sex-matched healthy volunteers (77.8% female). 43/56 (77%) SLE patients received influenza vaccine in the past vs. 4/18 (22%) healthy controls (p<0.001).	All participants received a single dose of trivalent inactivated seasonal influenza vaccine (H1N1/H3N2/B-HK). Group A - No meds (n=12), Group B - HCQ >=400mg daily (n=17), Group C - AZA >= 50 mg daily (n=13), Group D - Prednisone >= 10 mg daily (n=14) Patients in Group B (HCQ) & Group C (AZA) were allowed prednisone <10 mg daily.	**GMT pre/post vaccination:** <u>H1N1:</u> SLE (n=56): 32.4 / 142 Controls (n=17): 6.93 / 130 <u>H3N2:</u> SLE (n=56): 50 / 183 Controls (n=17): 21.7 / 272 <u>Influenza B:</u> SLE (n=56): 16.2 / 64.0 Controls (n=17): 5.65 / 49 Pre-vaccine GMT significantly higher in SLE patients vs. controls for all 3 antigens (p<0.001 for H1N1 & B; p=0.036 for H3N2). GMT increased at 30 days post-vaccine for all antigens. Post-vaccine GMTs did not differ significantly between SLE & controls. Vaccine efficacy & seroprotection rates similar between SLE patients on medication (HCQ, AZA, or GC; n=44) vs. not on medication (n=12) for all 3 antigens.
7655 Milanetti (2014) [20]	Prospective, single-center, cohort study	6 months post-vaccination	30 patients with RA with low-moderate disease activity (DAS<3.7) and stable disease.	All participants received a single dose of trivalent non-adjuvanted 2009-2010 seasonal influenza vaccine	Pandemic & seasonal influenza vaccines met all three CPMP criteria in both RA patients & HCs at T1 for all three antigens (seroconversion rate >40%, seroprotection rate >70%, seroconversion factor > 2.5 at T1). At T2, seroprotection rate >70% only maintained for seasonal vaccine (all 3 antigens in HCs, only B-influenza in RA patients). <u>Seroconversion factor at T1:</u> npH1N1: 4.1 in RA patients vs. 3.7 in HCs

			Mean (SD) age 50 (10) years, mean (SD) baseline DAS 2.33 (0.8) 13 healthy controls, Mean (SD) age 41.8 (12) years 6/30 (20%) RA patients and 3/13 (23%) controls received influenza vaccination in the prior season.	(H1N1/H3N2/B-Brisbane) and a single dose of the pandemic monovalent adjuvanted H1N1 vaccine on the same day. All RA patients were taking a biologic DMARD. Concomitant low-dose corticosteroids (prednisone <10mg daily) and csDMARDs (mostly MTX 10-15mg weekly) permitted.	H3N2: 6.4 in RA patients vs. 6.2 in HCs B-influenza: 4.9 in RA patients vs. 4.8 in HCs pH1N1: 8.5 in RA patients vs. 5.1 in HCs <u>GMTs in RA patients & HCs at T0/T1/T2:</u> npH1N1 - RA: 22/174/57 vs. HC: 15/107/72 H3N2 – RA: 11/61/31 vs. HC: 32/113/93 B-influenza – RA:45/263/148 vs. HC: 68/302/195 pH1N1 – RA: 8/100/33 vs. HC: 7/50/24 Between T0 and T1, GMT values increased significantly for all antigens in RA patients ($p<0.05$), with reduction at T2. Slight increase in activated cytokine-producing T cells at T1 compared to T0, followed by reduction at T2 in both RA patients & HCs. Mean values not significantly different in RA patients vs. HCs at all timepoints.
7864 Richi (2019) [51]	Prospective cohort study	At least 4 weeks FU post-vaccine [mean (SD) 33 (8) days]	17 PsA and AS patients on secukinumab for mean (SD) duration 8.9 (5.8) months vs. 13 healthy controls. 10/17 (58.8%) patients on concomitant csDMARDs.	All participants received one standard dose of seasonal inactivated trivalent influenza vaccine (H1N1/H3N2/B-Brisbane).	GMT at baseline / post-vaccine in AS & PsA patients vs. healthy controls for each antigen: H1N1: AS & PsA patients: 60 / 276 (4.6-fold increase) Controls: 107 / 428 (4.0-fold increase) H3N2: AS & PsA patients: 65 / 91 (1.4-fold increase) Controls: 85 / 86 (1.0-fold increase) Influenza B: AS & PsA patients: 20 / 74 (3.7-fold increase) Controls: 32 / 171 (5.3-fold increase)
8096 Abu-Shakra	Case series	12 weeks post-vaccine	24 SLE patients Mean age 46.1 years (range 20-74), 100%	All participants received one standard dose of trivalent subunit	<u>Vaccine response:</u> At 6 weeks post-vaccination, 18/24 (75%) SLE patients had **immune response (>=4 fold rise in titer or seroconversion)** to at least 1/3 influenza strains: 5/24 (20.8%) responded to 1/3 strains

(2002) [75]			females. Mean disease duration 9.1 years. Baseline seroprotection for H3N2/H1N1/B in SLE (20.8/8.3/66.7 %) similar to healthy age-matched female controls (n=30; 20/16.7/63.3%) . Healthy controls <u>not</u> evaluated post-vaccine.	influenza vaccine (H1N1/H3N2/B-Influenza). <u>SLE therapies:</u> Oral steroids (n=17), mean prednisone dose 12 mg HCQ 400 mg daily (n=9) AZA 100 mg daily (n=3) MTX (n=4) mean dose 10mg weekly	8/24 (33.4%) responded to 2/3 strains 5/24 (20.8%) responded to 3/3 strains 6/24 (25%) did not respond to any strains. All 6 were taking oral steroids (mean dose 15.8 mg). Response to H3N2 in 14/24 (58.3%), H1N1 in 9/24 (37.5%) and B-influenza in 15/24 (62.5%). <u>Seroprotection:</u> Prior to vaccination, patients had protective antibodies **(HI titer >= 1:40)** against a mean of 0.96 of 3 influenza strains. This increased to a mean of 1.92 at 6 weeks post-vaccine and then decreased slightly to a mean of 1.6 at 12 weeks post-vaccine. <u>Rate of seroprotection by number of strains:</u> 0/3: 2/24 (8.3%) at 6 wks, 4/24 (16.7%) at 12 wks 1/3: 6/24 (25%) at 6 wks, 8/24 (33.3%) at 12 wks 2/3: 8/24 (33.3%) at 6 wks, 6/24 (25%) at 12 wks 3/3: 8/24 (33.3%) at 6 wks, 6/24 (25%) at 12 wks <u>Rate of seroprotection by influenza strain:</u> H3N2: 16/24 (66.7%) at 6 weeks; 14/24 (58.3%) at 12 weeks H1N1: 8/24 (33.3%) at 6 weeks; 6/24 (25%) at 12 weeks B-influenza: 22/24 (91.6%) at 6 weeks, 18/24 (75%) at 12 weeks Mean number of immune responses to the 3 influenza antigens, stratified by age, SLEDAI score, and use of prednisone, MTX, or AZA: Overall mean # of immune responses = 1.5/3 <u>Age:</u> Mean 1.33 for 50+ years, 1.6 for < 50 years. <u>Prednisone:</u> Mean 1.14 if 10+ mg daily vs. 1.65 if < 10 mg daily or none. <u>AZA:</u> Mean 1.33 if taking AZA vs. 1.6 if no AZA. No association of <u>MTX therapy</u> or <u>SLEDAI scores</u> with mean number of immune responses.

8187 Holvast (2009) [6]	Prospective cohort study	Follow-up to 3-4 months post-vaccine	80 adult patients with SLE: 54 vaccinated vs. 24 nonvaccinated. Two patients excluded after randomization. Vaccinated SLE patients (n=54): 18.5% male, mean age 44.8 years, 34/54 (63%) prior vaccination. Nonvaccinated SLE patients (n=24): 8.3% male, mean age 45.5 years, 9/24 (37.5%) prior vaccination. Age- and sex-matched healthy individuals (n=54): 20.4% male, mean age 43.1 years, 3/54 (5.6%) prior vaccination. For cellular responses: 38	SLE patients randomized 2:1 to influenza vaccination vs. nonvaccinated patient control group. All healthy controls vaccinated. Vaccination with single standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B). Vaccinated SLE patients (n=54): 5/54 (9.3%) no medications, 28/54 (51.9%) prednisone (median 5mg daily), 30/54 (55.6%) HCQ (median 400mg daily), 17/54 (31.5%) AZA (median 125mg daily), 6/54 (11.1%) MTX. Nonvaccinated SLE patients (n=24): 5/24 (20.8%) no medications, 10/24 (41.7%) prednisone (median 6.25mg daily), 10/24	**Cellular responses:** Prior to vaccination, SLE patients had fewer H1N1-specific & H3N2-specific IFNy spot-forming cells. In both SLE patients & controls, significant increases in H1N1- & H3N2-specific IFNy spot-forming cells from pre-vaccine to 28-days post-vaccine. Post-vaccine, fewer H1N1- and H3N2-specific IFNy spot-forming cells in SLE patients vs. controls. **Geometric mean titers (GMT):** H1N1 T=0: 18.9 in SLE vs. 10.9 in Controls ($p<0.01$) T=D28: 76.5 SLE vs. 98.2 Controls ($p<0.001$) T=3-4 months: 51.3 SLE vs. 62.7 Controls H3N2 T=0: 15.8 in SLE vs. 12.4 in Controls T=D28: 86.4 SLE vs. 138 in Controls ($p<0.01$) T=3-4 months: 55.8 in SLE vs. 76 in Controls **GMT fold increase at Day 28:** H1N1: 4.0 SLE vs. 9.0 in Controls ($p<0.001$) H3N2: 5.5 SLE vs. 11.1 in Controls ($p<0.01$)

			vaccinated SLE patients vs. 38 age- & sex-matched controls.	(41.7%) HCQ (median 400mg daily), 6/24 (25%) AZA (median 87.8 mg), no MTX.	
8953 Litinksy 2012 [76]	case control		26 consecutive SSc patients (12 diffuse, 14 CREST) VS healthy controls Mean age of SSc pts: 52 years, male:female ratio 1:5.5, mean disease duration 8.3 years+/-6.28, 34.6% with digital ulcers, 27% with PAH, 58% with GI involvement, 42% with MSK involvement, 100% with Raynaud's, 27% on immunosuppressive tx	trivalent influenza subunit vaccine (H1N1, H3N2, TGA)	Geometric mean titers of haemagglutination inhibition (HI) antibodies (µg/ml) against influenza antigens in scleroderma (SSc) patients and controls before and six weeks after vaccination. (SD not provided) Week 0 to 6, SSc n=26 H1N1 29.35 to 356 p<0.0001 H3N2 3.28 to 51.3 p<0.001 B 62.9 to 198 p<0.0001 Week 0 to 6, Controls n=16 H1N1 33.63 to 76.6, p=0.02 41.77 to 113.13, p=<0.01 80 to 153.21, p=0.04 Geometric mean titers of haemagglutination inhibition (HI) antibodies (µg/ml) against influenza antigens in scleroderma patients (SSc) subgroups with regard to the use of immunosuppressive drugs, before and six weeks after vaccination. SSc with IS n=7 Week 0 to Week 6 H1N1 4.18 to 5.66 p=0.036 H3N2 1.58 to 2.63, p=1.04 B 4.18 to 4.87, p=0.017 SSc without IS n=19 Week 0 to Week 6

					H1N1: 3.08 to 5.95, p<0.0001 H3N2: 1.04 to 4.41, p<0.0001 B: 4.12 to 5.43, p=0.0001 "The combination therapy of iloprost and calcium channel blockers significantly increased the humoral response to the H1N1 and B antigens (p<0.0001 and p=0.0007, respectively)."
8961 Kobashigawa 2013 [77]	Cohort study	6 months	3529, 4518, 4816, and 4872 RA patients in the 2000/01, 2001/02, 2002/03, and 2006/07 seasons Vaccinated = 12.2%, 17.0%, 20.9%, 38.7% of corresponding cohort	Seasonal influenza vaccination Patient survey results	PICO 3 Immunogenicity - RR 0.83 (0.71-0.95, p<0.01) of developing influenza in vaccinated vs unvaccinated population - no separate data for vaccinated patients who developed influenza subsequently available for analysis (displayed in bar graph) PICO 13 - no separate data for different disease activity groups PICO 15 - no separate data for different medications
9056 Rehnberg 2010 [56]	Case-control	21 days	RA patients (Post-rituximab (n = 11) Pre-rituximab (n = 8) and Controls (n = 10)	Influenza (Afluria) and Pneumo23 vaccines were given 6 months after rituximab (post-RTX group, n = 11) or 6 days before rituximab treatment (pre-RTX group; n = 8). RA patients never exposed to RTX composed the control group (n = 10).	On day 6 after vaccination, formation of influenza-specific B cells was lower in post-RTX group as compared with the pre-RTX group and controls (p = 0.04). Polysaccharide-specific B cells were found in 27% to 50%, being equally distributed between the groups. On day 21, the impairment of humoral responses was more pronounced with respect to influenza as compared with the pneumococcal vaccine and affected both IgG and light-chain production. Total absence of influenza-specific IgG production was observed in 55% of the post-RTX group.

9273 Bjork 2020 [78]	Prospective cohort	90 days	25 Sjogren's patients (anti SSA seropositive and fulfilling the American-European consensus group criteria) [17 were untreated, 8 patients on HCQ] 16 age and sex matched healthy controls	Seasonal influenza vaccination Fluarix,GlaxoSmithKline, Solna, Sweden) containing inactivated A/California/7/2009 (H1N1)-, A/Switzerland/9715293/2013 (H3N2), and B/Phuket/3073/2013-like strains.	**Vaccine specific antibody titers** We observed higher levels of vaccine-specific IgG titres in pSSUntr compared with controls ($p<0.01$), but not in pSSHCQ compared with controls. There was no statistically significant difference in antibody titres comparing pSSUntr and pSSHCQ (data not shown). Vaccine-specific IgA and IgM titres did not differ between pSSUntr and controls and neutralizing anti-hemagglutinin antibody levels were comparable for two of the strains, but higher in pSSUntr compared with controls for the A/Switzerland/9715293/2013-like strain.
9426 Adler 2012 [38]	Nonrandomized comparative	6 months	149 patients: 47 RA, 59 SpA, 15 vasculitis, 28 CTD vs. 40 healthy controls; % of patients >60 was 51% RA, 14% SpA, 40% VAS, 29% CTD, and 8% controls	Single dose of adjuvanted A/H1N1 influenza vaccine; medications included steroids, 93% were on DMARDs (mostly MTX), 46% were on TNFIs, 22% were on both MTX and TNFIs, 10 or fewer patients were each on rituximab, abatacept, tocilizumab, and CYC	PICO 3 and PICO 6 GMT peaked at 3 weeks post-vaccination in both RMD and controls, declined at 6 weeks for both groups, then reached levels below protection (mean increase of GMT <2.5 per CHMP criteria) at 6 months for RMD patients. 3 weeks (GMT/GMT ratio; **met CHMP criteria**) GMT: 47.7/**5.6 RMD**, 116.0/**13.3** controls 6 weeks GMT: 36.2/**4.3 RMD**, 93.0/**10.7** controls 6 months GMT: 19.6/2.3 RMD, 51.0/**5.9** controls Seroprotection (%) at 3 weeks, 6 weeks, 6 months (**CHMP criteria in at least 70% of patients**): MTX (n=28): 50, 41, 25 TNFIs (n=35): **91, 78**, 36 MTX+TNFIs (n=33): 63, 61, 20

					Glucocorticoids (n=50): 66.5, 57, 27.5 Other DMARDs (n=28): **79, 76**, 39 Abatacept (n=20): 45, 35, 20 Rituximab (n=8): 25, 25, 25 <u>GMT/GMT ratio at 3 weeks, 6 weeks, and 6 months; (**CHMP criteria ≥2.5 for GMT ratio)**</u>: MTX: 32.5/**3.8**, 26.1/**3.0**, 18.6/2.2 TNFIs: 83.3/**10.5**, 57.8/**7.3**, 22.4/**2.8** MTX+TNFIs: 37.6/**5.4**, 28.3/**4.1**, 14.3/2.1 Glucocorticoids: 55.2/**5.2**, 38.7/**3.7**, 21.8/2.1 Other DMARDs: 73.4/**7.7**, 55.4/**5.8**, 26.9/**2.8** Abatacept: 23.8/2.5, 24.2/**2.6**, 15.8/1.7 Rituximab: 21.0/2.1, 22.9/2.3, 16.2/1.6 <u>Seroconversion (%) at 3 weeks, 6 weeks, and 6 months (**CHMP criteria in at least 40% of patients**)</u>: MTX: **50**, 36, 29 TNFIs: **83, 66, 46** MTX+TNFIs: **64, 61**, 27 Glucocorticoids: **59.5, 43.5**, 26 Other DMARDs: **75, 64, 46** Abatacept: 35, 30, 10 Rituximab: 25, 25, 13
9428 Oren 2008 [79]	Nonrandomized comparative	4 weeks	29 RA (non-rituximab), 14 rituximab-treated RA (rituximab), and 21 healthy controls	Influenza: 0.5 ml split virion inactivated vaccine (Vaxigrip, Promedico) containing a 15 mg haemagglutinin (HA) dose of A/California /7/04 (CAL) (H3N2), B/Shanghai /361/02 (SHAN) and A/New Caledonian/20/99 (NC) (H1N1),	<u>PICO 3</u> At 4 weeks, both control groups (non-rituximab, healthy controls) demonstrated a satisfactory humoral response* with significant increases in GMT of HI antibody against 3 antigens tested (CAL, SHAN, NC). The rituximab arm demonstrated a significant rise for only 2 antigens (NC and CAL; data graphically presented). No significant difference between groups was reported for percent of responders to all 3 antigens or to none of them (data not shown).

				administered intramuscularly	
9442 Tarjan 2006 [80]	Case series	8 weeks	18 SLE patients	Influenza vaccine containing A/H1N1, A/H3N2, and B-type surface haemagglutinin (Influvac, Solvay Pharmaceuticals B.V., the Netherlands); individuals were on methylprednisone, azathioprine, and chloroquine	PICO 8 At 8 weeks, no increase in SLEDAI scores were noted.
307, Laestadius, 2019 [81]	Cohort study	3 and 10 months	78 children with rheumatic diseases; 22 healthy controls	Seasonal inactivated trivalent influenza vaccine given to 14 pts on MTX only, 36 pts on TNFi +/- MTX, and 11 pts on IL-1/IL-6 inhibitors; there were 17 RD pts not on any therapy	At 3 mo, no sig difference in vaccine response as measured[82] by GMT between any of the groups. Specific values were not reported for either GMT or seroprotection rates (shown in graphical form only). "A few children" on TNFi remained seronegative.
1173, Holvast, 2010 [82]	Cohort study	4 wks	25 GPA patients; 25 healthy controls	Seasonal inactivated trivalent influenza vaccine given to all	Specific values not reported – results shown in graphical form only At 4 wks, GPA and HC patients showed similar levels of: - Activated T cells (both CD4+ and CD8+ were measured) - Influenza-specific IFN-g release (as measured by ELISPOT) - Total IFN-g production in response to viral stimulation in vitro GPA patients on immunosuppressive drugs (n=11, drugs not specified) were not different from GPA patients not on immunosuppression (n=13)

2488, Gelinck, 2008 [58]	Cohort study	4 wks	64 pts on TNFi; 19 matched controls; 48 patients not on TNFi, with 18 matched controls. Both RMD and IBD patients were included	Seasonal inactivated trivalent influenza vaccine given to all	Specific values not reported – results shown in graphical form only At 4 wks, TNFi group had statistically lower GMTs for A/H3N2 and Flu B, but not statistically different for A/H1N1. Seroconversion rates (4-fold increase in titer) was lower for TNFi group for all 3 antigens. Seroprotection rates were similar in all groups, and generally excellent (>80%).
2643, Muller, 2013 [83]	Prospective cohort study	4 weeks after 2nd vaccination	16 patients who were treated with rituximab and had received first dose of influenza vaccine.	2nd dose of 2009 H1N1 influenza vaccine (Pandemrix) given 4 wks after first dose.	Significant anti-HA titers seen after 1st vaccine in 6/16 patients; this increased to 7/16 after the 2nd vaccine. In patients with low B cell numbers, the T cell response (as measured by virus-specific, IFN-g-producing T cell numbers) increased after booster vaccine. In patients with normal B cells, booster vaccine had no effect.
4124, Lakota, 2019 [34]	Prospective cohort study	>6 months post vaccination	137 patients (109 RA, 10 PsA, 15 AS, 1 MCTD, 1 JRA, 1 Still's) and 54 healthy controls. 72 patients who served as unvaccinated controls.	137 pts and 54 HC rec'd seasonal trivalent influenza vaccine (A/Brisbane/59/2007 (H1N1), A/Brisbane/10//2007 (H3N2), B/Brisbane/60/2008 (B)). Of these, 93 pts and 15 HC rec'd pandemic flu vaccine (A/California/7/2009 (H1N1pdm)) 3-5 wks later.	See RevMan for GMT, seroresponse, seroconversion, and seroprotection for seasonal flu vaccine comparing RD patients to healthy controls. "Patients used methotrexate, sulfasalazine, leflunomide, chloroquine, adalimumab, etanercept, rituximab, tocilizumab, infliximab, and methyl- prednisolone and combinations of drugs for therapy." Poorest seroprotection (56%) in patients having rituximab therapy, while methotrexate, adalimumab, etanercept, and tocilizumab treated patients were seroprotected in 86–91% and vaccinated controls 92%. Only 2 of 9 pts who rec'd rituximab had seroconversion to at least 1 antigen. Drop of antibody titer over time was not typically related to any medication used as we observed loss of seroresponse titers for H1N1, H3N2 and B in patients treated with methotrexate in 78% (7/9), 88% (7/8) and 100% (2/2), with adalimumab 70% (12/17), 62% (5/8), and 82% (9/11) and with etanercept 40% (6/15), 43% (3/7), and 90% (9/10), respectively

				Of these, 63 pts rec'd 2nd dose of pandemic flu vaccine another 3-5 wks later.	
4372 Bedognetti, 2011 [84]	Prospective cohort study	5 years	31 lymphoma patients treated with rituximab-based regimens, 34 healthy controls. Of the 31, 6 rec'd >6 doses of rituximab, and 25 rec'd ≤6 doses. Ritux was administered >1 year prior for 80% of patients. Almost all were also receiving concomitant chemotherapy	Seasonal trivalent virosomal flu vaccine. A/ Brisbane/10/2007 (H3N2), A/Brisbane/59/2007 (H1N1), and B/Florida/4/ 2006	Patients across the board had lower GMT, seroprotection, seroconversion rates as compared to controls. There were no statistically significant predictors of lower response to H1N1. However, for H3N2, history of fludarabine was a predictor of lower response. Dose of rituximab exposure was not a predictor. Patients had lower circulating CD27+ memory B cells, which correlated with vaccine response, and these remained low as long as 5 years post treatment.
4709, Kanakoudi-Tsakalidou 2001 [85]	Prospective cohort study	2 months	70 children w rheumatic disease (49 JIA, 11 SLE, 10 other). Divided into 4 treatment groups: 1) No treatment	"split type" influenza vaccine, Fluarix, 1 or 2 doses depending on age/size A/Beijing, A/Sydney, B/Beijing	Antibody titers at baseline, 1 month (before 2nd dose), and 1 month after 2nd dose. Patients had high seroconversion rates (74-100%) after just one influenza dose, and almost complete seroconversion after 2 doses. ANOVA evaluation showed statistically significant differences between treatment groups for A/Sydney and B/Beijing serotypes. Lowest GMT was in group 4, but direct statistical comparisons were not made between 2 groups. No statistically significant difference in GMT between JIA and SLE groups.

			2) Prednisone + MTX/cyclosporine/azathioprine 3) Prednisone + MTX + Cyclosporine 4) MTX/cyclosporine/azathioprine without steroids Also 5 healthy controls (siblings of patients)		
7213 Nii, 2009 [86]	Prospective cohort study	1 year	RA patients 1 yr after flu vax. 26 out of 27 RA pts on biologic (almost all TNFi), 25 of 36 RA patients not on biologic, and 28 of 52 healthy controls	A/ New Caledonia/20/99 (H1N1) (A-NC), A/Hiroshima/52/2005 (H3N2) (A-Hiro), and B/Malaysia/2506/2004	Data provided in graphical form only. In original study, antibody titers to influenza antigens was not different between RA and control. At 1 year, all 3 groups showed decline in titer, but there was not statistically significant differences between the groups. Titers against, measles, mumps, and EBNA were also measured – all similar except RA pts on biologics had *higher* anti-measles antibody. "No significant effects of prednisolone, methotrexate, or other DMARDs" on titers
7489 Yri, 2011 [87]	Prospective cohort study	6 months	67 lymphoma patients, 51 controls. All had received rituximab; only 7 received rituximab as monotherapy. All were either during or within	Adjuvanted monovalent H1N1 vaccine (Pandemrix)	Only 5 of the 67 lymphoma patients had a measurable antibody response to vaccination (was measurable but not seroprotective in any patients), as compared to seroprotection rate of 82.4% in healthy controls. The rituximab monotherapy patients were not broken out separately, but none of them developed protective response.

			6 months of treatment.		
4693 Williams 1978 [88]	Double blind, randomized, placebo controlled	20 weeks	40 pts with SLE randomly assigned flu vs normal saline vaccination; 21 healthy controls	Bivalent whole vaccine from influenza A/NJ/11/76 (Hsw 1 N 1) and A/Victoria/3/75 (H 3 N 2) influenza strains	Alternate-day steroid therapy (six patients) was associated with the greatest increase in specific antibody (+ 2.8). Nonsteroidal anti-inflammatory agents (two patients, +0.7) and high-dose steroids, >20 mg/day (two patients, +0.8), were associated with the smallest increases. Immunosuppressive drugs (five patients, +1.5) and low-dose prednisone (four patients, +1.5) were associated with intermediate levels of specific antibody. The group of patients receiving immuno-suppressive drugs was also on alternate-day or low-dose daily prednisone therapy, and these individuals' antibody responses seemed to correlate more closely with the dose of steroids than with the dose or type of immunosuppression.

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Haemophilus Influenza Type B (HiB) Vaccine

Summary: Four observational studies were included that described the impact of a drug of interest on HiB vaccine response for individuals with RMD.

Battafarano et al (1) found that among 73 patients with SLE, there was a trend toward decreased antibody response in patients treated with CYC, AZA, or prednisone, although this was not statistically significant. There was no significant difference for any individual medication or combination of medications, or by medication dosage.

Brogan et al (2) found that among 17 pediatric patients with CAPS and confirmed NLRP3 mutations on canakinumab, the available vaccine response data demonstrated antibody titers above protective levels at subsequent visits 4-8 weeks later.

Morgan et al (3) found that among 92 patients with small and/or medium vessel vasculitis, there was significant improvement in the percentage of patients who had antibody titers above the threshold. Titers increased in 26% of patients pre-vaccination to 68% post-vaccination.

Summaries of results that do not specifically comment on drug impact:

Dotan et al (4) found that among 43 patients with IBD treated with thiopurines, there was no significant suppressive effect on the systemic cellular and humoral immune responses after HiB vaccine.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
459 Battafarao 1998	Cohort	12 weeks	73 SLE 5.5% male/94.5 % female; mean age 43 (18-76) 48% on antimalarial agents , NSAIDS 34%, AZA 10%, IV CYC 10%, oral MTX 1% 74% on steroids, with 85% oral prednisone <10mg per day	Pneumococcal (pneumovax 23), tetanus toxoid and haemophilus influenza type B	61 (84%) achieved 4-fold AB response to at least 1 antigen, with 100% achieving at least a 2-fold response to at least 1 antigen. 14 (19%) developed 4-fold response to all 3 antigens, with >50% developing at least 2-fold response to all 3 antigens. Majority developed protective Abs to tetanus and HiB irrespective of their increase in titer; 65 (90%) had protective levels of tetanus AB (≥0.01 IU/ml). and 64 (88%) had protective levels of HIB antibody *(*≥1, pg/ml). For the polyvalent pneumococcal vaccine, only total antibody levels could be measured. % of patients with protective levels of AB HiB preimm 37 (51%) / postimm 64 (88%) TT preimm 36 (50%) / post imm 65 (90%) Pneumo pre/post Not determined

					Patients with 3-fold increase in AB titers post-immunization: those who were not receiving AZA, CYC and prednisone, all developed 3-fold increases to a mean of almost 2 (1.9) of the 3 vaccines. Trend toward decreased antibody response in patients treated with CYC, AZA or prednisone, although this was not statistically significant. There was no significant difference for any individual medication or combination of medications, or by medication dosage.
7047 Brogan 2019	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood vaccination programs. No live vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days	In core study, 7/17 (41%) patients received a total of 31 vaccine injections (10 different types of inactivated vaccines). Vaccine response data available for 18/31 (58.1%) injections. All showed a positive response (Ab titers increased above protective level). For all 31 vaccine injections, including those without a pre-dose Ab titer, protective post-vaccine Ab titers were maintained throughout the trial. In the extension study, 4/17 (24%) patients received a total of 20 vaccine injections (8 different types of inactivated vaccines). 17/20 (85%) of injections had data available to assess vaccine response. In 16/17 (94.1%) cases, protective Ab titers were achieved post-vaccine. For 19/20 (95%) vaccine injections, including those without a pre-dose Ab titer, protective post-vaccine Ab titers were maintained throughout the extension study

				after vaccination ("Pre-dose"), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). <u>Included vaccines:</u> HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	
647 Morgan 2016	Cohort-case control	Median FU post vaccination 4.6 years, total patient FU was 363 patient-years (none lost to FU)	92 patients with small or medium-sized systemic vasculitis (EGPA- 7 patients, GPA-59 , MPA-22 or classical PAN- 4) in stable remission > 6 months (BVAS = 0), s/p CYC and steroid induction but not within 6 months, had not received RTX within 6 months, on <10mg of prednisone per day, currently on no more than 1 immunosuppressant + prednisolone, no active infections,	*7-valent conjugate pneumococcal vaccine (Prevnar)* Haemophilus influenzae type b (Hib) *Meningococcal (Men) group C conjugate vaccine and Men polysaccharide groups A, C, Y, and W135 vaccine*	Median AB titers for all the vaccine components increased at 4 weeks postvaccination 4 weeks postvaccination, significant improvement in the percentage of patients who had AB titers above the threshold, although there was variability in the response between antigens (antibody response above the protective threshold for each antigen median of 46% [IQR 39–58%]) Serotype PreVacc Post Vacc P Hib 26 68 0.001

			not pregnant, no hx of previous severe reaction to vaccination or received vaccination to proposed vaccines; age 66 (53-74) 81 patients still taking prednisolone at median of 5mg/day at time of vaccination. 9 patients on Rituxan, 35 on AZA, 35 on mycophenalate		
5898, Dotan, 2012[4]	Prospective cohort	n/a	43 patients with IBD on thiopurines (31 with Crohn's, 12 with UC)	Pneumonia, tetanus, HiB	The post-therapy average 6-MP dose was 1.05 +/- 0.30 mg/kg. There was no significant suppressive effect on the systemic cellular and humoral immune responses after HiB vaccine. Post-therapy white blood cell counts decreased significantly from baseline values ($p<0.002$).

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Pneumococcal Vaccines

Summary**:** Literature searches identified a total of 6 randomized controlled trials and 46 observational studies that addressed this question for pneumonia vaccines.

There are six observational studies (1-6) and three RCTs (7-10) that addressed this PICO for PCV23 vaccine and appear in GradePro Tables 1-25 (several additional studies appear in Table 26 and are discussed below).

In an RCT comparing RA patients on MTX+TCZ therapy to MTX monotherapy, the response rate to PCV23 vaccine was slightly in favor of patients on MTX monotherapy but the result was imprecise (9). Comparing RA patients 51-64 and 18-50 years old years old on MTX+TCZ therapy to MTX monotherapy, response rate to PCV23 vaccine was slightly in favor of patients on MTX monotherapy but the result was imprecise (9).

One RCT comparing effects of PPV23 vaccine in patients on MTX or TA+MTX vs patients on TAC showed favorable outcomes for patients on TAC, but between patients on TA+MTX and patients on MTX showed no difference in outcomes except for GM-OIs 23F, which favored patients on MTX (7).

In a study comparing RA patients on MTX vs RA patients on TCZ the outcomes after PPV23 were more favorable to RA patients on TCZ, in comparison of RA patients on MTX+TCZ vs RA patients on MTX the outcomes were similar in both groups, but between MTX+TCZ and TCZ the outcomes favored TCZ (1).

An RCT comparing RA patients treated with ETN or MTX versus RA patients not treated with ETN or MTX showed slightly favorable outcomes for patients not treated with compared medications with imprecise results for ETN vs no ETN and statistically significant differences for MTX vs no MTX. For RA patients treated with ETN and RA patients treated with MTX, the results showed statistically significant differences in outcomes in favor of patients treated with ETN (8).

One study comparing patients on TNFi versus not on TNFi treatment had similar outcomes on seroprotection for different serotypes, but more favorable outcomes on seroconversion at 2 months for patients on TNFi treatment with high imprecision, and similar outcomes for seroprotection and seroconversion at 12 months for different serotypes between groups (2).

In a study comparing cancer patients on rituximab vs not on rituximab, the outcomes were in favor of patients not on rituximab (3).

In a study comparing seroconversion and seroprotection between age groups, the outcomes for all age groups were more favorable in patients not on MTX but the results were imprecise; 2-fold increase in patients age < 50 was slightly more favorable in patients on MTX, while in patients age > 60 more favorable in patients not on MTX, but the results were very imprecise (4).

In a study comparing SLE patients given PCV23 prior to treatment with belimumab therapy versus those vaccinated at week 24 of treatment the outcome on antibody titer increase was not different (5).

Another RCT examined response to PPSV23 in RA patients receiving rituximab; 69 patients received rituximab with methotrexate and 34 received methotrexate alone. They found a decreased response to PPSV23 in the rituximab group (57% of patients had a 2-fold rise in titer in response to ≥1 serotype, compared with 82% of patients treated with MTX alone). Rituxumab plus MTX substantially reduced the response for every serotype compared to MTX alone, suggesting PPSV23 should be administered prior to start of rituximab therapy (10).

In a study (6) comparing the number of serotypes with 2-fold increase in patients on rituximab vs healthy controls the difference was statistically significant in favor of healthy controls, while in comparison of abatacept and DMARD's versus healthy controls the outcomes favored healthy controls but the results were not statistically significant. In comparing seroprotection (IgG >/=1.3) in patients either on rituximab, abatacept or DMARDs vs healthy controls the outcomes were in favor of healthy controls but the results were imprecise. In comparing PCV13+PPV23 boost at 8 weeks - Serotypes with 2-fold increase in patients on rituximab vs healthy controls the differences in outcomes were statistically significant in favor of healthy controls, while for abatacept and DMARDs versus healthy controls the outcomes tended to favor healthy controls but the difference was not statistically significant. In comparing PCV13+PPV23 boost at 8 weeks - Seroprotection (IgG >/= 1.3) in patients on rituximab vs healthy controls the difference in outcomes was statistically significant in favor of healthy controls, while in comparison of abatacept and DMARDs versus healthy controls the outcomes favored healthy controls but the difference was not statistically significant.

Summary for study data not entered into RevMan (Table 26):

In observational studies similar results were seen for RTX: patients treated with RTX had the poorest antibody responses to pneumoccal vaccines (11-16).

Patients on TNFi had better response rates compared to patients on MTX or TNFi+MTX, patients on MTX had slightly better results than patients on TNFi+MTX, patients on TNFi had similar or poorer results than healthy controls, as well patients with SpA had better results than patients with RA (17-23). Another study (34) observed that among patients with RA treated with TNFi+MTX, similar rates of protection were found up to 24 months utilizing antibody titers via ELISA, though a decrease in functional antibody measurements was observed via OPA. However, one study reported no difference in PPSV23 vaccine response between patients taking IFX+MTX and MTX monotherapy (24).

Caskurlu et al[2848] observed that among patients with inflammatory arthritis on ADA, 24/32 patients doubled antibody titers and 8/32 patients tripled antibody titers 4 weeks after vaccination.

In one study patients with concomitant use of prednisone had better results than patients with MTX (18) while in other studies prednisone as well AZA or CYC did not correlate with antibody response (25) or had a decreased antibody response, but the results were statistically

insignificant (26). In patients with RA, a study nested within an RCT to evaluate effectiveness of PPSV23 in reducing the incidence of pneumonia, a higher GMC was observed in the MTX group compared to the ABT group (33). Alten et al (35) observed that 94/112 patients with RA treated with ABT achieved protective antibody titer levels for pneumococcal antigens. Caporuscio et al (38) observed that among patients with RA treated on prednisone, MTX, TNFi, or MTX+TNFi, there was no difference in antibody response to PCV13. Coulson et al (39) observed that among patients with RA treated with MTX, there was no correlation between pneumococcal antibody levels and MTX dose or duration. Nielsen et al (40) observed an association between MTX use and a protective antibody level in patients with inflammatory arthritis.

In an RCT, patients on TOFA had the same outcomes for GMFR as patients on MTX, but lower than patients on no DMARDs and higher than patients on TOFA+MTX (27). In a single-arm study, Winthrop et al (45) observed that among patients with psoriasis treated with TOFA, most patients were able to mount a T-cell-dependent response to PCV13.

In one study, there was no significant difference in antibody response and GMT increase over time between RMD patients on immunosuppressants (IS) and not on IS (28). There was a significant difference between RA patients on MTX and OA patients as controls in measuring antibody fold increase (2.63-fold in the RA and 6.13-fold in the control group) (29).

For SLE patients, one study showed significant increase in antibody level after 23 valent pneumococcal vaccine, comparable to control patients with asthma (30), while in other study the antibody response in SLE patients, both immunosuppressed and not immunosuppresed, was low (31). In one RCT, SLE patients who received PPSV23 vaccine before and after starting belimumab had similar results for vaccine response outcome (32). Another study (46) observed that in patients with SLE treated with belimumab there was no impairment in antibody response. Another study (36) observed that in patients with RA and SLE treated with prednisone, HCQ, MTX, AZA, SSZ, minocycline, or CYC had significant increases in GMT of specific serotypes one month post-PPSV23 vaccination. Jarrett et al (37) observed that among patients with SLE on low-dose prednisone, high-dose prednisone, or high-dose prednisone+AZA, there was no significant difference between the three treatment groups in antibody response to the 14 valent pneumococcal vaccine. Grabar et al (41) observed that in patients with stable SLE there was no difference in response to PPSV based on IS. Elkayem et al (42) observed that in patients with SLE there was no difference in measure of disease activity or autoantibodies after vaccination. Stohl et al (44) observed in pooled data from BLISS-52 and BLISS-76, there was no difference in antibody titers across treatment groups in response to pneumococcal vaccination, though a lower titer was noted for subtype 12F.

Brogan et al (43) observed that in patients with CAPS treated with canakinumab, 16/17 patients achieved protective antibody titers after vaccination.

Overall quality of evidence across all critical outcomes*:* Very low for most comparisons.

Table 1: PCV23 responders TCZ+MTX v MTX monotherapy compared to placebo for TCZ + MTX versus MTX for rheumatoid arthritis refractory to TNF (9).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
PCV23 response, TCZ+MTX v MTX												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	30/50 (60.0%)	17/24 (70.8%)	**RR 0.85** (0.60 to 1.19)	**106 fewer per 1,000** (from 283 fewer to 135 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Open-label

b. Wide CI crosses significant effect and no-effect lines

Table 2: PCV23 response in patients 51-64 years, TCZ+MTX v MTX monotherapy compared to placebo for TCZ + MTX versus MTX for rheumatoid arthritis refractory to TNFi (9).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
PCV23 response ages 51-64 years, TCZ+MTX v MTX monotherapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	18/32 (56.3%)	10/15 (66.7%)	**RR 0.84** (0.53 to 1.35)	**107 fewer per 1,000** (from 313 fewer to 233 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Open-label

b. Wide CI crosses significant effect and no-effect lines

Table 3: PCV23 response ages 18-50, TCZ+MTX versus MTX monotherapy compared to placebo for TCZ + MTX versus MTX for rheumatoid arthritis refractory to TNF (9)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
PCV23 response ages 18-50, TCZ+MTX v MTX monotherapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12/18 (66.7%)	7/9 (77.8%)	**RR 0.86** (0.53 to 1.38)	**109 fewer per 1,000** (from 366 fewer to 296 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Open-label

b. Wide CI crosses significant effect and no-effect lines

Table 4: MTX compared to Tacrolimus in RA patients getting PCV23 vaccine (7).

Quality of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	Tacrolimus	Relative (95% CI)	Absolute (95% CI)		
IgG GMCs, µg/ml, 6B												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	Tacrolimus	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	55	29	-	MD **3.99 lower** (9.72 lower to 1.74 higher)	⨁⨁⨁◯ Moderate	

IgG GMCs,µg/ml 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	55	29	-	MD **9.32 lower** (18.32 lower to 0.32 lower)	⨁⨁⨁◯ Moderate	Favors tacrolimus

GM-OIs, 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	55	29	-	MD **1442.25 lower** (2427.98 lower to 456.52 lower)	⨁⨁⨁◯ Moderate	Favors tacrolimus

GM-OIs, 23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	Tacrolimus	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	55	29	-	MD **858.48 lower** (1721.04 lower to 4.08 higher)	⊕⊕⊕◯ Moderate	

Antibody response for IgG 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	31/55 (56.4%)	25/29 (86.2%)	**RR 0.65** (0.50 to 0.86)	**302 fewer per 1,000** (from 431 fewer to 121 fewer)	⊕⊕⊕◯ Moderate	Favors tacrolimus

Antibody response for OIs 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	19/55 (34.5%)	17/29 (58.6%)	**RR 0.59** (0.37 to 0.95)	**240 fewer per 1,000** (from 369 fewer to 29 fewer)	⊕⊕⊕◯ Moderate	Favors tacrolimus

Antibody response for IgG 23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	Tacrolimus	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	36/55 (65.5%)	27/29 (93.1%)	**RR 0.70** (0.57 to 0.87)	**279 fewer per 1,000** (from 400 fewer to 121 fewer)	⨁⨁⨁◯ Moderate	Favors tacrolimus

Antibody response for OIs 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	24/55 (43.6%)	24/29 (82.8%)	**RR 0.53** (0.37 to 0.74)	**389 fewer per 1,000** (from 521 fewer to 215 fewer)	⨁⨁⨁◯ Moderate	Favors tacrolimus

Antibody response for IgG 6B+23F

1	randomised trials	not serious	not serious	not serious[a]	serious[a]	none	28/55 (50.9%)	23/29 (79.3%)	**RR 0.64** (0.47 to 0.88)	**286 fewer per 1,000** (from 420 fewer to 95 fewer)	⨁⨁⨁◯ Moderate	Favors tacrolimus

Antibody response for OIs 6B+23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	Tacrolimus	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	14/55 (25.5%)	13/29 (44.8%)	**RR 0.57** (0.31 to 1.04)	**193 fewer per 1,000** (from 309 fewer to 18 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide CI crosses significant effect and no-effect lines and/or less than 200 patients per arm

Table 5: TAC+MTX compared to Tacrolimus in RA patients getting PCV23 vaccine (7).

Quality of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	TAC	Relative (95% CI)	Absolute (95% CI)		
IgG GMCs,µg/ml 6B												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	TAC	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	14	29	-	MD **3.54 higher** (10.35 lower to 17.43 higher)	⨁⨁⨁◯ Moderate	

IgG GMCs,µg/ml 23F

1	randomised trials	not serious	not serious	not serious	serious[b]	none	14	29	-	MD **11.79 lower** (20.71 lower to 2.87 lower)	⨁⨁⨁◯ Moderate	Favors tacrolimus

GM-OI, 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	14	29	-	MD **1310.69 lower** (2526.35 lower to 95.03 lower)	⨁⨁⨁◯ Moderate	Favors tacrolimus

GM-OI, 23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	TAC	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	14	29	-	MD **1491.9 lower** (2272.55 lower to 711.25 lower)	⨁⨁⨁◯ Moderate	Favors tacrolimus

Antibody response for IgG 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	5/14 (35.7%)	25/29 (86.2%)	**RR 0.41** (0.20 to 0.85)	**509 fewer per 1,000** (from 690 fewer to 129 fewer)	⨁⨁⨁◯ Moderate	Favors tacrolimus

Antibody response for IgG 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	9/14 (64.3%)	27/29 (93.1%)	**RR 0.69** (0.46 to 1.03)	**289 fewer per 1,000** (from 503 fewer to 28 more)	⨁⨁⨁◯ Moderate	

Antibody response for IgG 6B+23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	TAC	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	4/14 (28.6%)	23/29 (79.3%)	**RR 0.36** (0.15 to 0.84)	**508 fewer per 1,000** (from 674 fewer to 127 fewer)	⨁⨁⨁◯ Moderate	Favors tacrolimus

Antibody response for OIs 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	5/14 (35.7%)	17/29 (58.6%)	**RR 0.61** (0.28 to 1.31)	**229 fewer per 1,000** (from 422 fewer to 182 more)	⨁⨁⨁◯ Moderate	Favors tacrolimus

Antibody response for OIs 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	3/14 (21.4%)	23/29 (79.3%)	**RR 0.27** (0.10 to 0.75)	**579 fewer per 1,000** (from 714 fewer to 198 fewer)	⨁⨁⨁◯ Moderate	Favors tacrolimus

Antibody response for OIs 6B+23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	TAC	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	2/14 (14.3%)	13/29 (44.8%)	**RR 0.32** (0.08 to 1.22)	**305 fewer per 1,000** (from 412 fewer to 99 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide CI crosses significant effect and no-effect lines and less than 200 patients per arm

Table 6: TAC+MTX compared to MTX in RA patients getting PCV23 vaccine (7).

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
IgG GMCs, µg/ml 6B												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	14	55	-	MD **7.53 higher** (5.48 lower to 20.54 higher)	⨁⨁⨁◯ Moderate	

IgG GMCs, µg/ml 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	14	55	-	MD **2.47 lower** (6.32 lower to 1.38 higher)	⨁⨁⨁◯ Moderate	

GM-OIs, 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	14	55	-	MD **131.56 higher** (701.89 lower to 965.01 higher)	⨁⨁⨁◯ Moderate	

GM-OIs 23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	14	55	-	MD **633.42 lower** (1024.06 lower to 242.78 lower)	⨁⨁⨁◯ Moderate	Favors MTX

Antibody response for IgG 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	5/14 (35.7%)	31/55 (56.4%)	**RR 0.63** (0.30 to 1.33)	**209 fewer per 1,000** (from 395 fewer to 186 more)	⨁⨁⨁◯ Moderate	

Antibody response for IgG 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	9/14 (64.3%)	36/55 (65.5%)	**RR 0.98** (0.64 to 1.52)	**13 fewer per 1,000** (from 236 fewer to 340 more)	⨁⨁⨁◯ Moderate	

Antibody response for IgG 6B+23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TAC+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	2/14 (14.3%)	28/55 (50.9%)	**RR 0.28** (0.08 to 1.04)	**367 fewer per 1,000** (from 468 fewer to 20 more)	⨁⨁⨁◯ Moderate	

Antibody response for OIs 6B

1	randomised trials	not serious	not serious	not serious	serious[a]	none	5/14 (35.7%)	19/55 (34.5%)	**RR 1.03** (0.47 to 2.28)	**10 more per 1,000** (from 183 fewer to 442 more)	⨁⨁⨁◯ Moderate	

Antibody response for OIs 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	3/14 (21.4%)	24/55 (43.6%)	**RR 0.49** (0.17 to 1.40)	**223 fewer per 1,000** (from 362 fewer to 175 more)	⨁⨁⨁◯ Moderate	

Antibody response for OIs 6B+23F

1	randomised trials	not serious	not serious	not serious	serious[a]		2/14 (14.3%)	14/55 (25.5%)	**RR 0.56** (0.14 to 2.19)	**112 fewer per 1,000** (from 219 fewer to 303 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Wide CI crosses significant effect and no-effect lines and less than 200 patients per arm

Table 7: MTX compared to TCZ in RA patients (1)

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	TCZ	Relative (95% CI)	Absolute (95% CI)		
IgGGMCs (µg/ml) 6B fold increase												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	62	50	-	MD **1.3 lower** (2.72 lower to 0.12 higher)	⊕◯◯◯ Very low	
IgGGMCs (µg/ml) 23F fold increase												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	62	50	-	MD **0.8 lower** (2.99 lower to 1.39 higher)	⊕◯◯◯ Very low	
GM OIs 6B fold increase												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	TCZ	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	62	50	-	MD **7.5 lower** (16.47 lower to 1.47 higher)	⨁◯◯◯ Very low	

GM OIs 23F fold increase

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	62	50	-	MD **11.8 lower** (28.06 lower to 4.46 higher)	⨁◯◯◯ Very low	

IgG 6B antibody response rate

1	observational studies	serious[a]	not serious	not serious	not serious	none	23/62 (37.1%)	28/50 (56.0%)	**RR 0.66** (0.44 to 0.99)	**190 fewer per 1,000** (from 314 fewer to 6 fewer)	⨁◯◯◯ Very low	Favors TCZ

IgG 23F antibody response rate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	TCZ	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	35/62 (56.5%)	36/50 (72.0%)	**RR 0.78** (0.59 to 1.04)	**158 fewer per 1,000** (from 295 fewer to 29 more)	⨁◯◯◯ Very low	

IgG 6B+23F antibody response rate

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	20/62 (32.3%)	23/50 (46.0%)	**RR 0.70** (0.44 to 1.12)	**138 fewer per 1,000** (from 258 fewer to 55 more)	⨁◯◯◯ Very low	

OIs 6B antibody response rate

1	observational studies	serious[a]	not serious	not serious	not serious	none	21/62 (33.9%)	28/50 (56.0%)	**RR 0.60** (0.40 to 0.93)	**224 fewer per 1,000** (from 336 fewer to 39 fewer)	⨁◯◯◯ Very low	Favors TCZ

OIs 23F antibody response rate

1	observational studies	serious[a]	not serious	not serious	not serious	none	23/62 (37.1%)	29/50 (58.0%)	**RR 0.64** (0.43 to 0.95)	**209 fewer per 1,000** (from 331 fewer to 29 fewer)	⨁◯◯◯ Very low	Favors TCZ

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	TCZ	Relative (95% CI)	Absolute (95% CI)		
OIs 6B+23F antibody response rate												
1	observational studies	serious[a]	not serious	not serious	not serious	none	10/62 (16.1%)	17/50 (34.0%)	**RR 0.47** (0.24 to 0.94)	**180 fewer per 1,000** (from 258 fewer to 20 fewer)	⨁◯◯◯ Very low	Favors TCZ

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Non-randomized open-label study

b. Wide CI crosses significant effect and no-effect lines

Table 8: MTX compared to MTX+TCZ in RA patients (1)

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	MTX+TCZ	Relative (95% CI)	Absolute (95% CI)		
IgGGMCs (µg/ml) 6B fold increase												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	MTX+TCZ	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	None	62	54	-	MD **0.1 lower** (0.65 lower to 0.45 higher)	⊕◯◯◯ Very low	

IgGGMCs (µg/ml) 23F fold increase

1	observational studies	serious[a]	not serious	not serious	serious[b]	None	62	54	-	MD **0.3 lower** (2.44 lower to 1.84 higher)	⊕◯◯◯ Very low	

GM OIs 6B fold increase

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	62	54	-	MD **2.3 lower** (8.35 lower to 3.75 higher)	⊕◯◯◯ Very low	

GM OIs 23F fold increase

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	MTX+TCZ	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	62	50	-	MD **11.8 lower** (28.06 lower to 4.46 higher)	⊕◯◯◯ Very low	

IgG 6B antibody response rate

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23/62 (37.1%)	13/54 (24.1%)	**RR 1.54** (0.87 to 2.74)	**130 more per 1,000** (from 31 fewer to 419 more)	⊕◯◯◯ Very low	

IgG 23F antibody response rate

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	35/62 (56.5%)	30/54 (55.6%)	**RR 1.02** (0.74 to 1.40)	**11 more per 1,000** (from 144 fewer to 222 more)	⊕◯◯◯ Very low	

IgG 6B+32F antibody response

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	20/62 (32.3%)	10/54 (18.5%)	**RR 1.74** (0.90 to 3.39)	**137 more per 1,000** (from 19 fewer to 443 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	MTX+TCZ	Relative (95% CI)	Absolute (95% CI)		
OIs 6B antobody response												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	21/62 (33.9%)	22/54 (40.7%)	**RR 0.83** (0.52 to 1.34)	**69 fewer per 1,000** (from 196 fewer to 139 more)	⊕◯◯◯ Very low	
OIs 23F antibody response rate												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23/62 (37.1%)	19/54 (35.2%)	**RR 1.05** (0.65 to 1.71)	**18 more per 1,000** (from 123 fewer to 250 more)	⊕◯◯◯ Very low	
OIs 6B+23F antibody response rate												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/62 (16.1%)	12/54 (22.2%)	**RR 0.73** (0.34 to 1.55)	**60 fewer per 1,000** (from 147 fewer to 122 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Non-randomized open-label study

b. Wide CI crosses significant effect and no-effect lines

Table 9: TCZ compared to MTX+TCZ in RA patients (1)

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	MTX+TCZ	Relative (95% CI)	Absolute (95% CI)		
IgG 6B antibody response rate												
1	observational studies	serious[a]	not serious	not serious	not serious	none	28/50 (56.0%)	13/54 (24.1%)	**RR 2.33** (1.36 to 3.97)	**320 more per 1,000** (from 87 more to 715 more)	⊕◯◯◯ Very low	Favors TCZ
IgG 23F antibody response rate												
1	observational studies	serious[a]	not serious	not serious	not serious	none	36/50 (72.0%)	30/54 (55.6%)	**RR 1.30** (0.97 to 1.74)	**167 more per 1,000** (from 17 fewer to 411 more)	⊕◯◯◯ Very low	
IgG 6B+23F antibody response rate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ	MTX+TCZ	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	23/50 (46.0%)	11/54 (20.4%)	**RR 2.26** (1.23 to 4.14)	**257 more per 1,000** (from 47 more to 640 more)	⊕◯◯◯ Very low	Favors TCZ

OIs 6B antobody response

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	28/50 (56.0%)	22/54 (40.7%)	**RR 1.37** (0.92 to 2.06)	**151 more per 1,000** (from 33 fewer to 432 more)	⊕◯◯◯ Very low	

OIs 23F antibody response rate

1	observational studies	serious[a]	not serious	not serious	not serious	none	29/50 (58.0%)	19/54 (35.2%)	**RR 1.65** (1.07 to 2.54)	**229 more per 1,000** (from 25 more to 542 more)	⊕◯◯◯ Very low	Favors TCZ

OIs 6B+23F antibody response rate

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/50 (34.0%)	12/54 (22.2%)	**RR 1.53** (0.81 to 2.88)	**118 more per 1,000** (from 42 fewer to 418 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Non-randomized open-label study

b. Wide CI crosses significant effect and no-effect lines

Table 10: ETN compared to no ETN for health problem or population (8)

Level of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETN	no ETN	Relative (95% CI)	Absolute (95% CI)		
2-fold increase 9V												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	47/94 (50.0%)	53/90 (58.9%)	**RR 0.85** (0.65 to 1.11)	**88 fewer per 1,000** (from 206 fewer to 65 more)	⊕⊕⊕◯ Moderate	
2-fold increase 14												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	55/94 (58.5%)	56/90 (62.2%)	**RR 0.94** (0.74 to 1.19)	**37 fewer per 1,000** (from 162 fewer to 118 more)	⊕⊕⊕◯ Moderate	
2-fold increase 18C												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETN	no ETN	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/94 (61.7%)	56/90 (62.2%)	**RR 0.99** (0.79 to 1.24)	**6 fewer per 1,000** (from 131 fewer to 149 more)	⨁⨁⨁◯ Moderate	No difference

2-fold increase 19F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	33/94 (35.1%)	36/90 (40.0%)	**RR 0.88** (0.60 to 1.28)	**48 fewer per 1,000** (from 160 fewer to 112 more)	⨁⨁⨁◯ Moderate	

2-fold increase 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	48/94 (51.1%)	52/90 (57.8%)	**RR 0.88** (0.68 to 1.15)	**69 fewer per 1,000** (from 185 fewer to 87 more)	⨁⨁⨁◯ Moderate	

4-fold increase 9V

1	randomised trials	not serious	not serious	not serious	serious[a]	none	32/94 (34.0%)	41/90 (45.6%)	**RR 0.75** (0.52 to 1.07)	**114 fewer per 1,000** (from 219 fewer to 32 more)	⨁⨁⨁◯ Moderate	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETN	no ETN	Relative (95% CI)	Absolute (95% CI)		
4-fold increase 14												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	40/94 (42.6%)	41/90 (45.6%)	**RR 0.93** (0.67 to 1.29)	**32 fewer per 1,000** (from 150 fewer to 132 more)	⨁⨁⨁◯ Moderate	
4-fold increase 18C												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	38/94 (40.4%)	42/90 (46.7%)	**RR 0.87** (0.62 to 1.21)	**61 fewer per 1,000** (from 177 fewer to 98 more)	⨁⨁⨁◯ Moderate	
4-fold increase 19F												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18/94 (19.1%)	20/90 (22.2%)	**RR 0.86** (0.49 to 1.52)	**31 fewer per 1,000** (from 113 fewer to 116 more)	⨁⨁⨁◯ Moderate	
4-fold increase 23F												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETN	no ETN	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	25/94 (26.6%)	30/90 (33.3%)	**RR 0.80** (0.51 to 1.25)	**67 fewer per 1,000** (from 163 fewer to 83 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Wide CI crosses significant effect and no-effect lines and less than 200 patients per arm

Table 11: MTX compared to no MTX (8)

Quality of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	no MTX	Relative (95% CI)	Absolute (95% CI)		

2-fold increase 9V

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	no MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	27/83 (32.5%)	72/101 (71.3%)	**RR 0.46** (0.33 to 0.64)	**385 fewer per 1,000** (from 478 fewer to 257 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

2-fold increase 14

1	randomised trials	not serious	not serious	not serious	serious[a]	none	31/83 (37.3%)	80/101 (79.2%)	**RR 0.47** (0.35 to 0.63)	**420 fewer per 1,000** (from 515 fewer to 293 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

2-fold increase 18C

1	randomised trials	not serious	not serious	not serious	serious[a]	none	35/83 (42.2%)	79/101 (78.2%)	**RR 0.54** (0.41 to 0.71)	**360 fewer per 1,000** (from 461 fewer to 227 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

2-fold increase 19F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	no MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	22/83 (26.5%)	47/101 (46.5%)	**RR 0.57** (0.38 to 0.86)	**200 fewer per 1,000** (from 289 fewer to 65 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

2-fold increase 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	29/83 (34.9%)	70/101 (69.3%)	**RR 0.50** (0.37 to 0.69)	**347 fewer per 1,000** (from 437 fewer to 215 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

4-fold increase 9V

1	randomised trials	not serious	not serious	not serious	serious[a]	none	19/83 (22.9%)	53/101 (52.5%)	**RR 0.44** (0.28 to 0.67)	**294 fewer per 1,000** (from 378 fewer to 173 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

4-fold increase 14

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	no MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18/83 (21.7%)	62/101 (61.4%)	**RR 0.35** (0.23 to 0.55)	**399 fewer per 1,000** (from 473 fewer to 276 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

4-fold increase 18C

1	randomised trials	not serious	not serious	not serious	serious[a]	none	20/83 (24.1%)	59/101 (58.4%)	**RR 0.41** (0.27 to 0.63)	**345 fewer per 1,000** (from 426 fewer to 216 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

4-fold increase 19F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	11/83 (13.3%)	27/101 (26.7%)	**RR 0.50** (0.26 to 0.94)	**134 fewer per 1,000** (from 198 fewer to 16 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

4-fold increase 23F

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	no MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	15/83 (18.1%)	41/101 (40.6%)	**OR 0.32** (0.16 to 0.64)	**227 fewer per 1,000** (from 307 fewer to 102 fewer)	⨁⨁⨁◯ Moderate	Favors patients not on MTX

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Table 12: ETN compared to MTX in RA patients (8)

Quality of Evidence: Moderate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETN	MTX	Relative (95% CI)	Absolute (95% CI)		
4-fold increase 9V												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	47/94 (50.0%)	27/83 (32.5%)	**OR 2.07** (1.12 to 3.82)	**174 more per 1,000** (from 25 more to 323 more)	⨁⨁⨁◯ Moderate	Favors patients on ETN
2-fold increase 14												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETN	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	55/94 (58.5%)	31/83 (37.3%)	**RR 1.57** (1.13 to 2.17)	**213 more per 1,000** (from 49 more to 437 more)	⨁⨁⨁◯ Moderate	Favors patients on ETN

2-fold increase 18C

1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/94 (61.7%)	35/83 (42.2%)	**RR 1.46** (1.09 to 1.97)	**194 more per 1,000** (from 38 more to 409 more)	⨁⨁⨁◯ Moderate	Favors patients on ETN

2-fold increase 19F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	33/94 (35.1%)	22/83 (26.5%)	**RR 1.32** (0.84 to 2.08)	**85 more per 1,000** (from 42 fewer to 286 more)	⨁⨁⨁◯ Moderate	

2-fold increase 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	48/94 (51.1%)	29/83 (34.9%)	**RR 1.46** (1.03 to 2.08)	**161 more per 1,000** (from 10 more to 377 more)	⨁⨁⨁◯ Moderate	Favors patients on ETN

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETN	MTX	Relative (95% CI)	Absolute (95% CI)		
4-fold increase 9V												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	32/94 (34.0%)	19/83 (22.9%)	**RR 1.49** (0.92 to 2.41)	**112 more per 1,000** (from 18 fewer to 323 more)	⊕⊕⊕◯ Moderate	
4-fold increase 14												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	40/94 (42.6%)	18/83 (21.7%)	**RR 1.96** (1.22 to 3.14)	**208 more per 1,000** (from 48 more to 464 more)	⊕⊕⊕◯ Moderate	Favors patients on ETN
4-fold increase 18C												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	38/94 (40.4%)	20/83 (24.1%)	**RR 1.68** (1.07 to 2.64)	**164 more per 1,000** (from 17 more to 395 more)	⊕⊕⊕◯ Moderate	Favors patients on ETN
4-fold increase 19F												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETN	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18/94 (19.1%)	11/83 (13.3%)	**RR 1.44** (0.73 to 2.88)	**58 more per 1,000** (from 36 fewer to 249 more)	⨁⨁⨁◯ Moderate	

4-fold increase 23F

1	randomised trials	not serious	not serious	not serious	serious[a]	none	25/94 (26.6%)	15/83 (18.1%)	**RR 1.47** (0.83 to 2.60)	**85 more per 1,000** (from 31 fewer to 289 more)	⨁⨁⨁◯ Moderate	

Poor response

1	randomised trials	not serious	not serious	not serious	serious[a]	none	56/94 (59.6%)	64/83 (77.1%)	**RR 0.77** (0.63 to 0.95)	**177 fewer per 1,000** (from 285 fewer to 39 fewer)	⨁⨁⨁◯ Moderate	Favors patients on ETN

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Wide CI crosses significant effect and no-effect lines and less than 200 patients per arm

Table 13: Seroprotection of PPSV23 at 2months between patients on TNFi versus not on TNFi treatment (2)

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No TNFi	TNFi	Relative (95% CI)	Absolute (95% CI)		
Seroprotection for serotype 4												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/10 (50.0%)	7/17 (41.2%)	**RR 1.21** (0.52 to 2.82)	**86 more per 1,000** (from 198 fewer to 749 more)	⊕◯◯◯ Very low	
Seroprotection for serotype 6B												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	10/17 (58.8%)	**RR 0.68** (0.29 to 1.60)	**188 fewer per 1,000** (from 418 fewer to 353 more)	⊕◯◯◯ Very low	
Seroprotection for serotype 9V												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	12/17 (70.6%)	**RR 0.57** (0.25 to 1.29)	**304 fewer per 1,000** (from 529 fewer to 205 more)	⊕◯◯◯ Very low	
Seroprotection for serotype 14												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No TNFi	TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/10 (70.0%)	14/17 (82.4%)	**RR 0.85** (0.54 to 1.35)	**124 fewer per 1,000** (from 379 fewer to 288 more)	⊕◯◯◯ Very low	

Seroprotection for serotype 18C

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/10 (80.0%)	11/17 (64.7%)	**RR 1.24** (0.77 to 1.97)	**155 more per 1,000** (from 149 fewer to 628 more)	⊕◯◯◯ Very low	

Seroprotection for serotype 19F

1	observational studies	serious[a]	not serious	not serious	serious[a]	none	3/10 (30.0%)	9/17 (52.9%)	**RR 0.57** (0.20 to 1.62)	**228 fewer per 1,000** (from 424 fewer to 328 more)	⊕◯◯◯ Very low	

Seroprotection for serotype 23F

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/10 (60.0%)	11/17 (64.7%)	**RR 0.93** (0.50 to 1.72)	**45 fewer per 1,000** (from 324 fewer to 466 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 14: Seroconversion of PPSV23 at 2months between patients on or not on TNFi treatment (2)

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No TNFi	TNFi	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for serotype 4												
1	observational studies	serious[a]	not serious	not serious	not serious	None	4/10 (40.0%)	8/17 (47.1%)	**RR 0.85** (0.34 to 2.11)	**71 fewer per 1,000** (from 311 fewer to 522 more)	⨁◯◯◯ Very low	
Seroconversion for serotype 6B												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/10 (30.0%)	7/17 (41.2%)	**RR 0.73** (0.24 to 2.20)	**111 fewer per 1,000** (from 313 fewer to 494 more)	⨁◯◯◯ Very low	
Seroconversion for serotype 9V												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No TNFi	TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	9/17 (52.9%)	**RR 0.76** (0.31 to 1.82)	**127 fewer per 1,000** (from 365 fewer to 434 more)	⨁◯◯◯ Very low	

Seroconversion for serotype 14

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	11/17 (64.7%)	**RR 0.62** (0.27 to 1.43)	**246 fewer per 1,000** (from 472 fewer to 278 more)	⨁◯◯◯ Very low	

Seroconversion for serotype 18C

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/10 (30.0%)	9/17 (52.9%)	**RR 0.57** (0.20 to 1.62)	**228 fewer per 1,000** (from 424 fewer to 328 more)	⨁◯◯◯ Very low	

Seroconversion for serotype 19F

1	observational studies	serious[a]	not serious	not serious	serious[a]	none	3/10 (30.0%)	7/17 (41.2%)	**RR 0.73** (0.24 to 2.20)	**111 fewer per 1,000** (from 313 fewer to 494 more)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No TNFi	TNFi	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for serotype 23F												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/10 (30.0%)	10/17 (58.8%)	**RR 0.51** (0.18 to 1.42)	**288 fewer per 1,000** (from 482 fewer to 247 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 15: Seroprotection of PPSV23 at 12 months between patients on or not on TNFi treatment (2)

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunogenicity of PPSV23 at 12mo_PICO 3,6	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroprotection for serotype 4												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	3/14 (21.4%)	**RR 1.87** (0.53 to 6.57)	**186 more per 1,000** (from 101 fewer to 1,000 more)	⊕◯◯◯ Very low	
Seroprotection for serotype 6B												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/10 (50.0%)	7/14 (50.0%)	**RR 1.00** (0.44 to 2.25)	**0 fewer per 1,000** (from 280 fewer to 625 more)	⊕◯◯◯ Very low	
Seroprotection for serotype 9V												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	7/14 (50.0%)	**RR 0.80** (0.32 to 2.01)	**100 fewer per 1,000** (from 340 fewer to 505 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunogenicity of PPSV23 at 12mo_PICO 3,6	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroprotection for serotype 14												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/10 (80.0%)	10/14 (71.4%)	**RR 1.12** (0.71 to 1.76)	**86 more per 1,000** (from 207 fewer to 543 more)	⊕◯◯◯ Very low	
Seroprotection for serotype 18C												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/10 (70.0%)	8/14 (57.1%)	**RR 1.23** (0.67 to 2.25)	**131 more per 1,000** (from 189 fewer to 714 more)	⊕◯◯◯ Very low	
Seroprotection for serotype 19F												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/10 (60.0%)	10/14 (71.4%)	**RR 0.84** (0.46 to 1.54)	**114 fewer per 1,000** (from 386 fewer to 386 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunogenicity of PPSV23 at 12mo_PICO 3,6	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroprotection for serotype 23F												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	6/10 (60.0%)	9/14 (64.3%)	**RR 0.93** (0.49 to 1.77)	**45 fewer per 1,000** (from 328 fewer to 495 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 16: Seroconversion at 12months between patients on TNFi versus not on TNFi treatment (2)

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunogenicity of PPSV23 at 12mo_PICO 3,6	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for serotype 4												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	2/10 (20.0%)	3/14 (21.4%)	**RR 0.93** (0.19 to 4.60)	**15 fewer per 1,000** (from 174 fewer to 771 more)	⊕◯◯◯ Very low	
Seroconversion for serotype 6B												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/10 (30.0%)	6/14 (42.9%)	**RR 0.70** (0.23 to 2.15)	**129 fewer per 1,000** (from 330 fewer to 493 more)	⊕◯◯◯ Very low	
Seroconversion for serotype 9V												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	6/14 (42.9%)	**RR 0.93** (0.35 to 2.46)	**30 fewer per 1,000** (from 279 fewer to 626 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunogenicity of PPSV23 at 12mo_PICO 3,6	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for serotype 14												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	9/14 (64.3%)	**RR 0.62** (0.26 to 1.46)	**244 fewer per 1,000** (from 476 fewer to 296 more)	⊕◯◯◯ Very low	
Seroconversion for serotype 18C												
1	observational studies	serious[a]	not serious	not serious	serious[a]	none	4/10 (40.0%)	6/14 (42.9%)	**RR 0.93** (0.35 to 2.46)	**30 fewer per 1,000** (from 279 fewer to 626 more)	⊕◯◯◯ Very low	
Seroconversion for serotype 19F												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/10 (30.0%)	4/14 (28.6%)	**RR 1.05** (0.30 to 3.69)	**14 more per 1,000** (from 200 fewer to 769 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunogenicity of PPSV23 at 12mo_PICO 3,6	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for serotype 23F												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/10 (40.0%)	5/14 (35.7%)	**RR 1.12** (0.40 to 3.15)	**43 more per 1,000** (from 214 fewer to 768 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 17: RTX compared to no RTX in cancer patients (3)

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTX	no RTX	Relative (95% CI)	Absolute (95% CI)		
Serotype-specific protective pneumococcal antibodies												
1	observational studies	serious[a]	not serious	not serious	not serious	none	8	55	-	MD **5.9 lower** (8.81 lower to 2.99 lower)	⊕◯◯◯ Very low	Favors patients not on RTX
Response to pneumococcal vaccination												
1	observational studies	serious[a]	not serious	not serious	not serious	none	8	55	-	MD **6.1 lower** (7.26 lower to 4.94 lower)	⊕◯◯◯ Very low	Favors patients not on RTX

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational study

Table 18: MTX compared to no MTX in RA patients age < 50 or > 60 (4).

Level of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	no MTX	Relative (95% CI)	Absolute (95% CI)		
Seroconversion												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11/20 (55.0%)	15/20 (75.0%)	**RR 0.74** (0.46 to 1.19)	**195 fewer per 1,000** (from 405 fewer to 142 more)	⨁◯◯◯ Very low	
Seroconversion - age < 50												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/10 (60.0%)	7/10 (70.0%)	**RR 0.86** (0.45 to 1.64)	**98 fewer per 1,000** (from 385 fewer to 448 more)	⨁◯◯◯ Very low	
Seroconversion - age > 60												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/10 (50.0%)	8/10 (80.0%)	**RR 0.63** (0.31 to 1.25)	**296 fewer per 1,000** (from 552 fewer to 200 more)	⨁◯◯◯ Very low	
2-fold increase												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	no MTX	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/20 (65.0%)	14/20 (70.0%)	**RR 0.92** (0.59 to 1.42)	**56 fewer per 1,000** (from 287 fewer to 294 more)	⊕◯◯◯ Very low	

2-fold increase - age < 50

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/10 (70.0%)	6/10 (60.0%)	**RR 1.17** (0.61 to 2.23)	**102 more per 1,000** (from 234 fewer to 738 more)	⊕◯◯◯ Very low	

2-fold increase - age > 60

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/10 (60.0%)	8/10 (80.0%)	**RR 0.75** (0.41 to 1.36)	**200 fewer per 1,000** (from 472 fewer to 288 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Open-label trial

b. Wide CI crosses significant effect and no-effect lines

Table 19: Antibody titer increase in SLE patients given PCV23 prior to treatment with belimumab therapy versus those vaccinated at week 24 of treatment (5).

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients vaccinated prior to treatment with belimumab therapy	SLE patients vaccinated at week 24 of treatment	Relative (95% CI)	Absolute (95% CI)		
New Outcome												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	33/34 (97.1%)	44/45 (97.8%)	**RR 0.99** [0.92, 1.07]	**7 fewer per 1,000** (from 290 fewer to 20 more)	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 20: PICO 3 Effect on TNFi on immune responses to pneumococcal vaccine in RA and AS (33).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proportion of Patients Responding to Pneumococcal Vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		
Proportion of Patients Responding (>1um/mL increase) to Pneumococcal Vaccination, **Serotype 14**												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/16 (56.3%)	13/17 (76.5%)	**RR 0.74** (0.30 to 1.11)	**199 fewer per 1,000** (from 535 fewer to 84 more)	⨁◯◯◯ Very low	
Proportion of Patients Responding (>1um/mL increase) to Pneumococcal Vaccination, **Serotype 23F**												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/16 (43.8%)	12/17 (70.6%)	**RR 0.62** (0.23 to 1.08)	**268 fewer per 1,000** (from 544 fewer to 56 more)	⨁◯◯◯ Very low	
Proportion of Patients Responding (>1um/mL increase) to Pneumococcal Vaccination, **Serotype 4**												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/16 (37.5%)	11/17 (64.7%)	**RR 0.58** (0.20 to 1.10)	**272 fewer per 1,000** (from 518 fewer to 65 more)	⨁◯◯◯ Very low	
Proportion of Patients Responding (>1um/mL increase) to Pneumococcal Vaccination, **Serotype 8**												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proportion of Patients Responding to Pneumococcal Vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/16 (56.3%)	12/17 (70.6%)	**RR 0.80** (0.34 to 1.20)	**141 fewer per 1,000** (from 466 fewer to 141 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (>1um/mL increase) to Pneumococcal Vaccination, **Serotype 9N**

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/16 (56.3%)	12/17 (70.6%)	**RR 0.80** (0.34 to 1.20)	**141 fewer per 1,000** (from 466 fewer to 141 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (>1um/mL increase) to Pneumococcal Vaccination, **Serotype 7F**

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/16 (56.3%)	14/17 (82.4%)	**RR 0.69** (0.27 to 1.05)	**255 fewer per 1,000** (from 601 fewer to 41 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (>1um/mL increase) to Pneumococcal Vaccination, **Serotype 2**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proportion of Patients Responding to Pneumococcal Vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/16 (50.0%)	11/17 (64.7%)	**RR 0.78** (0.30 to 1.24)	**142 fewer per 1,000** (from 453 fewer to 155 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (2-fold increase) to Pneumococcal Vaccination , **Serotype 14**

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/16 (43.8%)	9/17 (52.9%)	**RR 0.83** (0.32 to 1.42)	**90 fewer per 1,000** (from 360 fewer to 222 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (2-fold increase) to Pneumococcal Vaccination , **Serotype 23F**

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	2/16 (12.5%)	9/17 (52.9%)	**RR 0.24** (0.04 to 0.86)	**402 fewer per 1,000** (from 508 fewer to 74 fewer)	⨁◯◯◯ Very low	

Proportion of Patients Responding (2-fold increase) to Pneumococcal Vaccination , **Serotype 4**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proportion of Patients Responding to Pneumococcal Vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/16 (18.8%)	6/17 (35.3%)	**RR 0.53** (0.13 to 1.51)	**166 fewer per 1,000** (from 307 fewer to 180 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (2-fold increase) to Pneumococcal Vaccination, **Serotype 8**

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/16 (50.0%)	12/17 (70.6%)	**RR 0.71** (0.27 to 1.14)	**205 fewer per 1,000** (from 515 fewer to 99 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (2-fold increase) to Pneumococcal Vaccination , **Serotype 9N**

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/16 (25.0%)	10/17 (58.8%)	**RR 0.42** (0.11 to 1.01)	**341 fewer per 1,000** (from 524 fewer to 6 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (2-fold increase) to Pneumococcal Vaccination , **Serotype 7F**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proportion of Patients Responding to Pneumococcal Vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/16 (43.8%)	12/17 (70.6%)	**RR 0.62** (0.23 to 1.08)	**268 fewer per 1,000** (from 544 fewer to 56 more)	⨁◯◯◯ Very low	

Proportion of Patients Responding (2-fold increase) to Pneumococcal Vaccination , **Serotype 2**

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/16 (37.5%)	10/17 (58.8%)	**RR 0.64** (0.21 to 1.20)	**212 fewer per 1,000** (from 465 fewer to 118 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not randomized
b. Less than 200 patients per arm

Table 21: MTX plus RTX vs MTX in RA patients.(10)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
Response at 4 weeks (at least 1 serotype)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	36/63 (57.1%)	23/28 (82.1%)	**RR 0.70** (0.53 to 0.92)	**246 fewer per 1,000** (from 386 fewer to 66 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (at least 2 serotypes)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	27/63 (42.9%)	23/28 (82.1%)	**RR 0.52** (0.37 to 0.73)	**394 fewer per 1,000** (from 518 fewer to 222 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (at least 3 serotypes)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	24/63 (38.1%)	22/28 (78.6%)	**RR 0.48** (0.34 to 0.70)	**409 fewer per 1,000** (from 519 fewer to 236 fewer)	⨁⨁◯◯ Low	Favors MTX

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
Response at 4 weeks (at least 4 serotypes)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	21/63 (33.3%)	21/28 (75.0%)	**RR 0.44** (0.30 to 0.67)	**420 fewer per 1,000** (from 525 fewer to 247 fewer)	⊕⊕◯◯ Low	Favors MTX
Response at 4 weeks (at least 5 serotypes)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/63 (23.8%)	19/28 (67.9%)	**RR 0.35** (0.21 to 0.58)	**441 fewer per 1,000** (from 536 fewer to 285 fewer)	⊕⊕◯◯ Low	Favors MTX
Response at 4 weeks (at least 6 serotypes)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12/63 (19.0%)	17/28 (60.7%)	**RR 0.31** (0.17 to 0.57)	**419 fewer per 1,000** (from 504 fewer to 261 fewer)	⊕⊕◯◯ Low	Favors MTX

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
Response at 4 weeks (serotype 1)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	8/63 (12.7%)	12/28 (42.9%)	**RR 0.30** (0.14 to 0.64)	**300 fewer per 1,000** (from 369 fewer to 154 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (serotype 3)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	6/63 (9.5%)	8/28 (28.6%)	**RR 0.33** (0.13 to 0.87)	**191 fewer per 1,000** (from 249 fewer to 37 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (serotype 4)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	8/63 (12.7%)	17/28 (60.7%)	**RR 0.21** (0.10 to 0.43)	**480 fewer per 1,000** (from 546 fewer to 346 fewer)	⨁⨁◯◯ Low	Favors MTX

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
Response at 4 weeks (serotype 6B)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	24/63 (38.1%)	17/28 (60.7%)	**RR 0.63** (0.41 to 0.97)	**225 fewer per 1,000** (from 358 fewer to 18 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (serotype 8)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	21/63 (33.3%)	16/28 (57.1%)	**RR 0.58** (0.36 to 0.94)	**240 fewer per 1,000** (from 366 fewer to 34 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (serotype 9N)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	14/63 (22.2%)	17/28 (60.7%)	**RR 0.37** (0.21 to 0.63)	**382 fewer per 1,000** (from 480 fewer to 225 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (serotype 12F)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	7/63 (11.1%)	14/28 (50.0%)	**RR 0.22** (0.10 to 0.49)	**390 fewer per 1,000** (from 450 fewer to 255 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 14)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	19/63 (30.2%)	17/28 (60.7%)	**RR 0.50** (0.31 to 0.80)	**304 fewer per 1,000** (from 419 fewer to 121 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 19F)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/63 (25.4%)	15/28 (53.6%)	**RR 0.47** (0.27 to 0.82)	**284 fewer per 1,000** (from 391 fewer to 96 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 23F)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	13/63 (20.6%)	10/28 (35.7%)	**RR 0.58** (0.29 to 1.16)	**150 fewer per 1,000** (from 254 fewer to 57 more)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 7F)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/63 (25.4%)	17/28 (60.7%)	**RR 0.42** (0.25 to 0.70)	**352 fewer per 1,000** (from 455 fewer to 182 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 18C)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	13/63 (20.6%)	16/28 (57.1%)	**RR 0.36** (0.20 to 0.65)	**366 fewer per 1,000** (from 457 fewer to 200 fewer)	⨁⨁◯◯ Low	Favors MTX

CI: confidence interval; **RR:** risk ratio

Explanations

a. No allocation concealment or blinding

b. Small sample size

Table 22: PCV13 (alone) - Serotypes with 2-fold increase (6)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13 (alone)	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Number of serotypes with >/= 2-fold increase from prevaccination, RTX vs HC												
1	observational studies	serious[a]	not serious	not serious	not serious	none	1/30 (3.3%)	10/28 (35.7%)	**RR 0.09** (0.01 to 0.68)	**325 fewer per 1,000** (from 354 fewer to 114 fewer)	⨁◯◯◯ Very low	Favors healthy controls
Number of serotypes with >/= 2-fold increase from prevaccination, Abatacept vs HC												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/23 (26.1%)	10/28 (35.7%)	**RR 0.73** (0.31 to 1.71)	**96 fewer per 1,000** (from 246 fewer to 254 more)	⨁◯◯◯ Very low	
Number of serotypes with >/= 2-fold increase from prevaccination, DMARD vs HC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13 (alone)	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/27 (25.9%)	10/28 (35.7%)	**RR 0.73** (0.32 to 1.63)	**96 fewer per 1,000** (from 243 fewer to 225 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 23: PCV-13 (alone), Number of Serotypes with IgG >/=1.3 (6)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13 (alone) Seroprotection (IgG >/=1.3)	placebo	Relative (95% CI)	Absolute (95% CI)		

Number of Serotypes with IgG >/=1.3, RTX vs HC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13 (alone) Seroprotection (IgG >/=1.3)	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/30 (10.0%)	7/28 (25.0%)	**RR 0.40** (0.11 to 1.40)	**150 fewer per 1,000** (from 223 fewer to 100 more)	⊕◯◯◯ Very low	

Number of Serotypes with IgG >/=1.3, Abatacept vs HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/23 (26.1%)	7/28 (25.0%)	**RR 1.04** (0.41 to 2.67)	**10 more per 1,000** (from 148 fewer to 418 more)	⊕◯◯◯ Very low	

Number of Serotypes with IgG >/=1.3, DMARD vs HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/27 (14.8%)	7/28 (25.0%)	**RR 0.59** (0.20 to 1.80)	**103 fewer per 1,000** (from 200 fewer to 200 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 24: PCV13+PPV23 boost at 8 weeks - Serotypes with 2-fold increase (6)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13+PPV23 boost at 8 weeks - Serotypes with 2-fold increase	placebo	Relative (95% CI)	Absolute (95% CI)		
Number of serotypes with >/= 2-fold increase from prevaccination after prime + boost, RTX vs HC												
1	observational studies	serious[a]	not serious	not serious	not serious	none	1/30 (3.3%)	11/28 (39.3%)	**RR 0.08** (0.01 to 0.62)	**361 fewer per 1,000** (from 389 fewer to 149 fewer)	⨁◯◯◯ Very low	Favors healthy controls
Number of serotypes with >/= 2-fold increase from prevaccination after prime + boost, Abatacept vs HC												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/23 (34.8%)	11/28 (39.3%)	**RR 0.89** (0.43 to 1.83)	**43 fewer per 1,000** (from 224 fewer to 326 more)	⨁◯◯◯ Very low	
Number of serotypes with >/= 2-fold increase from prevaccination after prime + boost, DMARD vs HC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13+PPV23 boost at 8 weeks - Serotypes with 2-fold increase	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/27 (33.3%)	11/28 (39.3%)	**RR 0.85** (0.42 to 1.72)	**59 fewer per 1,000** (from 228 fewer to 283 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 25: PCV13+PPV23 boost at 8 weeks - Seroprotection (IgG >/= 1.3) (6)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13+PPV23 boost at 8 weeks - Seroprotection (IgG >/= 1.3)	placebo	Relative (95% CI)	Absolute (95% CI)		

Number of Serotypes with IgG >/=1.3, RTX vs HC

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCV13+PPV23 boost at 8 weeks - Seroprotection (IgG >/= 1.3)	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	3/30 (10.0%)	10/28 (35.7%)	**RR 0.28** (0.09 to 0.91)	**257 fewer per 1,000** (from 325 fewer to 32 fewer)	⊕◯◯◯ Very low	Favors healthy controls

Number of Serotypes with IgG >/=1.3, Abatacept vs HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/23 (26.1%)	10/28 (35.7%)	**RR 0.73** (0.31 to 1.71)	**96 fewer per 1,000** (from 246 fewer to 254 more)	⊕◯◯◯ Very low	

Number of Serotypes with IgG >/=1.3, DMARD vs HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/27 (25.9%)	10/28 (35.7%)	**RR 0.73** (0.32 to 1.63)	**96 fewer per 1,000** (from 243 fewer to 225 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 26: Additional data from observational studies and RCTs not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
10159 Berho 2021[10159]	Single-center, observational case series	Unclear	19 patients with JIA on treatment with TNFi. Mean age 13.8 years, mean disease duration 46.2 months.	**All patients received pneumococcal vaccination prior to starting TNFi:** - 9/19 (47.3%) received one dose PCV13 & one dose PPSV23 at 8 weeks - 8/19 (42.2%) received single dose of PPSV23 - 2/19 (10.5%) received single dose of PCV13 Mean time from last vaccine to TNFi start was 3 months. **Treatment at time of vaccination:** 17/19 (89.4%) on immunosuppression 16/19 (84.2%) on MTX 8/19 (42.1%) on prednisone 7/19 (41.1%) on MTX + prednisone 1/19 on SSZ + azathioprine **Treatment at time of serology:** All 19 on TNFi:	Specific IgG antibodies against 10 pneumococcal serotypes measured by ELISA at unspecified time post-vaccination. **Response to each serotype** defined as an IgG antibody titer >1.3 ug/ml post-vaccination. **Vaccine response** defined as response to 50% or more of the serotypes if age <6 years, or to 70% or more serotypes if age 6 years or older. 18/19 (94.7%) were vaccine responders One nonresponder (female patient with RF+ JIA on MTX + GC at time of single-dose of PPSV23) **Response rates to individual serotypes:** Serotype 1: 12/19 (63.1%) Serotype 3: 14/19 (73.6%) Serotype 4: 13/19 (68.4%) Serotype 5: 18/19 (94.7%) - Nonresponder received single PCV13 Serotype 6B: 18/19 (94.7%) Serotype 9V: 17/19 (89.4%) Serotype 14: 19/19 (100%) Serotype 18C: 18/19 (94.7%) Serotype 19F: 19/19 (100%) Leukocyte, lymphocyte, immunoglobulin, and complement levels were normal for all patients.

				- 13/19 (68.5%) adalimumab - 6/19 (31.5%) etanercept All 19 receiving additional immunosuppression: - 18/19 (94.7%) MTX - 10/19 (52.6%) glucocorticoids 9/18 (50%) MTX + glucocorticoids	Lower mean lymphocyte count in non-responders to serotype 4 compared to responders (2344/uL vs. 3535/uL; p=0.054).
10245, Jensen L, 2021[10245]	Prospective cohort study	median 77 days after PCV13, and 71 days after PPV23	27 children with rheumatic disease (SLE/MCTD most common, followed by JIA and a mix of others); excluded rituximab.	Prevnar 13, followed 8 wks later by Pneumovax	Samples collected at baseline, post-PCV13, and post-PPV23. Seroprotection for each serotype was defined as IgG ≥0.35 µg/mL. Relatively high seroprotection (>6 serotypes) noted at baseline, thought to be due to prior infectious exposure as all children were unvaccinated for *S. pneumococcus*. After PCV13, an increase in the antibody titres compared with pre-vaccination was found for all serotypes, and for 9/12 serotypes, the increase was significant. After PPV23, all serotypes except serotype 23F were seen to increase compared with post-PCV13 but none of the increases reached significance. Patients were on varying combinations of glucocorticoids, MTX, TNFi, azathioprine, MMF, and hydroxychloroquine, but results were not broken out by individual medication or disease type. 4 children were on no immunosuppressant.
100730 Nived 2021[100730]	Case-control	7 days	RA patients on MTX=11 RA patients not on meds=12 HC=13	RMD and HC received the PCV-13 vaccine	T cell % was similar amongst all groups, although CD4+CD45RO+ T cells were lower in MTX patients (14/3) than in HCs (21/3) or RA patients not on meds (22.7%) B cell % was similar in HCs (5.7%) and RA patients on DMARDS (4.8%), but higher in RA on MTX patients (10.2%).

					In addition, there were far fewer exhausted B cells (11.5% & 12.5% in the RA patients (off & on MTX) compared to HCs (22.5%). There were slightly more plasmablasts in HCs (9.5%) compared to RA patients 6.2 & 6.8% (off & on MTX).
9496 Rasmussen 2021[9496]	Observational cohort	3 months	224 patients with autoimmune inflammatory rheumatic disease cared for at an outpatient clinic in Denmark who were identified to have low pneumococcal antibody levels in DANBIO database 144 RA 34 PsA 46 SpA Patients on RTX were excluded	PCV 23 – pneumococcal antibodies	Antibody measure of anti-pneumococcal IgG to 12 serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) – Geometric mean level >=1 was considered protective. Post-vaccination measurement of pneumococcal antibody level revealed that only 80 patients (36%) achieved a protective level of antibodies. In univariate logistic regression, likelihood of achieving a protective antibody level higher in patients with a previous vaccination history vs. without: 30% versus 43%, respectively (p = 0.05). When comparing patients with a history of vaccination less than 5 years ago (n = 77) with patients with a history of vaccination 5 years ago or more (n = 49), a significant difference in achieving a protective antibody level occurred in disfavour of the former group, the figures being 21% versus 45%, respectively (p = 0.005). In multivariable model, when comparing patients with a history of vaccination 5 years ago or more with patients without a history of vaccination, there was no difference in achieving a protective antibody level between the two groups (OR 0.976, 95% CI 0.437–2.179). **MTX:** The group of patients receiving MTX alone or as part of a DMARD regimen (n = 124) was observed to have a lower prevalence of protective antibody levels compared to the group of patients not receiving MTX (n = 100), the figures being 26% versus 48% (p < 0.001). Patients achieving a protective anti- body level had no significant difference in median MTX from the patients not achieving a protective antibody level. Among patients not previously vaccinated and not receiving MTX at the time of vaccination, 64%

					achieved a protective level of antibodies at follow-up, whereas this was achieved by only 17% of the patients who were treated with MTX at the time of vaccination in addition to being previously vaccinated with PPV23 within the last 5 years. In a multivariable logistic regression model, revaccination with PPV23 within the last 5 years [odds ratio (OR) 0.291, 95% confidence interval (CI) 0.123– 0.689] and MTX treatment at the time of vaccination (OR 0.290, 95% CI 0.139–0.604) remained significantly associated with a non-protective status after vaccination with PPV23 **bDMARD, steroids:** There was no similar difference with respect to the use of prednisolone, TNFi, or other bDMARD treatment regimens. Patients achieving a protective anti-body level had no significant difference in median prednisolone dose from the patients not achieving a protective antibody level. **PsA vs. others:** A diagnosis with PsA was significantly associated with a non-protective status after PPV23 vaccination (OR 0.348, 95% CI 0.123–0.981) in multivariable model.
9946, Richi, 2021[9946]	Noninterventional, multicenter, cohort study	The recruitment period started in October 2014 and the follow-up period finished when the last serological test was	Patients older than 18 years, suffering from an AIIRD such as RA, PsA, PsO or IBD. In addition, patients had to be on current biological treatment; N=182	Patients completed protocol combining PCV13 and PPV23 following international recs. Blood samples were collected on entry in the study and at least 4 weeks after the last vaccine was given. Immune response to serotypes 1, 3, 7F, 14, 19A, 19F were assessed.	RA and SpA were 70.4% of the diagnoses. 85% were receiving TNFi. Before entering the study, PPV23 had been administered in 115 subjects (63.2%), PCV13 in 21 subjects (12.1%) and only 9 with both vaccines. Analysis of the antibody response confirmed that at least one third of the patients achieved Opsonophagocytic titer (OT) against each pneumococcal serotype (Table 2). We found no correlation between age and the immune response (p = 0.907). We also observed no influence of the gender (number of serotypes with OT response in men median (IQR): 2 (2.5) vs. 3 (3) in women, p = 0.374). Hence, we did not see differences in the number of serotypes with OT response between the group of patients who had

		performed, at least 4 weeks after the last vaccine was administrated.			received another biological agent, and those who had been treated with the same biological DMARD since the beginning (median [IQR]: 3 (3) vs. 2 (2), p = 0.206). As a result, the regression analysis confirmed that age, gender and having received a previous biological DMARD, did not affect the immune response. Among biological DMARDs, etanercept showed a tendency to higher OT response compared to the other therapies (median [IQR]: 3 (2.5), p = 0.066) whereas adalimumab had lower OT levels (median (IQR): 1 (2), p = 0.015). Rituximab did not show a worse OT response when compared with the other biological agents (median (IQR): 3.5 (2.3), p = 0.088). Interestingly, patients treated with etanercept tended to achieve higher OT levels against serotype 3 (57.9% of patients on etanercept vs. 42.3% of subjects on other biologics, p = 0.052). In fact, almost 40% of patients with an OT response against serotype 3 were treated with etanercept in comparison to patients based in other biological therapies (Figure 3). Remarkably, Rituximab was other biological DMARD that was associated to a good immunological response against pneumococcus with at least 50% of the patients developing functional antibodies against the majority of serotypes investigated (Figure 3). Twenty-six patients (14.3%) did not achieve OT against any of the serotypes studied. None of the biological agents exhibited association with this absence of response. Methotrexate, which was the most frequent synthetic DMARD used, did not interfere with the immune response in patients treated with biological agents. In this sense, the number of serotypes with positive response, was similar in patients treated or not with methotrexate (median (IQR): 2.3 (2.0) in patients on methotrexate vs. 2.0 (3.0) in those without MTX, p=0.73. Similar results with other csDMARDs. GCs did not interfere with immune response to any serotype, nor with the number of serotypes against which

					OT were achieved. The small group of five patients who received a daily dose of prednisone higher than 7.5 mg, showed a lower number of serotypes with OT than subjects untreated with glucocorticoids (median (IQR): 0 (2.0) vs. 3.0 (3.0), p = 0.023). Overall, our study shows that patients with autoimmune inflammatory diseases treated with biological agents, including rituximab, had a functional antibody phagocytic response after a correct program of vaccination using PCV13 and PPV23. These results reinforce the importance of increasing the coverage rates of pneumococcal vaccines in these patients.
2481 Migita 2015 (34)	Study was nested within a random-ized, double-blind, controlled trial designed to evaluate the effectivenes s of the PPSV23 in reducing the incidence of pneumonia as a primary endpoint.	6 weeks	Patients with clinically diagnosed RA were recruited in Japanese National Hospital Organization (NHO) hospitals across Japan (n = 32) from September 2010 to December 2012. The study population was classified into three groups: DMARD treatment only (RA control group; n = 35), MTX monotherapy (MTX alone group, n = 55), and ABT treat-ment (n = 24, mean dose; 547 + 127.9 mg/4 weeks).	0.5 ml (25 μg) of PPSV23 (Pneumovax NP, Merck Sharp & Dohme Corp., Tokyo, Japan) or 0.5 ml of a placebo (sodium chloride) subcutaneously in the upper arm.	After vaccination with PPSV23, the geometric mean concentrations (GMCs) of both serotype 6B- and 23F-specific IgG were increased in all groups. (, there were large differences in the fold induction of GMC responses among the groups with regard to treatments; for 6B serotypes, a higher post-GMC was obtained in the control (2.38 times) and MTX alone (1.75 times) groups compared with that in the ABT (1.23 times, no significant increase) group. In a subgroup analysis, the pneumococcal serotype-specific IgG responses were significantly lower in both serotypes (6B and 23F) in the ABT/MTX group; however, the OI responses in the ABT group were not different from the control group. There was no association between the pneumococcal serotype-specific IgG and OI responses for the 6B serotype in patients receiving ABT in contrast to the control or MTX alone patients.

2540 Nazi 2013 (11)	Secondary analysis of Arnold et al. 2007 (RCT)	6 months	14 patients with immune thrombocytopenia (ITP)	23-valent pneumococcal polysaccharide vaccine (Pneumovax-23; Merck) and the Hib conjugate vaccine (ActHIB; Aventis); rituximab received 6 months prior to vaccinations	Antibody response Within 1 month of vaccinations, a fourfold increase in anti-pneumococcal and anti-Hib antibodies was achieved in 3 (21%) and 4 (29%) patients, respectively. 3 (21%) patients failed to respond to both vaccines by any criteria. T-cell response Following vaccinations, the mean number of IFN-y–producing T cells was 38 cells per 5 x 10^5 total cells at 1 week and 14 cells per 5 x 10^5 total cells at 1 month. B-cell subsets *Peripheral blood CD191 B cells:* rapidly depleted by rituximab, remained depleted 1 year later *Resting memory B cells:* significantly lower vs. baseline after rituximab, remained 80% depleted 1 year later *Naive B cells*: slightly reduced 1 month after rituximab and recovered to baseline levels by 1 year *CD31 T-cell levels*: unaffected Authors concluded that antibody responses were "impaired for at least 6 months after rituximab" and "cellular immunity was reduced in parallel with depleted B-cell pools." Adequate response was defined as a fourfold increase in antibody concentration from baseline within the 1st month after vaccinations.
2542 Rosema n 2012 (17)	Open label, non controlled, clinical trial	6 weeks	RA+MTX (or other DMARD) (n=85), RA+TNF (n=79), RA+MTX (or other DMARD)+TNF (n=89), SpA+TNF (n=83), SpA+MTX (or other DMARD) (n=83), SpA+NSAIDs (n=86)	pneumococcal vaccine (7-valent pneumococcal conjugate vaccine)	The primary study goal was to investigate effects of smoking and alcohol consumption on immune response to pneumococcal vaccine in 6 pre-specified subgroups defined by inflammatory arthritis type (RA or SpA) and treatment. No statistical test compared the groups (see population description). Numerically, immune responses measured for **23F** (mean fold-increase in titer) were highest in SpA+NSAIDs (6.6), followed by SpA on TNFi (4.8), RA on TNFi (3.4), SpA on TNF+MTX (3.0), RA on MTX (2.5) and lowest in RA on TNF+MTX (2.2). The same order for responses was observed with the outcome of IR for **6B** subunit: SpA+NSAIDs (3.3), followed by SpA on TNFi (3.1), RA on TNFi (2.7), SpA on

					TNF+MTX (1.8), RA on MTX (1.8) and lowest in RA on TNF+MTX (1.6) Proportion of patients with protective antibody levels for both 23F and 6B, 4-6 weeks after vaccination: - RA on MTX: 21.2% - RA on TNFi: 36.7% - RA on TNF+MTX: 15.7% - SpA on TNFi: 50.6% - SpA on TNF+MTX: 20.5% SpA on NSAIDs: 47.7%
2545 Winthrop 2016 (27)	Randomized, double-blind, placebo-controlled, phase II study	64 days (35 days post-vaccination)	200 tofacitinib-naive adult patients with RA Median age 53 years, 77% female. Patients excluded if previous influenza vaccine within 6 months or previous pneumococcal vaccine within last 5 years. Four exposure groups: No DMARDs (n=43), MTX monotherapy (n=55), TOFA monotherapy (n=45), MTX+TOFA (n=57)	Participants randomized 1:1 to receive tofacitinib 10 mg BID (n=102) vs. placebo (n=98), stratified by background MTX use (defined as continuous use >4 months with stable dose of 10-25 mg weekly for 6+ weeks). Background MTX in 57/102 (55.9%) of TOFA group, 55/98 (56.1%) placebo group. Prednisone use (<10 mg daily) in 38/102 (37.3%) and 31/98 (31.6%) of placebo group. No changes in MTX, prednisone dosing permitted during study. All participants received one dose of PPSV-23 and one dose of 2011-2012 seasonal trivalent influenza vaccine (H1N1/H3N2/B-Brisbane) at 4 weeks after initiation of study treatment.	GMFR - Fold increase in geometric mean titer (GMT) from pre- to 35 days post-vaccine For majority of pneumococcal serotypes, highest GMFR in No DMARD group, intermediate GMFR in MTX or TOFA monotherapy groups, and lowest GMFR in TOFA+MTX group.

2847 Akamatsu 2015 (28)	Non-randomized, open label comparative	Up to 3 years	22 patients with pulmonary disease receiving steroids and/or immunosuppressant agents (MTX 2, AZA 2, Cyclosporine 2, CYC 1, tacro 1, mizoribine 1); sarcoidosis (n=4), CTD-associated ILD (7), GPA (n=1), eGPA (n=1) remainder no RMD lung disease; and controls with pulmonary diseases not on immunosuppression (n=23)	23-valent pneumococcal polysaccharide vaccine (all participants received intervention)	(1) Baseline Ab level**:** pneumococcal Ab GMT at baseline was not different between immunosuppressive (IS) group and controls (58.6 mg/L (95% confidence interval: 40.5–84.9 mg/L) and 62.5 mg/L, 95% CI: 45.6–85.7 mg/L), respectively. (2) GMT, 1 month**:** In the IS group, 1 month after vaccination GMT: 553.4 mg/L (95% CI: 334.2–916.2 mg/L), which were significantly increased over those before vaccination ($p < 0.05$). (3) Fold Increase, 1 month: No significant difference between IS and controls in fold increase titer at 1 month post vaccine**:** The geometric mean increases (n-fold) between pre- and 1 month post-vaccination were 9.4 (95% CI: 5.7–15.6) and 8.8 (95% CI: 5.8–13.2) in the IS and control groups, respectively ($p = 0.813$). (4) In the IS group, the GMT at 6, 12, 24, and 36 months after vaccination were 385.5, 375.0, 331.1, and 221.8 mg/L, respectively, all significantly increased over baseline levels. There was no significant difference between IS and controls in GMT levels at any time point except at 24 months (data presented as graph only). (5) 20 of 22 patients in the IS group (90.9%) and 21 of 23 in the control group (91.3%) were responders for anti-pneumococcal antibody 1 month after vaccination. There was no statistically significant change in the proportion of responders during the time course between the groups.
2848 Caskurlu 2020 (2848)	Observational cohort	4 weeks	36 patients with inflammatory arthritis receiving Adalimumab (RA n=16, PsA n=2, AS n=18) who had not previously received pneumococcal vaccine "Patients with rheumatoid arthritis had used corticosteroids during their follow-up." Otherwise no mention is	PCV 13	1. Proportion with "protective" anti-pneumococcal IgG antibody levels (>=250 mU/ml) at baseline: 32 of 26 patients had protective pre-vaccination titers. 2. Of 4 patients who did not have protective pre-vaccine titers, all 4 had titers >=250 at 4 weeks post vaccine. 3. Of the 32 patients with baseline protective Ab levels, Ab titers doubled in 24 patients, and tripled in 8 patients at 4 weeks post vaccination. 4. Pre and post vaccination IgG titers (full cohort), median (IQR): (1) Measured with 405nm Pre: 636.7 (413.3-2065.8) Post 2413.3 (1295.0-320.0)

			made re: other medications such as MTX		(2) measured with 450 nm Pre: 1121.1 (462.4-2372.0) Post: 2915.5 (1564.9-3803.6)
2877 Rákóczi 2016 (29)	Nonrandomized trial	2 months	22 RA patients on etanercept in combination with methotrexate (MTX) (n = 15) or monotherapy (n = 7) for at least one year and 24 controls (with OA)	PC13 vaccine (Prevnar)	<u>Response at 1 month</u> 1. One month after vaccination, antibody levels (IgG t=1) increased in both groups (RA: 247.7 ± 155.6 mg/l; controls: 417.7 ± 198.3 mg/l) compared to baseline (P < 0.001). The mean increase in antibody levels between baseline and 4weeks were 2.63-fold in the RA and 6.13-fold in the control group (P = 0.016). 2. Mean fold-increase in antibody levels after <u>4 weeks</u> vs baseline: RA: 2.6-fold vs. Control: 6.13-fold (p=0.016) 3. RA patients receiving ETA-MTX combination (n = 15) vs. ETA monotherapy (n = 7): <u>1 month fold increase</u> not sig different: - Combined group: (2.89-fold increase) - Monotherapy group: (2.07-fold increase) Between group difference P = 0.503
3481 Kapetanovic 2011 (19)	Controlled clinical trial, not randomized	4-6 weeks	RA (N=253 given PCV7 and N=149 given PPV23) and healthy controls (N=47 given PPV23) RA patients further divided into 3 treatment groups: RA on MTX with or without other DMARDS (N=122), RA on TNFi monotx (N=141), RA on TNFi+MTX (N=139)	Pneumococcal conjugate vaccine (PCV7) or 23-valent polysaccharide vaccine (PPV23)	1. <u>Levels of serotype specific IgG 23F and 6B</u> - "significant" increase in Ab levels for 23F and 6B vs pre-vaccine levels in each treatment group ("p value range between <0.001 and 0.035). 2. <u>Antibody response ratio (ARR)= ratio between post- and pre-vaccine Ab levels.</u> <u>PCV7 (N=253 patients with RA)</u> <u>ARR 6B (median (range))</u> RA on MTX (n=85): 1.4 (0.4-100) RA on TNFi (n=79): 1.8 (0.5-58) RA on MTX+TNFi (n=89): 1.3 (0.4-75) <u>ARR 23F (median (range))</u> RA on MTX (n=85): 1.9 (0.7-740) RA on TNFi (n=79): 2.5 (0.7-181) RA on MTX+TNFi (n=89): 1.5 (0.5-77)

					PPV23 (N=196, RA and HC): ARR 6B (median (range)) RA on MTX (n=37): 1.6 (0.8-20) RA on TNFI (n=62): 3.4 (0.8-280) RA on TNFi+MTX (n=50): 1.8 (0.9-44) Healthy controls (n=47): 2.2 (0.4-75) ARR 23F (median (range)) RA on MTX (n=37): 1.4 (0.3-15) RA on TNFI (n=62): 2.8 (0.9-68) RA on TNFi+MTX (n=50): 2.0 (0.7-36) Healthy controls (n=47): 2.3 (0.2-91) There were no statistical significant differences in ARR between corresponding treatment groups for neither 23F nor 6B serotype (p value between 0.079 and 0.946; ANOVA, adjusted for differences in age, gender and prevaccination antibody levels). 3. Positive antibody response (pAR) = at least 2-fold increase in pre-vaccine Ab level - Lowest % of responders found in the MTX alone or MTX+TNFi group, regardless of vaccine type (data shown visually). However, no significant differences observed between corresponding treatment groups. Univariate regression model: - Higher age (p = 0.030) and ongoing MTX treatment (p < 0.001) predicted impaired posAR for both serotypes. - Concomitant prednisolone (p = 0.002) and anti-TNF treatment (p = 0.006) predicted better posAR. Multivariable models: adjusted for age, gender and "baseline disease characteristics" and antibody levels for both 23F and 6B - Patients with ongoing MTX treatment was associated with lower odds of antibody response (OR 0.361 95% CI 0.206, 0.633).

					- Concomitant prednisolone use was associated with higher odds of posAR (OR 1.807, 95% CI 1.107, 2.949). Ongoing TNFi had no significant impact on posAR for any antibody subtype (OR 1.081, 95% CI 0.570, 2.050).
399 Kapetanovic 2011 (18)	Case-control, prospective	4-6 weeks post-vaccination	505 adult patients (253 w RA, 121 PsA, 78 Ank Spond, 53 another form SpA) RA + MTX; age 61.5 +/-14 RA + anti-TNF + MTX; age 60.1 +/- 10 RA + TNF; age 59.8 +/- 14 SpA + anti-TNF + MTX; age 50.4 +/- 11 SpA anti-TNF; age 49.2 +/- 12 SpA + NSAIDs +/- analgesics = control group; age 51.6 +/- 12	7-valent conjugate pneumococcal vaccine	Post vaccination serotype-specific IgG increased significantly for both serotypes in all groups compared to baseline. No. (%) of patients with 2-fold increase in prevaccination antibody levels for both serotypes (n=85) RA + MTX 18 (21.2) RA + TNF + MTX 14 (15.7) RA + TNF 29 (36.7) SpA + Anti-TNF + MTX 22 (26.5) SpA + TNF 42 (50.6) SpA + Nsaids/analgesics 41 (47.7) No. (%) of patients with 4-fold increase in prevaccination antibody levels for both serotypes RA + MTX 9 (10.6) RA + TNF + MTX 3(3.4) RA + TNF 17(21.5) SpA + Anti-TNF + MTX 9 (10.8) SpA + TNF 24 (28.9) SpA + Nsaids/analgesics 23(26.7) <u>MTX and TNFIs:</u> • ARR was higher in controls vs groups of patients treated with MTX (*P* 0.046 for 6B and *P* 0.002 for 23F) or MTX combined with TNFIs (*P* 0.002 for 6B and *P* 0.001 for 23F). • Significantly lower ARRs were found for both serotypes in patients on MTX vs. pts not on MTX (*P* 0.001 in both). TNFIs as monotherapy: • No significant difference for ARRs for both serotypes vs controls.

					• No difference in ARRs between patients treated with TNFIs vs those not on TNFIs for either serotype tested. In RA patients, higher age [-0.033, p= 0.013, OR 0.97 (0.94-0.99)] and MTX treatment [-1.134, p=0.006, OR 0.32 (0.44-0.73)] were predictors of impaired antibody response both in univariate and multivariate regression analysis. In SpA patients, only concomitant MTX treatment [-1/006, p= 0.011, OR 0.37 (0.17-0.80)] was predictive of an impaired antibody response for both serotypes.
402, Nived 2018 (25)	Cohort, case control	6 weeks	60 patients w RA (50 without DMARD, 10 on MTX); 58% on prednisolone (median dose 5 mg daily, range 0–15 mg) vs 15 patients with primary Sjogren's syndrome (pSS) without DMARD vs 49 controls	13-valent pneumococcal conjugate vaccine (PCV13)	Prednisolone dose did not correlate with antibody response or percentage change in OPA.
4026 Bahuaud 2018 (35)	cohort	24 months	24 RA patients	PCV13 followed 2 months later by PPSV23 (prime-boost) Primary outcome: Seroconversion for 7 serotypes common to both vaccines, and 3 included only in PPSV23 measured at baseline, 4, 12 and 24 months post-vaccine	Similar percentages of protection were found at 4 months (63 vs 55%), 12 months (54 vs 50%) and 24 months (53 vs 55%) for the 7 common and 3 uncommon serotypes
405 Allen 2016 (36)	Observational	28 days	125 RA patients (77 from ACQUIRE and 48 from ATTUNE) received PPSV23. mean age 45.7 (13.8), 85% female.	PPSV23 and the 2011–2012 trivalent seasonal influenza vaccine; abatacept and DMARDs	Patients achieving protective antibody levels (antibody titer ≥1.6 µg/mL for pneumococcal antigens. Pneumococcal (≥3 of 5 antigens): 94/112 (83.9%, 95% CI: 77.1 to 90.7)

			191 RA patients from the ACQUIRE study received influenza vaccine; mean age 44.9 (12.6), 90% female.		
4078 Elkayam 2002 (37)	Case control	2 months	42 RA patients, 24 SLE patients, 20 controls Prednisone, HCQ, MTX, AZA, SSZ, minocycline, CYC	PPSV23	Notes: 1 month post- vaccine both RA and SLE groups had significant increases in GMT of specific serotypes as well as mean fold-increase in antibody levels to all 7 serotypes compared with pre-vaccine levels. 35-71% of RA patients and 36-86% of SLE patients responded to pneumococcal vaccination within 1 month
4103_Alyasin 2016 (30)	Case control	3 weeks	30 children with SLE 30 age matched control(asthma)	23 valent pneumococcal vaccine IgG anti-PCP Titers before and 3 weeks later using ELISA	Both groups had significant increases in anti-pneumococcal antibody level, with mean fold of 7.01 in SLE and 9.6 in control group. Although a trend toward decreased post-immunization antibody level and immune response in patients treated with different medications was seen in comparison with those patients who did not receive such treatments this was not statistically significant
4119_Rezende 2016 (31)	Prospective open label study	1 year	54 patients with SLE(divided into immunosuppressed and non immunosuprressed) 14 excluded from initial group of 68	23 valent pneumococcal polysaccharide	No significant difference in the response rate to each criterion between the treatment groups (p -0.62 and p - 0.44, respectively (both by chi-square) Antibody responses to PPSV23 were overall lower among lupus patients undergoing immunosuppressive treatment, with the vaccine being insufficiently immunogenic even among those not receiving immunosuppressants
4125 Gorelik 2018 (12)	Observational cohort	40 weeks	26 pediatric SLE patients vs. 21 healthy controls mean age: 15.7 pLE, 10 controls	26 received PCV13. Of these, 22 went onto receive PPSV23 100% on HCQ, 54% corticosteroids, 50% mycophenolate, 19%	PICO 3: 17/26 (65%) achieved primary endpoint (>70% vaccinated serotype Ab levels >1.3mcg.dL) following PCV13 and 13/22 (59%) following PPSV23, compared to 100% in retrospective healthy controls.

				azathioprine, 35% rituximab, 4% abatacept, 12% MTX/LEF	- rituximab in preceding 6 months was associated with not achieving protective levels Sequential PCV13 and PPSV23 achieved protective status for ~2/3 of pediatric SLE patients in this population
4126 van Aalst 2020 (20)	Prospective cohort	8 weeks	141 IBD patients on 4 different med regimens: - 37 no IS - 40 TNFi - 29 combo TNF + conventional drugs 35 Conventional immunomodulators: pred > 10 mg, thiopurines, MTC	PCV13 followed by PPSV23 2 months later Assessing serotype-specific IgG concentrations at baseline, and 4-8 weeks post-vaccination	Adequate response to vaccine (seroconversion/SCR), which was defined as post-vaccination Ab concentration ≥1.3 mcg/mL for 70% of measured serotypes. <u>No IS group</u> SCR all 23 serotypes 81% (CI 68-93) SCR PCV13 serotypes 84% (CI 71-94) SCR PPSV23 only 81% (CI 67-92) <u>TNFi group</u> SCR all 23 serotypes 63% (CI 46-78), OR 0.39(0.14-1.10) SCR PCV13 serotypes 58% (CI 42-73), OR 0.26(.09-0.77) SCR PPSV23 only 80% (CI 64-91). OR 0.8(0.27-2.43) <u>Combo group</u> SCR all 23 serotypes 52% (CI 33-71), OR 0.25(0.08-0.75) SCR PCV13 serotypes 41% (CI 23-60), OR 0.14(0.04-.43) SCR PPSV23 only 55% (CI 37-74) OR 0.29(0.10-0.86) <u>Conventional meds group</u> SCR all 23 serotypes 60% (CI 42-75), OR 0.35(0.12-1.02) SCR PCV13 serotypes 49% (CI 31-64), OR 0.18(0.06-.55) SCR PPSV23 only 74% (CI 60-88) OR 0.67(0.22-2.06) <u>Groups 1-3 combined (any type of IS</u> SCR all 23 serotypes 59% (CI 49-68), OR 0.33(0.13-0.82) SCR PCV13 serotypes 50% (CI 40-59), OR 0.19(0.07-.50) SCR PPSV23 only 70% (CI 61-79) OR 0.55(0.22-1.38) After adjusting for disease type, only the use of a combination of immunosuppressive drugs was significantly associated with impaired seroconversion (OR 0.32 [CI, 0.10-0.98]).
4362 Jarrett 1980 (38)	Case control	6 months	38 SLE (37 female) 5 no meds 29 on prednisone alone 9 on pred/AZA Group 1: prednisone <20mg/day	Pneumococcal vaccine (14 valent)	Post-immunization AB levels at 1 month were far lower in SLE patients than in normal control subjects for serotypes 1,4, 6A,7,8,14,18C,23F (P value at least *<0.05).* All three groups had significantly lower mean post-

			Group 2: prenidone>20mg/day Group 3: both prednisone + AZA vs 23 pts who refused vaccination (22 female) vs 17 healthy volunteers		immunization antibody levels than normal control subjects. There was no significant difference between the three treatment groups in AB response. In patients with SLE off any treatment at time of immunization, mean post-immunization Ab level was 1,290+/-472ng/AbN/ml, compared to a lower value (exact value not provided) in patients only on >20mg/day of prednisone (group II), and in patients on prednisone and AZA ($p<0.05$) combined.
459 Battafarao 1998 (26)	Cohort	12 weeks	73 SLE 5.5% male/94.5 % female; mean age 43 (18-76) 48% on antimalarial agents , NSAIDS 34%, AZA 10%, IV CYC 10%, oral MTX 1% 74% on steroids, with 85% oral prednisone <10mg per day	Pneumococcal (pneumovax 23), tetanus toxoid and haemophilus influenza type B	61 (84%) achieved 4-fold AB response to at least 1 antigen, with 100% achieving at least a 2-fold response to at least 1 antigen. 14 (19%) developed 4-fold response to all 3 antigens, with >50% developing at least 2-fold response to all 3 antigens. Majority developed protective Abs to tetanus and HiB irrespective of their increase in titer; 65 (90%) had protective levels of tetanus AB (≥0.01 IU/ml). and 64 (88%) had protective levels of HIB antibody *(*≥1, pg/ml). For the polyvalent pneumococcal vaccine, only total antibody levels could be measured. <u>% of patients with protective levels of AB</u> HiB preimm 37 (51%) / postimm 64 (88%) TT preimm 36 (50%) / post imm 65 (90%) Pneumo pre/post Not determined <u>PICO 3 and 4</u> Patients with 3-fold increase in AB titers post-immunization: those who were not receiving AZA, CYC and prednisone, all developed 3-fold increases to a mean of almost 2 (1.9) of the 3 vaccines. Trend toward decreased antibody response in patients treated with CYC, AZA or prednisone, although this was not statistically significant. There was no significant difference

					for any individual medication or combination of medications, or by medication dosage.
4782 Ngyuen 2017 (13)	Randomized control trial of RA patients on biologics given 3 pneumococcal vaccine strategies compared to RA patients on MTX receiving the standard vaccine strategy	4 weeks following PPV23 boost dose	35 DMARD patients (91% MTX) who received PCV13 followed by PPV23 16 wks later 65 biologic patients (59% on TNFis, 21% on abatacept, 14% on IL-6is, 6% on RTX → of all of these, 68% were also on MTX) who received: Grp 1A: PCV13 + PPV23 16 wks later Grp 1B: PCV13 + PPV23 24 weeks later Grp 2: double-dose of PCV13 + PPV23 16 weeks later	PCV13 and PPV23	Figure 3: When considering the DMARD patients (most of whom were MTX) vs the biologic patients as a whole (most of whom were TNFi), the DMARD patients had less response to the pneumococcal vaccines (when considering (response defined as IgG >0.35mg/l or 4-fold rise) … specifically, both groups tended to show a response to at least 7 serotypes, but more biologic patients had a response to 8,9,10,11, or 12 serotypes than did patients on DMARDs alone. When looking at the specific biologic … anti-IL6 and abatacept patients had very good responses (often 11 or 12 serotypes), with anti-TNF response still pretty good, but the rituximab patient response poorest (most ritux patients mounted a response for 5 serotypes, and no ritux patients mounted a response for more than 7 serotypes). Ritux significantly impaired serologic response Fig 3B: for patients on biologics, responses to the 3 vaccine strategies were similar, with Grp 1A appearing best, group 2A appearing next best, and Grp 2 appearing worst. For TNFi patients, their response was very slightly impaired by also being on MTX. For IL6i patients, response to 10,11, or 12 serotypes was blunted by also being on MTX, but all patients (with or without MTX) responded to at least 9 serotypes. For patients on abatacept, being on MTX was associated with an IMPROVED response to the vaccine (no explanation provided by the authors).
509 Caporuscio 2018 (39)	Case control	12 months	38 RA patients (mean age 62.4 ys) on IS vs. 20 healthy controls mean age 62.7 yrs) RA patients were on a stable dose of oral steroids	Antibodies to all PCV13 serotypes were measured pre vaccine, then at 1, 6 and 12 months	Antibody response was not influenced by RA therapy (prednisone/methotrexate/TNFi) The percentage of responding subjects to each 13 serotypes did not differ between the two groups

			(mean pred 7.5 mg/d) and mean MTX 15 mg/week. 14(37%) TNFi. 13(34%) TNFi+MTX		
5147_Broyde 2016(21)	Retrospective cohort	10 years	145 pts with Rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), or inflammatory bowel disease (IBD)-associated spondyloarthropathy (SpA) On biologics [tumor necrosis factor-α (TNF-α) or interleukin 6 (IL-6) receptor inhibitors] or methotrexate (MTX)	PPSV 23	No association between the use of TNF-α blockers, tocilizumab, or low-dose prednisone. Use of MTX was associated with significantly lower antibody levels (187 mg/l vs 289 mg/l for no MTX, p = 0.037). A higher but nonsignificant proportion of MTX users had non-protective levels of antibodies (13% vs 7% for non-treated patients)
6278_Crnkik 2013 (22)	Retrospective cohort	1.5 years after vaccination	398 RA(163), SPA(139)	PCV 7 Divided into 6 groups based on Tx Seroprotection: Antibody levels > =1 mg/L	SpA (only NSAIDs): significantly higher antibody levels at 4/6 weeks and at 1.5 years (84%) Lowest level of protective antibody levels was seen in RA+ anti-TNF+MTX (52%) Lower in RA vs SpA Concomitant anti-TNF treatment and treatment with MTX were identified as negative predictors of persistence of protective antibody levels for both serotypes tested (P = 0.024 and 0.065, respectively).
6438 Coulson 2011 (40)	Retrospective cohort	10 years	152 RA patients on MTX - 124 prev. received PPSV23 28 not vaccinated	Assayed pneumococcal antibody levels	PICO 3: no correlation found between pneumococcal antibody levels and methotrexate dose or duration

6439 Nielsen 2020 (41)	Cross sectional study	1.5 years of measurement of antibody titers	346 pts RA/SPA or PSA with antibody measurement Compare vaccinated and unvaccinated pts	PPV 23(given prior to initiation of bDMARD therapy) Levels of specific antibodies added to normal blood sample procedure as a part of the clinic visit	Methotrexate use was associated with a protective antibody level (P - 0.03)
647 Morgan 2016 (14)	Cohort-case control	Median FU post vaccination 4.6 years, total patient FU was 363 patient-years (none lost to FU)	92 patients with small or medium-sized systemic vasculitis (EGPA- 7 patients, GPA-59 , MPA-22 or classical PAN- 4) in stable remission > 6 months (BVAS = 0), s/p CYC and steroid induction but not within 6 months, had not received RTX within 6 months, on <10mg of prednisone per day, currently on no more than 1 immunosuppressant + prednisolone, no active infections, not pregnant, no hx of previous severe reaction to vaccination or received vaccination to proposed vaccines; age 66 (53-74) 81 patients still taking prednisolone at median of 5mg/day at time of vaccination. 9 patients on Rituxan, 35 on AZA, 35 on mycophenalate	7-valent conjugate pneumococcal vaccine (Prevnar) *Haemophilus influenzae type b (Hib)* *Meningococcal (Men) group C conjugate vaccine and Men polysaccharide groups A, C, Y, and W135 vaccine*	Median AB titers for all the vaccine components increased at 4 weeks postvaccination 4 weeks postvaccination, significant improvement in the percentage of patients who had AB titers above the threshold, although there was variability in the response between antigens (antibody response above the protective threshold for each antigen median of 46% [IQR 39–58%]) Serotype PreVacc Post Vacc P Pn4 23 42 <0.001 Pn6B 48 67 <0.001 Pn9V 55 82 <0.001 Pn14 55 74 <0.001 Pn18C 70 88 <0.001 Pn19F 59 77 <0.001 Pn23F 50 74 <0.001

6472 Grabar 2017 (42)	Double-blind RCT	52 weeks	SLE patients Age (median (IQR): 39.5 (33.3-50.7)	25 received PPSV23 17 received PCV7 followed by PPSV23 24 weeks later primary endpoint: rate of responders at week 28 to at least 5 of 7 serotypes shared by both vaccines	PICO 3: At week 28, (4 weeks after PPSV23) primary endpoint achieved by 18/25 (72%) in the PPSV23 group and 13/17 (76%) in the PCV7-PPSV23 group. No differences by IS.
6474 Elkayam 2005 (43)	Cohort	2 months	24 consecutive SLE pts fulfilling ACR criteria (mean age 39, 83% female, mean disease duration 7 years; 67% on HCQ, 46% on <10mg of prednisone, 17% on >10mg of prednisone, 8% on NSAIDs, 17% on mtx, 4% on CYC)	Pneumovax given to all SLE pts	No significant changes in measures of disease activity were shown after the pneumococcal vaccination: The mean +/- SD SLEDAI score was 4.41+/-2.92 at the time of vaccination and 4.47+/-3.11 at 2 months apart. Levels of ESR, CRP, WBC, C3, C4, IgG, IgM and IgA remained stable. The mean serum levels of anti-dsDNA, -Ro/SSA, -La/SSB, -nRNP, -Sm, IgG and IgM aCL, C3and C4 did not significantly change after vaccination At time of vaccination, 10 patients had increased levels of anti-dsDNA, 9 had anti-Ro/SSA, 4 anti-La/SSB, 4 IgG and IgM aCL, and 2 had anti-Sm and 5 anti-nRNP antibodies. Two months after vaccination, no change was observed in the proportion of patients with anti-Sm, anti-nRNP, anti-Ro/SSA and aCL IgM. A single patient developed aCL IgG and another one turned anti-nRNP negative
7041 Chatham 2017 (32)	RCT, open-label	32 weeks	79 SLE patients receiving belimumab mean age: 39.6 (12.40)	34 received PPSV23 4 weeks before starting belimumab 45 received PPSV23 24 weeks after starting belimumab	No significant differences between groups. At week 4 post-vaccination, 97% of the pre-belimumab and 97.6% of the post-belimumab had a positive response to >=1 of 23 pneumococcal serotypes. Proportions were also comparable across broader response from >=2 to 23 serotypes.
7047 Brogan 2019 (44)	Core study: 56-week, multicenter, open label phase III trial	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment.	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise	In core study, 7/17 (41%) patients received a total of 31 vaccine injections (10 different types of inactivated vaccines). Vaccine response data available for 18/31 (58.1%) injections. All showed a positive response (Ab titers increased above protective level).

	Long-term extension (LTE): 6-24 months additional treatment & follow-up		Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood vaccination programs. No live vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination ("Pre-dose"), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). <u>Included vaccines:</u> HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	For all 31 vaccine injections, including those without a pre-dose Ab titer, protective post-vaccine Ab titers were maintained throughout the trial. In the extension study, 4/17 (24%) patients received a total of 20 vaccine injections (8 different types of inactivated vaccines). 17/20 (85%) of injections had data available to assess vaccine response. In 16/17 (94.1%) cases, protective Ab titers were achieved post-vaccine. For 19/20 (95%) vaccine injections, including those without a pre-dose Ab titer, protective post-vaccine Ab titers were maintained throughout the extension study
7331 Visvana than 2007 (24)	Analysis of ASPIRE substudy	38 weeks	70 RA patients: -20 IFX 3mg/kg+MTX -36 IFX 6mg/kg+MTX -14 placebo + MTX ASPIRE (RCT) enrolled 1049 RA patients with no	PPSV23 given 34 weeks after start of IS Antibody responses were assessed 4 weeks post-vaccination.	<u>N</u>o significant difference in response to PPSV23 was observed between any of the 3 groups. 80-85% responded to at least one serotype.

			prior treatment with MTX or TNFI		
7485 Kapetanovic 2013 (15)	Prospective cohort	6 weeks	88 RA patients: 55 RTX - 26 MTX 17 ABA -13 MTX 16 TCZ -9 MTX 85 MTX Vs. 86 controls (SpA pts not on IS)	PCV7 Primary outcome: IgG against 23F and 6B serotypes checked at vaccination, and 4-5 weeks after. Antibody response (AR) was defined as ratio between post- and pre-vaccine Ab levels, and positive AR was >=2	RTX-treated patients had significantly lower AR for each serotype, no difference if they were taking methotrexate or not. RTX pts had significantly impaired positive AR compared to MTX, TCZ and controls ABA-treated patients TCZ-treated patients – immune response comparable to that of controls *Treatment with ritux and ABA was associated with diminished AR response and was most pronounced for rituximab, regardless of MTX use*
8281 Gelinck 2008 (23)	Retrospective cohort	4 weeks	93 patients with RA or IBD - 52 TNFi - 41 DMARD Median age 50 18 healthy controls Median age 47	PPSV23	PICO 3: response rates, defined as post-vaccination titer ≥35 mcg/ml in combination with at least 2-fold increase in antibody titer to PPS 6B, 9V, 19F and 23F ** the figures in this paper were difficult to interpret, but response to PPSV23 was significantly impaired in patients treated with methotrexate, and furthermore if methotrexate combined with TNFi, compared to controls
840_Stohl 2012 (45)	Case Series Pooled data from 2 phase III trials, the Study of Belimumab in subjects with SLE 52 week (BLISS-52) and 76 week (BLISS-76) trials	Within 5 years of start of treatment in BLISS-76 study	Substudy of BLISS-76: Evaluated for IgG antipneumococcal AB levels 26 tx w placebo 28 tx belimumab 1mg/kg 22 tx w belimumab 10mg/kg Evaluated for IgG anti-tetanus toxoid 33 tx w placebo 33 tx belimumab 1mg/kg	Pneumococcal or tetanus vaccine	At week 52, no significant differences across Tx groups in percentages of pts maintain IgG anti-pneumococcal AB titers to 5 serotypes; of the 7 additional pneumococcal vaccine serotypes, significantly lower titers noted only for serotype 12F AG serotype Placebo 9N -10.20 +/- 6.39 (0.00) 14 -8.70 +/- 6.49 (-10.37) 19F -5.28 +/-6.64 (-3.30) 23F -8.32 +/- 7.84 (-2.30)

			25 tx w belimumab 10mg/kg [BLISS-52 (n=865); placebo vs belimumab 1mg/kg] [BLISS-76 (n=819); placebo vs belimumab 10mg/kg All patients had active SLE and were on standard therapy for SLE (steroids, immunosuppressive agents [aza, mmf, mtx] and/or antimalarial agents alone or in combination)]		26B -13.30+/-5.12 (-6.79) AG serotype Belimumab 1mg/kg 9N -1.49 +/- 7.47 (0.00) 14 -1.20 +/- 4.04 (0.00) 19F -3.45 +/-5.81 (-2.60) 23F -2.35 +/- 6.43 (0.00) 26B -6.36 +/- 4.13 (0.00) AG serotype Belimumab 10mg/kg 9N -11.90 +/-3.28 (0.00) 14 -10.10 +/-5.10 (-10.26) 19F -10.27 +/- 5.09 (-7.92) 23F -6.61 +/- 3.92 (0.00) 26B -10.05 +/- 3.43 (0.00) IgG anti-tetanus toxoid AB not significantly decreased Tetanus toxoid vaccine Placebo AG -10.43 +/-4.67 (-10.59) AG Belimumab 1mg/kg 28.14 +/- 33.39 (-15.33) AG Belimumab 10mg/kg -13.52 +/- 7.07 (-16.84)
8424 Winthrop 2018 (46)	Single-arm study	4 weeks after vaccination	60 patients completing at least 3 months' continuous treatment with tofacitinib 10 mg twice daily	PCV-13 and tetanus vaccines.	Geometric mean fold rise from baseline for the 13 PCV serotypes at 4 weeks postvaccination varied from 8.3 (serotype 3) to 101.9 (serotype 6A). GM titers ranged from 66.1 to 2782.2 at 4 weeks postvaccination.
8703 Nagel 2017 (47)	Case-control study	6 weeks	47 SLE patients treated with: 1) no DMARD = 7, 2) AZA or DMARD other than HCQ = 9	All immunized with a single dose of 13-valent conjugated pneumococcal vaccine.	Fold increase of 12 serotype specific antibody log transformed levels and confidence intervals: Belimumab vs Healthy Controls: 0.40 (-0.25-1.05) HCQ or AZA or other DMARD vs Healthy Controls: 0.57 (-0.04 - 1.19)

			3) AZA + HCQ = 10, 4) HCQ only = 10, 5) belimumab + other treatment = 11, and 21 healthy controls		AZA+HCQ vs Healthy Controls: 1.11 (0.40-1.83)
8944 Groh 2017 (16)	Case-control	Follow-up up to 27 months	19 AAV patients	PCV13 and PPV23 vaccination in 9 patients during AAV remission induction with CYC or rituximab therapy (group A); 10 patients during AAV maintenance therapy or absence of IS (group B)	1 out of 9 patients (11%) from group A and 7 out of 10 patients (70%) from group B had protective residual anti-pneumococcal immunity.

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Bacteriophage Vaccine

Summary: One comparative cohort study described the impact of a drug of interest on the bacteriophage ΦX174 vaccine response in an RMD population. Niwa et al (1) found that the primary and secondary serum response was diminished two weeks after vaccine administration in 47 individuals with RMD. Steroids alone did not influence immune response to anti- ΦX.

A non-RMD RCT in patients with type 1 diabetes showed that RTX diminished the immune response to phiX174 vaccine compared to no RTX (2).

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies and RCTs not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2538 Pescovitz 2011	RCT, blinded	56 weeks	Patients with type 1 diabetes treated with RTX (n=46) or placebo (n=29), healthy controls also contributed data for the bacteriophage studies	Hepatitis A, Tetanus/diphtheria vaccines, bacteriophage phiX174 administered at 12 months	Bacteriophage phiX174: PBO patients had responses to first and second vaccine dose similar to HC, both of which were greater than that of the RTX-treated group, RTX subjects developed responses after 3rd and 4th doses that were similar to those seen in the PBO group after the 1st and 2nd dose. Results log-transformed and cannot be added to RevMan. Below is geometric mean of Kv Primary Response: **7 days:** RTX (n=20): 0.02 (0-0.53); Control (n=15): 10 (2-49), healthy subjects (n=52): 9 (1.5-50) **14 days**: RTX (n=20): 0.03 (0-1.2); Control (n=15): 37 (2-577), healthy subjects (n=52): 114 (9-1461) **28 days**: RTX (n=20): 0.03 (0-0.53); Control (n=15): 17 (0.76-400), healthy subjects (n=52): 65 (9-565) p≤0.0001 for RTX vs. placebo control p=0.0186 for placebo control vs. healthy subjects p≤0.0001 for RTX vs healthy subjects Secondary Response: **7 days:** RTX (n=20): 0.02 (0-0.27), Control (n=15): 325 (34-3152), healthy subjects (n=52): 550 (165-1827) **14 days**: RTX (n=20): 0.03 (0-0.62), Control (n=15): 187 (15-2272), healthy subjects (n=52): 357 (113-1126)

					28 days: RTX (n=20): 0.02 (0-0.18), Control (n=15): 69 (5-953), healthy subjects (n=52): 183 (60-555) p≤0.0001 for RTX vs. placebo control p=0.0155 for placebo control vs. healthy subjects p≤0.0001 for RTX vs healthy subjects <u>Tertiary Response:</u> **7 days:** RTX (n=16): 4.74 (0.18-123), Control (n=15): 926 (200-4293), healthy subjects (n=19): 878 (214-3603) **14 days**: RTX (n=16): 51 (3.5-754), Control (n=15): 1022 (255-4103), healthy subjects (n=19): 704 (156-3171) **28 days**: RTX (n=16): 32 (0.92-643), Control (n=15): 579 (123-2715), healthy subjects (n=19): 664 (103-4285) p≤0.0001 for RTX vs. placebo control p=0.7423 for placebo control vs. healthy p≤0.0001 for RTX vs healthy subjects <u>Quaternary Response:</u> **7 days:** RTX (n=13): 902 (186-4378), Control (n=15): 555 (91-3389), healthy subjects: NA **14 days**: RTX (n=13): 768 (181-3267), Control (n=15): 687 (128-3693), healthy subjects: NA **28 days**: RTX (n=13): 338 (85-1346), Control (n=15): 450 (89-2286), healthy subjects: NA P=0.87 for RTX vs placebo control
3853 Niwa 1978	Cohort study	Varied by treatment; some outcomes evaluated at 5 days others up to 3 months	47 patients with autoimmune diseases (SLE n=22; DLE n=15; diffuse scleroderma n=10; 50 patients with “dermatosis” on steroids for non-autoimmune	**Bacteriophage ΦX174**: Primary response: Serum obtained at baseline and 2 weeks after. Secondary response: dilution of the virus given 3 months after primary immunization and anti-bacteriophage titer measured before and 5 days after booster	**Bacteriophage ΦX174** - No Anti-ΦX titers present at baseline - SLE: primary and secondary response diminished - Secondary Anti-ΦX titers in all patients with autoimmune diseases were depressed - Steroids alone did not influence immune response to anti- ΦX

			diseases, and 50 healthy controls		

References

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Hepatitis A Vaccine

Summary: Five observational studies were included that described the efficacy of hepatitis A vaccine in the setting of a drug of interest for individuals with RMD. One study (Erguven et al (1)) described vaccine non-response in 8.5% (4 of 47) of a population of individuals with JIA; all four patients who did not respond were male patients with active JIA on a TNFi (no other individuals were on TNFi in the study). Maritsi et al (2017) (2) studied patients with JIA on MTX vs. HC and found JIA patients have lower seroprotection rate after first vaccine (vs. HC) but similar seroprotection rates at 7 and 18 months. Belderok et al (3) described a mixed cohort of patients with HIV and RMD on various medications including MTX, TNFi, anakinra, steroids, azathioprine, cyclosporine, and found no differences in proportion of responders by medication type ($p > 0.118$). Similarly, Mertoglu et al (4) found no difference in response rates in patients with SE using vs not using steroids, hydroxychloroquine or rituximab. Maritsi et al (2019) (5) found that use of steroids or NSAIDs did not impact seroconversion and seroprotection among individuals with PFAPA.

Overall quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2861 Erguven 2011	Open label comparative study	8 months	Juvenile idiopathic arthritis (n=47) and 67 healthy controls with no history of	Hepatitis A vaccine: 2 doses of hepatitis A vaccine at 6-month intervals, disease	No statistical tests comparing treatment effect on vaccine response were performed. 4 of 47 patients with JIA in the study did not have a vaccine response – all were male patients with active systemic JIA on TNFi. Only those 4 patients were on TNFi in the entire study cohort.

			previous Hepatitis A vaccination	activity (CHAQ), adverse effects	
2862 Belderok 2013	Interventional comparative study (phase IV)	Up to 36 weeks	Children with HIV (N=100) and children using immunosuppressive medication for rheumatic diseases (N=140): (71, 89%) JIA; 3 (4%) uveitis; 2 (3%) SLE; 1 (1%) panuveitis; 1 (1%) auto-inflammatory syndrome; and 1 (1%) juvenile dermatomyositis	Combined HAV and HBV vaccine twice (at week 0 and again between week 26-30)	Outcome: An anti-HAV concentration ≥20 mIU/mL was considered protective for HAV; subjects who went from negative to protective Ab levels = "responders" For patients with rheumatic diseases on immunosuppressants: Most children (42, 53%) were using only methotrexate, 28 (35%) methotrexate in combination with an anti- TNF agent (n=24), both an anti-TNF and prednisone (n=2), anakinra (n = 1), or prednisone (n = 1), and 10 (13%) used another immunosuppressive regimen (including only anti-TNF (n=4); anti-TNF in combination with cyclosporine (n=1); anakinra (n = 1); azathioprine (n = 1); cyclosporine (n = 1); mycophenolate mofetil (n = 1), or mycophenolate mofetil in combination with prednisone (n = 1)) No differences in proportion of responders by medication type (p > 0.118). HAV response (seroconversion), 1st dose: MTX only: 23 of 40 (58% MTX combined: 9 of 20 (45%) Other treatment: 5 of 7 (71%) HAV response (seroconversion), 2nd dose: MTX only: 37 of 37 (100%) MTX combined: 21 of 21 (100%) Other treatment: 7 of 7 (100%)

3428 Mertoglu 2019	Controlled clinical trial, prospective, not randomized	Jan 2016 – Mar 2017	30 childhood onset SLE ; age 16.7 +/-3.2 yrs antimalarials 27 (90) prednisolone 11 (36.6) immunosuppressive tx 15 (50) vs 39 healthy participants; age 12.2 +/- 3.3	Hepatitis A vaccine Subjects between 1 and 18 years of age received two doses of licensed pediatric formulation of hepatitis A vac- cine (720 EL.U/0.5 ml HAVRIX) Those over 18 years of age received the adult form (1440 EL.U/1 ml) of HAVRIX,	PICO 3: seroconversion rates, % (n) Prednisolone Positive (n=11) 72.7 (8) Negative (n=19) 78.9 (15) Immunosuppresive agents Positive (n=15) 66.6 (10) Negative (n= 19) 93.3 (14) Hydroxychloroquine Pos (n=27) 81.5 (22) Neg (n=3) 66.6 (2) Rituximab Pos (n=2) 50.0 (1) Neg (n=28) 82.1 (23) All p values > 0.05
4088 Martsi 2017	Cohort/case control, non-randomized	Nov 2011-Nov 2014	83 JIA (6.3 +/-2.3)/66% females, on MTX (mean dose 12.5mg/week) Vs 76 Healthy controls-age (5.3 +/-2.7)/sex (45% females) matched	Two inactivated anti-HAV vaccine	Seroconversion rates Month 1 p 0.07 JIA 60 (72.3%) Control 62 (81.6%) Seroprotection rates Month 1 p 0.05 JIA 40 (48.2%) Control 49 (65%) GMT of Anti HAV AB titers 1 month p0.001 JIA 0.00 Control 47.92 The seroconversion rates were similar at all time points for both groups. After primary immunisation, the seroprotection rate was signicantly lower in the JIA group (*p*=0.050). The rates of seroprotection were similar in both groups at 7 and 18 months. The GMT of anti-HAV-IgG titres were signicantly lower in the JIA group at all time points (*p*<0.001);

					Anti-HAV- IgG antibody titres increased signicantly from 1 to 7 months and from 1 to 18 months for both groups (p<0.01).
4097 Martisi 2019	Case- control, prospective observational	Nov 2012- Nov 2014	28 periodic fever, aphthous stomatitis, pharyngitis, and adenitis **(**PFAPA) patients (age 4.4 _/- 2.3)/(43% female) For flare: NSAID 13 pts (46%) NSAID + CS 9 (32%) CS 3 (10%) No med 3 (10%) Vs 76 Healthy controls (age 4.75_/- 2.7)/(45% female)	HAV vaccination	Seroprotection 1 month p = 0.07 PFAPA 27 (92.9%) Control 59 (77.6%) In both groups, seroprotection rates remained elevated 12 months after completion of the study. IgG titer 1 month p=0.3 PFAPA 110 +/- 54 Control 96 +/-34 Mean IgG concentration was not significantly different between the PFAPA and control groups at 1 (P = 0.3), 7 (P = 0.8) and 18 months (P = 0.2). On subgroup analysis of the PFAPA group, the use of CS or NSAID did not affect seroconversion and sero- protection rates or mean anti-HAV-IgG antibody titers. Seroprotection was 89% in PFAPA patients treated with CS vs 92% in patients treated with NSAID, 1 month after the second dose; 98% vs. 100% at 7 months; and 98% vs. 100% at 18 months.

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2. Maritsi DN, Coffin SE, Argyri I, Vartzelis G, Spyridis N, Tsolia MN**.** Immunogenicity and safety of the inactivated hepatitis A vaccine in children with juvenile idiopathic arthritis on methotrexate treatment: a matched case-control study. Clin Exp Rheumatol. 2017;35(4):711-5.
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5. Maritsi DN, Syrmou A, Vartzelis G, Diamantopoulos S, Tsolia MN**.** Immunogenicity and side-effects of the inactivated hepatitis A vaccine in periodic fever, aphthous stomatitis, pharyngitis, and adenitis patients. Pediatr Int. 2019;61(1):104-6.

Hepatitis B Vaccines

Summary: The searches identified 26 observational studies that described the impact of a drug of interest on hepatitis B virus vaccine response for individuals with RMD.

In a study comparing seroconversion after HBV in patients with JIA not on biologics vs on biologics, the outcome was in favor of patients not on biologics but the results are imprecise [(1)].

In a study comparing seroconversion after HBV vaccine in patients with Behcet disease on colchicine to healthy controls, the outcome was similar in both groups [(2)].

Kohagura et al[(3)] found that among 26 children with rheumatic disease vaccinated against HBV while immunosuppressed, 15/26 patients produced anti-HBV antibody after primary vaccinations. 8 of 10 patients (80%) taking MTX and 3 of 11 (27%) taking MMF were seropositive. MMF was independently associated with lower odds of seroconversion when adjusting for dose of prednisone.

Okay et al[(4)] found that among 187 patients with chronic inflammatory disease on TNFi, the effective response rate was found to be significantly lower in certolizumab (0%) and infliximab (27.9%) (p=0.031) than in the other anti-TNF agents (etanercept, golimumab, adalimumab). The adequate response rate was found to be low in certolizumab (33.3%) and infliximab (52.5%), though this was not statistically significant. Use of infliximab and certolizumab, and vaccination 6 months and later after the initiation of anti-TNF therapy were identified as the risk factors of non-response to HBV vaccine. In patients vaccinated >= 6 months after initiation of TNFi, vaccine non-response rate (90.3%) was statistically significantly higher than the vaccine response rate (69.3%)

Belderok et al[(5)] found that among 140 children with RMD on immunosuppression, there was no difference in response to HAV or HBV vaccination based on medication. After the second dose of HBV vaccination, seroconversion rates were 37/40 on methotrexate alone, 25/27 for MTX + combination therapy, and 9/10 in patients on other therapy.

Richi et al(6) found that in 187 RMD patients on immunosuppressive therapy, 153 (81.82%) of 187 patients on biological therapy achieved seropositivity. 39 of 48 responded in the csDMARD group. There was no difference if patients on biologics with or without DMARDS or steroids. Patients on etanercept were more likely to respond to the vaccine than those subjects on the other biologics. Being on RTX was associated with lower odds of response. The seroconversion rate in the biologics group was lower than in the synthetic DMARD group and trended to be lower than in the healthy group. Sixty-four patients on biologics and six on synthetic DMARDs needed a booster (34.22% vs. 12.50%). 44 patients on biologics and 4 on synthetic DMARD required a second vaccination series (23.53% vs. 8.33%).

Kasapcopur et al(7) found that among 39 patients with JIA, 38/39 patients developed an effective antibody response to HBV vaccine. Vaccine responsiveness was not influenced by either methotrexate or prednisolone treatment.

Aytac et al(8) found that among 20 patients with juvenile SLE not immunized to hepatitis B who then received the recombinant HBV vaccine, 80% of patients developed a positive antibody response one month after the third vaccination. Vaccine responsiveness not influenced either from prednisone or AZA treatment.

Moxey-Mims et al(9) found that among 23 pediatric patients on hemodialysis, three of which had lupus nephritis, only the three SLE patients did not response to the Heptavax-B vaccine. All SLE patient were receiving oral corticosteroids.

Haykir Solay et al(10) found that among 109 patients on biologic DMARDs who received the hepatitis B vaccine, only 58/109 (53.2%) of patients responded to HBV vaccination. The highest rate of response was for etanercept (8/9; 88.9%), and the lowest rate of response was with infliximab (2/12; 16.7%). Intermediate rates were noted for adalimumab (30/62; 48.2%) and ustekinumab (18/25; 72%). The one patient on golimumab was a non-responder.

Urganci et al(11) found that among 47 children with IBD, seroconversion rates to HAB and HBV vaccination was lower after primary vaccination series compared to healthy children. No correlation was established between initial vaccine response and the treatment given.

Pratt et al (2018)(12) found that among 391 patients with IBD on immunosuppressive therapy, patients treated with infliximab remained significantly less likely to have seroprotective response to HBV vaccination after adjusting for simultaneous treatment with immunomodulator/corticosteroid therapy (OR 0.38; 95% CI 0.21–0.67; $P < 0.01$). patient at time of vaccination, there was no association between patient exposure to adalimumab and seroprotective HBsAb concentration.

Watts et al(13) found that among pediatric IBD patients who received the HBV vaccine, there was no significant association with the mode of immunosuppression.

Gibsert et al(14) found that among 100 patients with IBD on TNFi or azathioprine, patients on TNFi had a higher cumulative incidence of loss of anti-HBs titers. Risk of losing protective anti-HBs titers was 3-fold higher among patients on anti-TNF therapy compared to azathioprine.

Colucci et al(15) found that among 27 pediatric patients with nephrotic syndrome on anti-CD20 therapy, median anti-HBV IgG titers were significantly reduced at last follow-up compared to baseline. 5/27 patients (19%) were re-immunized against HBV after a mean time of 51 months from the last anti-CD20 infusion, and 11/27 patients (41%) were re-immunized against tetanus after a mean time of 36 months treatment

Belle et al(16) found that among 96 patients with IBD vaccinated against HBV, none of the baseline characteristics of IBD patients, including immunomodulators and antitumor necrosis factor therapy, influenced the vaccine response.

Pratt et al (2019)(17) found that among 149 patients with IBD who underwent vaccination against HBV, patients who received 3 additional doses of vaccine were more likely to achieve seroprotective HBsAb levels than patients who received 1 or 2 doses, after adjusting for age, sex, race, immunosuppressive medication exposure, time between vaccine/titer.

Jaffe et al(18) found that among 292 patients with AHSCT, 64% of patients underwent seroconversion after vaccination for HBV. Response was adversely effected by age and history of GVHD,) but not by donor type or by use of T-cell depletion, adoptive immunotherapy, or rituximab.

Summaries of results that do not specifically comment on drug impact:

Szczygielska et al (2020)(19) found that among 56 patients treated with biologic medications, 22/56 patients had no protective concentration of anti-HBs antibodies. Szczygielska et al (2015)(20) found that among 50 children with RMD on immunosuppressive therapy and vaccinated against HBV with Engerix-B, 25/50 patients had no protective anti-HBsAb concentration.

Haykir et al(21) found that among 75 patients with RMD on biologic medications who underwent vaccination with either standard or high dose Engerix-B, 38/75patients were responders and 37/75 were non-responders.

Brogan et al(22) found that among 17 pediatric patients with CAPS and confirmed NLRP3 mutations on canakinumab, the available vaccine response data demonstrated antibody titers above protective levels at subsequent visits 4-8 weeks later.

Elkayam et al(23) found that among 22 patients with RA who underwent HBV vaccination, 15/22 (68%) patients responded to vaccination with an antibody level of more than 10 IU/l after six months.

Altunoz et al(24) found that among 102 patients with IBD who underwent HBV vaccination, 43% of whom were on immunosuppressive therapy, adequate and effective immune responses were significantly lower in patients compared to controls.

<u>Overall Quality of Evidence: Very low</u>

Table 1: Seroconversion rate of HBV vaccine in JIA patients on biologics compared to patients not on biologics (1)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion in JIA not on biologics	Seroconversion in JIA on biologics	Relative (95% CI)	Absolute (95% CI)		
Seroconversion in JIA on biologics vs not post HBV vaccine												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	6/7 (85.7%)	13/18 (72.2%)	**OR 2.31** (0.22 to 24.32)	**135 more per 1,000** (from 358 fewer to 262 more)	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 2: Seroconversion rate of HBV vaccine in Behcet's disease patients on colchicine compared to healthy controls (2)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Behcet's on Colchicine	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion on day 28 to Hepatitis B												
1	observational studies	serious[a]	not serious	not serious	not serious	none	12/13 (92.3%)	0.0%	**RR 0.99** (0.80 to 1.22)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

Table 3: Additional observational study data not entered into RevMan.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
9766, Khagura, 2022[9766]	Retrospective study	3.5 years	26 children with rheumatic disease (JIA, SLE, JDM, MCTD, or MPA) on immunosuppressive therapy (prednisolone, methotrexate,	Primary HBV series (3 doses); if remained seronegative then a second series was given	15/26 patients (58%) produced anti-hepatitis B surface antibody (anti-HBs) after the primary vaccinations. In 6/7 patients (86%) who received a secondary series of vaccinations, anti-HBs were produced. <u>Proportion of seroconversion by treatment</u> Prednisolone: 10/20 (p = 0.197) Methotrexate: 8/10 (p = 0.109)

<table>
<tr><td></td><td></td><td></td><td>mycophenolate, azathioprine, cyclosporine, adalimumab, and/or tocilizumab)</td><td></td><td>Mycophenolate: 3/11 (p = 0.015)
Azathioprine: 2/2 (p = 0.492)
Cyclosporine: 1/2 (p = 1.000)
Adalimumab: 3/4 (p = 0.614)
Tocilizumab: 1/1 (p = 1.000)
JIA: 8/10 (p = 0.109)
SLE: 3/8 (p = 0.218)
JDM: 3/4 (p = 0.614)
MCTD: 0/3 (p = 0.063)
MPA: 1/1 (p = 1.000)
One medicine: 4/5 (p = 0.356)
Two or more medicines: 11/21 (p = 0.356)

Multivariate analysis showed MMF was a factor impeding seroconversion (OR 0.093, 95% CI 0.014–0.615), not prednisolone.</td></tr>
<tr><td>9785, Okay, 2021[9785]</td><td>Cross-sectional retrospective study</td><td>1 year</td><td>274 total patients
- 187 with chronic inflammatory disease (UC, Crohn’s, AS, RA, psoriasis) on TNFi (IFX, ADA, ETN, GOL, SER)

- 87 healthy controls</td><td>HBV vaccination</td><td><u>Comparison between anti-TNF agents regarding the hepatitis B virus vaccine response</u>
Mean value of anti-HBS (p = 0.139)
IFX: 14
ADA: 43
ETN: 48
GOL: 293
SER: 7

<u>Comparison between the type of chronic inflammatory diseases regarding the hepatitis B virus vaccine response</u>
Mean value of anti-HBS (p = 0.124)
IBD: 15
Rheum: 67
Psoriasis: 33

<u>Univariate analysis of the factors affecting the nonresponse rate of hepatitis B virus vaccine</u>
<table>
<tr><td></td><td>Anti-HBS <10</td><td>Anti-HBS >10</td><td>p value</td></tr>
<tr><td>Age</td><td>43.35</td><td>38.55</td><td>0.003</td></tr>
<tr><td>Male</td><td>50</td><td>62</td><td>0.043</td></tr>
<tr><td>Smoking</td><td>34</td><td>36</td><td>0.048</td></tr>
<tr><td>IFX</td><td>30</td><td>31</td><td>0.331</td></tr>
</table>
</td></tr>
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					ADA 26 47 ETN 17 28 SER 3 0 GOL 1 4 Vax >6 months after TNFi 65 79 0.005 <u>Logistic regression analysis of factors affecting the non-response rate of hepatitis B virus vaccine</u> B OR (95% CI) p value Male -0.896 0.408 (0.201-0.830) 0.013 Vax >6 mo -1.498 0.224 (0.083-0.602) 0.003 IFX 0.991 2.694 (1.203-6.035) 0.016 SER 1.196 3.307 (1.287-8.498) 0.013 Infliximab and sertoluzimab usage, male sex, and vaccination after anti-TNF treatment were risk factors of nonresponse.
2623 Kohagura 2021[3]	Retrospective cohort study	Antibodies measured at 1 month after 1 series of HB vaccinations	26 children with rheumatic diseases who had been vaccinated against hepatitis B during immunosuppressive treatment (Pred, MTX, MMF, Azathioprine, CsA, ADA, TCZ)	Hepatitis B	(A) 15 of 26 (58%) produced anti HBV Ab after primary vaccinations. (B) 8 of 10 patients (80%) taking methotrexate and 3 of 11 (27%) taking mycophenolate mofetil (MMF) were seropositive. (C) MMF was independently associated with lower odds of seroconversion when adjusting for dose of prednisone (odds ratio 0.093, 95% confidence interval 0.014–0.615; p=0.013). (D) In six of seven patients (86%) who received a secondary series of vaccinations, anti-HBs were produced. (E) PSL had no effect on the proportion of seropositive patients (OR 1.030, 95% CI 0.03-34.7; p=0.988).
2857 Okay 2020 (4)	Cohort study	Cross-sectional	187 patients with chronic inflammatory diseases	Hepatitis B vaccine	1) The response rate for anti-HBs of >10IU/L (adequate immune response) was 60.4 and 94.3% (P<0.001) in patients with CID and controls, respectively, and 37.9 and 75.9% (P<0.001) for anti-HBs >100IU/L (effective immune response). See RevMan File.

			(RA=4, AS=33, PsO=94, IBD=56), 87 healthy controls		(2) The median value of anti-HBs (IQR) was significantly higher in the control group (324IU/L (759IU/L)) than in the patients with CID (32IU/L (205IU/L)) (P<0.001). (3) Comparison between anti-TNF agents regarding the hepatitis B virus vaccine response: The effective response rate was found to be significantly lower in certolizumab (0 %) and infliximab (27.9%) (P=0.031) than in the other anti-TNF agents (etanercept, golimumab, adalimumab). The adequate response rate was found to be low in certolizumab (33.3%) and infliximab (52.5%). However, there was no statistical significance (P=0.374). There were no significant differences in median anti-HBs level between TNF (P=0.139). Use of infliximab (OR, 2.694; 95% CI, 1.203– 6.035; P=0.016) and certolizumab (OR, 3.307; 95% CI, 1.287–8.498; P=0.013), and vaccination 6months and later after the initiation of anti-TNF therapy (OR, 0.224; 95% CI, 0.083–0.602; P=0.003) were identified as the risk factors of nonresponse to HBV vaccine. (5) Timing of TNF: In patients vaccinated >= 6 months after initiation of anti-TNF, vaccine nonresponse rate (90.3%) was statistically significantly higher than the vaccine response rate (69.3%) (P=0.005).
2862 Belderok 2013 [5]	Interventional comparative study (phase IV)	Up to 36 weeks	Children with HIV (N=100) and children using immunosuppressive medication for rheumatic diseases	Combined HAV and HBV vaccine twice (at week 0 and again between week 26-30)	Outcome: An anti-HAV concentration ≥20 mIU/mL or an anti-HBs concentration ≥10 mIU/mL was considered protective for HAV or HBV infection respectively; subjects who went from negative to protective Ab levels = "responders" For patients with rheumatic diseases on immunosuppressants: Most children (42, 53%) were using only methotrexate, 28 (35%) methotrexate in combination with an anti- TNF agent (n=24), both an anti-TNF and prednisone (n=2), anakinra (n = 1), or prednisone

			(N=140): (71, 89%) JIA; 3 (4%) uveitis; 2 (3%) SLE; 1 (1%) panuveitis; 1 (1%) auto-inflammatory syndrome; and 1 (1%) juvenile dermatomyositis		(n = 1), and 10 (13%) used another immunosuppressive regimen (including only anti-TNF (n=4); anti-TNF in combination with cyclosporine (n=1); anakinra (n = 1); azathioprine (n = 1); cyclosporine (n = 1); mycophenolate mofetil (n = 1), or mycophenolate mofetil in combination with prednisone (n = 1)) No differences in proportion of responders by medication type (p > 0.118). HBV seroconversion, after 1st dose: MTX only: 5 of 40 (13%) MTX combined: 7 of 26 (27%) Other treatment: 1 of 10 (10%) HBV seroconversion, after 2nd dose: MTX only: 37 of 35 (95%) MTX combined: 25 of 27 (93%) Other treatment: 9 of 10 (90%)
2876 Richi 2020 (6)	Cohort study	Healthy control data collected retrospectively; patient data collected between 2014-2016	187 patients on biologic therapy (RA=58, SpA=73, PsA=30, PsO=9, IBD=6, others=12); (Etanercept=58, adalimumab-55, infliximab=22, golimumab=17, rituximab=14, tocizumab=9, certolizumab=	Hepatitis B vaccine	Seroconversion was considered with anti-HBs titer was >10 <u>Patients on biologics</u>: (1) 153 (81.82%) of 187 patients on biological therapy achieved seropositivity. 39 of 48 responded in the csDMARD group (See Revman for comparison file). (2) No difference if patients on biologics with or without DMARDS or steroids: 81.69% of patients on DMARDs and 88.00% of those not on DMARDs were responders (p = 0.222), 86.36% of subjects on steroids vs. 78.79% of those not on steroid treatment became seropositive (p = 0.285). (3) Patients on etanercept were more likely to respond to the vaccine than those subjects on the other biologics (OR, 3.074, 95% CI, 1.124–8.405, p = 0.023) (4) Being on RTX was associated with lower odds of response (OR, 0.064, 95% CI, 0.019–0.222, p < 0.001)

			8, abatacept=3, anakinra-1), 48 patients on synthetic DMARD, 49 healthy controls.		(5) The seroconversion rate in the biologics group was lower than in the synthetic DMARD group (p = 0.043) and tended to be lower than in the healthy group (p = 0.056) (6) Sixty-four patients on biologics and six on synthetic DMARDs needed a booster (34.22% vs. 12.50%, p = 0.003) (7) 44 patients on biologics and 4 on synthetic DMARD required a second vaccination series (23.53% vs. 8.33%, p = 0.023). Drug, n Responders, n (%) Etanercept, n = 58. -- 53 (91.38) – p=0.023 Adalimumab, n = 55 -- 47 (85.45) Infliximab, n = 22 -- 15 (68.18) Golimumab, n = 17 -- 17 (100.00) – p=0.046 Rituximab, n = 14 -- 4 (28.57) – p<0.001 Tocilizumab, n = 9 -- 7 (77.78) Certolizumab, n = 8 -- 8 (100.00) Abatacept, n = 3 -- 2 (66.67) Anakinra, n = 1 -- 0 (0.00) P>0.05, if not otherwise mentioned. Synthetic DMARDS: (1) Seroconversion was achieved in 93.75% of patients on synthetic DMARDs and 97.96% of healthy controls (p=ns).
3438_Kasapcopur_2004 [7]	Controlled clinical trial not randomized	3 to 6 months	39 JIA (21 male, 18 female); 11 with systemic JIA, 11 with oligoarticular JIA, 10 with polyarticular JIA, and seven	Hepatitis B vaccination (DNNA recombinant vaccine) Alternating two groups: Group I: were	With the exception of one child with systemic JIA, all the children (38/39) developed an effective antibody response. GMT of the anti- HBs concentrations was 134.2 mIU/ml in patients with oligoarticular JIA, 122.2 mIU/ml in patients with polyarticular JIA, 135.91 mIU/ml in patients with systemic JIA, and 93.1 mIU/ml in patients with enthesitis related arthritis. The vaccine responsiveness was not influenced by either

			with enthesitis related arthritis – all in remission 10 male, 10 female were on CS (range 2.5-10mg/dayl mean 6.05mg); 19 patients not on CS 22 (11 male, 11 female) on MTX (10mg/m2/week), 17 were not on MTX vs control group 41 healthy children (21 female, 20 male)	vaccinated at 0,1,and 3 months Group IIL were vaccinated at 0,1,and 6 months	methotrexate or prednisolone treatment. The GMT of patients receiving these drugs, no different from that of children not receiving immunosuppressant treatment: prednisolone, GMT 109.7 IU/ml (n = 20) vs not on prednisolone, GMT 141.05 IU/ml (n = 19); Methotrexate, GMT 114.4 IU/ml (n = 22) vs not on methotrexate, GMT 137 IU/ml (n = 17).
3439 Aytac 2011 [8]	Controlled clinical trial not randomized	7 months	20 juvenile SLE patients were non immunized to hep B (16 female, 4 male; age 13.2 +/- 2.58 yrs)	Recombinant Hepatitis B vaccine Day 0, 1 and 6 months	One month after the third vaccination, 16 of the SLE patients (80%) and all of the healthy controls developed positive antibody response. Vaccine responsiveness not influenced either from prednisone or AZA treatment. The GMT of patients who on prednisone and/or AZA and of patients who were without treatment did not show any statistical

			17 on prednisone (mean 6.25mg; range 2.5-12.5mg/day) 11 on AZA (mean dose 100mg/day) , 3 on MMF (mean dose 1000mg/day) and 2 on HCQ (mean dose 200mg/day) 3 patients not taking any meds. vs 24 Healthy controls (12 female, 12 male; age 8.83+/- 2.72)		significance [prednisone using GMT: 282.6 IU/ml (n=17), prednisone not using GMT: 411.7 IU/ml (n=3), AZA using GMT: 282.8 IU/ml (n=11), AZA not using GMT: 316.2 IU/ml (n=9)]. However, there was an insignificant negative correlation between prednisone dosage and anti-HBs titer (r=-0.08, *p*=0.81).
3482 MoxeyMims 1990 [9]	clinical trial, not randomized	Not reported	Pediatric dialysis patients with negative HepBs Ab (N=23; 3 of whom had SLE nephritis)	Heptavax-B (given at a dose of 2x that recommended in healthy individuals)	Vaccine response: positive anti-HBs antibody - Only the 3 SLE patients did not respond to the vaccine (p=0.0006). All SLE patients were also receiving oral steroids. The one non-SLE patient in the study taking oral steroids responded to the vaccine. - "The effect of steroids on response to the vaccine was significant (p=0.0023)"
3536	Prospective cohort study	One month follow-up	109 patients aged 18 years	All participants received three	<u>Vaccine response (Anti-HBs titer > 10 ug/ml) at one month after last vaccine dose:</u>

Haykir Solay 2019 (10)		after last vaccine dose	or older on biologic DMARDs with baseline seronegativity for HBsAg, anti-HBs and anti-HBc IgG. 57/109 (52%) male, mean (SD) age 44.8 (10.3) years, 49/109 (45%) smokers, 29/109 (27%) obese (BMI 30+). All patients were of Turkish descent. Indications for bDMARD therapy: PsO (n=83), Crohn's disease (n=12), RA (n=6), UC (n=3), hidradenitis suppurativa (n=3), Behcet's	doses (0, 4, 24 weeks) of hepatitis B vaccine, either at standard vaccine dose (20ug/ml; n=73) or high vaccine dose (40 ug/ml; n=36) (unclear how patients were assigned to receive standard vs. high dose vaccine). Biologic DMARDs: adalimumab (n=62), ustekinumab (n=25), infliximab (n=12), etanercept (n=9), golimumab (n=1). No concomitant immunosuppressive medications.	Overall, only 58/109 (53.2%) of patients responded to HBV vaccination. Highest rate for ETN (8/9; 88.9%). Lowest rate for INF (2/12; 16.7%). Intermediate rates for ADA (30/62; 48.2%) and UST (18/25; 72%). The one patient on golimumab was a non-responder. No significant differences in response rates by age, gender, BMI, smoking status, or disease. No difference in response rates by duration of bDMARD therapy (52.2% vs. 54.8%; p=0.797).

			disease (n=1), or AS (n=1).		
4017_Urganci_2013 (11)	Cohort/ case control, prospective	2000-2012	47 children w IBD; all on 5-aminosalicylic acid. 13 pts on CS (prednisolone 1-2mg/kg/day,max 60mg); AZA (2mg/kg/day) in 8 pts age ranged 3-17 yrs; male: female ratio 1.13 47 pts without evidence of earlier exposure to Hep B received Hep B vaccine; 23 of them neg for HAV AB received Hep A vacc vs 50 healthy controls; age-sex matched (17 girls, 33 boys; mean	For those patients not immune to HAV or HBV: (no one received combined hep A/B vacc) Hepatitis A vaccine— 2 doses given 6 months apart Hepatitis B vaccine – 3 doses at months 0,1, and 6	Seroconversion rate of patients with IBD was lower after primary vaccination series vs healthy children (70.2% vs 90%) Overall seroconversion rates 1 month after a single booster dose were 85.1% in patients with IBD and 96% in controls. No correlation was established between initial vaccine response and the treatment given. Also, no reduction in AB response was observed during treatment among patients with IBD. Response to HB primary Vacc Pt group, (n=47) 33/47 (70.2) Control group (n=50) 45/50 (90) p 0.02 Overall response to HBV after single booster dose Pt group 40/47 (85) Control group 48/50 (96) p 0.08 Response to HBV in primary nonresponders after single booster dose Pt group 7/14 (50) Control group 3/5 (60) p 0.67

			age 9.2+/- 1.7 yrs)		
403 Pratt, 2018 [12]	retrospective cohort study	January 2000 and December 2014	IBD, n=391	EMR review of Hep B vaccination. Patients grouped by type(s) of medication prescribed during the 6 month time-period of interest: (i) anti-TNF: adalimumab (ADA), infliximab (IFX), certolizumab pegol (CZP) or golimumab (GLM); (ii) immuno-modulator (IMM): 6-mercaptopurine (6MP), azathioprine (AZA), or methotrexate (MTX); (iii) both anti-TNF and IMM (ie, dual therapy); and (iv) 5-ASA/none of the above (reference arm)	In our multivariate analysis of medication-specific exposures (see Table 4, Fig. 2), patients treated with IFX remained significantly less likely to have seroprotective HBsAb ≥10 IU/l after adjusting for simultaneous treatment with immunomodulator/corticosteroid therapy (OR 0.38; 95% CI 0.21–0.67; P < 0.01). This significant association remained after adjusting for patient age at time of titer measurement (OR 0.30; 95% CI 0.16–0.56; P < 0.001) and interval time since vaccination. After adjusting for simultaneous medication exposure and age of patient at time of vaccination, there continued to be no association between patient exposure to ADA and seroprotective HBsAb concentration.
4463 Watts 2017 [13]	Prospective cohort	One year	IBD 5-18 years old	Previously received full series of the hepatitis B vaccine	PICO 3 There was no significant association with the mode of immunosuppression: corticosteroids (P=0.88), immunomodulators (P=0.19), and biologics (P=0.26).

5011_Gisbert 2013 [14]	Retrospective cohort	Unclear	100 pts with IBD. Thiopurines v/s anti TNF	HBV 0,1,2 mo.	Univariate analysis TNF: a higher cumulative incidence of loss of anti-HBs titers if tx with anti-TNF drugs. This was not noted on pts with thiopurine. Multivariate analysis: Tx with anti-TNF only factor associated with a higher risk of loss of anti-HBs titers Risk of losing protective anti-HBs titers was 3-fold higher among patients on anti-TNF therapy Cumulative incidence of loss of anti-HBs titers was 2% after 6 months and 15% after 12 months. Incidence rate of loss of protective anti-HBs titers was 18% per patient-year. Baseline (after vaccination) anti-HBs titers were lower among patients whose titers became negative during the follow-up than among those who maintained them >10 IU/L (191 versus 515 IU/L; p<0.001). Treatment with anti-TNFs was the only factor associated with a higher risk of loss of anti-HBs (hazard ratio 3.1, p=0.03).
616 Szczygielska, 2020 [19]	Cross-sectional study	N/A	Patients with JIA treated with biologic drugs, n=56	All children were vaccinated according to the 0, 1, 6 months schedule with the Engerix-B vaccine (GlaxoSmithKline) or Euvax-B (LG Chem Life Sciences, Po-land) or Hepavax-Gene TF (Janssen-Cilag International).	Of 56 patients studied, 22 (39.33%) had no protective concentration of anti-HBs antibodies (the concentration was lower than 10 mIU/ml) and in the remaining 34 cases (60.7%) seroprotection was confirmed (anti-HBs antibody concentration >10 mIU/ml). No comparison group.

627 Szczygielska, 2015 [20]	Cross-sectional study	N/A	children receiving immunosuppressive therapy due to inflammatory systemic connective tissue diseases and vaccinated against hepatitis B in infancy, N=50 Control group=50 healthy children	All children were vaccinated according to the 0, 1, 6 months schedule with the Engerix-B vaccine	In the group of children with AIRDs, in 25 (50%) cases no protective anti-HBsAb concentration was found, including concentration below 10 mIU/ml in 18 (36%) children, and the absence of anti-HBsAb (0 mIU/ml) in 7 (14%) children. In the control group, seroprotection was found in 48 children (96%): in 32 children (62%) the concentration was > 10 mIU/ml and in 16 children (34%) it was < 10 mIU/ml. In 2 children (4%) no anti-HBsAb concentration (0 mIU/ml) was detected. The differences were statistically significant ($p < 0.0001$).
641, Haykir, 2020 [21]	Cohort study		N=75 patients using biologic drugs with negative serology of HBV admitted to the outpatient clinic of Infection Disease and Clinical Microbiology between January and December 2018 were	20 µg as standard dose or 40 µg as high dose of HBV vaccine intramuscularly (Engerix-B 20 µg/mL, GlaxoSmithKline) in a three dose schedule (of 0, 4 and 24 weeks).	Forty-one (54.7%) patients received standard dose HBV vaccine, and 34 (45.3%) patients re-ceived high dose HBV vaccine. In all participants, 38 (50.7%) patients were “responders” and 37 (49.3%) were “non-responders”. Twenty-three (60.5%) of the patients who received standard dose HBV vaccine were “responders” and 15 (39.5%) of the patients who received high dose HBV vaccine were “non-responders”.

			included into this study.		
6852 Colucci 2019 [15]	Case-series	81 months	27 frequently-relapsing (n = 2) or steroid-dependent nephrotic syndrome (n = 25) pediatric patients.	HBV, tetanus and measles/mumps/rubella (MMR) vaccines (not a primary intervention)	Anti-CD20 treatment reduced the mean number of relapses/year from 3.4 (range1–5) to 0.6 (range0–2) at last follow-up. Serum immunoglobulin concentrations at last follow-up for median levels of IgG compared to baseline levels: 701 vs. 610mg/dl at baseline; p=0.19) and IgA (138 vs.124mg/dl at baseline; p=0.53). Light reduction was observed for IgM median levels (76 vs. 104 mg/dl at baseline; p=0.05). Median anti-HBV IgG titers were significantly reduced at last follow-up compared to baseline. 5/27 patients (19%) were re-immunized against HBV after a mean time of 51 months (range23–81 months) from the last anti-CD20infusion, and 11/27 patients (41%) were re-immunized against tetanus after a mean time of 36 months (range10–82months).
7047 Brogan 2019 [22]	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID.	In core study, 7/17 (41%) patients received a total of 31 vaccine injections (10 different types of inactivated vaccines). Vaccine response data available for 18/31 (58.1%) injections. All showed a positive response (Ab titers increased above protective level). For all 31 vaccine injections, including those without a pre-dose Ab titer, protective post-vaccine Ab titers were maintained throughout the trial. In the extension study**,** 4/17 (24%) patients received a total of 20 vaccine injections (8 different types of inactivated vaccines). 17/20 (85%) of injections had data available to assess vaccine response. In 16/17 (94.1%) cases, protective Ab titers were achieved post-vaccine.

			least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	Patients received inactivated vaccinations as part of national childhood vaccination programs. No live vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination ("Pre-dose"), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). <u>Included vaccines:</u> HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	For 19/20 (95%) vaccine injections, including those without a pre-dose Ab titer, protective post-vaccine Ab titers were maintained throughout the extension study

7620 Elkayam 2002 [23]	Case control	7 months	22 pts with RA who received hep B vaccination and 22 pts with RA who refused the vaccine.	Hepatitis b vaccine (3 doses)	Fifteen of 22 (68%) patients responded to vaccination with an antibody level of more than 10 IU/l after six months—the mean (SD) antibody level of the responders after six months was 302 (SD 54) IU/l. Humoral response to hepatitis B vaccination is expected to be more than 85% in young healthy adults [as per a reference]
4338, Belle, 2015[16]	Case-control	6 months	96 patients with IBD 68 healthy controls	HBV	Level of anti-HBs was greater than 10 IU/l in 80.2 and 94.1% (p=0.0115) of IBD patients and healthy controls, respectively. Anti-HBs levels greater than 100 IU/l were seen in 45.8 versus 77.9% (p<0.0001) of IBD patients and healthy controls, respectively. The median level of anti-HBs was significantly higher in healthy controls (497.0 ± 386.2) than in IBD patients (253.9 ± 34.5) (p<0.0001). None of the baseline characteristics of IBD patients, including immunomodulators and antitumor necrosis factor therapy, influenced the vaccine response (p values not given). Ileal disease was the only factor associated with a lower response to the vaccine (odds ratio = 3.2; 95% confidence interval = 1.0–9.7; p=0.049). IBD patients with no immunomodulator and no anti-TNF therapy (N = 16) as reference; patients on immunomodulators (thiopurine or MTX) (N = 48); patients on anti-TNF drugs (infliximab or adalimumab) (N = 73); and patients on combination therapy (N = 42). - There was no difference in terms of vaccine response rate between these four subgroups when using anti-HBs more

					than 10 IU/l or more than 100 IU/l to define vaccine response. - Median titers of anti-HBs did not differ between these four subgroups, being, respectively, 246.25 ± 330.88, 275.93 ± 369.99, 273.54 ± 357.58, and 306.91 ± 385.49 (p values not significant/not reported)
4388, Pratt, 2019[17]	Retrospective cohort	n/a	149 patients with IBD (57% on AZA, 6MP, or MTX; 46.3% on TNFi; 26.2% on dual therapy; 17.4% on glucocorticoids)	HBV	Patients of all ages and age ≥ 40 years, who received 3 additional doses of vaccine, were more likely to achieve seroprotective HBsAb levels than patients who received 1 or 2 doses (OR 1.77, P = 0.01; OR 1.9, P = 0.03, respectively, after adjusting for age, sex, race, immunosuppressive medication exposure, time between vaccine/titer).
6205, Altunoz, 2012 [24]	Prospective cohort	Two years	102 patients with IBD (39 with Crohn's, 63 with UC) 52 healthy controls	HBV	AIR and EIR were significantly lower in patients than in controls (p<0.001), but similar between patients with CD and UC (p=0.302). 43% patients were on immunosuppressive therapy before vaccination. After vaccination, 76% of patients had AIRs and 53% of patients had EIRs, whereas 100% of the controls had AIRs and 87% of the controls had EIRs, respectively (p<0.001 and p<0.001, respectively). AIR = adequate immune response EIR = effective immune response
4123, Jaffe, 2006 [18]	Observational study	12 months	292 patients with allogeneic hematopoietic cell transplants	HBV (recombinant)	64% of patients seroconverted - Response was adversely affected by age older than 18 years (p<.01) and history of prior chronic GVHD (p<.001) but not by donor type or by use of T-cell depletion, adoptive immunotherapy, or rituximab.

					25 patients vaccinated with rHBV received rituximab after HCT - 16/25 patients lacked anti-HBs at transplantation, 23/25 lacked detectable anti-HBs titers at the time of vaccination. - 12 patients seroconverted, 11 did not respond, and 2 patients retained immunity following rHBV.

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Human Papillomavirus Vaccines (HPV)

Summary: Six observational studies addressed this question for the HPV vaccine. (1-5)[10055] Two observational studies that compared SLE patients to healthy controls (1, 2) showed no significant difference in most measures for immunogenecity of HPV vaccine between the groups. Esposito et al.(3) found that among 21 females with JIA, there was no difference in vaccine response between the group on NSAIDs, MTX or Etanercept. Soybilgic(4) et al studied 27 patients with SLE (taking hydroxychloroquine (100%); prednisone (59.2%); mycophenolate mofetil (33.3%); azathioprine (33.3%); methotrexate (22.2%); at 7 months (n=16), seropositivity post-vaccine was >94% for HPV 6, 11, 16 and 18. Anti-

HPV 6 and 18: 94.4% seropositivity, Anti-HPV 11 and 16: 100% seropositivity. Heijstek et al.(5) found that among 68 patients with JIA who underwent HPV vaccination, there was no effect of methotrexate on HPV16 antibodies (p=0.79) or HPV18 antibodies (p=0.37) detected. All patients on methotrexate except for one (67/68) were seropositive at 12 months after the first vaccination. All patients on anti-TNF treatment were seropositive after vaccination. Finally, one large retrospective study of pediatric patients with rheumatic diseases or IBD received an HPV single dose booster; 68% of patients seroconverted and medication (anti-TNF/IL-6, DMARDs) was not associated with non-response (age >11 years was the only factor significantly associated with non-response to booster).[10055]

Overall quality of evidence across all critical outcomes: Very low

Table 1: HPV vaccine in SLE patients compared to healthy controls (1).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
seroconversion for HPV-6 at 12 months												
1	observational studies	serious[a]	not serious	not serious	not serious	none	32/39 (82.1%)	44/45 (97.8%)	**RR 0.84** (0.72 to 0.98)	**156 fewer per 1,000** (from 274 fewer to 20 fewer)	⊕◯◯◯ Very low	Favors controls
Seroconversion for HPV-11 at 12 months												
1	observational studies	serious[a]	not serious	not serious	not serious	none	34/38 (89.5%)	43/44 (97.7%)	**RR 0.92** (0.81 to 1.03)	**78 fewer per 1,000** (from 186 fewer to 29 more)	⊕◯◯◯ Very low	No difference
Seroconversion for HPV-16 at 12 months in SLE v controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	37/39 (94.9%)	43/44 (97.7%)	**RR 0.97** (0.89 to 1.06)	**29 fewer per 1,000** (from 107 fewer to 59 more)	⊕◯◯◯ Very low	No difference

Seroconversion for HPV-18 at 12 months in SLE v controls

1	observational studies	serious[a]	not serious	not serious	not serious	none	29/38 (76.3%)	32/40 (80.0%)	**RR 0.95** (0.75 to 1.21)	**40 fewer per 1,000** (from 200 fewer to 168 more)	⊕◯◯◯ Very low	

Persistence of HPV-6 response at 5 years in SLE v controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/27 (88.9%)	32/33 (97.0%)	**RR 0.92** (0.79 to 1.06)	**78 fewer per 1,000** (from 204 fewer to 58 more)	⊕◯◯◯ Very low	No difference

Persistence of HPV-11 at 5 years, SLE v controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	26/31 (83.9%)	32/33 (97.0%)	**RR 0.86** (0.73 to 1.02)	**136 fewer per 1,000** (from 262 fewer to 19 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Persistence of HPV-16 immunogenicity at 5 years, SLE v controls												
1	observational studies	serious[a]	not serious	not serious	not serious	none	32/34 (94.1%)	32/32 (100.0%)	**RR 0.94** (0.85 to 1.04)	**60 fewer per 1,000** (from 150 fewer to 40 more)	⊕◯◯◯ Very low	No difference
Persistence of HPV-18 immunogenicity at 5 years, SLE v control												
1	observational studies	serious[a]	not serious	not serious	not serious	none	24/25 (96.0%)	23/24 (95.8%)	**RR 1.00** (0.89 to 1.12)	**0 fewer per 1,000** (from 105 fewer to 115 more)	⊕◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosses significant effect and no-effect lines

Table 2: HPV vaccine in cSLE patients compared to healthy controls (2)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cSLE	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seropositivity HPV 16 after 2/2 doses cSLE vs Healthy Control												
1	observational studies	serious[a]	not serious	not serious	not serious	none	14/14 (100.0%)	28/30 (93.3%)	**RR 1.05** (0.91 to 1.21)	**47 more per 1,000** (from 84 fewer to 196 more)	⨁◯◯◯ Very low	No difference
Seropositivity HPV 18 after 2/2 doses cSLE vs Healthy Control												
1	observational studies	serious[a]	not serious	not serious	not serious	none	14/14 (100.0%)	25/30 (83.3%)	**RR 1.18** (0.97 to 1.42)	**150 more per 1,000** (from 25 fewer to 350 more)	⨁◯◯◯ Very low	
Seropositivity HPV 16 after 2/3 doses cSLE vs Healthy Control												
1	observational studies	serious[a]	not serious	not serious	not serious	none	14/14 (100.0%)	126/142 (88.7%)	**RR 1.09** (0.98 to 1.22)	**80 more per 1,000** (from 18 fewer to 195 more)	⨁◯◯◯ Very low	No difference
Seropositivity HPV 18 after 2/3 doses cSLE vs Healthy Control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	cSLE	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	14/14 (100.0%)	112/142 (78.9%)	**RR 1.23** (1.08 to 1.40)	**181 more per 1,000** (from 63 more to 315 more)	⨁◯◯◯ Very low	

Seropositivity HPV 16 after 3/3 doses cSLE vs Healthy Control

1	observational studies	serious[a]	not serious	not serious	not serious	none	31/31 (100.0%)	119/123 (96.7%)	**RR 1.02** (0.97 to 1.08)	**19 more per 1,000** (from 29 fewer to 77 more)	⨁◯◯◯ Very low	No difference

Seropositivity HPV 18 after 3/3 doses cSLE vs Healthy Control

1	observational studies	serious[a]	not serious	not serious	not serious	none	31/31 (100.0%)	112/123 (91.1%)	**RR 1.08** (1.01 to 1.17)	**73 more per 1,000** (from 9 more to 155 more)	⨁◯◯◯ Very low	Favors cSLE

CI: confidence interval; **RR:** risk ratio

Explanations

a. Open-label study

Table 3: Additional data not entered into RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
10055, Aljaberi, 2021[10055]	Retrospective chart review	Jan 2011-Jan 2017; timepoint of ab check post-vaccine was not defined	354 peds rheum, 226 IBD patients screened for HBV surface antibody titers -41-44% on TNFi -11-18% on nonbiologic DMARDs	HPV single dose booster	>40% of patients were on TNFi 71% of patients were nonimmune to HBV on screening (409 patients). Age 11-18 was assoc/ with lower baseline seroprotection; pts on medications had lower rates of immunity as well (p=0.08) 291 of these patients rec'd single dose HBV booster 68% of patients who rec'd booster seroconverted. Age >11 was the only factor associated w/ non-response to booster (p=0.01) Diagnosis, medication (anti-TNF/IL-6, DMARDs) were all not significant
4138 Esposito 2014(3)	Cohort	7 months	21 female patients aged 12-25 years w stable JIA - 10 (47.6%) NSAIDs - 5 (23.8%) MTX - 6 (28.6%) etanercept vs 21 healthy females	HPV vaccine (cervarix)	It did not seem that anti-rheumatic drugs influenced the immune response to bivalent HPV vaccine. No significant difference was observed comparing the 10 JIA patients who were receiving daily NSAID drugs, and the 5 JIA patients treated with methotrexate. No significant difference found considering together the 15 JIA patients treated with non-steroidal anti-inflammatory drugs or methotrexate and comparing them with the 6 JIA patients treated with etanercept. <u>GMT</u> *Before the third dose (month 6)*: HPV 16 JIA group 274.40 (6.0) HPV 16 healthy 487.43 (12.2) HPV 18 JIA group: 302.03 (7.6) HPV 18 healthy 463 (11.6) *One month s/p 3rd dose (month 7):* HPV 16 JIA group 6834.38 (170.9); p<0.05 vs. controls HPV 16 healthy 12,177.48 (304.4) HPV 18 JIA group 5120 (128)

					HPB 18 healthy 6347.86 (158.7)
7676 Soybilgic 2013(4)	Cohort	7 months	27 SLE patients (aged 12 to 26 years), 100% female; 16 evaluable at 7 months. Treatments included hydroxychloroquine (100%); prednisone (59.2%); mycophenolate mofetil (33.3%); azathioprine (33.3%); methotrexate (22.2%). The mean prednisone dose was 12.6 mg (range 0–36).	3 doses of 0.5 ml of recombinant, quadrivalent HPV vaccine (Gardasil)	At 7 months (n=16), seropositivity post-vaccine was >94% for HPV 6, 11, 16 and 18. Anti-HPV 6 and 18: 94.4% seropositivity Anti-HPV 11 and 16: 100% seropositivity
4084, Heijstek, 2014 (5)	Observational cohort	6 months	68 patients with JIA 55 healthy controls	HPV (bivalent 16/18)	All participants were seropositive for HPV16 and HPV18 at 7 months. One patient (1/68) turned seronegative at 12 months for HPV16/18. No significant differences were found between patients and controls in HPV-specific antibody concentrations; however, antibody concentrations were consistently lower in patients. No effect of methotrexate on HPV16 antibodies (p=0.79) or HPV18 antibodies (p=0.37) was detected. All patients on methotrexate except for one (67/68) were seropositive at 12 months after the first vaccination. All patients on anti-TNFα treatment were seropositive after vaccination. HPV vaccination did not aggravate JIA disease.

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Meningococcal Vaccines

Summary: Three observational studies were included that described the impact of a drug of interest on meningococcal vaccine response for individuals with RMD. Stoof et al (1) found that among 127 patients with JIA, methotrexate did not affect the the decline of MenC-specific IgG concentrations. Biological treatment induced a trend towards accelerated decay in MenC-specific antibodies.

Summaries of results that do not specifically comment on drug effect:
Ronaghy et al (2) found that PBMC T-cell proliferative responses to vaccine antigens increased after vaccination among 28 patients with JIA, mostly in the poly-JIA subgroup and not the oligoarticular subgroup.

Morgan et al (3) found that among 92 patients with small and/or medium vessel vasculitis, there significant improvement in the percentage of patients who had antibody titers above the threshold. For MenA, titers increase in 33% of patients to 79%. For MenC, titers increased from 9% to 54% of patients.

Table 1. Data from observational studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
5014_Stoof 2014	Retrospective cohort	8 years	127 pts with JIA 1527 controls Pts on methotrexate, biologics (TNF and IL6), steroids	Meningococcal serogroup C(MenC)	Methotrexate treatment did not affect the decline of MenC-specific IgG concentrations Biological treatment induced a trend towards accelerated decay in MenC-specific antibodies, with a faster predicted decay rate in 92.6% of patients.
9018 Ronaghy 2011	Case-control	2 months	28 polyarticular JIA patients and 20 healthy adults	MenC vaccination	PBMC T-cell proliferative responses to vaccine antigens increased after vaccination in the Healthy Controls (1.9±1.8 rose to 6.8±6.7, change 4.9, p=0.001, N=13) and the JIA patients (4.2±1.9 to 15.3±8.9, change 11.1, p=0.005, N=16), but mostly in PolyJIA subgroup (6.1±5.0 to 23.4±18.2, change 17.3, p=0.02, N=8) and not the oligoarticular JIA (2.3±1.3 to 7.2±4.6, change 4.9, p=0.066, N=8).
647 Morgan 2016	Cohort-case control	Median FU post vaccination 4.6 years, total patient FU was 363	92 patients with small or medium-sized systemic vasculitis (EGPA- 7 patients, GPA-59 , MPA-22 or classical PAN- 4) in stable	7-valent conjugate pneumococcal vaccine (Prevnar) Haemophilus	Median AB titers for all the vaccine components increased at 4 weeks postvaccination 4 weeks postvaccination, significant improvement in the percentage of patients who had AB titers above the threshold, although there was variability in the response between antigens (antibody response above the protective threshold for each

		patient-years (none lost to FU)	remission > 6 months (BVAS = 0), s/p CYC and steroid induction but not within 6 months, had not received RTX within 6 months, on <10mg of prednisone per day, currently on no more than 1 immunosuppressant + prednisolone, no active infections, not pregnant, no hx of previous severe reaction to vaccination or received vaccination to proposed vaccines; age 66 (53-74) 81 patients still taking prednisolone at median of 5mg/day at time of vaccination. 9 patients on Rituxan, 35 on AZA,	influenzae type b (Hib) Meningococcal (Men) group C conjugate vaccine and Men polysaccharide groups A, C, Y, and W135 vaccine	antigen median of 46% [IQR 39–58%]) Serotype PreVacc Post Vacc P MenA 33 79 0.029 MenC 9 54 0.006 MenW135 2 23 0.4 MenY 12 49 0.001

			35 on mycophenalate		

References

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3. David Morgan M, Richter A, Al-Ali S, Flint J, Yiannakis C, Drayson M, et al. Association of Low B Cell Count and IgG Levels With Infection, and Poor Vaccine Response With All-Cause Mortality in an Immunosuppressed Vasculitis Population. Arthritis Care Res (Hoboken). 2016;68(6):853-60.

Measles, Mumps, Rubella (MMR) Vaccines

Summary: Four observational studies were included that described the impact of a drug of interest on MMR vaccine response for individuals with RMD.

Ingelman-Sundberg et al (1) found that among 50 pediatric patients with RMD, titers to measles and rubella did not differ between subjects treated with any DMARD (MTX or MTX + TNFi) compared to NSAID-treated patients, though tetanus titers were significantly lower in the DMARD-treated group. For children who had received a tetanus booster, patients treated with any DMARD had lower tetanus serum IgG compared to healthy controls and NSAID-treated patients.

Borte et al (2) found that among 15 pediatric patients with JIA who received the MMR vaccine, there was no statistically significant difference in antibody titer or virus-specific IFN-producing T cells in patients treated with low-dose MTX for at least 6 months prior to vaccination (n=5) compared to heathy controls. Among patients treated with low-dose MTX +TNFi, there was a trend towards a decline of virus-specific IFN-producing T cells.

Maritsi et al (3) found that among 41 patients with ERA, longer duration with TNFi treatment directly correlated to a lower antibody concentration after MMR vaccination. There was no difference detected between patients on anti-TNF monotherapy compared to combined treatment with a synthetic DMARD.

Caldera et al (4) found that among 46 patients with IBD who underwent MMR vaccination, there was no difference in antibody concentrations were found among the IBD treatment groups (azathioprine monotherapy, TNFi monotherapy, or combination therapy).

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2297 Ingelman-Sundberg 2016	Cross-sectional study		50 patients (age 2.9–18.3) were recruited from the rheumatology clinic at Astrid Lindgren Children's hospital, Stockholm, Sweden. 31 healthy age-matched controls All patients and healthy controls were included and sampled between November 2011 and June 2014.	All children in the tetanus group had received 3 doses of diphtheria–tetanus–pertussis (DTP) vaccine, given before the age of 1 year, and the corresponding measles/rubella group had received 1 dose of measles–mumps–rubella (MMR) vaccine, given at the age of 18 months. The booster doses of the studied vaccines are given at preschool/school age in Sweden, within a time span	4 groups here with NSAID group having only 8 patients. We compared all subjects with any DMARD treatment (MTX + anti-TNFi therapy or MTX only) to all subjects without DMARD (healthy controls or NSAID-treated patients). The measles and rubella titres did not differ between these groups (data not shown), but the tetanus titres were significantly lower in DMARD-treated patients with booster. Subsequent analysis of protection rate revealed that DMARD-treated patients were not more likely to have sub-protective levels (<0.1 IU/ml), compared to individuals without DMARD treatment (data not shown). For children who had received a tetanus booster, patients treated with any DMARD had lower tetanus serum IgG compared to healthy controls and NSAID-treated patients. Patients without a measles booster had lower levels of measles-specific memory B cells, but all vaccine-specific memory B cells were preserved in patients with booster. We furthermore found that the mature B cell compartment was phenotypically similar between patients and healthy controls.

				of either 2 (DTP) or 3 years (MMR). Due to the retrospective study design, it was not possible to determine the exact duration between vaccination and inclusion in all cases.	
2629 Borte 2009	prospective nested case control		15 patients w JIA (ages 6-17); on low dose MTX alone or MTX +etanercept group 1: (n=5) JIA w completed MMR I and II vacc, tx w low dose MTX (!0mg.m2 body surface, once weekly, SD 7.5-15mg/person) group 2A: (n=5)JIA s/p MMR vacc while tx w low dose MTX > 6 months prior to vaccc date group 2b: (=5)JIA + low-dose MTX + TNF RA etacercept (0.4mg/kg body wt, twice weekly 22 healthy controls	MMR	PICO 3: (mean value and interquartile range) Humoral immunity Group 1 vs control Measles 194.3 (0-410) vs 1231.7 (461-1730) p=0.045 Mumps 588.6 (0-760) vs 974.3 (310-990) p=0.258 Rubella 19.4 (14-19) vs 49.2 (21-73) p=0.110 Humoral immunity Group 2a vs control Measles 652 (0-600) vs 1372 (1320-1460) p=0.116 Mumps 996 (720-1000) vs 1352 (920-1760) p=0.465 Rubella 36 (20-46) vs 41.2 (24-56) p=0.530 Humoral immunity Group 2b vs control Measles 944 (640-1320) vs 744 (460-600) p=0.346 Mumps 1276 (540-1760) vs 824 (720-820) p=0.675 Rubella 36 (20-46) vs 34.8 (18-56) p=0.834 Cellular immunity Group 1 vs control Measles 32.3 (26.5-41) vs 14.3 (5.5-21) p=0.038 Mumps 45.4 (31.5-47) vs 31.8 (22-42.5) p=0.522 Rubella 14.1 (8-20) vs 8.7 (5.5-11.5) p= 0.176 Cellular immunity Group 2a vs control Measles8.4 (3-16) vs 11 (4-15) p=0.675 Mumps 15.2 (4-24) vs 24.8 (18-26) p=0.530 Rubella 6.9 (4-11) vs 8 (4-13) p= 0.599

					Cellular immunity Group 2b vs control Measles 5.4 (2-5) vs 16.6 (8-23) p=0.076 Mumps 14.4 (4-22) vs 24.2 (20-27) p=0.142 Rubella 5.8 (4-6) vs 9.6 (7-13) p= 0.171 Group 2a: whilst receiving MMR revaccination we observed no statistical relevant differences in antibody titres or virus-specific IFN- producing T cells when compared with untreated healthy controls Group 2b tended towards a decline of virus-specific IFN- producing T cells, but not within the range of statistical significance. Humoral immunity, in terms of virus-specific IgG antibodies, on the other hand seemed to be slightly increased
5156 Maritsi	Prospective cohort	3 years	41 - ERA 149 controls	MMR received at age 2 and age 5	- Longer duration with anti TNFa treatment directly correlated to lower antibody concentration. - No differences detected between patients on anti TNF monotherapy vs combined treatment with a synthetic DMARD
4246, Caldera, 2019[4]	Cross-sectional studyl	8 months	46 patients with IBD (16 patients on thiopurine monotherapy, 15 patients on anti-TNF therapy, 15 patients on combination therapy) 20 healthy controls	MMR	All subjects had measurable antibody concentrations to the three vaccine viruses. No difference in the antibody concentration among the groups <u>Measles</u> (p=0.45) - IBD 667 mIU/ml - HC 744 mIU/ml <u>Mumps</u> (p = 0.62) - IBD 339 EU/ml - HC 402 EU/ml <u>Rubella</u> (p=0.11) - IBD 26 mIU/ml - HC 62 mIU/ ml No differences in antibody concentrations were found among the IBD treatment groups <u>Measles</u> (p=0.25) - AZA 767 mIU/ml - TNF 1610 mIU/ml

					- Combo 375 mIU/ml Mumps (p=0.09) - AZA 394 mIU/ml - TNF 362 mIU/ml - Combo 270 mIU/ml Rubella (p=0.80) - AZA 32 mIU/ml - TNF 29 mIU/ml - Combo 14 mIU/ml

References

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Polio Vaccines

Summary: One observational study evaluated the effect of corticosteroid on immunity to polio and found no association with steroid use and lack of humoral immunity to polio (1).

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational study

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
6208 Marchand-Janssen 2011	Cross-sectional study	Looking for humoral immunity to diptheria, tetanus, and poliomyelitis in mixed RMD popul.	186 mixed RMD patients in total, on a variety of immunosuppressant medications.	n/a	Of the 55 pts documented to be up-to-date for polio, 100% had high-level immunity (>/= 8). CS was not associated with lack of humoral immunity to tetanus or poliomyelitis

References

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Tetanus, Diphtheria, Pertussis (TDaP) Vaccine

Summary: Eighteen observational studies and two RCTs described the impact of a drug of interest on Tdap vaccine response for individuals with RMD.

Ingelman-Sundberg et al [1] found that among 50 pediatric patients with RMD, titers to measles and rubella did not differ between subjects treated with any DMARD (MTX or MTX + TNFi) compared to NSAID-treated patients, though tetanus titers were significantly lower in the DMARD-treated group. For children who had received a tetanus booster, patients treated with any DMARD had lower tetanus serum IgG compared to healthy controls and NSAID-treated patients.

Niwa et al [2]found that among 22 patients with SLE only 1/22 patients did not develop antibody formation. Steroids alone did not influence secondary responses to diphtheria toxoid.

Battafarano et al [3] found that among 73 patients with SLE, there was a trend toward decreased antibody response in patients treated with CYC, AZA, or prednisone, although this was not statistically significant. There was no significant difference for any individual medication or combination of medications, or by medication dosage.

Marchand-Janssen et al [4] found that among 186 patients with RMD, factors associated with absent humoral immunity to diphtheria were age >50 years and corticosteroid therapy. Corticosteroid use was not associated with lack of humoral immunity to tetanus or poliomyelitis.

Holmes et al [5] demonstrated that among 98 patients with rheumatoid arthritis, female sex and methotrexate use were correlated with reduced immunity to pertussis.

Stohl et al [6] found that in pooled data from BLISS-52 and BLISS-76, patients with SLE treated with belimumab did not have a significantly decreased IgG anti-tetanus toxoid antibody after vaccination.

Winthrop et al [7] found that in 60 patients with RMD treated with tofacitinib, 51 (88%) of patients had greater than 2-fold and 35 (60%) patients had greater 4-fold rise in antibody concentration to the tetanus toxoid four weeks after vaccination.

Puissant-Lubrano et al [8] found that among 13 kidney transplants previously treated with rituximab compared to 26 kidney transplants not previously treated, the patients previously treated with RTX displayed lower CD19 than those who did not. Responders to the tetanus toxoid vaccination were slightly fewer in RTX (4/13) than in the non-RTX group (16/26), but the intensity of the anti-tetanus toxoid response was not significantly different between the two.

Summaries of results that do not specifically comment on drug impact:

Peracchi et al [9] found that among 26 adolescents with juvenile SLE there was a significant increase in tetanus ($p<0.001$), diphtheria ($p<0.001$), and pertussis antibody titers ($p<0.001$) in jSLE patients. Notably, the increase in antibody titers for diphtheria was significantly lower in jSLE patients than in the control group at all timepoints analyzed. Over time, a distinct pattern of response in antibody titers for tetanus and pertussis was observed ($p<0.001$ and $p<0.001$, respectively), though not for diphtheria.

Fawcett et al [10] found that among 18 patients with Hashimoto's disease, a significant increase in tetanus toxoid antibodies was observed in only 50% of patients. Among responders, there was no correlation was found between the tetanus toxoid antibody increment and the antibody levels prior to immunization.

Kashef et al [11] found that among 40 pediatric patients with SLE there was no significant difference in anti-tetanus titers compared to control patients.

Brogan et al [12] found that among 17 pediatric patients with CAPS and confirmed NLRP3 mutations on canakinumab, the available vaccine response data demonstrated antibody titers above protective levels at subsequent visits 4-8 weeks later.

Brinkman et al [13] found that among 19 children with RMD undergoing ASCT and 10 adults with multiple sclerosis, all but one pediatric patient and all adult MS patients responded to TT vaccination pre-ASCT. After ASCT conditioning, anti-TT IgG levels in pediatric RMD patients decreased to the same level as before first DTP vaccination. A significant and increasing response to the tetanus toxoid was found after subsequent vaccinations post-ASCT. All evaluable pediatric RMD patients could be classified as vaccine responders within 1-3 booster doses post-ASCT.

Jaeger et al [14] found that among 68 patients with definite CAPS treated with canakinumab who received multiple vaccinations, antibody titer measurements post-vaccination performed in only 4 patients, all following PPV injections. Seroprotection was achieved in all four patients.

Ayaslioglu et al [15] found that among 82 patients with Behcet's on immunosuppression, 92.7% of patients had protective antibody titers against tetanus after booster that was not significantly different from controls. There was a significant inverse correlation between anti-toxin titers and age in patient and control groups.

Dotan et al [16] found that among 43 patients with IBD treated with thiopurines, there was no significant suppressive effect on the systemic cellular and humoral immune responses after tetanus vaccine.

Summary of comparative studies with data in RevMan/GradePro tables:

Two observational studies [17, 18] and two RCTs [19][20] were tabled in GradePro tables 1 through 5 below. One study [17] compared outcomes for tetanus and diphteria vaccines in mixed RMD patients, as well as subgroups by disease (RA, SpA, vasculitis) and by medications (MTX, csDMARD's, biologics, MTX+TNFi, Rituximab, glucocorticoids) to healthy controls or patients not on studied medications. Healthy controls had more favorable outcomes compared to RMD patients, and patients not on studied medications had more favorable outcomes compared to patients on studied medications, except for patients on TNFi who had slightly more favorable outcomes than patients not on TNFi, but the results are imprecise. For diphteria vaccine there was no statistically significant differences between any comparisons except for RA patients versus healthy controls on GMC after first month of diphteria vaccination which was in favor of healthy controls, and for patients on TNFi who had more favorable outcomes one month after diphteria vaccination compared to patients not taking TNFi [17].

In an RCT comparing RA patients on MTX+TCZ therapy versus on MTX monotherapy, the response rate to tetanus vaccine was slightly in favor of patients on MTX monotherapy but the result was imprecise [19]. Another RCT found a poor response to tetanus vaccine for RA patients receiving MTX and a similar (but slightly lower) response in RA patients receiving MTX plus rituximab [20]. Again, the results were imprecise.

In a study comparing JIA patients on TNFi versus not on TNFi, the GMT outcomes on tetanus, diphteria and pertussis were in favor of patients on TNFi with high imprecision, but seroconversion rates were similar [18].

<u>Overall Quality of Evidence across all critical outcomes:</u> Very low

Table 1: Mixed RMD patients and subgroups by disease (RA, SpA, vasculitis) and by medications (MTX, csDMARD's, biologics, MTX+TNFi, Rituximab, glucocorticoids) versus healthy controls or patients not on studied medications [17]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Response to tetanus in mixed RMDs v healthy controls, GMC, 1 month												
1	observational studies	serious[a]	not serious	not serious	not serious	none	284	253	-	MD **2.15 lower** (3.21 lower to 1.09 lower)	⊕◯◯◯ Very low	Favors healthy controls
Response to tetanus in mixed RMDs v healthy controls, GMC, 3 months												
1	observational studies	serious[a]	not serious	not serious	not serious	none	284	253	-	MD **1.56 lower** (2.24 lower to 0.88 lower)	⊕◯◯◯ Very low	Favors healthy controls
Response to tetanus vaccine in RA pts v healthy controls, 1 month												
1	observational studies	serious[a]	not serious	not serious	not serious	none	131	253	-	MD **3.36 lower** (6.98 lower to 0.26 higher)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Response to tetanus vaccine in RA pts v healthy controls, 3 months												
1	observational studies	serious[a]	not serious	not serious	not serious	none	131	253	-	MD **2.27 lower** (3.04 lower to 1.5 lower)	⊕◯◯◯ Very low	Favors healthy controls
Vaccine response to tetantus in vasculitis pts v healthy controls, 1 month												
1	observational studies	serious[a]	not serious	not serious	not serious	none	39	253	-	MD **2.92 lower** (4.73 lower to 1.11 lower)	⊕◯◯◯ Very low	Favors healthy controls
Vaccine response to tetantus in vasculitis pts v healthy controls, 3 months												
1	observational studies	serious[a]	not serious	not serious	not serious	none	39	253	-	MD **2.04 lower** (3.09 lower to 0.99 lower)	⊕◯◯◯ Very low	Favors healthy controls
Vaccine response to tetanus in SpA/PsA pts v healthy controls, 1 month												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	114	253	-	MD **0.15 higher** (1.19 lower to 1.49 higher)	⊕◯◯◯ Very low	

Vaccine response to teatnus in SpA/PsA pts v healthy controls, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	114	253	-	MD **0.25 lower** (1.13 lower to 0.63 higher)	⊕◯◯◯ Very low	

Response to tetanus in patients on GCs v no medication, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	12	31	-	MD **0.75 lower** (3.18 lower to 1.68 higher)	⊕◯◯◯ Very low	

Response to tetanus in patients on GCs v no medication, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	12	31	-	MD **0.87 higher** (3.7 lower to 5.44 higher)	⊕◯◯◯ Very low	

Vaccine response to tetanus in pts on MTX v no medication, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	41	31	-	MD **2.77 lower** (5.43 lower to 0.11 lower)	⊕◯◯◯ Very low	Favors patients not on MTX

Vaccine response to tetanus in pts on MTX v no medication, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	41	31	-	MD **2.09 lower** (3.72 lower to 0.46 lower)	⊕◯◯◯ Very low	Favors patients not on MTX

Response to tetanus vaccine in pts on csDMARDs v healthy controls, 1 month

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	26	31	-	MD **1.84 lower** (4.99 lower to 1.31 higher)	⊕◯◯◯ Very low	

Response to tetanus vaccine in pts on csDMARDs v healthy controls, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	26	31	-	MD **1.66 lower** (3.57 lower to 0.25 higher)	⊕◯◯◯ Very low	

Vaccine response to tetanus in pts on TNFi v no medication, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	81	31	-	MD **0.39 higher** (1.23 lower to 2.01 higher)	⊕◯◯◯ Very low	

Vaccine response to tetanus in pts on TNFi v no medication, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	81	31	-	MD **1.26 higher** (1.42 lower to 3.94 higher)	⊕◯◯◯ Very low	

Vaccine response to tetanus in pts receiving rituximab v no medication

1	observational studies	serious[a]	not serious	not serious	not serious	none	11	31	-	MD **3.32 lower** (4.92 lower to 1.72 lower)	⊕◯◯◯ Very low	Favors patients not on RTX

Vaccine response to tetanus in pts receiving rituximab v no medication, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	11	31	-	MD **5.27 lower** (7.79 lower to 2.75 lower)	⊕◯◯◯ Very low	Favors patients not on RTX

Vaccine response to tetanus in pts on biologic DMARDs v no medication, 1 month

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	47	31	-	MD **0.44 lower** (3.39 lower to 2.51 higher)	⊕◯◯◯ Very low	

Vaccine response to tetanus in pts on biologic DMARDs v no medication, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	47	31	-	MD **0.11 higher** (1.84 lower to 2.06 higher)	⊕◯◯◯ Very low	

Vaccine response to tetanus in pts on MTX + TNFi v no medication

1	observational studies	serious[a]	not serious	not serious	not serious	none	35	31	-	MD **0.85 lower** (3.62 lower to 1.92 higher)	⊕◯◯◯ Very low	

Vaccine response to tetanus in pts on MTX + TNFi v no medications, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	35	31	-	MD **1.06 lower** (2.84 lower to 0.72 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. Observational study

Table 2: Response to diphtheria titers in mixed RMDs v healthy controls [17]

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Response to diphtheria vaccine in mixed RMD v healthy controls, 1 month												
1	observational studies	serious[a]	not serious	not serious	not serious	none	284	253	-	MD **0.16 lower** (0.26 lower to 0.06 lower)	⊕◯◯◯ Very low	Favors healthy controls
Response to diphtheria vaccine in mixed RMD v healthy controls, 3 months												
1	observational studies	serious[a]	not serious	not serious	not serious	none	284	253	-	MD **0.13 lower** (0.2 lower to 0.06 lower)	⊕◯◯◯ Very low	Favors healthy controls
Response to diphtheria in RA pts v healthy controls, GMC, 1 month												
1	observational studies	serious[a]	not serious	not serious	not serious	none	131	253	-	MD **0.26 lower** (0.37 lower to 0.15 lower)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Response to diphtheria in RA pts v healthy controls, GMC, 3 months												
1	observational studies	serious[a]	not serious	not serious	not serious	none	131	253	-	MD **0.2 lower** (0.26 lower to 0.14 lower)	⊕◯◯◯ Very low	Favors healthy controls
Response to diphtheria in SpA/PsA pts v healthy controls, 1 month												
1	observational studies	serious[a]	not serious	not serious	not serious	none	114	253	-	MD **0.01 lower** (0.14 lower to 0.12 higher)	⊕◯◯◯ Very low	
Response to diphtheria in SpA/PsA pts v healthy controls, 3 months												
1	observational studies	serious[a]	not serious	not serious	not serious	none	114	253	-	MD **0.01 lower** (0.12 lower to 0.1 higher)	⊕◯◯◯ Very low	
Response to diphtheria vaccine in vasculitis pts v healthy controls, 1 month												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	39	253	-	MD **0.15 lower** (0.32 lower to 0.02 higher)	⊕◯◯◯ Very low	

Response to diphtheria vaccine in vasculitis pts v healthy controls, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	39	253	-	MD **0.14 lower** (0.25 lower to 0.03 lower)	⊕◯◯◯ Very low	Favors healthy controls

Vaccine response in pts on GCs v no medication, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	12	31	-	MD **0** (0.15 lower to 0.15 higher)	⊕◯◯◯ Very low	

Vaccine response in pts on GCs v no medication, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	12	31	-	MD **0.17 higher** (0.09 lower to 0.43 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on MTX v no medication, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	41	31	-	MD **0.02 lower** (0.17 lower to 0.13 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on MTX v no medication, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	41	31	-	MD **0.02 lower** (0.13 lower to 0.09 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on csDMARDs v no medication, 1 month

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	26	31	-	MD **0.09 higher** (0.11 lower to 0.29 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on csDMARDs v no medication, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	26	31	-	MD **0.04 higher** (0.1 lower to 0.18 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on TNFi v no medication, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	81	31	-	MD **0.35 higher** (0.17 higher to 0.53 higher)	⊕◯◯◯ Very low	Favors TNFi

Vaccine response to diphtheria in pts on TNFi v no medication, 3 months

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	8	31	-	MD **0.2 higher** (0.08 higher to 0.32 higher)	⊕◯◯◯ Very low	Favors TNFi

Vaccine response to diphtheria in pts receiving rituximab v no medication, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	11	31	-	MD **0.03 higher** (0.19 lower to 0.25 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts receiving rituximab v no medication, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	11	31	-	MD **0.01 higher** (0.15 lower to 0.17 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on biologic DMARDs v no medication, 1 month

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	47	31	-	MD **0.01 higher** (0.14 lower to 0.16 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on biologic DMARDs v no medication, 1 month

1	observational studies	serious[a]	not serious	not serious	not serious	none	47	31	-	MD **0.01 higher** (0.14 lower to 0.16 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on biologic DMARDs v no medication, 3 months

1	observational studies	serious[a]	not serious	not serious	not serious	none	47	31	-	MD **0.01 higher** (0.11 lower to 0.13 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on MTX+TNFi v no medication, 1 month

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	25	31	-	MD **0.11 higher** (0.03 lower to 0.25 higher)	⊕◯◯◯ Very low	

Vaccine response to diphtheria in pts on MTX+TNFi v no medication, 3 months

0	observational studies	serious[a]	not serious	not serious	not serious	none	35	31	-	MD **0.11 higher** (0.08 lower to 0.3 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. Observational study

Table 3: Response to tetanus, TCZ+MTX v MTX compared to placebo for TCZ + MTX versus MTX for rheumatoid arthritis refractory to TNF [19]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCZ+MTX	MTX	Relative (95% CI)	Absolute (95% CI)		
Response to tetanus, TCZ+MTX v MTX												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	21/50 (42.0%)	9/23 (39.1%)	**RR 1.07** (0.59 to 1.97)	**27 more per 1,000** (from 160 fewer to 380 more)	⊕⊕◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Open-label

b. Wide CI crosses significant effect and no-effect lines

Table 4: TNFi compared to no TNFi in JIA patients receiving TDAP vaccine [18].

Quality of Evidence: Very low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	no TNFi	Relative (95% CI)	Absolute (95% CI)		
GMT Tetanus day 28												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	19	18	-	MD **19.04 lower** (45.81 lower to 7.73 higher)	⊕◯◯◯ Very low	
GMT Diphteria day 28												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	19	18	-	MD **4.22 higher** (8.49 lower to 16.93 higher)	⊕◯◯◯ Very low	
GMT Pertussis day 28												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	19	18	-	MD **4.19 higher** (34.32 lower to 42.7 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TNFi	no TNFi	Relative (95% CI)	Absolute (95% CI)		
Seroconversion tetanus day 28												
1	observational studies	serious[a]	not serious	not serious	not serious	none	17/17 (100.0%)	19/19 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⊕◯◯◯ Very low	No difference
Seroconversion diphteria day 28												
1	observational studies	serious[a]	not serious	not serious	not serious	none	17/17 (100.0%)	19/19 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⊕◯◯◯ Very low	No difference
Seroconversion pertussis day 28												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11/15 (73.3%)	15/19 (78.9%)	**RR 0.93** (0.63 to 1.36)	**55 fewer per 1,000** (from 292 fewer to 284 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Observational studies

b. Wide CI crosse significant effect and no-effect lines

Table 5: MTX compared to MTX + RTX: RA patients treated with MTX have slightly better outcomes for 4-fold and 2-fold titer increase at 4 weeks after tetanus immunization, but the results are imprecise[20].

Level of Evidence: Low

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	MTX + RTX	Relative (95% CI)	Absolute (95% CI)		
Patients with 4-fold titer increase 4 weeks (tetanus)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	11/26 (42.3%)	25/64 (39.1%)	RR 1.08 (0.63 to 1.86)	**31 more per 1,000** (from 145 fewer to 336 more)	⊕⊕◯◯ Low	
Patients with 2-fold titer increase 4 weeks (tetanus)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/26 (61.5%)	34/64 (53.1%)	RR 1.16 (0.79 to 1.70)	**85 more per 1,000** (from 112 fewer to 372 more)	⊕⊕◯◯ Low	
GMT 4 weeks after tetanus vaccine												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX	MTX + RTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	26	64	-	MD **1.3 higher** (1.74 lower to 4.34 higher)	⊕⊕◯◯ Low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

b. Open label
c. Wide CI crosses significant effect and no-effect lines

Table 6- Data from observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
158 Peracchi 2021	Case control-prospective	24 months	26 adolescents w juvenile SLE and 26 age/sex matched healthy control adolescents (age between 10-20 years) Inclusion criteria for both groups was 3 doses	Tdap Booster	There was a significant increase in tetanus (p<0.001), diphtheria (p<0.001) and pertussis antibody titers (p<0.001) in both the jSLE patients and the control group on D14 and D28. Increase in antibody titers for diphtheria was significantly lower in jSLE patients than in the control group at all timepoints analyzed (p=0.007). Over time a distinct pattern of response in antibody titers for tetanus and pertussis was observed

			and 2 booster doses of the DTwP vaccine, the last booster at least with a minimum 3 year-interval from the study entry. jSLE patients also had to be on stable immunosuppressives for at least 3 months.		(p<0.001 and p<0.001, respectively) but not for diphtheria when the two groups were compared (p=0.912). In control group, protective titers for tetanus were found on D14 (p= 1.000) but subsequently were noticed in both groups at D28 (no p value), D6m (no p value), and D12m (no p value). For diphtheria, protective titers were demonstrated in both groups at D28 (no p value) but not beyond this time point in the jSLE cohort. No significant differences were found between jSLE patients and controls regarding tetanus and diphtheria protective titers. Higher frequency of pertussis seroconversion in the control group than in the jSLE group on D14 (p= 0.009), D28 (p= 0/023), D12m (p=0.015)and D24m (p=0.004) Cellular immunity to Bordetella pertussis showed that IFNc levels were significantly lower in jSLE patients than in controls (p < 0.001). Higher levels of IL10 (p = 0.001), IL12 (p =0.002), IL21 (p =0.038) and TNFa (p = 0.008) were observed in jSLE patients when compared to the control group at all assessment at D0, D14. For IL2, there was a reduction in D14 for both groups when compared to D0 (p = 0.008). Geometric mean concentrations of T follicular helper cells did not show any differences between jSLE patients and controls at any of the times analyzed. Similarly, the percentage of Tfh cells and their subsets did not vary between D0 and D14 (unable to access Supplemental Table 1).

2059 Fawcett 1984	Cohort	10 weeks	18 patients with Hashimoto's disease	10 Limes flocculation units of tetanus toxoid absorbed on aluminium hydroxide (Wellcome Reagents Ltd).	A marked increase in tetanus toxoid antibodies was observed in 9 (50%) patients; response most prominent at 4 weeks. No correlation was found between the tetanus toxoid antibody increment and the antibody levels prior to immunization (r = 0.17, p>0.10) in responders.
2297 Ingelman-Sundberg 2016	Cross-sectional study		50 patients (age 2.9–18.3) were recruited from the rheumatology clinic at Astrid Lindgren Children's hospital, Stockholm, Sweden. 31 healthy age-matched controls All patients and healthy controls were included and sampled between November 2011 and June 2014.	All children in the tetanus group had received 3 doses of diphtheria–tetanus–pertussis (DTP) vaccine, given before the age of 1 year, and the corresponding measles/rubella group had received 1 dose of measles–mumps–rubella (MMR) vaccine, given at the age of 18 months. The booster doses of the studied vaccines are given at preschool/school age in Sweden, within a time span of either 2 (DTP) or 3 years (MMR). Due to the retrospective study design, it was not possible to determine the exact duration between vaccination and inclusion in all cases.	4 groups here with NSAID group having only 8 patients. We compared all subjects with any DMARD treatment (MTX + anti-TNFi therapy or MTX only) to all subjects without DMARD (healthy controls or NSAID-treated patients). The measles and rubella titres did not differ between these groups (data not shown), but the tetanus titres were significantly lower in DMARD-treated patients with booster. Subsequent analysis of protection rate revealed that DMARD-treated patients were not more likely to have sub-protective levels (<0.1 IU/ml), compared to individuals without DMARD treatment (data not shown). For children who had received a tetanus booster, patients treated with any DMARD had lower tetanus serum IgG compared to healthy controls and NSAID-treated patients. Patients without a measles booster had lower levels of measles-specific memory B cells, but all vaccine-specific memory B cells were preserved in patients with booster. We furthermore found that the mature B cell compartment was phenotypically similar between patients and healthy controls.
2538 Pescovitz 2011	RCT, blinded	56 weeks	Patients with type 1 diabetes treated with RTX (n=46) or placebo (n=29), healthy controls	Hepatitis A, Tetanus/diphtheria vaccines, bacteriophage phiX174	Tetanus: No difference between groups in proportion of patients with response to tetanus (see RevMan file)

			also contributed data for the bacteriophage studies	administered at 12 months	Diphtheria: No difference between groups in proportion of patients with response to diphtheria (see RevMan file)
3853 Niwa 1979	Cohort	Varied by treatment; some outcomes evaluated at 5 days others up to 3 months	47 patients with autoimmune diseases (SLE n=22; DLE n=15; diffuse scleroderma n=10; 50 patients with "dermatosis" on steroids for non-autoimmune diseases, and 50 healthy controls	Diphtheria toxoid: 2 injections given IM 1 week apart, Antibody formation measured; solution injected intradermal 1 week after last injection of diphtheria toxoid, if patient had an injection site reaction >10mm they were non responders.	Diphtheria toxoid - Only 1 of 22 SLE patients did not develop an antibody formation vs 0 of 18 normal controls (p>0.05) - Steroids alone did not influence secondary responses to diphtheria toxoid
458 Kashef 2008	Case-control	N/A	40 pediatric SLE patients (mean age of 14 years, range 7-21 yrs) + 60 age and sex matched controls in Iran. Mean SLEDAI 4.9.	Tetanus vaccine, with a standard protocol of 3 primary doses and 2 boosters by the age of 6. SLE patients were on aza (13), CYC (10), aza+CYC (5), MMF (8); all patients were on prednisolone (dosage not reported).	No signficant difference detected between anti-tetanus titers in control patients (2.00±1.24 IU/mL) and SLE patients (1.90±1.33 IU/mL).
459 Battafara o 1998	Cohort	12 weeks	73 SLE 5.5% male/94.5 % female; mean age 43 (18-76) 48% on antimalarial agents , NSAIDS 34%, AZA 10%, IV CYC 10%, oral MTX 1%	Pneumococcal (pneumovax 23), tetanus toxoid and haemophilus influenza type B	61 (84%) achieved 4-fold AB response to at least 1 antigen, with 100% achieving at least a 2-fold response to at least 1 antigen. 14 (19%) developed 4-fold response to all 3 antigens, with >50% developing at least 2-fold response to all 3 antigens. Majority developed protective Abs to tetanus irrespective of their increase in titer; 65 (90%) had protective levels of tetanus AB (≥0.01 IU/ml). TT preimm 36 (50%) / post imm 65 (90%)

			74% on steroids, with 85% oral prednisone <10mg per day		Patients with 3-fold increase in AB titers post-immunization: those who were not receiving AZA, CYC and prednisone, all developed 3-fold increases to a mean of almost 2 (1.9) of the 3 vaccines. Trend toward decreased antibody response in patients treated with CYC, AZA or prednisone, although this was not statistically significant. There was no significant difference for any individual medication or combination of medications, or by medication dosage.
5223_Brunner 2020	Single-arm, open-label, multicenter phase 3 Trial	24 months	Polyarticular JIA Age 2-5 years ≥2 continuous months of weekly subcutaneous abatacept (with/without methotrexate and/or low-dose corticosteroids)	DT vaccine prior to enrolment Protective antibody levels to diphtheria/ tetanus (> 0.1 IU/mL), and safety, were assessed Protective antibody levels to diphtheria and tetanus were defined as > 0.1 IU/mL	Concomitant use of methotrexate and/or low-dose corticosteroids had no evident effect on antibody levels.
6208 Marchand-Janssen 2011	Cross-sectional study	Looking for humoral immunity to diptheria, tetanus, and poliomyelitis in mixed RMD popul.	186 mixed RMD patients in total, on a variety of immunosuppressant medications.	n/a	Of the 48 pts documented to be up-to-date for diphtheria, 18 (37%) had no immunity, 22 (46% had intermediate immunity, and 8 (17%) had high immunity (>/=1 IU/ml). Of the 70 pts documented to be up-to-date for tetanus, 7 (10%) had no immunity, 16 (23%) had intermediate immunity, and 47 (67%) had high immunity (>/= 0.5 IU/ml). In the multivariate analysis, factors associated with no humoral immunity to diphtheria were age >50 years [odds ratio (OR) 5.9; 95% CI 3.09, 11.12; P <

					0.001)] and CS therapy (OR 5.04; 95% CI 1.72, 14.76; P = 0.003). CS was not associated with lack of humoral immunity to tetanus or poliomyelitis
6852 Colucci 2019	Case-series	81 months	27 frequently-relapsing (n = 2) or steroid-dependent nephrotic syndrome (n = 25) pediatric patients.	HBV, tetanus and measles/mumps/rubella (MMR) vaccines (not a primary intervention)	Anti-CD20 treatment reduced the mean number of relapses/year from 3.4 (range1–5) to 0.6 (range0–2) at last follow-up. Serum immunoglobulin concentrations at last follow-up for median levels of IgG compared to baseline levels: 701 vs. 610mg/dl at baseline; p=0.19) and IgA (138 vs.124mg/dl at baseline; p=0.53). Light reduction was observed for IgM median levels (76 vs. 104 mg/dl at baseline; p=0.05). 11/27 patients (41%) were re-immunized against tetanus after a mean time of 36 months (range10–82months).
7047 Brogan 2019	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood	In core study, 7/17 (41%) patients received a total of 31 vaccine injections (10 different types of inactivated vaccines). Vaccine response data available for 18/31 (58.1%) injections. All showed a positive response (Ab titers increased above protective level). For all 31 vaccine injections, including those without a pre-dose Ab titer, protective post-vaccine Ab titers were maintained throughout the trial. In the extension study**,** 4/17 (24%) patients received a total of 20 vaccine injections (8 different types of inactivated vaccines). 17/20 (85%) of injections had data available to assess vaccine response. In 16/17 (94.1%) cases, protective Ab titers were achieved post-vaccine.

			from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	vaccination programs. No live vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination ("Pre-dose"), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). <u>Included vaccines:</u> HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	For 19/20 (95%) vaccine injections, including those without a pre-dose Ab titer, protective post-vaccine Ab titers were maintained throughout the extension study.
7197 Holmes 2019	Retrospecti ve cohort	Within 10 years	98 Rheumatoid arthritis 71 Controls Excluded those who had received rituximab	Tdap vaccine within 10 years of the blood collection for the biorepository	Female sex and methotrexate use, <u>but not TNF inhibiting medications,</u> correlated with reduced immunity to pertussis.
7309 Brinkman (2007)	Prospective cohort study	Follow-up to 2 years post-ASCT	19 children with RMD undergoing ASCT for treatment of their disease (13 sJIA, 4 pJIA, 2 SLE); median age 9 years (range 4-15), 36.8% female, median	All patients underwent autologous stem cell transplantation (ASCT) according to EULAR & EBMT guidelines. Immunosuppressive medications were	<u>Humoral response to DTP vaccine:</u> All but one pediatric RMD patient & all MS patients responded to TT vaccination pre-ASCT. For most patients, anti-TT IgG concentrations were within range of TT booster responses in healthy adult controls.

			disease duration 70 months (range 24-144 months) pre-ASCT. 10 adults with MS undergoing ASCT; median age 37 years (range 23-50), 70% female, median MS duration 60 months (range 24-144). Reference data from 18 healthy volunteers; median age 31 years (range 19-49), 50% female; received single dose of rabies vaccine with one booster dose 3 months later.	stopped at one month prior to marrow harvest. All patients received one dose of rabies neoantigen vaccine immediately after bone marrow harvest (4 weeks pre-conditioning) and one dose at 6 months post-ASCT. One dose of DTP (diphtheria, tetanus, polio) vaccination was given at least 1 month before marrow harvest (TT0), with 3 subsequent DTP vaccinations given at 3 months (TT1), 4 months (TT2), and 5 months (TT3) post-ASCT.	After ASCT conditioning, anti-TT IgG levels in pediatric RMD patients decreased to the same level as before first DTP vaccination. A significant & increasing response to TT was found after subsequent vaccinations @ 3, 4, 5 months post-ASCT. All evaluable pediatric RMD patients could be classified as vaccine responders within 1-3 booster doses post-ASCT. <u>T cell responses to DTP vaccine:</u> Data available for 6 JIA patients. Proliferative response to tetanus (stimulation index > 3) in all JIA patients pre-ASCT. After conditioning, significant decrease in SI found at 3 months post-ASCT in JIA patients. No anti-specific proliferative response detected in 50% of JIA patients post-ASCT & before revaccination. After one TT revaccination, a proliferative T cell response found in all JIA patients.
7772 Jaeger (2017)	Case series based on prospective, multicenter observational patient registry (β-CONFIDENT)	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period. Patients without definite CAPS, not receiving vaccines, or	All patients treated with canakinumab. Total of 159 vaccine injections 43/68 (63%) patients received multiple vaccine injections	Antibody titer measurements post-vaccination performed in only 4 patients, all following PPV injections. Seroprotection achieved in all four patients (details not reported).

			with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	Influenza: 107 injections in 55/68 (81%) patients Pneumococcal: 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	
840_Stohl PICO 3	Case Series Pooled data from 2 phase III trials, the Study of Belimumab in subjects with SLE 52 week (BLISS-52) and 76 week (BLISS-76) trials	Within 5 years of start of treatment in BLISS-76 study	Substudy of BLISS-76: Evaluated for IgG anti-tetanus toxoid 33 tx w placebo 33 tx belimumab 1mg/kg 25 tx w belimumab 10mg/kg [BLISS-52 (n=865); placebo vs belimumab 1mg/kg] [BLISS-76 (n=819); placebo vs belimumab 10mg/kg	Pneumococcal or tetanus vaccine	IgG anti-tetanus toxoid AB not significantly decreased Tetanus toxoid vaccine Placebo AG -10.43 +/-4.67 (-10.59) AG Belimumab 1mg/kg 28.14 +/- 33.39 (-15.33) AG Belimumab 10mg/kg -13.52 +/- 7.07 (-16.84)

			All patients had active SLE and were on standard therapy for SLE (steroids, immunosuppressive agents [aza, mmf, mtx] and/or antimalarial agents alone or in combination)]		
8424 Winthrop 2021	Single-arm study	4 weeks after vaccination	60 patients completing at least 3 months' continuous treatment with tofacitinib 10 mg twice daily	PCV-13 and tetanus vaccines.	For tetanus toxoid, 51 (88%) patients had > 2-fold and 35 (60%) patients had > 4-fold rise in antibody concentration.
8450 Ayaslioglu 2003	Case-control	10 years	82 patients with Behcet's disease on immunosuppresive medications and 79 healthy individuals	Tetanus booster	Behcet's disease (92.7%) and 74 healthy controls (93.7%) had protective antibody titres against tetanus, with geometric mean levels of 1.02/1.28 and 1.39/1.65 IU/ml, respectively, with no statistically significant differences. There was a significant inverse correlation between antitoxin titres and age in patient and control groups.
4347, Puissant-Lubrano, 2010	Case-control	n/a	39 kidney- transplant recipients (13 previously received RTX- group 1, 26 had not- group 2) 30 healthy controls	Tetanus	At baseline: - Neither of the 2 patient groups differed significantly from the healthy controls for IgG, IgA, IgM serum levels, or CD8 T-cell counts - Both patient groups displayed lower peripheral CD3+CD4+ and lower CD19+ counts than healthy blood donors - Patients from group 1 (rituximab) displayed lower CD19 than those from group 2 ($P <$ .0001) - The two patient groups did not differ in their CD4, CD8, or NK counts. - Complete CD19+ B-cell depletion occurred for all patients who had received rituximab therapy (group 1)

					Responders to the tetanus toxoid vaccination were slightly fewer in group 1 (4/13) than in group 2 (16/26), but the intensity of the anti-tetanus toxoid response was not significantly different between these 2 groups. None of the parameters studied at the time of vaccination (anti-tetanus toxoid level, peripheral B or CD4 T-cell count, memory B-cell subsets, treatment with rituximab, time since transplant) were associated with an ability to respond to vaccination. The ability to respond to vaccination and graft outcomes were not correlated in each patient group.
5898, Dotan, 2012	Prospective cohort	n/a	43 patients with IBD on thiopurines (31 with Crohn's, 12 with UC)	Pneumonia, tetanus, HiB	The post-therapy average 6-MP dose was 1.05 +/- 0.30 mg/kg. There was no significant suppressive effect on the systemic cellular and humoral immune responses after tetanus vaccine. Post-therapy white blood cell counts decreased significantly from baseline values ($p<0.002$).

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Typhoid Vaccine

Summary: One observational study described duration of post vaccine titer according to medication effect and reported no effect of immunosuppressants evaluated (methotrexate, steroids, biologic DMARD, non-biologic DMARD) on duration of vaccine response/antibody titer (1). Another study demonstrated that corticosteroids alone did not impair typhoid vaccine response (2).

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7602_von Asmuth 2019	Retrospective study	4 years	40 pts with rheumatoid disease	Previous receipt of Vi-PS vaccination	No statistically significant effect on methotrexate, steroid, biologic DMARD or non-biologic DMARD use on titer half-life.
3853 Niwa 1979	Comparative, interventional	Varied by treatment; some outcomes evaluated at 5 days others up to 3 months	47 patients with autoimmune diseases (SLE n=22; DLE n=15; diffuse scleroderma n=10; 50 patients with "dermatosis" on steroids for non-autoimmune diseases, and 50 healthy controls	**Typhoid vaccine**: injected 5 times at weekly intervals and agglutinin titer to typhoid "O" Ag measured 2 weeks after each injection; titer >=1:40 indicated response and further immunization stopped after	**Typhoid vaccine** - In patients with SLE, O agglutinin titers were "not greatly impaired." 2 SLE did not respond and one SLE finally showed titer above 1:40 after last vaccination ($p>0.05$ when compared with healthy controls and patients on steroids). - Steroids alone did not influence secondary responses to typhoid vaccine.

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Varicella Zoster Vaccines

Summary: One RCT and 7 observational studies addressed this question for varicella zoster vaccines.

One study comparing mixed RMD patients on MTX to healthy controls, seroconversion rate was in favor of healthy controls but the results are imprecise, and seroprotection at 4-6 weeks and 1 year was similar in both groups (1).

Speth et al (2) found that among 30 patients with rheumatic disease, 21 patients showed a positive vaccination response to VZV. Two patients (7%) receiving high-intensity immunosuppression failed to raise positive VZV-IgG, despite booster immunization.

An RCT by Winthrop et al. (3) found that tofacitinib did not diminish the immune response to live attenuated zoster vaccine compared to placebo in RA patients; post-vaccination IgG increase trended higher in the tofacitinib arm.

Summaries of results that do not specifically comment on drug impact:
Guthridge et al (4) found that among 10 patients with SLE, there was no change in antibody titers over time compared to healthy controls.

Zhang et al (5) found that among 44,115 patients over the age of 50 with RMD, with or without immunosuppressive therapy, the incidence rate of HZ were similar in vaccinated patients compared to unvaccinated patients.

Boldingh and Nordall (6) found that among 21 patients with JIA who underwent VZV vaccination, 5 patients were seropositive after 1 dose, and an additional 10 patients were seropositive after 2 doses.

Chakravarty et al (7) found that among 4260 patients at increased risk for incident Zoster, 1485 with SLE and 2775 with MSK disorders, vaccination rates varied by diagnosis. The number of vaccinated individuals were too small to perform meaningful subanalyses.

Takahashi et al (8) found that among 16 elderly patients, including 10 patients with SLE on steroids, who underwent VZV vaccination, 8/12 elderly subjects (conversion rate 66.6%) and 4/6 patients with collagen vascular diseases (conversion rate 66.6%), who were VZV-skin test negative but purified protein derivative tuberculin test-positive, became VZV skin test-positive.

Quality of Evidence across all critical outcomes: Very low

Table 1: Immunogenicity of Varicella vaccine in mixed RMD patients on MTX versus healthy controls (1)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 3 Mixed RMD on MTX	control	Relative (95% CI)	Absolute (95% CI)		
Seroconversion 4-6 weeks VZV												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/20 (50.0%)	13/18 (72.2%)	**RR 0.69** (0.41 to 1.17)	**224 fewer per 1,000** (from 426 fewer to 123 more)	⊕◯◯◯ Very low	
Seroprotection 4-6 weeks VZV												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	15/25 (60.0%)	11/17 (64.7%)	**RR 0.93** (0.58 to 1.49)	**45 fewer per 1,000** (from 272 fewer to 317 more)	⊕◯◯◯ Very low	
Seroprotection 1 year VZV												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11/22 (50.0%)	8/16 (50.0%)	**RR 1.00** (0.53 to 1.90)	**0 fewer per 1,000** (from 235 fewer to 450 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Wide CI crosse significant effect and no-effect lines

Table 2. Observational Studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3510 Guthridge 2013	Case control	12 weeks (weeks 2, 6, 12)	10 SLE Medications: - 7 HCQ - 2 MTX - Prednisone <10mg/d 10 controls	Zostavax, live attenuated vaccine	Some data presented as bar graph only, without numerical values. - Cellular immunity ELISPOT: proportion with a > 50% increase comparable between both groups (no extractable data) - Antibody titers: 'no change in SLE over time' vs 'statistically increased from baseline at all timepoint in controls' ($p<0.05$)
7664 Winthrop 2017	RCT, double-blinded, placebo	up to 14 weeks post-vaccination	RA patients >50 years, 55 Tofacitinib (5mg twice daily) vs 57 placebo 2-3 weeks after vaccination Medications: - All continued MTX - concomitant prednisone <10mg/day allowed	Zoster, live attenuated vaccine	No significant difference in geometric mean fold rise (GMFR) in VZV-specific IgG levels at 6 weeks and 14 weeks post-vaccination. 6 weeks: 2.11 (80% CI: 1.87 to 2.37) tofacitinib (n=54) vs. 1.74 (80% CI: 1.55 to 1.95) placebo (n=53) 14 weeks: 1.64 (80% CI: 1.45 to 1.85) tofacitinib (n=48) vs. 1.50 (80% CI: 1.32 to 1.69) placebo (n=44) Percent of patients with ≥1.5-fold post-vaccination increase in IgG at 6 weeks post-vaccination trended higher with patients receiving tofacitinib (57.4% vs. 43.4%).
8919 Zhang 2011	Case-control	Follow-up at least 183 days	44,115 patients aged 50 years and older, with the mixed rheumatic diseases, with or without csDMARDs, bDMARDs, GC therapies, vaccinated and unvaccinated	551 (1.2%) received herpes zoster vaccine	The incidence rates of HZ were similar in vaccinated and unvaccinated patients (standardized incidence ratio: 0.99 (95% CI = 0.29 to 3.43))
9241 Speth 2018	Case-series	12 weeks	30 patients with pediatric rheumatic diseases at risk for severe chickenpox, on their current low-	Varicella zoster virus (VZV) vaccine	21 patients (91%) showed a positive vaccination response. 2 patients (7%) in the HIIS group failed to raise positive VZV-IgG, despite booster immunization. There were no cases of rash or other vaccine induced varicella disease symptoms and no evidence of PRD flare.

			intensity and high-intensity immunosuppression, including biological agents		
9437 Boldingh and Nordall 2011	Case series	NR	21 JIA patients	Varicella zoster vaccine (VZV); on DMARDs (unspecified)	Of 21 JIA patients receiving VZV, 5 patients were seropositive after 1 dose, and an additional 10 patients were seropositive after 2 doses.
4477, Chakravarty, 2013	Prospective cohort	10 years	4260 participants at risk for incident herpes zoster available for analysis (1485 patients with SLE; 2775 patients with MSK disorders)	Zoster (study examines rate of infection, some patients received vaccine)	Data on HZ vaccination since vaccine licensure in 2006 were available for 1601 participants >=60 years old. - 186 (11.6%) of participants reported vaccination - Vaccination rates varied by diagnosis (7.1% of age-eligible SLE patients reporting vaccination compared to 13% for those with MSK disorders (p=0.001)) - Mean age at vaccination was 70 years for SLE and 74 years for MSK - Numbers of vaccinated individuals were too small to perform meaningful subanalyses.
3971, Takahashi, 1992[5]	Observational	Unknown	16 elderly patients (age>60) 10 with collagen vascular disease (SLE on steroids)	Varicella	After two doses of VZV vaccine, 8/12 elderly subjects (conversion rate 66.6%) and 4/6 patients with collagen vascular diseases (conversion rate 66.6%), who were VZV-skin test negative but purified protein derivative tuberculin test-positive, became VZV skin test-positive.

References:

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Yellow Fever Vaccine

Summary: Six observational studies were included that described the impact of a drug of interest on yellow fever vaccine response for individuals with RMD. Wieten et al. compared the seroprotection outcome of yellow fever vaccine between mixed RMD on MTX and healthy controls (1), which was in favor of RMD patients with yellow fever vaccine but the result is imprecise.

Ferreira et al(2) found that among 122 patients with RA, csDMARD therapy did not affect the duration of protective immunity induced by the 17DD-YF vaccine compared to that of healthy controls. csDMARD in combination with bDMARD therapy induced a premature depletion in the main determinants of the vaccine protective response.

Tonacio et al[9919] reported that 84.3% of patients with ARD seroconverted following vaccination with yellow fever vaccine. Medication (prednisone, methotrexate) was not significantly associated with seroconversion (only viremia was significantly associated with seroconversion).

Summaries of results that do not specifically comment on drug impact:

Valim et al(3) found that among 227 patients with RMD, patients had significantly lower PRNT levels compared to healthy controls. Yellow fever viral RNAemia peak was slightly later and lower in patients with RMD compared to healthy controls. Scheinberg et al(4) found that among 17 patients with RA on MTX and TNFi, there was a trend toward a lower antibody response rate compared to controls, but not statistically significant due to the small number of patients. Costa Richa et al.[10330] also reported lower seropositivity rates among RMD patients compared to healthy controls following yellow fever vaccination.

Overall Quality of Evidence across all critical outcomes: Very low

Table 1: Seroprotection, Yellow Fever vaccine in mixed RMD on MTX patients versus healthy controls(1)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMD on MTX	control	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11/11 (100.0%)	10/12 (83.3%)	**RR 1.19** (0.89 to 1.59)	**131 more per 1,000** (from 298 fewer to 165 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Observational study

b. Small number of patients, very wide confidence interval

Table 2: Additional data from observational studies not entered into RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
10330 da Costa-Rocha 2021[10330]	Case-control	28 days	RA=38 SpA=51 SLE=21 SS=30 Healthy control=21	RMD and HCs were vaccinated with 17DD-YF yellow fever vaccine Meds were held "as specified by Brazillian recommendations" (Ref for holding protocol is Pileggi 2019)	Seropositivity and GMs were: Patient Group — Seropos rate — GM (95% CI) HC — 95% (20/21) — 448(285-705) Mixed RMD — 77% (108/140) — 170(133-219) RA — 87% (33/38) — 291(194-436)

			RMD patients were in remission or had minimal disease. 1/3 of patients were on MTX; 1/4 were on a biologic; <10% were on steroids	Blood was drawn at regular intervals following vaccination and ex vivo experiments were performed	SpA 73% (37/51) 112(73-170) SLE 71% (15/21) 133(55-321) SS 77% (23/30) 209(115-378)
9919 Tonacio 2021[9919]	Prospective, case control	Jan 2018 to April 2018	318 participants= 159 Autoimmune rheumatic disease (ARD) and 159 healthy controls; age ≥18 or ≤ 60 years old ARD group: low or inactive disease; low immunosuppression (hydroxychloroquine, sulfasalazine, prednisone 20 mg/day, methotrexate up to 0.4mg/kg/week(maximum of 20 mg/week) and leflunomide 20 mg/day without other drugs or associated with prednisone 7.5mg/day or hydroxychloroquine or sulfasalazine)	Yellow fever vaccine	ARD seroprotection rate 124/147 (84.3) ARD GMT 731.0 (593.6–900.2) ARD seroconversion rate 118/141 (83.7) Medication (prednisone, methotrexate) was not significantly associated with seroconversion (only viremia was significantly associated with seroconversion).
4352, de Castro Ferreira, 2019 (2)	Cohort	2 years	122 patients with RA 226 healthy controls	Yellow fever (17DD)	***most data presented in bar graph form without clear numbers csDMARD therapy did not affect the duration of protective immunity induced by the 17DD-YF vaccine compared to that of health controls

					- Both presented a significant time-dependent decline at 10 years after vaccination. cs+bDMARD therapy induced a premature depletion in the main determinants of the vaccine protective response - Diminished PRNT seropositivity levels between 5 and 9 years and impaired effector memory in CD8+ T cells as early as 1–5 years after 17DD-YF vaccination.
6419 Valim (2020) (3)	Prospective single-center cohort study	28 days post-vaccine	227 patients aged 18 years or older with autoimmune diseases (AID), including RA (n=79), SpA (n=59), SSc (n=8), SLE (n=27), and pSS (n=54). All patients had low disease activity or were in remission. Mean (SD) age 51 (14) years; 71.8% female. 51 healthy controls [mean (SD) age 56 (15) years, 56.9% female]. Exclusion criteria for both groups: HIV, organ transplant, PID, cancer, previous YF vaccination or pre-vaccine seropositivity for anti-YF antibodies (PRNT >1:50)	All participants received one dose of the live attenuated 17DD-Yellow Fever (YF) vaccine. Patients on "low level" immunosuppression did not withdraw therapy prior to vaccination, including prednisone 20mg or less daily (n=27), MTX 20mg or less weekly (n=65), AZA 2mg or less daily, LEF (n=21), HCQ (n=39), or SSZ (n=11). Patient on "high level" immunosuppression were instructed to withdraw therapy prior to vaccination, including patients on bDMARDs (n=42), CYC (n=5), CNI (n=1), MMF (n=3), high-dose AZA, or prednisone >20mg daily (n=6). Recommended intervals between withdrawal & YF vaccination: >3 months for CYC, MMF, AZA, CNI; >6 months for rituximab; > 5.5 half-lives for other bDMARDs.	GMT for anti-YF Ab @ Day 28 (95%CI): HC (n=23): 440 (291-665) AID (n=160): 181 (144-228) p=0.005 vs. HC RA (n=46): 270 (183-401) SpA (n=51): 112 (73-170) p<0.001 vs. HC SSc (n=6): 206 (60-711) SLE (n=22): 143 (61-332) p=0.01 vs. HC pSS (n=35): 223 (133-376) Kinetic Timeline of anti-YF Ab (PRNT) levels: AID patients had significantly lower PRNT levels than HC at Day 5, Day 14, and Day 28. No significant differences in PRNT levels between AID patients & HC on Day 0, 3, 4, 6, or 7. Kinetic Timeline of 17DD-YF viremia: YF viral RNAemia peak was slightly later (Day 6 vs. Day 5) and lower in AID patients vs. HC. Similar viremia peak at Day 5-6 across all AIDs. Viremia was undetectable in SSc subgroup.

9398 Scheinberg 2010 (4)	Case-control	N/A	17 RA on MTX and TNFi and 15 healthy controls	Yellow fever revaccination after the 10-year period and 1 month after the last anti-TNF infusion	A comparison between the antibody test titers seen in patients and controls showed a trend toward lower response in patients, but due to the small number of patients a formal statistical analysis was not performed. Before revaccination: Titer 1:800 in controls – 0, in patients – 0, 1:400 in controls – 0, in patients – 0, 1:200 in controls – 3, in patients – 3, 1:100 in controls – 12, in patients - 10 Negative in controls – 0, in patients – 2 After revaccination: Titer 1:800 in controls – 6, in patients – 0 1:400 in controls – 6, in patients – 6 1:200 in controls – 2, in patients – 6 1:100 in controls – 0, in patients - 4 Negative in controls – 1, in patients – 1

References:

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PICO 4: In RMD patients, does the immunogenicity or efficacy of Vaccine Z differ in patients taking high-dose steroids as compared to those using lower doses of steroids or those not using steroids?

Summary:
Pneumococcal vaccine. We identified 13 observational studies and 2 RCTs that addressed this question for pneumococcal vaccines. In an open label long term extension of vaccine RA-BEYOND (NCT01885078) sub-study (1), the percentage of patients with satisfactory responses was similar for PCV-13 regardless of a baricitinib 2-mg or 4-mg dose, concomitant corticosteroids (71%), and SDAI response. Among observational studies, most of the study populations were RA, SpA or SLE (2-12). One study (11) included patients with small or medium vessel vasculitis. These studies consistently reported that the immunogenicity of the vaccine did not differ among patients on high or lower dose of glucocorticoids. In a substudy of the ASPIRE RC, PPSV23 given 34 weeks after start of immunosuppression in a subset of RA patients. Antibody responses were assessed 4 weeks post-vaccination. In the IFX + MTX combined arm (n=56), significantly more patients receiving oral corticosteroids (11/26, 42.3%) were responders vs those not receiving oral corticosteroids (2/30, 6.7%)(13). In a double blind RCT (14) addressing this question among patients with SLE, 25 patients received PPSV23, 17 received PCV7 followed by PPSV23 24 weeks later. No differences between rates of responders were observed in either group (PCV17 or PPSV23) in patients treated with and without IS and in those receiving < or > 10 mg prednisone.

Tetanus toxoid vaccine. In the long-term extension study by Winthrop et al (n=106), the immune responses to tetanus toxoid vaccine (TTV) were also examined. Authors found that for TTV, 33% (95% CI 15.2, 58.3) of patients taking baricitinib 2 mg showed a humoral response compared to 45% (95% CI 34.8, 55.3) of those taking baricitinib 4 mg; the percentages were 52% (95% CI 34.8, 68.0) and 39% (95% CI 28.9, 51.1) for those taking and not taking concomitant corticosteroids, respectively.

Influenza vaccine. We identified 14 observational studies evaluating this PICO question for influenza vaccine. Aikawa et al (15) studied 237 patients with juvenile autoimmune rheumatic diseases and 91 controls for immunogenicity after H1N1 vaccination. Three weeks after immunization, seroprotection rate (81.4% vs 95.6%; p = 0.0007), sero-conversion rate (74.3 vs 95.6%; p < 0.0001), and the factor-increase in GMT (12.9 vs 20.3; p = 0.012) were significantly lower in patients with juvenile ARD versus controls. Glucocorticoid use and lymphopenia were associated with lower seroconversion rates (60.4 vs 82.9%; p = 0.0001; and 55.6 vs 77.2%; p = 0.012). Multivariate logistic regression including diseases, lymphopenia, glucocorticoid, and immunosuppressants demonstrated that only glucocorticoid use (OR 0.20 (0.06–0.70), p = 0.012) remained significant. In other (mostly smaller) studies addressing this question (3, 16-26), the majority concluded that the dose of prednisone did not impact the immunogenicity of influenza vaccine.

Other vaccines. Only one study each on the following vaccines pertaining to this PICO: Hepatitis B and live zoster vaccine. In a retrospective study (27) with mixed RMD populations (n=84), double-dose HBV vaccine (40 µg) was given on months 0, 1, 2 and 6, and response rates were assessed. thirty-nine (46.4%) patients were using immunomodulatory therapies such as methotrexate and prednisolone before starting on biological agents. Use of these therapies prior to biological agents had no effect on vaccine response (p=0.392).

In study by Yun et al (29), 59,627 mixed RMD patients who had received live zoster vaccine, identified by ICD coding, and who had received ≥ 12 months continuous Medicare coverage before vaccination and throughout follow up were matched to 119,254 in an unvaccinated cohort. The outcome of interest was the first HZ event during follow up. Herpes zoster incidence rate in the vaccine group increased from 0.75/100 PY in the first-year post vaccine to 1.25/100 PY in the 7th year post-vaccine whereas HZ IR in unvaccinated group remained consistent through 7 years (1.3-1.7/100 PYs). Subgroup analysis stratified by glucocorticoid dose (14% of study population on prednisone < 7.5 mg/d, 2.5% receiving ≥ 7.5 mg/d) yielded consistent trends with main analysis.

Quality of evidence across all critical outcomes: Low for pneumococcal vaccines, Very low for other vaccines.

Table 1: Impact of steroids on immunogenicity of PPSV23 vaccine at d28 in RA patients (3) Alten 2016.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	No steroids	Relative (95% CI)	Absolute (95% CI)		
Impact of steroids (any dose) on PPSV23 seroprotection												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	50/63 (79.4%)	44/49 (89.8%)	**RR 0.88** (0.76 to 1.03)	**108 fewer per 1,000** (from 216 fewer to 27 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. No randomization
b. Small sample size

Table 2: IFX + MTX on corticosteroids vs off corticosteroids in RA patients vaccinated with PPSV23 (13) Visvanathan 2007

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX + MTX (on steroids)	IFX + MTX (no steroids)	Relative (95% CI)	Absolute (95% CI)		
Responders to PPSV23, 4 weeks												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	11/26 (42.3%)	2/30 (6.7%)	**RR 6.35** (1.55 to 26.05)	**357 more per 1,000** (from 37 more to 1,000 more)	⨁⨁◯◯ Low	Favors steroids

CI: confidence interval; **RR:** risk ratio

Explanation

a. Non-randomized subgroup analysis in two combined trial arms
b. Small sample size and wide CI

Table 3: Impact of steroids on immunogenicity of Seasonal Flu vaccine at d28 in RA patients (3) Alten 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	No steroids	Relative (95% CI)	Absolute (95% CI)		
Impact of steroid (any dose) on influenza vaccine seroprotection												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	No steroids	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	95/114 (83.3%)	56/70 (80.0%)	**RR 1.04** (0.90 to 1.20)	**32 more per 1,000** (from 80 fewer to 160 more)	⨁◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

Explanations

a. No randomization
b. Small sample size

Table 4: Immunogenicity of 2009 H1N1 in SLE based on medications compared to placebo in SLE (on various meds, including pred >20mg) and in HC (18) Borba 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pred >/=20 mg/day + DMARD	Pred >/=20 mg/day + DMARD	Relative (95% CI)	Absolute (95% CI)		
Seroprotection: SLE on pred >/=20mg/day with and without DMARD												
1		serious[a]	not serious	not serious	serious[b]	none	152 participants			-		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pred >/=20 mg/day + DMARD	Pred >/=20 mg/day + DMARD	Relative (95% CI)	Absolute (95% CI)		
	observational studies						-		**RR 0.98** (0.77 to 1.25)		⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. No randomization
b. Small sample size

Table 5: Impact of prednisone on immunogenicity, low responders vs high responders to trivalent subunit seasonal influenza vaccines (21) **Crowe 2011**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low responders on pred (>/=10 mg/day)	High responders on pred (>/=10 mg/day)	Relative (95% CI)	Absolute (95% CI)		
Number of low responders vs high responders taking prednisone (>/=10mg pred/day)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low responders on pred (>/=10 mg/day)	High responders on pred (>/=10 mg/day)	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/36 (66.7%)	17/36 (47.2%)	**RR 1.41** (0.93 to 2.14)	**194 more per 1,000** (from 33 fewer to 538 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. No randomization
b. Small sample size

Table 6: RA-steroids compared to RA-no steroids following pH1N1 vaccination [(22)] Ribeiro (2011)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	RA-no steroids	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	RA-no steroids	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	146/247 (59.1%)	56/93 (60.2%)	**RR 0.98** (0.81 to 1.19)	**12 fewer per 1,000** (from 114 fewer to 114 more)	⨁◯◯◯ Very low	No difference
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	247	93	-	MD **1.1 lower** (3.22 lower to 1.02 higher)	⨁◯◯◯ Very low	
Seroconversion												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	122/247 (49.4%)	51/93 (54.8%)	**RR 0.90** (0.72 to 1.13)	**55 fewer per 1,000** (from 154 fewer to 71 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. No randomization
b. Small sample size

Table 7: Prednisone compared to No medications in SLE patients; all participants received a single dose of trivalent inactivated seasonal influenza vaccine (H1N1/H3N2/B-HK). [(23)] Holvast (2006)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⊕◯◯◯ Very low	
Vaccine efficacy - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⊕◯◯◯ Very low	
Vaccine efficacy - B-influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/14 (35.7%)	7/12 (58.3%)	**RR 0.61** (0.26 to 1.43)	**228 fewer per 1,000** (from 432 fewer to 251 more)	⊕◯◯◯ Very low	

Seroprotection - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/14 (92.9%)	11/12 (91.7%)	**RR 1.01** (0.81 to 1.27)	**9 more per 1,000** (from 174 fewer to 248 more)	⊕◯◯◯ Very low	

Seroprotection - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/14 (85.7%)	12/12 (100.0%)	**RR 0.87** (0.67 to 1.11)	**130 fewer per 1,000** (from 330 fewer to 110 more)	⊕◯◯◯ Very low	

Seroprotection - B-influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/14 (57.1%)	11/12 (91.7%)	**RR 0.62** (0.38 to 1.01)	**348 fewer per 1,000** (from 568 fewer to 9 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. No randomization
b. Small sample size

Table 8: SLE on GCs compared to SLE not on GCs; all participants received one standard dose of trivalent seasonal influenza vaccine (H1N1/H3N2/B-Malaysia). [(24)] **Wallin (2009)**

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on GCs	SLE not on GCs	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine antibody titer - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	24	-	MD **320 lower** (895.03 lower to 255.03 higher)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on GCs	SLE not on GCs	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine antibody titer - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	24	-	MD **182.6 lower** (765.01 lower to 399.81 higher)	⨁◯◯◯ Very low	
Post-vaccine antibody titer - B-Malay												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	24	-	MD **536.9 lower** (892.88 lower to 180.92 lower)	⨁◯◯◯ Very low	Favors no GCs

CI: confidence interval; **MD:** mean difference

Explanations

a. No randomization
b. Small sample size

Table 9. Data from other observational studies for Pneumococcal vaccine

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
9946, Richi, 2021[9946]	Nonintervent ional, multicenter, cohort study	The recruitmen t period started in October 2014 and the follow-up period finished when the last serological test was performed, at least 4 weeks after the last vaccine was administrat ed.	Patients older than 18 years, suffering from an AIIRD such as RA, PsA, PsO or IBD. In addition, patients had to be on current biological treatment; N=182	Patients completed protocol combining PCV13 and PPV23 following international recs. Blood samples were collected on entry in the study and at least 4 weeks after the last vaccine was given. Immune response to serotypes 1, 3, 7F, 14, 19A, 19F were assessed.	RA and SpA were 70.4% of the diagnoses. 85% were receiving TNFi. Before entering the study, PPV23 had been administered in 115 subjects (63.2%), PCV13 in 21 subjects (12.1%) and only 9 with both vaccines. Analysis of the antibody response confirmed that at least one third of the patients achieved Opsonophagocytic titer (OT) against each pneumococcal serotype (Table 2). GCs did not interfere with immune response to any serotype, nor with the number of serotypes against which OT were achieved. The small group of five patients who received a daily dose of prednisone higher than 7.5 mg, showed a lower number of serotypes with OT than subjects untreated with glucocorticoids (median (IQR): 0 (2.0) vs. 3.0 (3.0), p = 0.023).
2866, Winthrop, 2019 [2866]	Open label long term extension trial's vaccine sub-study	12 weeks	Patients from the phase 3 LTE trial for baricitinib (RA-BEYOND; NCT0188507 8) were invited to participate in this vaccine substudy (n=106); 89%	PCV-13	For the PCV-13 vaccine at week 5, a majority of patients (68%) achieved a ≥ 2-fold increase in concentration in ≥ 6 serotypes; week 12 responses were similar to week 5 responses. The percentage of patients with satisfactory responses was similar for PCV-13 regardless of a baricitinib 2-mg or 4-mg dose, concomitant corticosteroids (71%), and SDAI response.

			on concomitant MTX		
402, Nived 2018 (2)	Cohort, case control	6 weeks	60 patients w RA (50 without DMARD, 10 on MTX); 58% on prednisolone (median dose 5 mg daily, range 0–15 mg) vs 15 patients with primary Sjogren's syndrome (pSS) without DMARD vs 49 controls	13-valent pneumococcal conjugate vaccine (PCV13)	PICO 4 Prednisolone dose did not correlate with antibody response or percentage change in OPA.
4103_Alyasin 2016 (4)	Case control	3 weeks	30 children with SLE 30 age matched control(asthma)	23 valent pneumococcal vaccine IgG anti-PCP Titers before and 3 weeks later using ELISA	PICO 4: The efficacy difference between those taking low and high dose steroids was insignificant

4362 Jarrett 1980 (5)	Case control	6 months	38 SLE (37 female) 5 no meds 29 on prednisone alone 9 on pred/AZA Group 1: prednisone <20mg/day Group 2: prednisone>20mg/day Group 3: both prednisone + AZA vs 23 pts who refused vaccination (22 female) vs 17 healthy volunteers	Pneumococcal vaccine (14 valent)	All three groups had significantly lower mean post-immunization antibody levels than normal control subjects. There was no significant difference between the three treatment groups in AB response.
459 Battafarao 1998 (6)	Cohort	12 weeks	73 SLE 5.5% male/94.5 % female; mean age 43 (18-76) 48% on antimalarial agents , NSAIDS 34%,	Pneumococcal (pneumovax 23), tetanus toxoid and haemophilus influenza type B	<u>PICO 4</u> Patients with 3-fold increase in AB titers post-immunization: those who were not receiving AZA, CYC and prednisone, all developed 3-fold increases to a mean of almost 2 (1.9) of the 3 vaccines. Trend toward decreased antibody response in patients treated with CYC, AZA or prednisone, although this was not statistically significant. There was no significant difference for any individual medication or combination of medications, or by medication dosage.

			AZA 10%, IV CYC 10%, oral MTX 1% 74% on steroids, with 85% oral prednisone <10mg per day		
6278_Crnkik 2013 (7)	Retrospective cohort	1.5 years after vaccination	398 RA(163), SPA(139)	PCV 7 Divided into 6 groups based on Tx Seroprotection: Antibody levels > =1 mg/L	PICO 6: At 1.5 years GML for each serotype lower than at 4 - 6 weeks((P between 0.035 and <0.001;) Lower than prevaccination, but only significant for RA +Anti TNF+ MTX) Lower proportions of patients with protective antibody levels for both serotypes (P < 0.001). PICO 3 SpA (only NSAIDs): significantly higher antibody levels at 4/6 weeks and at 1.5 years (84%) Lowest level of protective antibody levels was seen in RA+ anti-TNF+MTX (52%) Lower in RA vs SpA Concomitant anti-TNF treatment and treatment with MTX were identified as negative predictors of persistence of protective antibody levels for both serotypes tested (P = 0.024 and 0.065, respectively). PICO 4 Use of steroids: no significant differences in both groups
631, Nagel 2015 (9)	Cohort study	Antibody levels measured 4-6 weeks later	248 Patients with RA , 249 with SpA	single dose of 0.5 ml of PCV7 intramuscularly (between May 2008 and June 2009)	Between May 2008 and 31 December 2012, 27 serious infections were identified in 23 patients (four patients had two infections), Table 1. Out of these 27 infections, 23 occurred in RA patients and four in SpA patients (of which only one in SpA patients on NSAIDs without DMARDs). Patients with serious infections after vaccination received oral prednisolone to a larger extent. Mean daily prednisolone dose (range) in patients with and without history of serious infection was 3.8 (0 to

					10) mg and 1.1 (0 to 20) mg, respectively. The majority of patients with serious infections were on higher prednisolone doses (fourth quartile that is ≥7.5 mg daily). Ongoing MTX, anti-TNF or combination of these treatments at vaccination were not associated with serious infections after vaccination, and there were no significant differences in disease duration at vaccination or between men and women. Prednisolone treatment vaccination (yes/no) remained a statistically significant predictor of serious infections after adjustment for age (P <0.001) as well as higher prednisolone doses (P <0.001)
6439 Nielsen 2020 (10)	Cross sectional study	1.5 years of measurement of antibody titers	346 pts RA/SPA or PSA with antibody measurement Compare vaccinated and unvaccinated pts	PPV 23(given prior to initiation of bDMARD therapy) Levels of specific antibodies added to normal blood sample procedure as a part of the clinic visit	PICO 4: Percent of patients on prednisolone did not differ between patients with seroprotection and patients without seroprotection at time of vaccination (27% vs 28%, p = 0.89) or at blood sampling (2% vs 6%, p = 0.17).
647 Morgan 2016 (11)	Cohort-case control	Median FU post vaccination 4.6 years, total patient FU was 363 patient-years (none lost to FU)	92 patients with small or medium-sized systemic vasculitis (EGPA- 7 patients, GPA-59 , MPA-22 or classical PAN-4) in stable remission > 6 months	7-valent conjugate pneumococcal vaccine (Prevnar) Haemophilus influenzae type b (Hib) Meningococcal (Men) group C	<u>PICO 4</u> Previous cumulative steroid dose correlated with the overall infection rate (r 5 0.21, P 5 0.043) but not the serious infection rate (r 5 0.18, P 5 0.097)

			(BVAS = 0), s/p CYC and steroid induction but not within 6 months, had not received RTX within 6 months, on <10mg of prednisone per day, currently on no more than 1 immunosuppressant + prednisolone, no active infections, not pregnant, no hx of previous severe reaction to vaccination or received vaccination to proposed vaccines; age 66 (53-74) 81 patients still taking prednisolone at median of	conjugate vaccine and Men polysaccharide groups A, C, Y, and W135 vaccine	

			5mg/day at time of vaccination. 9 patients on Rituxan, 35 on AZA, 35 on mycophenalate		
7485 Kapetanovic 2013 (12)	Prospective cohort	6 weeks	88 RA patients: 55 RTX - 26 MTX 17 ABA -13 MTX 16 TCZ -9 MTX 85 MTX Vs. 86 controls (SpA pts not on IS)	PCV7 Primary outcome: IgG against 23F and 6B serotypes checked at vaccination, and 4-5 weeks after. Antibody response (AR) was defined as ratio between post- and pre-vaccine Ab levels, and positive AR was >=2	PICO 4: concomitant prednisolone dose had no effect on vaccine response

Table 10. Data from double-blind RCT for pneumococcal vaccine

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
6472 Grabar 2017 (14)	Double-blind RCT	52 weeks	SLE patients Age (median (IQR): 39.5 (33.3-50.7)	25 received PPSV23 17 received PCV7 followed by PPSV23 24 weeks later primary endpoint: rate of responders at week 28 to at least 5 of 7 serotypes shared by both vaccines	PICO 3: At week 28, (4 weeks after PPSV23) primary endpoint achieved by 18/25 (72%) in the PPSV23 group and 13/17 (76%) in the PCV7-PPSV23 group. No differences by IS. PICO 4: no differences between rates of responders in either group in patients treated with and without IS and in those receiving < or > 10 mg prednisone PICO 8: no significant risk of flare detected PICO 20: *Sequential administration of PCV17 followed by PPSV23 is safe and shows short term immunological efficacy in patients with SLE but was not superior to PCV7 alone*

Table 11. Data from observational studies for Tetanus toxoid vaccine (TTV)

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2866, Winthrop, 2019 [2866]	Open label long term extension trial's vaccine sub-study	12 weeks	Patients from the phase 3 LTE trial for baricitinib (RA-BEYOND; NCT01885078) were invited to participate in this vaccine substudy (n=106); 89% on concomitant MTX	TTV	Less than half of patients (43%) achieved ≥ 4-fold increase in concentration at week 5; a greater percentage of patients achieved a ≥ 2-fold concentration increase (74%). For TTV, both ≥ 2-fold and ≥ 4-fold week 12 responses were lower than week 5 responses). However, for TTV, 33% (95% CI 15.2, 58.3) of patients taking baricitinib 2 mg showed a humoral response compared to 45% (95% CI 34.8, 55.3) of those taking baricitinib 4 mg; the percentages were 52% (95% CI 34.8, 68.0) and 39% (95% CI 28.9, 51.1) for those taking and not taking concomitant corticosteroids, respectively.

Table 12. Data from observational studies for Hepatitis B

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2874, Aydin 2020 (27)	Retrospective study	Patients' anti-HBs titers were investigated one	Mixed RMD patients, n=84	Double-dose HBV vaccine (40 µg) on months 0, 1, 2 and 6, and response	Thirty-nine (46.4%) patients were using immunomodulatory therapies such as methotrexate and prednisolone before starting on biological agents. Use of these therapies prior to biological agents had no effect on vaccine response (p=0.392).

		month after completion of the vaccine schedule. Study period: Jan 2017-July 2018		rates were assessed.	

Table 13. Data from observational studies for Influenza vaccine

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3267, Aikawa, 2011 (15)	Prospective, open study. The study was registered with clinical-trials.gov under NCT01151644.	March 2010-April 2010	237 patients with juvenile autoimmune rheumatic diseases ; 91 controls	Single intramuscular dose (0.5 ml) of H1N1 A/California/7/2009 -like virus vaccine (A/California/7/2009/Butantan Institute/Sanofi Pasteur)	Three weeks after immunization, seroprotection rate (81.4% vs 95.6%; p = 0.0007), sero-conversion rate (74.3 vs 95.6%; p < 0.0001), and the factor-increase in GMT (12.9 vs 20.3; p = 0.012) were significantly lower in patients with juvenile ARD versus controls. Glucocorticoid use and lymphopenia were associated with lower seroconversion rates (60.4 vs 82.9%; p = 0.0001; and 55.6 vs 77.2%; p = 0.012). Multivariate logistic regression including diseases, lymphopenia, glucocorticoid, and immunosuppressants demonstrated that only glucocorticoid use (OR 0.20 (0.06–0.70), p = 0.012) remained significant.

3531 Campos 2013 (16)	Prospecti ve open-label cohort study,	3 weeks	pSLE and healthy controls	2009 H1N1 vaccine 92 on antimalarials, 83 on prednisone (mean SD dosage of 18.8 17 mg/day), 72 on immunosuppressive drugs (44 azathioprine, 15 mycophenolate mofetil, and 14 methotrexate).	3 weeks post-vaccination, GMT and factor increase in GMT were both significantly reduced in pSLE patients versus controls. GMT: 90.8, 95% CI: 67.8 to 121.7 pSLE, 237.3, 95% CI: 188.8 to 298.3 controls; p<0.001 Factor increase in GMT: 8.1, 95% CI: 6.3 to 10.5 pSLE, 19.9, 95% CI: 15.6 to 25.4; p<0.001 <u>PICO 4, 13 and 14</u> Multivariate logistic regression indicated that SLEDAI-2K score ≥8 was significantly associated with nonseroconversion (OR 0.42, 95% CI: 0.18 to 0.98; p=0.045), while current prednisone dose was not. SLEDAI-2K score ≥8: 48.8% nonseroconverted, 24% seroconverted; p=0.008 Prednisone dosage (mean±SD mg/day): 18±21.4 non-seroconverted, 10.5±12.5 seroconverted; p=0.018

4351 Gabay 2011 (17)	Prospective cohort study	3-4 weeks	82 with rheumatoid arthritis, 45 with spondylarthritis, 46 with other inflammatory rheumatic diseases and 138 control subjects	Controls received 1 dose of adjuvanted influenza A/09/H1N1 vaccine, and patients received 2 doses of the vaccine. Post-dose 1: 138 patients, 131 healthy controls Post-dose 2: 148 patients 138 on DMARDs (73 MTX, 41 SSZ or HCQ, 23 LEF, 28 AZA or CYC or MMF, 3 other) 22 on Rituximab 67 on oral steroids (46 on <10 mg/day, 21 on ≥10 mg/day)	<u>PICO 4 and 14</u> Use of prednisone was not associated with lower antibody titers (Note: only 21 patients were taking a daily dose ≥10 mg).

4717 Herron 1979 (19)	Case control	4 months (pt with RA were studies for an additional 3 weeks for flares)	32 healthy individuals, 20 pts with SLE, 17 with RA, 8 with DJD, 17 with other rheumatic diseases	All received IM inj of whole bivalent influenza virus vaccine: 200 chick-cell agglutinating(CCA) units of type A/NewJersey/76 (A/NJ) and 200CCA units of type A/Victoria/75 (A/Vict) antigens (MerckSharp&Dohme)	PICO 4 A/New Jersey/76 Age <57 years GMT with glucocorticoids = 16 GMT no glucocorticoids = 71 (p = 0.02) Age ≥57 years GMT with glucocorticoids = 2.4 GMT no glucocorticoids = 16 (p >0.05<0.10, NS) A/Victoria/75 (all ages) GMT with glucocorticoids = 7.3 GMT no glucocorticoids = 14 (p>0.10<0.20, NS)
4721 Mercado 2004 (20)	Single-arm intervention	8 weeks	18 SLE patients in Baja Mexico; 17 patients on pred (mean dose of 14mg/day, range of 2.5-50mg/day); mean Mex-SLEDAI of 5.5	2001-2002 Fluarix trivalent inactivated seasonal influenza vaccine	PICO 4 and 14 There was no significant correlation between antibody response to A/ Moskow, A/New Caledonia, and B/Sichuan with prednisone treatment.

8096 Abu-Shakra 2002 (25)	Case series	12 weeks post-vaccine	24 SLE patients Mean age 46.1 years (range 20-74), 100% females. Mean disease duration 9.1 years. Baseline seroprotection for H3N2/H1N1/B in SLE (20.8/8.3/66.7%) similar to healthy age-matched female controls (n=30; 20/16.7/63.3%). Healthy controls <u>not</u> evaluated post-vaccine.	All participants received one standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B-Influenza). <u>SLE therapies:</u> Oral steroids (n=17), mean prednisone dose 12 mg HCQ 400 mg daily (n=9) AZA 100 mg daily (n=3) MTX (n=4) mean dose 10mg weekly	Mean number of immune responses to the 3 influenza antigens, stratified by age, SLEDAI score, and use of prednisone, MTX, or AZA: Overall mean # of immune responses = 1.5/3 <u>Age:</u> Mean 1.33 for 50+ years, 1.6 for < 50 years. <u>Prednisone:</u> Mean 1.14 if 10+ mg daily vs. 1.65 if < 10 mg daily or none. <u>AZA:</u> Mean 1.33 if taking AZA vs. 1.6 if no AZA. No association of <u>MTX therapy</u> or <u>SLEDAI scores</u> with mean number of immune responses.

9426 Adler 2012 (26)	Nonrandomized comparative	6 months	149 patients: 47 RA, 59 SpA, 15 vasculitis, 28 CTD vs. 40 healthy controls; % of patients >60 was 51% RA, 14% SpA, 40% VAS, 29% CTD, and 8% controls	Single dose of adjuvanted A/H1N1 influenza vaccine; medications included steroids, 93% were on DMARDs (mostly MTX), 46% were on TNFIs, 22% were on both MTX and TNFIs, 10 or fewer patients were each on rituximab, abatacept, tocilizumab, and CYC	Glucocorticoids (mean dose of 7.4 mg/day) did not significantly impair antibody response even when separating for doses <10 and ≥10 mg/day (p=0.11). No significant effect of oral GCs (n=50; mean dose 7.4mg daily) on antibody response (p=0.11). Seroprotection rate: 10.5% T1, 66.5% T2, 57% T3, 27.5% T4 Seroconversion rate: 59.5% T2, 43.5% T3, 26% T4 GMT ratio: 5.2 T2, 3.7 T3, 2.1 T4

Table 14. Data from observational studies for live zoster vaccine

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
5144 Yun 2017 (29)	Cohort study	Up to 7 years after vaccination (retrospective)	59,627 patients who had received live zoster vaccine, identified by ICD coding, and who had received ≥ 12 months continuous Medicare coverage before vaccination and throughout follow up - 53.1% RA - 31.6% PsO - 4.7% PsA	Live zoster vaccine 11% had any biologic use prior to index date 83.5% on no steroids 14% on < 7.5 mg/d	Outcome: first HZ event during follow up. HZ IR in the vaccine group increased from 0.75/100 PY in the first year post vaccine to 1.25/100 PY in the 7th year post-vaccine. whereas HZ IR in unvaccinated group remained consistent through 7 years (1.3-1.7/100 PYs) RR for HZ during years 3-5 in study group ranged from 0.74-0.77. protective effect was not significant after 5 years. Subgroup analysis stratified by glucocorticoid dose (14% of study population on prednisone < 7.5 mg/d, 2.5% receiving ≥ 7.5 mg/d) yielded consistent trends with main analysis.

			- 20.9% IBD - 1.4% AS Mean age 73.5±7.3. Matched to 119,254 in unvaccinated cohort; mean age 73.5±7.3.	2.5% on ≥ 7.5 mg/d	

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PICO 5: In RMD patients on drug Y, do immune responses to neo-antigens (not vaccines) differ from responses seen in the general population?

Summary: The literature search identified two small observational studies addressing this question. Denman et al (1) studied patients with RA or Still's disease on (n=20) and not on cytotoxic drugs (n=39); also had 20 healthy controls. Alternate patients were immunized either with polyvalent influenza vaccine, "Flugen" (Antigen 1), or with tetanus toxoid (Antigen 2). Patients receiving cytotoxic drug therapy for longer than 10 weeks were immunized with a third antigen, brucella vaccine (Antigen 3). Cytotoxic drugs failed to suppress skin reactivity and production of

circulating antibody. Lymphocyte transformation in vitro after stimulation with antigens was not suppressed and may even have been enhanced. Authors concluded that cytotoxic drugs were not demonstrably immunosuppressive in patients with RA and that Ag sensitive and Ab producing lymphocytes escape inactivation despite the concomitant peripheral lymphopenia.

Brinkman et al (2) studied 19 children with RMD undergoing ASCT, 10 adults with MS undergoing ASCT, and reference data from 18 healthy volunteers was also obtained. All patients received one dose of rabies neoantigen vaccine immediately after bone marrow harvest (4 weeks pre-conditioning) and one dose at 6 months post-ASCT. The results of this study indicate that immunoablative conditioning may be sufficient to eliminate immunological memory generated against a neoantigen given after graft harvest and before conditioning. On the other hand, as illustrated by the secondary humoral response to tetanus toxoid in 60% of the children after ASCT, the same transplant procedure including moderately stringent T cell depletion of the graft was insufficient to eliminate immunological memory for a recall antigen boosted before graft harvest.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2989 Denman, 1970	Observational study	March 1966-Jan 1969	Patients with RA on (n=39) and not on cytotoxic drugs (n=20). Also had 20 healthy controls	Influenza vaccine, tetanus toxoid, brucella antigen	Immunological responses of 20 patients with RA or Still's disease were studied before and during treatment with AZA or chlorambucil and were compared with those of 39 patients with same diseases not on cytotoxic drugs and 20 HCs. Cytotoxic drugs failed to suppress skin reactivity and production of circulating antibody. Lymphocyte transformation in vitro after stimulation with antigens was not suppressed and may even have been enhanced. Authors concluded that cytotoxic drugs were not demonstrably immunosuppressive in patients with RA and that Ag sensitive and Ab producing lymphocytes escape inactivation despite the concomitant peripheral lymphopenia.
7309 Brinkman (2007)	Prospective cohort study	Follow-up to 2 years post-ASCT	19 children with RMD undergoing ASCT for treatment of their disease (13 sJIA, 4 pJIA, 2 SLE); median age 9 years (range 4-15), 36.8% female,	All patients underwent autologous stem cell transplantation (ASCT) according to EULAR & EBMT	Humoral response to rabies vaccine: 86% (12/14) of pediatric RMD patients responded to rabies vaccine before ASCT. Anti-rabies Ab titers decreased to pre-vaccine levels in all pediatric RMD patients after ASCT conditioning.

			median disease duration 70 months (range 24-144 months) pre-ASCT. 10 adults with MS undergoing ASCT; median age 37 years (range 23-50), 70% female, median MS duration 60 months (range 24-144). Reference data from 18 healthy volunteers; median age 31 years (range 19-49), 50% female; received single dose of rabies vaccine with one booster dose 3 months later.	guidelines. Immunosuppressive medications were stopped at one month prior to marrow harvest. All patients received one dose of rabies neoantigen vaccine immediately after bone marrow harvest (4 weeks pre-conditioning) and one dose at 6 months post-ASCT	100% of evaluable pediatric RMD patients responded to booster vaccine at 6 months post-ASCT. <u>T cell response to rabies vaccine:</u> 2/5 JIA patients showed proliferative T cell response (SI >3) at 4 weeks after first rabies vaccine pre-ASCT. 1/5 JIA patients showed proliferative T cell response at four weeks after booster rabies vaccination at 6 months post-ASCT.

References:

1. Denman EJ, Denman AM, Greenwood BM, Gall D, Heath RB. Failure of cytotoxic drugs to suppress immune responses of patients with rheumatoid arthritis. Ann Rheum Dis. 1970;29(3):220-31.
2. Brinkman DM, Jol-van der Zijde CM, ten Dam MM, te Boekhorst PA, ten Cate R, Wulffraat NM, et al. Resetting the adaptive immune system after autologous stem cell transplantation: lessons from responses to vaccines. J Clin Immunol. 2007;27(6):647-58.

PICO 6: In patients with [Disease X], is the duration of the immune response to [Vaccine Z] diminished compared to [healthy controls]?

Summary: The literature search revealed 1 RCT and 27 observational studies that addressed this PICO question. Most studies had a small number of patients enrolled and the quality of evidence was very low.

Tetanus: A retrospective study (1) comparing adolescents with juvenile SLE and controls who had received the Tdap booster, noted that protective titers were demonstrated against diphtheria until day 28. Cellular immunity to pertussis was lower in jSLE compared to controls. The authors of a retrospective study (2) of 98 Rheumatoid arthritis and 71 Controls who had received TdaP in the last 10 years noted no significant difference in tetanus IgG titers. In a study (3) of 284 patients with mixed RMD, response to tetanus was lower in mixed RMD population compared to healthy control but the difference was insignificant.

Hepatitis A vaccine: In a study(4) of 47 pts and 67 controls with JIA who received the hepatitis A vaccine, 2 months after 2nd vaccine dose, 91.5% of the study group had +anti-HAV IgG antibody. In another study(5) of 83 JIA patients compared to 76 Healthy controls, between 7 to 18 months the anti-HAV- IgG antibody levels increased significantly for the control (p=0.04) but not for the JIA group (p>0.05).

Pneumococcal vaccine: Studies of patients with SLE(6), RA(7), PsA(7), and other mixed rheumatic diseases (8) have suggested that IgG anti PCP titers remain elevated for between 8-10 years and that outcomes are comparable to controls. A non-randomized single-arm (9) trial of 22 RA patients and 24 controls who received the Prevnar Vaccine revealed that after two months, antibody levels (IgG t = 2) somewhat decreased in both groups; however, they remained significantly higher compared to baseline (RA: 207.6 ± 127.6 mg/l; control: 356.4 ± 171.2 mg/l).

Influenza vaccine: One study of 81 patients with SLE and 81 healthy controls reported higher GMT levels in the SLE group at baseline and 30 days post-vaccination; seroconversion and seroprotection did not differ significantly between groups at 30 days [9980]. In a study of 29 patients with SLE and 17 healthy controls who received non-adjuvanted seasonal influenza vaccination. Patients with SLE had significantly higher antibody titers compared to controls in the first month, and remained higher at 3 months post-vaccination. In a similar study (10) of 21 SLE patients on immunosuppressive drugs who were compared to 15 healthy controls who received the H1N1 vaccination, at 6 months evaluation of GMT, the percentages of seroprotection and seroconversion rate among these groups was different and was dependent on the immunosuppressive medication used. In a study(11) of 69 pts and 69 controls with MCTD who received the IM dose of the H1N1 vaccine, at 21 days, the immune response as measured by seroprotection, seroconversion and GMT was comparable. In a study(12) of 62 SLE on medications vs 47 healthy control who received the inactivated influenza vaccine, the GMT at 4, 12 weeks and the mean fold increase at 4 and 12 weeks tended to be lower in patients compared to controls. A non-randomized comparative study of 149 patients with RMDs (13) who received a single dose of adjuvant A/H1N1 influenza vaccine indicated significantly higher rates for seroprotection and seroconversion in healthy controls vs. RMD patients at all time points (3 weeks, 6 weeks, 6 months). In another prospective cohort study(14) of SLE patients who received the influenza vaccination, GMT titers at D28, 3-4 mo and fold increased at D28 remained lower in the SLE group compared to controls.

Hepatitis B: A study (15) of 262 treatment naïve JIA patients who had received the hepatitis B vaccine revealed that seroprotection was much lower in the JIA group compared to controls over a 4 year duration.

Zostavax: An observational study comparing controls to patients with RA(16) revealed that antibody titers were comparable between the 2 groups at 12 weeks. In a placebo-controlled RCT of 57 RA patients (17) on Tofacitinib who received Zostavax, there was no significant difference in geometric mean fold rise (GMFR) in VZV-specific IgG levels at 6 weeks (about 1 and a half months) and 14 weeks (about 3 months) post-vaccination.

HPV: Another study(18) of 21 female patients stable JIA vs 21 healthy females revealed both at month 6 and month 7 post-vaccine the GMT among cases was lower than that with controls. Two cohort studies(19),(20)of SLE patients who had received the 3 dose Gardasil vaccine concluded seroconversion at 7 months was similar for all serotypes. Another study(21) analysed long term immunogenicity of individual HPV serotypes, persistence of immunogenicity tended to be lower in SLE compared to controls – but the difference was insignificant.

Meningococcal vaccine: In a retrospective cohort study(22) of 127 pts with JIA compared to 1527 controls, at 4.2 years after vaccination, the MenC-specific IgG concentrations were similar to controls.

MMR: In a study (23) of 41 patients with enthesitis-related arthritis and 149 controls who received the MMR at age 2 and age 5, at 1 and 4 years after vaccination, the ERA group had a greater significant decrease in antibody levels.

Overall, these studies suggested that the duration of immune response was comparable between cases and controls, but some findings were inconsistent. While most studies included patients with SLE, RA, JIA and mixed RMD populations – several diseases were underrepresented.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies and RCT data not suitable for GradePro

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
158_peracchi_2021(1)	Case control-prospective	24 months	26 adolescents w juvenile SLE and 26 age/sex matched healthy control adolescents (age between 10-20 years) Inclusion criteria for both groups was 3 doses and 2 booster doses of the DTwP vaccine, the last	Tdap Booster	PICO 6 In control group, protective titers for tetanus were found on D14 (p= 1.000) but subsequently were noticed in both groups at D28 (no p value), D6m (no p value), and D12m (no p value). For diphtheria, protective titers were demonstrated in both groups at D28 (no p value) but not beyond this time point in the jSLE cohort.

			booster at least with a minimum 3 year-interval from the study entry. jSLE patients also had to be on stable immunosuppressives for at least 3 months.		No significant differences were found between jSLE patients and controls regarding tetanus and diphtheria protective titers. Higher frequency of pertussis seroconversion in the control group than in the jSLE group on D14 (p= 0.009), D28 (p= 0/023), D12m (p=0.015)and D24m (p=0.004)
7197_Holmes 2019(2)	Retrospective cohort	Within 10 years	98 Rheumatoid arthritis 71 Controls Excluded those who had received rituximab Tdap vaccine within 10 years of the blood collection for the biorepository	Tdap vaccine within 10 years of the blood collection for the biorepository	PICO 6 no significant difference in tetanus IgG titers was observed between rheumatoid arthritis subjects and controls Compared to controls, rheumatoid arthritis subjects had lower titers against pertussis, but not tetanus, and reduced immunity to pertussis. These results were even more prominent at 5–10 years post-vaccination, when rheumatoid arthritis patients had 50% lower titers than controls and 2.5x more rheumatoid arthritis subjects were not considered immune to pertussis.
2861 Erguven 2011(4)	Open label comparative study	8 months	Juvenile idiopathic arthritis (n=47) and 67 healthy controls with no history of previous Hepatitis A vaccination	Hepatitis A vaccine: 2 doses of hepatitis A vaccine at 6-month intervals, disease activity (CHAQ), adverse effects	2 months after 2nd (and final) vaccine dose, 91.5% of study group and 100% of control group had +anti-HAV IgG antibody (p=0.027).
4088_ Martsi 2017 PICO 3,6,8(5)	Cohort/case control, non-randomized	Nov 2011- Nov 2014	83 JIA (6.3 +/-2.3)/66% females, on MTX (mean dose 12.5mg/week) Vs 76 Healthy controls- age (5.3 +/-2.7)/sex (45% females) matched	Two inactivated anti-HAV vaccine	PICO 6: From 7 to 18 months the anti-HAV- IgG antibody levels increased significantly for the control (p=0.04) but not for the JIA group (p>0.05).

4103_Alyasin 2016(6)	Case control	3 weeks	30 children with SLE 30 age matched control(asthma)	23 valent pneumococcal vaccine IgG anti-PCP Titers before and 3 weeks later using ELISA	PICO 6: significant increases in anti-pneumococcal antibody level after vaccination (p≤0.001). 77.7% of SLE, 86.2% of controls had at least 2-fold increase in titer (p≥0.05). Significant correlations between the level of post-immunization antibody with the age of children with SLE (p=0.02) and their age of disease onset (p=0.02)
6439 Nielsen 2020(7)	Cross sectional study	1.5 years of measurement of antibody titers	346 pts RA/SPA or PSA with antibody measurement Compare vaccinated and unvaccinated pts	PPV 23(given prior to initiation of bDMARD therapy) Levels of specific antibodies added to normal blood sample procedure as a part of the clinic visit	PICO 6: Out of 346, 61 (18%) Had seroprotection 59 (30%) vaccinated patients versus two (1%) unvaccinated patients (p < 0.0001). GMLs of antibodies were significantly higher in the vaccinated patients compared with the unvaccinated patients for each of the 12 different serotypes included in the analysis Antibody response did not significantly decline with time since vaccination, which was up to 8 years for some patients, but this was not a specific data point to analyses.
5147_Broyde (8)	Retrospective cohort	10 years	145 pts with Rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), or inflammatory bowel disease (IBD)-associated	PPSV 23	Antibody levels had been preserved after 10 years Nonsignificant trend toward lower antibody levels among patients who were vaccinated > 5 years before study entry

			spondyloarthropathy (SpA) On biologics [tumor necrosis factor-α (TNF-α) or interleukin 6 (IL-6) receptor inhibitors] or methotrexate (MTX)		
10001 Bjork 2021(10001)	Prospective cohort	90 days	29 pts with SLE, 17 controls	Seasonal influenza, non adjuvanted Vaccine specifici IgG Antibody titers measured using ELISA	Patients with SLE had significantly higher titers compared to controls. Increase from Day 0 to Day 28 was higher in patients compared to controls (p= 0.002 quantile regression, p=0.02 mixed model), titers remained higher at day 90.
3345 Lu 2011[3345]	Controlled clinical trial, not randomized	6 months s/p vaccination	21 SLE; age 34.3 +/- 11.8, all taking one or more immunosuppresives- prednisolone (17), HCQ (15), disease-modifying antirheumatic drugs ,or cytotoxic agents i.e AZA (18), CYC vs 15 healthy controls; sex, age matched	Split-virion inactivated monovalent A/H1N1 vaccination between Dec 2009- Jan 2010	SLE (n=21) vs controls (n=15) GMT T= 0 day 28.28 vs 28.28 T = 21 days 148.74 vs 116.19 T= 6 months 60.14 vs 44.50 Seroprotection rate T= 0 day 9.5% (2/21) vs 6.7% (1/15) T = 21 days 76.2% (16/21) vs 80.0% (12/15) (<0.001) T= 6 months 66.7% (14/21) vs 60.0% (9/15) (<0.001) Seroconversion rate 21 days 76.2% (16/21) vs 80.0% (12/15) 6 months 52.4% (11/21) vs 53.3% (8/15) PICO 6: Prednisolone (n=17), AZA (n=18), HCQ (n=15) GMT T=0 days 30.31 vs 30.31 vs 25.20

					T= 21 days 127.0 vs 113.1 vs 58/.10 T = 6 months 55.08 vs 53.84 vs 58.10 Seroprotection rate T= 0 days 5.9% (1) vs 5.6 % (1) vs 0 T= 21 days 70.6% (12) vs 72.2% (13) vs 80.0% (12) (<0.0001) T= 6 months 64.7% (11) vs 61.1% (11) vs 73.3% (11) (<0.0001) Seroconversion rate T=21 days 70.6% (12) vs 72.2% (13) vs 80.0% (12) T= 6 months 47.1% (8) vs 55.6% (10) vs 66.7% (10) No difference was found in the GMT, the percentages of seroprotection and seroconversion rate among these three groups Prednisolone & AZA (n=15) GMT T= 0 33.6 T=21 days 99.0 T=6 months 48.3 Seroprotection rates T= 0 5.9% (1) T=21 days 70.6% (12) (<0.0001) T= 6 months 60% (9) (<.0001) Seroconversion rates T=21 days 66.7% (10) T = 6 months 40.0% (6) AZA & HCQ (n=12) GMT T= 0 28.3 T=21 days 109.6 T=6 months 49.2 Seroprotection rates T= 0 5.6% (1) T=21 days 75.0% (9) (<0.0001) T= 6 months 66.6% (8) (<.0001) Seroconversion rates T=21 days 75.0% (9) T = 6 months 58.3% (7)

					HCQ & Prednisolone (n=13) GMT T= 0 28.3 T=21 days 134.5 T=6 months 51.51 Seroprotection rates T= 0 0 T=21 days 76.9% (10) (<0.0001) T= 6 months 69.2% (9) (<.0001) Seroconversion rates T=21 days 76.9% (10) T = 6 months 61.5% (8) Evaluation of GMT, the percentages of seroprotection and seroconversion rate among these three groups revealed no specific differences
489 Wiesik-Szewczyk 2010(12)	Case control	12 weeks	62 SLE on medications vs 47 healthy control	Inactivated Influenza vaccine 15ug HA each of A/H1N1, A/H3N2, and B	PICO 3, 6 and 15 GMT at 4 weeks (SLE, controls) H1N1: 39.06, 104.32; p<0.0011 H3N2: 42.97, 91.36; p=0.001 Type B: 50.80, 81.19; p=0.05 GMT at 12 weeks (SLE, controls) H1N1: 24.21, 69.03; p<0.001 H3N2: 25.71, 60.45; p=0.0001 Type B: 28.28, 52.16; p=0.0008 Mean fold increase at 4 weeks (SLE, controls) H1N1: 6.23, 16.48; p=0.000002

					H3N2: 6.61, 14.23; p<0.0001 Type B: 7.02, 11.9; p=0.0002 Mean fold increase at 12 weeks (SLE, controls) H1N1: 3.86, 10.91; p=0.000005 H3N2: 3.96, 9.42; p=0.0001 Type B: 3.91, 7.65; p=0.000086
6910 Adler (2012)(13)	Prospective, single-center, cohort study	Follow-up to 6 months post-vaccine	149 RMD patients (57.7% female; Age: 24.2% <40 years, 45% 40-59 years, 30.8% 60+ years). Includes 47 RA patients, 59 SpA, 15 vasculitis, and 28 CTD patients. 40 healthy controls (65% female; Age: 38% <40 years, 55% 40-59 years, 8% 60+ years). Seasonal influenza vaccine in 127/149 (85.2%) patients vs. 28/40 (70%) controls (mean 4 vs. 3.7 weeks prior to study)	All participants received one standard dose of adjuvanted H1N1 vaccine (2009 pandemic). vaccination (T1), and 3 weeks (T2), 6 weeks (T3) and 6 months (T4) Seroprotection was defined as specific antibody titre 51 : 40 (i.e. HAI), seroconversion as a 4-fold titre increase and the respective seroconversion rate	CHMP criteria: HI titers 1:40 or greater in >70%, seroconversion in >40%, mean increase in GMT >2.5 All three criteria met at all timepoints for controls. None of the criteria met in RMD patients at T4 (6 months). By disease group, CHMP criteria met at T2, T3 in RA, SpA, vasculitis, CTD. CHMP criteria met at T4 in SpA group only.
8187 Holvast (2009)(14)	Prospective cohort study	Follow-up to 3-4 months post-vaccine	80 adult patients with SLE: 54 vaccinated vs. 24 nonvaccinated. Two patients	SLE patients randomized 2:1 to influenza vaccination vs. nonvaccinated patient	Cellular responses: Geometric mean titers (GMT):

			excluded after randomization. Vaccinated SLE patients (n=54): 18.5% male, mean age 44.8 years, 34/54 (63%) prior vaccination. Nonvaccinated SLE patients (n=24): 8.3% male, mean age 45.5 years, 9/24 (37.5%) prior vaccination. Age- and sex-matched healthy individuals (n=54): 20.4% male, mean age 43.1 years, 3/54 (5.6%) prior vaccination. For cellular responses: 38 vaccinated SLE patients vs. 38 age- & sex-matched controls. Mean age 43.4 years, 24% males	control group. All healthy controls vaccinated. Vaccination with single standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B). Vaccinated SLE patients (n=54): 5/54 (9.3%) no medications, 28/54 (51.9%) prednisone (median 5mg daily), 30/54 (55.6%) HCQ (median 400mg daily), 17/54 (31.5%) AZA (median 125mg daily), 6/54 (11.1%) MTX. Nonvaccinated SLE patients (n=24): 5/24 (20.8%) no medications, 10/24 (41.7%) prednisone (median 6.25mg daily), 10/24 (41.7%) HCQ (median 400mg daily), 6/24 (25%) AZA (median 87.8 mg), no MTX.	<u>H1N1</u> T=0: 18.9 in SLE vs. 10.9 in Controls (p<0.01) T=D28: 76.5 SLE vs. 98.2 Controls (p<0.001) T=3-4 months: 51.3 SLE vs. 62.7 Controls <u>H3N2</u> T=0: 15.8 in SLE vs. 12.4 in Controls T=D28: 86.4 SLE vs. 138 in Controls (p<0.01) T=3-4 months: 55.8 in SLE vs. 76 in Controls GMT fold increase at Day 28: H1N1: 4.0 SLE vs. 9.0 in Controls (p<0.001) H3N2: 5.5 SLE vs. 11.1 in Controls (p<0.01)
5318 Maritsi 2013(15)	Prospective case control	One year	89 newly diagnosed JIA patients and 89 controls	Three doses of the HBV vaccine given at 2, 4 and 6–18 months of age-completed at the time of diagnosis with JIA or enrollment into study	The proportion of JIA patients with evidence of HBV immunity was significantly lower than their healthy counterparts. JIA group 55% (49/89) : HBV immune (anti-HBs level ≥10 IU/L) control group : 92% (82/89) HBV immune

					mean concentration of anti-HBs levels in JIA patients was 18.3 IU/L versus 82.6 IU/L in the control group (p<0.001) No differences in seroprotection rates against different JIA subtypes
5014_Stoof 2014 (22)	Retrospective cohort	8 years	127 pts with JIA 1527 controls Pts on methotrexate, biologicals (TNF and IL6), steroids	Meningococcal serogroup C(MenC)	PICO 6: At 4.2 years after MenCC vaccination, the Estimated MenC-specific IgG concentrations similar to controls Adolescents - highest GMCs (patients 2.3 µg/ml (95% PI 1.2–4.7) versus healthy controls 2.3 µg/ml (95% CI 2 to 2.8)). The youngest age group showed the lowest MenC-specific IgG concentrations 4.2 years after MenCC vaccination, again with comparable levels between patients (GMC 0.2 µg/ml (95% PI 0.1–0.5)) and healthy controls (GMC 0.2 µg/ml (95% CI 0.2 to 0.3)).'
2877 Rákóczi 2016(9)	Nonrandomized, single arm trial	2 months	22 RA patients on etanercept in combination with methotrexate (MTX) (n = 15) or monotherapy (n = 7) for at least one year and 24 controls (with OA)	PC13 vaccine (Prevnar)	Duration of response at 2 months 1. After two months, antibody levels (IgG t = 2) somewhat decreased in both groups, however, still remained significantly higher compared to baseline (RA: 207.6 ± 127.6 mg/l; control: 356.4 ± 171.2 mg/l). 2. Mean fold-increase in antibody levels after 8 weeks vs baseline: RA: 2.08-fold vs. Control: 5.2-fold (p=0.039) 3. RA patients receiving ETA-MTX combination (n = 15) vs. ETA monotherapy (n = 7):

					2 month fold increase not sig different: • Combined group: (2.22-fold increase) • Monotherapy group: (1.76-fold increase) Between group difference P = 0.245
3345_Lu_2011 (24)	Controlled clinical trial, not randomized	6 months s/p vaccination	21 SLE; age 34.3 +/- 11.8, all taking one or more immunosuppresives- prednisolone (17), HCQ (15), disease-modifying antirheumatic drugs ,or cytotoxic agents i.e AZA (18), CYC vs 15 healthy controls; sex, age matched	Split-virion inactivated monovalent A/H1N1 vaccination between Dec 2009- Jan 2010	SLE (n=21) vs controls (n=15) GMT T= 0 day 28.28 vs 28.28 T = 21 days 148.74 vs 116.19 T= 6 months 60.14 vs 44.50 Seroprotection rate T= 0 day 9.5% (2/21) vs 6.7% (1/15) T = 21 days 76.2% (16/21) vs 80.0% (12/15) (<0.001) T= 6 months 66.7% (14/21) vs 60.0% (9/15) (<0.001) Seroconversion rate 21 days 76.2% (16/21) vs 80.0% (12/15) 6 months 52.4% (11/21) vs 53.3% (8/15) PICO 6: Prednisolone (n=17), AZA (n=18), HCQ (n=15) GMT T=0 days 30.31 vs 30.31 vs 25.20 T= 21 days 127.0 vs 113.1 vs 58/.10 T = 6 months 55.08 vs 53.84 vs 58.10 Seroprotection rate T= 0 days 5.9% (1) vs 5.6 % (1) vs 0 T= 21 days 70.6% (12) vs 72.2% (13) vs 80.0% (12) (<0.0001) T= 6 months 64.7% (11) vs 61.1% (11) vs 73.3% (11) (<0.0001) Seroconversion rate T=21 days 70.6% (12) vs 72.2% (13) vs 80.0% (12)

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7664 Winthrop 2017(17)	RCT, double-blinded, placebo	up to 14 weeks post-vaccination	RA patients >50 years, 55 Tofacitinib (5mg twice daily) vs 57 placebo 2-3 weeks after vaccination Medications: - All continued MTX - concomitant prednisone <10mg/day allowed	Zoster, live attenuated vaccine	No significant difference in geometric mean fold rise (GMFR) in VZV-specific IgG levels at 6 weeks and 14 weeks post-vaccination. 6 weeks: 2.11 (80% CI: 1.87 to 2.37) tofacitinib (n=54) vs. 1.74 (80% CI: 1.55 to 1.95) placebo (n=53) 14 weeks: 1.64 (80% CI: 1.45 to 1.85) tofacitinib (n=48) vs. 1.50 (80% CI: 1.32 to 1.69) placebo (n=44) Percent of patients with ≥1.5-fold post-vaccination increase in IgG at 6 weeks post-vaccination trended higher with patients receiving tofacitinib (57.4% vs. 43.4%).

4138 Esposito 2014(18)138 Esposito 2014(18)	Cohort	7 months	21 female patients aged 12-25 years w stable JIA - 10 (47.6%) NSAIDs - 5 (23.8%) MTX - 6 (28.6%) etanercept vs 21 healthy females	HPV vaccine (cervarix)	MT *Before the third dose (month 6)*: HPV 16 JIA group 274.40 (6.0) HPV 16 healthy 487.43 (12.2) HPV 18 JIA group: 302.03 (7.6) HPV 18 healthy 463 (11.6) *One month s/p 3rd dose (month 7):* HPV 16 JIA group 6834.38 (170.9); p<0.05 vs. controls HPV 16 healthy 12,177.48 (304.4) HPV 18 JIA group 5120 (128) HPB 18 healthy 6347.86 (158.7)

7676 Soybilgic 2013(19)	Cohort	7 months	27 SLE patients (aged 12 to 26 years), 100% female; 16 evaluable at 7 months	3 doses of 0.5 ml of recombinant, quadrivalent HPV vaccine (Gardasil) Treatments included hydroxychloroquine (100%); prednisone (59.2%); mycophenolate mofetil (33.3%); azathioprine (33.3%); methotrexate (22.2%). The mean prednisone dose was 12.6 mg (range 0–36).	At 7 months (n=16), seropositivity post-vaccine was >94% for HPV 6, 11, 16 and 18. Anti-HPV 6 and 18: 94.4% seropositivity Anti-HPV 11 and 16: 100% seropositivity
4047 Mok 2012(20)	Case control	18 months	50 patients with SLE and 50 health controls, aged 18-35 years, with stable disease	GARDASIL IM at baseline, month 2 and month 6 given to stable lupus patients on the following medications: - Prednisolone 70% - HCQ 66% - AZA 48% - MMF 18% - CSA 4% - Tac 10% MTX 6%	At month 7 seroconversion rates of anti-HPV types 6, 11, 16 and 18 in SLE patients and controls were 74%, 76%, 92%, 76% and 96%, 95%, 98%, 93%, respectively. At month 12, rates were 82%, 89%, 95%, 76% for SLE and 98%, 98%, 98% and 80% for controls.
7786 Koh 2018(16, 25)	Observational cohort study	Oct 2014 to Dec 2015	41 pts with RA, 28pts with OA RA pts: median age 60, 93% female, 93% with seropositive RA, 61% on GC (median dose 2.5mg (IQR 0-5), 93% on MTX (median dose 10 (7.5-12.5), 7% on SSZ, 22% on LEF, 22% on HCQ. [pts	Live attenuated HZ vaccine	<u>VZV specific ELISPOT SFU for RA vs OA:</u> Baseline: Median in RA 5 (IQR 3-10) vs median in OA 9 (3-35), p=0.056 12 weeks: median in RA 18 (9-53) vs 56 (20-119), p=0.001 <u>Anti-VZV IgG INDEX value for RA vs OA:</u> BL: 5.5 (2.6-8) vs 8 (4.8-10), p=0.022

			taking biologics, CYC, prednisolone >=20mg within 3 mo of enrollment were excluded] OA median age 62 years, 86% female.		12 weeks: (exact values cannot be estimated as they are presented on graph). In text: "Because the values at 12 weeks after vaccination were increased in all participants, the anti-VZV IgG index values were not significantly different between the 2 groups".
5156_Maritsi_PICO 3_6(26)	Prospective cohort	3 years	41 - ERA 149 controls	MMR received at age 2 and age 5	PICO 6: Measles: • Seroprotection: similar in ERA and control • IgG: • Lower in the ERA (P < 0.05) at 1 and 3 years' follow-up, but not at diagnosis • GMC: lower at 3 years Rubella: • Seroprotection: similar in ERA and control • IGG: • Lower in the ERA (P < 0.05) at 1 and 3 years' follow-up, but not at diagnosis (P < 0.01) • GMC: lower at 3 years During the follow-up period, the ERA group had greater decrease in antibody levels as indicated from the significant interaction effect of analysis (both measles and rubella).

Table 2. Response to tetanus vaccine in mixed RMDs v healthy controls, GMC at 3 months compared to placebo. 7670 Buhler 2019. (3)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mixed RMDs	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Response to tetanus in mixed RMDs v healthy controls, GMC at 3 months												
1	observational studies	not serious	not serious	not serious	serious[a]	none	284	253	-	MD **1.56 lower** (2.24 lower to 0.88 lower)	⨁◯◯◯ Very Low	Favors healthy controls

CI: confidence interval; **MD:** mean difference

a. Small sample size

Table 3. Hepatitis A vaccine in patients with JIA versus healthy controls . 2861_Erguven_2011_PICO_6. (4)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Response to Hep A vaccine (positive anti-HAV Ab titer)												
1			not serious	not serious		none	47 JIA 67 controls		-			

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
	observational studies	not serious			Serious(small sample size)				**OR 0.07** (0.00 to 1.36)		⊕◯◯◯ Very Low	

CI: confidence interval; **OR:** odds ratio

Table 4. IgG level 2 months after PCV13 vaccination in patients with RA. 2877_Rákóczi_2016 (9)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IgG level 2 months after vaccination in RA	Control	Relative (95% CI)	Absolute (95% CI)		
RA vs Control												
1	observational studies	not serious	not serious	not serious	serious[a]	none	22	24	-	MD **148.8 lower** (235.76 lower to 61.84 lower)	⊕◯◯◯ Very Low	Favors control
RA+TNF monotherapy vs RA+combination therapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IgG level 2 months after vaccination in RA	Control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	7	15	-	MD **29.7 lower** (128.31 lower to 68.91 higher)	⊕◯◯◯ Very Low	

CI: confidence interval; **MD:** mean difference

a. Small sample size

Table 5. SLE compared to Healthy controls, week 12 (influenza vaccine). 489 Wiesik-Szewczyk 2010. (12)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 6 SLE	Healthy controls, week 12	Relative (95% CI)	Absolute (95% CI)		
Seroconversion week 12 H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 6 SLE	Healthy controls, week 12	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	20/62 (32.3%)	37/47 (78.7%)	**RR 0.41** (0.28 to 0.61)	**464 fewer per 1,000** (from 567 fewer to 307 fewer)	⊕◯◯◯ Very Low	Favors healthy controls

Seroconversion week 12 H3N2

1	observational studies	not serious	not serious	not serious	serious[a]	none	25/62 (40.3%)	33/47 (70.2%)	**RR 0.57** (0.40 to 0.82)	**302 fewer per 1,000** (from 421 fewer to 126 fewer)	⊕◯◯◯ Very Low	Favors healthy controls

Seroconversion week 12 Type B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 6 SLE	Healthy controls, week 12	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	23/62 (37.1%)	30/47 (63.8%)	**RR 0.58** (0.39 to 0.86)	**268 fewer per 1,000** (from 389 fewer to 89 fewer)	⊕◯◯◯ Very Low	Favors healthy controls

Seroprotection week 12 H1N1

1	observational studies	not serious	not serious	not serious	serious[a]	none	27/62 (43.5%)	44/47 (93.6%)	**RR 0.47** (0.35 to 0.62)	**496 fewer per 1,000** (from 609 fewer to 356 fewer)	⊕◯◯◯ Very Low	Favors healthy controls

Seroprotection week 12 H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 6 SLE	Healthy controls, week 12	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	32/62 (51.6%)	43/47 (91.5%)	**RR 0.56** (0.44 to 0.73)	**403 fewer per 1,000** (from 512 fewer to 247 fewer)	⊕◯◯◯ Very Low	Favors healthy controls

Seroprotection week 12 Type B

1	observational studies	not serious	not serious	not serious	serious[a]	none	33/62 (53.2%)	37/47 (78.7%)	**RR 0.68** (0.51 to 0.89)	**252 fewer per 1,000** (from 386 fewer to 87 fewer)	⊕◯◯◯ Very Low	Favors healthy controls

CI: confidence interval; **RR:** risk ratio

a. Small sample size

Table 6. Response to H3N2 vaccine at 30 days in SLE patients vs healthy controls [9980]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
GMT in SLE compared to HC D0 (pre-vaccination)												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	81	81	-	MD **74.3 higher** (47.85 higher to 100.75 higher)	⨁◯◯◯ Very low	Favors SLE
GMT in SLE vs Healthy Controls D30 post vaccination												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	81	81	-	MD **145.4 higher** (91.28 higher to 199.52 higher)	⨁◯◯◯ Very low	Favors SLE
Seroprotection D0 between SLE and HC												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	72/81 (88.9%)	62/81 (76.5%)	**OR 2.45** (1.03 to 5.81)	**123 more per 1,000** (from 5 more to 184 more)	⨁◯◯◯ Very low	Favors SLE

Seroprotection D30 between SLE and HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	77/81 (95.1%)	74/81 (91.4%)	**OR 1.82** (0.51 to 6.48)	**37 more per 1,000** (from 70 fewer to 72 more)	⨁◯◯◯ Very low	

Seroconversion D30 between SLE and HC

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/81 (16.0%)	9/81 (11.1%)	**OR 1.53** (0.61 to 3.81)	**49 more per 1,000** (from 40 fewer to 211 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. observational study

b. small sample

Table 7. RMD patients compared to healthy controls (A/H1N1 vaccination). 9426 Adler (2012) (13)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection rate - T1												
1	observational studies	not serious	not serious	not serious	serious[a]	none	15/149 (10.1%)	4/40 (10.0%)	**RR 1.01** (0.35 to 2.87)	**1 more per 1,000** (from 65 fewer to 187 more)	⨁◯◯◯ Very Low	
Seroprotection rate - T2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	101/149 (67.8%)	39/40 (97.5%)	**RR 0.70** (0.62 to 0.78)	**293 fewer per 1,000** (from 371 fewer to 214 fewer)	⊕◯◯◯ Very Low	

Seroprotection rate - T3

1	observational studies	not serious	not serious	not serious	serious[a]	none	88/149 (59.1%)	38/40 (95.0%)	**RR 0.62** (0.53 to 0.72)	**361 fewer per 1,000** (from 446 fewer to 266 fewer)	⊕◯◯◯ Very Low	

Seroprotection rate - T4

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	40/149 (26.8%)	30/40 (75.0%)	**RR 0.36** (0.26 to 0.49)	**480 fewer per 1,000** (from 555 fewer to 383 fewer)	⊕◯◯◯ Very Low	

Seroconversion rate - T2

1	observational studies	not serious	not serious	not serious	serious[a]	none	95/149 (63.8%)	34/40 (85.0%)	**RR 0.75** (0.63 to 0.90)	**213 fewer per 1,000** (from 315 fewer to 85 fewer)	⊕◯◯◯ Very Low	

Seroconversion rate - T3

1	observational studies	not serious	not serious	not serious	serious[a]	none	80/149 (53.7%)	32/40 (80.0%)	**RR 0.67** (0.54 to 0.83)	**264 fewer per 1,000** (from 368 fewer to 136 fewer)	⊕◯◯◯ Very Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion rate - T4												
1	observational studies	not serious	not serious	not serious	serious[a]	none	49/149 (32.9%)	26/40 (65.0%)	**RR 0.51** (0.37 to 0.70)	**319 fewer per 1,000** (from 410 fewer to 195 fewer)	⨁◯◯◯ Very Low	
Seroprotection rate, 3 weeks												
1	observational studies	not serious	not serious	not serious	serious[a]	none	101/149 (67.8%)	39/40 (97.5%)	**RR 0.70** (0.62 to 0.78)	**293 fewer per 1,000** (from 371 fewer to 214 fewer)	⨁◯◯◯ Very Low	
Seroprotection rate, 6 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	88/149 (59.1%)	38/40 (95.0%)	**RR 0.62** (0.53 to 0.72)	**361 fewer per 1,000** (from 446 fewer to 266 fewer)	⊕◯◯◯ Very Low	

Seroprotection rate, 6 months

1	observational studies	not serious	not serious	not serious	serious[a]	none	40/149 (26.8%)	30/40 (75.0%)	**RR 0.36** (0.26 to 0.49)	**480 fewer per 1,000** (from 555 fewer to 383 fewer)	⊕◯◯◯ Very Low	

Seroconversion, 3 weeks

1	observational studies	not serious	not serious	not serious	serious[a]	none	95/149 (63.8%)	34/40 (85.0%)	**RR 0.75** (0.63 to 0.90)	**213 fewer per 1,000** (from 315 fewer to 85 fewer)	⊕◯◯◯ Very Low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, 6 weeks												
1	observational studies	not serious	not serious	not serious	serious[a]	none	95/149 (63.8%)	34/40 (85.0%)	**RR 0.75** (0.63 to 0.90)	**213 fewer per 1,000** (from 315 fewer to 85 fewer)	⨁◯◯◯ Very Low	
Seroconversion, 6 months												
1	observational studies	not serious	not serious	not serious	serious[a]	none	49/149 (32.9%)	26/40 (65.0%)	**RR 0.51** (0.37 to 0.70)	**319 fewer per 1,000** (from 410 fewer to 195 fewer)	⨁◯◯◯ Very Low	

CI: confidence interval; **RR:** risk ratio

a.Small sample size

Table 8. Vaccinated SLE patients compared to healthy controls (subunit influenza vaccines). 8187_Holvast (2009) (14)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - T0 - H1N1												
1	observational studies	not serious	not serious	not serious	serious[a]	none	15/54 (27.8%)	8/54 (14.8%)	**RR 1.88** (0.87 to 4.05)	**130 more per 1,000** (from 19 fewer to 452 more)	⊕◯◯◯ Very Low	
Seroprotection - T0 - H3N2												
1	observational studies	not serious	not serious	not serious	serious[a]	none	8/54 (14.8%)	9/54 (16.7%)	**RR 0.89** (0.37 to 2.13)	**18 fewer per 1,000** (from 105 fewer to 188 more)	⊕◯◯◯ Very Low	
Seroprotection - Day 28 - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	44/54 (81.5%)	48/54 (88.9%)	**RR 0.92** (0.78 to 1.07)	**71 fewer per 1,000** (from 196 fewer to 62 more)	⨁◯◯◯ Very Low	

Seroprotection - Day 28 - H3N2

1	observational studies	not serious	not serious	not serious	serious[a]	none	41/54 (75.9%)	50/54 (92.6%)	**RR 0.82** (0.69 to 0.97)	**167 fewer per 1,000** (from 287 fewer to 28 fewer)	⨁◯◯◯ Very Low	Favors healthy controls

Seroprotection - 3-4mths - H1N1

1	observational studies	not serious	not serious	not serious	serious[a]	none	36/54 (66.7%)	39/54 (72.2%)	**RR 0.92** (0.72 to 1.19)	**58 fewer per 1,000** (from 202 fewer to 137 more)	⨁◯◯◯ Very Low	

Seroprotection - 3-4 mths - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccinated SLE patients	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	37/54 (68.5%)	45/54 (83.3%)	**RR 0.82** (0.66 to 1.02)	**150 fewer per 1,000** (from 283 fewer to 17 more)	⨁◯◯◯ Very Low	

CI: confidence interval; **RR:** risk ratio

a. Small sample size

Table 9. Persistence of immunogenicity of HPV-11 at 5 years, SLE v controls. 5154 Mok 2018. (21)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	controls	Relative (95% CI)	Absolute (95% CI)		
Persistence of HPV-11 at 5 years, SLE v controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	26/31 (83.9%)	32/33 (97.0%)	**RR 0.86** (0.73 to 1.02)	**136 fewer per 1,000** (from 262 fewer to 19 more)	⨁◯◯◯ Very Low	

CI: confidence interval; **RR:** risk ratio

a. Small sample size

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PICO 7. Do patients with [Disease X] have higher rates of adverse events following [Vaccine Z] compared to [healthy controls]?

This question was part of the initial project plan but later dropped based on the consensus of the Core Team.

PICO 8: Do patients with [Disease X] experience flares of their underlying RMD after immunization with [Vaccine Z]?

The literature search identified randomized controlled trials and/or observational studies addressing this question for the following vaccines: influenza, haemophilus influenza, pneumococcal, hepatitis A and B, HPV, meningococcal, MMR, polio, shingles, Tdap, typhoid, and yellow fever. This document contains separate summary sections for each of the vaccines listed above (in that order).

Influenza Vaccine

Summary: The literature search identified 3 randomized controlled trials[1-3] and 63 observational[4-64][9980][10045] studies that addressed PICO question 8 regarding the influenza vaccine.

In a double-blind study of 40 pts with SLE who were randomly assigned to receive inactivated bivalent influenza vaccine or saline, the flare rate was similar between the two groups at 20 weeks (2/21 in the influenza vaccinated group and 2/19 in the saline group)[1]. In ANCA vasculitis, 31 patients in remission for 3 months or more were randomized 3:1 to receive trivalent influenza or no vaccine (n=27 and n=7 respectively). No significant change in disease activity occurred in vaccinated individuals compared to unvaccinated, and no increase in ANCA, Creatinine, or CRP levels was seen at 28 days. There was a single disease relapse episode in one MPA patient at 6 months post vaccine compared to none in the non-vaccinated group[2]. In SLE, 80 patients were randomized 2:1 to receive influenza vaccination or not (n=54 and n=24, respectively). There were no significant differences noted between vaccinated and non-vaccinated patients in SLEDAI or VAS at baseline, 28 days and 3-4 months of follow up[3].

However, most of the studies that reported on risk of flare and clinical or laboratory parameters of disease activity post vaccination were observational. In an observational nested case control study, 25 patients with PsA on anti-TNFa treatment, who were vaccinated with an adjuvanted vaccine for seasonal influenza, and matched for age, sex, disease activity and therapy with non-vaccinated PsA patients, vaccinated PsA patients showed a significant increase in tender joint count, ESR, HAQ, PtGA and PhGA at 1 month compared to the non-vaccinated PsA patients, and at 3 months for ESR and PtGA (but not TJC, HAQ or PhGA)[53]. When 24 patients with low or stable disease activity (14 with SLE and 10 with RA), who were immunized with trivalent split influenza vaccine without adjuvant, were compared against 24 age- and sex-matched non-vaccinated patients (14 with SLE and 10 with RA), no significant difference was observed on the clinical activity or auto-antibodies before and after vaccination (90 and 180 days)[50]. In a prospective, open, monocenter, vaccine phase III study on 199 patients with autoimmune diseases (vasculitis, systemic sclerosis, SLE, Sjogrens, others) subjects received either seasonal and/or non-adjuvant HFV (A/H1N1) flu vaccines. Within 30 days of inoculation, 6 flares were reported, mostly mild[39]. In a retrospective nested case-control study of 230 consecutive ANCA vasculitis patients with at least 1 year of follow up it was shown that the relapse rate per 100 patients at risk was lower in vaccinated patients compared to unvaccinated (3.4 vs 6.3) when analyzed for the entire year and for every quarter of the year. Disease free survival per separate year according to vaccination status was lower in all 5 years in patients who had been vaccinated (statistically significant in two years)[16]. Similarly, a study that utilized within persons comparison and self-controlled case series methodology showed that among 14,928 cases of autoimmune rheumatic diseases (80% RA) there was no association between vaccination and primary care consultation for RA flare, corticosteroid prescription, fever or vasculitis. Vaccination was association with reduced primary care consultation for joint pain in the subsequent 90 days (incidence rate ratio 0.91, 95% CI 0.87-0.94)[30]. In a prospective randomized parallel-group trial that investigated whether temporary discontinuation of methotrexate in patients with RA (n=199) improves the efficacy of seasonal influenza vaccination, RA flares occurred in 24%, 21%, 34% and 39% in groups of patients 1 to 4 respectively at 16 weeks post vaccination (group 1: continue MTX, group 2: suspend MTX for 4 weeks before vaccination, group 3: suspend MTX for 2 weeks before and 2 weeks after vaccination, and group 4: suspend MTX for 4 weeks after vaccination), which was not statistically significant despite methotrexate being held for 4 weeks in groups 2-4 for 4 weeks at different timings around vaccination[27]. To the contrary, a cross sectional study of 101 SLE patients that were matched to 101 controls (all received seasonal influenza vaccination) a flare rate of 43% (43/101) was reported at 12 weeks post-vaccination. The study also showed new onset transient aCL development post vaccination at similar rates among patients and controls[7]. In conclusion, most of the observational studies showed no increased risk of disease flare after vaccination against influenza with some exceptions. Severe flares were very rare post vaccination.

Children:

Among children with rheumatic diseases prospective cohort studies do not support increased risk of flare after administration of influenza vaccine. Ninety-one JIA patients who received a single dose monovalent influenza vaccine had no worsening in the median number of active joint or acute phase reactants or CHAQ score at 3 weeks post vaccination compared to prior to vaccination[61]. No flares were noted at 6 months post vaccination in 35 JIA patients (15 on TNFi, 4 on anakinra and 6 on tocilizumab) after one or two doses of trivalent non-adjuvanted influenza vaccine over two seasons (JADAS score increased in 6/35, however)[55], or in 70 children with rheumatic diseases (49 with JIA, 11 with SLE, 10 other) after one or two doses of split type influenza vaccine (Fluarix) at 2 months[41]. In 49 children with pediatric rheumatic disease (most on prednisolone at varying doses, usually <0.2mg/kg) two had a disease flare within two weeks of influenza HA vaccination (2 doses, 1-4 weeks apart)[29]. In 55 patients with definite CAPS treated with canakinumab and followed at 14 centers in 9 countries, influenza vaccination did not result in CAPS reactivation[43]. Additionally, 17 patients with CAPS on canakinumab (aged 28 days to 60 months with confirmed NLRP3 mutations, body weight>=2.5kg and active disease at enrollment), who received inactivated vaccinations as part of the national vaccination program, were not noted to have increased frequency of flares within 8 weeks from vaccination[56]. From a nationwide survey in Germany, 90 children with rheumatic diseases from 16 pediatric rheumatological sites who received ASO3 adjuvanted H1N1 did not have increase in disease activity before and after influenza vaccination at median follow of 4 weeks. However, 4 patients (4.4%) sustained a flare in 2-5 weeks after vaccination[19]. Finally, among 31 children with JIA (10 boys, 21 girls, mean age of 11 years) on various therapies who received the annual influenza vaccine Begrivac 2008/2009, 4/31 (13%) experienced a flare of JIA in one month and 7/31 (23%) in 5 months post vaccination[12].

Quality of evidence across all critical outcomes: Low

Table 1. Data from RCTs and observational studies not suitable for RevMan

RefID, Author, Year	Study type	Duration	Population Description	Treatment given to relevant population	Results
10045 Milanovic 2022 [10045]	Cross-sectional , case- control	6 months	50 patients with autoimmune rheumatic diseases (Systemic Lupus Erythematosus—24; Rheumatoid Arthritis—15; and Sjögren's Syndrome—11), who were at least 65 years old or whose relative disease duration (disease duration/age) was greater than 1/8	Trivalent inactivated non-adjuvant influenza vaccine- 34 patients No vaccine- control group, 16 patients	Vaccine well tolerated by all SLE, RA and SS patients. No exacerbation of the underlying disease was observed.
9980 Formiga 2021[9980]	Prospective longitudinal	30 days	81 consecutive SLE patients and 81 age- and sex-matched healthy controls (HC)	H3N2 vaccine	Based on SLEDAI 2K scores, no significant changes were observed at D0 and D30

			The mean age (40.4 ± 11.6 vs 40.1 ± 10.9 years,p= 0.851), and frequencies of female sex (86% vs 86%, p= 1.000), and current smoking (4% vs 4%, p= 1.000) were similar in SLE patients and HC. SLE patients had higher frequencies of non-Caucasian race (56(69) vs 31 (38), p= 0.0001) and higher body mass index than HC (27.7 (16.2–42.3) vs 25.0 (18.4–47.3), p= 0.004). The mean disease duration for SLE patients was 12.2 ± 7.4 years.		[2 (0min-16max) vs 2 (0min-14max), p=0.665] No differences in current use and dose of HCQ, GC, AZA, cyclophosphamide, mtx,MMF, LEF were identified btw D0 and D30.
1351_Louie 1978	Case series	3 months	11 SLE pts, age 18-56 years, 10 women 8 controls, age 27-40 years, 5 women	Influenza whole bivalent A /New Jersey/76 (Hsw1N1) and A/Victoria/75 (H3N2)	Only one patient w significant change in clinical activity within 3 month observation period-fatigue, erythematous skin lesions, lab abnl and bx c/w diffuse, proliferative GN
1671 Launay 2013	Cohort	30 days	27 SLE SLEDAI = 0 5 SLEDAI 1-4 = 17 SLEDAI >4 = 5	2009–2010 seasonal trivalent inactivated influenza vaccine (Mutagrip®, Sanofi Pasteur Paris, France): A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2) and B/Brisbane/60/2008	- SLEDAI 3.9 ± 3.8 D0 and 3.3 ± 3.7 D30 - ANA 3036.2 ± 3670.2 D0 vs 3239.2 ± 3924.5 D30 (p=NS) - IgG anti-dsDNA Abs levels 109.0 ± 171.9 A.U D0 vs 120.4 ± 210.9 A.U D30 (p=NS)
2503_Jain_2017	Cohort, case control, prospective	Feb- March 2014	DMARD group: 51 patients w RA on MTX ≥ 15mg/wk x 3 months or more (concurrent SSZ, HCQ and/or prednisolone ≤ 7.5mg/day were continued); age 49.4 +/- 10.5, 98% females vs DMARD-naïve group:	Inactivated seasonal trivalent influenza vaccine (containing A/California/7/2009-H1N1 and A/Vicotria/361/2011- H3N2 and one B strain – B Massachusetts/2/2012)	The mean disease activity was reduced in the DMARD group during post-vaccination period. However, the reduction in DAS28 score (ΔDAS28 - 0.42) was not clinically significant.

			51 RA patients DMARD naïve (tx NSAIDS & IA or low dose PO steroids [prednisolone 7.5mg/day or less]; age 43.4 +/-12.2; 84.3 % females vs 45 Healthy controls; age 41.4+/-6.7; 62.2% females		DAS28 reduction in DMARD-naïve group, was clinically significant (ΔDAS28 - 1.41). Disease activity worsened post-vaccination in five (9.80%) patients and remained the same in two (3.92%) patients in DMARD group, while it increased in three patients (5.88%) in DMARD-naïve group.
2526 Park 2017	Prospective single-center randomized single-blind parallel-group intervention study	20 weeks (4 weeks pre-vaccine, 16 weeks postvaccine)	277 patients with RA aged 18 years or older and on a stable dose of MTX for 6 weeks or longer	All participants received one dose of inactivated seasonal trivalent influenza vaccine (H1N1/H3N2/B-Yamagata). Randomized 1:1:1:1 to: Group 1 (n=69) continue MTX; Group 2 (n=68) suspend MTX for 4 weeks before vaccination; Group 3 (n=71) suspend MTX for 2 weeks before & 2 weeks after vaccination; Group 4 (n=69) suspend MTX for 4 weeks after vaccination.	Primary analysis performed on per-protocol population (n=199): Group 1 (n=54), Group 2 (n=44), Group 3 (n=49), Group 4 (n=52). <u>Noncomparative data:</u> Group 1 (n=54) RA patients receiving influenza vaccine while continuing MTX. 46.3% on GC (mean dose 2.2 mg daily), mean MTX dose (12.7 mg weekly), 9.3% SZZ, 18.5% HCQ, 25.9% LEF, 9.3% TNFi. <u>RA flares:</u> (Flare = Increase in DAS28 of >1.2, or >0.6 if baseline DAS28 was 3.2 or greater) RA flare occurred in 24.1%, 21.2%, 34.1% and 38.8% in groups 1, 2, 3 and 4, respectively (p=NS).
2613_Elkayam_2011	Cohort, case control	Nov 2009-Jan 2010	41 RA patients (age 52.6 +/-14.5); MTX 25 (61%), prednisone 19	Adjuvanted H1N1v monovalent	Parameters of disease activity

			(46.3%), TNF 13 (31.7%), HCQ 6 (14.6%) 21 SLE (41.7 +/-11.5); MTX 3 (14.3%), prednisone 15 (71.4%), TNF none, HCQ 15 (71.4%) 17 PsA (48.5 +/-11.8); MTX 7 (41.2%), prednisone 3(17.6%), TNF 14 (82.4%), HCQ none 15 ASpond (47.2 +/- 13.3); MTX 1 (6.7%), prednisone none, TNF 12 (80%), HCQ none 25 healthy controls age (46.5 + /- 12.1) and sex matched	influenza vaccine	remained stable among the RA, SLE, PsA, and AS patients
2479_Holvast_ 2009	Controlled clinical trial, not randomized, open prospective	Oct-Dec 2007	52 SLE patients w quiescent disease; mean age 45.2 +/- 10 yrs; 17.3% males Most used immunosuppresives especially prednisone (31 pts), HCQ (25 pts) , and AZA (15 pts); 5 not on meds 7 on other immunosuppressive drugs: 4 on MTX, 2 MMF, 1 cyclosporin vs 28 Healthy control age and sex matched Subanalysis for PICO 3: 28 pts on prednisone and/or AZA vs 17 pts using no immunosuppressives or HCQ only. 7 pts using other immunosuppressive drugs then prednisone, AZA and HCQ (excluded)	trivalent subunit influenza vaccine s/p 4 weeks only SLE patients received a second booster dose of vaccination	SLEDAI scores and levels of anti-dsDNA AB did not increase following vaccinations, levels of C3 and C4 remained stable 19.6% of SLE pts experienced erythema after both 1st and 2nd vaccination, compared to controls (0%, p=0.013)
3062 Setti 2009	Open-label, cohort study	12 months	46 scleroderma 20 controls age- and gender-matched	Trivalent seasonal influenza vaccine: 15 ug of hemagglutinin (HA) for A/Wisconsin/67/2005 (H3N2); A/New Caledonia/20/99	*no standard disease activity scores used - laboratory profiles: ESR, CRP, Fibrinogen, Ferritin, C3, C4, ANA, WBC

				(H1N1); B/Malaysia/2506/2004	'no major change, in particular no worsening was Observed' in T0 to T12 - graphical representation on clinical status 'organ involvement score' changes 'Changes were few, modest, insignificant and mainly in the direction of improvement'
3345_Lu_2011	Controlled clinical trial, not randomized	6 months s/p vaccination	21 SLE; age 34.3 +/- 11.8, all taking one or more immunosuppresives-prednisolone (17), HCQ (15), disease-modifying antirheumatic drugs ,or cytotoxic agents i.e AZA (18), CYC vs 15 healthy controls; sex, age matched	Split-virion inactivated monovalent A/H1N1 vaccination between Dec 2009- Jan 2010	No neurological or psychiatric manifestations of SLE before and after this vaccination. Only one SLE patient w optic neuritis 4 yrs prior to vaccination experienced malaise, sore throat, fever, blurred vision 2 weeks after vaccination; dx with sle flare w b/l optic neuritis and demyelination. None of the other vaccinated SLE patients experienced significant flares or increase in SLEDAI score
3731 van Assen 2010	Prospective cohort study	28 days post-vaccine	23 adult patients with RA on RTX (Mean age 55.5 years, 70% female, 12/23 (52%) influenza vaccine in preceding year, median RA duration 13.8 years) 20 patients with RA on MTX (Mean age 57.1, 55% female, 10/20 (50%)	All participants received one standard dose of trivalent inactivated seasonal influenza vaccination. RA-RTX group (n=23): RTX 1000 mg IV x 2 doses, 2 weeks apart, except 375 mg/m2 IV wekly x 4 doses. First RTX cycle	DAS28 measured at baseline, Day 7, and Day 28 post-vaccination & reported as medians (range): <u>MTX group (n=20):</u> Baseline: 3.04 (0.77-5.17) Day 7: 2.93 (0.49-3.71) Day 28: 2.59 (1.00-4.22)

			influenza vaccine in preceding year, median RA duration 8.7 years) 29 healthy volunteers (Mean age 46.5 years, 79% female, 21/29 (72%) influenza vaccine in preceding year) Baseline CD19+ cells significantly higher in healthy controls & RA-MTX group compared to RA-RTX group ($p<0.001$)	in 11/23 (48%), second cycle in 5/23 (22%). Median MTX dose 17.5 mg weekly, median prednisone dose 8.75mg OD Vaccination 4-8 wks post-RTX in 11 patients (Early) vs. 6-10 months post-RTX in 12 patients (Late). Baseline CD19+ B cell numbers similar in both subgroups. RA-MTX (n=20): Median MTX dose 16.3 mg weekly, one patient on SSZ, one patient on LEF, no corticosteroids	P=0.287 <u>RTX group (n=23):</u> Baseline: 3.95 (2.15-5.71) Day 7: 3.97 (2.15-6.26) Day 28: 4.02 (2.04-6.77) P=0.834 No significant differences in DAS28 scores between timepoints in either group.
3904_Zhou 2021	Cohort, case control	3 months s/p vacc	17 pts w Primary Sjogrens syndrome (pSS)(16 female, 1 male); mean age 49.23 +/- 14.37 yrs vs 16 healthy controls; age and sex matched (15 female, 1 male)	Influenza vaccine	Changes in disease activity scores, including ESSDAI and ESSPRI, were observed 3 months after vaccination in pSS patients
4703 Vista 2012	Cross sectional observational study	Case control	101 SLE patients and age, race, and sex matched healthy controls	Seasonal flu vaccine	43 out of 101 (42.6%) patients developed disease flares after vaccination
4080 Kostianovsky 2012	Cohort	6 months (4.5 months after 2nd dose of H1N1)	199 mixed adult RMD patients (SNV, SScl, SLE, SS, and others	<u>seasonal flu (SFV)</u> – Mutagrip, a trivalent, inactivated-influenza single-dose vaccine and <u>H1N1 flu (HFV)</u> – Panenza, a monovalent, inactivated split-virion, A/H1N1 vaccine	6 flares were reported as temporally related to vaccination (within 30 days of inoculation): • polyneuritis in a CSS patients 3 days after 1st HFV dose • arthritis and purpura in a Wegener's

					disease patient at day 20 after 1st HFV dose • skin rash in a SS patient at day 10 after SFV • aphthae in a patient with Behcet's disease at day 1 after HFV dose • arthralgias in a patient with AS at day 2 after 1st HFV dose • asymptomatic hypereosinophilia in a CSS patient at day 3 post 1st HFV dose 13 mild flares were regarded as temporally unrelated to vaccination.
4351 Gabay 2011	Prospective cohort study	3-4 weeks	82 with rheumatoid arthritis, 45 with spondylarthritis, 46 with other inflammatory rheumatic diseases and 138 control subjects	Controls received 1 dose of adjuvanted influenza A/09/H1N1 vaccine, and patients received 2 doses of the vaccine. Post-dose 1: 138 patients, 131 healthy controls Post-dose 2: 148 patients 138 on DMARDs (73 MTX, 41 SSZ or HCQ, 23 LEF, 28 AZA or CYC or MMF, 3 other) 22 on Rituximab	An increase in the DAS28-CRP (increase of ≥1.2 and final score >3.2) occurred in 14 (17%) of RA patients, but was correlated only with an increase in the RADAI (≥1.0) and/or HAQ score (≥0.17) in 3 patients in whom oral prednisone and/or MTX were being gradually withdrawn. The BASDAI increased significantly (≥2.0) in 1 SpA patient with axial involvement.

				67 on oral steroids (46 on <10 mg/day, 21 on ≥10 mg/day)	
4354 Park 2018	Prospective multicenter randomized investigator-blind, parallel-group intervention study	4 weeks post-vaccine for serology; 1-year FU post-vaccine for influenza-like illness	320 patients with RA aged 19 years or older and on the same dose of MTX for 6 weeks or longer	All participants received one standard dose of the 2016-2017 seasonal quadrivalent inactivated influenza vaccine (H1N1/H3N2/B-Yamagata/B-Victoria). Participants randomized 1:1 to continue MTX (n=159) vs. discontinue MTX for 2 weeks after vaccination (n=161).	Primary analysis performed on modified ITT population (n=316; Continue MTX n=156, Hold MTX for 2 weeks post-vaccination n=160). <u>Noncomparative data</u> 156 RA patients receiving influenza vaccine while continuing MTX. Mean age 52.2 years, 82.7% female. 52.6% on GC (mean dose 1.8 mg daily), mean MTX dose (13.3 mg weekly), 5.1% SZZ, 22.4% HCQ, 21.2% LEF, 1.3% TAC, 7.1% TNFi, 2.6% TOCI, 0.6% abatacept, 0.6% RTX <u>RA flares:</u> Mean (SD) change in DAS28 pre-vaccine to post- vaccine: + 0.1 (0.7) 8/156 (5.1%) had RA flare within 4 weeks post-vaccine (Flare = Increase in DAS28 of >1.2, or >0.6 if baseline DAS28 was 3.2 or greater)
4428 Turner-Stokes 1988	Prospective cohort	4 weeks	28 pts with SLE 10 with RA 4 MCTD 2 RA/SLE crossover	Influenza vaccine Anti-influenza antibody assay levels conducted at 7 day intervals up to 28 days	No flares noted

4706 Stassen 2008	Nested case control (retrospective)	1999-2004	230 pts with at least one year of follow up (GPA, MPA, EGPA and renal limited vasculitis)	No treatment given. Relapse rate of AAV compared in pts who got vaccinated against influenza at least once vs those who didn't	The relapse rate per 100 patients at risk over the period 1999–2004 was lower in patients who had been vaccinated within the previous year (3.4) than in pa-tients who had not been vaccinated against influenza (6.3), both during the entire year and in every trimester. Disease-free survival in vaccinated vs unvaccinated Year 1999: chi square 1.13 (p=0.29) HR 0.64 (95% CI 0.25-1.51) Year 2000: chi square 3.25 (p=0.07), HR 0.55 (95% CI 0.25-1.06) Year 2001:chi square 5.69 (p=0.0171) HR 0.44 (95% CI 0.19-0.85) Year 2002 chi square 12.79 (p=0.0003) HR 0.32 (95% CI 0.14-0.56) Year 2003 chi square 0.85 (p=0.36), HR 0.77 (95% CI 0.4-1.39) Pts who were vaccinated were older, duration of disease before start of study was longer in the vaccinated pts. Dosage of IS meds in month of Oct-Nov was slightly lower in vaccinated group vs unvaccinated.

					34 pts were not vaccinated every year during the study period. In this group of pts, the relapse rate per 100 pt at risk was lower (6.2) in years after a vaccination than in years in which these patients were not vaccinated (10.1).
4708 Milanovic 2013	Cross sectional study	6 months	47 patients with SLE (N=19), RA(N=15) and Sjogrens (n=13) that were immunized vs 52 that refused to be immunized (SLE N=11, RA N=22, Sjogren's n=19)	Inactivated trivalent split vaccine containing 15 µg HA A/California/7/2009 (H1N1), 15 µg HA A/Perth/16/2009 (H3N2) and 15 µg HA B/Brisbane/60/2008.	Vaccine was well tolerated In all 3 groups of patients (RA/SLE/SjS) that were vaccinated. There were no registered cases of exacerbation of underlying disease.
4716 Tavana 2011	Cohort	6 months safety	23 patients with sarcoidosis (SP) and 26 healthy controls (HC). Antibody titers mean age SP: 45.83, mean age controls: 42	0.5 ml of the trivalent influenza vaccine (influvac; Solvay Pharma, Weesp, Netherlands)	After 6 months of follow-up, no sign of disease flare-up was observed.
4717 Herron 1979	Case control	4 months (pt with RA were studies for an additional 3 weeks for flares)	32 healthy individuals, 20 pts with SLE, 17 with RA, 8 with DJD, 17 with other rheumatic diseases	All received IM inj of whole bivalent influenza virus vaccine: 200 chick-cell agglutinating(CCA) units of type A/NewJersey/76 (A/NJ) and 200CCA units of type A/Victoria/75 (A/Vict) antigens (MerckSharp&Dohme)	1/32 healthy individuals developed trochanteric bursitis 4/20 SLE pts had flareup (1/4 serious/flare of lupus nephritis that was preexisting) 3/17 other rheum diseases had flares 6/17 RA pts had flares in the first 3 weeks of study (one was severe) Total flares were noted in 13/54 (serious flare ups in 3 pts) Given the high rate of flares, the 13 individuals were re-

					examined at 0,1,3 weeks at 4 month follow up (no therapeutic changes or immunizations were permitted). Flares occurred in 7/13 individuals. Authors concluded that since similar proportions of pts had flares ups during both study periods, its unlikely that exacerbations during the first period were due to vaccination
4721 Mercado 2004	Single-arm intervention	8 weeks	18 SLE patients in Baja Mexico; 17 patients on pred (mean dose of 14mg/day, range of 2.5-50mg/day); mean Mex-SLEDAI of 5.5	2001-2002 Fluarix trivalent inactivated seasonal influenza vaccine	Anti-dsDNA measurements were the same pre-vaccination, 4 weeks post-vaccination, and 8 weeks post-vaccination. However, Mex-SLEDAI scores were higher pre-vaccination (5.6±4.5) compared to at 4 weeks (3.1±2.4) or 8 weeks (2.8±1.9).
4722 Ristow 1978	Cohort	8 weeks	29 SLE (28 females) and 29 control subjects matched for age and prevaccination antibody titer	A/New Jersey/76 HswINI influenza virus vaccine	Increase in disease activity in only 1 patient with active lupus erythematosus who developed nephritis during the observation period when her disease was clinically and serologically improving. Renal function subsequently returned to normal after a short course of increased prednisone therapy.
4723 Stojanovich 2006	Case control	1 year	69 pts with SLE, 54 pts with RA which were divided as follows: -SLE1 (23 pts) and RA1 (23 pts) who received vaccine	Flu shot in Nov 2003	No flares in RA or SLE patients who were vaccinated (group 1).

			-SLE2 (46 pts) and RA2 (31pts) who did not receive vaccine		
2555 Aikawa 2013	Prospective cohort study	21 days	95 JIA patients, 91 healthy controls	Single dose monovalent influenza vaccine (A/California/7/2009 (H1N1))	At 3 weeks post vaccination: The median number of active joints [0 (0–28) vs. 0 (0–18), p=0.552)], CRP values [1.9 (0.1–137.3) vs. 2.7 (0.2– 122.8) mg/dL, p = 0.073], and CHAQ score [0.123 (0–3) vs. 0 (0–3), p = 0.058] remained stable throughout the study. However, the medians for ESR [19 (1–83) vs. 15 (0–83) mm/1st hour, p =0.016], patient VAS [10 (0–80) vs. 8.5 (0–80), p = 0.001], and physician VAS [10 (0–90) vs. 6 (0–80), p = 0.002] were statistically lower in the postvaccination evaluation CHAD: Childhood Health Assessment Questionnaire
4278 Crowe 2011	Single-arm intervention	12 weeks	72 SLE patients (and 72 healthy controls) in Oklahoma 58 on steroids, 69 on antimalarials, 51 on combination steroids and antimalarials	2005-2006 or 2007-2008 trivalent subunit seasonal influenza vaccines	Amongst the 36 of patients classified as “low responders,” an increased rate of “lupus disease flare” (SELENA SLEDAIs reportedly scored, but no scores given) was noted 6 weeks following the vaccine, in comparison to “high responders.” At 6 weeks, 7 low responders (20%) were reported to have mild/moderate flare (compared to 3 of the high

					responders), and another 3 (8%) were reported to have a severe flare (compared to 1 of the high responders). This difference was not noted at 12 weeks following the vaccine, when the two groups were equal with 8 (22%) mild/moderate flares in each group, and 1-2 (3-6%) severe flares in each group.
489 Wiesik-Szewczyk 2010	Case control	12 weeks	62 SLE on medications vs 47 healthy control	Inactivated Influenza vaccine 15ug HA each of A/H1N1, A/H3N2, and B	SLE group - 1 severe exacerbation - 6 mild and moderate exacerbation 'As assessed by SLEDAI, we did not find significant alterations of disease activity in the group as a whole.'
5711 Sbidian 2014	Case series	3 months following vaccination	Cases of new psoriasis or flare of preexisting psoriasis were identified by emailing French Dermatologists (approx. 3,000 MDs). Also cases identified through reports to 31 pharmacovigilance regional centers of the French Health products Safety Agency at the end of 2009-10 antiflu vaccination campaigning	2009 monovalent H 1 N 1 /seasonal vaccination	-7 patients with new onset psoriasis presented within a median of 8 days (range 6-74 days) -3 patients with worsening of previously diagnosed psoriasis; time from vaccination 6, 15, and 30 days
6151 Martins de Medeiros 2014	Case control	6 months	-45 primary APS patients who were included in a large (n=1668), prospective rheumatic-disease cohort conducted at a single site in Sao Paulo, Brazil (Rheumatology Division,Hospital das Clí nicas da Universidade de Sa˜oPaulo), between March 2010 and April 2010 -33 healthy subjects	All vaccinated with pandemic 2009 influenza vaccine (A/California/7/2009/Butantan Institute/Sanofi Pasteur) -monovalent, nonadju-vanted, inactivated, split-virus vaccine produced by Butantan Institute/Sanofi Pasteur (Sao Paulo, Brazil)	No statistically significant difference in frequency of aPL before vaccination, at 3 weeks and at 6 months in patients and controls. At 3 weeks, 2 PAPS pts developed a new but transient

					aPL (one developed mod titer aCL IgG, the other one IgM). At 6 months new aPL were observed in 6 PAPS pts (3 mod titer aCL IgM, 1 mod titer ab2GPI IgM, one low antiphosphatidyl serine IgG, and one low titer antiprothrombin IgG.
6154 Shinjo 2012	Cohort	21 days	dermatomyositis (DM, n=37) and polymyositis (PM, n=21), age-and gender-[matched healthy controls (n=116); mean age: 43.1 ± 9.9 DM/PM vs. 43.8 ± 8.4 healthy controls	Sanofi Pasteur 2009 influenza A (H1N1) was a novel monovalent adjuvant-free vaccine (A/California/7/2009/Butantan Institute/Sanofi Pasteur)	PICO 8 No significant difference was reported for pre- versus post-vaccination disease and muscle parameters for DM/PM patients. Patient's VAS (0-10): 0 [0-1] vs. 0 [0-1], p=1.00 Physician's VAS (0-10): 0 [0-1] vs. 0 [0-1], p=1.00 MMT-8 (0-80): 80 [80] vs. 80 [80], p=0.500 Creatine kinase, IU/L (24-173): 145.5 [121-186] vs. 167.5 [98-321], p=0.200 Aldolase, IU/L (1.0-7.5): 4.6 [3.6-5.5] vs. 4.4 [3.4-7.7], p=0.980
636 Nakafero 2019	Case series	90 days	≥ 18 years with RA (11953, 80.07%), SpA (2347, 15.72%), SLE (628, 4.21%) = 14,928 total cases and on DMARDs	Inactivated influenza vaccine	PICO 8: 14-day prevaccination period associated with significantly more primary care consultations for joint pain and new corticosteroid prescriptions. 15 day prevaccination: 788 events, 169775 person-time

					(days), 1.29 (1.20-1.39) IRR (95%CI), p <0.001. Post vaccination intervals 0-14 days 479 events, 150314 person-time, 0.84 (0.77-0.92) IRR , p<0.001 15/30\- days 567 events, 160842 person-time, 0.94(0.86-1.02) IRR, p= 0.127 31-60 days 1121 events, 321024 person-time, 0.93(0.88-0.99)IRR , p= 0.025 61-90 days 1069 events, 319890 person-time, 0.90 (0.84-0.96) IRR, p=0.001 There were no significant associations between vaccination and other adverse outcomes in this study: RA flare, vasculitis, unexplained fever.
700 Urowitz 2011	Case series	3 months postvaccination	103 SLE patients (94 women, 9 men) Mean age at vaccination 43.9 +/- 15.2 years. Mean disease duration 14.2 +/- 11.0. Mean SLEDAI-2K score 4.38 +/- 4.28 Mean SD SDI score 1.26 +/- 1.52	H1N1 (with or without adjuvant)	68 patients with SLEDAI-2K values prior to and following second post-vaccination visit Mean SD SLEDAI-2K prevaccination 4.22 +/- 4.41 Mean postvaccination SD SLEDAI-2K 3.90 +/- 4.06 (paired

			64% on steroids, 79% on antimalarials, 62% on immunosuppressants		*t*-test P 0.39) At next followup clinic visit (mean SD 4.5 +/- 1.7) 11.5% of patient had a flare of their disease, with SLEDAI-2K score increased by 4. In their database, 10.5% of patient had a flare between 2 consecutive visits (P= 0.78).
7029 Jeffs 2015	Open, single-center, prospective cohort study	28 days post-vaccine	31 adult patients (45.2% female) with AAV (20 GPA & 11 MPA) in clinical remission for 3+ months (BVAS <2). 67 healthy individuals (68.7% female) recruited from hospital staff members & medical trainees. Median age significantly older in vaccinated AAV patients (62 yrs) vs. healthy controls (23 yrs).	AAV patients randomized 3:1 to receive trivalent (H1N1/H3N2/B influenza) seasonal influenza vaccine (n=24) versus no vaccination (n=7). Healthy individuals also randomized 3:1 to receive vaccine (n=53) versus no vaccine (n=14). Vaccinated AAV patients: 25% no immunosuppression, 33% AZA, 8% CYC, 4% MTX, 13% HCQ, 13% MMF, 58% oral steroids; 29% one medication, 42% two medications, 4% three medications. Non-vaccinated AAV patients: 57% AZA, 14% MTX, 14% MMF, 86% prednisolone; 29% on one medication, 71% on two medications.	From Day 0 to Day 28 post-vaccine: No significant change in ANCA titers, CRP, creatinine, or BVAS scores in vaccinated AAV patients (n=24) compared to non-vaccinated AAV patients (n=7); p>0.05 for all comparisons. Single disease relapse episode in one MPA patient at 6 months post-vaccine. No relapses within 6 months of follow-up in non-vaccinated group.

7034 Evison 2009	Randomized double blind trial	4-6 weeks	304 total: 131 HIV, 47 mixed RMD (28 RA, 13 AS, 3 SLE, 2 Sarcoidosis, 1 vasculitis), 74 renal transplant, 47 hemodialysis, 5 nephrologic disease	Trivalent seasonal 2005-2006 influenza subunit vaccine (Influvac; Solvay Pharma AG) vs the virosomal vaccine (Influvac plus; Solvay Pharma AG): 15 mg of A/California/20/99 (H3N2), A/New Caledonia/20/99 (H1N1), B/Shanghai/361/2002	- 24 RA: mean DAS change -0.4 subunit vaccine, -0.9 virosomal vaccine - 13 AS: mean BASDAI change -0.9 subunit vaccine, -0.9 virosomal vaccine - 3 SLE: mean DAS change 0 subunit vaccine, 0 virosomal vaccine - 2 GPA: mean DEI change 2 subunit vaccine, 0 virosomal vaccine
7047 Brogan 2019	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood vaccination programs. No live vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination (“Pre-dose”), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination).	No disease flares induced by vaccination

				Included vaccines: HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	
7199 Ribeiro 2011	Prospective single-center cohort study	21 days post-vaccine	340 patients with RA aged 18 years or older on stable RA medications vs. 234 healthy controls. Mean age 55.8 years in RA vs. 36.6 years in controls; 86.8% female in RA vs. 66.8% in controls. RA patients: Mean RA disease duration 16.7 yrs, mean DAS28-ESR 3.66.	All participants received a single dose of pH1N1 vaccine. RA patients: 72.6% on oral corticosteroids (mean dose 8.6mg daily); 63.2% on MTX (mean dose 19.2 mg weekly); 42.9% on LEF, 36.5% on chloroquine, 13.8% on TNFi, 3.2% not on DMARDs.	331/340 (97.4%) RA patients reported no change in disease activity post-vaccination; 9 patients (2.6%) reported worsening symptoms post-vaccine. Mean (SD) DAS28-ESR 3.66 (1.35) pre-vaccine vs. 3.49 (1.36) at 21 days post-vaccine ($p>0.05$).
7615 Holvast 2006	Prospective, single center, cohort study	Follow-up to 30 days post-vaccine	56 adult patients (89.3% female) with SLE and quiescent disease (SLEDAI 5 or less) VS. 18 age- and sex-matched healthy volunteers (77.8% female). 43/56 (77%) SLE patients received influenza vaccine in the past vs. 4/18 (22%) healthy controls ($p<0.001$). 34/56 SLE patients received influenza vaccine in the previous season vs. 1/18 healthy controls ($p<0.001$).	All participants received a single dose of trivalent inactivated seasonal influenza vaccine (H1N1/H3N2/B-HK). SLE patients grouped by treatment: Group A - No meds (n=12) Group B - HCQ >=400mg daily (n=17) Group C - AZA >= 50 mg daily (n=13) Group D - Prednisone >= 10 mg daily (n=14) Patients taking MTX (n=5) or other immunosuppressives (CYC, CNI, MMF; n=12) were excluded from the study.	SLEDAI scores pre- vs. post-vaccine were not significantly different in any SLE group. In AZA group, patient VAS scores were significantly lower post-vaccination. No significant change pre- vs. post-vaccination in the other 3 SLE groups.

				Median dose HCQ in Group B = 400 mg daily; median dose AZA in Group C = 100 mg daily; median dose prednisone in Group D = 10 mg daily. Patients in Group B (HCQ) & Group C (AZA) were allowed prednisone <10 mg daily. All prednisone doses were "stable" for at least 2 months pre-vaccination. All four SLE groups similar with respect to age, sex, SLE duration, baseline SLEDAI, and baseline VAS. More patients in AZA group received influenza vaccine in the previous season vs. other SLE groups (p=0.026)	
7772 Jaeger 2017	Case series based on prospective, multicenter observational patient registry (β-CONFIDENT)	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period. Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	All patients treated with canakinumab. Total of 159 vaccine injections 43/68 (63%) patients received multiple vaccine injections <u>Influenza:</u> 107 injections in 55/68 (81%) patients <u>Pneumococcal:</u> 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients <u>Tetanus/Diphtheria:</u> 12 injections in 12/68 (18%) patients	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days. No cases of CAPS reactivation reported for other vaccines.

				Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	
790 Ritterhouse 2011	Case series	3 months	60 female w SLE (meeting at leat 4 ACR classification criteria for SLE) Medicaitons (prednisone, AZA, HCQ, MMF, MTX, CYC) 60 healthy individuals	Influenza vaccine	White SLE patients w elevated BLyS levels had higher SLEDAI (median score 8 (IQR 5-12)), physician's global assessment (60 (IQR 39-72)) and SLAM scores (11 (IQR 9-15)) vs those w NL BLyS levels: median SLEDAI score 2 (IQR 0-6), physicians global assessment score 23 (IQR 9-39), and SLAM 7(IQR 5-10)) (P=0.035, P=0/016 and P= 0.018, respectively). African Americans w elevated BLyS levels did not have increased disease activity scores: SLEDAI 4 (IQR 2-8), Physicians global assessment score 47 (IQR 19-53) and SLAM 11 (IQR 6-15) vs to African Americans with normal levels: SLEDAI 5 (IQR 2-8), physicians global assessment score 43 (IQR 12-59) and SLAM 9 (IQR 6-11) (p=1.000, p=0.837, p= 0.225, respectively)

					There were no differences between patients with elevated BLyS levels and patients w NL BlyS levels with regard to active disease features that were determined as part of SLEDAI eval (number of individuals with each active disease feature was low). 22 patients had mild/moderate flare at either 6 or 12 weeks after baseline. 3 patients had a severe flare. 50% of SLE pts with elevated BLyS levels had a flare during 12 week FU, 38% with nl BLyS at baseline had a flare during this time (OR 1.6 [95% CI0.5-5.0]) (p=0.409).
8096 Abu-Shakra 2002	Case series	12 weeks post-vaccine	24 SLE patients Mean age 46.1 years (range 20-74), 100% females. Mean disease duration 9.1 years. Baseline seroprotection for H3N2/H1N1/B in SLE (20.8/8.3/66.7%) similar to healthy age-matched female controls (n=30; 20/16.7/63.3%). Healthy controls <u>not</u> evaluated post-vaccine.	All participants received one standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B-Influenza). <u>SLE therapies:</u> Oral steroids (n=17), mean prednisone dose 12 mg HCQ 400 mg daily (n=9) AZA 100 mg daily (n=3) MTX (n=4) mean dose 10mg weekly	<u>Mean SLE disease activity index (SLEDAI) scores:</u> Enrollment: 18 (range 4-59) At vaccination: 6.6 (range 0-36) At 6 weeks post: 4.9 (range 0-28) At 12 weeks post: 5.1 (range 0-24)

8256 Sengler 2014	Nationwide survey (Germany)	Nov 2009 to Feb 2010	Children with rheumatic disease 90 cases 66% female Median age 12 JIA in 85% SLE in 7% DM in 3% MCTD in 1% Non bacterial OM in 2% Lyme arthritis in 1% 59% of pts on mtx, 24% on etanercept, 9% on cyclosporin, 7% on antimalarials and others, 5% on MMF, adalimumab or tocilizumab, 4% on AZA, anakinra and Leflunomide	AS03 adjuvanted H1N1	16 ped rheum sites documented 90 patients. At median f/u of 4 weeks, no difference in disease activity before and after influenza vaccination was seen. 4 pts (4.4%) sustained a flare in 2-5 weeks after vaccination.
9273 Bjork 2020	Prospective cohort against healthy controls	90 days	25 Sjogren's patients (anti SSA seropositive and fulfilling the American-European consensus group criteria) [17 were untreated, 8 patients on HCQ] 16 age and sex matched healthy controls	Seasonal influenza vaccination Fluarix,GlaxoSmithKline, Solna, Sweden) containing inactivated A/California/7/2009 (H1N1)-, A/Switzerland/9715293/2013 (H3N2)-, and B/Phuket/3073/2013-like strains.	Potential changes in disease activity during the study period were followed through self-reported clinical parameters. No significant changes in EULAR Sjogren's Syndrome Patient Reported Index or other disease-related parameters were noted
9428 Oren 2008	Nonrandomized comparative	4 weeks	29 RA (non-rituximab), 14 rituximab-treated RA (rituximab), and 21 healthy controls	Influenza: 0.5 ml split virion inactivated vaccine (Vaxigrip, Promedico) containing a 15 mg haemagglutinin (HA) dose of A/California /7/04 (CAL) (H3N2), B/Shanghai /361/02 (SHAN) and A/New Caledonian/20/99 (NC) (H1N1), administered intramuscularly	No significant difference was reported before versus after influenza vaccination for disease activity (tender joints, swollen joints, morning stiffness, day and night pain, ESR) in all RA patients.

9442 Tarjan 2006	Case series	8 weeks	18 SLE patients	Influenza vaccine containing A/H1N1, A/H3N2, and B-type surface haemagglutinin (Influvac, Solvay Pharmaceuticals B.V., the Netherlands); individuals were on methylprednisone, azathioprine, and chloroquine	At 8 weeks, no increase in SLEDAI scores were noted.
2643, Muller, 2013	Prospective cohort study	4 weeks after 2nd vaccination	16 patients who were treated with rituximab (within past 36 months) and had received first dose of influenza vaccine.	2nd dose of 2009 H1N1 influenza vaccine (Pandemrix) given 4 wks after first dose.	Disease flares were not reported in any of the patients.
3893, Tsuru, 2014	Prospective cohort study	3 months	38 pts on tocilizumab, 15 pts on TNFi+MTX, 24 pts on DMARDs (MTX, SSZ, or cyclosporine)	Seasonal trivalent inactivated influenza vaccine (A(New Caledonia (NC):H1N1), A(Hiroshima (HIR):H3N2) and B(Malaysia (MAL))	No disease flares were seen.
4073, Camacho, 2017	Prospective cohort study	6 months	35 JIA patients and 6 healthy controls. Of the JIA patients,15 on TNFi, 4 on anakinra, 6 on tocilizumab	1 or 2 doses of Trivalent non-adjuvanted influenza vaccine over 2 seasons. Season 1: A/California/7/2009-H1N1, A/Victoria/361/2011-H3N2, B/ Massachusetts/2/2012. Season 2: A/California/7/2009 (H1N1)pdm, A/ Texas/50/2012 (H3N2), B/Massachusetts/2/2012.	JADAS score increased in 6 of 35 patients from baseline. However, none of these met criteria for flare.
4115, Ogimi, 2011	Prospective cohort study	2-4 weeks after 2nd dose	49 children with pediatric rheumatic disease, 36 controls. Most PRD patients were on prednisolone at varying doses, usually <0.2 mg/kg.	Influenza HA vaccine, not otherwise specified. 2 doses given, 1-4 weeks apart	2 pediatric RD patients had disease flares within 2 wks of vaccination.
4709, Kanakoudi-Tsakalidou 2001	Prospective cohort study	2 months	70 children w rheumatic disease (49 JIA, 11 SLE, 10 other). Divided into 4 treatment groups: 1) No treatment 2) Prednisone + MTX/cyclosporine/azathioprine 3) Prednisone + MTX + Cyclosporine	"split type" influenza vaccine, Fluarix, 1 or 2 doses depending on age/size A/Beijing, A/Sydney, B/Beijing	No worsening of underlying disease was reported.

			4) MTX/cyclosporine/azathioprine without steroids Also 5 healthy controls (siblings of patients)		
4832 Bjork, 2021	Prospective cohort study	90 days	28 SLE patients, of whom 15 were on HCQ. All had low or no disease activity. 17 healthy controls	Non-adjuvanted seasonal flu vaccine (Vaxigrip)	"Vaccine-specific IgG" measured by ELISA at baseline, 28 days, 90 days, no details provided. Measured multiple autoantibodies (dsDNA, Sm, RNP, chromatin, etc) and found no difference before/after vaccination. Global VAS not different before/after vaccination.
4478 Fragoulis 2021	Cross sectional observational study		1015/1046 (97%) of patients with ARD who responded to phone call (60% with inflammatory arthritides, 30% with CTD)	Inquiry about whether pt received flu vaccine	Self-reported disease flares after vaccination were <1%. For 2019/20 period: 2/771 (0.3%) For 2020/21 period 6/843 (0.7%)
4693 Williams 1978	Double blind, randomized, placebo controlled	20 weeks	40 pts with SLE randomly assigned flu vs normal saline vaccination; 21 healthy controls	Bivalent whole vaccine from influenza A/NJ/11/76 (Hsw 1 N 1) and A/Victoria/3/75 (H 3 N 2) influenza strains	2/19 in the SLE vaccinated group (an additional pt developed patchy alopecia and arthritis 4 mo after immunization) 2/21 in the SLE unvaccinated group
8187 Holvast 2009	Prospective cohort study	Follow-up to 3-4 months post-vaccine	80 adult patients with SLE: 54 vaccinated vs. 24 nonvaccinated. Two patients excluded after randomization.	SLE patients randomized 2:1 to influenza vaccination vs. nonvaccinated patient control group. All healthy controls vaccinated. Vaccination with single standard dose of trivalent	No significant differences between vaccinated & nonvaccinated SLE patients in SLEDAI or VAS scores at any timepoint.

			Vaccinated SLE patients (n=54): 18.5% male, mean age 44.8 years, 34/54 (63%) prior vaccination. Nonvaccinated SLE patients (n=24): 8.3% male, mean age 45.5 years, 9/24 (37.5%) prior vaccination. Age- and sex-matched healthy individuals (n=54): 20.4% male, mean age 43.1 years, 3/54 (5.6%) prior vaccination. For cellular responses: 38 vaccinated SLE patients vs. 38 age- & sex-matched controls. Mean age 43.4 years, 24% males	subunit influenza vaccine (H1N1/H3N2/B). Vaccinated SLE patients (n=54): 5/54 (9.3%) no medications, 28/54 (51.9%) prednisone (median 5mg daily), 30/54 (55.6%) HCQ (median 400mg daily), 17/54 (31.5%) AZA (median 125mg daily), 6/54 (11.1%) MTX. Nonvaccinated SLE patients (n=24): 5/24 (20.8%) no medications, 10/24 (41.7%) prednisone (median 6.25mg daily), 10/24 (41.7%) HCQ (median 400mg daily), 6/24 (25%) AZA (median 87.8 mg), no MTX.	<u>Visit 1 (T=0):</u> SLEDAI – median (range): 2 (0-8) in vaccinated vs. 2 (0-12) not vaccinated VAS (0-10) – median (range): 2.2 (0-5.6) in vaccinated vs. 1.6 (0-6.6) not vaccinated <u>Visit 2 (T=Day 28):</u> SLEDAI – median (range): 2 (0-13) in vaccinated vs. 2 (0-8) not vaccinated VAS (0-10) – median (range): 1.4 (0-8.1) in vaccinated vs. 2.1 (0-7.4) not vaccinated <u>Visit 3 (T=3-4 months):</u> SLEDAI – median (range): 2 (0-10) in vaccinated vs. 2 (0-4) not vaccinated VAS (0-10) – median (range): 1.8 (0-9.4) in vaccinated vs. 2.2 (0-8.9) not vaccinated
7655 Milanetti 2014 (**SEE GRADEPRO TABLE BELOW)**	Prospective, single-center, cohort study	6 months post-vaccination	30 patients with RA (1987 ACR criteria) with low-moderate disease activity (DAS<3.7) and stable disease (no increase in therapy required in past 6 months). Mean (SD) age 50 (10) years, 77% female, mean (SD) baseline DAS 2.33 (0.8)	All participants received a single dose of trivalent non-adjuvanted 2009-2010 seasonal influenza vaccine (H1N1/H3N2/B-Brisbane) and a single dose of the pandemic monovalent adjuvanted H1N1 vaccine on the same day. All RA patients were taking a biologic DMARD	No statistically significant changes in ANA titers, RF, ESR, or CRP levels between T0, T1, T2.

			13 healthy controls, matched for age and sex. Mean (SD) age 41.8 (12) years, 62% female. 6/30 (20%) RA patients and 3/13 (23%) controls received influenza vaccination in the prior season.	(13 etanercept, 7 adalimumab, 4 infliximab, 6 abatacept). Concomitant low-dose corticosteroids (prednisone <10mg daily) and csDMARDs (mostly MTX 10-15mg weekly) permitted. Details not reported.	
6910 Adler 2012 (Duplicate with 9426)	Prospective, single-center, cohort study	Follow-up to 6 months post-vaccine	149 RMD patients (57.7% female; Age: 24.2% <40 years, 45% 40-59 years, 30.8% 60+ years). Includes 47 RA patients, 59 SpA, 15 vasculitis, and 28 CTD patients. 40 healthy controls (65% female; Age: 38% <40 years, 55% 40-59 years, 8% 60+ years). Seasonal influenza vaccine in 127/149 (85.2%) patients vs. 28/40 (70%) controls (mean 4 vs. 3.7 weeks prior to study)	All participants received one standard dose of adjuvanted H1N1 vaccine (2009 pandemic). RMD patients: 10.7% no medications, 24.2% steroids (<10mg), 7.4% steroids (10+ mg). 62.4% on DMARDs: SSZ/HCQ (n=14), MTX (n=61), LEF (n=6), AZA (n=6), CSA (n=4), MMF (n=2), TNFi 45.6%, MTX+TNFi 22.1%. RTX (5 RA, 3 vasculitis), Abatacept (10 RA, 6 SpA, 4 CTD), Tocilizumab (5 RA), CYC (1 RA, 1 vasc, 1 CTD)	Increase in disease activity observed in 32/149 RMD patients (15 RA, 12 SpA, 1 VAS, 4 CTD) during entire study period. Occurred in first 2 months post-vaccine in 8 patients. Three patients required change in therapy: IA GC injections in 2 patients, PO steroids in one patient.
4918 Kogure 2014	Single-arm intervention	4 weeks	57 RA patients in Japan	2011-2012 trivalent subunit seasonal influenza vaccine	The DAS28 did not change after vaccination. There was no adverse reaction of influenza vaccination in our observation.
4753 Brodman 1978	Case control	2 months	46 pts with SLE and 58 controls (family members and lab personnel)	Patients were vaccinated with 0.5 ml of Influenza Virus Vaccine Monovalent, Type A, which contained 200 chick-cell agglutinating (CCA) units of A/New Jersey/8/76(HswlNl) (Merrell-National Laboratories, Cincinnati, Ohio, Lot #1497FK).	Symptoms related to sLE occurred in 11/46 pts after 1st vaccination and 13/37 pts after 2nd vaccination. All symptoms were mild, no major flares occurred.

				One month later the patients were then vaccinated with 0.5 ml of Influenza Virus Vaccine Bivalent, Types A, which contained 200 CCA units of A/ Victoria/3/75(H3N2) and 200 CCA units of A/New Jersey/8/ 76/(HswlNl) (Merrell-National Laboratories, Cincinnati, Ohio, Lot # 1494FK).	

Table 2: RA disease activity: Pre-vaccine compared to Post-vaccine in trivalent seasonal influenza vaccination. 1177-Arad (2011)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA disease activity: Pre-vaccine	Post-vaccine	Relative (95% CI)	Absolute (95% CI)		
DAS28												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	46	46	-	MD **0.1 lower** (0.74 lower to 0.54 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. not randomized, not blinded, small number of participants
b. CI cross null value, relatively small number of participants

Table 3. Pre-vaccine compared to Post-vaccine (4-6 weeks). 2516_Elkayam (2010)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-vaccine	Post-vaccine (4-6 weeks)	Relative (95% CI)	Absolute (95% CI)		
Disease activity: DAS in RA patients												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	43	43	-	MD **0.25 lower** (0.85 lower to 0.35 higher)	⊕◯◯◯ Very low	
Disease activity: BASDAI in AS patients												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	18	18	-	MD **0.15 lower** (1.72 lower to 1.42 higher)	⊕◯◯◯ Very low	
Disease activity: CRP in RA patients												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	43	43	-	MD **1 lower** (5.82 lower to 3.82 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-vaccine	Post-vaccine (4-6 weeks)	Relative (95% CI)	Absolute (95% CI)		
Disease activity: ESR in RA patients												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	43	43	-	MD **6 higher** (0.56 lower to 12.56 higher)	⨁◯◯◯ Very low	
Disease activity: CRP in AS patients												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	18	18	-	MD **5.4 higher** (9.11 lower to 19.91 higher)	⨁◯◯◯ Very low	
Disease activity: ESR in AS patients												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	18	18	-	MD **1 higher** (1.03 lower to 3.03 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. not randomized, not blinded, small number of patients
b. CI cross zero, small number of patients

Table 4: Influenza compared to placebo for DM. Vaccine for DM. 6154 Shinjo 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza	placebo	Relative (95% CI)	Absolute (95% CI)		
Flare s/p Influenza, not defined												
1	observational studies	very serious[a]	not serious	not serious	not serious	none	46/134 (34.3%)	28/76 (36.8%)	**OR 0.90** (0.50 to 1.61)	**24 fewer per 1,000** (from 143 fewer to 116 more)	⊕◯◯◯ Very low	
Swine flu, H1N1												
1	observational studies	very serious[a]	not serious	not serious	not serious	none	34/134 (25.4%)	16/76 (21.1%)	**OR 1.27** (0.65 to 2.50)	**42 more per 1,000** (from 63 fewer to 189 more)	⊕◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. not randomized, not blinded, recall bias possible (survey)

Table 5: Flares in RA/SLE after immunization or without compared to placebo. 4731 Del Porto 2006

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flares in RA/SLE after immunization or without	placebo	Relative (95% CI)	Absolute (95% CI)		
Flares in SLE based on immunization status												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	2/14 (14.3%)	1/10 (10.0%)	**OR 1.50** (0.12 to 19.24)	**43 more per 1,000** (from 87 fewer to 581 more)	⊕◯◯◯ Very low	
Flares in RA after immunization or without												
1	observational studies	serious [a]	not serious	not serious	not serious	none	2/10 (20.0%)	3/10 (30.0%)	**OR 0.58** (0.07 to 4.56)	**101 fewer per 1,000** (from 271 fewer to 362 more)	⊕◯◯◯ Very low	
Flares in both RA/SLE in immunized vs not immunized												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flares in RA/SLE after immunization or without	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious [a]	not serious	not serious	not serious	none	4/24 (16.7%)	4/20 (20.0%)	**OR 0.80** (0.17 to 3.71)	**33 fewer per 1,000** (from 159 fewer to 281 more)	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. no randomized, not blinded, small sample size
b. wider confidence interval

Table 6. PICO 8 RA vaccinated compared to RA non-vaccinated. 4732 Salemi 2010

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 8 RA vaccinated	RA non-vaccinated	Relative (95% CI)	Absolute (95% CI)		
Increase in DAS day 30-day0												
1	observational studies	serious[a]	not serious	not serious	not serious	none	28	20	-	MD **0.09 higher** (0.05 higher to 0.13 higher)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PICO 8 RA vaccinated	RA non-vaccinated	Relative (95% CI)	Absolute (95% CI)		
Increase in DAS day 180-day0												
1	observational studies	serious[a]	not serious	not serious	not serious	none	28	20	-	MD **0.27 lower** (0.31 lower to 0.23 lower)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. non randomized, not blinded, small sample

Table 7. Disease activity in SSc before and after vaccination (6 weeks) PICO 8 compared to placebo. 8953 Litinsky 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Disease activity in SSc before and after vaccination (6 weeks) PICO 8	placebo	Relative (95% CI)	Absolute (95% CI)		
Tender Joints												
1		serious[a]	not serious	not serious	serious[b]	none						

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Disease activity in SSc before and after vaccination (6 weeks) PICO 8	placebo	Relative (95% CI)	Absolute (95% CI)		
	observational studies						26	26	-	**MD 0.02 higher** (0.71 lower to 0.75 higher)	⨁◯◯◯ Very low	
Swollen joints												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	- 26	26	-	**MD 0.18 higher** (0.71 lower to 0.35 higher)	⨁◯◯◯ Very low	
Digital ulcers												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	- 26	26	-	**MD 0.88 higher** (0.40 lower to 2.16 higher)	⨁◯◯◯ Very low	
Rodnan score												
1		serious[a]	not serious	not serious	serious[b]	none	-					IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Disease activity in SSc before and after vaccination (6 weeks) PICO 8	placebo	Relative (95% CI)	Absolute (95% CI)		
	observational studies						26	26	-	**MD 0.12 lower** (5.76 lower to 5.52 higher)	⨁◯◯◯ Very low	
PDAI (VAS) pt disease activity index												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-		-	**MD 0.76 lower** (2.18 lower to 0.66 higher)	⨁◯◯◯ Very low	IMPORTANT
							26	26				
PHDAI (VAS) physician disease activity												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-		-	**MD 0.20 higher** (1.06 lower to 1.46 higher)	⨁◯◯◯ Very low	IMPORTANT
							26	26				
ESR												
1		serious[a]	not serious	not serious	serious[b]	none	-					

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Disease activity in SSc before and after vaccination (6 weeks) PICO 8	placebo	Relative (95% CI)	Absolute (95% CI)		
	observational studies						26	26	-	**MD 0.35 lower** (10.31 lower to 9.61 higher)	⨁◯◯◯ Very low	
CRP												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-		-	**MD 0.76 higher** (1.67 lower to 3.19 higher)	⨁◯◯◯ Very low	
							26	26				

CI: confidence interval; **RR:** risk ratio

Explanations

a. case control study
b. relatively small sample size

Table 8. Flare year before vaccination compared to year after vaccination in SS compared to placebo for seasonal flu vaccine, primary Sjogren's Syndrome/controls. 8002 Pasoto 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flare year before vaccination compared to year after vaccination in SS	placebo	Relative (95% CI)	Absolute (95% CI)		
Parotitis												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	2/36 (5.6%)	3/36 (8.3%)	**RR 0.67** (0.12 to 3.75)	**27 fewer per 1,000** (from 73 fewer to 229 more)	⊕◯◯◯ Very low	
Arthritis												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	2/36 (5.6%)	6/36 (16.7%)	**RR 0.33** (0.07 to 1.54)	**112 fewer per 1,000** (from 155 fewer to 90 more)	⊕◯◯◯ Very low	
Anti-Ro (seeum level, in units +/- SD)												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	20	20	-	MD **14.1 higher** (10.97 lower to	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flare year before vaccination compared to year after vaccination in SS	placebo	Relative (95% CI)	Absolute (95% CI)		
										39.17 higher)		
Anti-La (SSB) (in serum, U +/- SD)												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	20	20	-	MD **12.1 higher** (15.59 lower to 39.79 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. low population, cohort study
b. small sample size

Table 9. RA disease activity compared to placebo. 7655_Milanetti(2014)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA disease activity	placebo	Relative (95% CI)	Absolute (95% CI)		
DAS-T0 vs. DAS-T1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	30	30	-	MD **0.15 lower** (0.55 lower to 0.25 higher)	⨁◯◯◯ Very low	
DAS-T0 vs. DAS-T2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	30	30	-	MD **0.09 lower** (0.52 lower to 0.34 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. single center cohort study
b. small sample size

Table 10. SLE disease activity: Pre- compared to Post-vaccine. 7624_Wallin (2009)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE disease activity: Pre-	Post-vaccine	Relative (95% CI)	Absolute (95% CI)		
SLEDAI scores: Pre- vs. Post-vaccine												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	47	47	-	MD **0.41 lower** (1.35 lower to 0.53 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. prospec cohort study
b. small sample size

Table 11. JIA flare with seasonal flu vaccine, 6 months compared to placebo. 7614 Toplak 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA flare with seasonal flu vaccine, 6 months	placebo	Relative (95% CI)	Absolute (95% CI)		
JIA flare within 6 months following vaccine (compared to same 6-mo interval in unvaccinated JIA patients)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA flare with seasonal flu vaccine, 6 months	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11/31 (35.5%)	7/31 (22.6%)	**RR 1.57** (0.70 to 3.52)	**129 more per 1,000** (from 68 fewer to 569 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. observational study
b. small sample size

Table 12. JIA doesn't flare 30, 60, or 90 days after flu vaccination compared to placebo. 6879 Carvalho 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA doesn't flare 30, 60, or 90 days after flu vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		

Physician global scores before and 30 days following seasonal flu vaccine (2006/2007 strains)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA doesn't flare 30, 60, or 90 days after flu vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	44	44	-	MD **0.45 lower** (0.99 lower to 0.09 higher)	⨁◯◯◯ Very low	
ESR doesn't bump 30 days post-vaccination												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	44	44	-	MD **1.7 higher** (2.24 lower to 5.64 higher)	⨁◯◯◯ Very low	
Active joint count												
1	observational studies	serious	not serious	not serious	serious[b]	none	44	44	-	MD **0.2 lower** (1.12 lower to 0.72 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

Explanations

a. prospective cohort study
b. small sample size

Table 13. Constitutional symptoms after monovalent vaccination compared to placebo. 4753 Brodman 1978

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Constitutional symptoms after monovalent vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		
Constitutional symptoms												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/46	9/58	**OR 1.32** (0.48 to 3.66)	-	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. case control study
b. relatively small sample size

Table 14. Constitutional symptoms after monovalent vaccination compared to placebo. 4753 Brodman 1978

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Constitutional symptoms after bivalent vaccination	placebo	Relative (95% CI)	Absolute (95% CI)		
Constitutional symptoms												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/37	9/42	**OR 1.99** (0.73 to 5.40)	-	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. case control study
b. small sample size

Table 15. Flares in PsA on monotx anti-TNFa after vaccination compared to without vaccination. 4738 Caso 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flares in PsA on monotx anti-TNFa after vaccination	without	Relative (95% CI)	Absolute (95% CI)		
Tender joint counts												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 2.48 higher** (0.91 higher to 4.05 higher)	⨁◯◯◯ Very low	Favors without vaccination
Swollen Joint Count												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 0.04 higher** (0.15 lower to 0.23 higher)	⨁◯◯◯ Very low	
BASDAI												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flares in PsA on monotx anti-TNFa after vaccination	without	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 0.36 higher** (0.47 lower to 1.19 higher)	⨁◯◯◯ Very low	

BASFI

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 0.58 higher** (0.43 lower to 1.59 higher)	⨁◯◯◯ Very low	

MASES

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 0.04 higher** (0.79 lower to 0.87 higher)	⨁◯◯◯ Very low	

PASI

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flares in PsA on monotx anti-TNFa after vaccination	without	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 0.39 higher** (1.55 lower to 2.33 higher)	⨁◯◯◯ Very low	
HAQ												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 0.32 higher** (0.05 lower to 0.59 higher)	⨁◯◯◯ Very low	
PtGA												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 15.40 higher** (3.72 higher to 27.08 higher)	⨁◯◯◯ Very low	Favors without vaccination
PhGA												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flares in PsA on monotx anti-TNFa after vaccination	without	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 9.40 higher** (1.39 higher to 17.41 higher)	⨁◯◯◯ Very low	Favors without vaccination
ESR (mm/h)												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25	-	**MD 4.20 higher** (1.28 higher to 7.12 higher)	⨁◯◯◯ Very low	Favors without vaccination
CRP												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	25	25		- **MD 0.05 higher** (0.07 lower to 0.17 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. nested case control
b. small sample size

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Haemophilus influenza (Hib) vaccine

Summary: The literature search identified no randomized control trials, two observational studies [1,2] and one open label phase III trial [4] that addressed PICO 8 regarding Haemophilus influenza (Hib) vaccine. All the studies had small samples sizes and no changes in disease flares or relapse rates were seen status post the Hib vaccine.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
647 Morgan 2016 [1]	Cohort-case control	Median FU post vaccination 4.6 years, total patient FU was 363 patient-years (none lost to FU)	92 patients with small or medium-sized systemic vasculitis (EGPA- 7 patients, GPA-59 , MPA-22 or classical PAN- 4) in stable remission > 6 months (BVAS = 0), s/p CYC and steroid induction but not within 6 months, had not received RTX within 6 months, on <10mg of prednisone per day, currently on no more than 1 immunosuppressant + prednisolone, no active infections, not pregnant, no hx of previous severe reaction to vaccination or received vaccination to proposed vaccines; age 66 (53-74) 81 patients still taking prednisolone at median of 5mg/day at time of vaccination. 9 patients on Rituxan, 35 on AZA, 35 on mycophenalate	7-valent conjugate pneumococcal vaccine (Prevnar) Haemophilus influenzae type b (Hib) Meningococcal (Men) group C conjugate vaccine and Men polysaccharide groups A, C, Y, and W135 vaccine	No change in relapse rate in the 2 years following vaccination (prevaccination 0.15 per patient-year; postvaccination 0.12 per patient-year, p>0.05).
7047 Brogan 2019 [2]	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood vaccination programs. No live vaccines	No disease flares induced by vaccination

				permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination ("Pre-dose"), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). Included vaccines: HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	
459 Battafarao 1998 [3]	Cohort	12 weeks	73 SLE 5.5% male/94.5 % female; mean age 43 (18-76)4 48% on antimalarial agents , NSAIDS 34%, AZA 10%, IV CYC 10%, oral MTX 1% 74% on steroids, with 85% oral prednisone <10mg per day	Pneumococcal (pneumovax 23), tetanus toxoid and haemophilus influenza type B	None had clinical flare of SLE, no significant increase in disease activity scores measured by SLEDAI or LACC Six patients (8%) had increase in disease activity scores but didn't meet criteria for flare.

References:

[1] Morgan M, Richter A, Al-Ali S et al. Association of Low B Cell Count and IgG LevelsWith Infection, and Poor Vaccine Response WithAll-Cause Mortality in an ImmunosuppressedVasculitis Population. *Art Care & Research.* 2016;68(6): 853-860.

[1] Battafarano D, Battafarano N, Larsen L et al. Antigen-specific antibody responses in lupus patients following immunization. *Art Rheum.* 1998;41(10):1828-1834.

[11]Brogan P, Hofer M, Kuemmerle-Deschner J et al. Rapid and Sustained Long- Term Efficacy and Safety of Canakinumab in Patients With Cryopyrin- Associated Periodic Syndrome Ages Five Years and Younger. *Art Rheumatology.* 2019;71(11):1955-1963

Pneumococcal vaccine

Summary: The literature search identified three randomized controlled trials (RCTs) and 12 observational studies that addressed PICO 8 regarding the pneumococcal vaccine. The evidence base is relatively consistent in finding no increased risk of flares in RMD patients following pneumococcal vaccination.

An observational study of 38 patients with SLE who received the pneumococcal vaccination (14-valent purified pneumococcal capsular polysaccharide).[1] During the 6-month follow-up period post vaccination, 3 of 38 vaccinated SLE patients had a major flare compared to 2 of 23 non-vaccinated SLE patients. With such a small sample it is difficult to definitively make conclusions in regards to flare rate status post vaccination in this study.

Another observational study looked at 27 JIA patients who received the 23-valent polysaccharide pneumococcal vaccine (PPSv23) and found no increase in disease activity or flares status post immunization.[2]

A randomized, double blind, placebo control trial of 32 Sjogrens patients who received the PPSv23 vaccine found no increased risk in disease flare post vaccination.[3]

A case control study of a mixed RMD population, included 505 adult patients (253 w RA, 121 PsA, 78 Ank Spond, 53 another form SpA) received the 7-valent conjugate pneumococcal vaccine and found that 34 patients reported a disease flare post immunization.[1] Another case control study examined 60 patients with RA and 15 patients with Sjogrens received the 13-valent pneumococcal conjugate vaccine (PCV13) and subsequently reported no increase in their disease activity or flares.[5]
In a cohort study, PPSv23 was given to 42 RA patients and 24 SLE patients.[6] This study also found no association between the vaccination and RA or SLE flares.

Several studies found no flares or worsening of disease activity in SLE patients. A prospective cohort study of 21 SLE patients who received PCV13 followed by PPSV23 8 weeks later[7], a randomized control trial of 40 SLE patients who received the PPSv23 vaccine[8] , a cohort study of 73 SLE patients who received the PPSv23 vaccine[9], a case control of 18 SLE patients who received the PPSv23 vaccine[10], and another randomized control trial of SLE patients, 25 who received PPSV23 and 17 received PCV7 followed by PPSV23 24 weeks later[11], all found no flares status post vaccination.

A quality improvement study on 86 patients with childhood SLE who received PCV13, PPSV32, also found no disease flares status post vaccination.[12]

A cohort study in 92 patients with small or medium-sized systemic vasculitis who received the 7-valent conjugate pneumococcal vaccine (Prevnar) also found no disease flare post immunization.[13]

Two studies of pneumococcal vaccination in patients with cryopyrin-associated auto-inflammatory syndromes (CAPS), the first with a small sample size of 17 patients[14] and the second with 68 patients (19 received pneumococcal vaccine)[15], did not show any changes in disease activity or flares of their disease.

Quality of evidence across all critical outcomes: Low

Table 1: Flares after pneumococcal vaccination compared to no vaccination in patients with SLE. [1] 4373_Jarrett_1980

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccine	No vaccine	Relative (95% CI)	Absolute (95% CI)		
Flares												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/38	2/23	**OR 0.90** (0.14 to 5.83)	-	⨁◯◯◯ Very low	

CI: confidence interval; OR: odds ratio

Explanations

a. observational study - case control
b. Small sample size and wide confidence interval

Table 2: Disease activity in JIA patients pre- vs. post-immunization with pneumoccal vaccine. [2] 8003_Aikawa_2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-vaccine	Pre-vaccine	Relative (95% CI)	Absolute (95% CI)		
JADAS in JIA with anti-TNF 2mo vs baseline												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17	17	-	**MD 7.56 lower** (20.69 lower to 5.57 higher)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Post-vaccine	Pre-vaccine	Relative (95% CI)	Absolute (95% CI)		
JADAS in JIA without anti-TNF 2mo vs baseline												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10	10	-	**MD 2.31 lower** (22.22 lower to 17.60 higher)	⨁◯◯◯ Very low	
JADAS in JIA with anti-TNF 12mo vs baseline												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17	17	-	- **MD 7.81 lower** (21.05 lower to 5.43 higher)	⨁◯◯◯ Very low	
JADAS in JIA without anti-TNF 12mo vs baseline												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10	10	-	**MD 2.25 lower** (21.86 lower to 17.37 higher)	⨁◯◯◯ Very low	

CI: confidence interval; RR: risk ratio

Explanations

a. nested case control study
b. small sample size

Table 3. Data from RCTs and observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4373_Jarrett 1980 [1]	Case control	6 months	38 SLE (37 female) 5 no meds 29 on prednisone alone 9 on pred/AZA Group 1: prednisone <20mg/day Group 2: prenidone>20mg/day Group 3: both prednisone + AZA vs 23 pts who refused vaccination (22 female) vs 17 healthy volunteers	Pneumococcal vaccine (14 valent)	During the 6-month period following immunization, 3 of 38 vaccinated SLE patients had a major clinical flare.
3970 Karsh 1980 [3]	Randomized Double blind placebo controlled	6 months	32 patients with Sjogren's – 16 received PPSV23, 16 got PBO 6 in vaccine group were taking prednisone, doses < 0.25mg/kg	PPSv23	no increased risk of disease flare was observed following vaccination.
399 Kapetanovic 2011 [4]	Case-control, prospective	4-6 weeks post-vaccination	505 adult patients (253 w RA, 121 PsA, 78 Ank Spond, 53 another form SpA) RA + MTX; age 61.5 +/-14 RA + anti-TNF + MTX; age 60.1 +/- 10	7-valent conjugate pneumococcal vaccine	Disease flare was reported in 34 patients; most experienced transitory worsening of joint pain lasting a week post-vaccination. Worsening of existing arthritis (observed

			RA + TNF; age 59.8 +/- 14 SpA + anti-TNF + MTX; age 50.4 +/- 11 SpA anti-TNF; age 49.2 +/- 12 SpA + NSAIDs +/- analgesics = control group; age 51.6 +/- 12		by a rheumatologist) was reported in 1 patient.
402, Nived 2018 [5]	Cohort, case control	6 weeks	60 patients w RA (50 without DMARD, 10 on MTX); 58% on prednisolone (median dose 5 mg daily, range 0–15 mg) vs 15 patients with primary Sjogren's syndrome (pSS) without DMARD vs 49 controls	13-valent pneumococcal conjugate vaccine (PCV13)	None of the patients reported increased disease activity or relapse after vaccination.
4078 Elkayam 2002 [6]	Case control	2 months	42 RA patients, 24 SLE patients, 20 controls Prednisone, HCQ, MTX, AZA, SSZ, minocycline, CYC	PPSV23	no association between PPSV23 administration and SLE or RA flares
4370 Sacre 2018 [7]	Prospective cohort	1 year	21 patients with SLE	PCV13 followed by PPSV23 8 weeks later	No SLE flare was observed during the 12 months following pneumococcal vaccination.
1675_Klippel_1979 [8]	RCT	1 month	40 SLE patients; avg age 32 (range 14-61), 39 females Meds, various doses: 31 pts on CS 20 on NSAIDs 17 on antimalarials, either HCQ or chloroquine 5 on NO medicaitons No patients on cytotoxic drugs	Polyvalent pneumococcal polysaccharide vaccine (pneumovax) or isotonic saline solution w 0.25% phenol	No flares: composite lupus activity indexes at time of vaccination and one month later showed no differences between placebo and vaccine treated patients for clinical, laboratory or serologic measure

459 Battafarao 1998 [9]	Cohort	12 weeks	73 SLE 5.5% male/94.5 % female; mean age 43 (18-76)4 48% on antimalarial agents , NSAIDS 34%, AZA 10%, IV CYC 10%, oral MTX 1% 74% on steroids, with 85% oral prednisone <10mg per day	Pneumococcal (pneumovax 23), tetanus toxoid and haemophilus influenza type B	None had clinical flare of SLE, no significant increase in disease activity scores measured by SLEDAI or LACC Six patients (8%) had increase in disease activity scores but didn't meet criteria for flare.
5875 Tarjan 2009 [10]	Case control	28 days	18 SLE patients randomly selected from a cohort of Szolnok County Hospital in Hungary Inclusion criteria: established disease of mild activity -9 healthy women served as controls	Pneumovax vaccine given to SLE and healthy women	No disease flares were observed and SLEDAI scores remained almost unchanged.
6472 Grabar 2017 [11]	Double-blind RCT	52 weeks	SLE patients Age (median (IQR): 39.5 (33.3-50.7)	25 received PPSV23 17 received PCV7 followed by PPSV23 24 weeks later primary endpoint: rate of responders at week 28 to at least 5 of 7 serotypes shared by both vaccines	no significant risk of flare detected
6782 Sivaraman 2020 [12]	Quality improvement	Jan 2016-June 2018	86 pts with childhood SLE (median age 18 years, 87% female, 50% White, 35% African American, 15% Hispanic and other; 31% with LN at any time; 29% on CYC at any time, 10% on anti B cell biologics in preceding year, 10% on steroids >=20mg/day, 41% on steroids <20mg/day)	PCV13, PPSV32 92.7% of pts ended up getting vaccinated with at least pneumococcal vaccine and 87.3% with both.	No disease flares related to timing of vaccination were observed.
647 Morgan 2016 [13]	Cohort-case control	Median FU post vaccination 4.6 years, total patient FU was 363 patient-years (none lost to FU)	92 patients with small or medium-sized systemic vasculitis (EGPA- 7 patients, GPA-59 , MPA-22 or classical PAN- 4) in stable remission > 6 months (BVAS = 0), s/p CYC and steroid induction but not within 6 months, had not received RTX within 6 months, on <10mg of prednisone per day, currently on no more than 1 immunosuppressant + prednisolone, no active infections, not pregnant, no hx of previous severe reaction	7-valent conjugate pneumococcal vaccine (Prevnar) Haemophilus influenzae type b (Hib) Meningococcal (Men) group C conjugate vaccine and Men polysaccharide groups A, C, Y, and W135 vaccine	No change in relapse rate in the 2 years following vaccination (prevaccination 0.15 per patient-year; postvaccination 0.12 per patient-year, p>0.05).

			to vaccination or received vaccination to proposed vaccines; age 66 (53-74) 81 patients still taking prednisolone at median of 5mg/day at time of vaccination. 9 patients on Rituxan, 35 on AZA, 35 on mycophenalate		
7047 Brogan 2019 [14]	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood vaccination programs. No live vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination (“Pre-dose”), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). Included vaccines: HBV, HiB, TdaP, influenza, pneumococcal, meningococcal.	No disease flares induced by vaccination

				No data on timing of vaccinations with respect to canakinumab dosing.	
7772 Jaeger (2017) [15]	Case series based on prospective, multicenter observational patient registry (β-CONFIDENT)	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period. Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	All patients treated with canakinumab. Total of 159 vaccine injections 43/68 (63%) patients received multiple vaccine injections Influenza: 107 injections in 55/68 (81%) patients Pneumococcal: 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days. No cases of CAPS reactivation reported for other vaccines.

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1. Jarrett M, Schiffman G, Barland Peter, Grayzel A. Impaired response to pneumococcal vaccine in systemic lupus erythematosus. Art Rheum. 1980;23(11): 1287- 1293.

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13. Morgan M, Richter A, Al-Ali S et al. Association of Low B Cell Count and IgG LevelsWith Infection, and Poor Vaccine Response WithAll-Cause Mortality in an ImmunosuppressedVasculitis Population. Art Care & Research. 2016;68(6): 853-860.

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15. Jaeger V, Hoffman H, van der Poll T et al. Safety of vaccination in patients with cryopyrin-associated periodic syndromes: a prospective registry based study. Rheumatology. 2017;56:1484. doi:10.1093/rheumatology/kex185.

Hepatitis A Vaccine

Summary: The literature search identified six observational studies that addressed PICO 8 in regard to the hepatitis A vaccine.

Two observational studies looked at post-vaccination flares in JIA patients.[1,2] Both had small sample sizes. The open label comparative study did not find any disease flares in the 47 JIA patients studied post-vaccination.[3] The case control study of 83 JIA patients found 15 JIA disease flares during the total follow-up period, but these were not considered to be related to the vaccination.[1] No JIA flare was reported during the three-month monitoring period after the vaccinations.

One prospective controlled clinical trial of 30 patients with childhood-onset SLE showed no disease flares post vaccination.[5]

A case control study of 28 patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) showed a disease flare in 3 patients (14.2%). Overall the vaccination in this study was considered well tolerated.[6]

In the prospective case series, only five hepatitis A vaccines were given to patients with a cryopyrin-associated autoinflammatory syndromes (*CAPS*) and no disease flares were seen status post vaccination.[1]

The last cohort study included non-RMD patients, 47 children with IBD, and no flares were seen post vaccination.[1]

Quality of evidence across all critical outcomes: Low

Table 1. Data from RCTs and observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2861 Erguven 2011 [1]	Open label comparative study	8 months	Juvenile idiopathic arthritis (n=47) and 67 healthy controls with no history of previous Hepatitis A vaccination	Hepatitis A vaccine: 2 doses of hepatitis A vaccine at 6-month intervals, disease activity (CHAQ), adverse effects	No patient with JIA had clinical worsening or disease activation after vaccination. No increment in CHAQ score.
4088_ Martsi 2017 [2]	Cohort/case control, non-randomized	Nov 2011- Nov 2014	83 JIA (6.3 +/-2.3)/66% females, on MTX (mean dose 12.5mg/week) Vs 76 Healthy controls- age (5.3 +/-2.7)/sex (45% females) matched	Two inactivated anti-HAV vaccine	15 JIA disease flares during the total follow-up period. Two patients developed a flare after the first dose (mean time 4.3 months) and 13 after the second dose (mean time 8 months). These flares were not considered to relate to vaccinations. No JIA flare was reported during the three-month

					monitoring period after each vaccine.
3428_Mertoglu_2019 [3]	Controlled clinical trial, prospective, not randomized	Jan 2016 – Mar 2017	30 childhood onset SLE ; age 16.7 +/-3.2 yrs antimalarials 27 (90) prednisolone 11 (36.6) immunosuppressive tx 15 (50) vs 39 healthy participants; age 12.2 +/- 3.3	Hepatitis A vaccine Subjects between 1 and 18 years of age received two doses of licensed pediatric formulation of hepatitis A vac- cine (720 EL.U/0.5 ml HAVRIX) Those over 18 years of age received the adult form (1440 EL.U/1 ml) of HAVRIX,	No flare of SLE seen in any patient in study
4097_Martisi 2019 [4]	Case- control, prospective observational	Nov 2012- Nov 2014	28 periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) patients (age 4.4 _/- 2.3)/(43% female) For flare: NSAID 13 pts (46%) NSAID + CS 9 (32%) CS 3 (10%) No med 3 (10%) Vs 76 Healthy controls (age 4.75_/- 2.7)/(45% female)	HAV vaccination	Disease flare in 3 pts (14.2%)
7772 Jaeger (2017) [5]	Case series based on prospective, multicenter observational patient registry (β-CONFIDENT)	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period. Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	All patients treated with canakinumab. Total of 159 vaccine injections 43/68 (63%) patients received multiple vaccine injections Influenza: 107 injections in 55/68 (81%) patients Pneumococcal: 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days. No cases of CAPS reactivation reported for other vaccines.

				Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	
4017_Urganci_2013 [6]	Cohort/ case control, prospective	2000-2012	47 children w IBD; all on 5-aminosalicylic acid. 13 pts on CS (prednisolone 1-2mg/kg/day,max 60mg); AZA (2mg/kg/day) in 8 pts age ranged 3-17 yrs; male: female ratio 1.13 47 pts without evidence of earlier exposure to Hep B received Hep B vaccine; 23 of them neg for HAV AB received Hep A vacc vs 50 healthy controls; age-sex matched (17 girls, 33 boys; mean age 9.2+/- 1.7 yrs)	For those patients not immune to HAV or HBV: (no one received combined hep A/B vacc) Hepatitis A vaccine— 2 doses given 6 months apart Hepatitis B vaccine – 3 doses at months 0,1, and 6	no flares, disease activity remained stable after vaccination

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6. Urganci N, Kalyonuc D. Immunogenicity of hepatitis A and B vaccination in pediatric patients with inflammatory bowel disase. JPGN. 2013;56:412-415

Hepatitis B Vaccine

Summary: The literature search identified 12 observational studies that addressed PICO 8 in regards to the hepatitis B vaccine.

An online survey of 210 patients with juvenile dermatomyositis (DM) (n=164) and adult DM (n=46) who received any of the vaccines listed in the study was assessed, which included the Hepatitis B vaccine.[1] Results showed 63.8% (103 juvenile, 31 adults) experienced a flare within the past 6 months. Patients who flared were more likely to have received HPV vaccine within 6 months of the flare, while other vaccines (including hepatitis B vaccine) did not differ in frequency between those who did or did not flare.

A cohort study of 22 patients with RA who received the hepatitis vaccination found that vaccination was not associated with any significant worsening of any clinical or laboratory measure of disease activity.[2] The different measures used to assess disease activity of patients with RA and controls were not statistically different. Another cohort study of 46 patients with RA had similar findings of no disease worsening either clinically or by laboratory data status post vaccination with hepatitis B.[3]

A retrospective study of 26 children with rheumatic diseases found no worsening of their disease after hepatitis B vaccination.[1] No flares were also seen in a nonrandomized clinic controlled trial, which included 39 JIA patients who received the hepatitis B vaccination.[5]

Another nonrandomized clinical controlled study of 20 juvenile SLE patients who received this vaccination found that 15% of patients had a flare of their disease, however this flare rate was not different than the 18% flare rate of other juvenile SLE patients on follow-up.[6]

A larger retrospective cohort study of 262 JIA patients who underwent hepatitis B vaccination found no flares of their disease.[7] No flares were also seen in an open label phase III trial of 17 patients with CAPS post hepatitis B vaccination.[8] A prospective cohort study of 25 JIA patients found no flares post hepatitis B vaccination.[9]

A case control study of 13 patients with Behcet's disease did not find disease activity post vaccination.[10] Laboratory data was not significantly different pre and post vaccination. There was no reactivation or worsening of arthritis in these patients. Eruption of minor oral aphtae was seen in 23.1% of patients.

In a prospective case series, only six hepatitis B vaccines were given to patients with a cryopyrin-associated autoinflammatory syndromes (*CAPS*); it reported no disease flares status post vaccination.[11] The last cohort study included non-RMD patients, 7 children with IBD, and no flares were seen post vaccination.[12]

Quality of evidence across all critical outcomes: Low

Table 1: Hepatitis B compared to placebo for DM. [1] 2740_Mamyrova_2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hepatitis B	placebo	Relative (95% CI)	Absolute (95% CI)		
Flare s/p Hep B												
1	observational studies	very serious[a]	not serious	not serious	serious[b]	none	10/134 (7.5%)	2/76 (2.6%)	**OR 2.98** (0.64 to 13.99)	**48 more per 1,000** (from 9 fewer to 248 more)	⨁◯◯◯ Very low	

CI: confidence interval; OR: odds ratio

Explanations

a. recall bias (survey), not randomized, not blinded
b. Wide confidence intervals

Table 2. Clinical measures of activity in pts with RA and hep B vaccine compared to without vaccine. [2] 7620 Elkayam 2002

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical measures of activity in pts with RA and hep B vaccine	without vaccine	Relative (95% CI)	Absolute (95% CI)		
Daytime pain 0 weeks												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical measures of activity in pts with RA and hep B vaccine	without vaccine	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-		**-**	**MD 0.55 lower** (1.88 lower to 0.78 higher)	⨁◯◯◯ Very low	
Morning stiffness (min) 0 weeks												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-		**-**	**MD 19.10 lower** (48.73 lower to 10.53 higher)	⨁◯◯◯ Very low	
Number of Tender jts week 0												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%		- **MD 1.40 lower** (4.43 lower to 1.63 higher)	⨁◯◯◯ Very low	
Number of Swollen joints week 0												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical measures of activity in pts with RA and hep B vaccine	without vaccine	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	**-**	**MD 0.76 lower** (2.65 lower to 1.13 higher)	⊕◯◯◯ Very low	
CRP (mg/L) week 0												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	0 cases 0 controls		**-**	**MD 0.79 lower** (2.02 lower to 0.44 higher)	⊕◯◯◯ Very low	
							-	0.0%				
ESR week 0												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none			**RR --**	**MD 10.80 lower** (21.41 lower to 0.19 lower)	⊕◯◯◯ Very low	Favors hep B vaccine
							-	0.0%				
Daytime pain 1 month												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none			**-**	**MD 0.90 lower** (2.23 lower to 0.43 higher)	⊕◯◯◯ Very low	
							-	0.0%				

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical measures of activity in pts with RA and hep B vaccine	without vaccine	Relative (95% CI)	Absolute (95% CI)		
Morning stiffness 1 month												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 32.70 lower** (63.53 lower to 1.87 lower)	⨁◯◯◯ Very low	Favors hep B vaccine
No of tender joints 1 month												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 1.10 lower** (3.47 lower to 1.27 higher)	⨁◯◯◯ Very low	
No of swollen joints 1 month												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 0.70 lower** (2.16 lower to 0.76 higher)	⨁◯◯◯ Very low	
CRP (mg/L) 1 month												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical measures of activity in pts with RA and hep B vaccine	without vaccine	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 0.70 lower** (1.56 lower to 0.16 higher)	⊕◯◯◯ Very low	
ESR 1 month												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%		**MD 5.60 lower** (15.57 lower to 4.37 higher)	⊕◯◯◯ Very low	IMPORTANT
Daytime pain Month 7												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 1.10 lower** (2.34 lower to 0.14 higher)	⊕◯◯◯ Very low	
Morning stiffness (min) 7 mo												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 39.40 lower** (69.84 lower to 8.96 lower)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical measures of activity in pts with RA and hep B vaccine	without vaccine	Relative (95% CI)	Absolute (95% CI)		
No of tender joint month 7												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 1.20 lower** (3.75 lower to 1.35 higher)	⨁◯◯◯ Very low	IMPORTANT
No of swollen joints month 7												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 1.20 lower** (2.68 lower to 0.28 higher)	⨁◯◯◯ Very low	
CRP (mg/L) 7 months												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	-	0.0%	-	**MD 1.10 lower** (2.17 lower to 0.03 higher)	⨁◯◯◯ Very low	
ESR 7 months												
1		serious[a]	not serious	not serious	serious[b]	none				-		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clinical measures of activity in pts with RA and hep B vaccine	without vaccine	Relative (95% CI)	Absolute (95% CI)		
	observational studies						-	0.0%	-	**MD 4.70 lower** (15.38 lower to 5.98 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. case control study
b. small sample size

Table 1. Data from observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2607 Intongkam 2019 [3]	Prospective cohort	24 weeks	46 RA patients (33 receiving cDMARDS, 13 cDMARDS+bDMARDs) vs 37 treatment-matched controls (34 on cDMARDs, 13 on cDMARDs+bDMARDs) who did not get vaccination	20 ug Hepatitis B vaccine at 0, 4, and 24 wks	Hepatitis B vaccination was not associated with a significant worsening of any clinical or laboratory measure of disease. No other statistically significant differences in disease activity, as measured by total joint count, ESR, DAS28, Patient global Results at week 0, 4, and 32: Tender joint count: 2.6, 1.9, 2.0 Swollen joint count: 2.2, 1.7, 2.1

					Patient global assessment: 27.4, 24.3, 27.7 ESR, mm/h: 54.2, 60, 49.9 DAS28: 3.97, 3.91, 3.9
2623 Kohagura 2021 [4]	Retrospective cohort study	Antibodies measured at 1 month after 1 series of HB vaccinations	26 children with rheumatic diseases who had been vaccinated against hepatitis B during immunosuppressive treatment (Pred, MTX, MMF, Azathioprine, CsA, ADA, TCZ)	Hepatitis B	No worsening of the underlying disease by HB vaccination
3438_Kasapcopur_2004 [5]	Controlled clinical trial not randomized	3 to 6 months	39 JIA (21 male, 18 female); 11 with systemic JIA, 11 with oligoarticular JIA, 10 with polyarticular JIA, and seven with enthesitis related arthritis – all in remission 10 male, 10 female were on CS (range 2.5-10mg/dayl mean 6.05mg); 19 patients not on CS 22 (11 male, 11 female) on MTX (10mg/m2/week), 17 were not on MTX vs control group 41 healthy children (21 female, 20 male)	Hepatitis B vaccination (DNNA recombinant vaccine) Alternating two groups: Group I: were vaccinated at 0,1,and 3 months Group IIL were vaccinated at 0,1,and 6 months	None of the JIA patients experienced a flare up or clinical deterioration related to the vaccination.
3439_Aytac 2011 [6]	Controlled clinical trial not randomized	7 months	20 juvenile SLE patients were non immunized to hep B (16 female, 4 male; age 13.2 +/- 2.58 yrs) 17 on prednisone (mean 6.25mg; range 2.5-12.5mg/day) 11 on AZA (mean dose 100mg/day) , 3 on MMF (mean dose 1000mg/day) and 2 on HCQ (mean dose 200mg/day)	Recombinant Hepatitis B vaccine Day 0, 1 and 6 months	3 patients (15%) were considered to have a flare and their treatment protocol was revised by increasing the prednisone dose. (The 15% flare rate of the study patients was not different than the 18% flare rate of other juvenile SLE patients on follow-up)

			3 patients not taking any meds. vs 24 Healthy controls (12 female, 12 male; age 8.83+/-2.72)		
3441_Cakmak 2021 [7]	Retrospective cohort	4 years	262 treatment naïve JIA 276 controls patients who received chemotherapy, immunomodulatory therapy, - excluded	None, Anti Hep B Surface antibody titers studied Seroprotection: Anti-HBs titers >10 IU/L If Anti-HBs titers < 10IU/L - revaccinated	There was no correlation between disease activity at the diagnosis and anti-Hbs titer (p=0.31).
7047 Brogan 2019 [8]	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood vaccination programs. No live vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination (“Pre-dose”), and	No disease flares induced by vaccination

				on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). Included vaccines: HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	
7335 Erkek 2005 [9]	Case control	28 days after each dose of vaccine	13 Behcet's disease (7 women, 6 men; mean age, 33.54 ± 9.863 years); vs 15 healthy controls (12 female, 3 males; mean age, 32.87 ± 10.267 years)	Hepatitis B vaccine 3-doses 0, 1, 6 months Colchicine at a dose of 0.6–1.8 mg/day.	Behcet's patients disease activity ESR andCRP values before and after vaccination were not sig-nificantly different (P = 0.818 and P= 0.912). 3/13 (23.1%) had minor oral aphtae on the third and twenty-eighth days of follow-up after the second dose of vacci-nation. 4/13 (30.8%) had positive pathergy reaction
7608 Nerome 2015 [10]	Prospective cohort	7 months	25 JIA disease controlled pts (=unchanged treatment for at least 3 months), 18 pts on biologics, 7 not on biologics (etanercept, infliximab, adalimumab, tocilizumab). Average age 16, 28% treated with CS, 76% on mtx, 72% on biologics	HBV at 0,1,6 mo	No flares of JIA were observed
7772 Jaeger (2017) [11]	Case series based on prospective, multicenter observational patient registry	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period.	All patients treated with canakinumab. Total of 159 vaccine injections	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days.

	(β-CONFIDENT)		Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	43/68 (63%) patients received multiple vaccine injections Influenza: 107 injections in 55/68 (81%) patients Pneumococcal: 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	No cases of CAPS reactivation reported for other vaccines.
4017_Urganci_2013 [12]	Cohort/ case control, prospective	2000-2012	47 children w IBD; all on 5-aminosalicylic acid. 13 pts on CS (prednisolone 1-2mg/kg/day,max 60mg); AZA (2mg/kg/day) in 8 pts age ranged 3-17 yrs; male: female ratio 1.13 47 pts without evidence of earlier exposure to Hep B received Hep B vaccine; 23 of them neg for HAV AB received Hep A vacc vs 50 healthy controls; age-sex matched (17 girls, 33 boys; mean age 9.2+/- 1.7 yrs)	For those patients not immune to HAV or HBV: (no one received combined hep A/B vacc) Hepatitis A vaccine— 2 doses given 6 months apart Hepatitis B vaccine – 3 doses at months 0,1, and	no flares, disease activity remained stable after vaccination

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Human Papilloma Virus (HPV) Vaccine

Summary: The literature search identified nine observational studies that addressed PICO 8 in regards to the HPV vaccine.

An online survey of 210 patients with juvenile DM (n=164) and adult DM (n=46) who received any of the vaccines listed in the study was assessed, which included the HPV vaccine. Results showed 63.8% (103 juvenile, 31 adults) experienced a flare within the past 6 months. Patients who flared were more likely to have received HPV vaccine within 6 months of the flare (8.2%, P = 0.03; OR = 10.0, 95% CI: 0.6, 175.5).[1]

One cohort study examined a small sample size of 21 patients with JIA and found no changes in disease activity or flares status post HPV vaccination.[2]

Several studies addressed HPV vaccination in SLE patients. A case control study with 50 SLE patients between the ages of 18-35 years, identified 1 mild/moderate flare at months 0-2, two flares at months 3-6 and six flares at months 7-12 during followup post HPV vaccination.[3] A causal relationship between the vaccine and flares was unclear. A cohort study of 27 SLE patients found 9/27 had a mild-moderate flare during the study period.[1] A controlled, clinical trial that was not randomized included 37 women with SLE aged 18-50 years and found no SLE flares post vaccination.[5] A small cohort study of 27 SLE patients aged 12 to 26 years found 9/27 (33.3%) patients developed a mild or moderate lupus flare during their study period.[6] Each of these studies had a small sample size and conclusions in regards to disease flare rate status post vaccination cannot be definitively made. The largest multicenter, interventional prospective study examined 256 patients with childhood onset SLE.[7] In 9% of these patients, their SLEDAI scores increased from 3 to 12 after the two doses of the vaccine, indicating mild-moderate disease worsening. After the 3rd dose, only 5% of the patients remained with a significantly higher score in comparison to their baseline visit.

Another multicenter, interventional prospective study examined 47 patients with juvenile DM.[8] Disease activity remained stable or even improved during the study status post HPV vaccination. Childhood Myositis Activity Score did not worsen. Only 2.5% of the study population had worsening or new onset or a rash, 2.5% worsening/new onset of gottron's papules and 5% had worsening or new onset of heliotrope rash.

In the prospective case series, only one HPV vaccine was given to patients with a cryopyrin-associated autoinflammatory syndromes (*CAPS*) and with such a small sample size, conclusions in regards to disease flare rate status post vaccination cannot be definitively made.[9]

Quality of evidence across all critical outcomes: Very low

Table 1. HPV compared to placebo for DM. [1] 2740_Mamyrova_2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HPV	placebo	Relative (95% CI)	Absolute (95% CI)		
Flare s/p HPV												
1	observational studies	very serious[a]	not serious	not serious	serious[b]	none	9/134 (6.7%)	0/76 (0.0%)	**OR 11.58** (0.66 to 201.83)	-	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. recall bias (survey), not randomized, not blinded
b. Wide confidence intervals, crosses zero

Table 2. Data from observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4138 Esposito 2014 [2]	Cohort	7 months	21 female patients aged 12-25 years w stable JIA - 10 (47.6%) NSAIDs - 5 (23.8%) MTX - 6 (28.6%) etanercept vs 21 healthy females	HPV vaccine (cervarix)	No significant change in JADAS-27 scores or laboratory test results following HPV vaccination.

4047 Mok 2012 [3]	Case control	18 months	50 patients with SLE and 50 health controls, aged 18-35 years, with stable disease	GARDASIL IM at baseline, month 2 and month 6 given to stable lupus patients on the following medications: - Prednisolone 70% - HCQ 66% - AZA 48% - MMF 18% - CSA 4% - Tac 10% - MTX 6%	No significant changes in dsDNA, anti-C1q, C3, C4, SLEDAI and PGA scores from baseline to months 2, 6 and 12. There was 1 mild/mod flare at months 0-2, two at months 3-6 and six at months 7-12. Two SLE patients had sever flares at months 7-12. Causal relationship between vaccine and flare was unclear. No withdrawals due to flare. Overall flare rate was 0.22/pt/yr which was not statistically different compared to a cohort of SLE patients who did not participate in the study.
7613 Borba 2013 [4]	Cohort	20 months	27 SLE patients - 7 patients did not complete study Medications: hydroxychloroquine (100%); prednisone (59.2%; mean 12.6mg range 0-36; mycophenolate mofetil (33.3%); azathioprine (33.3%); methotrexate (22.2%)	HPV vaccine 3-dose Gardasil	20 SLE completed follow-up: Mean SLEDAI 6.14 pre-vaccination to 4.49 post-vaccination at month 7 (p- 0.010; 95% CI:- 2.85 to −0.44) - 9/27 had mild-moderate flare during study period
7669 Dahr 2017 [5]	Controlled clinical trial, not randomized	7 months	37 women ages 18-50 yrs with history of mild to moderate SLE and minimally active or inactive SLE	Quadrivalent HPV vaccine at standard dosing schedule	No patient experienced any SLE flare, change in autoantibody levels, thrombosis, or generation of thrombogenic antibodies.
7676 Soybilgic 2013 [6]	Cohort	7 months	27 SLE patients (aged 12 to 26 years), 100% female; 16 evaluable at 7 months	3 doses of 0.5 ml of recombinant, quadrivalent HPV vaccine (Gardasil) Treatments included hydroxychloroquine (100%); prednisone (59.2%); mycophenolate mofetil (33.3%); azathioprine (33.3%); methotrexate (22.2%). The	9/27 (33.3%) patients had mild or moderate lupus flares during the study period. Results indicated a significant reduction in mean SLEDAI scores at 7 months (n=20) followup (6.14±3.7 vs. 4.49±2.8; p=0.01).

				mean prednisone dose was 12.6 mg (range 0–36).	HPV vaccination did not result in increases in mean SLEDAI scores.
7677 Herta Rotstein Gren 2020 [7]	Multi-center, interventional, prospective	March 2014-2016	256 childhood onset SLE and 41 healthy controls. cSLE 53/234 with active disease (Sledai>4), 61% on prednisone, 89.5% on hcq, 26% on AZA, 33% on cellcept, 7% on mtx, 6% on cyclosporine, 4.5% on CYC, 4% on no meds; Median age at dx of SLE was 11.8 years.	2 doses of Gardasil or 3 doses of Gardasil	182 BL visits 200 visits after the 2nd dose 182 visits after the 3rd dose Median SELENA SLEDAI at all these visits was 2. Disease remained stable in 76% after 2 doses, in 82% after receiving 3 doses compared to baseline. In 12% disease activity improved after 2 and 3 doses compared to baseline. One pt had score of 40 at BL visit which decreased to 0 at 2nd study visit. In 9% of pts SLEDAI scores increased from 3 to 12 after two doses of the vaccine (mild-mod disease worsening). After the 3rd dose, only 5% remained with a significantly higher score in comparison to baseline visit. 1 patient had severe worsening of scores during the study (increased up to 16) but this was related to poor compliance with treatment.

7678 Grein 2020 [8]	Multi-center, interventional, prospective	March 2014-2016 6 months	47 Juvenile DM (aged 9 to 20 years) and 41 healthy controls	3 doses of Gardasil	Muscular activity at V1 (BL), V2 (1 mo after 2nd dose), V3 (1mo after 3rd dose) and V4 (6 mo after 3rd dose). CMAS (childhood myositis activity score), median: 50 (V1, N=42), 51.5 (V2, N=42), 50 (V3, N=40), 50 (V4, N=26) Cutaneous activity: Rash: 9/42 (V1), 7/42 (v2), 4/40 (v3), 1/26 (v4) Gottron's papules: 12/42 V1, 9/42 V2, 10/40 v3, 3/26 V4 Heliotrope: 7/42 V1, 4/42 v2, 5/40 v3, 1/26 V4 CMAS improvement after 3rd HPV dose: 5/40 CMAS worsening after 3rd HPV dose: 0/40 Improvement of rash after 3rd HPV dose 5/40 (!2.5%), of Gottron's papules 3/40 (7.5%), of heliotrope rash 3/40 (7.5%). Worsening or new onset of cutaneous lesion after 3rd HPV dose compared to baseline for rash 1/40 (2.5%), for Gottron's papules 1/40 (2.5%) and for heliotrope rash 2/40 (5%).
7772 Jaeger (2017) [9]	Case series based on prospective, multicenter observational patient registry	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period.	All patients treated with canakinumab. Total of 159 vaccine injections 43/68 (63%) patients received multiple vaccine injections	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days.

	(β-CONFIDENT)		Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	Influenza: 107 injections in 55/68 (81%) patients Pneumococcal: 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	No cases of CAPS reactivation reported for other vaccines.

References:

1. Mamyrova G, Rider L, Ehrlich A et al. Environmental factors associated with disease flare in juvenile and adult dermatomyositis. Rheumatology. 2017;56:1342-1347: doi:10.1093/rheumatology/kex162.

2. Esposito S, Corona F, Barzon L et al. Immunogenicity, safety and tolerability of a bivalent human papillomavirus vaccine in adolescents with juvenile idiopathic arthritis. Expert Review Vaccines. 2014; 13(11): 1387-1393: DOI:10.1586/14760584.2014.943195.

3. Mok C, Ho L, Fong L et al. Immunogenicity and safety of a quadrivalent humran papillomavirus vaccine in patients with systemic lupus erythematosus: a case- control study. Ann Rheum Dis. 2013;72:659–664. doi:10.1136/annrheumdis-2012-201393.
4. Kuruma K, Borba E, Lopes M et al. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. Lupus. 2007;16:350–354

5. Dhar J, Essenmacher L, Dhar R et al. The safety and immunogenicity of quadrivalent HPV (qHPV) vaccine in systemic lupus erythematosus. Vaccine. 2017; 2642-2646.

6. Soybilgic A, Onel K, Utset T et al. Safety and immunogenicity of the quadrivalent HPV vaccine in female systemic lupus erythematosus patients aged 12 to 26 years. Ped Rheum. 2013;11(29): 1-7.

7. Herta Rotstein Grein I, Ferreira Pinto N, Lobo A et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in patients with childhood systemic lupus erythematosus: a real world interventional multi-center study. Lupus. 2020; 29 (8): 934-942.

8. Herta Rotstein Grein I, Ferreira Pinto N, Groot N et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in patients with juvenile dermatomyositis: a real-world multicenter study. Ped Rheum. 2020;18(87): 1-12

9. Jaeger V, Hoffman H, van der Poll T et al. Safety of vaccination in patients with cryopyrin-associated periodic syndromes: a prospective registry based study. Rheumatology. 2017;56:1484. doi:10.1093/rheumatology/kex185.

Meningococcal Vaccine

Summary: The literature search identified one observational study[1] and one open label phase III trial[2] that addressed PICO 8 in regards to the meningococcal vaccine. Both studies had small samples sizes and no changes in disease flares or relapse rates were seen status post the administered vaccine.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
647 Morgan 2016 [1]	Cohort-case control	Median FU post vaccination 4.6 years, total patient FU was 363 patient-years (none lost to FU)	92 patients with small or medium-sized systemic vasculitis (EGPA- 7 patients, GPA-59 , MPA-22 or classical PAN- 4) in stable remission > 6 months (BVAS = 0), s/p CYC and steroid induction but not within 6 months, had not received RTX within 6 months, on <10mg of prednisone per day, currently on no more than 1 immunosuppressant + prednisolone, no active infections, not pregnant, no hx of previous severe reaction to vaccination or received vaccination to proposed vaccines; age 66 (53-74) 81 patients still taking prednisolone at median of 5mg/day at time of vaccination. 9 patients on Rituxan, 35 on AZA, 35 on mycophenalate	7-valent conjugate pneumococcal vaccine (Prevnar) Haemophilus influenzae type b (Hib) Meningococcal (Men) group C conjugate vaccine and Men polysaccharide groups A, C, Y, and W135 vaccine	No change in relapse rate in the 2 years following vaccination (prevaccination 0.15 per patient-year; postvaccination 0.12 per patient-year, p>0.05).

7047 Brogan 2019 [2]	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype: 4 NOMID, 12 MWS, 1 FCAS patient.	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood vaccination programs. No live vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination (“Pre-dose”), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). Included vaccines: HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	No disease flares induced by vaccination

References:

1. Morgan M, Richter A, Al-Ali S et al. Association of Low B Cell Count and IgG LevelsWith Infection, and Poor Vaccine Response WithAll-Cause Mortality in an ImmunosuppressedVasculitis Population. Art Care & Research. 2016;68(6): 853-860.

2. Brogan P, Hofer M, Kuemmerle-Deschner J et al. Rapid and Sustained Long- Term Efficacy and Safety of Canakinumab in Patients With Cryopyrin- Associated Periodic Syndrome Ages Five Years and Younger. Art Rheumatology. 2019;71(11):1955-1963

Measles, Mumps, Rubella (MMR) Vaccine

Summary: The literature search identified one randomized controlled trial[1] and four observational studies[2-5] that addressed PICO question 8 regarding the MMR vaccine. In the randomized, multicenter, open-label clinical equivalence trial 137 JIA patients (4-9 years old) were assigned to receive the MMR booster (n=63) whereas 69 JIA patients served as a control group. The relative risk of a flare in revaccinated patients vs controls was 0.9 (95% CI, 0.4-2.0) at 3 months and 1.3 (95% CI, 0.8-2.1) during total follow-up. Similar results were found in patients using methotrexate or biologics, however, small patient numbers precluded definitive conclusions[1].

A prospective nested case-control of 15 JIA patients (ages 6-17) on low dose methotrexate with or without use of etanercept (control: 22 healthy children) receiving MMR revaccination showed no worsening of mean disease activity parameters over the period of 6 months after MMR revaccination, when compared with 6 months before vaccination date. There was no increase in medication use observed for oral or IA steroids or MTX[2]. A physician survey sent to recruit patients with autoinflammatory diseases on IL-1 or IL-6 blocking medications who had received live vaccination, identified 17 patients, of which 8 had received the MMR booster (in 1/8 MMR booster was combined with varicella zoster live vaccine). Two out of 8 patients experienced a flare of their autoinflammatory condition (one of two requiring hospitalization)[5]. In a retrospective observational multicenter cohort study of 314 patients with JIA who received MMR vaccine, no increase in disease activity, flares, or medication use was seen in the 6 months after MMR vaccination, including in patients using methotrexate (n=49)[3]. In conclusion, there was no significant evidence that MMR vaccination leads to flares of underlying RMD.

Quality of evidence across all critical outcomes: Low

Table 1. Data from RCTs and observational studies not suitable for RevMan

RefID, Author, Year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2596_Heijstek_2013	Randomized multicenter, open-label clinical equivalence trial	May 2008-July 2011	137 JIA patients; ages 4-9 years MMR booster group (n=63); 46 (73%)females, oligoart, persistent JIA 32 (51%), oligo art extended 8 (13%), polyart 14 (22%), systemic onset 6 (10%), PsA 3 (5%)	MMR booster vaccination vs no vaccination	The mean JADAS-27 during the total follow-up period did not differ significantly between revaccinated patients and control patients→ JADAS-27 difference was within the equivalence margin of 2.0 points (JADAS-27 difference over time, 0.4; 95% CI, 0.5 to 1.2) ; This was also true for patients taking methotrexate (JA- DAS-27 difference over time, 0.02; 95% CI, 1.1 to 1.2) or biologics (JADAS-27 difference over time, 0.6; 95% CI, 1.2 to 2.4) (Figure 2C) and for various JIA subtypes

			MTX 29 (46%) NSAID 38 (60%) LEF 1 (2%) TNF 6 (10%) IL-1R 3 (5%) Oral CS 2 (3%) Control group (n=69); 41 (60% females), oligoart persistent 40(59%), oligoart extended 4 (6%), polyart 13 (19%), systemic onset 9 (13%), PsA 2 (3%) MTX 31 (46%) NSAID 36 (53%) LEF 1 (1%) TNF 4 (6%) IL-1 2 (3%) Oral GC 1 (2%)		The mean number of flares per patient did not differ significantly between the MMR booster group (0.44; 95% CI, 0.28-0.61) vs control group (0.34; 95% CI, 0.20-0.49), nor did the % of patients with 1 or more flares during follow-up SEE REVMAN: The relative risk of a flare in revaccinated patients vs controls was 0.9 (95% CI, 0.4-2.0) at 3 months and 1.3 (95% CI, 0.8-2.1) during total follow-up Similar results were found in patients using methotrexate or biologics →small patient numbers precluded definite conclusions.
2629_Borte_2009	prospective nested case control		15 patients w JIA (ages 6-17); on low dose MTX alone or MTX +etanercept group 1: (n=5) JIA w completed MMR I and II vacc, tx w low dose MTX (!0mg.m2 body surface, once weekly, SD 7.5-15mg/person) group 2A: (n=5)JIA s/p MMR vacc while tx w low dose MTX > 6	MMR	No worsening of mean disease activity parameters was seen over the period of 6 months after MMR revaccination when compared with 6 months before vaccination date, No increase in medication use was observed for oral or IA steroids or MTX.

			months prior to vaccc date group 2b: (=5)JIA + low-dose MTX + TNF RA etacercept (0.4mg/kg body wt, twice weekly 22 healthy controls		
7743 Jeyaratnam 2018	Cohort	Cross-sectional only	17 autoinflammatory diseases - 7 systemic JIA, 5 CAPS, 4 MKD, 1 FMF Medications on anti-IL1 or anti-IL6: - 10 Anakinra - 4 Canakinumab - 3 Tocilizumab	Received 1-2 live attenuated vaccines - 7 MMR - 5 Varicella zoster booster - 4 Yellow fever - 1 oral polio	- 7/17 disease flare after vaccination
7772 Jaeger (2017)	Case series based on prospective, multicenter observational patient registry (β-CONFIDENT)	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period. Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	All patients treated with canakinumab. Total of 159 vaccine injections 43/68 (63%) patients received multiple vaccine injections <u>Influenza:</u> 107 injections in 55/68 (81%) patients <u>Pneumococcal:</u> 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days. No cases of CAPS reactivation reported for other vaccines.

				Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	
7745 Heijstek 2007 (**ALSO SEE BELOW GRADEPRO TABLES)**	Retrospective cohort study	1 year	49 patients with JIA who were using methotrexate	MMR	Median active joints 6 mo before MMR: 1 (range: 0 to 24), median active joints 6mo after MMR: 1 (0 to 14), p=0.016 Median limited (in ROM) joints 6mo before MMR:1 (0 to 12), median limited joints 6mo after MMR: 1 (0 to 3) 0.198 Median PGA before MMR: 0.7 (0 to 2.7) after MMR 0.4 (0 to 1.8) p=0.004 Median ESR before MMR 12 (2 to 32) after MMR 10 (2 to 33, p=0.016 Flares per patient before MMR 0 (0 to 3), after MMR 0 (0 to 2) p=0.186

Table 2. Number of flares before and after MMR vaccine in JIA pts compared to placebo. 7745 Heijstek 2007

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of flares before and after MMR vaccine in JIA pts	placebo	Relative (95% CI)	Absolute (95% CI)		
Number of flares 6mo before and 6 mo after MMR in JIA pts												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	36/40 (90.0%)	50/56 (89.3%)	**RR 1.01** (0.88 to 1.16)	-	⨁◯◯◯ Very low	No difference

CI: confidence interval; **OR:** odds ratio

Explanations

a. retrospective cohort study
b. small sample size

Table 3. Disease activity 6 mo before and 6 mo after MMR in JIA on MTX compared to placebo. 7745 Heijstek 2007

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Disease activity 6mo before and 6mo after MMR in JIA on MTX	placebo	Relative (95% CI)	Absolute (95% CI)		
Patients with>=1 flare												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Disease activity 6mo before and 6mo after MMR in JIA on MTX	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/49 (26.5%)	21/49 (42.9%)	**OR 0.48** (0.21 to 1.13)	**164 fewer per 1,000** (from 293 fewer to 30 more)	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. retrospective observational study
b. small sample size

References:

1. Heijstek MW, Kamphuis S, Armbrust W, et al. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. *JAMA.* 2013;309(23):2449-2456.
2. Borte S, Liebert UG, Borte M, et al. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. *Rheumatology (Oxford).* 2009;48(2):144-148.
3. Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. *Ann Rheum Dis.* 2007;66(10):1384-1387.
4. Jaeger VK, Hoffman HM, van der Poll T, et al. Safety of vaccinations in patients with cryopyrin-associated periodic syndromes: a prospective registry based study. *Rheumatology (Oxford).* 2017;56(9):1484-1491.
5. Jeyaratnam J, Ter Haar NM, Lachmann HJ, et al. The safety of live-attenuated vaccines in patients using IL-1 or IL-6 blockade: an international survey. *Pediatr Rheumatol Online J.* 2018;16(1):19.

Polio Vaccine

Summary: The literature search identified three observational studies that addressed PICO question 8 regarding the polio vaccine[1-3]. A letter questionnaire sent to 242 patients with SLE (response rate 60%) with responses confirmed by telephone call and examination of patients' medical records, determined that flare in lupus disease activity occurred in 5% (4/73) of patients under 45 years of age within three months from immunization against poliomyelitis following a nationwide campaign after the Israeli outbreak of 1988 (injected killed poliovaccine [IPV] in 3/49 patients and oral live attenuated (OPV) vaccine in 1/24)[3]. In the other two studies[1,2] only one patient in each study received the polio vaccine, which would not allow for definitive conclusions with respect to flare rate post vaccination.

Quality of evidence across all critical outcomes: Very low

Table 1. Flares in SLE pts who received OPV or IPV compared to SLE pts who did not at 4months. 6493_Schattner 1992

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flares in SLE pts who received OPV or IPV	SLE pts who did not at 4months	Relative (95% CI)	Absolute (95% CI)		
Flares in SLE who received OPV/IPV vs SLE who did not												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/73	0/37	**OR 4.86** (0.25 to 92.65)	-	⊕◯◯◯ Very low	
Flares in SLE who received OPV vs SLE who did not												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	1/24	0/37	**OR 4.79** (0.19 to 122.47)	-	⊕◯◯◯ Very low	
Flares in SLE who received IPV vs SLE who did not												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/49	0/37	**OR 5.65** (0.28 to 112.74)	-	⊕◯◯◯ Very low	
Flares in SLE who received OPV vs SLE who received IPV												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flares in SLE pts who received OPV or IPV	SLE pts who did not at 4months	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	1/24	3/49	**OR 0.67** (0.07 to 6.77)	-	⨁◯◯◯ Very low	

CI: confidence interval; **OR:** odds ratio

Explanations

a. observational case control study
b. relatively small sample size and very wide confidence intervals

Table 2. Data from observational studies not suitable for RevMan

RefID, Author, Year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7743 Jeyaratnam 2018	Cohort	Cross-sectional only	17 autoinflammatory diseases - 7 systemic JIA, 5 CAPS, 4 MKD, 1 FMF Medications on anti-IL1 or anti-IL6: - 10 Anakinra - 4 Canakinumab - 3 Tocilizumab	Received 1-2 live attenuated vaccines - 7 MMR - 5 Varicella zoster booster - 4 Yellow fever - 1 oral polio	- 8/17 disease flare after vaccination
7772 Jaeger 2017	Case series based on prospective, multicenter observational patient registry	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9	All patients treated with canakinumab. Total of 159 vaccine injections	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days.

	(β-CONFIDENT)		countries and receiving at least one vaccine during study period. Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	43/68 (63%) patients received multiple vaccine injections Influenza: 107 injections in 55/68 (81%) patients Pneumococcal: 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	No cases of CAPS reactivation reported for other vaccines.

References:

1. Jaeger VK, Hoffman HM, van der Poll T, et al. Safety of vaccinations in patients with cryopyrin-associated periodic syndromes: a prospective registry based study. *Rheumatology (Oxford).* 2017;56(9):1484-1491.
2. Jeyaratnam J, Ter Haar NM, Lachmann HJ, et al. The safety of live-attenuated vaccines in patients using IL-1 or IL-6 blockade: an international survey. *Pediatr Rheumatol Online J.* 2018;16(1):19.
3. Schattner A, Ben-Chetrit E, Schmilovitz H. Poliovaccines and the course of systemic lupus erythematosus--a retrospective study of 73 patients. *Vaccine.* 1992;10(2):98-100.

Shingles Vaccine

Summary: The literature search identified eight observational studies and one RCT that addressed PICO 8 regarding the shingles vaccine. One case control studied a small sample of SLE patients who received the live attenuated vaccine and did not find any flares post vaccination in these patients.[1] The second case control study analyzed a small sample of a mixed RMD population who received the varicella vaccine and found no increase in disease activity post vaccination in this study population.[2] In one small cross sectional study, only five varicella vaccines were given to patients with auto-inflammatory diseases.[3] With such a small study sample, conclusions in regards to disease flare rate status post vaccination cannot be definitively made.

A retrospective cohort study of 359 patients with immune mediated inflammatory diseases (IMID) received the recombinant zoster vaccine.[1] This study found 16% of the study population had a flare of their disease, with subpopulation percentages of flares seen as listed in the corresponding table. A retrospective case series looked at 403 RMD patients (239 with RA, 164 with other systemic rheumatic dseases [SRD]) who received the zoster recombinant adjuvanted vaccine and found flares in 6.7% of patients, specifically incidence rates of flares in 7.1% in SLE patients and 8.0% in RA patients.[5]

Another study examined a small population of RA patients who received the live attenuated varicella vaccine and found that 14.6% of their study population had a flare post-vaccination.[6]

Two other studies evaluated a mixed population of patients with rheumatic disease. One found no significant difference in disease flare rates before versus after vaccination with recombinant adjuvanted zoster vaccine.[10065] The other study reported that mild flares were not uncommon in the first 12 weeks post-vaccination, but did not compare it to flare rates pre-vaccination [10299].

The RCT included 368 patients with RA divided into varicella zoster vaccine and placebo groups. Disease activity did not worsen at 6 weeks (median change in Clinical Disease Activity was 0 in both vaccinated and placebo groups)[10292].

Quality of evidence across all critical outcomes: Very low

Table 1. Data from RCTs and observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
10292 Curtis 2021 [10292]	RCT	6 weeks	617 patient on TNFi - 368 RA, 154 PsA, 50 AS, 23 IBD-arthritis, 39 other inflammatory arthritis, 3 reactive arthritis, 2 undifferentiated - 83 non-RMD TNFi - 202 Adalimumab, 193 Infliximab, 131 Etanercept, 56 Golimumab, 35 Certolizumab	310 Varicella Zoster Vaccine - 190 RA 307 Placebo - 178 RA	Disease activity for 368 RA patients did not worsen. - median change in Clinical Disease Activity Index (CDAI) in both vaccinated and placebo group=0, p=0.73 - median change in Routine Assessment of Patient Index 3 (RAPDI3) score =0; p=0.99
10065 Gupta 2021[10065]	Retrospective chart review	January 1, 2018 and March 11, 2020	65 patients White (78.5%) female (86.2%) median age of 68 years (range, 44–89 years) Most common dx: rheumatoid arthritis 30.8%	Recombinant adjuvanted zoster vaccine	Disease flare incidence before and after vaccination All patients (n=65) Baseline vs after ZRA (reported as flares per 100 person-years) 5.6 vs 2.1, p=0.3 Nonbiologic DMARDS (n=29)

			polymyalgia rheumatica 18.5%, and Sjögren syndrome 9.2% 69.2% on a DMARD (45pts) 29/45 on a nonbiologic DMARD 16/45 on biologic DMARD 7 pts on prednisone monotherapy 12 pts on both prednisone and DMARD 52.3% of pts received both doses of ZRA		6.3 vs 1.6, p=0.3 Biologic DMARDS (n=16) 5.7 vs 2.9, p=0.5
10299 Lenfant 2021[10299]	Retrospective cohort	Median follow up 36 weeks	622 patients seen in rheumatology Of which 359 had immune mediated inflammatory disease including 88 RA, 50 vasculitis, 29 PMR	IMID flare defined as (i) documentation in rheum office notes, phone encounter or communication portal of worsening/new symptoms felt by treating rheumatologist to be attributed to their IMID and/or (ii) start or increase in dose of prednisone daily dose by treating rheumatologist, occurring in the 12-week period following each vaccine. For small vessel vasculitis patients, BVAS collected before and after shingrix vaccine	Mild flares were not uncommon in the 12 weeks post-vaccine 59/359 IMID patients flare after shingrix: - 34 after the first vaccine, 17 flared after the 2nd vaccine and 8 after both doses - Median time to flare was 31 days for those who flared after 1st vaccine, and 45 days for those who flared after 2nd vaccine 21/88 RA patients (24%) 5/29 PMR (17%) 4/24 SLE (17%) RA patients had the highest flare rate Flares occurred in temporal relation to a treatment change in 18 (31%) 27 (45%) treated with steroids 15 (25%) required a change in immunosuppressive therapy A time-to-flare survival analysis (Cox-model) showed that steroids was a significant predictor of IMID flare after 1st RZV dose [HR 2.4 (1.3-4.5, p=0.0039] and that a flare after the first dose was associated with flaring after the 2nd vaccine dose [HR 3.9 (1.7-9), p=0.0015]

3510 Guthridge 2013 [1]	Case control	12 weeks (weeks 2, 6, 12)	10 SLE Medications: - 7 HCQ - 2 MTX - Prednisone <10mg/d 10 controls	Zostavax, live attenuated vaccine	0/10 SLE receiving vaccine had disease flare
7684 Pileggi 2010 [2]	Case control	36 months	25 mixed RMD on meds - 17 JIA: 10 polyarticular, 5 systemic, 2 oligoarticular - 4 Juvenile Dermatomyositis - 3 Juvenile Scleroderma - 1 Vasculitis Medications - all on MTX (mean 16.4mg/m2/week) - 13 Prednisone (mean 4.2mg/d) - 5 other DMARDS 18 healthy controls	Varicella vaccine 1 dose	All RMD patients received vaccine - 25/25 no increase in disease activity - In 17 JIA: active joint count -1.4 (p=0.009), LROM joint count -0.1 (0.94), CHAQ -0.1 (p=0.19), Parent's global assessment -0.5 (p=0.23), Physician's global assessment -0.7 (0.077)
7743 Jeyaratnam 2018 [3]	Cohort	Cross-sectional only	17 autoinflammatory diseases - 7 systemic JIA, 5 CAPS, 4 MKD, 1 FMF Medications on anti-IL1 or anti-IL6: - 10 Anakinra - 4 Canakinumab - 3 Tocilizumab	Received 1-2 live attenuated vaccines - 7 MMR - 5 Varicella zoster booster - 4 Yellow fever - 1 oral polio	8/17 disease flare after vaccination
7756 Lenfant 2021 [4]	Retrospective cohort	Feb 2018-March 2020	359 patients with an IMID and 263 patients with non-IMID (osteoarthritis, bone metabolism, fibromyalgia etc) Among iMID: 25% with RA, 14% with vasculitis, 8% with PMR, 8% with gout, 7% with SLE, 6% with PsA, 5% with inflammatory arthritis, 5% with Sjogren's, 5% with SpA, 4% with CPPD, 3% with	Recombinant zoster vaccine	59/359 IMID pts (16%) had a flare of their disease: 21/88 (24%) of RA pts, 5/29 (17%) of PMR 4/24 (17%) of SLE

			myositis, 3% with scleroderma, 2% with IBD related arthritis, 7% with Other IMID Median age 66, 66% female, 84% white, 14% black.		3/19 (16%) of inflammatory arthritis 2/17 of SpA (12%) 2/20 of PsA (10%) 3/14 (21%) CPPD 5/28 (18%) gout 5/50 (10%) of vasculitis 34/59 pts flared after 1st RZV dose (after a median of 31 days) 17/59 after 2nd RZV dose (after a median of 45 days) 8/59 flared after both doses (17 d after 1st and 40 d after 2nd/medians) Flares occurred in temporal relation to a tx change in 18 cases (31%). Flares were most often treated with GC (n=27, 45%) median dose 20mg/day. 15 (25%) required change in IS therapy Univariate analysis among IMID patients revealed higher incidence of flares in pts on GC (p=0.002) and JAK inhibitors (p=0.032), and in RA pts (p=0.03). In multivariate logistic analysis only GC use at time of vaccine remained significantly a/w flares (OR 2.31, 1.3-4.1, P=0.004) after controlling for JAK inhibitors and RA. A secondary analysis excluded patients who had received RZV in the same time period

					as an immunosuppressant medication change (switching or discontinuing biologics, adjusting daily dosages, tapering GC in the time around RZV and before the onset of the IMID flare), and the exposure to glucocorticoids at the time of RZV was no longer a significant risk factor associated to flares. A time-to-flare survival analysis was conducted using a multivariate Cox-model: glucocorticoids use at the time of vaccine remained the only significant predictor of an IMID flare after the first RZV dose [hazard ratio (HR)=2.4(1.3–4.5),P=0.0039]. A second Cox-model applied to the 263 IMID patients who received both RZV doses showed that experiencing a flare after the first dose was significantly associated with a flare after the second dose [HR=3.9 (1.7–9),P=0.0015].
7765 Stevens (2020) [5]	Retrospective single-center chart review (case series)	Minimum follow-up 12 weeks post-vaccine	403 patients (239 with RA, 164 with SRD) who received at least one dose of ZRA vaccine Feb. 1st 2018-Feb. 1st 2019. Mean (SD) age 67.3 (10.6) years, 75% female, 86% white	78.4% on immunosuppressive medication, which were not held before or after vaccine. 37.2% on multiple drugs. 35.5% on MTX (mean 17.1 mg weekly), 26.3% on prednisone (mean 4.7 mg daily), 12.9% on tofacitinib, 26.1% on TNFi, 12.2% other biologics, 12.2% other non-biologic DMARDs. 55.1% received both first & second ZRA dose during study. Mean (SD) time between doses 18.3 (8.5) weeks.	Flares in 27/403 (6.7%) patients; 23 (5.7%) after first dose, 5 (1.2%) after second dose. Incidence rate of flares 7.1% in SLE, 8.0% in RA Flares commonly treated with prednisone taper, all were mild and self-limited, responded to steroids & did not require change in DMARDs.
7786 Koh 2018 [6]	Observational cohort study	Oct 2014 to Dec 2015	41 pts with RA, 28pts with OA RA pts: median age 60, 93% female, 93% with seropositive RA, 61% on GC (median dose 2.5mg (IQR 0-5), 93% on MTX (median	Live attenuated HZ vaccine	RA pts: Median DAS28 CRP BL: 1.1 (IQR 1.1-1.5) and at 12 weeks: 1.4 (IQR 1.1-1.7), p=0.506.

			dose 10 (7.5-12.5), 7% on SSZ, 22% on LEF, 22% on HCQ. [pts taking biologics, CYC, prednisolone >=20mg within 3 mo of enrollment were excluded] OA median age 62 years, 86% female.		ESR and CRP did not change significantly from BL to 12 weeks. At 12 weeks after HZ vaccination, 36 pts (88%) remained in remission, 3 (7.3%) showed low level disease activity (3.2<das28<=5.1) and 2 (4.9%) showed mod disease activity (3.2<das28<=5.1). 6 pts with RA (14.6%) had a flare (delta DAS28 >1.1) between 6 and 12 weeks after HZ vaccination. 4/6 had transient arthritis and recovered spontaneously or after tx with extra low dose GC, whereas the other 2 were switched to anti-TNFa.

References:

1. Guthridge J, Cogman A, Merrill J et al. Herpes zoster vaccination in SLE: a pilot study of immunogenicity. J Rheum. 2013;40:11; doi:10_3899/jrheum.130170

2. Pileggi G, Sandoval de Souza C, Ferriani V. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Art Care Research. 2010;62(7):1034-1039; doi 10.1002/acr.20183

3. Jeyaratnam J, M. ter Haar N, Lachmann H et al. The safety of live-attenuated vaccines inpatients using IL-1 or IL-6 blockade: aninternational survey. Pediatric Rheumatology (2018) 16:19 https://doi.org/10.1186/s12969-018-0235-z

4. Lenfant T, Jin Y, Kirchner E et al. Safety of recombinant zoster vaccine: a retrospective study of 622 rheumatology patients. Rheumatology. 2021;0:1-9; doi:10.1093/rheumatology/keab139.

5. Stevens E, Weinblatt M, Massarotti E et al. Safety of the zoster vaccine recombinant adjuvanted in rheumatoid arthritis and other systemic rheumatic disease patients: a single center's experience with 400 patients. ACR Open Rheum. 2020;2(6):357-361; doi SEP10.1002/acr2.11150.

6. Koh J, Lee J, Kim S et al. Safety, and humoral and cell-mediated immune responses to herpes zoster vaccine in patients with rheumatoid arthritis. J Rheum. 2018; 45:465-9; doi:10.3899/jrheum.170936.

Tetanus, Diphtheria, Pertussis (Tdap) Vaccine

Summary: The literature search identified five observational studies that addressed PICO 8 regarding the Tdap vaccine.

An online survey of 210 patients with juvenile DM (n=164) and adult DM (n=46) who received any of the vaccines listed in the study was assessed, which included tetanus vaccine. Results showed 63.8% (103 juvenile, 31 adults) experienced a flare within the past 6 months. It was found that flares were reported more post HPV vaccination and that the other vaccines, including tetanus, did not differ in frequency between those that did or did not flare.[1]

A small study of 26 adolescents with juvenile SLE who received the Tdap booster vaccine did not find any changes in their disease activity.[2]

Two studies of Tdap vaccination in patients with cryopyrin-associated auto-inflammatory syndromes (CAPS), the first with a small sample size of 17 patients[3] and the second with 68 patients,[1] did not show any changes in disease activity or flares of their disease.

A cohort study of 73 SLE patients who received the tetanus toxoid vaccine, found no flares status post vaccination.[5]

Quality of evidence across all critical outcomes: Very low

Table 1. Tetanus compared to placebo for DM. [1] 2740_Mamyrova_2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tetanus	placebo	Relative (95% CI)	Absolute (95% CI)		
Flare s/p tetanus												
1	observational studies	serious[a]	not serious	not serious	serious	none	6/134 (4.5%)	5/76 (6.6%)	OR 0.67 (0.20 to 2.26)	21 fewer per 1,000 (from 52 fewer to 72 more)	⨁◯◯◯ Very low	

CI: confidence interval; OR: odds ratio

Explanations

a. not randomized, not blinded, recall bias

Table 2. Data from observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
158 Peracchi 2021 [2]	Case control-prospective	24 months	26 adolescents w juvenile SLE and 26 age/sex matched healthy control adolescents (age between 10-20 years) Inclusion criteria for both groups was 3 doses and 2 booster doses of the DTwP vaccine, the last booster at least with a minimum 3 year-interval from the study entry. jSLE patients also had to be on stable immunosuppressives for at least 3 months.	Tdap Booster	No difference in disease activity, assessed with SLEDAI found on D28 (p=0.151), D6m (p=0.782) and D12m (p=0.812) vs time of vaccination (D0).
7047 Brogan 2019 [3]	Core study: 56-week, multicenter, open label phase III trial Long-term extension (LTE): 6-24 months additional treatment & follow-up	Follow-up of 3 years total	17 patients with CAPS, aged 28 days to 60 months with confirmed NLRP3 mutations, body weight >= 2.5 kg, & active disease at enrollment. Patients completing the core study with no major protocol deviations & at least 1 year of age were enrolled in LTE study. Median age 31 (1-59) months, 12/17 (71%) male, 16/17 (94%) Caucasian, mean time from diagnosis 2.6 years. CAPS phenotype:	Patients received SC canakinumab every 8 weeks for entire study period Patients without complete response eligible for stepwise dose up-titration (max 8 mg/kg). Starting dose 2 mg/kg; Higher starting dose 4 mg/kg if previous anti-IL-1 agent or if NOMID. Patients received inactivated vaccinations as part of national childhood vaccination programs. No live	No disease flares induced by vaccination

			4 NOMID, 12 MWS, 1 FCAS patient.	vaccines permitted during treatment with canakinumab. Vaccination response was assessed if antibody titer was measured 0-14 days after vaccination ("Pre-dose"), and on at least 1 subsequent visit (at 4 weeks and/or 8 weeks after vaccination). Included vaccines: HBV, HiB, TdaP, influenza, pneumococcal, meningococcal. No data on timing of vaccinations with respect to canakinumab dosing.	
7772 Jaeger (2017) [4]	Case series based on prospective, multicenter observational patient registry (β-CONFIDENT)	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period. Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	All patients treated with canakinumab. Total of 159 vaccine injections 43/68 (63%) patients received multiple vaccine injections Influenza: 107 injections in 55/68 (81%) patients Pneumococcal: 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days. No cases of CAPS reactivation reported for other vaccines.
459 Battafarao 1998 [5]	Cohort	12 weeks	73 SLE 5.5% male/94.5 % female; mean age 43 (18-76)4	Pneumococcal (pneumovax 23), tetanus toxoid and haemophilus influenza type B	None had clinical flare of SLE, no significant increase

			48% on antimalarial agents , NSAIDS 34%, AZA 10%, IV CYC 10%, oral MTX 1% 74% on steroids, with 85% oral prednisone <10mg per day		in disease activity scores measured by SLEDAI or LACC Six patients (8%) had increase in disease activity scores but didn't meet criteria for flare.

References:

1. Mamyrova G, Rider L, Ehrlich A et al. Environmental factors associated with disease flare in juvenile and adult dermatomyositis. Rheumatology. 2017;56:1342-1347: doi:10.1093/rheumatology/kex162.

2. Peracchi O, Nicacio A, Yamada J et al. Adequate tetanus but poor diphtheria and pertussis response to a Tdap booster in adolescents with juvenile systemic lupus erythematosus. Lupus. 2021;30(2): 299-306.

3. Brogan P, Hofer M, Kuemmerle-Deschner J et al. Rapid and Sustained Long- Term Efficacy and Safety of Canakinumab in Patients With Cryopyrin- Associated Periodic Syndrome Ages Five Years and Younger. Art Rheumatology. 2019;71(11):1955-1963

4. Jaeger V, Hoffman H, van der Poll T et al. Safety of vaccination in patients with cryopyrin-associated periodic syndromes: a prospective registry based study. Rheumatology. 2017;56:1484. doi:10.1093/rheumatology/kex185

5. Battafarano D, Battafarano N, Larsen L et al. Antigen-specific antibody responses in lupus patients following immunization. Art Rheum. 1998;41(10):1828-1834.

Typhoid Vaccine

Summary: The literature search identified one observational study in a RMD population[1] and one observational study in a non-RMD population[2] that addressed PICO 8 in regards to the typhoid vaccine. In the first study[1], only three typhoid vaccines were given to patients with a cryopyrin-associated autoinflammatory syndromes (*CAPS*). The second study[2] had a small sample size of non-RMD patients who were given the typhoid vaccine, with only one patient experiencing a flare post vaccination. With such a small population samples in both studies, any conclusions in regards to disease flare rates status post vaccination cannot be definitively made.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7772 Jaeger (2017) [1]	Case series based on prospective, multicenter observational patient registry (β-CONFIDENT)	Vaccination data collected July 2010 to December 2015	68 patients with definite CAPS treated with canakinumab, followed at 14 centers in 9 countries and receiving at least one vaccine during study period. Patients without definite CAPS, not receiving vaccines, or with missing data for vaccines and/or vaccine reactions were excluded - 217/285 (81%) of registry patients excluded.	All patients treated with canakinumab. Total of 159 vaccine injections 43/68 (63%) patients received multiple vaccine injections Influenza: 107 injections in 55/68 (81%) patients Pneumococcal: 19 injections (15 PPV, 2 PCV, 2 unknown type) in 18/68 (26%) patients Tetanus/Diphtheria: 12 injections in 12/68 (18%) patients Other vaccines: 21 injections in 11/68 (16%) patients (including 6 HBV, 5 HAV, 3 typhoid, 1 polio, 1 MMR, 1 HPV, 1 Lyme, 1 cholera, & 1 tick born encephalitis)	In 2 patients with MWS, PPV exposure was associated with symptoms attributable to CAPS reactivation. Events resolved over 10-18 days. No cases of CAPS reactivation reported for other vaccines.
5117 Nysaeter 2008 [2]	Case series	90 days	10 pts with IBD (7 with UC, 3 with Crohn's) IBD activity index <=10 for the past 2 weeks.	oral vaccine containing the Salmonella Ty21a strain (Vivotif®, Berna) using the standard dosage for such vaccination against typhoid fever	1 UC patient on 10 mg daily of prednisolone had a flare after 15 days and had to increase prednisolone to 30mg daily. "Disease activity was only slightly changed for the patients with Crohn's disease."

References

1. Jaeger V, Hoffman H, van der Poll T et al. Safety of vaccination in patients with cryopyrin-associated periodic syndromes: a prospective registry based study. Rheumatology. 2017;56:1484. doi:10.1093/rheumatology/kex185.

2. Nysaeter G, Berstad A. Live typhoid vaccine for IBD-patients – Well tolerated and with possible therapeutic effect. Drug Target Insights. 2008;3:119-123.

Yellow Fever Vaccine

Summary: The literature search identified four observational studies that addressed PICO 8 regarding the yellow fever vaccine.[1,[9919][10325][10485]] In the first study only four yellow fever vaccines were given to patients with auto-inflammatory diseases,[1] and with such a small study sample, conclusions in regards to disease flare rate status post vaccination cannot be definitively made. The second study reported no flares among 159 patients with ARD who received the yellow fever vaccine [9919]. Another study reported no flares among 12 patients with RA; one patient experienced a fever [10325]. The remaining study enrolled juvenile ARD patients and reported no change in disease activity parameters at 30 days following vaccination [10485].

Quality of evidence across all critical outcomes: Very low.

Table 1. Data from observational studies not suitable for RevMan

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
10485 Aikawa 2021[10485]	Prospective controlled, open label	All JARD patients and healthy controls were evaluated on the day of vaccination and 30 days later	16 patients had JIA, 6 HSP, 4 JSLE, 3 JDM and 1 JSS v healthy controls	Yellow fever vaccine	Disease activity parameters of JARD patients remained unchanged from D0 to D30: JADAS71 [6.5 (1–22) vs. 6 (1–31), p = 0.744], SLEDAI-2 K [1 (0–2) vs. 0 (0–2), p = 1.000], CMAS [52 (52) vs. 52 (52), p = 1.000], DAS [0 (0–1) vs. 0 (0), p = 0.500] and MMT [80 (80) vs. 80 (80), p = 1.000]. Erythrocyte sedimentation rates [6 (1–27) vs. 5.5 (1–31) mm/1st hour, p = 0.874] and CRP levels [0.3 (0–4.16) vs. 0.3 (0.3–3.4) mg/dL, p = 0.489] remained stable 30 days after YFV. HSP and JSS patients persisted stable throughout the study.
10325 Soares dos Reis 2021[10325]	Prospective cohort	46-212 weeks	12 pts with RA. 10 Leflunomide, 7 methotrexate, 6 biologics, 6 prednisone, 1 tofacitnib	Single dose yellow fever vaccine, fractionated dose Serum conversion and antibody production measured by plaque reduction	No flares reported. One patient experienced a fever

				neutralization test in cell culture(PRNT 50)	
9919 Tonacio 2021[9919]	Prospective, case control	Jan 2018 to April 2018	318 participants= 159 Autoimmune rheumatic disease (ARD) and 159 healthy controls; age ≥18 or ≤ 60 years old ARD group: low or inactive disease; low immunosuppression (hydroxychloroquine, sulfasalazine, prednisone 20 mg/day, methotrexate up to 0.4mg/kg/week(maximum of 20 mg/week) and leflunomide 20 mg/day without other drugs or associated with prednisone 7.5mg/day or hydroxychloroquine or sulfasalazine)	Yellow fever vaccine	No flares reported
7743 Jeyaratnam 2018 [1]	Cohort	Cross-sectional only	17 autoinflammatory diseases - 7 systemic JIA, 5 CAPS, 4 MKD, 1 FMF Medications on anti-IL1 or anti-IL6: - 10 Anakinra - 4 Canakinumab - 3 Tocilizumab	Received 1-2 live attenuated vaccines - 7 MMR - 5 Varicella zoster booster - 4 Yellow fever - 1 oral polio	8/17 patients had disease flare after vaccination

References:

1. Jeyaratnam J, M. ter Haar N, Lachmann H et al. The safety of live-attenuated vaccines inpatients using IL-1 or IL-6 blockade: aninternational survey. *Pediatric Rheumatology* (2018) 16:19 https://doi.org/10.1186/s12969-018-0235-z

PICO 9. In RMD patients age 65 and older, is high dose (Fluzone high dose) influenza vaccine more effective than seasonal regular dose influenza vaccine?

Summary: The literature search did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 10. In RMD patients age 65 and older, is adjuvanted influenza vaccine (FLUAD) more effective than seasonal regular dose influenza vaccine?

Summary: The literature search did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 11: In RMD patients under age 65 years, is high dose (Fluzone) vaccine more effective than seasonal regular dose influenza vaccine?

Summary: The literature search identified 2 randomized controlled trials [1-2] and no observational studies that addressed this PICO in the RMD population, both of which looked at patients with rheumatoid arthritis (RA). First, Stapleton *et al* [1], is a double-blind, Phase II RCT conducted in mostly-white adults with RA and mostly white healthy control patients; median age ranged from 49.0 years to 55.5 years, depending on the arm. 25 RA patients and 25 health controls each received the standard dose (15mcg) trivalent seasonal influenza vaccine IM, while another 26 RA patients and 26 healthy controls each received the high-dose (60mcg) trivalent seasonal influenza vaccine IM. Geometric mean titers (GMTs) were compared for each serotype at day 21 and at day 180. Most relevant to PICO 11, influenza seroconversion and GMT values were higher among RA subjects receiving high dose, compared to standard dose, for every serotype and at both time points, with a RR that ranged from 1.52 H1N1 at Day 21) to 8.31 (H1N1 at day 180). In addition, in Colmegna *et al* [2], a randomized, double blind treatment-stratified trial, the standard dose (15 mcg) quadrivalent seasonal influenza vaccine IM was compared to the high dose (60mcg) trivalent seasonal influenza vaccine IM in patients with RA on a wide variety of medications, including steroids, DMARDs, biologics, and small molecules. 139 (HD) and 140 patients (SD) were enrolled. Based on both haemagglutination-inhibition and microneutralization assays, seroconversion at day 28 was greater in the HD dose, for all serotypes, compared to SD.

Quality of evidence across all critical outcomes: Moderate

Table 1. High-dose compared to standard-dose for H1N1 in RA on anti-TNF vs Healthy Controls (HC) at Day 21[1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose	Standard Dose for H1N1 on anti-TNF and HC at Day 21	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for RA patients												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	19/26 (73.1%)	12/25 (48.0%)	**RR 1.52** (0.95 to 2.44)	**250 more per 1,000** (from 24 fewer to 691 more)	⨁⨁⨁◯ Moderate	
Seroconversion for health control patients												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	13/26 (50.0%)	7/25 (28.0%)	**RR 1.79** (0.85 to 3.73)	**221 more per 1,000** (from 42 fewer to 764 more)	⨁⨁⨁◯ Moderate	

a. CI crosses null value line AND small sample size

Table 2. High-dose compared to standard-dose for H1N1 in RA on anti-TNF vs HC at Day 180[1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose	Standard Dose for H1N1 on anti-TNF and HC at Day 180	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for RA patients												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	9/26 (34.6%)	1/24 (4.2%)	**RR 8.31** (1.14 to 60.78)	**305 more per 1,000** (from 6 more to 1,000 more)	⨁⨁⨁◯ Moderate	Favors high dose
Seroconversion for healthy control patients												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	3/25 (12.0%)	5/25 (20.0%)	**RR 0.60** (0.16 to 2.25)	**80 fewer per 1,000** (from 168 fewer to 250 more)	⨁⨁⨁◯ Moderate	

a. small sample size

Table 3. High-dose compared to standard-dose for A/H3N2 in RA on anti-TNF vs HC at Day 21[1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose	standard dose for A/H3N2 on anti-TNF and HC at Day 21	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for RA patients												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	16/26 (61.5%)	10/25 (40.0%)	**RR 1.54** (0.87 to 2.72)	**216 more per 1,000** (from 52 fewer to 688 more)	⨁⨁⨁◯ Moderate	
Seroconversion for healthy control patients												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	17/26 (65.4%)	10/25 (40.0%)	**RR 1.63** (0.94 to 2.85)	**252 more per 1,000** (from 24 fewer to 740 more)	⨁⨁⨁◯ Moderate	

a. CI crosses null value line AND small sample size

Table 4. High-dose compared to standard-dose for A/H3N2 in RA on anti-TNF vs HC at Day 180[1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose	standard dose for A/H3N2 on anti-TNF and HC at Day 180	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for RA patients												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	9/26 (34.6%)	5/24 (20.8%)	**RR 1.66** (0.65 to 4.26)	**137 more per 1,000** (from 73 fewer to 679 more)	⨁⨁⨁◯ Moderate	
Seroconversion for healthy control patients												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	6/25 (24.0%)	3/25 (12.0%)	**RR 2.00** (0.56 to 7.12)	**120 more per 1,000** (from 53 fewer to 734 more)	⨁⨁⨁◯ Moderate	

a. CI crosses null value line AND small sample size

Table 5. High-dose compared to standard-dose for Influenza B in RA on anti-TNF vs HC at Day 21[1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose	standard dose for B on anti-TNF and HC at Day 21	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for RA patients												
1	randomised trials	not serious	not serious	not serious	serious[a,]	none	15/26 (57.7%)	7/24 (29.2%)	**RR 1.98** (0.98 to 4.00)	**286 more per 1,000** (from 6 fewer to 875 more)	⨁⨁⨁◯ Moderate	
Seroconversion for healthy control patients												
1	randomised trials	not serious	not serious	not serious	Serious[a]	none	10/26 (38.5%)	6/25 (24.0%)	**RR 1.60** (0.68 to 3.75)	**144 more per 1,000** (from 77 fewer to 660 more)	⨁⨁⨁◯ Moderate	

a. CI crosses null value line AND small sample size

Table 6. High-dose compared to standard-dose for Influenza B in RA on anti-TNF vs HC at Day 180[1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose	standard dose for B on anti-TNF and HC at Day 180	Relative (95% CI)	Absolute (95% CI)		
Seroconversion for RA patients												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	5/26 (19.2%)	2/24 (8.3%)	**RR 2.31** (0.49 to 10.80)	**109 more per 1,000** (from 42 fewer to 817 more)	⨁⨁◯◯ Low	
Seroconversion for healthy control patients												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	3/25 (12.0%)	2/25 (8.0%)	**RR 1.50** (0.27 to 8.22)	**40 more per 1,000** (from 58 fewer to 578 more)	⨁⨁◯◯ Low	

a. CI cross null value line and are extremely wide, plus small sample size

Table 7. SD-QIV vs HD-TIV in RA patients[2]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SD-QIV	HD-TIV	Relative (95% CI)	Absolute (95% CI)		
Seroconversion (Haemagglutination-inhibition antibodies) for A/Hong Kong/4801/2014												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SD-QIV	HD-TIV	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	12/136 (8.8%)	31/138 (22.5%)	**RR 0.39** (0.21 to 0.73)	**137 fewer per 1,000** (from 177 fewer to 61 fewer)	⊕⊕⊕◯ Moderate	Favors HD-TIV

Seroconversion (Haemagglutination-inhibition antibodies) for B/Brisbane/60/2008

1	randomised trials	not serious	not serious	not serious	serious[a]	none	40/136 (29.4%)	62/138 (44.9%)	**RR 0.65** (0.48 to 0.90)	**157 fewer per 1,000** (from 234 fewer to 45 fewer)	⊕⊕⊕◯ Moderate	Favors HD-TIV

Seroconversion (Haemagglutination-inhibition antibodies) for A/California/7/2009 (year 1)

1	randomised trials	not serious	not serious	not serious	serious[a]	none	18/71 (25.4%)	36/69 (52.2%)	**RR 0.49** (0.31 to 0.77)	**266 fewer per 1,000** (from 360 fewer to 120 fewer)	⊕⊕⊕◯ Moderate	Favors HD-TIV

Seroconversion (Haemagglutination-inhibition antibodies) for A/Michigan/45/2015 (year2) @ day 28

1	randomised trials	not serious	not serious	not serious	serious[a]	none	17/65 (26.2%)	32/69 (46.4%)	**RR 0.56** (0.35 to 0.91)	**204 fewer per 1,000** (from 301 fewer to 42 fewer)	⊕⊕⊕◯ Moderate	Favors HD-TIV

Seroconversion (Microneutralization antibodies) for A/Hong Kong/4801/2014 @ day 28

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SD-QIV	HD-TIV	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a,b]	none	45/136 (33.1%)	61/138 (44.2%)	**RR 0.75** (0.55 to 1.01)	**111 fewer per 1,000** (from 199 fewer to 4 more)	⨁⨁⨁◯ Moderate	

Seroconversion (Microneutralization antibodies) for B/Brisbane/60/2008

1	randomised trials	not serious	not serious	not serious	serious[a]	none	26/136 (19.1%)	58/138 (42.0%)	**RR 0.45** (0.31 to 0.68)	**231 fewer per 1,000** (from 290 fewer to 134 fewer)	⨁⨁⨁◯ Moderate	Favors HD-TIV

Seroconversion (Microneutralization antibodies) for A/California/7/2009

1	randomised trials	not serious	not serious	not serious	serious[a]	none	20/71 (28.2%)	37/69 (53.6%)	**RR 0.53** (0.34 to 0.81)	**252 fewer per 1,000** (from 354 fewer to 102 fewer)	⨁⨁⨁◯ Moderate	Favors HD-TIV

Seroconversion (Microneutralization antibodies) for A/Michigan/45/2015

1	randomised trials	not serious	not serious	not serious	serious[a]	none	26/65 (40.0%)	42/69 (60.9%)	**RR 0.66** (0.46 to 0.94)	**207 fewer per 1,000** (from 329 fewer to 37 fewer)	⨁⨁⨁◯ Moderate	Favors HD-TIV

Explanations

a. small sample size
b. CI touches the null value line

References:

1. Stapleton J, Wagner N, et al. High dose trivalent influenza vaccine compared to standard dose vaccine in patients with rheumatoid arthritis receiving TNF-alpha inhibitor therapy and healthy controls: Results of the DMID 10-0076 randomized clinical trial. *Vaccine* 2020; 38;393403941.

2. Colmega I, Useche M., et al. Immunogenicity and safety of high-dose versus standard-dose inactivated influenza vaccine in rheumatoid arthritis patients: a randomised, double-blind, active-comparator trial. *Lancet Rheumatology* 2020; 2: e14-23.

PICO 12. In RMD patients *under* age 65 years, is adjuvanted influenza vaccine (FLUAD) more effective than seasonal regular dose influenza vaccine?

Summary: The literature search did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 13: In RMD patients, does the immunogenicity or efficacy of influenza vaccine differ in patients who have moderate to severely active underlying disease as compared to those in low-disease activity or remission?

Summary: The literature search identified no randomized controlled trials and 4 observational studies [1-4] that addressed this PICO question: 3 in SLE [1,2,4] and 1 in RA (3). A prospective open-label cohort pediatric SLE study with 118 participants [2] found a higher proportion of patients with SLEDAI-2K $\geq$ 8 in non-seroconverted (48.8%) compared to seroconverted (24%), p=0.008. A further multivariate logistic regression confirmed that SLEDAI-2K $\geq$ 8 was significantly associated with non-seroconversion (OR 0.42, 95% CI: 0.18 to 0.98; p=0.045). In contrast, one small SLE study [1] found no significant difference in immunogenicity (GMT) across three SLEDAI ranges (=0, 1-4, or >4). Another small SLE study [4] found SLEDAI scores were not associated with reduced mean number of immune responses to the 3 components of influenza vaccine. An observational study [3] with 57 RA participants found no significant differences in antibody titers based on any clinical measures of disease activity (peripheral lymphocyte count, CRP, ESR, IgM-RF, MMP-3, DAS28CRP, and DAS28ESR).

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies and RCT data not suitable for GradePro

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

1671, Launay, 2013 [1]	Cohort	30 days	27 SLE SLEDAI = 0 5 SLEDAI 1-4 = 17 SLEDAI >4 = 5	2009–2010 seasonal trivalent inactivated influenza vaccine (Mutagrip®, Sanofi Pasteur Paris, France): A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2) and B/Brisbane/60/2008	No significant difference in immunogenicity (GMT) in SLEDAI = 0, SLEDAI 1-4, SLEDAI >4
3531, Campos, 2013 [2]	Prospective open-label cohort study	3 weeks	118 cSLE and 102 healthy controls	H1N1 A/California/7/2009–like virus vaccine 92 on antimalarials, 83 on prednisone (mean SD dosage of 18.8 17 mg/day), 72 on immunosuppressive drugs (44 azathioprine, 15 mycophenolate mofetil, and 14 methotrexate).	- SLEDAI-2K score ≥8: 21/43 (48.8%) nonseroconverted, 18/75 (24%) seroconverted; p=0.008 Multivariate logistic regression: SLEDAI-2K score ≥8 was significantly associated with nonseroconversion (OR 0.42, 95% CI: 0.18 to 0.98; p=0.045)
4918, Kogure, 2014 [3]	Single-arm intervention	4 weeks	57 RA DAS28CRP 3.08±0.73 DAS28ESR 3.69±0.86	2011-2012 trivalent subunit seasonal influenza vaccine	No significant differences were noted in the three kinds of antibody titers based on any clinical measures of disease activity ((peripheral lymphocyte count, CRP, ESR, IgM-RF, MMP-3, DAS28CRP, and DAS28ESR)
8096. Abu-Shakra, 2002 [4]	Case series	12 weeks post-vaccine	24 SLE patients Mean age 46.1 years (range 20-74), 100% females. Mean disease duration 9.1 years. Mean SLEDAI 18 (range 4-59)	One standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B-Influenza). SLE therapies: Oral steroids (n=17), mean prednisone dose 12 mg HCQ 400 mg daily (n=9) AZA 100 mg daily (n=3) MTX (n=4) mean dose 10mg weekly	SLEDAI scores were not associated with reduced mean number of immune responses to the 3 components of influenza vaccine

References

1. Launay O, Paul S, Servettaz A, et al. Control of humoral immunity and auto-immunity by the CXCR4/CXCL12 axis in lupus patients following influenza vaccine. *Vaccine*. 2013;31(35):3492-3501. doi:10.1016/j.vaccine.2013.05.095
2. Campos LM, Silva CA, Aikawa NE, et al. High disease activity: an independent factor for reduced immunogenicity of the pandemic influenza a vaccine in patients with juvenile systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2013;65(7):1121-1127. doi:10.1002/acr.21948
3. Kogure T, Harada N, Tatsumi T, Fujinaga H. Investigation of clinical characteristics as predictive factors for the humoral immune response to the influenza vaccine in patients with rheumatoid arthritis. *Clin Rheumatol*. 2014;33(3):323-328. doi:10.1007/s10067-013-2483-0
4. Abu-Shakra M, Press J, Varsano N, et al. Specific antibody response after influenza immunization in systemic lupus erythematosus. *J Rheumatol*. 2002;29(12):2555-2557.

PICO 14: In RMD patients, does the immunogenicity or efficacy of influenza vaccine differ in patients taking high-dose steroids as composed to those using lower doses of steroids or those not using steroids?

Summary: The literature identified no randomized controlled trials and 13 observational studies that addressed this PICO in the RMD population, with 7 studies looking specifically at SLE [2,4,5,8,9,11,13], 2 at RA [1,7], 2 at inflammatory myositis [3,6], 1 at primary Sjogren's syndrome [10], and 1 at a mixed RMD population that was comprised predominantly of inflammatory arthritis [12]. Some studies examined seasonal influenza [1,5,8,9,13] and others pandemic influenza [2,3,4,6,7,10,11,12]. The studies that compared *any* dose of prednisone to no prednisone did not find that prednisone blunted vaccine immunogenicity [1,7,10, 12]. Most studies that compared <10mg daily prednisone to ≥10mg daily prednisone *did* find prednisone to reduce influenza vaccine immunogenicity [4,5,13], whereas one study only identified a trend in that direction, with p=0.11 [12]. Shinjo et al, who defined high-dose steroids as ≥0.5mg/kg, also did not find high-dose prednisone to diminish patients' response to the influenza vaccine [6], likely because they compared high-prednisone to all patients (rather than comparing high-dose prednisone to no prednisone), with a very small number of patients meeting criteria for high-dose prednisone. Nevertheless, several studies that defined high-dose prednisone as ≥20mg daily did observe high-dose prednisone to blunt patients' response to the influenza vaccine [2,3,11]. Similarly, Campos and colleagues compared the mean prednisone dose of those who did seroconvert versus those who did not seroconvert and found a significant difference (10.5mg versus 18mg, respectively; p=0.018) [2]. Overall, the studies with larger numbers of patients and the studies that evaluated higher doses of prednisone found that prednisone impairs RMD patients' response to the influenza vaccine, likely appreciable at doses of 10mg or higher, but most consistently evident at doses of 20mg or higher. In addition, the two studies that examined prednisone as a continuous variable [2,3] identified a dose-response suggesting prednisone is more likely to blunt the immunogenicity of the influenza vaccine at higher doses, while suggesting against a specific dose threshold.

Quality of evidence across all critical outcomes: Very low

TABLE 1. No blunting of immunogenicity seen at 28 days in RA patients receiving seasonal influenza vaccines – but no data on steroid dosing. [Alten 405]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact of MTX and steroids on immunogenicity of Seasonal Flu vaccine at d28 in RA	Control	Relative (95% CI)	Absolute (95% CI)		
Impact of steroid (any dose) on influenza vaccine seroprotection												
1	observational	serious[a]	not serious	not serious	serious[b,c]	none	57/114 (50.0%)	34/70 (48.6%)	**RR 1.03** (0.76 to 1.39)	**15 more per 1,000** (from 117 fewer to 189 more)	⨁◯◯◯ Very low	

Explanations

a. observational study
b. CI crosses null value
c. small sample size

TABLE 2. pSLE patients on higher doses of prednisone were less likely to have seroconverted 21 days after the 2009 H1N1 (pandemic influenza A) vaccine. [Campos 3531]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion (or not) based on prednisone dose or other meds (pSLE)	Control	Relative (95% CI)	Absolute (95% CI)		
Prednisone (continuous variable – mean dose in seroconverted group was 10.5mg and mean dose in non-seroconverted group was 18mg) … p=0.018												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion (or not) based on prednisone dose or other meds (pSLE)	Control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b,c]	none	-/43	0.0%	**RR 7.50** (0.51 to 14.49)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	
Pred dose >/= 20mg per day												
1	observational studies	serious[a]	not serious	not serious	serious[b,c]	none	18/43 (41.9%)	0.0%	**RR 1.43** (0.87 to 2.35)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	

Explanations

a. observational study
b. CI crosses null value
c. small sample size

TABLE 3. High dose but not low dose prednisone (20+mg) did reduce immunogenicity of influenza A H1N1/2009 vaccine in JDM patients at day 21. [Guissa 4674]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroid use in JDM patients who did or did not seroconvert	Control	Relative (95% CI)	Absolute (95% CI)		
Users of low-dose prednisone												
1	observational studies	serious[a]	not serious	not serious	serious[c,d]	none	2/4 (50.0%)	10/26 (38.5%)	**RR 1.30** (0.44 to 3.88)	**115 more per 1,000** (from 215 fewer to 1,000 more)	⊕◯◯◯ Very low	
Users of high dose (>20mg/day) prednisone												
1	observational studies	serious[a,b]	not serious	not serious	serious[d]	none	2/4 (50.0%)	1/26 (3.8%)	**RR 13.00** (1.50 to 112.42)	**462 more per 1,000** (from 19 more to 1,000 more)	⊕◯◯◯ Very low	
Prednisone dose in mg												
1	observational studies	serious[a,b]	not serious	not serious	not serious[d]	dose response gradient	4	26	-	MD **1.8 higher** (1.7 lower to 5.3 higher)	⊕⊕◯◯ Low	

Explanations

a. single-arm observational study

b. only 3 patients on high-dose steroids
c. CI crosses null value
d. small sample size

TABLE 4. High dose prednisone (10+mg) did reduce immunogenicity of influenza vaccine (1976 formulation) in SLE patients at day 28. [Ristow 4722]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients	Control patients	Relative (95% CI)	Absolute (95% CI)		
response to vaccine in SLE pts on pred >9mg compared to controls												
1	observational studies	serious[a]	not serious	not serious	serious[b,c]	none	18	18	-	MD **1.5 lower** (3.8 lower to 0.8 higher)	⨁◯◯◯ Very low	

Explanations

a. observational, small study
b. small sample size
c. CI crosses null value

TABLE 5. Prednisone (≥10mg) did not impact immunogenicity of seasonal influenza vaccine in primary SLE patients. [Crowe 4728]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact of medications on immunogenicity in primary SLE	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Impact of prednisone (>/=10mg pred/day)												
1	observational studies	serious[a,b]	not serious	not serious	not serious	none	24/36 (66.7%)	17/36 (47.2%)	**RR 1.41** (0.93 to 2.14)	**194 more per 1,000** (from 33 fewer to 538 more)	⨁◯◯◯ Very low	

Explanations

a. observational
b. small sample size

TABLE 6. High dose prednisone (≥0.5mg/kg) did not reduce immunogenicity of pandemic influenza vaccine in DM/PM patients at day 21. [Shinjo 6154]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion to H1N1/2009 for Myositis (DM/PM) based on Immunosuppression	Control	Relative (95% CI)	Absolute (95% CI)		
Impact of high-dose steroids												
1	observational studies	serious[a,b]	serious[c]	not serious	serious[d,e]	none	8/9 (88.9%)	34/48 (70.8%)	**RR 1.25** (0.94 to 1.68)	**177 more per 1,000** (from 43 fewer to 482 more)	⨁◯◯◯ Very low	

Explanations

a. observational study
b. small sample size
c. findings opposite other studies' findings
d. CI crosses null value
e. small sample size

TABLE 7. Prednisone (any dose) was associated with a very subtle reduction in immunogenicity of the H1N1 pandemic influenza vaccine in RA patients at day 21. [Ribeiro 7199]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	RA-no steroids	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	not serious	not serious	not serious	serious[a]	none	146/247 (59.1%)	56/93 (60.2%)	**RR 0.98** (0.81 to 1.19)	**12 fewer per 1,000** (from 114 fewer to 114 more)	⨁◯◯◯ Very low	
Factor increase GMT												
1	observational studies	not serious	not serious	not serious	not serious	none	247	93	-	MD **1.1 lower** (3.22 lower to 1.02 higher)	⨁⨁◯◯ Low	
Seroconversion												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	RA-no steroids	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	not serious	not serious	not serious	serious[a]	none	122/247 (49.4%)	51/93 (54.8%)	**RR 0.90** (0.72 to 1.13)	**55 fewer per 1,000** (from 154 fewer to 71 more)	⨁◯◯◯ Very low	

Explanations

a. CI crosses null value

TABLE 8. Prednisone (any dose) was associated with a very subtle reduction in immunogenicity of the seasonal influenza vaccine in SLE patients at day 30. [Holvast 7615]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												
1	observational studies	serious[a,b]	not serious	not serious	serious[b,c]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⨁◯◯◯ Very low	
Vaccine efficacy - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a,b]	not serious	not serious	serious[b,c]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⊕◯◯◯ Very low	

Vaccine efficacy - B-influenza

1	observational studies	serious[a,b]	not serious	not serious	serious[b,c]	none	5/14 (35.7%)	7/12 (58.3%)	**RR 0.61** (0.26 to 1.43)	**228 fewer per 1,000** (from 432 fewer to 251 more)	⊕◯◯◯ Very low	

Seroprotection - H1N1

1	observational studies	serious[a,b]	not serious	not serious	serious[b,c]	none	13/14 (92.9%)	11/12 (91.7%)	**RR 1.01** (0.81 to 1.27)	**9 more per 1,000** (from 174 fewer to 248 more)	⊕◯◯◯ Very low	

Seroprotection - H3N2

1	observational studies	serious[a,b]	not serious	not serious	serious[b,c]	none	12/14 (85.7%)	12/12 (100.0%)	**RR 0.87** (0.67 to 1.11)	**130 fewer per 1,000** (from 330 fewer to 110 more)	⊕◯◯◯ Very low	

Seroprotection - B-influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a,b]	not serious	not serious	serious[b,c]	none	8/14 (57.1%)	11/12 (91.7%)	**RR 0.62** (0.38 to 1.01)	**348 fewer per 1,000** (from 568 fewer to 9 more)	⊕◯◯◯ Very low	

Explanations

a. observational
b. small study size
c. CI crosses null value

TABLE 9. Prednisone (any dose) was associated with decreased seroprotection for the influenza B component of the seasonal flu vaccine in SLE patients at 6 weeks. [Wallin 7624]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on GCs	SLE not on GCs	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine antibody titer - H1N1												
1	observational studies	serious[a,b,]	not serious	not serious	serious[c,d]	none	23	24	-	MD **320 lower** (895.03 lower to 255.03 higher)	⊕◯◯◯ Very low	
Post-vaccine antibody titer - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on GCs	SLE not on GCs	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a,b]	not serious	not serious	serious[c]	none	23	24	-	MD **182.6 lower** (765.01 lower to 399.81 higher)	⨁◯◯◯ Very low	

Post-vaccine antibody titer - B-Malay

1	observational studies	serious[a,b]	not serious	not serious	serious[c,d]	none	23	24	-	MD **536.9 lower** (892.88 lower to 180.92 lower)	⨁◯◯◯ Very low	

Explanations

a. observational
b. small sample size
c. CI crosses null value

TABLE 10. Prednisone (any dose) did not impact immunogenicity of H1N1 pandemic influenza vaccine in primary Sjogren's patients at 21 days. [Pasoto 8002]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Medications depending on seroconversion at day 21 in Sjogren's patients	No seroconversion	Relative (95% CI)	Absolute (95% CI)		
Of SS patients, # on prednisone (by seroconversion or no seroconversion)												
1	observational studies	serious[a,b,c]	serious[d]	not serious	serious[b,e]	none	8/28 (28.6%)	0/8 (0.0%)	**RR 5.28** (0.34 to 82.72)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	

Explanations

a. observational
b. small sample size
c. small doses of prednisone
d. opposite findings
e. CI crosses null value

TABLE 11. Prednisone ≥ 20mg daily reduced the immunogenicity of the H1N1 pandemic influenza vaccine in SLE patients at 21 days compared to healthy controls. [Borba 4677]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immunogenicity of 2009 H1N1 in SLE based on medications	SLE no medication	Relative (95% CI)	Absolute (95% CI)		
Seroprotection: SLE on pred >/=20mg/day vs no medications												
1	observational studies	serious[a,b]	not serious	not serious	serious[b]	none	41/76 (53.9%)	54/75 (72.0%)	**RR 0.75** (0.58 to 0.96)	**180 fewer per 1,000** (from 302 fewer to 29 fewer)	⨁◯◯◯ Very low	Favors no medication

Explanations

a. observational study
b. small sample size

Table 12. Influenza vaccination in RMD patients vs. controls

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
6910 Adler (2012)	Prospective, single-center, cohort study	Follow-up to 6 months post-vaccine	149 RMD patients (57.7% female; Age: 24.2% <40 years, 45% 40-59 years, 30.8% 60+ years). Includes 47 RA patients, 59 SpA, 15 vasculitis, and 28 CTD patients. 40 healthy controls (65% female; Age: 38% <40 years, 55% 40-59 years, 8% 60+ years).	All participants received one standard dose of adjuvanted H1N1 vaccine (2009 pandemic). RMD patients: 10.7% no medications, 24.2% steroids (<10mg), 7.4% steroids (10+ mg). 62.4% on DMARDs: SSZ/HCQ (n=14), MTX (n=61), LEF (n=6), AZA (n=6), CSA (n=4), MMF (n=2), TNFi 45.6%, MTX+TNFi 22.1%.	No significant effect of oral GCs (n=50; mean dose 7.4mg daily) on antibody response (p=0.11). Seroprotection rate: 10.5% T1, 66.5% T2, 57% T3, 27.5% T4 Seroconversion rate: 59.5% T2, 43.5% T3, 26% T4 GMT ratio: 5.2 T2, 3.7 T3, 2.1 T4

			Seasonal influenza vaccine in 127/149 (85.2%) patients vs. 28/40 (70%) controls (mean 4 vs. 3.7 weeks prior to study)	RTX (5 RA, 3 vasculitis), Abatacept (10 RA, 6 SpA, 4 CTD), Tocilizumab (5 RA), CYC (1 RA, 1 vasc, 1 CTD)	

Table 13. Influenza vaccination in RA patients on RTX vs. RA patients on MTX vs. healthy controls

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
8096 Abu-Shakra (2002)	Case series	12 weeks post-vaccine	24 SLE patients Mean age 46.1 years (range 20-74), 100% females. Mean disease duration 9.1 years. Baseline seroprotection for H3N2/H1N1/B in SLE (20.8/8.3/66.7%) similar to healthy age-matched female controls (n=30; 20/16.7/63.3%). Healthy controls <u>not</u> evaluated post-vaccine.	All participants received one standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B-Influenza). <u>SLE therapies:</u> Oral steroids (n=17), mean prednisone dose 12 mg HCQ 400 mg daily (n=9) AZA 100 mg daily (n=3) MTX (n=4) mean dose 10mg weekly	Mean number of immune responses to the 3 influenza antigens, Overall mean # of immune responses = 1.5/3 <u>Prednisone:</u> Mean 1.14 if 10+ mg daily vs. 1.65 if < 10 mg daily or none.

Table 14. Influenza vaccine, mixed RMD and healthy controls mostly on MTX

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
9426 Adler 2012	Nonrandomized comparative	6 months	149 patients: 47 RA, 59 SpA, 15 vasculitis, 28 CTD vs. 40 healthy controls; % of patients >60 was 51% RA, 14% SpA, 40%	Single dose of adjuvanted A/H1N1 influenza vaccine; medications included steroids, 93% were on DMARDs (mostly MTX), 46% were on TNFIs, 22% were on both MTX and TNFIs, 10 or fewer patients were each	Glucocorticoids (mean dose of 7.4 mg/day) did not significantly impair antibody response even when separating for doses <10 and ≥10 mg/day (p=0.11). <u>Seroprotection (%) at 3 weeks, 6 weeks, 6 months (CHMP criteria in at least 70% of patients):</u> Glucocorticoids (n=50): 66.5, 57, 27.5

			VAS, 29% CTD, and 8% controls	on rituximab, abatacept, tocilizumab, and CYC	GMT/GMT ratio at 3 weeks, 6 weeks, and 6 months; (CHMP criteria ≥2.5 for GMT ratio): Glucocorticoids: 55.2/5.2, 38.7/3.7, 21.8/2.1 Seroconversion (%) at 3 weeks, 6 weeks, and 6 months (CHMP criteria in at least 40% of patients): Glucocorticoids: 59.5, 43.5, 26

CHMP: Committee for Human Medicinal Products

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PICO 15: In RMD patients, does the immunogenicity or efficacy of influenza vaccine differ in patients taking Drug Y as compared to those not using drug Y at the time of vaccination?

This evidence summary is divided into 5 sections according to medication type: 1) Biologicals*:* TNFi/tocilizumab/secukinumab; 2) Conventional DMARDs (cDMARDs)*:* methotrexate, leflunomide, azathioprine, hydroxychloroquine; 3) Rituximab*;* 4) JAK inhibitors; 5) Glucocorticoids; 6) Abatacept*.* Gradepro tables are included with each section, but the Word table summarizing additional evidence is appended at the end.

Biologicals: TNFi / Tocilizumab / Secukinumab

Summary:

TNFi: Many prospective observational studies were identified, all of which demonstrated largely similar responses to influenza vaccine in patients taking TNF inhibitors [1-10]. In some cases, there may have been one or more parameters in which patients in the TNFi group had lower response (e.g. response to 1 out of 3 influenza vaccine antigens was lower, or seroprotection was similar while seroconversion was lower). Overall, however, there was no consistent trend toward lower response in patients receiving TNFi. This held true even in patients taking combination TNFi and cDMARD therapy [11]. Two RCTs of RA patients were identified. In the first, patients were randomized to receive adalimumab or placebo on days 1, 15, and 29; influenza vaccine was administered on day 8 [12]. Seroprotection rate was similar between both adalimumab and placebo groups. In the second, patients were randomized to receive certolizumab or placebo at weeks 0, 2, and 4; influenza vaccine was administered at week 2 [13]. Vaccine responses were similar between both certolizumab and placebo groups. Overall quality of evidence across all critical outcomes*:* Low

Tocilizumab: A small prospective observational study of tocilizumab in RA patients found no difference in response to influenza vaccine compared to either healthy controls or RA patients on other medications [14]. An even smaller observational study in SJIA patients on tocilizumab similarly found effect on response to influenza vaccine [15]. Overall quality of evidence across all critical outcomes*:* Very low

Secukinumab: One very small prospective observational study was identified. In AS/PsA patients on secukinumab, no significant differences were noted in response to influenza vaccine as compared to healthy controls [16]. Overall quality of evidence across all critical outcomes*:* Very low

Table 1. RA patients on certolizumab had SIMILAR response to influenza vaccine as compared to RA patients who received placebo. LOWER response to H3N2 antigen.[13]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	certolizumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Satisfactory humoral response to Influenza vaccine, week 6												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	54/107 (50.5%)	59/109 (54.1%)	**RR 0.93** (0.72 to 1.20)	**38 fewer per 1,000** (from 152 fewer to 108 more)	⊕⊕⊕◯ Moderate	
Antibody titer change, Influenza antigen H1N1												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	86	83	-	MD **139.8 lower** (285.44 lower to 5.84 higher)	⊕⊕⊕◯ Moderate	
Antibody titer change, Influenza antigen H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	certolizumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	86	83	-	MD **355.6 lower** (648.15 lower to 63.05 lower)	⨁⨁⨁◯ Moderate	Favors placebo
Antibody titer change, Influenza antigen B, Brisbane												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	86	83	-	MD **28.5 lower** (144.17 lower to 87.17 higher)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Small sample size

Table 2. Mixed RMD patients on biological DMARDs had SIMILAR response to influenza vaccine as compared to healthy controls. ("seropositivity" not clearly defined). [17]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - Ag A - Adjusted												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	63/68 (92.6%)	44/48 (91.7%)	**RR 1.01** (0.91 to 1.13)	**9 more per 1,000** (from 82 fewer to 119 more)	⨁◯◯◯ Very low	

Seroprotection - Ag B - Adjusted

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	44/68 (64.7%)	36/48 (75.0%)	**RR 0.86** (0.68 to 1.10)	**105 fewer per 1,000** (from 240 fewer to 75 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. small sample size

Table 3. Mixed RMD patients on combination therapy (biological plus conventional DMARDs) had LOWER GMT responses; SIMILAR seroprotection to 3/3 antigens, and SIMILAR seroconversion to 2/3 antigens as compared to healthy controls. [11]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs+DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Cal H1N1 bDMARDs+DMARDs vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	110	15	-	MD **133.6 lower** (235.89 lower to 31.31 lower)	⨁◯◯◯ Very low	Favors controls
GMT, A/Swi H3N2 bDMARDs+DMARDs vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	110	15	-	MD **104.7 lower** (151.45 lower to 57.95 lower)	⨁◯◯◯ Very low	Favors controls
GMT, B/Phu Yamagata bDMARDs+DMARDs vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	110	15	-	MD **36.6 lower** (68.43 lower to 4.77 lower)	⨁◯◯◯ Very low	Favors controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs+DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/Cal H1N1 bDMARDs+DMARDs vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	98/99 (99.0%)	13/13 (100.0%)	**RR 1.02** (0.92 to 1.13)	**20 more per 1,000** (from 80 fewer to 130 more)	⨁◯◯◯ Very low	No difference
Seroprotection, A/Swi H3N2 bDMARDs+DMARDs vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	96/99 (97.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	No difference
Seroprotection, B/Phu Yamagata bDMARDs+DMARDs vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	99/99 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	No difference

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs+DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A/Cal H1N1 bDMARDs+DMARDs vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/86 (27.9%)	3/9 (33.3%)	**RR 0.84** (0.31 to 2.24)	**53 fewer per 1,000** (from 230 fewer to 413 more)	⨁◯◯◯ Very low	
Seroconversion, A/Swi H3N2 bDMARDs+DMARDs vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/86 (19.8%)	6/9 (66.7%)	**RR 0.30** (0.16 to 0.56)	**467 fewer per 1,000** (from 560 fewer to 293 fewer)	⨁◯◯◯ Very low	Favors controls
Seroconversion, B/Phu Yamagata bDMARDs+DMARDs vs controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs+DMARDs	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/86 (5.8%)	2/9 (22.2%)	**RR 0.26** (0.06 to 1.16)	**164 fewer per 1,000** (from 209 fewer to 36 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 4. Mixed RMD patients on biological monotherapy had LOWER GMT responses; SIMILAR seroprotection to 3/3 antigens, and SIMILAR seroconversion to 2/3 antigens as compared to healthy controls. [11]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Cal H1N1 bDMARDs mono vs controls												
1	observational studies	serious[a,b]	not serious	not serious	serious[b]	none	80	15	-	MD **145.1 lower** (247.78 lower to 42.42 lower)	⨁◯◯◯ Very low	Favors controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Swi H3N2 bDMARDs mono vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	80	15	-	MD **89 lower** (137.22 lower to 40.78 lower)	⨁◯◯◯ Very low	Favors controls
GMT, B/Phu Yamagata bDMARDs mono vs controls												
1	observational studies	serious[b]	not serious	not serious	serious[b]	none	80	15	-	MD **35.1 lower** (67.35 lower to 2.85 lower)	⨁◯◯◯ Very low	Favors controls
Seroprotection, A/Cal H1N1 bDMARDs mono vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66/66 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	No difference
Seroprotection, A/Swi H3N2 bDMARDs mono vs controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	65/66 (98.5%)	13/13 (100.0%)	**RR 1.01** (0.91 to 1.13)	**10 more per 1,000** (from 90 fewer to 130 more)	⨁◯◯◯ Very low	No difference

Seroprotection, B/Phu Yamagata bDMARDs mono vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	66/66 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.90 to 1.11)	**0 fewer per 1,000** (from 100 fewer to 110 more)	⨁◯◯◯ Very low	No difference

Seroconversion, A/Cal H1N1 bDMARDs mono vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/58 (13.8%)	3/9 (33.3%)	**RR 0.41** (0.13 to 1.28)	**197 fewer per 1,000** (from 290 fewer to 93 more)	⨁◯◯◯ Very low	

Seroconversion, A/Swi H3N2 bDMARDs mono vs controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bDMARDs monotherapy	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/58 (15.5%)	6/9 (66.7%)	**RR 0.23** (0.11 to 0.50)	**513 fewer per 1,000** (from 593 fewer to 333 fewer)	⨁◯◯◯ Very low	Favors controls

Seroconversion, B/Phu Yamagata bDMARDs mono vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/58 (5.2%)	2/9 (22.2%)	**RR 0.23** (0.04 to 1.21)	**171 fewer per 1,000** (from 213 fewer to 47 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 5. RA patients on TNFi had SIMILAR responses to influenza vaccine as compared to RA patients not on TNFi, and had HIGHER seroconversion rates. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-TNFi	RA-no TNFI	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/47 (68.1%)	172/293 (58.7%)	**RR 1.16** (0.93 to 1.44)	**94 more per 1,000** (from 41 fewer to 258 more)	⊕◯◯◯ Very low	
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	47	293	-	MD **2.8 higher** (1.41 lower to 7.01 higher)	⊕◯◯◯ Very low	
Seroconversion												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/47 (68.1%)	149/293 (50.9%)	**RR 1.34** (1.07 to 1.68)	**173 more per 1,000** (from 36 more to 346 more)	⊕◯◯◯ Very low	Favors RA-TNFi

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 6. RA patients on TNFi had SIMILAR responses to influenza vaccine compared to healthy controls. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-TNFi	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/47 (68.1%)	194/234 (82.9%)	**RR 0.82** (0.67 to 1.01)	**149 fewer per 1,000** (from 274 fewer to 8 more)	⨁◯◯◯ Very low	
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	47	234	-	MD **3.6 lower** (8.19 lower to 0.99 higher)	⨁◯◯◯ Very low	
Seroconversion												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-TNFi	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/47 (68.1%)	180/234 (76.9%)	**RR 0.89** (0.72 to 1.09)	**85 fewer per 1,000** (from 215 fewer to 69 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 7. RA patients on biologics had SIMILAR response to influenza vaccine compared to RA patients not on biologics (biologics included both TNFi and tocilizumab). [5]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on biologics	RA not on biologics	Relative (95% CI)	Absolute (95% CI)		
RA on biologics vs RA not on biologics - seroprotecton												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on biologics	RA not on biologics	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/36 (47.2%)	32/53 (60.4%)	**RR 0.78** (0.52 to 1.18)	**133 fewer per 1,000** (from 290 fewer to 109 more)	⨁◯◯◯ Very low	

RA on biologics vs RA not on biologics - seroresponse

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	14/36 (38.9%)	31/53 (58.5%)	**RR 0.66** (0.42 to 1.06)	**199 fewer per 1,000** (from 339 fewer to 35 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small numbers

Table 8. JIA patients on biologicals (TNFi, IL-6 inhibitors) had SIMILAR seroprotection response compared to JIA patients not on biologicals. [6]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biological	no biological	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/H1N1, bio vs no bio												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/25 (96.0%)	10/10 (100.0%)	**RR 0.99** (0.84 to 1.16)	**10 fewer per 1,000** (from 160 fewer to 160 more)	⨁◯◯◯ Very low	No difference
Seroprotection, A/H3N2, bio vs no bio												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/25 (96.0%)	10/10 (100.0%)	**RR 0.99** (0.84 to 1.16)	**10 fewer per 1,000** (from 160 fewer to 160 more)	⨁◯◯◯ Very low	No difference
Seroprotection, B, bio vs no bio												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	22/25 (88.0%)	9/10 (90.0%)	**RR 0.98** (0.76 to 1.26)	**18 fewer per 1,000** (from 216 fewer to 234 more)	⨁◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 9. JIA pts on biologicals had SIMILAR seroconversion to 2 out of 3 influenza vaccine antigens as compared to JIA patients not on biologicals [6]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biological	no biological	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A/H1N1, bio vs no bio												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	15/25 (60.0%)	8/10 (80.0%)	**RR 0.75** (0.48 to 1.17)	**200 fewer per 1,000** (from 416 fewer to 136 more)	⨁◯◯◯ Very low	
Seroconversion, A/H3N2, bio vs no bio												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	15/25 (60.0%)	7/10 (70.0%)	**RR 0.86** (0.51 to 1.44)	**98 fewer per 1,000** (from 343 fewer to 308 more)	⨁◯◯◯ Very low	
Seroconversion, B, bio vs no bio												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Biological	no biological	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/25 (36.0%)	8/10 (80.0%)	**RR 0.45** (0.25 to 0.83)	**440 fewer per 1,000** (from 600 fewer to 136 fewer)	⨁◯◯◯ Very low	Favors no biological

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 10. RA pts treated with adalimumab had SIMILAR seroprotection response to influenza vaccine compared to those treated with placebo. [12]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adalimumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, influenza, >=2 out of 3 antigens												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	97/99 (98.0%)	103/109 (94.5%)	**RR 1.04** (0.98 to 1.09)	**38 more per 1,000** (from 19 fewer to 85 more)	⨁⨁⨁◯ Moderate	No difference

CI: confidence interval; **RR:** risk ratio

a. Small sample size

Table 11. RA pts treated with adalimumab had SIMILAR seroconversion response to influenza vaccine compared to those treated with placebo. [12]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adalimumab	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, influenza, >=2 out of 3 antigens												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	51/99 (51.5%)	69/109 (63.3%)	**RR 0.81** (0.64 to 1.03)	**120 fewer per 1,000** (from 228 fewer to 19 more)	⊕⊕⊕◯ Moderate	
Seroconversion, influenza, H1N1												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	50/99 (50.5%)	61/109 (56.0%)	**RR 0.90** (0.70 to 1.17)	**56 fewer per 1,000** (from 168 fewer to 95 more)	⊕⊕⊕◯ Moderate	
Seroconversion, influenza, H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	adalimumab	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/99 (58.6%)	74/109 (67.9%)	**RR 0.86** (0.70 to 1.06)	**95 fewer per 1,000** (from 204 fewer to 41 more)	⨁⨁⨁◯ Moderate	

Seroconversion, influenza, B (Hong Kong)

1	randomised trials	not serious	not serious	not serious	serious[a]	none	48/99 (48.5%)	66/109 (60.6%)	**RR 0.80** (0.62 to 1.03)	**121 fewer per 1,000** (from 230 fewer to 18 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **RR:** risk ratio

a. Small numbers

Table 12. JIA pts on MTX/TNFi/both had SIMILAR seroprotection response to influenza vaccine compared to healthy controls. [7]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A/solomon Islands H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	26/31 (83.9%)	5/10 (50.0%)	**RR 1.68** (0.89 to 3.18)	**340 more per 1,000** (from 55 fewer to 1,000 more)	⊕◯◯◯ Very low	
Seroprotection, A/Wisconsin H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27/31 (87.1%)	9/10 (90.0%)	**RR 0.97** (0.76 to 1.24)	**27 fewer per 1,000** (from 216 fewer to 216 more)	⊕◯◯◯ Very low	
Seroprotection, B/Malaysia												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27/31 (87.1%)	9/10 (90.0%)	**RR 0.97** (0.76 to 1.24)	**27 fewer per 1,000** (from 216 fewer to 216 more)	⊕◯◯◯ Very low	
Seroprotection, A/Brisbane H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/15 (86.7%)	6/6 (100.0%)	**RR 0.91** (0.68 to 1.22)	**90 fewer per 1,000** (from 320 fewer to 220 more)	⊕◯◯◯ Very low	

Seroprotection, A/Brisbane H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/15 (66.7%)	4/6 (66.7%)	**RR 1.00** (0.51 to 1.95)	**0 fewer per 1,000** (from 327 fewer to 633 more)	⊕◯◯◯ Very low	

Seroprotection, B/Florida

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/15 (60.0%)	4/6 (66.7%)	**RR 0.90** (0.45 to 1.81)	**67 fewer per 1,000** (from 367 fewer to 540 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small numbers

Table 13. JIA pts on MTX/TNFi/both had SIMILAR seroconversion responses to influenza vaccine compared to healthy controls. [7]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A/solomon Islands H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/12 (58.3%)	4/5 (80.0%)	**RR 0.73** (0.38 to 1.39)	**216 fewer per 1,000** (from 496 fewer to 312 more)	⊕◯◯◯ Very low	
Seroconversion, A/Wisconsin H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/13 (46.2%)	6/8 (75.0%)	**RR 0.62** (0.30 to 1.25)	**285 fewer per 1,000** (from 525 fewer to 188 more)	⊕◯◯◯ Very low	
Seroconversion, B/Malaysia												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/14 (57.1%)	2/4 (50.0%)	**RR 1.14** (0.39 to 3.36)	**70 more per 1,000** (from 305 fewer to 1,000 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	JIA pts on MTX/TNFi/both	healthy control	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A/Brisbane H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/6 (66.7%)	1/1 (100.0%)	**RR 0.86** (0.32 to 2.27)	**140 fewer per 1,000** (from 680 fewer to 1,000 more)	⨁◯◯◯ Very low	
Seroconversion, A/Brisbane H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/9 (44.4%)	3/5 (60.0%)	**RR 0.74** (0.27 to 2.06)	**156 fewer per 1,000** (from 438 fewer to 636 more)	⨁◯◯◯ Very low	
Seroconversion, B/Florida												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/12 (50.0%)	2/3 (66.7%)	**RR 0.75** (0.28 to 2.00)	**167 fewer per 1,000** (from 480 fewer to 667 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small numbers

Table 14. Seroprotection response to influenza vaccine was SIMILAR in JIA pts compared to healthy controls; SIMILAR in JIA on MTX vs no MTX; SIMILAR in JIA on TNFi vs no TNFi. [8]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroprotection		Relative (95% CI)	Absolute (95% CI)		
JIA vs healthy control												
1	observational studies	serious[a]	not serious	not serious	not serious	none	84/95 (88.4%)	87/91 (95.6%)	**RR 0.92** (0.85 to 1.01)	**76 fewer per 1,000** (from 143 fewer to 10 more)	⊕◯◯◯ Very low	No difference
JIA on MTX vs JIA not on MTX												
1	observational studies	serious[a]	not serious	not serious	not serious	none	41/47 (87.2%)	43/48 (89.6%)	**RR 0.97** (0.84 to 1.13)	**27 fewer per 1,000** (from 143 fewer to 116 more)	⊕◯◯◯ Very low	No difference
JIA on TNFi vs JIA not on TNFi												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroprotection		Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	16/16 (100.0%)	68/79 (86.1%)	**RR 1.13** (1.00 to 1.28)	**112 more per 1,000** (from 0 fewer to 241 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

Table 15. Seroconversion in response to influenza vaccine was LOWER in JIA pts vs healthy controls; SIMILAR in JIA pts on MTX vs not on MTX; SIMILAR in JIA pts on TNFi vs not on TNFi. [8]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion	placebo	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, total												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seroconversion	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	79/95 (83.2%)	87/91 (95.6%)	**RR 0.87** (0.79 to 0.96)	**124 fewer per 1,000** (from 201 fewer to 38 fewer)	⨁◯◯◯ Very low	Favors control

Seroconversion, MTX in JIA patients

1	observational studies	serious[a]	not serious	not serious	not serious	none	39/47 (83.0%)	40/48 (83.3%)	**RR 1.00** (0.83 to 1.19)	**0 fewer per 1,000** (from 142 fewer to 158 more)	⨁◯◯◯ Very low	No difference

Seroconversion, TNFi in JIA pts

1	observational studies	serious[a]	not serious	not serious	not serious	none	15/16 (93.8%)	64/79 (81.0%)	**RR 1.16** (0.98 to 1.37)	**130 more per 1,000** (from 16 fewer to 300 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

Table 16. GMT in response to influenza vaccine was SIMILAR between JIA and healthy control; SIMILAR between JIA pts on MTX vs not on MTX; SIMILAR between JIA pts on TNFi vs not on TNFi. [8].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GMT	placebo	Relative (95% CI)	Absolute (95% CI)		
GMT, total												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	95	91	-	MD **35 lower** (112.06 lower to 42.06 higher)	⊕◯◯◯ Very low	
GMT, MTX in JIA												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	47	48	-	MD **8.1 lower** (112.26 lower to 96.06 higher)	⊕◯◯◯ Very low	
GMT, TNFi in JIA												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	GMT	placebo	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16	79	-	MD **105.4 higher** (42.4 lower to 253.2 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

a. No randomization

b. Very wide ranges

Table 17. No significant difference in seroconversion or GMT in RA pts on infliximab compared to RA patients not on infliximab (vaccine given same day as infliximab) [2]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
Humoral response - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/22 (45.5%)	11/23 (47.8%)	**RR 0.95** (0.51 to 1.78)	**24 fewer per 1,000** (from 234 fewer to 373 more)	⊕◯◯◯ Very low	

Humoral response - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	14/22 (63.6%)	16/23 (69.6%)	**RR 0.91** (0.60 to 1.39)	**63 fewer per 1,000** (from 278 fewer to 271 more)	⊕◯◯◯ Very low	

Humoral response - B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/22 (40.9%)	10/23 (43.5%)	**RR 0.94** (0.47 to 1.87)	**26 fewer per 1,000** (from 230 fewer to 378 more)	⊕◯◯◯ Very low	

Post-vaccine GMT - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	22	23	-	MD **0.6 lower** (1.52 lower to 0.32 higher)	⊕◯◯◯ Very low	

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	22	23	-	MD **1 lower** (1.96 lower to 0.04 lower)	⊕◯◯◯ Very low	

Post-vaccine GMT - B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	RA-Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	22	23	-	MD **1.2 lower** (2.51 lower to 0.11 higher)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. No randomization

b. Small numbers and wide confidence intervals

Table. No sig difference in seroconversion or GMT in RA pts on infliximab compared to healthy controls (vaccine given same day as infliximab) [2]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
Humoral response - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious	none	10/22 (45.5%)	8/17 (47.1%)	**RR 0.97** (0.49 to 1.91)	**14 fewer per 1,000** (from 240 fewer to 428 more)	⊕◯◯◯ Very low	

Humoral response - H3N2

1	observational studies	not serious	not serious	not serious	serious	none	14/22 (63.6%)	10/17 (58.8%)	**RR 1.08** (0.65 to 1.80)	**47 more per 1,000** (from 206 fewer to 471 more)	⊕⊕◯◯ Low	

Humoral response - B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious	none	9/22 (40.9%)	5/17 (29.4%)	**RR 1.39** (0.57 to 3.39)	**115 more per 1,000** (from 126 fewer to 703 more)	⨁◯◯◯ Very low	

Post-vaccine GMT - H1N1

1	observational studies	serious[a]	not serious	not serious	serious	none	22	16	-	MD **0.7 lower** (1.69 lower to 0.29 higher)	⨁◯◯◯ Very low	

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	serious	none	22	16	-	MD **0.9 lower** (1.79 lower to 0.01 lower)	⨁◯◯◯ Very low	

Post-vaccine GMT - B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given same day)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious	none	22	16	-	MD **2.2 lower** (3.29 lower to 1.11 lower)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. No randomization

Table 18. No sig difference in seroconversion or GMT in RA pts on infliximab compared to healthy controls (vaccine 3 wks after infliximab) [2]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
Humoral response - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/16 (43.8%)	8/17 (47.1%)	**RR 0.93** (0.44 to 1.97)	**33 fewer per 1,000** (from 264 fewer to 456 more)	⊕◯◯◯ Very low	

Humoral response - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/16 (50.0%)	10/17 (58.8%)	**RR 0.85** (0.45 to 1.60)	**88 fewer per 1,000** (from 324 fewer to 353 more)	⊕◯◯◯ Very low	

Humoral response - B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/16 (50.0%)	5/17 (29.4%)	**RR 1.70** (0.70 to 4.12)	**206 more per 1,000** (from 88 fewer to 918 more)	⨁◯◯◯ Very low	

Post-vaccine GMT - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16	16	-	MD **0.4 lower** (1.57 lower to 0.77 higher)	⨁◯◯◯ Very low	

Post-vaccine GMT - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16	16	-	MD **0.6 lower** (1.74 lower to 0.54 higher)	⨁◯◯◯ Very low	

Post-vaccine GMT - B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX-(vax given 3 wks later)	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16	16	-	MD **1.8 lower** (2.94 lower to 0.66 lower)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. No randomization

b. Small numbers and wide confidence intervals

Table 19. RA patients on TNFi had similar or HIGHER responses to influenza vaccine compared to healthy controls. Response defined as seropositive OR seroconversion at 4-6 weeks. [9]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on TNFi	HC	Relative (95% CI)	Absolute (95% CI)		
Response, A/H1N1/New Caledonia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on TNFi	HC	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/27 (44.4%)	9/52 (17.3%)	**RR 2.57** (1.24 to 5.32)	**272 more per 1,000** (from 42 more to 748 more)	⨁◯◯◯ Very low	Favors RA on TNFi

Response, A/H3N2/Hiroshima

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/27 (44.4%)	13/52 (25.0%)	**RR 1.78** (0.94 to 3.34)	**195 more per 1,000** (from 15 fewer to 585 more)	⨁◯◯◯ Very low	

Response, B/Malaysia

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/27 (29.6%)	5/52 (9.6%)	**RR 3.08** (1.12 to 8.51)	**200 more per 1,000** (from 12 more to 722 more)	⨁◯◯◯ Very low	Favors RA on TNFi

CI: confidence interval; **RR:** risk ratio

a. No randomization

b. Small numbers

Table 20. RA patients on TNFi had SIMILAR responses to influenza vaccine compared to RA not on TNFi. Response defined as seropositive OR seroconversion at 4-6 weeks. [9]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on TNFi	RA not on TNFi	Relative (95% CI)	Absolute (95% CI)		
Response, A/H1N1/New Caledonia												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/27 (44.4%)	8/36 (22.2%)	**RR 2.00** (0.95 to 4.20)	**222 more per 1,000** (from 11 fewer to 711 more)	⊕◯◯◯ Very low	
Response, A/H3N2/Hiroshima												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/27 (44.4%)	12/36 (33.3%)	**RR 1.33** (0.71 to 2.49)	**110 more per 1,000** (from 97 fewer to 497 more)	⊕◯◯◯ Very low	
Response, B/Malaysia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA on TNFi	RA not on TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/27 (29.6%)	8/36 (22.2%)	**RR 1.33** (0.57 to 3.10)	**73 more per 1,000** (from 96 fewer to 467 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. No randomization

b. Small numbers

Table 21. RA pts on tocilizumab had SIMILAR or LOWER seroconversion response compared to RA pts on conventional DMARDs [14]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on Tocilizumab	RA pts on DMARD	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A(NC) Toci vs DMARD												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on Tocilizumab	RA pts on DMARD	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/38 (44.7%)	18/24 (75.0%)	**RR 0.60** (0.39 to 0.91)	**300 fewer per 1,000** (from 458 fewer to 67 fewer)	⊕◯◯◯ Very low	Favors RA on DMARD

Seroconversion, A(HIR) Toci vs DMARD

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	18/38 (47.4%)	13/24 (54.2%)	**RR 0.87** (0.53 to 1.44)	**70 fewer per 1,000** (from 255 fewer to 238 more)	⊕◯◯◯ Very low	

Seroconversion, B(MAL) Toci vs DMARD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on Tocilizumab	RA pts on DMARD	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious	none	24/38 (63.2%)	19/24 (79.2%)	**RR 0.80** (0.58 to 1.10)	**158 fewer per 1,000** (from 333 fewer to 79 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small numbers

Table 22. RA pts on tocilizumab had SIMILAR seroconversion response to RA pts on TNFi. [14]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on TNFi	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A(NC) Toci vs TNFi												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	17/38 (44.7%)	6/15 (40.0%)	**RR 1.12** (0.55 to 2.28)	**48 more per 1,000** (from 180 fewer to 512 more)	⊕◯◯◯ Very low	

Seroconversion, A(HIR) Toci vs TNFi

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	18/38 (47.4%)	8/15 (53.3%)	**RR 0.89** (0.50 to 1.59)	**59 fewer per 1,000** (from 267 fewer to 315 more)	⊕◯◯◯ Very low	

Seroconversion, B(MAL) Toci vs TNFi

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/38 (63.2%)	4/15 (26.7%)	**RR 2.37** (0.99 to 5.67)	**365 more per 1,000** (from 3 fewer to 1,000 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small numbers and wide confidence intervals

Table 23. RA pts on tocilizumab had SIMILAR seroprotection response to influenza vaccine compared to RA pts on conventional DMARDs. [14]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on DMARDs	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A(NC) Toci vs DMARD												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	36/38 (94.7%)	22/24 (91.7%)	**RR 1.03** (0.90 to 1.19)	**28 more per 1,000** (from 92 fewer to 174 more)	⊕◯◯◯ Very low	No difference
Seroprotection, A(HIR) Toci vs DMARD												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	35/38 (92.1%)	23/24 (95.8%)	**RR 0.96** (0.85 to 1.09)	**38 fewer per 1,000** (from 144 fewer to 86 more)	⊕◯◯◯ Very low	No difference
Seroprotection, B(MAL) Toci vs DMARD												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on DMARDs	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/38 (84.2%)	21/24 (87.5%)	**RR 0.96** (0.78 to 1.18)	**35 fewer per 1,000** (from 192 fewer to 157 more)	⨁◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small numbers

Table 24. RA pts on tocilizumab had SIMILAR seroprotection response to influenza vaccine compared to RA pts on TNFi. [14]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on TNFi	Relative (95% CI)	Absolute (95% CI)		
Seroprotection, A(NC) Toci vs TNFi												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA pts on tocilizumab	RA pts on TNFi	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	36/38 (94.7%)	11/15 (73.3%)	**RR 1.29** (0.94 to 1.77)	**213 more per 1,000** (from 44 fewer to 565 more)	⊕◯◯◯ Very low	

Seroprotection, A(HIR) Toci vs TNFi

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	35/36 (97.2%)	12/15 (80.0%)	**RR 1.22** (0.94 to 1.57)	**176 more per 1,000** (from 48 fewer to 456 more)	⊕◯◯◯ Very low	

Seroprotection, B(MAL) Toci vs TNFi

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/38 (84.2%)	8/15 (53.3%)	**RR 1.58** (0.96 to 2.59)	**309 more per 1,000** (from 21 fewer to 848 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small numbers and wide confidence intervals

Table 25. SJIA patients on tocilizumab, as compared to healthy controls, had higher GMT to 1/3 influenza antigens, lower GMT to 2/3 influenza antigens, and SIMILAR seroprotection and seroconversion rates. [15]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
GMT, A/H1N1, SJIA/toci vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27	17	-	MD **18.5 higher** (15.42 higher to 21.58 higher)	⊕◯◯◯ Very low	Favors SJIA on tocilizumab
GMT, A/H3N2, SJIA/toci vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27	17	-	MD **133.4 lower** (135.64 lower to 131.16 lower)	⊕◯◯◯ Very low	Favors controls
GMT, B, SJIA/toci vs control												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	27	17	-	MD **10.2 lower** (13.16 lower to 7.24 lower)	⊕◯◯◯ Very low	Favors controls

Seroprotection, A/H1N1, SJIA/toci vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	24/27 (88.9%)	13/17 (76.5%)	**RR 1.16** (0.87 to 1.56)	**122 more per 1,000** (from 99 fewer to 428 more)	⊕◯◯◯ Very low	

Seroprotection, A/H3N2, SJIA/toci vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23/27 (85.2%)	17/17 (100.0%)	**RR 0.86** (0.72 to 1.03)	**140 fewer per 1,000** (from 280 fewer to 30 more)	⊕◯◯◯ Very low	

Seroprotection, B, SJIA/toci vs control

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	11/27 (40.7%)	6/17 (35.3%)	**RR 1.15** (0.52 to 2.54)	**53 more per 1,000** (from 169 fewer to 544 more)	⊕◯◯◯ Very low	

Seroconversion, A/H1N1, SJIA/toci vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/27 (48.1%)	8/17 (47.1%)	**RR 1.02** (0.54 to 1.94)	**9 more per 1,000** (from 216 fewer to 442 more)	⊕◯◯◯ Very low	

Seroconversion A/H3N2, SJIA/toci vs control

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/27 (37.0%)	9/17 (52.9%)	**RR 0.70** (0.36 to 1.36)	**159 fewer per 1,000** (from 339 fewer to 191 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SJIA on tocilizumab	healthy control	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, B, SJIA/toci vs control												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/27 (14.8%)	2/17 (11.8%)	**RR 1.26** (0.26 to 6.15)	**31 more per 1,000** (from 87 fewer to 606 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 26. AS/PsA patients on secukinumab had SIMILAR response to influenza vaccine as compared to healthy controls (seroconversion). [16]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AS/PsA patients on secukinumab	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Vaccine Response - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AS/PsA patients on secukinumab	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	10/17 (58.8%)	7/13 (53.8%)	**RR 1.09** (0.58 to 2.07)	**48 more per 1,000** (from 226 fewer to 576 more)	⊕◯◯◯ Very low	

Vaccine Response - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	2/17 (11.8%)	1/13 (7.7%)	**RR 1.53** (0.15 to 15.09)	**41 more per 1,000** (from 65 fewer to 1,000 more)	⊕◯◯◯ Very low	

Vaccine Response - B-Brisbane

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/17 (35.3%)	6/13 (46.2%)	**RR 0.76** (0.32 to 1.83)	**111 fewer per 1,000** (from 314 fewer to 383 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size and wide confidence intervals

Conventional DMARDs

Summary: Two relevant RCTs were identified. RA patients on baseline MTX therapy were assigned in a 1:1:1:1 ratio to either continue MTX, suspend for 4 weeks before vaccination, suspend for 2 weeks before and 2 weeks after, or suspend for 4 weeks after vaccination [18](see data for Park 2017 in Table 56). All four groups showed high rates of satisfactory responses to at least 1 out of 3 influenza vaccine antigens; the group that suspended MTX 2 wks before and 2 wks afterwards seemed to have the best response, especially when looking at antibody titers compared to the group which continued MTX throughout [18]. Therefore, the results suggest that MTX has a modest effect on influenza vaccine response. Another RCT by Park [19] compared responses to the quadrivalent inactivated influenza vaccine for RA patients on MTX randomized to continue MTX or discontinue MTX for 2 weeks after vaccination. While the overall vaccine response was good, it was significantly better in patients with the 2-week MTX discontinuation (see data for [19] in Table 56). Results from meta-analyses of these two RCTs appear in Table 27; the quality of evidence is moderate.

Many additional observational studies also addressed MTX either directly or indirectly. The most compelling of these was a prospective cohort study of 215 RA patients on MTX and 125 RA patients not on MTX [4]. At 3 weeks post-vaccination, 53% of RA patients on MTX were seroprotected, compared to 72% of RA patients not on MTX. Increase in GMT and seroconversion rates were similarly lower in patients on MTX. Other observational studies were mixed, with most (but not all) showing similar rates of seroprotection and seroconversion in response to influenza vaccine in patients taking MTX [3, 10, 20-25]. However, even in the studies that showed statistically similar rates, the rates were generally lower in the MTX group. Many of these studies addressed the question of MTX effect indirectly; all had small cohorts and thus quality is very low. However, the overall findings are consistent with the findings in the higher-quality RCTs.

Extremely limited observational data for hydroxychloroquine, leflunomide, and azathioprine demonstrated no significant differences in response to influenza vaccination [4, 17, 22, 23].

Overall quality of evidence across all critical outcomes: Low for MTX, Very low for other csDMARDs

Table 27. MTX continuation versus MTX temporary discontinuation (holding) in patients with RA.[2526][4354]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX continue	MTX hold	Relative (95% CI)	Absolute (95% CI)		
Fold change in H1N1 antibody titres												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX continue	MTX hold	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a]	not serious	not serious	not serious	none	210	209	-	MD **2.33 lower** (3.77 lower to 0.88 lower)	⊕⊕⊕◯ Moderate	Favors MTX hold

Fold change in H3N2 antibody titres

2	randomised trials	serious[a]	not serious	not serious	not serious	none	210	209	-	MD **4.35 lower** (6.55 lower to 2.14 lower)	⊕⊕⊕◯ Moderate	Favors MTX hold

Fold change in B-Yamagata antibody titres

2	randomised trials	serious[a]	not serious	not serious	not serious	none	210	209	-	MD **2.28 lower** (3.13 lower to 1.43 lower)	⊕⊕⊕◯ Moderate	Favors MTX hold

Fold change in B-Victoria antibody titres

1	randomised trials	serious[a]	not serious	not serious	not serious	none	156	160	-	MD **2.8 lower** (3.74 lower to 1.86 lower)	⊕⊕⊕◯ Moderate	Favors MTX hold

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX continue	MTX hold	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine GMT, H1N1												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	156	160	-	MD **40 lower** (61 lower to 19 lower)	⨁⨁⨁◯ Moderate	Favors MTX hold
Post-vaccine GMT, H3N2												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	156	160	-	MD **40.4 lower** (57.18 lower to 23.62 lower)	⨁⨁⨁◯ Moderate	Favors MTX hold
Post-vaccine GMT, B-Yamagata												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	156	160	-	MD **45.2 lower** (67.17 lower to 23.23 lower)	⨁⨁⨁◯ Moderate	Favors MTX hold
Post-vaccine GMT, B-Victoria												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX continue	MTX hold	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	156	160	-	MD **26.8 lower** (38.06 lower to 15.54 lower)	⊕⊕⊕◯ Moderate	Favors MTX hold

Seroconversion, H1N1

1	randomised trials	serious[a]	not serious	not serious	not serious	none	79/156 (50.6%)	100/160 (62.5%)	**RR 0.81** (0.67 to 0.99)	**119 fewer per 1,000** (from 206 fewer to 6 fewer)	⊕⊕⊕◯ Moderate	Favors MTX hold

Seroconversion, H3N2

1	randomised trials	serious[a]	not serious	not serious	not serious	none	85/156 (54.5%)	114/160 (71.3%)	**RR 0.76** (0.64 to 0.91)	**171 fewer per 1,000** (from 257 fewer to 64 fewer)	⊕⊕⊕◯ Moderate	Favors MTX hold

Seroconversion, B-Yamagata

1	randomised trials	serious[a]	not serious	not serious	not serious	none	66/156 (42.3%)	104/160 (65.0%)	**RR 0.65** (0.52 to 0.81)	**227 fewer per 1,000** (from 312 fewer to 123 fewer)	⊕⊕⊕◯ Moderate	Favors MTX hold

Seroconversion, B-Victoria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX continue	MTX hold	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	64/156 (41.0%)	118/160 (73.8%)	**RR 0.56** (0.45 to 0.69)	**324 fewer per 1,000** (from 406 fewer to 229 fewer)	⨁⨁⨁◯ Moderate	Favors MTX hold

Seroprotection, H1N1

1	randomised trials	serious[a]	not serious	not serious	not serious	none	118/156 (75.6%)	138/160 (86.3%)	**RR 0.88** (0.79 to 0.98)	**104 fewer per 1,000** (from 181 fewer to 17 fewer)	⨁⨁⨁◯ Moderate	Favors MTX hold

Seroprotection, H3N2

1	randomised trials	serious[a]	not serious	not serious	not serious	none	97/156 (62.2%)	125/160 (78.1%)	**RR 0.80** (0.69 to 0.92)	**156 fewer per 1,000** (from 242 fewer to 62 fewer)	⨁⨁⨁◯ Moderate	Favors MTX hold

Seroprotection, B-Yamagata

1	randomised trials	serious[a]	not serious	not serious	not serious	none	116/156 (74.4%)	141/160 (88.1%)	**RR 0.84** (0.76 to 0.94)	**141 fewer per 1,000** (from 212 fewer to 53 fewer)	⨁⨁⨁◯ Moderate	Favors MTX hold

Seroprotection, B-Victoria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX continue	MTX hold	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	95/156 (60.9%)	121/160 (75.6%)	**RR 0.81** (0.69 to 0.94)	**144 fewer per 1,000** (from 234 fewer to 45 fewer)	⨁⨁⨁◯ Moderate	Favors MTX hold
Adverse events												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	64/210 (30.5%)	71/209 (34.0%)	**RR 0.91** (0.67 to 1.23)	**31 fewer per 1,000** (from 112 fewer to 78 more)	⨁⨁⨁◯ Moderate	
SAE												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	1/208 (0.5%)	2/209 (1.0%)	**RR 0.61** (0.08 to 4.92)	**4 fewer per 1,000** (from 9 fewer to 38 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Single-blind study

Table 28. RA patients on MTX monotherapy had SIMILAR response to influenza vaccine as compared to RA pts on no DMARDs "Vaccine response" = seroconversion (>4-fold increase in titer). "Seroconversion" = proportion of patients lacking baseline seroprotection that meet the above criteria for seroprotection at 35 days post-vaccination. [21]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - Influenza												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/55 (58.2%)	29/43 (67.4%)	**RR 0.86** (0.64 to 1.17)	**94 fewer per 1,000** (from 243 fewer to 115 more)	⊕◯◯◯ Very low	
Baseline seroprotection - Influenza												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	19/55 (34.5%)	13/43 (30.2%)	**RR 1.14** (0.64 to 2.04)	**42 more per 1,000** (from 109 fewer to 314 more)	⊕◯◯◯ Very low	
Seroprotection - Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX monotherapy	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	51/55 (92.7%)	39/43 (90.7%)	**RR 1.02** (0.91 to 1.15)	**18 more per 1,000** (from 82 fewer to 136 more)	⨁◯◯◯ Very low	No difference

Seroconversion - Influenza

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	32/36 (88.9%)	26/30 (86.7%)	**RR 1.03** (0.86 to 1.23)	**26 more per 1,000** (from 121 fewer to 199 more)	⨁◯◯◯ Very low	No difference

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 29. Among SLE patients, those on DMARDs had significantly LOWER seroprotection response to influenza vaccine compared to those on no medications. When broken down by medication, patients on azathioprine, methotrexate, and MMF all showed lower seroprotection responses, but these individual differences were not

statistically significant. Chloroquine was not associated with a difference in seroprotection response, regardless of whether used as monotherapy or in combination with a DMARD. SLE pts on pred >20 mg/day did not have a different seroprotection response to influenza vaccine. [22]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meds	no meds	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - SLE on chloroquine monotherapy vs no medications												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	82/105 (78.1%)	56/75 (74.7%)	**RR 1.05** (0.89 to 1.24)	**37 more per 1,000** (from 82 fewer to 179 more)	⨁◯◯◯ Very low	No difference
Seroprotection: SLE on DMARD vs no medications												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	49/95 (51.6%)	56/75 (74.7%)	**RR 0.69** (0.55 to 0.87)	**231 fewer per 1,000** (from 336 fewer to 97 fewer)	⨁◯◯◯ Very low	Favors no meds
Seroprotection: SLE on DMARD vs no medications - On aza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meds	no meds	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	21/38 (55.3%)	19/25 (76.0%)	**RR 0.73** (0.51 to 1.04)	**205 fewer per 1,000** (from 372 fewer to 30 more)	⨁◯◯◯ Very low	

Seroprotection: SLE on DMARD vs no medications - On mtx

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	14/27 (51.9%)	19/25 (76.0%)	**RR 0.68** (0.45 to 1.04)	**243 fewer per 1,000** (from 418 fewer to 30 more)	⨁◯◯◯ Very low	

Seroprotection: SLE on DMARD vs no medications - On mmf

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meds	no meds	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	14/30 (46.7%)	18/25 (72.0%)	**RR 0.65** (0.41 to 1.02)	**252 fewer per 1,000** (from 425 fewer to 14 more)	⊕◯◯◯ Very low	

Seroprotection: SLE on DMARD vs DMARD + chloroquine

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	56/95 (58.9%)	31/46 (67.4%)	**RR 0.87** (0.67 to 1.14)	**88 fewer per 1,000** (from 222 fewer to 94 more)	⊕◯◯◯ Very low	

Seroprotection: SLE on pred >/=20mg/day with and without DMARD

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Meds	no meds	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	47/76 (61.8%)	48/76 (63.2%)	**RR 0.98** (0.77 to 1.25)	**13 fewer per 1,000** (from 145 fewer to 158 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 30. Mixed RMD patients on conventional DMARDs had SIMILAR response to influenza vaccine as compared to healthy controls. ("seropositivity" not clearly defined) [17]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - Ag A - Adjusted												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	csDMARDs	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	38/46 (82.6%)	44/48 (91.7%)	**RR 0.90** (0.77 to 1.06)	**92 fewer per 1,000** (from 211 fewer to 55 more)	⨁◯◯◯ Very low	

Seroprotection - Ag B - Adjusted

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	28/46 (60.9%)	36/48 (75.0%)	**RR 0.81** (0.61 to 1.08)	**142 fewer per 1,000** (from 293 fewer to 60 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 31. SLE patients on azathioprine had SIMILAR post-vaccine titer to all 3 influena vaccine antigens, as compared to SLE patients not on azathioprine. [23]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on AZA	SLE not on AZA	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine antibody titer - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9	38	-	MD **179.6 higher** (648.78 lower to 1007.98 higher)	⊕◯◯◯ Very low	
Post-vaccine antibody titer - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9	38	-	MD **445.6 lower** (920.07 lower to 28.87 higher)	⊕◯◯◯ Very low	
Post-vaccine antibody titer - B-Malay												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9	38	-	MD **142.2 lower** (498.57 lower to 214.17 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference

a. Not randomized

b. Small sample size

Table 32. RA patients on chloroquine had SIMILAR response to influenza vaccine compared to RA patients not on chloroquine. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-CQ	RA-no CQ	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	not serious	none	73/124 (58.9%)	131/216 (60.6%)	**RR 0.97** (0.81 to 1.16)	**18 fewer per 1,000** (from 115 fewer to 97 more)	⊕◯◯◯ Very low	No difference
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	not serious	none	124	216	-	MD **0.9 lower** (2.94 lower to 1.14 higher)	⊕◯◯◯ Very low	
Seroconversion												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-CQ	RA-no CQ	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	61/124 (49.2%)	119/216 (55.1%)	**RR 0.89** (0.72 to 1.11)	**61 fewer per 1,000** (from 154 fewer to 61 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

Table 33. RA patients on leflunomide had SIMILAR GMT responses to influenza vaccine as compared to healthy controls. RA patients on leflunomide had LOWER seroconversion and seroprotection rates. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-LEF	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-LEF	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	95/146 (65.1%)	194/234 (82.9%)	**RR 0.78** (0.69 to 0.90)	**182 fewer per 1,000** (from 257 fewer to 83 fewer)	⊕◯◯◯ Very low	Favors healthy controls

Factor increase GMT

1	observational studies	serious[a]	not serious	not serious	not serious	none	146	234	-	MD **3.1 lower** (6.34 lower to 0.14 higher)	⊕◯◯◯ Very low	

Seroconversion

1	observational studies	serious[a]	not serious	not serious	not serious	none	84/146 (57.5%)	180/234 (76.9%)	**RR 0.75** (0.64 to 0.87)	**192 fewer per 1,000** (from 277 fewer to 100 fewer)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. No randomization

Table 34. RA patients on leflunomide had SIMILAR response to influenza vaccine compared to RA patients not on leflunomide. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-LEF	RA-no LEF	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	not serious	none	95/146 (65.1%)	110/194 (56.7%)	**RR 1.15** (0.97 to 1.36)	**85 more per 1,000** (from 17 fewer to 204 more)	⊕◯◯◯ Very low	
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	not serious	none	146	194	-	MD **4.5 higher** (1.83 higher to 7.17 higher)	⊕◯◯◯ Very low	Favors RA-LEF
Seroconversion												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-LEF	RA-no LEF	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	84/146 (57.5%)	98/194 (50.5%)	**RR 1.14** (0.94 to 1.39)	**71 more per 1,000** (from 30 fewer to 197 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

Table 35. RA patients on MTX had lower response to influenza vaccine compared to healthy controls. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	not serious	none	114/215 (53.0%)	194/234 (82.9%)	**RR 0.64** (0.56 to 0.73)	**298 fewer per 1,000** (from 365 fewer to 224 fewer)	⊕◯◯◯ Very low	Favors healthy controls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	not serious	none	215	234	-	MD **7.7 lower** (9.97 lower to 5.43 lower)	⨁◯◯◯ Very low	Favors healthy controls
Seroconversion												
1	observational studies	serious[a]	not serious	not serious	not serious	none	100/215 (46.5%)	180/234 (76.9%)	**RR 0.60** (0.52 to 0.71)	**308 fewer per 1,000** (from 369 fewer to 223 fewer)	⨁◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

Table 36. RA patients on MTX had LOWER responses to influenza vaccine compared to RA patients not on MTX. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	RA-no MTX	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	not serious	none	114/215 (53.0%)	90/125 (72.0%)	**RR 0.74** (0.62 to 0.87)	**187 fewer per 1,000** (from 274 fewer to 94 fewer)	⨁◯◯◯ Very low	Favors RA-no MTX
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	not serious	none	215	125	-	MD **5.9 lower** (9 lower to 2.8 lower)	⨁◯◯◯ Very low	Favors RA-no MTX
Seroconversion												
1	observational studies	serious[a]	not serious	not serious	not serious	none	100/215 (46.5%)	82/125 (65.6%)	**RR 0.71** (0.59 to 0.86)	**190 fewer per 1,000** (from 269 fewer to 92 fewer)	⨁◯◯◯ Very low	Favors RA-no MTX

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

Table 37. RA patients on chloroquine had LOWER responses to influenza vaccine compared to healthy control. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-CQ	healthy controls	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	not serious	none	73/124 (58.9%)	194/234 (82.9%)	**RR 0.71** (0.61 to 0.83)	**240 fewer per 1,000** (from 323 fewer to 141 fewer)	⊕◯◯◯ Very low	Favors healthy controls
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	not serious	none	124	234	-	MD **6.6 lower** (9.16 lower to 4.04 lower)	⊕◯◯◯ Very low	Favors healthy controls
Seroconversion												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-CQ	healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	not serious	none	62/124 (50.0%)	180/234 (76.9%)	**RR 0.65** (0.54 to 0.79)	**269 fewer per 1,000** (from 354 fewer to 162 fewer)	⨁◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

Table 38. SLE patients on methotrexate had LOWER post-vaccine antibody responses to 2/3 antigens of the influenza vaccine, as compared to SLE patients not on methotrexate. [23]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on MTX	SLE not on MTX	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine antibody titer - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on MTX	SLE not on MTX	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8	39	-	MD **467.9 lower** (1103.61 lower to 167.81 higher)	⊕◯◯◯ Very low	

Post-vaccine antibody titer - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8	39	-	MD **376.9 lower** (1079.28 lower to 325.48 higher)	⊕◯◯◯ Very low	

Post-vaccine antibody titer - B-Malay

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8	39	-	MD **339.2 lower** (631.41 lower to 46.99 lower)	⊕◯◯◯ Very low	Favors SLE not on MTX

CI: confidence interval; **MD:** mean difference

a. Not randomized

b. Small sample size

Table 39. RA pts on MTX have SIMILAR baseline seroprotection levels compared to healthy controls. Post-vaccination, RA pts on MTX have SIMILAR seroprotection levels compared to healthy controls. [20]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
Pre-vaccine seroprotection - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/20 (20.0%)	13/29 (44.8%)	**RR 0.45** (0.17 to 1.17)	**247 fewer per 1,000** (from 372 fewer to 76 more)	⊕◯◯◯ Very low	
Pre-vaccine seroprotection - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/20 (20.0%)	13/29 (44.8%)	**RR 0.45** (0.17 to 1.17)	**247 fewer per 1,000** (from 372 fewer to 76 more)	⊕◯◯◯ Very low	
Pre-vaccine seroprotection - B												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	1/20 (5.0%)	7/29 (24.1%)	**RR 0.21** (0.03 to 1.56)	**191 fewer per 1,000** (from 234 fewer to 135 more)	⨁◯◯◯ Very low	

Post-vaccine seroprotection - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/20 (65.0%)	25/29 (86.2%)	**RR 0.75** (0.53 to 1.07)	**216 fewer per 1,000** (from 405 fewer to 60 more)	⨁◯◯◯ Very low	

Post-vaccine seroprotection - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-MTX	Healthy Controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/20 (65.0%)	25/29 (86.2%)	**RR 0.75** (0.53 to 1.07)	**216 fewer per 1,000** (from 405 fewer to 60 more)	⊕◯◯◯ Very low	

Post-vaccine seroprotection - B

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/20 (25.0%)	14/29 (48.3%)	**RR 0.52** (0.22 to 1.21)	**232 fewer per 1,000** (from 377 fewer to 101 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

b. Small sample size and wide confidence intervals

Table 40. RA pts on MTX had SIMILAR seroconversion response to influenza compared to RA pts not on MTX [12].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX subgroup analysis	no MTX	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, influenza, MTX vs no MTX												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	62/114 (54.4%)	58/94 (61.7%)	**RR 0.88** (0.70 to 1.11)	**74 fewer per 1,000** (from 185 fewer to 68 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 41. SLE patients on azathioprine had SIMILAR seroconversion and seroprotection responses to influenza vaccine to SLE patients not on azathioprine. ("vaccine efficacy" = seroconversion and/or seroprotection). They had LOWER seroprotection to 1 out of 3 antigens. [26]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: AZA	SLE no medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: AZA	SLE no medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	4/13 (30.8%)	7/12 (58.3%)	**RR 0.53** (0.20 to 1.36)	**274 fewer per 1,000** (from 467 fewer to 210 more)	⊕◯◯◯ Very low	

Vaccine efficacy - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	1/13 (7.7%)	7/12 (58.3%)	**RR 0.13** (0.02 to 0.92)	**508 fewer per 1,000** (from 572 fewer to 47 fewer)	⊕◯◯◯ Very low	Favors SLE no medications

Vaccine efficacy - B-influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: AZA	SLE no medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	3/13 (23.1%)	7/12 (58.3%)	**RR 0.40** (0.13 to 1.19)	**350 fewer per 1,000** (from 508 fewer to 111 more)	⊕◯◯◯ Very low	

Seroprotection - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	9/13 (69.2%)	11/12 (91.7%)	**RR 0.76** (0.51 to 1.13)	**220 fewer per 1,000** (from 449 fewer to 119 more)	⊕◯◯◯ Very low	

Seroprotection - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: AZA	SLE no medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/13 (61.5%)	12/12 (100.0%)	**RR 0.63** (0.41 to 0.98)	**370 fewer per 1,000** (from 590 fewer to 20 fewer)	⊕◯◯◯ Very low	Favors SLE no medications

Seroprotection - B-influenza

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/13 (61.5%)	11/12 (91.7%)	**RR 0.67** (0.42 to 1.07)	**302 fewer per 1,000** (from 532 fewer to 64 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 42. SLE patients on hydroxychloroquine had SIMILAR seroconversion and seroprotection responses to influenza vaccine to SLE patients not on hydroxychloroquine. ("vaccine efficacy" = seroconversion and/or seroprotection). [26]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	7/17 (41.2%)	7/12 (58.3%)	**RR 0.71** (0.34 to 1.48)	**169 fewer per 1,000** (from 385 fewer to 280 more)	⊕◯◯◯ Very low	
Vaccine efficacy - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/17 (47.1%)	7/12 (58.3%)	**RR 0.81** (0.40 to 1.62)	**111 fewer per 1,000** (from 350 fewer to 362 more)	⊕◯◯◯ Very low	
Vaccine efficacy - B-influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/17 (47.1%)	7/12 (58.3%)	**RR 0.81** (0.40 to 1.62)	**111 fewer per 1,000** (from 350 fewer to 362 more)	⨁◯◯◯ Very low	

Seroprotection - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	14/17 (82.4%)	11/12 (91.7%)	**RR 0.90** (0.68 to 1.19)	**92 fewer per 1,000** (from 293 fewer to 174 more)	⨁◯◯◯ Very low	

Seroprotection - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	16/17 (94.1%)	12/12 (100.0%)	**RR 0.95** (0.80 to 1.14)	**50 fewer per 1,000** (from 200 fewer to 140 more)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine	No medications	Relative (95% CI)	Absolute (95% CI)		
Seroprotection - B-influenza												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/17 (70.6%)	11/12 (91.7%)	**RR 0.77** (0.54 to 1.09)	**211 fewer per 1,000** (from 422 fewer to 83 more)	⨁◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Rituximab

Summary: Only observational data with small cohorts were available for rituximab, although multiple prospective studies were identified with relatively consistent findings [11, 20, 27-30]. Almost all studies found lower geometric mean titers to influenza vaccine antigens, although in some studies the seroprotection and seroconversion rates were still similar. Most studies reported overall low rates of response to influenza vaccine in RMD patients receiving rituximab – notably, in RMD studies comparing different drug regimens, patients receiving rituximab generally had the lowest rates of response [3, 31][19]. One retrospective study with a relatively large cohort (681 adults with ITP exposed to rituximab) did not examine the typical seroprotection/seroconversion/GMT outcomes; rather, it examined rates of infection [32]. Although patients exposed to rituximab had significantly higher rates of serious infection compared to ITP patients on other regimens (HR 2.6, CI 1.67-4.03), influenza vaccination still had a protective effect in reducing infection (HR 0.42 compared to no vaccination).

Overall quality of evidence across all critical outcomes: Very low

Table 43. Seroconversion and seroprotection were clinically, but not statistically, LOWER in lymphoproliferative disease patients on rituximab. [28]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	No rituximab	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, rituximab vs no rituximab												
1	observational studies	serious[b]	not serious	serious[b]	serious[c]	none	2/14 (14.3%)	10/26 (38.5%)	**RR 0.37** (0.09 to 1.46)	**242 fewer per 1,000** (from 350 fewer to 177 more)	⊕◯◯◯ Very low	
Seroprotection, rituximab vs no rituximab												
1	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	3/14 (21.4%)	12/26 (46.2%)	**RR 0.46** (0.16 to 1.37)	**249 fewer per 1,000** (from 388 fewer to 171 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. No randomization

b. Non-RMD population

c. Small sample size and wide confidence intervals

Table 44. RA patients on rituximab had lower baseline GMT levels than healthy controls. Post-vaccination, RA pts on rituximab again had significantly LOWER GMT. [20]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
Pre-vaccine GMT - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious	none	23	29	-	MD **14.5 lower** (19.65 lower to 9.35 lower)	⊕◯◯◯ Very low	Favors healthy controls
Pre-vaccine GMT - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious	none	23	29	-	MD **12 lower** (13.36 lower to 10.64 lower)	⊕◯◯◯ Very low	Favors healthy controls
Pre-vaccine GMT - B												
1	observational studies	serious[a]	not serious	not serious	serious	none	23	29	-	MD **6.8 lower** (8.08 lower to 5.52 lower)	⊕◯◯◯ Very low	Favors healthy controls
Post-vaccine GMT - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	Healthy controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious	strong association	23	29	-	MD **30.1 lower** (31.4 lower to 28.8 lower)	⨁⨁◯◯ Low	Favors healthy controls

Post-vaccine GMT - H1N1

1	observational studies	serious[a]	not serious	not serious	serious	strong association	23	29	-	MD **55.1 lower** (56.46 lower to 53.74 lower)	⨁⨁◯◯ Low	Favors healthy controls

Post-vaccine GMT - B

1	observational studies	serious[a]	not serious	not serious	serious	strong association	23	29	-	MD **18.8 lower** (20.14 lower to 17.46 lower)	⨁⨁◯◯ Low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

Table 45. RA patients on rituximab had SIMILAR baseline GMT levels compared to RA pts on MTX. Post-vaccination, RA pts on rituximab had significantly LOWER GMT compared to RA pts on MTX. [20]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	RA-MTX	Relative (95% CI)	Absolute (95% CI)		
Pre-vaccine GMT - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious	none	23	20	-	MD **0.8 lower** (2.35 lower to 0.75 higher)	⊕◯◯◯ Very low	
Pre-vaccine GMT - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious	none	23	20	-	MD **0.4 higher** (0.97 lower to 1.77 higher)	⊕◯◯◯ Very low	
Pre-vaccine GMT - B												
1	observational studies	serious[a]	not serious	not serious	serious	none	23	20	-	MD **1.2 higher** (0 to 2.4 higher)	⊕◯◯◯ Very low	
Post-vaccine GMT - H3N2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-RTX	RA-MTX	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious	strong association	23	20	-	MD **19.8 lower** (21.12 lower to 18.48 lower)	⨁⨁◯◯ Low	Favors RA-MTX

Post-vaccine GMT - H1N1

1	observational studies	serious[a]	not serious	not serious	serious	strong association	23	20	-	MD **29.1 lower** (30.75 lower to 27.45 lower)	⨁⨁◯◯ Low	Favors RA-MTX

Post-vaccine GMT - B

1	observational studies	serious[a]	not serious	not serious	serious	none	23	20	-	MD **2.5 lower** (3.97 lower to 1.03 lower)	⨁◯◯◯ Very low	Favors RA-MTX

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

Table 46. Mixed RMD patients on rituximab had LOWER GMT responses but SIMILAR seroprotection and SIMILAR seroconversion to influenza vaccine as compared to healthy controls. [11]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
GMT, A/Cal H1N1 rituximab vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5	15	-	MD **182 lower** (285.83 lower to 78.17 lower)	⨁◯◯◯ Very low	Favors controls
GMT, A/Swi H3N2 rituximab vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5	15	-	MD **44.3 lower** (137.79 lower to 49.19 higher)	⨁◯◯◯ Very low	
GMT, B/Phu Yamagata rituximab vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5	15	-	MD **4.3 higher** (61.98 lower to 70.58 higher)	⨁◯◯◯ Very low	
Seroprotection, A/Cal H1N1 rituximab vs controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/5 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.77 to 1.30)	**0 fewer per 1,000** (from 230 fewer to 300 more)	⊕◯◯◯ Very low	

Seroprotection, A/Swi H3N2 rituximab vs controls

1	observational studies	serious[b]	not serious	not serious	serious[b]	none	5/5 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.77 to 1.30)	**0 fewer per 1,000** (from 230 fewer to 300 more)	⊕◯◯◯ Very low	

Seroprotection, B/Phu Yamagata rituximab vs controls

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/5 (100.0%)	13/13 (100.0%)	**RR 1.00** (0.77 to 1.30)	**0 fewer per 1,000** (from 230 fewer to 300 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
Seroconversion, A/Cal H1N1 rituximab vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	0/4 (0.0%)	3/9 (33.3%)	**RR 0.29** (0.02 to 4.52)	**237 fewer per 1,000** (from 327 fewer to 1,000 more)	⨁◯◯◯ Very low	
Seroconversion, A/Swi H3N2 rituximab vs controls												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	1/4 (25.0%)	6/9 (66.7%)	**RR 0.38** (0.06 to 2.18)	**413 fewer per 1,000** (from 627 fewer to 787 more)	⨁◯◯◯ Very low	
Seroconversion, B/Phu Yamagata rituximab vs controls												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Rituximab	controls	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	2/4 (50.0%)	2/9 (22.2%)	**RR 2.25** (0.47 to 10.78)	**278 more per 1,000** (from 118 fewer to 1,000 more)	⨁◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 47. RMD patients on rituximab had LOWER seroconversion rates in response to influenza vaccine as compared to healthy controls. Pre-vaccination antibody titers to influenza antigens were SIMILAR; post-vaccination titers were LOWER in the rituximab group. [27]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD-RTX	Healthy controls,	Relative (95% CI)	Absolute (95% CI)		
Seroconversion (1+/3 antigens)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD-RTX	Healthy controls,	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	2/12 (16.7%)	10/15 (66.7%)	**RR 0.25** (0.07 to 0.93)	**500 fewer per 1,000** (from 620 fewer to 47 fewer)	⊕◯◯◯ Very low	Favors healthy controls

Mean pre-vaccine Ab titer - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **38.33 lower** (80.86 lower to 4.2 higher)	⊕◯◯◯ Very low	

Mean pre-vaccine Ab titer - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **13.33 lower** (31.6 lower to 4.93 higher)	⊕◯◯◯ Very low	

Mean pre-vaccine Ab titer - B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD-RTX	Healthy controls,	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious	none	12	15	-	MD **55 lower** (97.88 lower to 12.12 lower)	⨁◯◯◯ Very low	Favors healthy controls

Mean post-vaccine Ab titer - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **60 lower** (115.5 lower to 4.5 lower)	⨁◯◯◯ Very low	Favors healthy controls

Mean post-vaccine Ab titer - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **103.33 lower** (191.77 lower to 14.89 lower)	⨁◯◯◯ Very low	Favors healthy controls

Mean post-vaccine Ab titer - B

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RMD-RTX	Healthy controls,	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **178.33 lower** (277.95 lower to 78.71 lower)	⊕◯◯◯ Very low	Favors healthy controls

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

b. Small sample size

JAKi

Summary There was only one study which directly examined the effect of tofacitinib on response to influenza vaccine in RA patients [21]. In this study, patients were randomized to either tofacitinib 10 mg BID or placebo, and then vaccinated 4 weeks later. Randomization was stratified according to background methotrexate use. While response to vaccine, as defined by increase in influenza vaccine titers, was similar between tofacitinib and placebo, rates of seroprotection overall was lower in patients who received tofacitinib. The combination tofactinib+MTX group had the lowest seroprotection rate (64.9%) when compared to the MTX monotherapy (92.7%), tofacitinib monotherapy (91.1%), or no DMARD (90.7%). Taken together, the study suggests a modest effect of tofacitinib on protective response to influenza vaccination.

Overall quality of evidence across all critical outcomes: Moderate

Table 48. RA patients on tofacitinib monotherapy had SIMILAR response to influenza vaccine as compared to RA patients on no DMARDs. [21]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA monotherapy	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	29/45 (64.4%)	29/43 (67.4%)	**RR 0.96** (0.71 to 1.29)	**27 fewer per 1,000** (from 196 fewer to 196 more)	⊕⊕⊕◯ Moderate	
Baseline seroprotection - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	10/45 (22.2%)	13/43 (30.2%)	**RR 0.74** (0.36 to 1.50)	**79 fewer per 1,000** (from 193 fewer to 151 more)	⊕⊕⊕◯ Moderate	
Seroprotection - Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA monotherapy	No DMARDs	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	41/45 (91.1%)	39/43 (90.7%)	**RR 1.00** (0.88 to 1.15)	**0 fewer per 1,000** (from 109 fewer to 136 more)	⨁⨁⨁◯ Moderate	No difference

Seroconversion - Influenza

1	randomised trials	not serious	not serious	not serious	serious[a]	none	31/35 (88.6%)	26/30 (86.7%)	**RR 1.02** (0.85 to 1.23)	**17 more per 1,000** (from 130 fewer to 199 more)	⨁⨁⨁◯ Moderate	No difference

CI: confidence interval; **RR:** risk ratio

a. Small sample size

Table 49. RA patients on tofacitinib monotherapy had SIMILAR response to influenza vaccine as compared to RA patients on MTX monotherapy. [21]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA monotherapy	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	29/45 (64.4%)	32/55 (58.2%)	**RR 1.11** (0.81 to 1.51)	**64 more per 1,000** (from 111 fewer to 297 more)	⨁⨁⨁◯ Moderate	
Baseline seroprotection - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	10/45 (22.2%)	19/55 (34.5%)	**RR 0.64** (0.33 to 1.24)	**124 fewer per 1,000** (from 231 fewer to 83 more)	⨁⨁⨁◯ Moderate	
Seroprotection - Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA monotherapy	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	41/45 (91.1%)	51/55 (92.7%)	**RR 0.98** (0.87 to 1.11)	**19 fewer per 1,000** (from 121 fewer to 102 more)	⨁⨁⨁◯ Moderate	No difference

Seroconversion - Influenza

1	randomised trials	not serious	not serious	not serious	serious[a]	none	31/35 (88.6%)	32/36 (88.9%)	**RR 1.00** (0.84 to 1.18)	**0 fewer per 1,000** (from 142 fewer to 160 more)	⨁⨁⨁◯ Moderate	No difference

CI: confidence interval; **RR:** risk ratio

a. Small sample size

Table 50. RA patients on tofacitinib+MTX combination therapy had LOWER response to influenza vaccine as compared to RA patients on MTX monotherapy [21]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	29/57 (50.9%)	32/55 (58.2%)	**RR 0.87** (0.62 to 1.23)	**76 fewer per 1,000** (from 221 fewer to 134 more)	⊕⊕⊕◯ Moderate	
Baseline seroprotection - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	10/57 (17.5%)	19/55 (34.5%)	**RR 0.51** (0.26 to 0.99)	**169 fewer per 1,000** (from 256 fewer to 3 fewer)	⊕⊕⊕◯ Moderate	Favors MTX monotherapy
Seroprotection - Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA+MTX	MTX monotherapy	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	37/57 (64.9%)	51/55 (92.7%)	**RR 0.70** (0.57 to 0.86)	**278 fewer per 1,000** (from 399 fewer to 130 fewer)	⊕⊕⊕◯ Moderate	Favors MTX monotherapy

Seroconversion - Influenza

1	randomised trials	not serious	not serious	not serious	serious[a]	none	27/47 (57.4%)	32/36 (88.9%)	**RR 0.65** (0.49 to 0.85)	**311 fewer per 1,000** (from 453 fewer to 133 fewer)	⊕⊕⊕◯ Moderate	Favors MTX monotherapy

CI: confidence interval; **RR:** risk ratio

a. Small sample size

Table 51. RA patients on tofacitinib monotherapy had LOWER response to influenza vaccine as compared to RA patients not on tofacitinib. [21]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA	PLACEBO (+/- background MTX)	Relative (95% CI)	Absolute (95% CI)		
Vaccine response - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/102 (56.9%)	61/98 (62.2%)	**RR 0.91** (0.73 to 1.15)	**56 fewer per 1,000** (from 168 fewer to 93 more)	⊕⊕⊕◯ Moderate	
Baseline seroprotection - Influenza												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	20/102 (19.6%)	32/98 (32.7%)	**RR 0.60** (0.37 to 0.98)	**131 fewer per 1,000** (from 206 fewer to 7 fewer)	⊕⊕⊕◯ Moderate	Favors placebo
Seroprotection - Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TOFA	PLACEBO (+/- background MTX)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	78/102 (76.5%)	90/98 (91.8%)	**RR 0.83** (0.74 to 0.94)	**156 fewer per 1,000** (from 239 fewer to 55 fewer)	⨁⨁⨁◯ Moderate	Favors placebo

Seroconversion - Influenza

1	randomised trials	not serious	not serious	not serious	serious[a]	none	58/82 (70.7%)	58/66 (87.9%)	**RR 0.80** (0.68 to 0.95)	**176 fewer per 1,000** (from 281 fewer to 44 fewer)	⨁⨁⨁◯ Moderate	Favors placebo

CI: confidence interval; **RR:** risk ratio

a. Small sample size

Glucocorticoids

Summary: There were few studies which directly addressed the effect of glucocorticoids on response to influenza vaccine in RMD populations. All were observational studies, with only one study having a sample size >200 [4, 15, 23, 26, 33]. This larger study demonstrated a slightly lower seroprotection response in patients on glucocorticoids [4]. The other smaller studies did not show significant differences in vaccine response related to glucocorticoid exposure, although one study of SLE patients reported lower seroprotection rates in patients receiving prednisone >10 mg/day [33].

Overall quality of evidence across all critical outcomes: Very low

Table 52. RA patients on steroid had SIMILAR seroprotection response to influenza compared to RA patients not on steroid. [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	RA-no steroids	Relative (95% CI)	Absolute (95% CI)		
Seroprotection												
1	observational studies	serious[a]	not serious	not serious	not serious	none	146/247 (59.1%)	56/93 (60.2%)	**RR 0.98** (0.81 to 1.19)	**12 fewer per 1,000** (from 114 fewer to 114 more)	⊕◯◯◯ Very low	No difference
Factor increase GMT												
1	observational studies	serious[a]	not serious	not serious	not serious	none	247	93	-	MD **1.1 lower** (3.22 lower to 1.02 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RA-steroids	RA-no steroids	Relative (95% CI)	Absolute (95% CI)		
Seroconversion												
1	observational studies	serious[a]	not serious	not serious	not serious	none	122/247 (49.4%)	51/93 (54.8%)	**RR 0.90** (0.72 to 1.13)	**55 fewer per 1,000** (from 154 fewer to 71 more)	⊕◯◯◯ Very low	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

a. Not randomized

Table 53. SLE patients on prednisone had SIMILAR seroconversion and seroprotection responses to influenza vaccine to SLE patients not on prednisone. ("vaccine efficacy" = seroconversion and/or seroprotection) [26]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⊕◯◯◯ Very low	

Vaccine efficacy - H3N2

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	6/14 (42.9%)	7/12 (58.3%)	**RR 0.73** (0.34 to 1.59)	**158 fewer per 1,000** (from 385 fewer to 344 more)	⊕◯◯◯ Very low	

Vaccine efficacy - B-influenza

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	5/14 (35.7%)	7/12 (58.3%)	**RR 0.61** (0.26 to 1.43)	**228 fewer per 1,000** (from 432 fewer to 251 more)	⊕◯◯◯ Very low	

Seroprotection - H1N1

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	13/14 (92.9%)	11/12 (91.7%)	**RR 1.01** (0.81 to 1.27)	**9 more per 1,000** (from 174 fewer to 248 more)	⊕◯◯◯ Very low	No difference

Seroprotection - H3N2

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE patients: Prednisone	No medications	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12/14 (85.7%)	12/12 (100.0%)	**RR 0.87** (0.67 to 1.11)	**130 fewer per 1,000** (from 330 fewer to 110 more)	⊕◯◯◯ Very low	

Seroprotection - B-influenza

1	observational studies	serious[a]	not serious	not serious	serious[b]	none	8/14 (57.1%)	11/12 (91.7%)	**RR 0.62** (0.38 to 1.01)	**348 fewer per 1,000** (from 568 fewer to 9 more)	⊕◯◯◯ Very low	

CI: confidence interval; **RR:** risk ratio

a. Not randomized

b. Small sample size

Table 54. SLE patients on glucocorticoids had SIMILAR post-vaccine antibody titers to 2 out of 3 influenza vaccine antigens as compared to SLE patients not on glucocorticoids. [23]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLE on GCs	SLE not on GCs	Relative (95% CI)	Absolute (95% CI)		
Post-vaccine antibody titer - H1N1												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	24	-	MD **320 lower** (895.03 lower to 255.03 higher)	⊕◯◯◯ Very low	
Post-vaccine antibody titer - H3N2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	24	-	MD **182.6 lower** (765.01 lower to 399.81 higher)	⊕◯◯◯ Very low	
Post-vaccine antibody titer - B-Malay												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	23	24	-	MD **536.9 lower** (892.88 lower to 180.92 lower)	⊕◯◯◯ Very low	Favors SLE not on GCs

CI: confidence interval; **MD:** mean difference

a. Not randomized

b. Small sample size

Table 55. In SJIA patients on tocilizumab, patients with prednisolone doses <0.2 mg/kg/d had HIGHER GMT response to influenza vaccine than patients with prednisolone doses >0.2 mg/kgd. [15]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisolone <0.2 mg/kg/d	Prednisolone >0.2 mg/kg/d	Relative (95% CI)	Absolute (95% CI)		
GMT, A/H1N1 Pred <0.2 vs Pred >0.2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **24.7 higher** (21.43 higher to 27.97 higher)	⨁◯◯◯ Very low	Favors lower dose prednisolone
GMT, A/H3N2 Pred <0.2 vs Pred >0.2												
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **223.2 higher** (219.83 higher to 226.57 higher)	⨁◯◯◯ Very low	Favors lower dose prednisolone
GMT, B Pred <0.2 vs Pred >0.2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prednisolone <0.2 mg/kg/d	Prednisolone >0.2 mg/kg/d	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	12	15	-	MD **7 higher** (4.88 higher to 9.12 higher)	⨁◯◯◯ Very low	Favors lower dose prednisolone

CI: confidence interval; **MD:** mean difference

a. Not randomized

b. Small sample size

Abatacept

Summary: One observational study by Alten [24] (see Table 55) included 191 RA patients receiving fixed-dose abatacept (125 mg/week) with background DMARDs who were vaccinated with the 2011-2012 trivalent seasonal influenza vaccine. Over 82% of patients achieved a protective antibody level (titer ≥1:40 to >2 of 3 antigens).

Overall quality of evidence across all critical outcomes: Very low

Table 56. Additional RCT and observational study data not entered into RevMan.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
307, Laestadius, 2019 [34]	Cohort study	3 and 10 months	78 children with rheumatic diseases; 22 healthy controls	Seasonal inactivated trivalent influenza vaccine given to 14 pts on MTX only, 36 pts on TNFi +/- MTX, and 11 pts on IL-1/IL-6 inhibitors; there	At 3 mo, no sig difference in vaccine response as measured by GMT between any of the groups. Specific values were not reported for either GMT or seroprotection rates (shown in graphical form only).

				were 17 RD pts not on any therapy	"A few children" on TNFi remained seronegative. No difference in GMT (peds RD vs healthy controls)
405 Alten 2016 [24]	Observational	28 days	125 RA patients (77 from ACQUIRE and 48 from ATTUNE) received PPSV23. mean age 45.7 (13.8), 85% female. 191 RA patients from the ACQUIRE study received influenza vaccine; mean age 44.9 (12.6), 90% female.	PPSV23 and the 2011–2012 trivalent seasonal influenza vaccine; All patients received fixed-dose abatacept (125 mg/week) and background DMARDs	Patients achieving protective antibody levels (antibody titer ≥1.6 µg/mL for pneumococcal antigens and ≥1:40 for influenza antigens): Pneumococcal (≥3 of 5 antigens): 94/112 (83.9%, 95% CI: 77.1 to 90.7) Influenza (≥2 of 3 antigens): 151/184 (82.1%, 95% CI: 76.5 to 87.6) Most RA patients receiving abatacept achieved a protective response.
489 Wiesik-Szewczyk 2010 [35]	Case control	12 weeks	62 SLE on medications vs 47 healthy control	Inactivated Influenza vaccine 15ug HA each of A/H1N1, A/H3N2, and B	GMT at 4 weeks (SLE, controls) H1N1: 39.06, 104.32; p<0.0011 H3N2: 42.97, 91.36; p=0.001 Type B: 50.80, 81.19; p=0.05 GMT at 12 weeks (SLE, controls) H1N1: 24.21, 69.03; p<0.001 H3N2: 25.71, 60.45; p=0.0001 Type B: 28.28, 52.16; p=0.0008 Mean fold increase at 4 weeks (SLE, controls) H1N1: 6.23, 16.48; p=0.000002 H3N2: 6.61, 14.23; p<0.0001 Type B: 7.02, 11.9; p=0.0002 Mean fold increase at 12 weeks (SLE, controls) H1N1: 3.86, 10.91; p=0.000005 H3N2: 3.96, 9.42; p=0.0001 Type B: 3.91, 7.65; p=0.000086 SLE pts had lower responses than control
1177 Arad 2011 [25]	Prospective cohort study	Follow-up to 4-6 weeks post-vaccine	29 RA patients on RTX (Mean age 61.8 years, 79.2% female, median RA duration 9.5 years, mean DAS28 4.5)	All participants received one dose of trivalent seasonal influenza vaccine (inactivated, standard dose).	Percentage of influenza-specific CD4+ cells: <u>Healthy controls:</u> Pre vaccine: Median 0.6% Post-vaccine: Median 0.3%

			17 RA patients on csDMARDs (Mean age 61.2 yrs, 70.6% female, median RA duration 9 yrs, mean DAS28 4.1) 16 healthy individuals (Mean age 44.5 years, 87.5% female). Rate of influenza vaccination in previous year significantly lower in HC group (3/16; 18.6%) vs. csDMARD group (8/17; 47.1%) and RTX group (15/29; 51.7%)	RTX group (n=29): Each patient received 1000 mg IV infusion x 2 doses; 41% on concomitant MTX (mean dose 14.5 mg weekly); 34% on prednisone (mean dose 13.2 mg daily). 16/29 vaccinated within 5 months of last RTX infusion, 13/29 vaccinated >5 months after last RTX. 25/29 (86.2%) of RTX patients had <1% CD19+ B cells at time of vaccination. In remaining 4 patients, interval from last RTX to vaccine ranged from 5.5-9 months post-RTX. csDMARD group (n=17): 69% MTX (mean dose 15 mg weekly); 77% prednisone (mean dose 8.2 mg daily). Significantly higher rate of prednisone use in csDMARD group vs. RTX group. Healthy individuals (n=16): No immunosuppressive drugs.	<u>RA-csDMARD:</u> Pre vaccine: Median 0.1% Post-vaccine: Median 0.2% <u>RA-RTX:</u> Pre vaccine: Median 0.1% Post-vaccine: Median 0.3% No significant differences between groups. No correlation of cellular response with age, prior influenza vaccine, use or dose of MTX or prednisone, or baseline DAS28. Geometric mean titers (GMT): No significant differences between groups in pre-vaccine GMTs for the 3 antigens Significant increase in GMT between pre- and post-vaccine for all antigens in healthy control & RA-csDMARD groups: <u>Healthy controls:</u> H1N1 p=0.02, H3N2 p<0.01, B p=0.04 <u>RA-csDMARD group:</u> H1N1 p<0.01, H3N2 p<0.01, B p<0.01 In RA-RTX group, significant increase in GMT for B antigen only. <u>RA-RTX group:</u> H1N1 p=0.11, H3N2 p=0.22, B p<0.01 Average percentage of vaccine responders across three antigens: Healthy controls: 41.7% RA-csDMARDs: 68.4% RA-RTX: 26.4% RA patients on conventional DMARDs had similar response as compared to controls. RA patients on ritux had increase in GMT for B antigen only.

1173, Holvast, 2010 [36]	Cohort study	4 wks	25 GPA patients; 25 healthy controls	Seasonal inactivated trivalent influenza vaccine given to all	Specific values not reported – results shown in graphical form only At 4 wks, GPA and HC patients showed similar levels of: - Activated T cells (both CD4+ and CD8+ were measured) - Influenza-specific IFN-g release (as measured by ELISPOT) - Total IFN-g production in response to viral stimulation in vitro GPA patients on immunosuppressive drugs (n=11, drugs not specified) were not different from GPA patients not on immunosuppression (n=13) GPA pts had similar responses to HC, regardless of immunosuppressive drug
2488, Gelinck, 2008 [1]	Cohort study	4 wks	64 pts on TNFi; 19 matched controls; 48 patients not on TNFi, with 18 matched controls. Both RMD and IBD patients were included	Seasonal inactivated trivalent influenza vaccine given to all	Specific values not reported – results shown in graphical form only At 4 wks, TNFi group had statistically lower GMTs for A/H3N2 and Flu B, but not statistically different for A/H1N1. Seroconversion rates (4-fold increase in titer) was lower for TNFi group for all 3 antigens. Seroprotection rates were similar in all groups, and generally excellent (>80%). Pts on TNFi had lower GMTs and seroconversion rates but similar seroprotection rates compared w/ matched controls not on TNFi.
2516 Elkayam 2010 [2]	Prospective, single-center, cohort study	4-6 weeks post-vaccine	43 patients with RA, 18 patients with AS, and 17 healthy controls matched for age and gender to the RA group (mean age 55 years, 76.5% female).	All participants received one standard dose of trivalent inactivated seasonal influenza vaccine (H1N1/H3N2/B). RA & AS patients treated with infliximab were	Significant increases in GMT titers for all 3 antigens were observed in all groups (IFX-T1, IFX-T2, RA controls, healthy controls) at 4-6 weeks post-vaccine compared to pre-vaccine. Proportion of participants with humoral response to each of the 3 influenza antigens was similar in IFX-T1, IFX-T2, RA controls, and healthy controls.

			20/43 RA patients (mean age 64 years, mean RA duration 22 years, 75% female) and all 18 AS patients (mean age 47 years, mean RA duration 16 years, 27.8% female) treated with infliximab 3 mg/kg IV q6-8 weeks for >6 months. 23 RA "control" patients were on csDMARDs (mean age 66 years, mean RA duration 17 years, 73.9% female). All patients on stable drug treatment for 3+ months pre-vaccine.	randomized into two groups: 22 patients vaccinated on the day of IFX (IFX-T1) versus 16 patients vaccinated 3 weeks after infliximab infusion (IFX-T2). RA+Infliximab (n=20): 17/20 (85%) MTX, mean dose 11.8mg weekly; 12/20 (60%) prednisone, mean dose 5.8mg daily; 5/20 (25%) on HCQ. AS+Infliximab (n=18): 8/18 (44%) MTX, mean dose 11.2mg weekly; 3/18 (16%) prednisone, mean dose 10 mg daily, 1/18 (5%) on SSZ. RA controls (n=23): 19/23 (82%) MTX, mean dose 16mg weekly; 8/23 (35%) prednisone, mean dose 5.2mg daily; 6/23 (26%) on HCQ, 2/23 (8%) on SSZ.	Predictors of response: No association with humoral response for the following predictor variables: age, sex, RA duration, SJC, TJC, ESR, CRP, use or dose of prednisone, use or dose of MTX. RA and AS patients on TNFi had similar responses compared to RA pts on conventional DMARDs.
2526 Park 2017 [18]	Prospective single-center randomized single-blind parallel-group intervention study	20 weeks (4 weeks pre-vaccine, 16 weeks postvaccine)	277 patients with RA aged 18 years or older and on a stable dose of MTX for 6 weeks or longer	All participants received one dose of inactivated seasonal trivalent influenza vaccine (H1N1/H3N2/B-Yamagata). Randomized 1:1:1:1 to: Group 1 (n=69) continue MTX; Group 2 (n=68) suspend MTX for 4 weeks before vaccination; Group 3 (n=71) suspend MTX for 2 weeks before & 2 weeks after vaccination; Group 4 (n=69) suspend MTX for 4 weeks after vaccination.	Primary analysis performed on per-protocol population (n=199): Group 1 (n=54), Group 2 (n=44), Group 3 (n=49), Group 4 (n=52). Group 1 (n=54) RA patients receiving influenza vaccine while continuing MTX. 46.3% on GC (mean dose 2.2 mg daily), mean MTX dose (12.7 mg weekly), 9.3% SZZ, 18.5% HCQ, 25.9% LEF, 9.3% TNFi. Vaccine response at 4 weeks post-vaccine (4-fold or greater increase in HI antibody titer): 1+ antigens: 42/54 (77.8%) 2+ antigens: 29/54 (53.7%) 3 antigens: 17/54 (31.5%)

					H1N1: 28/54 (51.9%) H3N2: 39/54 (72.2%) B-Yamagata: 21/54 (38.9%) Fold increase in GMT (mean, 95% CI): H1N1: 5.1 (3.4-7.8) H3N2: 5.9 (4.3-8.1) B- Yamagata: 2.9 (2.2-3.8) Seroconversion at 4 weeks post-vaccine: H1N1: 22/36 (61.1%) H3N2: 15/15 (100%) B-Yamagata: 18/33 (54.5%) Group 3 achieved higher satisfactory vaccine response against all three antigens than group 1 (51.0% vs 31.5%, p=0.044).
2545 Winthrop 2016 [21]	Randomized, double-blind, placebo-controlled, phase II study	64 days (35 days post-vaccination)	200 tofacitinib-naive adult patients with RA Median age 53 years, 77% female. Patients excluded if previous influenza vaccine within 6 months or previous pneumococcal vaccine within last 5 years.	Participants randomized 1:1 to receive tofacitinib 10 mg BID (n=102) vs. placebo (n=98), stratified by background MTX use (defined as continuous use >4 months with stable dose of 10-25 mg weekly for 6+ weeks). Background MTX in 57/102 (55.9%) of TOFA group, 55/98 (56.1%) placebo group. Prednisone use (<10 mg daily) in 38/102 (37.3%) and 31/98 (31.6%) of placebo group. No changes in MTX, prednisone dosing permitted during study. Four exposure groups: No DMARDs (n=43), MTX monotherapy (n=55),	GMFR - Fold increase in geometric mean titer (GMT) from pre- to 35 days post-vaccine For majority of pneumococcal serotypes, highest GMFR in No DMARD group, intermediate GMFR in MTX or TOFA monotherapy groups, and lowest GMFR in TOFA+MTX group. For influenza vaccination, lowest GMFR responses consistently observed for influenza B antigen, with similar GMFR across 4 groups. More robust GMFR responses to H1N1 and H3N2 antigens in all groups. Highest GMFR responses for H1N1 & H3N2 in No DMARD group; lower & similar responses in the MTX alone, TOFA alone, and TOFA+MTX groups. Highest responses in no DMARD group MTX / tofacitinib / tofa+MTX were all lower

				TOFA monotherapy (n=45), MTX+TOFA (n=57) All participants received one dose of PPSV-23 and one dose of 2011-2012 seasonal trivalent influenza vaccine (H1N1/H3N2/B-Brisbane) at 4 weeks after initiation of study treatment.	
2643, Muller, 2013 [29]	Prospective cohort study	4 weeks after 2nd vaccination	16 patients who were treated with rituximab and had received first dose of influenza vaccine.	2nd dose of 2009 H1N1 influenza vaccine (Pandemrix) given 4 wks after first dose.	Significant anti-HA titers seen after 1st vaccine in 6/16 patients; this increased to 7/16 after the 2nd vaccine. In patients with low B cell numbers, the T cell response (as measured by virus-specific, IFN-g-producing T cell numbers) increased after booster vaccine. In patients with normal B cells, booster vaccine had no effect. Fewer than half of pts on rituximab had response to vaccine 2nd dose of influenza vaccine did not significantly improve response in pts on rituximab.
3341 Trollmo 1994 [37]	Open labeled, controlled interventional study	7-10 days	Experiment 1: (oral) 25 patients with RA, 9 patients with AS, 19 health controls Experiment 2: (IV): 14 patients with RA, 9 patients with AS, 10 health controls	Oral influenza (Experiment 1) Parenteral influenza vaccine (Experiment 2)	<u>Oral Influenza Vaccine:</u> 1. RA, AS and HC groups all had similar patterns (shown only visually): No influenza-specific SFCs (spot forming cells) at day 0, a few at day 4, peak response at day 7, and decreasing number of SFCs at day 10 . 2. Immune response = >5 antigen specific SFC/16 PBMC detected at 7 days: see RevMan file. - RA: 15/25 (60%) - AS: 7/9 (78%) - HC: 14/19 (74%) 3. “No difference in B cell response in patients with RA treated with cytotoxic drugs [MTX, cyclosporin, podophyllotoxinum] vs. other

					pharmacotherapies" (steroids, sulphasalzin, auranofin, natrium-aurothiomalas) (data not shown). <u>Parenteral Influenza Vaccine:</u> 1. 7 days after vaccine, SFC were seen in: - 13 of 14 patients with RA - 9 of 9 patients with AS - 10 of 10 HC 2. number of SFCs was lower in RA vs controls ($p<0.01$) and patients with AS ($p<0.05$). Similar but not stat signnifcant trend was seen for IgA-specific B cell responses. IgM responses similar in all groups. 3. No differences in antigen specific B cell response in aptients with RA treated with cytotoxic drugs [MTX, cyclosporin, podophyllotoxinum] vs. other pharmacotherapies" (steroids, sulphasalzin, auranofin, natrium-aurothiomalas) (data not shown). T and B cell responses to influenza vaccine in RA, AS, HC groups all similar; no apparent differences dependent on medications.
3531, Campos, 2013 [38]	Prospective cohort study	21 days after vaccination	118 juvenile SLE 102 controls 92 patients (78%) were on antimalarials, 83 (70.3%) were on prednisone with a mean SD dosage of 18.8 17 mg/day, and 72 (61.0%) were taking immunosuppressive drugs (azathioprine [37.3%], mycophenolate mofetil [12.7%], and methotrexate [11.9%].	1 dose of 2009 H1N1 vaccine	Significantly lower seroprotection, seroconversion rates and lower GMT in SLE patients vs controls. Comparison of pts who seroconverted vs. those who did not seroconvert did not reveal any statistically significant differences according to demographics, steroid dose, or immunosuppressive medications. Data was not broken down the opposite way (i.e. seroconversion rate among those on azathioprine)

					Patients who did not seroconvert were more likely to have high disease activity though. SLE pts have lower vaccine responses than healthy controls.
3721, Long, 2012 [39]	Prospective cohort study	4-16 wks after vaccination	106 High risk and healthy pediatric pts age 6 mo – 22 years. Of these, 20 with SLE, 24 with solid organ transplant (SOT).	1 dose of seasonal inactivated trivalent influenza vaccine given to all	Of SLE pts, 7 on MMF, 3 on MTX, 1 on cyclophosphamide, 2 on solumedrol. Of SOT pts, 18 on MMF, 2 were treated for rejection, 2 rec'd solumedrol/IVIG/plasmapheresis. Specific values not reported – results shown in graphical form only SLE and SOT had lowest rates of seroprotection at both enrollment (before vaccination) and at f/u. SLE pts had significantly lower baseline and f/u T cell responses as measured by IFN-g ELISPOT. In healthy children, pts who had received influenza vaccine in prior 2 seasons had higher rates of seroprotection following this vaccine. However, this trend was not seen in SLE patients. SLE pts have lower vaccine responses than healthy controls.
3731 van Assen 2010 [20]	Prospective cohort study	28 days post-vaccine	23 adult patients with RA on RTX (Mean age 55.5 years, 70% female, 12/23 (52%) influenza vaccine in preceding year, median RA duration 13.8 years) 20 patients with RA on MTX (Mean age 57.1, 55% female, 10/20 (50%) influenza vaccine in preceding year, median RA duration 8.7 years) 29 healthy volunteers (Mean age 46.5 years, 79% female,	All participants received one standard dose of trivalent inactivated seasonal influenza vaccination. RA-RTX group (n=23): RTX 1000 mg IV x 2 doses, 2 weeks apart, except 375 mg/m2 IV wekly x 4 doses. First RTX cycle in 11/23 (48%), second cycle in 5/23 (22%). Median MTX dose 17.5 mg weekly, median prednisone dose 8.75mg OD	Fold increase in titers at 28 days post-vaccine compared to baseline – median (range): <u>Healthy controls (n=29):</u> H3N2: 1.4 (-1.4 to 16) H1N1: 2 (-1.4 to 128) B strain: 1.4 (-1.4 to 32) <u>RA-MTX (n=20):</u> H3N2: 2 (1 to 11.3) H1N1: 4 (1 to 16) B strain: 1 (-1.4 to 16) <u>RA-RTX (n=23):</u> H3N2: 1 (-2 to 2)

			21/29 (72%) influenza vaccine in preceding year) Baseline CD19+ cells significantly higher in healthy controls & RA-MTX group compared to RA-RTX group (p<0.001)	Vaccination 4-8 wks post-RTX in 11 patients (Early) vs. 6-10 months post-RTX in 12 patients (Late). Baseline CD19+ B cell numbers similar in both subgroups. RA-MTX (n=20): Median MTX dose 16.3 mg weekly, one patient on SSZ, one patient on LEF, no corticosteroids	H1N1: 1 (-2 to 8) B strain: 1 (-2 to 5.7) Compared to RA-RTX group, significantly higher fold increase in Ab titers in HC group for H1N1 and B strain; in RA-MTX group for H3N2 & H1N1 (all $p < 0.05$). Seroconversion: (Fourfold or greater increase from baseline in Ab titer to at least 1:40 post-vaccine): Higher rate of seroconversion in RA-MTX group vs. RA-RTX group for H3N2 (p=0.011) & H1N1 (p=0.020). Seroconversion to any of the 3 influenza strains occurred in only 3 RA-RTX patients, all in the Late vaccine subgroup. Directly comparing B cell numbers in Early vs. Late subgroups at Day 28 post-vaccine: Significantly more CD19+ B cells present in patients in Late RTX subgroup (p=0.004). Higher fold increase in Ab titers in HC group for H1N1 and B strain; in RA on methotrexate group for H3N2 & H1N1; all higher than RA patients on rituximab Higher rate of seroconversion in RA-MTX group vs. RA-RTX group for H3N2 & H1N1.
3893, Tsuru, 2014 [14]	Prospective cohort study	3 months	38 pts on tocilizumab, 15 pts on TNFi+MTX, 24 pts on DMARDs (MTX, SSZ, or cyclosporine)	Seasonal trivalent inactivated influenza vaccine (A(New Caledonia (NC):H1N1), A(Hiroshima (HIR):H3N2) and B(Malaysia (MAL))	Seroprotection and Seroconversion tabled in RevMan. GMT was presented in graphical format. Titers were checked at baseline, 1, 2, and 3 months after vaccination. There was no significant difference between tocilizumab, TNFi, and DMARD groups.
4080 Kostianovsky 2012 [40]	Prospective cohort study	4.5 months	199 mixed adult RMD patients Cohort included systemic vasculitis, scleroderma, and lupus patients	Seasonal flu and H1N1 flu vaccine	Tabled in RevMan but not broken out by medications.

			Non-IS: non-immunosuppressed (no treatment or <10 mg corticosteroids/day); IS: immunosuppressed (on =/>10 mg corticosteroids/day and/or immunosuppressants); bio: biotherapies (RTX, ADA, ETN, IFX)		For seasonal flu, no significant differences in seroprotection or seroconversion between non-IS, IS, or bio groups. For H1N1, the non-IS group had higher seroprotection rates than the bio group, but otherwise no significant differences seen. Mixed RMD cohort – similar seroprotection and seroconversion rates between immunosuppressed, non-immunosuppressed, and biological therapies groups
4082, Saad, 2011 [41]	Cohort study	21 days post vaccination	Adults w RMD n = 1668, healthy controls n = 234; SLE (n=572) RA (n=343) AS (n=152) SSc (n=127) PsA (n=101) BD (n=85), MCTD (n=69) PAPS (n=54) DM (n=45) pSS (n=36) TA (n=30) PM (n=28) WG (n=26)	single IM dose (0.5 ml) H1N1 A/California/7/2009-like virus (A/California/7/2009/Butantan Institute/Sanofi Pasteur)	Factor increase in GMT was significantly lower with RMD population vs. controls (8.9, 95% CI: 8.3 to 9.6 RD population vs. 13.2, 95% CI: 11.1 to 15.8 controls; p<0.0001).
4114 deBruyn 2016 [42]	Parallel group, prospective, randomized, open-label study	3-5 weeks post-vaccine	132 patients with IBD on maintenance infliximab therapy and between 9-60 years of age. 51.8% male, 16% pediatric, 84% CD, 70.8% inactive disease.	All participants received one standard dose of the seasonal 2012/2013 trivalent influenza vaccine (H1N1/H3N2/Influenza B) Participants randomized 1:1 to either receive vaccine at Time 0 (Day 0-4 after IFX infusion; n=69) vs. Time 1 (Day 21-28 after IFX infusion; n=68).	Some analyses excluded patients missing baseline titers (n=2 in Time 0 group; n=8 in Time 1 group), missing FU titers (n=2 in Time 0 group) 137 IBD patients receiving influenza vaccine while on maintenance IFX. Seroprotection at 3-5 weeks post-vaccine: H1N1: 89/135 (65.9%) H3N2: 62/135 (45.9%) B-Influenza: 100/135 (73.0%) Immunologic response (3-5 weeks post-vaccine) H1N1: 40/125 (32%)

				Baseline characteristics similar between groups: duration of IFX use (median 1.4 vs. 2.0 years), IFX dose (median 5.5 vs. 5.6 mg/kg), IFX frequency (median 8 weeks in both groups), and concomitant immunomodulator (MTX or AZA) use (50.7% vs. 48.5%).	H3N2: 32/125 (25.6%) B-Influenza: 46/125 (36.8%) IBD patients on maintenance infliximab – relatively low responses to vaccine but no comparative data.
4115, Ogimi, 2011 [43]	Prospective cohort study	2-4 weeks after 2nd dose	49 children with pediatric rheumatic disease, 36 controls. Most PRD patients were on prednisolone at varying doses, usually <0.2 mg/kg.	Influenza HA vaccine, not otherwise specified. 2 doses given, 1-4 weeks apart	GMT, seroconversion for peds RD vs control is tabled in RevMan. Not broken down by medications. 31 peds RD patients on immunosuppression were compared to controls – no difference in seroconversion rate seen (p>0.26). Peds RD patients on immunosuppression had similar responses to healthy controls.
4124, Lakota, 2019 [44]	Prospective cohort study	>6 months post vaccination	137 patients (109 RA, 10 PsA, 15 AS, 1 MCTD, 1 JRA, 1 Still's) and 54 healthy controls. 72 patients who served as unvaccinated controls.	137 pts and 54 HC rec'd seasonal trivalent influenza vaccine (A/Brisbane/59/2007 (H1N1), A/Brisbane/ 10//2007 (H3N2), B/Brisbane/60/2008 (B)). Of these, 93 pts and 15 HC rec'd pandemic flu vaccine (A/California/7/2009 (H1N1pdm)) 3-5 wks later. Of these, 63 pts rec'd 2nd dose of pandemic flu vaccine another 3-5 wks later.	See RevMan for GMT, seroresponse, seroconversion, and seroprotection for seasonal flu vaccine comparing RD patients to healthy controls. "Patients used methotrexate, sulfasalazine, leflunomide, chloroquine, adalimumab, etanercept, rituximab, tocilizumab, infliximab, and methyl- prednisolone and combinations of drugs for therapy." Poorest seroprotection (56%) in patients having rituximab therapy, while methotrexate, adalimumab, etanercept, and tocilizumab treated patients were seroprotected in 86–91% and vaccinated controls 92%. Only 2 of 9 pts who rec'd rituximab had seroconversion to at least 1 antigen.

					Drop of antibody titer over time was not typically related to any medication used as we observed loss of seroresponse titers for H1N1, H3N2 and B in patients treated with methotrexate in 78% (7/9), 88% (7/8) and 100% (2/2), with adalimumab 70% (12/17), 62% (5/8), and 82% (9/11) and with etanercept 40% (6/15), 43% (3/7), and 90% (9/10), respectively Variety of RD patients, on a variety of meds. Poorest seroprotection in pts on rituximab; most everyone else had good seroprotection.
4351 Gabay 2011 [45]	Prospective cohort study	3-4 weeks	82 with rheumatoid arthritis, 45 with spondylarthritis, 46 with other inflammatory rheumatic diseases and 138 control subjects	Controls received 1 dose of adjuvanted influenza A/09/H1N1 vaccine, and patients received 2 doses of the vaccine. Post-dose 1: 138 patients, 131 healthy controls Post-dose 2: 148 patients 138 on DMARDs (73 MTX, 41 SSZ or HCQ, 23 LEF, 28 AZA or CYC or MMF, 3 other) 22 on Rituximab 67 on oral steroids (46 on <10 mg/day, 21 on ≥10 mg/day)	<u>Post-dose 1, mixed RMD vs. healthy controls</u>: Significantly lower HIA-GMTs in mixed RMD vs patients (146 mixed RMD, 340 healthy controls; p<0.001). <u>Post-dose 2 mixed RMD vs post-dose 1 healthy controls</u>: Results indicated similar HIA-GMTs (287 mixed RMD vs. 340 healthy controls). Multivariate regression analysis indicated after 2 doses of H1N1 vaccine, use of TNFIs (-0.02. (SE 0.15); p=0.91) and some DMARDS (MTX, LEF, AZA, MMF, CYC) was significantly associated with lower antibody response. Use of HCQ and SSZ (0.11 (SE 0.14); p=0.45) was not significantly associated with lower antibody response. Mixed RMD pts with lower responses compared to HC with 1 dose of vaccine; similar responses with 2 doses of vaccine compared to HC. TNFi, MTX, leflunomide, azathioprine, MMC, cyclosporine associated with lower responses.
4354 Park 2018 [19]	Prospective multicenter randomized investigator-blind, parallel-group	4 weeks post-vaccine for serology; 1-year FU post-vaccine for	320 patients with RA aged 19 years or older and on the same dose of MTX for 6 weeks or longer	All participants received one standard dose of the 2016-2017 seasonal quadrivalent inactivated influenza vaccine (H1N1/H3N2/B-Yamagata/B-Victoria).	Primary analysis performed on modified ITT population (n=316; Continue MTX n=156, Hold MTX for 2 weeks post-vaccination n=160). <u>Noncomparative data for PICO 3/7/8/15:</u>

	intervention study	influenza-like illness		Participants randomized 1:1 to continue MTX (n=159) vs. discontinue MTX for 2 weeks after vaccination (n=161).	156 RA patients receiving influenza vaccine while continuing MTX. Mean age 52.2 years, 82.7% female. 52.6% on GC (mean dose 1.8 mg daily), mean MTX dose (13.3 mg weekly), 5.1% SZZ, 22.4% HCQ, 21.2% LEF, 1.3% TAC, 7.1% TNFi, 2.6% TOCI, 0.6% abatacept, 0.6% RTX Vaccine response at 4 weeks post-vaccine (4-fold or greater increase in HI antibody titer): 1+ antigens: 118/156 (75.6%) 2+ antigens: 85/156 (54.5%) 3+ antigens: 57/156 (36.5%) 4 antigens: 34/156 (21.8%) Vaccine response at 4 weeks post-vaccine (4-fold or greater increase in HI antibody titer): H1N1: 79/156 (50.6%) H3N2: 85/156 (54.5%) B-Yamagata: 66/156 (42.3%) B-Victoria: 64/156 (41.0%) Fold increase in GMT (mean, 95% CI): H1N1: 4.6 (3.7-5.7) H3N2: 4.3 (3.5-5.3) B-Yamagata: 3.1 (2.6-3.8) B-Victoria: 2.9 (2.4-3.4) Seroprotection at 4 weeks post-vaccine: H1N1: 118/156 (75.6%) H3N2: 97/156 (62.2%) B-Yamagata: 116/156 (74.4%) B-Victoria: 95/156 (60.9%) Influenza-like illness at one year: 3/156 (1.9%) Overall good responses to vaccine in RA pts on MTX, but better response in patients with a 2-week MTX discontinuation after vaccination:

					MTX-hold group 75.5% vs MTX-continue group 54.5%, p <0.001; difference 21.0% (95%CI 10.6% to 31.7%).
4372 Bedognetti, 2011 [46]	Prospective cohort study	5 years	31 lymphoma patients treated with rituximab-based regimens, 34 healthy controls. Of the 31, 6 rec'd >6 doses of rituximab, and 25 rec'd ≤6 doses. Ritux was administered >1 year prior for 80% of patients. Almost all were also receiving concomitant chemotherapy	Seasonal trivalent virosomal flu vaccine. A/ Brisbane/10/2007 (H3N2), A/Brisbane/59/2007 (H1N1), and B/Florida/4/ 2006	Patients across the board had lower GMT, seroprotection, seroconversion rates as compared to controls. There were no statistically significant predictors of lower response to H1N1. However, for H3N2, history of fludarabine was a predictor of lower response. Dose of rituximab exposure was not a predictor. Patients had lower circulating CD27+ memory B cells, which correlated with vaccine response, and these remained low as long as 5 years post treatment. Lymphoma pts on rituximab – lower responses compared to controls.
4571 Moulis, 2017 [32]	Retrospective observational study	3 year study period; mean f/u was 18.5 months	1805 adults with new ITP	681 exposed to rituximab; 1035 to IVIG; 90 to other drugs 312 got pneumococcal vaccine; 375 got influenza vaccine	161 patients (9.1%) had serious infections. Multivariate model showed that HR for corticosteroids was 3.83 (95% CI 2.76-5.31); HR for rituximab was 2.6 (1.67-4.03). Pneumococcal and influenza vaccines had protective effect (HR 0.38, 0.2-0.73 and HR 0.42, 0.27-0.64, respectively). 1227 (68%) patients had non-serious infections. HR 2.46 (2.19-2.76) for corticosteroids, HR 1.49 (1.28-1.74) for rituximab. Pneumococcal and influenza vaccines again were protective (HR 0.52, 0.43-0.65 and HR 0.49,0.41-0.59, respectively). Did not directly measure vaccine response.

4674 Guissa, 2012 [47]	Prospective cohort study	21 days	30 JDM patients and 81 healthy age-matched controls; females - 63% JDM, 41% controls	single intramuscular dose (0.5 ml) of H1N1 A/California/7/2009-like virus vaccine	Seroconversion rate was significantly lower in JDM patients vs controls (86.7%, 95% CI 74.9% to 99.3% vs. 97.5%, 95% CI 94.1% to 100.9%, p=0.044), whereas the seroprotection rate was similar (90%, 95% CI 79.6% to 101.1% vs. 97.5%, CI 94.1% to 100.9%, p=0.12). GMT was also similar in both groups.
4722 Ristow, 1978 [48]	Prospective cohort study	4 and 8 wks	29 lupus, 29 control patients	A/New Jersey/76 HswINI influenza virus vaccine.	Seroconversion (4-fold increase in titer) was similar at the 4 week followup: 14/29 SLE patients and 18/29 healthy controls. SLE patients had similar seroconversion rates compared to healthy controls.
4709, Kanakoudi-Tsakalidou 2001 [49]	Prospective cohort study	2 months	70 children w rheumatic disease (49 JIA, 11 SLE, 10 other). Divided into 4 treatment groups: 1) No treatment 2) Prednisone + MTX/cyclosporine/azathioprine 3) Prednisone + MTX + Cyclosporine 4) MTX/cyclosporine/azathioprine without steroids Also 5 healthy controls (siblings of patients)	"split type" influenza vaccine, Fluarix, 1 or 2 doses depending on age/size A/Beijing, A/Sydney, B/Beijing	Antibody titers at baseline, 1 month (before 2nd dose), and 1 month after 2nd dose. Patients had high seroconversion rates (74-100%) after just one influenza dose, and almost complete seroconversion after 2 doses. ANOVA evaluation showed statistically significant differences between treatment groups for A/Sydney and B/Beijing serotypes. Lowest GMT was in group 4, but direct statistical comparisons were not made between 2 groups. No statistically significant difference in GMT between JIA and SLE groups. Pediatric mixed RD population. Overall high seroconversion responses; lowest GMT seen in MTX/cyclosporin/azathioprine group.
4832 Bjork, 2021 [50]	Prospective cohort study	90 days	28 SLE patients, of whom 15 were on HCQ. All had low or no disease activity. 17 healthy controls	Non-adjuvanted seasonal flu vaccine (Vaxigrip)	“Vaccine-specific IgG” measured by ELISA, no details provided. SLE pts produced *higher* levels of vaccine-specific IgG as compared to controls (data

					presented in graphical form). No difference between HCQ and no HCQ (data not shown). SLE pts produced *higher* levels of vaccine-specific IgG as compared to controls. No difference between HCQ and no HCQ.
6153 Sampaio-Barrow 2018 [51]	Prospective cohort study	21 days	92 SSc patients. 53 pts (58%) were on immunosuppression. MTX in 21.7%, AZA in 19.6%, CYC in 8.7% and MMF in 6.5%. 92 age-matched controls	A(H1N1)pdm09 vaccine, a novel, monovalent, non-adjuvanted, inactivated and split-virus vaccine (equivalent antigen to A/California/7/2009)	SSc patients had higher GMT (mean 166 vs mean 104) but similar seroconversion and seroprotection rates compared to healthy controls. No significant differences seen in diffuse vs. limited scleroderma, or based on modified Rodnan skin score. Patients were not broken out according to medications, but GMT was similar between immunosuppressed and non-immunosuppressed groups (166 and 166). No statistical difference in seroconversion or seroprotection rates (p=0.6, p=0.2, respectively. Systemic sclerosis patients on immunosuppression had similar response to influenza vaccine compared to those not on immunosuppression. Overall also similar to healthy controls.
6154 Shinjo 2012 [52]	Cohort	21 days	dermatomyositis (DM, n=37) and polymyositis (PM, n=21), age-and gender-[matched healthy controls (n=116); mean age: 43.1 ± 9.9 DM/PM vs. 43.8 ± 8.4 healthy controls	Sanofi Pasteur 2009 influenza A (H1N1) was a novel monovalent adjuvant-free vaccine (A/California/7/2009/Butantan Institute/Sanofi Pasteur)	No significant difference in GMT and factor increase in GMT post-vaccination with DM/PM vs. controls. GMT: 119.0 (75.3-188.1) DM/PM vs. 102.8 (82.8-127.8) controls; p=0.573 Factor increase in GMT: 13.6 (9.1-20.3) DM/PM vs. 11.6 (9.3-14.4) controls; p=0.496 Seroconversion rates were comparable between the controls and patients undergoing treatment with glucocorticoid (GC) (p=0.969), GC

					>0.5mg/kg/day (p=0.395) and GC+immunosuppressors (p=0.285) Dermatomyositis/polymyositis had similar responses as compared to healthy controls. There was no difference based on degree of immunosuppression.
6910 Adler 2012 [3]	Prospective, single-center, cohort study	Follow-up to 6 months post-vaccine	149 RMD patients (57.7% female; Age: 24.2% <40 years, 45% 40-59 years, 30.8% 60+ years). Includes 47 RA patients, 59 SpA, 15 vasculitis, and 28 CTD patients. 40 healthy controls (65% female; Age: 38% <40 years, 55% 40-59 years, 8% 60+ years). Seasonal influenza vaccine in 127/149 (85.2%) patients vs. 28/40 (70%) controls (mean 4 vs. 3.7 weeks prior to study)	All participants received one standard dose of adjuvanted H1N1 vaccine (2009 pandemic). RMD patients: 10.7% no medications, 24.2% steroids (<10mg), 7.4% steroids (10+ mg). 62.4% on DMARDs: SSZ/HCQ (n=14), MTX (n=61), LEF (n=6), AZA (n=6), CSA (n=4), MMF (n=2), TNFi 45.6%, MTX+TNFi 22.1%. RTX (5 RA, 3 vasculitis), Abatacept (10 RA, 6 SpA, 4 CTD), Tocilizumab (5 RA), CYC (1 RA, 1 vasc, 1 CTD)	CHMP criteria: HI titers 1:40 or greater in >70%, seroconversion in >40%, mean increase in GMT >2.5 All three criteria met at all timepoints for controls. None of the criteria met in RMD patients at T4 (6 months). By disease group, CHMP criteria met at T2, T3 in RA, SpA, vasculitis, CTD. CHMP criteria met at T4 in SpA group only. Impaired antibody responses with use of RTX (p=0.045), abatacept (p=0.031), or MTX (p<0.001) in multivariable model. MTX (n=28): Seroprotection: 50% T2, 41% T3, 25% T4 Seroconversion: 50% T2, 36% T3, 29% T4 GMT ratio: 3.8 T2, 3.0 T3, 2.2 T4 Abatacept (n=20): Seroprotection: 45% T2, 35% T3, 20% T4 Seroconversion: 35% T2, 30% T3, 10% T4 GMT ratio: 2.5 T2, 2.6 T3, 1.7 T4 Rituximab (n=8): Seroprotection: 25% T2, 25% T3, 25% T4 Seroconversion: 25% T2, 25% T3, 13% T4 GMT ratio: 2.1 T2, 2.3 T3, 1.6 T4 TNFi had a less suppressive effect on antibody response: TNFi (n=35): Seroprotection: 91% T2, 78% T3, 36% T4

					Seroconversion: 83% T2, 66% T3, 46% T4 GMT ratio: 10.5 T2, 7.3 T3, 2.8 T4 Mixed RMD patients with lower responses across the board compared to healthy controls. Ritux, abatacept, MTX associated w/ lower antibody response. TNFi did not have much effect.
7029 Jeffs 2015 [53]	Open, single-center, prospective cohort study	28 days post-vaccine	31 adult patients (45.2% female) with AAV (20 GPA & 11 MPA) in clinical remission for 3+ months (BVAS <2). 67 healthy individuals (68.7% female) recruited from hospital staff members & medical trainees. Median age significantly older in vaccinated AAV patients (62 yrs) vs. healthy controls (23 yrs).	AAV patients randomized 3:1 to receive trivalent (H1N1/H3N2/B influenza) seasonal influenza vaccine (n=24) versus no vaccination (n=7). Healthy individuals also randomized 3:1 to receive vaccine (n=53) versus no vaccine (n=14). Vaccinated AAV patients: 25% no immunosuppression, 33% AZA, 8% CYC, 4% MTX, 13% HCQ, 13% MMF, 58% oral steroids; 29% one medication, 42% two medications, 4% three medications. Non-vaccinated AAV patients: 57% AZA, 14% MTX, 14% MMF, 86% prednisolone; 29% on one medication, 71% on two medications.	Vaccinated AAV patient group satisfies European CPMP guidelines for effective responses to all three influenza vaccine antigens (at least one of: seroprotection rate >70%, seroconversion rate >40%, seroconversion factor >2.5). Post hoc: No significant difference in number of immunosuppressive medications and post-vaccine GMT for either of the influenza A antigens. Patients on no immunosuppressives had higher post-vaccine GMT for B-Malaysia compared to patients on 2 or 3 drugs ($p<0.05$).
7194 Kim 2013 [54]	Prospective cohort study	Follow-up to 3-5 weeks post-vaccine	26 patients with NMO spectrum disorders (NMOSD), 9 with MS, and 8 healthy controls aged 18-65 years.	All participants received one standard dose of a monovalent adjuvant H1N1 influenza vaccine (2009 pandemic).	At T1, 3 (18.8%) patients in the rituximab group showed seropositivity, while 6 (37.5%) patients in the rituximab group seroconverted. Mean fold increase was 3.3±4.1. Pts with NMO and MS treated with rituximab; low rates of seropositivity/seroconversion.

			RTX group (n=16 NMOSD patients): Mean age 38.8 years, 81.25% female Fewer than 10 patients were included in the remaining arms (MTX, AZA, healthy controls) so data is not useable.	RTX (n=16): 375 mg/m2 once weekly x 4 doses, or 1000 mg infused twice, 2 weeks apart; mean duration of treatment 82.7 weeks; mean (SD) interval between last RTX infusion & vaccination was 19.7 (12.4) weeks (range 1-45 weeks).	
7213 Nii, 2009 [55]	Prospective cohort study	1 year	RA patients 1 yr after flu vax. 26 out of 27 RA pts on biologic (almost all TNFi), 25 of 36 RA patients not on biologic, and 28 of 52 healthy controls	A/ New Caledonia/20/99 (H1N1) (A-NC), A/Hiroshima/52/ 2005 (H3N2) (A-Hiro), and B/Malaysia/2506/2004	Data provided in graphical form only. In original study, antibody titers to influenza antigens was not different between RA and control. At 1 year, all 3 groups showed decline in titer, but there were no statistically significant differences between the groups. Titers against, measles, mumps, and EBNA were also measured – all similar except RA pts on biologics had *higher* anti-measles antibody. "No significant effects of prednisolone, methotrexate, or other DMARDs" on titers
7489 Yri, 2011 [56]	Prospective cohort study	6 months	67 lymphoma patients, 51 controls. All had received rituximab; only 7 received rituximab as monotherapy. All were either during or within 6 months of treatment.	Adjuvanted monovalent H1N1 vaccine (Pandemrix)	Only 5 of the 67 lymphoma patients had a measurable antibody response to vaccination (was measurable but not seroprotective in any patients), as compared to seroprotection rate of 82.4% in healthy controls. The rituximab monotherapy patients were not broken out separately, but none of them developed protective response.
7496 Westra 2014 [31]	Prospective cohort study	28 days post-vaccine	43 patients with RA (1987 ACR criteria) aged 18 years or older, 20 on MTX, 23 on RTX.	All participants received one standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B-Malaysia).	Significant increase in anti-influenza specific IgG and IgM antibody levels (for both H1N1 & H3N2) at 28 days post-vaccination compared to baseline for healthy controls & RA-MTX. No significant

			Mean (SD) age 55.5 (7.6) years in RA-RTX, 57.1 (6.7) years in RA-MTX. 16/23 (70%) female in RA-RTX, 11/20 (55%) in RA-MTX. Median RA duration 13.8 years in RA-RTX, 8.7 years in RA-MTX. 28 healthy controls (HC). Mean (SD) age 45.2 (11.3) years (significantly younger than both RA groups), 78.6% female. Previous influenza vaccination in 52% of RA-RTX, 50% RA-MTX, 71.4% HC.	<u>RA-RTX group (n=23):</u> 11/23 (48%) vaccinated early - 4-8 weeks after RTX, 12/23 (52%) vaccinated late - 6-10 months post-RTX. 10/23 on concomitant MTX (median dose 17.5 mg weekly); 15/23 on prednisone (median dose 8.75 mg daily), 1/23 on another concomitant DMARD (not specified). <u>RA-MTX group (n=20):</u> Median dose 16.3 mg weekly, 2/20 on another concomitant DMARD, no corticosteroids. Significantly lower baseline B cell levels ($p<0.001$) and total IgG levels ($p<0.05$) in RA-RTX group compared to the HC and RA-MTX groups.	increase in IgG or IgM levels post-vaccine for either influenza strain in the RA-RTX group. <u>IgG subclass responses to influenza vaccine:</u> Significant increase in IgG1 and IgG3 levels post-vaccination for H1N1 ($p=0.037$ & $p=0.007$) and H3N2 ($p=0.009$ & $p=0.010$) in "late" RTX group. "Early" RTX group showed no increase in IgG1 or IgG3 post-vaccine to either influenza strain.
7510 Eisenberg 2013 [27]	Prospective single-center cohort study	Follow-up to 6 months post-vaccine in RMD patients; follow-up to 8 weeks post-vaccine in controls	25 patients on active RTX therapy for autoimmune disease enrolled, 17/25 (68%) completed the study. 16/17 patients (94%) female, 11/17 (65%) Caucasian, mean age 49 years. Type of RMD: 8/17 (47%) RA, 6/17 (35%) pSS, 2/17 (12%) SLE, 2/17 (12%) PM, 1/17 (6%) GPA. A subset of 12/17 patients (70.6%) with synchronized studies were used to assess vaccine response.	All participants received one standard dose of trivalent inactivated seasonal influenza vaccine (four different vaccines used over four different influenza seasons: 2006-2007, 2007-2008, 2008-2009, 2009-2010). All RMD patients vaccinated between 7-9 months post-RTX treatment. Of 17 patients on active RTX therapy, 3/17 had received RTX previously; this was first RTX cycle in remaining 14 patients.	Overall B cell numbers: All patients had complete B-cell depletion at 4 weeks post-RTX, defined as an absolute B cell count <=5 cells/uL. Variable B-cell recovery at 7-9 months post-RTX, with reconstitution in a few patients. B-cell subsets: Significantly fewer IgM memory cells & switched memory cells in RMD-RTX patients vs. controls at baseline ($p<0.001$ for both). At 7-9 months post-RTX, switched memory B cells & non-switched memory B cells remained depleted at <10% starting values. T-cell subsets:

			15 adult, age-matched controls: 8/15 (53% female), 11/15 (73%) Caucasian.	All RMD patients were on concomitant immunosuppressive therapy, including low-dose prednisone (n=4), HCQ (n=4), LEF (n=2), AZA (n=1), MTX (n=1).	The number of naïve CD4+ cells (p=0.05), naïve CD8+ cells (p=0.01), effector CD4+ cells (p<0.01), and effector CD8+ cells (p<0.01) were all significantly lower in RMD-RTX patients vs. controls at baseline. T cell response to influenza: At baseline, T cell response was similar between RMD-RTX patients & healthy controls No increase in T cell response observed post-vaccination in the RMD-RTX group (data not shown). T cell repertoire among RMD-RTX patients: No changes in T cell repertoire observed between baseline, 4 weeks post-RTX, 7-9 months post-RTX (vaccination), 2-months post-vaccine, and 6-months post vaccination. Seroconversion (fourfold or greater increase in titer post-vaccination for at least 1/3 strains): 2/12 RMD-RTX patients (one strain each) vs. 10/15 controls (multiple strains in most cases); p=0.009. Pre-existing aggregate HI titers (defined as sum of titers to 3 serotypes): For individual RMD-RTX patients, aggregate HI titers varied little over the course of the study, from baseline to 6-months post-vaccination, suggesting pre-existing titers were retained post-RTX treatment.
7615 Holvast 2006 [26]	Prospective, single center, cohort study	Follow-up to 30 days post-vaccine	56 adult patients (89.3% female) with SLE and quiescent disease (SLEDAI 5 or less) VS. 18 age- and sex-matched healthy volunteers (77.8% female).	All participants received a single dose of trivalent inactivated seasonal influenza vaccine (H1N1/H3N2/B-HK). SLE patients grouped by treatment: Group A - No meds (n=12)	GMT pre/post vaccination: H1N1: SLE (n=56): 32.4 / 142 Controls (n=17): 6.93 / 130 H3N2: SLE (n=56): 50 / 183 Controls (n=17): 21.7 / 272 Influenza B: SLE (n=56): 16.2 / 64.0 Controls (n=17): 5.65 / 49

			43/56 (77%) SLE patients received influenza vaccine in the past vs. 4/18 (22%) healthy controls (p<0.001). 34/56 SLE patients received influenza vaccine in the previous season vs. 1/18 healthy controls (p<0.001).	Group B - HCQ >=400mg daily (n=17) Group C - AZA >= 50 mg daily (n=13) Group D - Prednisone >= 10 mg daily (n=14) Patients taking MTX (n=5) or other immunosuppressives (CYC, CNI, MMF; n=12) were excluded from the study. Median dose HCQ in Group B = 400 mg daily; median dose AZA in Group C = 100 mg daily; median dose prednisone in Group D = 10 mg daily. Patients in Group B (HCQ) & Group C (AZA) were allowed prednisone <10 mg daily. All prednisone doses were "stable" for at least 2 months pre-vaccination. All four SLE groups similar with respect to age, sex, SLE duration, baseline SLEDAI, and baseline VAS. More patients in AZA group received influenza vaccine in the previous season vs. other SLE groups (p=0.026)	Pre-vaccine GMT significantly higher in SLE patients vs. controls for all 3 antigens (p<0.001 for H1N1 & B; p=0.036 for H3N2). GMT increased at 30 days post-vaccine for all antigens. Post-vaccine GMTs did not differ significantly between SLE & controls. Vaccine efficacy & seroprotection rates similar between SLE patients on medication (HCQ, AZA, or GC; n=44) vs. not on medication (n=12) for all 3 antigens.
7655 Milanetti 2014 [57]	Prospective, single-center, cohort study	6 months post-vaccination	30 patients with RA (1987 ACR criteria) with low-moderate disease activity (DAS<3.7) and stable disease (no increase in therapy required in past 6 months).	All participants received a single dose of trivalent non-adjuvanted 2009-2010 seasonal influenza vaccine (H1N1/H3N2/B-Brisbane) and a single dose of the pandemic monovalent adjuvanted	<u>PICO #3, 6, 15:</u> Pandemic & seasonal influenza vaccines met all three CPMP criteria in both RA patients & HCs at T1 for all three antigens (seroconversion rate >40%, seroprotection rate >70%, seroconversion factor > 2.5 at T1). At T2, seroprotection rate >70% only maintained for seasonal vaccine (all 3 antigens in HCs, only B-influenza in RA patients).

			Mean (SD) age 50 (10) years, 77% female, mean (SD) baseline DAS 2.33 (0.8) 13 healthy controls, matched for age and sex. Mean (SD) age 41.8 (12) years, 62% female. 6/30 (20%) RA patients and 3/13 (23%) controls received influenza vaccination in the prior season.	H1N1 vaccine on the same day. All RA patients were taking a biologic DMARD (13 etanercept, 7 adalimumab, 4 infliximab, 6 abatacept). Concomitant low-dose corticosteroids (prednisone <10mg daily) and csDMARDs (mostly MTX 10-15mg weekly) permitted. Details not reported.	<u>Seroconversion factor at T1:</u> npH1N1: 4.1 in RA patients vs. 3.7 in HCs H3N2: 6.4 in RA patients vs. 6.2 in HCs B-influenza: 4.9 in RA patients vs. 4.8 in HCs pH1N1: 8.5 in RA patients vs. 5.1 in HCs <u>GMTs in RA patients & HCs at T0/T1/T2:</u> npH1N1 - RA: 22/174/57 vs. HC: 15/107/72 H3N2 – RA: 11/61/31 vs. HC: 32/113/93 B-influenza – RA:45/263/148 vs. HC: 68/302/195 pH1N1 – RA: 8/100/33 vs. HC: 7/50/24 Between T0 and T1, GMT values increased significantly for all antigens in RA patients ($p<0.05$), with reduction at T2. Slight increase in activated cytokine-producing T cells at T1 compared to T0, followed by reduction at T2 in both RA patients & HCs. Mean values not significantly different in RA patients vs. HCs at all timepoints.
7864 Richi 2019 [16]	Prospective cohort study	At least 4 weeks FU post-vaccine [mean (SD) 33 (8) days]	17 PsA and AS patients on secukinumab vs. 13 healthy controls. No demographic differences between groups (data not shown).	All 17 PsA and AS patients on secukinumab (dose & frequency not reported) for mean (SD) duration 8.9 (5.8) months. 10/17 (58.8%) patients on concomitant csDMARDs (5 on LEF, 4 on MTX, 1 on SSZ). All participants received one standard dose of seasonal inactivated trivalent influenza vaccine (H1N1/H3N2/B-Brisbane).	PICO 3 & PICO 15: GMT at baseline / post-vaccine in AS & PsA patients vs. healthy controls for each antigen: H1N1: AS & PsA patients: 60 / 276 (4.6-fold increase) Controls: 107 / 428 (4.0-fold increase) H3N2: AS & PsA patients: 65 / 91 (1.4-fold increase) Controls: 85 / 86 (1.0-fold increase) Influenza B: AS & PsA patients: 20 / 74 (3.7-fold increase) Controls: 32 / 171 (5.3-fold increase)
8096 Abu-Shakra 2002 [33]	Case series	12 weeks post-vaccine	24 SLE patients Mean age 46.1 years (range 20-74), 100% females. Mean disease duration 9.1 years.	All participants received one standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B-Influenza).	<u>Vaccine response:</u> At 6 weeks post-vaccination, 18/24 (75%) SLE patients had immune response (>=4 fold rise in titer or seroconversion) to at least 1/3 influenza strains:

			Baseline seroprotection for H3N2/H1N1/B in SLE (20.8/8.3/66.7%) similar to healthy age-matched female controls (n=30; 20/16.7/63.3%). Healthy controls <u>not</u> evaluated post-vaccine.	<u>SLE therapies:</u> Oral steroids (n=17), mean prednisone dose 12 mg HCQ 400 mg daily (n=9) AZA 100 mg daily (n=3) MTX (n=4) mean dose 10mg weekly	5/24 (20.8%) responded to 1/3 strains 8/24 (33.4%) responded to 2/3 strains 5/24 (20.8%) responded to 3/3 strains 6/24 (25%) did not respond to any strains. All 6 were taking oral steroids (mean dose 15.8 mg). Response to H3N2 in 14/24 (58.3%), H1N1 in 9/24 (37.5%) and B-influenza in 15/24 (62.5%). <u>Seroprotection:</u> Prior to vaccination, patients had protective antibodies (HI titer >= 1:40) against a mean of 0.96 of 3 influenza strains. This increased to a mean of 1.92 at 6 weeks post-vaccine and then decreased slightly to a mean of 1.6 at 12 weeks post-vaccine. <u>Rate of seroprotection by number of strains:</u> 0/3: 2/24 (8.3%) at 6 wks, 4/24 (16.7%) at 12 wks 1/3: 6/24 (25%) at 6 wks, 8/24 (33.3%) at 12 wks 2/3: 8/24 (33.3%) at 6 wks, 6/24 (25%) at 12 wks 3/3: 8/24 (33.3%) at 6 wks, 6/24 (25%) at 12 wks <u>Rate of seroprotection by influenza strain:</u> H3N2: 16/24 (66.7%) at 6 weeks; 14/24 (58.3%) at 12 weeks H1N1: 8/24 (33.3%) at 6 weeks; 6/24 (25%) at 12 weeks B-influenza: 22/24 (91.6%) at 6 weeks, 18/24 (75%) at 12 weeks Mean number of immune responses to the 3 influenza antigens, stratified by age, SLEDAI score, and use of prednisone, MTX, or AZA: Overall mean # of immune responses = 1.5/3 <u>Age:</u> Mean 1.33 for 50+ years, 1.6 for < 50 years. <u>Prednisone:</u> Mean 1.14 if 10+ mg daily vs. 1.65 if < 10 mg daily or none.

					AZA: Mean 1.33 if taking AZA vs. 1.6 if no AZA. No association of MTX therapy or SLEDAI scores with mean number of immune responses.
8187 Holvast 2009 [58]	Prospective cohort study	Follow-up to 3-4 months post-vaccine	80 adult patients with SLE: 54 vaccinated vs. 24 nonvaccinated. Two patients excluded after randomization. Vaccinated SLE patients (n=54): 18.5% male, mean age 44.8 years, 34/54 (63%) prior vaccination. Nonvaccinated SLE patients (n=24): 8.3% male, mean age 45.5 years, 9/24 (37.5%) prior vaccination. Age- and sex-matched healthy individuals (n=54): 20.4% male, mean age 43.1 years, 3/54 (5.6%) prior vaccination. For cellular responses: 38 vaccinated SLE patients vs. 38 age- & sex-matched controls. Mean age 43.4 years, 24% males	SLE patients randomized 2:1 to influenza vaccination vs. nonvaccinated patient control group. All healthy controls vaccinated. Vaccination with single standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B). Vaccinated SLE patients (n=54): 5/54 (9.3%) no medications, 28/54 (51.9%) prednisone (median 5mg daily), 30/54 (55.6%) HCQ (median 400mg daily), 17/54 (31.5%) AZA (median 125mg daily), 6/54 (11.1%) MTX. Nonvaccinated SLE patients (n=24): 5/24 (20.8%) no medications, 10/24 (41.7%) prednisone (median 6.25mg daily), 10/24 (41.7%) HCQ (median 400mg daily), 6/24 (25%) AZA (median 87.8 mg), no MTX.	PICO #3,6,15: Cellular responses: Prior to vaccination, SLE patients had fewer H1N1-specific & H3N2-specific IFNy spot-forming cells. In both SLE patients & controls, significant increases in H1N1- & H3N2-specific IFNy spot-forming cells from pre-vaccine to 28-days post-vaccine. Post-vaccine, fewer H1N1- and H3N2-specific IFNy spot-forming cells in SLE patients vs. controls. Geometric mean titers (GMT): H1N1 T=0: 18.9 in SLE vs. 10.9 in Controls (p<0.01) T=D28: 76.5 SLE vs. 98.2 Controls (p<0.001) T=3-4 months: 51.3 SLE vs. 62.7 Controls H3N2 T=0: 15.8 in SLE vs. 12.4 in Controls T=D28: 86.4 SLE vs. 138 in Controls (p<0.01) T=3-4 months: 55.8 in SLE vs. 76 in Controls GMT fold increase at Day 28: H1N1: 4.0 SLE vs. 9.0 in Controls (p<0.001) H3N2: 5.5 SLE vs. 11.1 in Controls (p<0.01)
8953 Litinksy 2012 [59]	case control		26 consecutive SSc patients (12 diffuse, 14 CREST) VS healthy controls Mean age of SSc pts: 52 years, male:female ratio 1:5.5, mean disease duration 8.3 years+/- 6.28, 34.6% with digital ulcers,	trivalent influenza subunit vaccine (H1N1, H3N2, TGA)	Geometric mean titers of haemagglutination inhibition (HI) antibodies (µg/ml) against influenza antigens in scleroderma (SSc) patients and controls before and six weeks after vaccination. (SD not provided) Week 0 to 6, SSc n=26 H1N1

			27% with PAH, 58% with GI involvement, 42% with MSK involvement, 100% with Raynaud's, 27% on immunosuppressive tx		29.35 to 356 p<0.0001 H3N2 3.28 to 51.3 p<0.001 B 62.9 to 198 p<0.0001 Week 0 to 6, Controls n=16 H1N1 33.63 to 76.6, p=0.02 41.77 to 113.13, p=<0.01 80 to 153.21, p=0.04 Geometric mean titers of haemagglutination inhibition (HI) antibodies (µg/ml) against influenza antigens in scleroderma patients (SSc) subgroups with regard to the use of immunosuppressive drugs, before and six weeks after vaccination. SSc with IS n=7 Week 0 to Week 6 H1N1 4.18 to 5.66 p=0.036 H3N2 1.58 to 2.63, p=1.04 B 4.18 to 4.87, p=0.017 SSc without IS n=19 Week 0 to Week 6 H1N1: 3.08 to 5.95, p<0.0001 H3N2: 1.04 to 4.41, p<0.0001 B: 4.12 to 5.43, p=0.0001 "The combination therapy of iloprost and calcium channel blockers significantly increased the humoral response to the H1N1 and B antigens (p<0.0001 and p=0.0007, respectively)."
9273 Bjork 2020 [60]	Prospective cohort	90 days	25 Sjogren's patients (anti SSA seropositive and fulfilling the American-European consensus	Seasonal influenza vaccination	Vaccine specific antibody titers We observed higher levels of vaccine-specific IgG titres in pSSUntr compared with controls (p<0.01), but not in pSSHCQ compared with controls. There

			group criteria) [17 were untreated, 8 patients on HCQ] 16 age and sex matched healthy controls	Fluarix,GlaxoSmithKline, Solna, Sweden) containing inactivated A/California/7/2009 (H1N1)-, A/Switzerland/9715293/2013 (H3N2)-, and B/Phuket/3073/2013-like strains.	was no statistically significant difference in antibody titres comparing pSSUntr and pSSHCQ (data not shown). Vaccine-specific IgA and IgM titres did not differ between pSSUntr and controls and neutralizing anti-hemagglutinin antibody levels were comparable for two of the strains, but higher in pSSUntr compared with controls for the A/Switzerland/9715293/2013-like strain.
9426 Adler 2012 [3]	Nonrandomized comparative	6 months	149 patients: 47 RA, 59 SpA, 15 vasculitis, 28 CTD vs. 40 healthy controls; % of patients >60 was 51% RA, 14% SpA, 40% VAS, 29% CTD, and 8% controls	Single dose of adjuvanted A/H1N1 influenza vaccine; medications included steroids, 93% were on DMARDs (mostly MTX), 46% were on TNFIs, 22% were on both MTX and TNFIs, 10 or fewer patients were each on rituximab, abatacept, tocilizumab, and CYC	Use of MTX (n=28; p<0.001)), rituximab (n=8; p=0.0031), and abatacept (n=20; p=0.045) significantly suppressed immune response while use of TNFIs (n=35; p=0.81), other DMARDs (n=28; p=0.06), and glucocorticoids (n=50; p=0.11) did not significantly suppress response. Use of TNFIs and DMARDS without MTX showed the 1st and 2nd best response rates, respectively. Lastly, use of tocilizumab and cyclophosphamide "significantly impaired immune reaction leading to insufficient immune response" (data not shown). <u>Seroprotection (%) at 3 weeks, 6 weeks, 6 months (CHMP criteria in at least 70% of patients):</u> MTX (n=28): 50, 41, 25 TNFIs (n=35): 91, 78, 36 MTX+TNFIs (n=33): 63, 61, 20 Glucocorticoids (n=50): 66.5, 57, 27.5 Other DMARDs (n=28): 79, 76, 39 Abatacept (n=20): 45, 35, 20 Rituximab (n=8): 25, 25, 25 <u>GMT/GMT ratio at 3 weeks, 6 weeks, and 6 months; (CHMP criteria ≥2.5 for GMT ratio):</u> MTX: 32.5/3.8, 26.1/3.0, 18.6/2.2 TNFIs: 83.3/10.5, 57.8/7.3, 22.4/2.8 MTX+TNFIs: 37.6/5.4, 28.3/4.1, 14.3/2.1 Glucocorticoids: 55.2/5.2, 38.7/3.7, 21.8/2.1 Other DMARDs: 73.4/7.7, 55.4/5.8, 26.9/2.8 Abatacept: 23.8/2.5, 24.2/2.6, 15.8/1.7 Rituximab: 21.0/2.1, 22.9/2.3, 16.2/1.6

					Seroconversion (%) at 3 weeks, 6 weeks, and 6 months (CHMP criteria in at least 40% of patients): MTX: 50, 36, 29 TNFIs: 83, 66, 46 MTX+TNFIs: 64, 61, 27 Glucocorticoids: 59.5, 43.5, 26 Other DMARDs: 75, 64, 46 Abatacept: 35, 30, 10 Rituximab: 25, 25, 13
9428 Oren 2008 [30]	Nonrandomized comparative	4 weeks	29 RA (non-rituximab), 14 rituximab-treated RA (rituximab), and 21 healthy controls	Influenza: 0.5 ml split virion inactivated vaccine (Vaxigrip, Promedico) containing a 15 mg haemagglutinin (HA) dose of A/California /7/04 (CAL) (H3N2), B/Shanghai /361/02 (SHAN) and A/New Caledonian/20/99 (NC) (H1N1), administered intramuscularly	At 4 weeks, both control groups (non-rituximab, healthy controls) demonstrated a satisfactory humoral response* with significant increases in GMT of HI antibody against 3 antigens tested (CAL, SHAN, NC). The rituximab arm demonstrated a significant rise for only 2 antigens (NC and CAL; data graphically presented). No correlation was determined between immunogenicity and weeks since rituximab in rituximab-treated RA patients. Antigen SHAN: 3 responders at 34.3±26 weeks, 11 non-responders at 31.5±2.8 weeks; p=0.875 Antigen NC: 5 responders at 32.8±21.4 weeks, 9 non-responders at 31.8±24.4 weeks; p=0.787 Antigen CAL: 3 responders at 25.3±23.4 weeks, 11 non-responders at 34±23 weeks; p=0.694

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PICO 16: Should patients with RMD taking drug Y hold their drug for a period of time prior to or after receiving (not live-attenuated) vaccines?

Summary: The literature search identified 3 RCTs [1-3] and one post-hoc analysis [4] of an included RCT [2] that addressed this PICO question. All 3 RCTs [1-3] included patients with RA as the study population. Two RCTs [1, 2] evaluated the impact of holding methotrexate in relation to receipt of seasonal influenza

vaccine, while the third RCT [3] assessed the effect of holding versus continuing tofacitinib in patients receiving both the seasonal influenza vaccine and the pneumococcal polysaccharide vaccine (PPSV-23).

Park et al. [1] conducted a single-blind RCT of adult RA patients on a stable dose of methotrexate receiving the seasonal trivalent influenza vaccine. Participants were randomized to continue methotrexate without interruption (Group 1), suspend methotrexate 4 weeks before vaccination (Group 2), suspend methotrexate for 2 weeks before and 2 weeks after vaccination (Group 3), or suspend methotrexate for 4 weeks after vaccination (Group 4). There were no significant differences in the primary outcome, vaccine response at 4 weeks post-vaccination, between Group 1 and Group 2 [1]. For Group 3 and Group 4, the rates of satisfactory vaccine response at 4 weeks post-vaccination were numerically higher compared to Group 1, although the only statistically significant difference observed was for the rate of satisfactory vaccine response to all 3 influenza antigens in Group 3 versus Group 1 (51.0% vs. 31.5%, p=0.044) [1]. Although the overall rate of disease flares was high (58/199, 29.1%), there were no statistically significant differences in the rate of RA flares between the four groups [1].

In a second RCT, Park et al. [2] enrolled 320 adult RA patients on a stable dose of methotrexate receiving the seasonal quadrivalent influenza vaccine. Participants were randomized to continue methotrexate without interruption (MTX-continue) versus holding methotrexate for 2 weeks after vaccination (MTX-hold). For the primary outcome, significantly more patients in the MTX-hold group achieved a satisfactory vaccine response at 4 weeks post-vaccination compared to the MTX-continue group (75.5% vs. 54.5%, p<0.001) [2]. The MTX-hold group was also superior to the MTX-continue group with respect to all secondary serological outcomes related to vaccine efficacy [2]. The rate of RA flares post-vaccination was numerically higher in the MTX-hold group (10.6%) compared to the MTX-continue group (5.1%), but this difference was not statistically significant (p=0.070) [2]. In a post-hoc analysis of the 160 RA patients who held methotrexate for 2 weeks post-vaccination, there was no significant association observed between vaccine efficacy and the timing of vaccination relative to the last methotrexate dose [4].

In a vaccine substudy of an open-label, multicenter, long-term extension study, Winthrop et al. [3] randomized adult RA patients taking tofacitinib 10 mg PO BID for at least 3 months to 1) Continue tofacitinib without interruption; or 2) Discontinue tofacitinib one week prior to vaccination and resume tofacitinib one week post-vaccination. All participants received one dose of seasonal trivalent influenza vaccine and one dose of PPSV-23 on the same day. For both vaccines, there were no significant differences between the two groups in the rate of satisfactory humoral response at 35 days post-vaccination [3]. Similar results were observed in a subgroup analysis stratified by background methotrexate use [3]. The rates of RA disease flares were not reported.

Quality of evidence across all critical outcomes: Moderate for MTX, Low for tofacitinib, Very low for other DMARDs

Table 1. Hold methotrexate for 4 weeks pre-vaccine vs. Continue methotrexate without interruption in RA patients who are receiving seasonal influenza vaccine [1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 2: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
Satisfactory vaccine response at 4 weeks post-vaccination - 1+/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	36/44 (81.8%)	42/54 (77.8%)	**RR 1.05** (0.86 to 1.28)	**39 more per 1,000** (from 109 fewer to 218 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - 2+/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	23/44 (52.3%)	29/54 (53.7%)	**RR 0.97** (0.67 to 1.42)	**16 fewer per 1,000** (from 177 fewer to 226 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - 3/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	10/44 (22.7%)	17/54 (31.5%)	**RR 0.72** (0.37 to 1.41)	**88 fewer per 1,000** (from 198 fewer to 129 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 2: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	28/44 (63.6%)	23/54 (42.6%)	**RR 1.49** (1.02 to 2.19)	**209 more per 1,000** (from 9 more to 507 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - H3N2												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	30/44 (68.2%)	39/54 (72.2%)	**RR 0.94** (0.73 to 1.23)	**43 fewer per 1,000** (from 195 fewer to 166 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - B-Yamagata												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/44 (36.4%)	21/49 (42.9%)	**RR 0.85** (0.51 to 1.41)	**64 fewer per 1,000** (from 210 fewer to 176 more)	⊕⊕◯◯ Low	
Seroconversion at 4 weeks post-vaccination - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 2: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	18/24 (75.0%)	22/36 (61.1%)	**RR 1.23** (0.87 to 1.74)	**141 more per 1,000** (from 79 fewer to 452 more)	⊕⊕◯◯ Low	
Seroconversion at 4 weeks post-vaccination - H3N2												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	19/21 (90.5%)	15/15 (100.0%)	**RR 0.91** (0.77 to 1.09)	**90 fewer per 1,000** (from 230 fewer to 90 more)	⊕⊕◯◯ Low	
Seroconversion at 4 weeks post-vaccination - B-Yamagata												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17/30 (56.7%)	18/33 (54.5%)	**RR 1.04** (0.67 to 1.62)	**22 more per 1,000** (from 180 fewer to 338 more)	⊕⊕◯◯ Low	
Adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 2: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	27/44 (61.4%)	30/54 (55.6%)	**RR 1.10** (0.79 to 1.54)	**56 more per 1,000** (from 117 fewer to 300 more)	⊕⊕◯◯ Low	
RA flare at any visit, up to 16 weeks post-vaccination (DAS28 increase by >1.2, or >0.6 if baseline DAS28 was 3.2 or higher)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/44 (34.1%)	13/54 (24.1%)	**RR 1.42** (0.76 to 2.65)	**101 more per 1,000** (from 58 fewer to 397 more)	⊕⊕◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Single RCT with no blinding of participants. Primary analysis was per-protocol, including only 199 (72%) of 277 randomized participants.
b. Single study with < 200 patients/arm. Underpowered based on sample size calculation.

Table 2. Hold methotrexate for 2 weeks pre-vaccine and 2 weeks post-vaccine vs. Continue methotrexate without interruption in RA patients who are receiving seasonal influenza vaccine [1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 3: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
Satisfactory vaccine response at 4 weeks post-vaccination - 1+/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	43/49 (87.8%)	42/54 (77.8%)	**RR 1.13** (0.95 to 1.35)	**101 more per 1,000** (from 39 fewer to 272 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - 2+/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	35/49 (71.4%)	29/54 (53.7%)	**RR 1.33** (0.98 to 1.80)	**177 more per 1,000** (from 11 fewer to 430 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - 3/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	25/49 (51.0%)	17/54 (31.5%)	**RR 1.62** (1.00 to 2.62)	**195 more per 1,000** (from 0 fewer to 510 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 3: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	32/49 (65.3%)	28/54 (51.9%)	**RR 1.26** (0.91 to 1.75)	**135 more per 1,000** (from 47 fewer to 389 more)	⨁⨁◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - H3N2												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	42/49 (85.7%)	39/54 (72.2%)	**RR 1.19** (0.97 to 1.45)	**137 more per 1,000** (from 22 fewer to 325 more)	⨁⨁◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - B-Yamagata												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	29/49 (59.2%)	21/54 (38.9%)	**RR 1.52** (1.01 to 2.29)	**202 more per 1,000** (from 4 more to 502 more)	⨁⨁◯◯ Low	Favors MTX hold
Seroconversion at 4 weeks post-vaccination - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 3: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	27/29 (93.1%)	22/36 (61.1%)	**RR 1.52** (1.15 to 2.01)	**318 more per 1,000** (from 92 more to 617 more)	⨁⨁◯◯ Low	Favors MTX hold
Seroconversion at 4 weeks post-vaccination - H3N2												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22/23 (95.7%)	15/15 (100.0%)	**RR 0.97** (0.84 to 1.11)	**30 fewer per 1,000** (from 160 fewer to 110 more)	⨁⨁◯◯ Low	
Seroconversion at 4 weeks post-vaccination - B-Yamagata												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	27/30 (90.0%)	18/33 (54.5%)	**RR 1.65** (1.18 to 2.30)	**355 more per 1,000** (from 98 more to 709 more)	⨁⨁◯◯ Low	Favors MTX hold
Adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 3: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	26/49 (53.1%)	30/54 (55.6%)	**RR 0.96** (0.67 to 1.36)	**22 fewer per 1,000** (from 183 fewer to 200 more)	⨁⨁◯◯ Low	
RA flare at any visit, up to 16 weeks post-vaccination (DAS28 increase by >1.2, or >0.6 if baseline DAS28 was 3.2 or higher)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	19/49 (38.8%)	13/54 (24.1%)	**RR 1.61** (0.89 to 2.91)	**147 more per 1,000** (from 26 fewer to 460 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Single RCT with no blinding of participants. Primary analysis was per-protocol, including only 199 (72%) of 277 randomized participants.
b. Single study with < 200 patients/arm. Underpowered based on sample size calculation.

Table 3. Hold methotrexate for 4 weeks post-vaccine vs. Continue methotrexate without interruption in RA patients who are receiving seasonal influenza vaccine [1]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 4: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
Satisfactory vaccine response at 4 weeks post-vaccination - 1+/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	46/52 (88.5%)	42/54 (77.8%)	**RR 1.14** (0.96 to 1.35)	**109 more per 1,000** (from 31 fewer to 272 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - 2+/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	34/52 (65.4%)	29/54 (53.7%)	**RR 1.22** (0.89 to 1.67)	**118 more per 1,000** (from 59 fewer to 360 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - 3/3 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	24/52 (46.2%)	17/54 (31.5%)	**RR 1.47** (0.90 to 2.40)	**148 more per 1,000** (from 31 fewer to 441 more)	⊕⊕◯◯ Low	
Satisfactory vaccine response at 4 weeks post-vaccination - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 4: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	32/52 (61.5%)	28/54 (51.9%)	**RR 1.19** (0.85 to 1.66)	**99 more per 1,000** (from 78 fewer to 342 more)	⊕⊕◯◯ Low	

Satisfactory vaccine response at 4 weeks post-vaccination - H3N2

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	40/52 (76.9%)	39/54 (72.2%)	**RR 1.07** (0.85 to 1.33)	**51 more per 1,000** (from 108 fewer to 238 more)	⊕⊕◯◯ Low	

Satisfactory vaccine response at 4 weeks post-vaccination - B-Yamagata

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	32/52 (61.5%)	21/54 (38.9%)	**RR 1.58** (1.06 to 2.35)	**226 more per 1,000** (from 23 more to 525 more)	⊕⊕◯◯ Low	Favors MTX hold

Seroconversion at 4 weeks post-vaccination - H1N1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 4: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	27/33 (81.8%)	22/36 (61.1%)	**RR 1.34** (0.99 to 1.82)	**208 more per 1,000** (from 6 fewer to 501 more)	⊕⊕◯◯ Low	
Seroconversion at 4 weeks post-vaccination - H3N2												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	22/24 (91.7%)	15/15 (100.0%)	**RR 0.93** (0.79 to 1.09)	**70 fewer per 1,000** (from 210 fewer to 90 more)	⊕⊕◯◯ Low	
Seroconversion at 4 weeks post-vaccination - B-Yamagata												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	31/41 (75.6%)	18/33 (54.5%)	**RR 1.39** (0.97 to 1.98)	**213 more per 1,000** (from 16 fewer to 535 more)	⊕⊕◯◯ Low	
Adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 4: Hold MTX	Group 1: Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17/52 (32.7%)	30/54 (55.6%)	**RR 0.59** (0.37 to 0.93)	**228 fewer per 1,000** (from 350 fewer to 39 fewer)	⨁⨁◯◯ Low	
RA flare at any visit, up to 16 weeks post-vaccination (DAS28 increase by >1.2, or >0.6 if baseline DAS28 was 3.2 or higher)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	11/52 (21.2%)	13/54 (24.1%)	**RR 0.88** (0.43 to 1.78)	**29 fewer per 1,000** (from 137 fewer to 188 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Single RCT with no blinding of participants. Primary analysis was per-protocol, including only 199 (72%) of 277 randomized participants.
b. Single study with < 200 patients/arm. Underpowered based on sample size calculation.

Table 4. Continue methotrexate without interruption vs. Hold methotrexate for 2 weeks post-vaccination in RA patients who are receiving seasonal influenza vaccine [2]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hold MTX	Continue MTX	Relative (95% CI)	Absolute (95% CI)		
Primary outcome: Satisfactory vaccine response at 4 weeks post-vaccination - 2+/4 influenza antigens												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	121/160 (75.6%)	85/156 (54.5%)	**RR 1.39** (1.17 to 1.64)	**212 more per 1,000** (from 93 more to 349 more)	⊕⊕⊕◯ Moderate	
Satisfactory vaccine response at 4 weeks post-vaccination - 1+/4 influenza antigens												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	143/160 (89.4%)	118/156 (75.6%)	**RR 1.18** (1.07 to 1.31)	**136 more per 1,000** (from 53 more to 234 more)	⊕⊕⊕◯ Moderate	
Satisfactory vaccine response at 4 weeks post-vaccination - 3+/4 influenza antigens												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	99/160 (61.9%)	57/156 (36.5%)	**RR 1.69** (1.33 to 2.15)	**252 more per 1,000** (from 121 more to 420 more)	⊕⊕⊕◯ Moderate	
Satisfactory vaccine response at 4 weeks post-vaccination - 4/4 influenza antigens												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hold MTX	Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	73/160 (45.6%)	34/156 (21.8%)	**RR 2.09** (1.49 to 2.95)	**238 more per 1,000** (from 107 more to 425 more)	⨁⨁⨁◯ Moderate	

Satisfactory vaccine response at 4 weeks post-vaccination - H1N1

1	randomised trials	not serious	not serious	not serious	serious[a]	none	100/160 (62.5%)	79/156 (50.6%)	**RR 1.23** (1.01 to 1.50)	**116 more per 1,000** (from 5 more to 253 more)	⨁⨁⨁◯ Moderate	

Satisfactory vaccine response at 4 weeks post-vaccination - H3N2

1	randomised trials	not serious	not serious	not serious	serious[a]	none	114/160 (71.3%)	85/156 (54.5%)	**RR 1.31** (1.10 to 1.56)	**169 more per 1,000** (from 54 more to 305 more)	⨁⨁⨁◯ Moderate	

Satisfactory vaccine response at 4 weeks post-vaccination - B-Yamagata

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hold MTX	Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	104/160 (65.0%)	66/156 (42.3%)	**RR 1.54** (1.24 to 1.91)	**228 more per 1,000** (from 102 more to 385 more)	⨁⨁⨁◯ Moderate	

Satisfactory vaccine response at 4 weeks post-vaccination - B-Victoria

1	randomised trials	not serious	not serious	not serious	serious[a]	none	118/160 (73.8%)	64/156 (41.0%)	**RR 1.80** (1.46 to 2.22)	**328 more per 1,000** (from 189 more to 501 more)	⨁⨁⨁◯ Moderate	

Seroprotection at 4 weeks post-vaccination - H1N1

1	randomised trials	not serious	not serious	not serious	serious[a]	none	138/160 (86.3%)	118/156 (75.6%)	**RR 1.14** (1.02 to 1.27)	**106 more per 1,000** (from 15 more to 204 more)	⨁⨁⨁◯ Moderate	

Seroprotection at 4 weeks post-vaccination

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hold MTX	Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	125/160 (78.1%)	97/156 (62.2%)	**RR 1.26** (1.08 to 1.46)	**162 more per 1,000** (from 50 more to 286 more)	⨁⨁⨁◯ Moderate	

Seroprotection at 4 weeks post-vaccination - B-Yamagata

1	randomised trials	not serious	not serious	not serious	serious[a]	none	141/160 (88.1%)	116/156 (74.4%)	**RR 1.19** (1.06 to 1.32)	**141 more per 1,000** (from 45 more to 238 more)	⨁⨁⨁◯ Moderate	

Seroprotection at 4 weeks post-vaccination - B-Victoria

1	randomised trials	not serious	not serious	not serious	serious[a]	none	121/160 (75.6%)	95/156 (60.9%)	**RR 1.24** (1.07 to 1.45)	**146 more per 1,000** (from 43 more to 274 more)	⨁⨁⨁◯ Moderate	

Influenza-like illness within one year post-vaccination

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hold MTX	Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	1/160 (0.6%)	3/156 (1.9%)	**RR 0.33** (0.03 to 3.09)	**13 fewer per 1,000** (from 19 fewer to 40 more)	⨁⨁⨁◯ Moderate	

Adverse events

1	randomised trials	not serious	not serious	not serious	serious[a]	none	45/160 (28.1%)	34/156 (21.8%)	**RR 1.29** (0.88 to 1.90)	**63 more per 1,000** (from 26 fewer to 196 more)	⨁⨁⨁◯ Moderate	

Mean change in DAS28 from pre-vaccination to 4 weeks post-vaccination

1	randomised trials	not serious	not serious	not serious	serious[a]	none	160	156	-	MD **0.1 higher** (0.07 lower to 0.27 higher)	⨁⨁⨁◯ Moderate	

RA flares within 4 weeks post-vaccination (Increase in DAS28 > 1.2, or > 0.6 if baseline DAS28 was 3.2 or higher)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hold MTX	Continue MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	17/160 (10.6%)	8/156 (5.1%)	**RR 2.07** (0.92 to 4.66)	**55 more per 1,000** (from 4 fewer to 188 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Single study with < 200 patients/arm.

Table 5. Seasonal influenza vaccination within 3 days after last methotrexate dose vs. 4-7 days after last methotrexate dose in RA patients holding methotrexate for 2 weeks post-vaccination [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccine 0-3 days after last MTX	Vaccine 4-7 days after last MTX	Relative (95% CI)	Absolute (95% CI)		
Satisfactory vaccine response at 4 weeks post-vaccination - 2+/4 influenza antigens												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	30/65 (46.2%)	43/95 (45.3%)	**RR 1.02** (0.72 to 1.44)	**9 more per 1,000** (from 127 fewer to 199 more)	⨁⨁◯◯ Low	
Seroprotection rate at 4 weeks post-vaccination - H1N1												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccine 0-3 days after last MTX	Vaccine 4-7 days after last MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	53/65 (81.5%)	85/95 (89.5%)	**RR 0.91** (0.80 to 1.04)	**81 fewer per 1,000** (from 179 fewer to 36 more)	⊕⊕◯◯ Low	

Seroprotection rate at 4 weeks post-vaccination - H3N2

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	49/65 (75.4%)	76/95 (80.0%)	**RR 0.94** (0.79 to 1.12)	**48 fewer per 1,000** (from 168 fewer to 96 more)	⊕⊕◯◯ Low	

Seroprotection rate at 4 weeks post-vaccination - B-Yamagata

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	55/65 (84.6%)	86/95 (90.5%)	**RR 0.93** (0.83 to 1.06)	**63 fewer per 1,000** (from 154 fewer to 54 more)	⊕⊕◯◯ Low	

Seroprotection rate at 4 weeks post-vaccination - B-Victoria

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaccine 0-3 days after last MTX	Vaccine 4-7 days after last MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	49/65 (75.4%)	72/95 (75.8%)	**RR 0.99** (0.83 to 1.19)	**8 fewer per 1,000** (from 129 fewer to 144 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Post-hoc analysis.
b. Single study with < 200 patients/arm.

Table 6. Continue tofacitinib 10 mg PO BID without interruption vs. Hold tofacitinib (1 week pre-vaccine, resume 1 week post-vaccine) in RA patients who are receiving seasonal influenza and PPSV-23 vaccines [3]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue TOF	Hold TOF	Relative (95% CI)	Absolute (95% CI)		
Satisfactory humoral response at 35 days post-vaccination - PPSV23												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	69/92 (75.0%)	77/91 (84.6%)	**RR 0.89** (0.77 to 1.03)	**93 fewer per 1,000** (from 195 fewer to 25 more)	⨁⨁◯◯ Low	
Satisfactory humoral response at 35 days post-vaccination - Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue TOF	Hold TOF	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	61/92 (66.3%)	58/91 (63.7%)	**RR 1.04** (0.84 to 1.29)	**25 more per 1,000** (from 102 fewer to 185 more)	⊕⊕◯◯ Low	

Seroprotection at 35 days post-vaccination - Influenza (2+/3 antigens)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	69/92 (75.0%)	75/91 (82.4%)	**RR 0.91** (0.78 to 1.06)	**74 fewer per 1,000** (from 181 fewer to 49 more)	⊕⊕◯◯ Low	

Seroconversion at 35 days post-vaccination - Influenza

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	47/70 (67.1%)	52/68 (76.5%)	**RR 0.88** (0.71 to 1.08)	**92 fewer per 1,000** (from 222 fewer to 61 more)	⊕⊕◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Single unblinded RCT. Details of randomization procedure and allocation concealment unclear. Results reported from per-protocol analysis of 183 (92%) of 199 enrolled patients.
b. Single study with < 200 patients/arm.

Table 7. Subgroup analysis: Continue tofacitinib 10 mg PO BID without interruption vs. Hold tofacitinib (1 week pre-vaccine, resume 1 week post-vaccine) in RA patients on background methotrexate who are receiving seasonal influenza and PPSV-23 vaccines [3]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue TOF+MTX	Hold TOF, Continue MTX	Relative (95% CI)	Absolute (95% CI)		
Satisfactory humoral response at 35 days post-vaccination - PPSV23												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	36/55 (65.5%)	44/55 (80.0%)	**RR 0.82** (0.65 to 1.03)	**144 fewer per 1,000** (from 280 fewer to 24 more)	⊕⊕◯◯ Low	
Satisfactory humoral response at 35 days post-vaccination - Influenza												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	38/55 (69.1%)	34/55 (61.8%)	**RR 1.12** (0.85 to 1.47)	**74 more per 1,000** (from 93 fewer to 291 more)	⊕⊕◯◯ Low	
Seroconversion at 35 days post-vaccination - Influenza												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	30/42 (71.4%)	32/44 (72.7%)	**RR 0.98** (0.75 to 1.28)	**15 fewer per 1,000** (from 182 fewer to 204 more)	⊕⊕◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Single unblinded RCT. Details of randomization procedure and allocation concealment unclear. Results reported for per-protocol analysis only.
b. Single study with < 200 patients/arm.

Table 8. Subgroup analysis: Continue tofacitinib 10 mg PO BID without interruption vs. Hold tofacitinib (1 week pre-vaccine, resume 1 week post-vaccine) in RA patients not on background methotrexate who are receiving seasonal influenza and PPSV-23 vaccines [3]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue TOF	Hold TOF	Relative (95% CI)	Absolute (95% CI)		
Satisfactory humoral response at 35 days post-vaccination - PPSV23												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	33/37 (89.2%)	33/36 (91.7%)	**RR 0.97** (0.84 to 1.13)	**28 fewer per 1,000** (from 147 fewer to 119 more)	⨁⨁◯◯ Low	
Satisfactory humoral response at 35 days post-vaccination - Influenza												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	23/37 (62.2%)	24/36 (66.7%)	**RR 0.93** (0.66 to 1.31)	**47 fewer per 1,000** (from 227 fewer to 207 more)	⨁⨁◯◯ Low	
Seroconversion at 35 days post-vaccination - Influenza												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Continue TOF	Hold TOF	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	17/28 (60.7%)	20/24 (83.3%)	**RR 0.73** (0.51 to 1.03)	**225 fewer per 1,000** (from 408 fewer to 25 more)	⨁⨁◯◯ Low	

CI: confidence interval; **RR:** risk ratio

Explanations

a. Single unblinded RCT. Details of randomization procedure and allocation concealment unclear. Results reported for per-protocol analysis only.
b. Single study with < 200 patients/arm.

Table 9. Additional data from observational studies and RCT data not suitable for GradePro – Pneumococcal polysaccharide vaccine.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2545 Winthrop 2016 [3]	RCT - Vaccine substudy of an ongoing open-label, multicenter, long-term extension study	43 days (35 days post-vaccination)	Per-protocol analysis: 183 adult patients with RA on tofacitinib 10 mg BID for at least 3 months prior to the vaccine substudy. Median age 54-57 years, 85.8% female. Patients excluded if previous PPSV-23 vaccine within last 5 years.	Participants randomized 1:1 to "Continuous" group - TOF without interruption (n=92) VS. "Withdrawn" group - TOF withdrawn 1 week prior to vaccination & resumed 1 week after vaccination (n=91). Background MTX in 55/92 (59.8%) of Continuous group, 55/91 (60.4%) of Withdrawn group. Prednisone (<10 mg daily) in 39/92 (42.4%) of Continuous group and 46/91 (50.5%) of Withdrawn group.	See **Table 6** for results of main analysis for satisfactory humoral response to PPSV-23 vaccine at 35 days post-vaccination. See **Table 7** for results of subgroup analysis for patients on background methotrexate. See **Table 8** for results of subgroup analysis for patients no on background methotrexate. **GMFR - Fold increase in GMT from pre-vaccination to 35 days post-vaccination:** Across all 12 pneumococcal subtypes tested: - The “Hold TOF monotherapy” group had the highest GMFR

				No changes in MTX or prednisone dosing permitted during study. Four exposure groups: Hold TOF monotherapy (n=36), Hold TOF, continue MTX (n=55), Continue TOF monotherapy (n=37), Continue MTX+TOF (n=55) All participants received one dose of PPSV-23 vaccine one week after study enrolment.	- The "Continuing TOF monotherapy" and "Holding TOF while continuing MTX" groups had diminished and similar GMFR responses - The lowest GMFR were observed in the "Continue TOF+MTX" group **No data for vaccine-related adverse events or RA disease flares were reported.**

Table 10. Additional data from observational studies and RCT data not suitable for GradePro – Seasonal influenza vaccine.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
2526 Park 2017 [1]	Randomized, single-blind, parallel-group trial	20 weeks (16 weeks post-vaccine)	Per-protocol population: 199 adult RA patients on a stable dose of MTX for at least 6 weeks. Mean age 58 years. 84.9% female.	Participants randomized 1:1:1:1 to one of four groups: Group 1 – Continue MTX (n=54) Group 2 – Hold MTX 4 weeks pre-vaccination (n=44) Group 3 – Hold MTX 2 weeks pre-vaccine, 2 weeks post-vaccine (n=49) Group 4 – Hold MTX 4 weeks post-vaccination (n=52) Mean MTX dose 13 mg weekly. Concomitant GC use in 115/199 (57.8%). Mean GC dose 2-3 mg daily. 31/199 (15.6%) on concomitant bDMARDs. All participants received one dose of seasonal trivalent influenza vaccine (H1N1/H3N2/B-Yamagata). All four groups were similar in terms of pre-vaccine antibody titers.	See **Table 1** for results from comparison of Group 2 vs. Group 1. See **Table 2** for results from comparison of Group 3 vs. Group 1. See **Table 3** for results from comparison of Group 4 vs. Group 1. **Fold increase in antibody titers at 4 weeks post-vaccination compared to pre-vaccine:** <u>H1N1:</u> Group 1: 5.1 (95% CI 3.4 – 7.8) Group 2: 5.0 (95% CI 3.2 – 7.8) Group 3: 8.7 (95% CI 5.3 – 14.5) Group 4: 8.1 (95% CI 5.3 – 14.4) <u>H3N2:</u> Group 1: 5.9 (95% CI 4.3 – 8.1) Group 2: 6.1 (95% CI 4.4 – 8.5) Group 3: 12.2 (95% CI 8.4 – 17.5) Group 4: 10.0 (95% CI 6.8 – 14.8)

					B-Yamagata: Group 1: 2.9 (95% CI 2.2 – 3.8) Group 2: 2.8 (95% CI 2.1 – 3.7) Group 3: 4.7 (95% CI 3.3 – 6.7) Group 4: 6.1 (95% CI 4.2 – 8.8) **No serious adverse events related to vaccination were reported during follow-up.**
4354 Park 2018 [2]	Prospective multicenter randomized investigator-blinded, parallel-group study	Four weeks post-vaccine for serology, RA flares. Up to 1 year post-vaccine for influenza-like illness.	320 adult patients with RA on a stable dose of MTX for 6 weeks or longer. Mean age 52-53 years, 85% female.	Participants randomized 1:1 to continue MTX (n=159) vs. discontinue MTX for 2 weeks after vaccination (n=161). 52.6% on concomitant GC (mean dose 1.8 mg daily). Mean MTX dose 13.3 mg weekly. All participants received one standard dose of the 2016-2017 seasonal quadrivalent inactivated influenza vaccine (H1N1/H3N2/B-Yamagata/B-Victoria). Primary analysis performed on modified ITT population (n=316; Continue MTX n=156, Hold MTX for 2 weeks post-vaccination n=160).	See **Table 4** for results from the comparison of primary and secondary outcomes between the MTX-hold and MTX-continue groups. **Fold increase in GMT from pre-vaccination to 4 weeks post-vaccination:** H1N1: MTX continue: 4.6 (95% CI 3.7 – 5.7) MTX hold: 6.7 (95% CI 5.4 – 8.3) p-value = 0.018 H3N2: MTX continue: 4.3 (95% CI 3.5 – 5.3) MTX hold: 8.0 (95% CI 6.4 – 9.9) p-value < 0.001 B-Yamagata: MTX continue: 3.1 (95% CI 2.6 – 3.8) MTX hold: 5.6 (95% CI 4.7 – 6.6) p-value < 0.001 B-Victoria: MTX continue: 2.9 (95% CI 2.4 – 3.4) MTX hold: 5.7 (95% CI 4.9 – 6.7) p-value < 0.001 **No serious adverse events related to vaccination were observed in either the MTX-hold group or the MTX-continue group.** **Subgroup analysis:** Vaccine responses did not differ between the MTX-continue group and the MTX-hold groups in the subset of patients who took MTX 7.5mg weekly or

					less. Significant differences between groups were observed in the subset of patients on MTX 15mg weekly or more.
9435 Park 2019 [4]	Post hoc analysis of RCT (4354 Park 2018)	Four weeks post-vaccine	160 adult RA patients on a stable dose of MTX for 6 weeks or longer. Mean age 53.7 yrs, 87.5% female.	All participants held MTX dose for two weeks post-vaccination. Mean MTX dose 13.1 mg weekly. Concomitant GC use in 46.3%, mean GC dose 1.7 mg daily. Concomitant bDMARDs in 10.6%. 0-3 days group: Received vaccination within 3 days of last MTX dose (n=65) 4-7 days group: Received vaccine 4-7 days after the last MTX dose (n=95). All participants received one standard dose of the 2016-2017 seasonal quadrivalent inactivated influenza vaccine (H1N1/H3N2/B-Yamagata/B-Victoria).	See **Table 5** for results from the comparison of vaccine response and seroprotection between the 0-3 days group and the 4-7 days group. **Fold increase in GMT from pre-vaccination to 4 weeks post-vaccination:** <u>H1N1:</u> 0-3 days: 7.0, 95% CI: 4.8 to 10.2 4-7 days: 6.5, 95% CI: 4.9 to 8.5 p=0.996 <u>H3N2:</u> 0-3 days: 8.7, 95% CI: 6.3 to 12.1 4-7 days: 7.5, 95% CI: 5.6 to 10.0 p=0.433 <u>B-Yamagata:</u> 0-3 days: 5.1, 95% CI: 3.9 to 6.7 4-7 days: 5.9, 95% CI: 4.7 to 7.4 p=0.390 <u>B-Victoria:</u> 0-3 days: 5.6, 95% CI: 4.4 to 6.7 4-7 days: 5.8, 95% CI: 4.7 to 7.1 p=0.899 **Results of dividing patients into 8 subgroups based on the number of days (0-7) between last MTX dose and influenza vaccination:** In logistic regression analysis, vaccine response, fold increase in HI antibody titers, and the rate of post-vaccination seroprotection were not associated with time between last MTX dose and time of vaccination.
2545 Winthrop 2016 [3]	RCT - Vaccine substudy of an open-label, multicenter, long-term extension study	43 days (35 days post-vaccination)	Per-protocol population: 183 adult patients with RA on tofacitinib 10 mg BID for at least 3	Participants randomized 1:1 to "Continuous" group - TOF without interruption (n=92) VS. "Withdrawn" group - TOF withdrawn 1 week prior to vaccination & resumed 1 week after vaccination (n=91).	See **Table 6** for results of main analysis for satisfactory humoral response, seroprotection, and seroconversion at 35 days post-vaccine. See **Table 7** for results of subgroup analysis for patients on background methotrexate.

			months prior to the vaccine substudy. Median age 54-57 years, 85.8% female. Patients excluded if previous influenza vaccine within last 6 months.	Background MTX in 55/92 (59.8%) of Continuous group, 55/91 (60.4%) of Withdrawn group. Prednisone (<10 mg daily) in 39/92 (42.4%) of Continuous group and 46/91 (50.5%) of Withdrawn group. No changes in MTX or prednisone dosing permitted during study. Four exposure groups: Hold TOF monotherapy (n=36), Hold TOF, continue MTX (n=55), Continue TOF monotherapy (n=37), Continue MTX+TOFA (n=55) All participants received one dose of 2011-2012 seasonal trivalent inactivated influenza vaccine (H1N1/H3N2/B-Brisbane) one week after study enrolment.	See **Table 8** for results of subgroup analysis for patients no on background methotrexate. **GMFR - Fold increase in GMT from pre-vaccination to 35 days post-vaccination:** For each of the three influenza antigens, similar GMFR responses were observed across the four TOF/MTX exposure groups with no statistically significant differences between groups. Of the three influenza antigens, the lowest GMFR responses were observed for influenza B antigen across all four groups. More robust GMFR responses observed for H1N1 & H3N2. **No data for vaccine-related adverse events or RA disease flares were reported.**

References:

1. Park JK, Lee MA, Lee EY, et al. Effect of methotrexate discontinuation on efficacy of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2017;76(9):1559-1565.
2. Park JK, Lee YJ, Shin K. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2018;77(6):898-904.
3. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis* 2016;75(4):687-695.
4. Park JK, Choi Y, Winthrop KL, et al. Optimal time between the last methotrexate administration and seasonal influenza vaccination in rheumatoid arthritis: post hoc analysis of a randomised clinical trial. *Ann Rheum Dis* 2019;78(9):1283-1284.

PICO 17: When should patients with RMD who are taking biologic medications with usual dosing schedules of monthly or longer* schedule (not live-attenuated) vaccine administration relative to next dose of medication?

Summary: The literature search identified no randomized controlled trials and 4 observational studies [1-4] that addressed this PICO question, all involving seasonal influenza vaccination administration relative to Rituximab (RTX). Study populations included 4 in RA [1-3], and 1 in mixed RMD including RA [4]. Data were not combined in GradePRO due to differences in immunogenicity outcomes and vaccination timing in relation to medication.

An Israeli prospective cohort [1] of 29 RA patients on RTX showed the increase in GMT (H1N1 p=0.015, H3N2 p=0.06, B p=0.22) was greater in late RTX (defined as vaccinated >5 months post RTX) compared to early RTX (defined as vaccinated within 5 months post RTX). A Dutch prospective cohort [2] with 23 RA patients on RTX showed significantly greater fold increase in titres for H3N2 and H1N1 ($p<0.05$), seroconversion, and increased CD19+ B cells (p=0.004) in late RTX (defined as vaccination 6-10 months post RTX) compared to early RTX (defined as vaccination 4-8 weeks post RTX). In a Swedish prospective cohort study [3] with 22/173 mixed-RMD patients on RTX, 10-fold higher GMT titers were observed in those receiving vaccination >24 weeks post RTX compared to those receiving vaccination <12 weeks post RTX (p= 0.04). Another Dutch prospective Dutch study [4] with 23 RA patients on RTX reported significant increases in IgG titres, and IgG1 and IgG3 subclass titres in late RTX (defined as vaccination 6-10 months post RTX) but not in early RTX (defined as 4-8 weeks post RTX). Together, these studies support an improved immune response in seasonal influenza vaccination administration months later after RTX.

Quality of evidence across all critical outcomes: Low for RTX

Table 1. Data from observational studies and RCT data not suitable for GradePro

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
1177, Arad, 2011 [1]	Prospective cohort study	4-6 weeks post-vaccine	29 RA patients on RTX (Mean age 61.8 years, 79.2% female, median RA duration 9.5 years, mean DAS28 4.5)	One dose of trivalent seasonal influenza vaccine (inactivated, standard dose). 16/29 early RTX: vaccinated within 5 months of last RTX infusion, 13/29 late RTX: vaccinated >5 months after last RTX	Late RTX group had greater increase in GMT compared to early RTX group for 3 antigens. H1N1: 2.1 vs. 1.1 H3N2: 1.7 vs. 1.3 B strain: 3.6 vs. 1.6 H1N1 p=0.015, H3N2 p=0.06, B p=0.22
3731, vanAssen, 2010 [2]	Prospective cohort study	28 days post-vaccine	23 adult patients with RA on RTX (Mean age 55.5 years, 70% female, 12/23 (52%) influenza vaccine in preceding	One standard dose of trivalent inactivated seasonal influenza vaccination. RA-RTX group (n=23): RTX 1000 mg IV x 2 doses, 2 weeks apart, except 375 mg/m2 IV weekly x 4 doses. First RTX cycle in 11/23 (48%), second cycle in 5/23 (22%).	Fold increase in titers at 28 days post-vaccine compared to baseline – median (range): RTX-Early vaccine (n=11): H3N2: 1 (-2 to 2), H1N1: 1 (-2 to 1.4), B strain: 1 (-1.4 to 2) RTX-Late (n=12): H3N2: 1 (-1.4 to 2), H1N1: 1.2 (-1.3 to 8), B strain: 1 (-2 to 5.7)

			year, median RA duration 13.8 years)	Median MTX dose 17.5 mg weekly, median prednisone dose 8.75mg OD Vaccination 4-8 weeks post-RTX in 11 patients (Early) vs. 6-10 months post-RTX in 12 patients (Late). Baseline CD19+ B cell numbers similar in both subgroups.	Significantly greater fold increase in titers in Late group vs. Early group for H3N2 & H1N1 ($p<0.05$) Seroconversion to any of the 3 influenza strains occurred in only 3 RA-RTX patients, all in the Late vaccine subgroup. No seroconversions in the Early vaccine subgroup for any strain. Significantly more CD19+ B cells present in patients in Late RTX subgroup ($p=0.004$).
4351, Gabay, 2011 [3]	Prospective cohort study	3-4 weeks	82 with RA, 45 with SpA, 46 with other inflammatory rheumatic diseases and 138 control subjects	Controls received 1 dose of adjuvanted influenza A/09/H1N1 vaccine, and patients received 2 doses of the vaccine. 22 on RTX	After 2 doses of vaccine, 10-fold lower titers were observed in patients to whom RTX had been administered <12 weeks before vaccination (HIA-GMT 33, 95% CI 0.2 to 5,533) vs those who received rituximab >24 weeks prior to vaccination (HIA-GMT 370, 95% CI 17.8 to 7,683]) ($p= 0.04$).
7496, Westra, 2014 [4]	Prospective cohort study	28 days post-vaccine	43 patients with RA, 20 on MTX, 23 on RTX Mean (SD) age 55.5 (7.6) years in RA-RTX, 57.1 (6.7) years in RA-MTX. 16/23 (70%) female in RA-RTX, 11/20 (55%) in RA-MTX. Median RA duration 13.8 years in RA-RTX, 8.7 years in RA-MTX.	One standard dose of trivalent subunit influenza vaccine (H1N1/H3N2/B-Malaysia). RA-RTX group (n=23): 11/23 (48%) vaccinated early - 4-8 weeks after RTX, 12/23 (52%) vaccinated late - 6-10 months post-RTX. 10/23 on concomitant MTX (median dose 17.5 mg weekly); 15/23 on prednisone (median dose 8.75 mg daily), 1/23 on another concomitant DMARD (not specified).	IgG & IgM responses to influenza vaccine: Significant increase in influenza-specific IgG antibodies at Day 28 in the "late" RTX group. Mean (SD) IgG to H1N1: 48.9 (35.5) on Day 0 vs. 137.9 (127) on Day 28 P=0.002 Mean (SD) IgG to H3N2: 39.6 (32.8) on Day 0 to 63.1 (49.8) on Day 28 P=0.001 No significant increase in influenza-specific IgG for either strain in the "early" RTX group. IgM responses were not observed for either strain in both "early" and "late" RTX groups. IgG subclass responses to influenza vaccine: Significant increase in IgG1 and IgG3 levels post-vaccination for H1N1 ($p=0.037$ & $p=0.007$) and H3N2 ($p=0.009$ & $p=0.010$) in "late" RTX group. "Early" RTX group showed no increase in IgG1 or IgG3 post-vaccine to either influenza strain.

References:

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2. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum*. 2010;62(1):75-81. doi:10.1002/art.25033
3. Gabay C, Bel M, Combescure C, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. *Arthritis Rheum*. 2011;63(6):1486-1496. doi:10.1002/art.30325
4. Westra J, van Assen S, Wilting KR, et al. Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients. *Clin Exp Immunol*. 2014;178(1):40-47. doi:10.1111/cei.12390

PICO 18: Should moderately to severely ill RMD patients with disease X defer vaccination (for NOT live-attenuated) until disease is better controlled?

Summary: The literature search revealed one prospective open label cohort study [1] and another open-label cohort study [2] that addressed this PICO question. The prospective cohort study included multivariate logistic regression indicating that higher level of disease activity in pediatric lupus patients (SLEDAI-2K score ≥ 8) was significantly associated with nonseroconversion. 24% of these patients seroconverted versus 48.8% who did not seroconvert (p=0.008). The second study showed that patients with "exacerbated" disease showed lower titers to bacteriophage ΦX174 at three months and five days after booster doses of vaccine.

Quality of evidence across all critical outcomes: Very low.

Table 1. Data from observational studies not suitable for GradePro

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
3531 Campos 2013[1]	Prospective open-label cohort study,	3 weeks	pSLE and healthy controls	2009 H1N1 vaccine 92 on antimalarials, 83 on prednisone (mean SD dosage of 18.8 17 mg/day), 72 on immunosuppressive drugs (44 azathioprine, 15 mycophenolate mofetil, and 14 methotrexate).	SLEDAI-2K score ≥8: 48.8% nonseroconverted, 24% seroconverted; p=0.008 Multivariate logistic regression indicated higher level of disease (SLEDAI-2K score ≥8) was significantly associated with nonseroconversion.

3853 Niwa 1979[2]	Open-label cohort study	Varied by treatment ; some outcomes evaluated at 5 days others up to 3 months	47 patients with autoimmune diseases (SLE n=22; DLE n=15; diffuse scleroderma n=10; 50 patients with "dermatosis" on steroids for non-autoimmune diseases, and 50 healthy controls	Bacteriophage ΦX174: Primary response: Serum obtained at baseline and 2 weeks after. Secondary response: dilution of the virus given 3 months after primary immunization and anti-bacteriophage titer measured before and 5 days after booster **Typhoid vaccine**: injected 5 times at weekly intervals and agglutinin titer to typhoid "O" Ag measured 2 weeks after each injection; titer >=1:40 indicated response and further immunization stopped after **Diphtheria toxoid**: 2 injections given IM 1 week apart, Antibody formation measured; solution injected intradermal 1 week after last injection of diphtheria toxoid, if patient had an injection site reaction >10mm they were non responders.	With exception of 2 SLE patients, all patients with autoimmune diseases whose clinical conditions were "exacerbated" showed remarkably low titers at 3 months and 5 days after booster shots vs. those in "good clinical condition." Data shown visually.

References:

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2. Niwa, Y. and T. Kanoh, Immune deficiency states and immune imbalance in systemic lupus erythematosus and other autoimmune diseases. Clin Immunol Immunopathol, 1979. **12**(3): p. 289-300.

PICO 19: Should RMD patients be vaccinated against HPV at ages greater than 26 years?

Summary: The literature search identified three studies that addressed this question, one case control [1], one study on baseline risk in SLE patients [2] and one non-randomized controlled trial [3].

Mok et al. 2013 [1] compared 50 SLE patients with stable disease with 50 healthy controls. Patients in this cohort were ages 18-35 years, mean age 25 years, and duration of follow up was 18 months. Gardasil vaccine was given to both groups at baseline, month 2 and month 6. Immunosuppressive medications in the SLE

group included systemic glucocorticoids in 70%, azathioprine in 48%, and mycophenolate in 18%, tacrolimus (10%), methotrexate (6%), cyclosporine (4%) and hydroxychloroquine in 66%. They found Gardasil vaccine was well tolerated and reasonably effective in SLE patients. Antibody titers did not correlate with age.

Feldman et al. 2017[2] examined baseline risk for high-grade cervical dysplasia or cancer in SLE patients who had newly started immunosuppression (methotrexate, azathioprine, cyclosporine, tacrolimus, abatacept, rituximab, cyclosporine, belimumab) or hydroxychloroquine in a population of 2,451 matched pairs of adult SLE patients identified using claims data from two US commercial health plans (mean age 45 years), and 7,690 matched pairs from a Medicaid database (mean age 39 years). Among women with SLE, there was a trend towards greater risk of high-grade cervical dysplasia and cervical cancer in those recently started on immunosuppression compared to those on hydroxychloroquine alone, but it was not statistically significant.

In a non-randomized controlled clinical trial, Dahr et al. 2017[3] evaluated 37 women with SLE, ages 18-50 years, with a history of mild-to-moderate, minimally active or inactive disease, assessing for immunogenic response after completing standard dosing schedule of quadrivalent HPV vaccine. Highly immunogenic responses were seen in all patients. The seroconversion rate was assessed for each HPV type (6, 11, 16, 18) and all were comparable to the mean GMTs reported in the Gardasil package insert for women ages 35-45 years.

Overall, these studies support benefit for the use of HPV vaccination in patients with SLE of any age; however, the quality of evidence is very low due to the lack of randomized control trial data, small studies, as well as studies only containing SLE patients and no other RMDs. Whether these data can be extrapolated to assume benefit in other RMD populations remains unknown, and in these settings decision to administer HPV vaccine series beyond the age of 26 should be driven by the same factors considered when vaccinating the non-RMD population against HPV.

Quality of evidence across all critical outcomes: Very low.

Table 1. Data from observational studies

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4047 Mok 2012[1]	Case control	18 months	50 patients with SLE and 50 health controls, aged 18-35 years, with stable disease	GARDASIL IM at baseline, month 2 and month 6 given to stable lupus patients on the following medications: - Prednisolone 70% - HCQ 66% - AZA 48% - MMF 18% - CSA 4% - Tac 10% - MTX 6%	At month 7 seroconversion rates of anti-HPV types 6, 11, 16 and 18 in SLE patients and controls were 74%, 76%, 92%, 76% and 96%, 95%, 98%, 93%, respectively. At month 12, rates were 82%, 89%, 95%, 76% for SLE and 98%, 98%, 98% and 80% for controls GARDISIL is well tolerated and reasonably effective in SLE patients age 18-35 and reasonably effective. Antibody titers did not correlate with age. Mean age was 25
7464 Feldman 2017[2]	Study on baseline risks in	n/a	2,451 matched pairs of SLE patients ≥ 18 yrs starting IS or HCQ	Identified high-grade cervical dysplasia or cancer in SLE patients newly started on IS	Among women with SLE, IS may be associated with a greater (not statistically significant) risk of high-grade cervical dysplasia and cervical cancer compared to patients receiving HCQ alone

	special population		identified using claims data from 2 US commercial health plans (mean age 45) and 7,690 matched pairs in Medicaid database (mean age 39)	including MTX, AZA, MMF, CYC, tac, ABA, ritux, cys or belimumab, propensity matched 1:1 to SLE patients newly starting HCQ	
7669 Dahr 2017[3]	Controlled clinical trial, not randomized	7 months	37 women ages 18-50 yrs with history of mild to moderate SLE and minimally active or inactive SLE	Quadrivalent HPV vaccine at standard dosing schedule	Highly immunogenic responses were seen in all patients. Seroconversion rate was assessed for each HPV type and comparable to mean GMTs reported in Gardasil package insert for women 35-45 years: - HPV 6 GMT 677.3 U/ml (397.3 package insert) - HPV 11 GMT 827.6 (512.8 package insert) - HPV 16 GMT 3052.1 (2129.5 package insert) - HPV 18 567.7 (324.6 package insert)

References:

1. Dhar, J. P., Essenmacher, L., Dhar, R., Magee, A., Ager, J., & Sokol, R. J. (2017). The safety and immunogenicity of Quadrivalent HPV (qHPV) vaccine in systemic lupus erythematosus. *Vaccine, 35*(20), 2642-2646. doi:10.1016/j.vaccine.2017.04.001
2. Feldman, C. H., Liu, J., Feldman, S., Solomon, D. H., & Kim, S. C. (2017). Risk of high-grade cervical dysplasia and cervical cancer in women with systemic lupus erythematosus receiving immunosuppressive drugs. *Lupus, 26*(7), 682-689. doi:10.1177/0961203316672928
3. Mok, C. C., Ho, L. Y., Fong, L. S., & To, C. H. (2013). Immunogenicity and safety of a quadrivalent human papillomavirus vaccine in patients with systemic lupus erythematosus: a case-control study. *Ann Rheum Dis, 72*(5), 659-664. doi:10.1136/annrheumdis-2012-201393

PICO 20: Should RMD patients receive vaccination against pneumococcus at ages less than 65 years?

Summary: The literature search identified five RCTs (1-5), eight cohort studies (6-11)[10159][10245], two case control studies (12, 13) and one open label trial(14) that addressed this PICO question. The data appear in tables 1 and 2 below, as well as GradePro tables 3-5. Very few studies specifically evaluated effectiveness of pneumococcal vaccine by age group, although the mean age of participants for the vast majority of these studies was < 65 years.

Multiple studies evaluated the “prime-boost” method of pneumococcal vaccination; pneumococcal conjugate (PC) vaccine followed by pneumococcal polysaccharide vaccine (PPSV). Bahuaud and colleagues examined 24 RA patients, of median age 63.5 years, who received PCV13 followed 2 months later by PPSV23 for seroconversion and seroprotection against 7 serotypes common to both vaccines, and 3 found only in PPSV23, over 24 months(6). Similar

percentages of protection were found for all serotypes at 4, 12 and 24 months, (63% vs. 55%, 54% vs 50% and 52% vs. 55%), however using functional antibody measurements only 19% of patients were protected at 24 months compared to 29% at baseline, questioning the advantage of prime-boost strategy in this population. In a prospective observational cohort of 26 pediatric SLE patients, Gorelik, et al. studied immunogenicity to PCV13 (received by all 26 SLE patients) followed by PPSV23 (in 22 patients) compared to a retrospective cohort of healthy controls(7). Sequential PCV13 and PPSV23 achieved protective status for about 2/3 of the study group - 17/65 (65%) achieved the primary endpoint of seroconversion following PCV13 and 13/22 (59%) following PPSV23, compared to 100% in retrospective controls. Rituximab in the 6 months preceding vaccination was associated with not meeting primary endpoint.

In an RCT, Nguyen, et al compared 65 RA patients after receiving one of 3 pneumococcal immunization strategies – a single dose of PCV13 followed by PPSV23 after 16 or 24 weeks, or double dose of PCV13 followed by PPSV23 after 16 weeks, to a comparison group of 35 RA patients on csDMARDs alone who received single dose PCV13 followed by PPSV23 16 weeks later (1). Median age in the csDMARD group was 59 years and was 62 years in the biologic group. There was no significant difference in primary endpoint between the 3 arms, however only 25% of rituximab patients reached primary endpoint (response to ≥6/12 pneumococcal serotypes 4 weeks after both vaccines) compared to ≥89% receiving other biologics. Another RCT examined SLE patients (median age < 42 years) who received PCV7 followed by PPSV23 24 weeks later and found that this prime boost strategy was immunogenic in the short term but was not superior to receipt of PCV7 alone, when examining rate of responders at week 28 (at least 5 of 7 serotypes shared by both vaccines)(2).

Caporuscio examined antibody response to PCV13 in RA patients on immunosuppression including steroids (mean prednisone 7.5 mg/d), methotrexate, TNF inhibitor and TNF inhibitor with methotrexate(12). The majority of patients were 60 years or older. Results of this study show similar immunogenicity of PCV13 in RA patients on immunosuppressive therapy, compared to healthy controls of mean age < 65 years. Response was not influenced by RA therapy, nor age. A retrospective cohort study by Coulson and colleagues examined pneumococcal antibody levels after PPSV23 vaccine in 124 RA patients on methotrexate, compared to 28 who were not vaccinated and found that those in the vaccinated group were 10 times less likely to develop pneumonia over a 10 year period(8). Mean age in the vaccinated group was 63 years.

A prospective cohort study of 88 RA patients receiving either rituximab, abatacept, tocilizumab with or without methotrexate and 85 patients on methotrexate monotherapy received PCV7 and were assessed for antibody response 4-5 weeks after vaccination(10). Treatment with rituximab and abatacept was associated with diminished response, and was most pronounced in rituximab-treated patients, regardless of methotrexate use. This study did not assess clinical outcomes, but did include patients younger than 65 years and supports vaccinating this group from a vaccine effectiveness standpoint. In a retrospective study of 93 patients with RA or IBD on TNF inhibitors or DMARD with median age of 50, response to PPSV23 was significantly impaired in patients treated with methotrexate, and even lower if combined with TNF inhibitor, compared to healthy controls(11).*(of note, this paper was old and the figure was really hard to read)*

As part of the ASPIRE study, 70 patients with early RA receiving either infliximab 3mg/kg with methotrexate, infliximab 6 mg/kg with methotrexate, or methotrexate alone received PPSV23 24 weeks after study initiation and assessed for antibody responses to 12 serotypes contained in the vaccine (5). They found that all 3 treatment groups had lower antibody responses than would be expected in immunocompetent persons, however addition of infliximab to methotrexate did not effect this response. Patients < 45 years of age and those on oral steroids appeared to respond better.

Two studies described risk of serious infection, including pneumococcal disease, in RMD patients receiving various degrees of immunosuppressive therapy. In a retrospective cohort of healthcare claims data, Shea et al reported increased rates of pneumococcal pneumonia and invasive pneumococcal disease in RA and

SLE patients compared to immunocompetent adults (9). Heusele and colleagues conducted a single-center case-control study of 69 patients who received rituximab for systemic autoimmune disease and followed them for 12 months(13). Twelve of 69 (17.4%) patients had at least one serious infection, and 3/13 serious infections were related to *Streprococcus pneumoniae* – all occurring in non-vaccinated patients.

In an RCT, Bingham et al. examined response to PPSV23 in RA patients receiving rituximab(4); 69 patients received rituximab with methotrexate and 34 received methotrexate alone. They found a decreased response to PPSV23 in the rituximab group (57% of patients had a 2-fold rise in titer in response to ≥1 serotype, compared with 82% of patients treated with MTX alone), suggesting PPSV23 should be administered prior to start of rituximab therapy. Age was not a predictor of immunization response.

One RCT assessed the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in RA patients receiving biologics or DMARDs in Japan (3). Out of 900 patients, similar numbers of patients in the vaccine and placebo groups developed pneumonia (3.7% vs. 3.4%), respectively). The authors' conclusion was that PPSV23 does not prevent against pneumonia overall in RA patients at relative risk for infection.

One small cohort study of 19 pediatric patients with JIA on treatment with TNFi reported a 94.7% response rate to pneumoccal vaccines (PCV13 and/or PPSV23). All patients received vaccination prior to starting TNFi [10159]. Another cohort study of 27 pediatric patients with a mixed group of rheumatic diseases reported significant increases in antibody titres to 9/12 serotypes following PCV13 vaccination. Antibody titres also increased upon follow-up vaccination with PPV23, but none of these increases was significant [10245].

Quality of evidence across all critical outcomes: Low

Table 1. RCT data not suitable for GradePro

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring in relevant population	Results
10159 Berho 2021[10159]	Single-center cohort study	Unclear	19 patients with JIA on treatment with TNFi. Mean age 13.8 years, mean disease duration 46.2 months.	**All patients received pneumococcal vaccination prior to starting TNFi:** - 9/19 (47.3%) received one dose PCV13 & one dose PPSV23 at 8 weeks - 8/19 (42.2%) received single dose of PPSV23	Specific IgG antibodies against 10 pneumococcal serotypes measured by ELISA at unspecified time post-vaccination. **Response to each serotype** defined as an IgG antibody titer >1.3 ug/ml post-vaccination. **Vaccine response** defined as response to 50% or more of the serotypes if age <6 years, or to 70% or more serotypes if age 6 years or older. 18/19 (94.7%) were vaccine responders One nonresponder (female patient with RF+ JIA on MTX + GC at time of single-dose of PPSV23) **Response rates to individual serotypes:** Serotype 1: 12/19 (63.1%) Serotype 3: 14/19 (73.6%) Serotype 4: 13/19 (68.4%) Serotype 5: 18/19 (94.7%)

				- 2/19 (10.5%) received single dose of PCV13 Mean time from last vaccine to TNFi start was 3 months. **Treatment at time of vaccination:** 17/19 (89.4%) on immunosuppression 16/19 (84.2%) on MTX 8/19 (42.1%) on prednisone 7/19 (41.1%) on MTX + prednisone 1/19 on SSZ + azathioprine **Treatment at time of serology:** All 19 on TNFi: - 13/19 (68.5%) adalimumab - 6/19 (31.5%) etanercept All 19 receiving additional immunosuppression: - 18/19 (94.7%) MTX	- Nonresponder received single PCV13 Serotype 6B: 18/19 (94.7%) Serotype 9V: 17/19 (89.4%) Serotype 14: 19/19 (100%) Serotype 18C: 18/19 (94.7%) Serotype 19F: 19/19 (100%) Leukocyte, lymphocyte, immunoglobulin, and complement levels were normal for all patients. Lower mean lymphocyte count in non-responders to serotype 4 compared to responders (2344/uL vs. 3535/uL; p=0.054).

				- 10/19 (52.6%) glucocorticoids 9/18 (50%) MTX + glucocorticoids	
10245, Jensen L, 2021[10245]	Prospective cohort study	median 77 days after PCV13, and 71 days after PPV23	27 children with rheumatic disease (SLE/MCTD most common, followed by JIA and a mix of others); excluded rituximab.	Prevnar 13, followed 8 wks later by Pneumovax	Samples collected at baseline, post-PCV13, and post-PPV23. Seroprotection for each serotype was defined as IgG ≥0.35 µg/mL. Relatively high seroprotection (>6 serotypes) noted at baseline, thought to be due to prior infectious exposure as all children were unvaccinated for *S. pneumococcus*. After PCV13, an increase in the antibody titres compared with pre-vaccination was found for all serotypes, and for 9/12 serotypes, the increase was significant. After PPV23, all serotypes except serotype 23F were seen to increase compared with post-PCV13 but none of the increases reached significance. Patients were on varying combinations of glucocorticoids, MTX, TNFi, azathioprine, MMF, and hydroxychloroquine, but results were not broken out by individual medication or disease type. 4 children were on no immunosuppressant.
4782 Mai T T Nguyen 2017	Randomized controlled trial of RA patients on biologics given 3 pneumococcal vaccine strategies compared to RA patients on MTX receiving	4 weeks following PPV23 boost dose	35 DMARD patients (91% MTX) who received PCV13 followed by PPV23 16 wks later 65 biologic patients (59% on TNFis, 21% on abatacept, 14% on IL-6is, 6% on RTX → of all of these, 68% were also on	PCV13 and PPV23	When considering the DMARD patients (most of whom were MTX) vs the biologic patients as a whole (most of whom were TNFi), the DMARD patients had less response to the pneumococcal vaccines (when considering (response defined as IgG >0.35mg/l or 4-fold rise) … specifically, both groups tended to show a response to at least 7 serotypes, but more biologic patients had a response to 8,9,10,11, or 12 serotypes than did patients on DMARDs alone. When looking at the specific biologic … anti-IL6 and abatacept patients had bery good responses (often 11 or 12 serotypes), with anti-TNF response still pretty good, but the ritux patient response poorest (most ritux patients mounted a response for 5 serotypes, and no ritux patients mounted a response for more than 7 serotypes). Ritux significantly impaired serologic response. (Figure 3 in publication).

	the standard vaccine strategy		MTX) who received: Grp 1A: PCV13 + PPV23 16 wks later Grp 1B: PCV13 + PPV23 24 weeks later Grp 2: double-dose of PCV13 + PPV23 16 weeks later		For patients on biologics, responses to the 3 vaccine strategies were similar, with Grp 1A appearing best, group 2A appearing next best, and Grp 2 appearing worst. (Figure 3B in publication) For TNFi patients, their response was very slightly impaired by also being on MTX. For IL6i patients, response to 10,11, or 12 serotypes was blunted by also being on MTX, but all patients (with or without MTX) responded to at least 9 serotypes. For patients on abatacept, being on MTX was associated with an IMPROVED response to the vaccine (no explanation provided by the authors). (Figure 4 in publication)
6472 Grabar 2017	Double-blind RCT	52 weeks	SLE patients Age (median (IQR): 39.5 (33.3-50.7)	25 received PPSV23 17 received PCV7 followed by PPSV23 24 weeks later primary endpoint: rate of responders at week 28 to at least 5 of 7 serotypes shared by both vaccines	PICO 3: At week 28, (4 weeks after PPSV23) primary endpoint achieved by 18/25 (72%) in the PPSV23 group and 13/17 (76%) in the PCV7-PPSV23 group. No differences by IS. PICO 4: no differences between rates of responders in either group in patients treated with and without IS and in those receiving < or > 10 mg prednisone PICO 20: *Sequential administration of PCV17 followed by PPSV23 is safe and shows short term immunological efficacy in patients with SLE but was not superior to PCV7 alone*
7331 Visvanathan 2007	RCT	38 weeks	70 RA patients: -20 IFX 3mg/kg+MTX -36 IFX 6mg/kg+MTX -MTX	PPSV23 given 34 weeks after start of IS Antibody responses were assessed	PICO 3: no significant difference in response to PPSV23 was observed between any of the 3 groups. 80-85% responded to at least one serotype PICO 4: patients receiving oral steroids generally *appeared* to respond better than those not receiving steroids PICO 20: all treatment groups had lower response to PPSV23 than would be expected in healthy persons, however addition of infliximab to MTX did not appear to affect response. patients < 45 years old appeared to respond better than those aged 45-65.

Table 2. Data from observational studies not suitable for GradePro

Ref ID, Author, year	Study type	Duration	Population Description	Monitoring in relevant population	Results
4125 Gorelik 2018	Cohort	40 weeks	26 pediatric SLE patients vs. 21 healthy controls mean age: 15.7 pLE, 10 controls	26 received PCV13. Of these, 22 went onto receive PPSV23 100% on HCQ, 54% corticosteroids, 50% mycophenolate, 19% azathioprine, 35% rituximab, 4% abatacept, 12% MTX/LEF	PICO 3: 17/26 (65%) achieved primary endpoint (>70% vaccinated serotype Ab levels >1.3mcg.dL) following PCV13 and 13/22 (59%) following PPSV23, compared to 100% in retrospective healthy controls. - rituximab in preceding 6 months was associated with not achieving protective levels Sequential PCV13 and PPSV23 achieved protective status for ~2/3 of pediatric SLE patients in this population
4026 Bahuaud 2018	cohort	24 months	24 RA patients	PCV13 followed 2 months later by PPSV23 (prime-boost) Primary outcome: Seroconversion for 7 serotypes common to both vaccines, and 3 included only in PPSV23 measured at baseline, 4, 12 and 24 months post-vaccine	PICO 3: similar percentages of protection were found at 4 months (63 vs 55%), 12 months (54 vs 50%) and 24 months (53 vs 55%) for the 7 common and 3 uncommon serotypes PICO 6: A decrease in protection was observed 24 months after vaccine, with only 19% of patients protected compared to 29% at baseline PICO 20: these results question the advantage of prime-boost strategy, as protection did not persist beyond 2 years, with levels of functional antibody decreasing to below pre-vaccine levels
509 Caporusci o 2018	Case control	12 months	38 RA patients (mean age 62.4 ys) on IS vs. 20 healthy controls mean age 62.7 yrs) RA patients were on a stable dose of oral steroids (mean	Antibodies to all PCV13 serotypes were measured pre vaccine, then at 1, 6 and 12 months	PICO 3: antibody response was not influenced by RA therapy (prednisone/methotrexate/TNFi) The percentage of responding subjects to each 13 serotypes did not differ between the two groups PICO 20: results of this study show a similar safety and immunogenicity of PCV13 in HC and RA patients on immunosuppressive therapy, of mean age < 65 years

			pred 7.5 mg/d) and mean MTX 15 mg/week. 14(37%) TNFi. 13(34%) TNFi+MTX		
6438 Coulson 2011	Retrospective cohort	10 years	152 RA patients on MTX - 124 prev. received PPSV23 28 not vaccinated	Assayed pneumococcal antibody levels	PICO 3: no correlation found between pneumococcal antibody levels and methotrexate dose or duration PICO 6: no correlation found between pneumococcal antibody levels and time since vaccination, although there was a trend for levels to fall from 7 years after vaccination PICO 20: these data show that vaccination of RA patients on MTX w/PPSV23 leads to increase in antibody levels, and suggests that patients who received PPSV23 were 10 times less likely to develop PNA over a 10- year period compared to those who have not been vaccinated. Mean age of RA patients in the vaccinated group was 63 (62 in non vaccinated)
7058 Shea 2014	Study on baseline risk, retrospective cohort	Data collection 2006-2010	Using data from 3 healthcare claims repositories to compare rates of pneumococcal disease in immunocompetent adults with chronic medical conditions (at-risk) and immunocompromised adults (high-risk)	Rates of all cause pneumonia were elevated in the high risk group, including RA, SLE, IBD, and risk increased with accumulation of at risk conditions and with age	PICO 20: risk for IPD and pneumococcal pneumonia is increased in high risk diagnoses compared to immunocompetent adults Pneumococcal pneumonia Rates of disease (per 100k) aged 18-49: 14 healthy, 59 RA, 100 SLE Rate ratios: 4.1, 95% CI: 3.3 to 5.2 RA; 7.1, 95% CI: 5.3 to 9.3 SLE Rates of disease (per 100k) aged 50-64: 25 healthy, 105 RA, 135 SLE Rate ratios: 4.1, 95% CI: 3.6 to 4.7 RA; 5.3, 95% CI: 4.2 to 6.7 SLE Rates of disease (per 100k) aged ≥65: 67 healthy, 271 RA, 272 SLE Rate ratios: 4.0, 95% CI: 3.6 to 4.5 RA; 4.0, 95% CI: 2.9 to 5.6 SLE IPD Rates of disease (per 100k) aged 18-49: 1.8 healthy, 11.4 RA, 26.5 SLE Rate ratios: 6.2, 95% CI: 3.7 to 10.5 RA; 14.4, 95% CI: 8.3 to 25.0 SLE Rates of disease (per 100k) aged 50-64: 4.5 healthy, 20.4 RA, 26.1 SLE Rate ratios: 4.6, 95% CI: 3.4 to 6.1 RA; 5.9, 95% CI: 3.4 to 10.1 Rates of disease (per 100k) aged ≥65: 8.3 healthy, 34.1 RA, 28.7 SLE Rate ratios: 4.1, 95% CI: 3.0 to 5.6 RA; 3.4, 95% CI: 1.3 to 9.2 SLE

7443 Heusele (2014)	Single-center case-control study	Follow-up for 12 months from the start of each RTX treatment course	All patients who received off-label RTX for systemic autoimmune disease between 2005 and 2011 (n=69) Mean (SD) age 51.4 (18.1) years, 81.2% female. 22 SLE, 14 pSS vasculitis, 9 AAV, 10 cryoglobulinemia, 12 hematologic, 3 IIM, 1 catastrophic APS. RTX course: 2 x 1000mg 2 weeks apart, or 4 x 375 mg/m2 weekly	Of 69 patients that received RTX: 55 received one course, 10 received two courses, 4 received 3 courses. Mean # RTX infusions = 2.9 Indications for RTX: 1. Refractory to GCs & 1+ immunosuppressive drug (n=64; 92.8%) 2. Dependent on high-dose GCs (prednisone >20mg OD) n=5; 7.2% Concomitant immunosuppressives drugs (n=26; 29.9%) Concomitant prednisone >15mg daily (n=41; 47.1%) 43/69 (62.3%) received pneumococcal vaccination (type not specified). 40 received vaccine prior to	12/69 patients (17.4%) experienced at least one serious infection during/after a RTX course. 5/12 patients died of infection – no deaths occurred in vaccinated patients. 13/87 (14.9%) RTX courses were associated with serious infections. 11/13 (12.6%) occurred within 6 months of start of RTX course. All were suspected or confirmed bacterial infections. Serious infection rate 18.7 per 100 patients-yrs. 3/13 serious infections were related to Streptococcus pneumoniae. All 3 occurred in nonvaccinated patients. Of patients who developed SIEs, 3/12 (25%) were vaccinated vs. 9/12 (75%) nonvaccinated. 3/43 (7.0%) vaccinated patients experienced serious infections vs. 9/26 (34.6%) nonvaccinated patients with serious infections. Odds of serious bacterial infection with pneumococcal infection: OR 0.11 (95% CI 0.03-0.41) p=0.0009 Mean (SD) age of patients with serious infection: 63.6 (18.8) years vs. 48.8 (16.7) years in patients without infections

				RTX, 3 after first RTX course.	
7485 Kapetanovic 2013	Prospective cohort	6 weeks	88 RA patients: 55 RTX - 26 MTX 17 ABA -13 MTX 16 TCZ -9 MTX 85 MTX Vs. 86 controls (SpA pts not on IS)	PCV7 Primary outcome: IgG against 23F and 6B serotypes checked at vaccination, and 4-5 weeks after. Antibody response (AR) was defined as ratio between post- and pre-vaccine Ab levels, and positive AR was >=2	<u>PICO 3</u>: RTX-treated patients had significantly lower AR for each serotype, no difference if they were taking methotrexate or not. RTX pts had significantly impaired positive AR compared to MTX, TCZ and controls ABA-treated patients TCZ-treated patients – immune response comparable to that of controls *Treatment with RTX and ABA was associated with diminished AR response and was most pronounced for rituximab, regardless of MTX use* <u>PICO 4</u>: concomitant prednisolone dose had no effect on vaccine response <u>PICO 20:</u> median age of patients was 68.9 yrs (RTX), 59.9 (RTX+MTX), 56.6 (ABA), 55.6 (TCZ), 61.5 (MTX) so did include patients < 65 – does not look at clinical effectiveness, but supports vaccinating those < 65 from a vaccine effectiveness standpoint
8281 Gelink 2008	Retrospective cohort	4 weeks	93 patients with RA or IBD - 52 TNFi - 41 DMARD Median age 50 18 healthy controls Median age 47	PPSV23	<u>PICO 3</u>: response rates, defined as post-vaccination titer ≥35 mcg/ml in combination with at least 2-fold increase in antibody titer to PPS 6B, 9V, 19F and 23F ** the figures in this paper were difficult to interpret, but response to PPSV23 was significantly impaired in patients treated with methotrexate, and furthermore if methotrexate combined with TNFi, compared to controls <u>PICO 20:</u> despite above, PPSV23 should not be withheld from patients on MTX and/or TNFi, and the median age in this group was 50 yrs

Table 3: MTX plus RTX vs MTX in RA patients(4).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
Response at 4 weeks (at least 1 serotype)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	36/63 (57.1%)	23/28 (82.1%)	**RR 0.70** (0.53 to 0.92)	**246 fewer per 1,000** (from 386 fewer to 66 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (at least 2 serotypes)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	27/63 (42.9%)	23/28 (82.1%)	**RR 0.52** (0.37 to 0.73)	**394 fewer per 1,000** (from 518 fewer to 222 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (at least 3 serotypes)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	24/63 (38.1%)	22/28 (78.6%)	**RR 0.48** (0.34 to 0.70)	**409 fewer per 1,000** (from 519 fewer to 236 fewer)	⨁⨁◯◯ Low	Favors MTX
Response at 4 weeks (at least 4 serotypes)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	21/63 (33.3%)	21/28 (75.0%)	**RR 0.44** (0.30 to 0.67)	**420 fewer per 1,000** (from 525 fewer to 247 fewer)	⊕⊕◯◯ Low	Favors MTX

Response at 4 weeks (at least 5 serotypes)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/63 (23.8%)	19/28 (67.9%)	**RR 0.35** (0.21 to 0.58)	**441 fewer per 1,000** (from 536 fewer to 285 fewer)	⊕⊕◯◯ Low	Favors MTX

Response at 4 weeks (at least 6 serotypes)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12/63 (19.0%)	17/28 (60.7%)	**RR 0.31** (0.17 to 0.57)	**419 fewer per 1,000** (from 504 fewer to 261 fewer)	⊕⊕◯◯ Low	Favors MTX

Response at 4 weeks (serotype 1)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	8/63 (12.7%)	12/28 (42.9%)	**RR 0.30** (0.14 to 0.64)	**300 fewer per 1,000** (from 369 fewer to 154 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 3)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	6/63 (9.5%)	8/28 (28.6%)	**RR 0.33** (0.13 to 0.87)	**191 fewer per 1,000** (from 249 fewer to 37 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 4)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	8/63 (12.7%)	17/28 (60.7%)	**RR 0.21** (0.10 to 0.43)	**480 fewer per 1,000** (from 546 fewer to 346 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 6B)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	24/63 (38.1%)	17/28 (60.7%)	**RR 0.63** (0.41 to 0.97)	**225 fewer per 1,000** (from 358 fewer to 18 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 8)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	21/63 (33.3%)	16/28 (57.1%)	**RR 0.58** (0.36 to 0.94)	**240 fewer per 1,000** (from 366 fewer to 34 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 9N)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	14/63 (22.2%)	17/28 (60.7%)	**RR 0.37** (0.21 to 0.63)	**382 fewer per 1,000** (from 480 fewer to 225 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 12F)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	7/63 (11.1%)	14/28 (50.0%)	**RR 0.22** (0.10 to 0.49)	**390 fewer per 1,000** (from 450 fewer to 255 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 14)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	19/63 (30.2%)	17/28 (60.7%)	**RR 0.50** (0.31 to 0.80)	**304 fewer per 1,000** (from 419 fewer to 121 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 19F)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/63 (25.4%)	15/28 (53.6%)	**RR 0.47** (0.27 to 0.82)	**284 fewer per 1,000** (from 391 fewer to 96 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 23F)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MTX + RTX	MTX	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	13/63 (20.6%)	10/28 (35.7%)	**RR 0.58** (0.29 to 1.16)	**150 fewer per 1,000** (from 254 fewer to 57 more)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 7F)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/63 (25.4%)	17/28 (60.7%)	**RR 0.42** (0.25 to 0.70)	**352 fewer per 1,000** (from 455 fewer to 182 fewer)	⨁⨁◯◯ Low	Favors MTX

Response at 4 weeks (serotype 18C)

1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	13/63 (20.6%)	16/28 (57.1%)	**RR 0.36** (0.20 to 0.65)	**366 fewer per 1,000** (from 457 fewer to 200 fewer)	⨁⨁◯◯ Low	Favors MTX

CI: confidence interval; **RR:** risk ratio

Explanations

a. No allocation concealment or blinding

b. Small sample size

Table 4: Should PPSv23 v placebo vs. placebo be used for pneumonia in RA (3)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PPSV23 v placebo	placebo	Relative (95% CI)	Absolute (95% CI)		
Pneumonia												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	17/464 (3.7%)	15/436 (3.4%)	**RR 1.06** (0.54 to 2.11)	**2 more per 1,000** (from 16 fewer to 38 more)	⊕⊕⊕◯ Moderate	
Pneumonia in patients with rheumatoid lung												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	10/81 (12.3%)	4/71 (5.6%)	**RR 2.19** (0.72 to 6.68)	**67 more per 1,000** (from 16 fewer to 320 more)	⊕⊕⊕◯ Moderate	
Pneumonia in patients receiving biologics												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	8/257 (3.1%)	6/253 (2.4%)	**RR 1.31** (0.46 to 3.73)	**7 more per 1,000** (from 13 fewer to 65 more)	⊕⊕⊕◯ Moderate	
Pneumonia in patients receiving immunosuppression												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PPSV23 v placebo	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	not serious	none	3/74 (4.1%)	2/70 (2.9%)	**RR 1.42** (0.24 to 8.24)	**12 more per 1,000** (from 22 fewer to 207 more)	⨁⨁⨁◯ Moderate	
Pneumonia in patients on >5mg/day steroids												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	5/130 (3.8%)	3/117 (2.6%)	**RR 1.50** (0.37 to 6.14)	**13 more per 1,000** (from 16 fewer to 132 more)	⨁⨁⨁◯ Moderate	
Pneumonia in patients w Steinbrocker stage 3 or 4												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	9/246 (3.7%)	9/239 (3.8%)	**RR 0.97** (0.39 to 2.41)	**1 fewer per 1,000** (from 23 fewer to 53 more)	⨁⨁⨁◯ Moderate	

CI: confidence interval; **RR:** risk ratio

Explanations

a. This study did not specifically assess clinical effectiveness of PPSV23 in patients less than 65 years of age

Table 5: Does PPSV23 response rate differ in RA patients on infliximab + MTX differ if < or ≥ 45 years(5)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IFX + MTX (aged <45 years	>/= 45 years)	Relative (95% CI)	Absolute (95% CI)		
Responders, 4 weeks												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	6/14 (42.9%)	7/42 (16.7%)	**RR 2.57** (1.04 to 6.37)	**262 more per 1,000** (from 7 more to 895 more)	⨁⨁◯◯ Low	Favors patients age <45 years

CI: confidence interval; **RR:** risk ratio

Explanations

a. Study did not specifically assess outcomes in patients 65 years and younger, but did assess in less than 45 years vs. 45 years and older
b. Small sample size

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PICO 21: Should RMD patients receive Shingrix vaccine at ages younger than 50 years?

Summary: The literature search did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 22. Should RMD patients receive standardized regimens of vaccine combinations?

Summary: The literature search did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low

PICO 23. Should RMD patients taking drug Y receive live-attenuated vaccines?

Summary: The literature search revealed 2 RCTs[1][10292] and 13 observational studies[2-13][9919] that addressed this PICO question.

Table 1 summarizes four observational studies that assessed development of yellow fever in patients with RMD after receiving the vaccine.[2-4][9919] There were no reports of development of yellow fever in any of the four studies. One cohort study[3] did compare patients on "low level" immunosuppression to "high level" immunosuppression. Patients on "low level" immunosuppression were not asked to taper or stop medications prior to receiving the vaccine compared to those with "high level" immunosuppression were asked to withdraw therapy prior to receiving the vaccine. There was no reported difference in the development of yellow fever after vaccine in these groups, but PRNT levels and peak RNAemia were both lower in RMD patients. Specifically, viremia was undetectable in SSc patients. A cohort study of 31 mixed RMD patients[3] who received the vaccine had no reported YF infections. Reports of a case control study[2] showed seroprotection and no infection in 15 mixed RMD patients.

Table 2 summarizes eight studies that addressed the development of varicella after receipt of the live vaccine in RMD patients.[1,5-10][10292] One RCT with 617 mixed RMD patients (310 received varicella zoster vaccine, 307 received placebo) reported no cases of confirmed varicella infection in either the vaccine or placebo group at 1 year follow-up. One case control study[5] resulted in no varicella infections in 10 SLE patients. Another case control study[6] compared a population of mixed RMD patients, non RMD patients and healthy controls, with hazard ratio less than one in RA patients with regards to the development of HZ. One cohort study of RA patients initiating tofacitinib[7] had <10% receipt of varicella vaccine and adjusted hazard ratio of 0.6 [95% CI 0.34–1.05]) for development of infection. A cohort study of RA patients on various medications[8] showed adjusted hazard ratio less than one with regards to the development of varicella after live vaccine. A third case control study of a mixed pediatric RMD population[9] showed that 2/25 patients on methotrexate developed zoster infection, compared to 0/18 healthy controls. A cohort of 17 patients with mixed autoinflammatory syndromes on either IL-1 or Il-6 blockade,[10] 1/5 who received varicella vaccine developed infection. Finally, a randomized controlled trial[1] of pediatric SLE patients included a total of 54 patients; none of those 28 vaccinated against varicella developed disease while 4/26 unvaccinated patients did develop disease.

Table 3 includes one cohort study[11] including 131 patients with Kawasaki disease who received IVIg within either 30 or 90 days of a live virus vaccine. None of these patients went on to develop infection.

Table 4 includes one retrospective cohort study[12] of 207 JIA patients (various types) who were vaccinated against MMR, none of the patients developed disease within one year. It also includes one observational cohort study[13] of mostly pediatric patients who received MMR and none went on to develop infection. A third cohort study[10] reported that one of 7 patients who received MMR vaccination developed pneumonia a week after vaccination; the patient had sJIA and was receiving canakinumab.

Quality of evidence across all critical outcomes: Very low

Table 1. Additional data from observational studies and RCT data not suitable for GradePro regarding yellow fever vaccine

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

9919 Tonacio 2021[9919]	Prospective, case control	Jan 2018 to April 2018	318 participants= 159 Autoimmune rheumatic disease (ARD) and 159 healthy controls; age ≥18 or ≤ 60 years old ARD group: low or inactive disease; low immunosuppression (hydroxychloroquine, sulfasalazine, prednisone 20 mg/day, methotrexate up to 0.4mg/kg/week(maximum of 20 mg/week) and leflunomide 20 mg/day without other drugs or associated with prednisone 7.5mg/day or hydroxychloroquine or sulfasalazine)	Yellow fever vaccine	No serious side effect reported in any ARD patient and no flares reported.
1562 Wieten 2016[2]	Case control	Up to 1407 days	15 mixed RMD patients: - 7 RA - 3 psoriatic arthritis - 2 psoriasis - 2 scleroderma - 1 pyoderma gangrenosum Medications: - 11/15 MTX 12 controls	Yellow Fever vaccine	Seroprotection: 15/15 mixed RMD on meds, 11/11 mixed RMD on MTX, 10/12 controls; *extracted data for groups n≥10

6419 Valim 2020[3]	Prospective single-center cohort study	28 days post-vaccine	227 patients aged 18 years or older with autoimmune diseases (AID), including RA (n=79), SpA (n=59), SSc (n=8), SLE (n=27), and pSS (n=54). All patients had low disease activity or were in remission. Mean (SD) age 51 (14) years; 71.8% female. 51 healthy controls [mean (SD) age 56 (15) years, 56.9% female]. Exclusion criteria for both groups: HIV, organ transplant, PID, cancer, previous YF vaccination or pre-vaccine seropositivity for anti-YF antibodies (PRNT >1:50)	All participants received one dose of the live attenuated 17DD-Yellow Fever (YF) vaccine. Patients on "low level" immunosuppression did not withdraw therapy prior to vaccination, including prednisone 20mg or less daily (n=27), MTX 20mg or less weekly (n=65), AZA 2mg or less daily, LEF (n=21), HCQ (n=39), or SSZ (n=11). Patient on "high level" immunosuppression were instructed to withdraw therapy prior to vaccination, including patients on bDMARDs (n=42), CYC (n=5), CNI (n=1), MMF (n=3), high-dose AZA, or prednisone >20mg daily (n=6). Recommended intervals between withdrawal & YF vaccination: >3 months for CYC, MMF, AZA, CNI; >6 months for rituximab; > 5.5 half-lives for other bDMARDs.	GMT for anti-YF Ab @ Day 28 (95%CI): HC (n=23): 440 (291-665) AID (n=160): 181 (144-228) p=0.005 vs. HC RA (n=46): 270 (183-401) SpA (n=51): 112 (73-170) p<0.001 vs. HC SSc (n=6): 206 (60-711) SLE (n=22): 143 (61-332) p=0.01 vs. HC pSS (n=35): 223 (133-376) Kinetic Timeline of anti-YF Ab (PRNT) levels: AID patients had significantly lower PRNT levels than HC at Day 5, Day 14, and Day 28. No significant differences in PRNT levels between AID patients & HC on Day 0, 3, 4, 6, or 7. Kinetic Timeline of 17DD-YF viremia: YF viral RNAemia peak was slightly later (Day 6 vs. Day 5) and lower in AID patients vs. HC. Similar viremia peak at Day 5-6 across all AIDs. Viremia was undetectable in SSc subgroup.
7926 Oliveira 2015[4]	Cohort	2 years	31 mixed RMD - 23 RA, 5 SLE, 2 SSc, 1 AS Medications - not reported for the whole group - for 23 RA: 16 MTX, 9 Leflunomide, 3 Infliximab, 3 Rituximab	Yellow fever vaccine	0/31 developed yellow fever infection

Table 2. Additional data from observational studies and RCT data not suitable for GradePro regarding varicella vaccine

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
10292 Curtis 2021 [10292]	RCT	1 year	617 patient on TNFi - 368 RA, 154 PsA, 50 AS, 23 IBD-arthritis, 39 other inflammatory arthritis, 3 reactive arthritis, 2 undifferentiated - 83 non-RMD TNFi - 202 Adalimumab, 193 Infliximab, 131 Etanercept, 56 Golimumab, 35 Certolizumab	310 Varicella Zoster Vaccine - 190 RA 307 Placebo - 178 RA	During 1 year of follow-up, no cases of confirmed varicella infection occurred in the vaccine or placebo group.
3510 Guthridge 2013[5]	Case control	12 weeks (weeks 2, 6, 12)	10 SLE Medications: - 7 HCQ - 2 MTX - Prednisone <10mg/d 10 controls	Zostavax, live attenuated vaccine	0/10 SLE on mixed medications developed HZ infection
7462 Yun 2016[6]	Case control; baseline population risk	3 years	50646 RA 8395 SLE 2629 PsA 1019 AS 58394 Gout Non-RMD: 7916 IBD 4299 PsO 214631 Diabetes 330727 Healthy controls	Live Zoster vaccine in 0.52% SLE, 1.10% RA, 0.80% PsA, 0.98% AS, 1.43% Gout	RA HZ vaccine unadjusted HR 0.74 (0.53-1.03) for development of HZ infection; adjusted model 1 (for age, sex, race) HR 0.71 (0.51–0.99); adjusted model 2 (for age, sex, race, biologics, steroids) 0.73 (0.52–1.02).

7448 Curtis 2019[7]	Cohort	5 years	8030 RA patients initiating Tofacitinib	Live Herpes Zoster vaccine in <10% (no actual number available)	Live zoster vaccine (adjusted HR 0.60 [95% CI 0.34–1.05]) for development of infection
7479 Yun 2015[8]	Cohort; Study on baseline population risk	5 years	29129 RA on new biologic treatment 28.7% abatacept 15.9% adalimumab 14.8% rituximab 12.4% infliximab 12.2% etanercept 6.1% tocilizumab 5.8% certolizumab 4.4% golimumab	2.29% Zoster vaccine before starting biologics	Vaccinated compared to unvaccinated risk of developing HZ infection HR 0.79 [95% CI 0.39–1.61]
7684 Pileggi 2010[9]	Case control	36 months	25 mixed RMD on meds - 17 JIA: 10 polyarticular, 5 systemic, 2 oligoarticular - 4 Juvenile Dermatomyositis - 3 Juvenile Scleroderma - 1 Vasculitis Medications - all on MTX (mean 16.4mg/m2/week) - 13 Prednisone (mean 4.2mg/d) - 5 other DMARDS 18 healthy controls	Varicella vaccine 1 dose	All RMD patients received vaccine Development of chickenpox infection: 2/25 mixed RMD on MTX receiving Varicella vaccine
7743 Jeyaratnam 2018[10]	Cohort	Cross-sectional only	17 autoinflammatory diseases - 7 systemic JIA, 5 CAPS, 4 MKD, 1 FMF Medications on anti-IL1 or anti-IL6: - 10 Anakinra	Received 1-2 live attenuated vaccines - 7 MMR - 5 Varicella zoster booster - 4 Yellow fever - 1 oral polio	Development of vaccine-induced infection: 1/5 developed Varicella

			- 4 Canakinumab - 3 Tocilizumab		
3881 Barbosa 2012[1]	Prospective RCT	Up to 360 days	54 pts w pSLE and 28 healthy controls; cohort of lupus patients had been previously exposed to the virus	Varicella zoster vaccine	0/28 vaccinated pSLE patients developed zoster while 4/26 unvaccinated pSLE patients developed zoster

Table 3. Additional data from observational studies and RCT data not suitable for GradePro regarding live virus vaccine

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7731 Lee 2017[11]	Cohort study	3 months	131 Kawasaki disease patients treated with Infliximab at Rady Children's in San Diego, CA between 2/2002 and 3/2016 who were under age 18 months or age 306 years at onset of KD, receiving infliximab	Retrospective review of serious infection or adverse events	38 patients received infliximab within 90 days of receiving a live virus vaccine and 14 of the 38 received their vaccine within 30 days before infliximab - and none had a serious infection.

Table 4. Additional data from observational studies and RCT data not suitable for GradePro regarding MMR vaccine

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7745 Heijstek 2007[12]	Retrospective cohort study	1 year	207 JIA patients (101 with persistent oligoarthritis, n=22 with extended oligoarthritis, n=55 with RF negative polyarthritis, n=5 with RF positive polyarthritis, n=17 with systemic arthritis, n=3 with enthesitis related arthritis, n=4 with PsA)	MMR	No MMR infections were reported (n=207). This was also true for patients using methotrexate (n=49)

5113 Uziel 2020[13]	Observational (pts who received MMR vaccine)	Unclear	234 mixed RMD peds patients (mostly JIA) from 10 countries. Of these, 124 were on methotrexate only, 39 were on biologics only, and 71 were on MTX+biolgoics	n/a	No severe AEs and no infections in any group.
7743 Jeyaratnam 2018[10]	Cohort	Cross-sectional only	17 autoinflammatory diseases - 7 systemic JIA, 5 CAPS, 4 MKD, 1 FMF Medications on anti-IL1 or anti-IL6: - 10 Anakinra - 4 Canakinumab - 3 Tocilizumab	Received 1-2 live attenuated vaccines - 7 MMR - 5 Varicella zoster booster - 4 Yellow fever - 1 oral polio	1/7 MMR recipients developed pneumonia 1 week after vaccination. The patient had sJIA and was receiving canakinumab.

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PICO 24: Should RMD patients taking drug Y hold the drug for a period of time prior to or after receiving live-attenuated vaccines?

Summary: The literature search identified 1 RCT [1] and 2 observational studies [2, 3] that addressed this PICO question. The RCT assessed the risk of herpes zoster infection among adult RA patients initiating tofacitinib 2-3 weeks after live zoster vaccination [1]. One observational study [3] assessed the safety and immunogenicity of live attenuated yellow fever (YF) vaccination in a mixed RMD population, while the second observational study [2] investigated the risk of serious infection among pediatric patients receiving infliximab for treatment of acute Kawasaki Disease (KD) within 3 months after receiving routine childhood live vaccinations (live rotavirus and/or MMR+VZV vaccines).

In a phase II RCT, Winthrop et al. [1] enrolled 112 patients aged 50 years or older with active RA on a stable background dose of methotrexate. All participants received a single dose of live zoster vaccine (LZV) and were randomized 1:1 to initiate tofacitinib 5 mg BID versus placebo 2-3 weeks after LZV vaccination [1]. Of the 55 patients randomized to initiate tofacitinib 2-3 weeks post-vaccination, one patient developed a disseminated cutaneous varicella infection 16 days after LZV vaccination and 2 days after starting tofacitinib [1]. Serology was consistent with a primary VZV infection. The cutaneous findings resolved after tofacitinib was discontinued and the patient received anti-viral treatment. There were no other serious vaccine-related adverse events or clinical HZ infections reported [1]. Overall, initiation of tofacitinib 2-3 weeks after LZV vaccination appeared safe, except for one patient who lacked pre-existing VZV immunity. Of note, these findings pertain specifically to initiation of tofacitinib post-vaccination and cannot be generalized to patients who are already taking tofacitinib pre-vaccination.

In a prospective, single-center observational study, Valim et al. [3] assessed the safety and immunogenicity of live attenuated YF vaccination in RMD patients versus healthy controls. The majority of RMD patients were on “low level” immunosuppression and were instructed to continue their medications without interruption during the vaccination period. A subset of RMD patients on “high level” immunosuppression were instructed to withdraw their medication prior to YF vaccination (see Table 2 for details). Among 211 RMD patients with clinical data available up to 28 days post-vaccination, only mild adverse events were reported [3]. There were no serious adverse events, including any YF infections [3]. Meanwhile, YF seropositivity at Day 28 occurred in 125/160 (78%) RMD patients with complete immunogenicity data [3]. Unfortunately, RMD patients on “low” versus “high” immunosuppression were not analyzed separately, limiting the conclusions that can be drawn from this study regarding continuing versus holding immunosuppressive medications prior to receipt of a live attenuated vaccine.

Finally, an observational study by Lee et al. [2] assessed the risk of serious vaccine-related infections in pediatric patients receiving infliximab for treatment of acute KD. They identified 38 patients who had received one or more live vaccines (rotavirus and/or MMR+VZV) within 90 days prior to receiving a single dose of infliximab, including 14 patients who received a live vaccine within 30 days prior to infliximab [2]. None of these patients experienced any serious infections in the 3 months post-discharge from their initial KD hospital admission [2], suggesting that the use of infliximab in children with acute KD who have recently received a live vaccine may be safe.

Quality of evidence across all critical outcomes: Very low

Table 1. RCT data not suitable for GradePro – Live zoster vaccine (LZV).

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
7664 Winthrop 2017[1]	RCT (Phase II double-blind, parallel-arm, placebo)	14 weeks post-vaccine	112 patients age >50 years, with active RA on stable background MTX. Randomized 1:1 to receive tofacitinib 5 mg BID (n=55) versus placebo (n=57), initiated 2-3 weeks post-vaccine. Tofacitinib group: Mean (SD) age 61.7 years, 76.4% female	All participants received a single dose of live zoster vaccine (LZV). 54/55 (98.2%) in TOF group on background MTX – mean (SD) dose 17.1 (4.7) mg weekly. 26/55 (47.3%) on daily prednisone – mean (SD) dose 5.9 (2.2) mg MTX, prednisone not held for vaccination.	Serious infections in the tofacitinib group (n=55): 1/55 patients developed disseminated cutaneous varicella infection 16 days post-vaccination (2 days after starting tofacitinib). This patient lacked pre-existing VZV immunity and serology was consistent with a primary VZV infection. The cutaneous findings resolved after tofacitinib was discontinued and patient received anti-viral treatment.

Table 2. Data from observational studies not suitable for GradePro – Live attenuated yellow fever (YF) vaccine.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

6419 Valim 2020[2]	Prospective, single-center cohort study	28 days post-vaccine	227 patients, aged 18 years or older with mixed RMD, including RA (n=79), SpA (n=59), SSc (n=8), SLE (n=27), and pSS (n=54). All patients had low disease activity or were in remission. Mean (SD) age 51 (14) years; 71.8% female. Compared to 51 healthy controls (HC), mean (SD) age 56 (15) years, 56.9% female Exclusion criteria for both groups: HIV, organ transplant, PID, cancer, previous YF vaccination or pre-vaccine seropositivity for anti-YF antibodies (PRNT >1:50)	All participants received one dose of the live attenuated 17DD-Yellow Fever (YF) vaccine. Patients on "low level" immunosuppression were instructed not to withdraw therapy prior to vaccination, including prednisone 20mg or less daily (n=27), MTX 20mg or less weekly (n=65), AZA 2mg or less daily, LEF (n=21), HCQ (n=39), or SSZ (n=11). Patient on "high level" immunosuppression were instructed to withdraw therapy prior to vaccination, including patients on bDMARDs (n=42), CYC (n=5), CNI (n=1), MMF (n=3), high-dose AZA, or prednisone >20mg daily (n=6). Recommended intervals between drug withdrawal & YF vaccination: >3 months for CYC, MMF, AZA, CNI; >6 months for rituximab; >5.5 half-lives for other bDMARDs.	<u>Immunosuppressive therapy in RMD patients:</u> Majority on “low level” immunosuppression. “High level” immunosuppression: 42/227 (18.4%) bDMARDs 13/227 (5.9%) AZA 6/227 (2.7%) High-dose prednisone (>20mg daily) 5/227 (2.3%) CYC 3/227 (1.3%) MMF 1/227 (0.4%) Cyclosporine-A Results for RMD patients on “low level” and “high level” immunosuppression reported in combination (no subgroup analyses). <u>Adverse events (AE) up to 28 days post-vaccine:</u> Data available for 211/227 RMD patients Local AE in 44/211 (21%) RMD patients Systemic AE in 67/211 (32%) RMD patients All AE were mild. No serious AE, including any cases of YF infection. <u>Immunogenicity of YF vaccine:</u> Seropositivity at Day 28 occurred in 125/160 (78%) RMD patients with available data. <u>Kinetic Timeline of 17DD-YF viremia:</u> Peak YF viremia level among RMD patients with available data (n=42) occurred on Day 6 at 5.9 (+/- 0.7) x 10^3 mean copies/mL. YF viral RNAemia peak and global maximum were detected at Day 5-6, regardless of RMD subgroup.

Table 3. Data from observational studies not suitable for GradePro – Live rotavirus vaccine.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

7731 Lee 2016[3]	Case series	3 months	Acute Kawasaki disease (KD) patients treated with infliximab at Rady Children's Hospital in San Diego, CA between 02/2002 and 03/2016, who were either under 18 months old or age 4-6 years at KD onset.	131 KD patients treated with a single dose of infliximab: - 5 mg/kg (n=114) - 10 mg/kg (n=17) All patients also treated with IVIG (2 g/kg). All live viral vaccines received within 90 days before infliximab were recorded Serious infections (requiring antimicrobials or hospitalization) within 3 months post-discharge from initial KD admission were recorded	<u>Live vaccinations:</u> Of 131 KD patients, 38 patients received a live viral vaccine within 90 days before infliximab: - 24 patients received a live vaccine between 31-90 days before infliximab - 14 patients received a live vaccine within 30 days before infliximab o 8 patients received a live vaccine within 14 days before infliximab <u>Rotavirus vaccine:</u> 13 patients received the live rotavirus vaccine within 1-30 days prior to infliximab - No serious infections requiring antimicrobials or hospitalization 17 patients received the live rotavirus vaccine within 31-90 days prior to infliximab - No serious infections requiring antimicrobials or hospitalization

Table 4. Data from observational studies not suitable for GradePro – Live MMR + VZV vaccination.

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

7731 Lee 2016[3]	Case series	3 months	Acute Kawasaki disease (KD) patients treated with infliximab at Rady Children's Hospital in San Diego, CA between 02/2002 and 03/2016, who were either under 18 months old or age 4-6 years at KD onset.	131 KD patients treated with a single dose of infliximab: - 5 mg/kg (n=114) - 10 mg/kg (n=17) All patients also treated with IVIG (2 g/kg). All live viral vaccines received within 90 days before infliximab were recorded Serious infections (requiring antimicrobials or hospitalization) within 3 months post-discharge from initial KD admission were recorded	<u>Live vaccinations:</u> Of 131 KD patients, 38 patients received a live viral vaccine within 90 days before infliximab: - 24 patients received a live vaccine between 31-90 days before infliximab - 14 patients received a live vaccine within 30 days before infliximab o 8 patients received a live vaccine within 14 days before infliximab <u>MMR+VZV vaccination:</u> One patient received the live MMR+VZV vaccine within 1-30 days prior to infliximab - No serious infections requiring antimicrobials or hospitalization 11 patients received the live MMR+VZV vaccine within 31-90 days prior to infliximab - No serious infections requiring antimicrobials or hospitalization

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2. Lee AM, Burns JC, Tremoulet AH. Safety of infliximab following live virus vaccination in Kawasaki disease patients. *The Pediatric Infectious Disease Journal* 2017;36(4):435-437.
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PICO question 25: Should neonates/infants with second and third trimester antenatal exposure to TNF inhibitors or Rituximab receive live-attenuated rotavirus vaccine in their first 6 months of life?

<u>Summary:</u> Evidence is extremely scant and limited to three observational studies in the IBD literature [1-3]. In total, data for 58 biologic-exposed children who received live rotavirus vaccines were reported; no clear adverse events occurred in any of these cases. However, as this was IBD literature, almost all biologics were TNF inhibitors. There is no data here on rituximab exposure.

Quality of evidence across all critical outcomes: Very low

Table 1. Data from observational studies not suitable for GradePro

Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
4659, Lee, 2019	Retrospective cross-sectional study	5 year span	18 women with IBD who had babies. 14 on infliximab, 1 on adalimumab, 2 on infliximab+azathioprine, 1 on adalimumab+azathioprine. Only 12 agreed to additional exam of children	BCG Rotavirus	4 children received BCG before 6 months of age 4 children received rotavirus before 6 months of age Total of 7 children who received live vaccines – no adverse reactions noted in any of these children. All 12 children received regularly scheduled HBV vaccine (0, 1, and 6 months). 4 of 12 did not seroconvert. 3 of the 4 who did not seroconvert were hospitalized for infection (bronchitis, colitis, pneumonia) before 12 months of age.
8206, Chiarella-Redfern, 2020	Retrospective cohort study	42 days post vaccination	157 infants both to mothers with IBD. Total of 14 biologic-exposed infants who rec'd rotavirus vaccine (13 full series, 1 partial) and 73 unexposed infants who received rotavirus vaccine	Rotavirus vaccine	Of the 14 biologic-exposed infants who received rotavirus vaccine, none had hospitalization. Rate of ED visits in vaccinated infants was similar (7.1% in biologic-exposed vs 6.9% of biologic-unexposed). Among biologic-unexposed infants, rate of ED visits for gastroenteritis was lower in those who were vaccinated vs. those who were not (5.5% vs 27.3%). Among biologic-exposed infants, ED visits for gastroenteritis were similar (14.3% vaccinated vs 10.2% unvaccinated)
8886, Beaulieu, 2018	Prospective registry	3 year span	153 biologic-exposed and 26 biologic-unexposed infants born to mothers with IBD	Standard vaccine schedule	No association between infliximab cord blood concentration and HiB or tetanus toxoid vaccine titers. 43 biologic-exposed infants rec'd rotavirus vaccine (data available for 40). Seven (17.5%) had reaction to vaccine (6 fever, 1 diarrhea). "comparable to the rates of fever or diarrhea reported in healthy infant." There was no correlation between level of biologic in cord blood and likelihood of adverse response.

References:

1. Beaulieu, D.B., et al., *Use of Biologic Therapy by Pregnant Women With Inflammatory Bowel Disease Does Not Affect Infant Response to Vaccines.* Clin Gastroenterol Hepatol, 2018. **16**(1): p. 99-105.
2. Chiarella-Redfern, H., et al., *Suboptimal Vaccination Administration in Mothers With Inflammatory Bowel Disease and Their Biologic-Exposed Infants.* Inflamm Bowel Dis, 2022. **28**(1): p. 79-86.

3. Lee, K.E., et al., *Influence of anti-tumor necrosis factor-alpha therapy to pregnant inflammatory bowel disease women and their children's immunity.* Intest Res, 2019. **17**(2): p. 237-243.

PICO 26: Should family members of RMD patients receive live-attenuated vaccines?

Summary: The literature search did not identify any studies that addressed this question.

Quality of evidence across all critical outcomes: Very low