OPEN ACCESS

KING'S College LONDON

King's Research Portal

DOI:
10.3899/jrheum.170710

Document Version
Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):
Subesinghe, S., Bechman, K., Rutherford, A. I., Goldblatt, D., & Galloway, J. B. (2018). A Systematic Review and Meta-Analysis of Anti-Rheumatic Drugs and Vaccine Immunogenicity in Rheumatoid Arthritis. *Journal of Rheumatology*, *45*(6), 733-744. https://doi.org/10.3899/jrheum.170710

Citing this paper
Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights
Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

•Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
•You may not further distribute the material or use it for any profit-making activity or commercial gain
•You may freely distribute the URL identifying the publication in the Research Portal

Take down policy
If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 04. Jan. 2025

The Journal of Rheumatology

0315-162X Meta-Analysis of Anti-Rheumatic Drugs and Vaccine Immunogenicity in Rheumatoid Arthritis

Journal:	*The Journal of Rheumatology*
Manuscript ID	2017-0710.R1
Manuscript Type:	Manuscript
Date Submitted by the Author:	27-Oct -2017
Keywords:	Rheumatoid arthritis, Vaccination, Biological therapy, Immunosuppression, Metaanalysis

Complete List of Authors: Subesinghe, Sujith; Academic Department of Rheumatology, King's College London
Bechman, Katie; Academic Department of Rheumatology, King's College London
Rutherford, Andrew; Academic Department of Rheumatology, King's College London
Goldblatt, David; University College London Medical School, Great Ormond Street Institute of Child Health
Galloway, James; Academic Department of Rheumatology, King's College London

SCHOLARONE™
Manuscripts

A Systematic Review and Meta-Analysis of Anti-Rheumatic Drugs and Vaccine Immunogenicity in Rheumatoid Arthritis

Short running footline: Immunosuppression and Vaccine Immunogenicity

Dr. Sujith Subesinghe [1]

Dr. Katie Bechman [1]

Dr. Andrew I Rutherford [1]

Prof. David Goldblatt [2]

Dr. James B Galloway [1]

1. Department of Academic Rheumatology, King's College London, Weston Education Centre, Cutcombe Road, Denmark Hill, London, SE5 9RJ
2. Institute of Child Health, University College London, 30 Guilford Street London, WC1N 1EH

S. Subesinghe BSc MBBS MSc MRCP. Clinical Research Fellow and Rheumatology Registrar

K. Bechman BSc MBBS MRCP. Clinical Research Fellow and Rheumatology Registrar

A.I. Rutherford BSc MBBS MSc MRCP. Clinical Research Fellow and Rheumatology Registrar

D. Goldblatt MBChB, FRCPCH, FRCP, PhD. Professor of Vaccinology and Immunology

J.B. Galloway MBChB, MSc, CHP, FRCP, PhD, FAcadMedEd. Senior Lecturer and Honorary Consultant Rheumatologist

Corresponding author: Dr James Galloway james.galloway@kcl.ac.uk

Department of Academic Rheumatology, King's College London, Weston Education Centre, Cutcombe Road, Denmark Hill, London, SE5 9RJ

Telephone (+44) 02078485203

Request for Reprints: Dr Sujith Subesinghe ssubesinghe@nhs.net

Department of Academic Rheumatology, King's College London, Weston Education Centre, Cutcombe Road, Denmark Hill, London, SE5 9RJ **Telephone** (+44) 02078485203

Key Words: Rheumatoid Arthritis, Biological therapy, Vaccinations, Immunosuppression, Meta-analysis

Disclaimers: The views expressed in the submitted article are the authors own and not an official position of their host institutions.

Source of support: No funding was received for preparation of this manuscript.

Competing interests: The authors have no competing interests to declare.

Word Count: 3488 words, Abstract 250 words

Tables and Figures: 3 tables (including 2 supplementary tables) and 3 figures

ABSTRACT

Objectives: Vaccination is a key strategy to reduce infection risk in RA patients and is advocated in internationally recognised rheumatology society guidelines. The aim was to evaluate to the impact of anti-rheumatic drugs on influenza and pneumococcal vaccine immunogenicity.

Methods: We conducted a systematic literature review and meta-analysis comparing the humoral response to influenza (pandemic and seasonal trivalent subunit vaccines) and pneumococcal (PPV23, PCV-7, PCV-13) vaccination in adult RA patients treated with anti-rheumatic drugs. Vaccine immunogenicity was assessed by seroprotection rates measured 3 to 6-weeks post immunisation. Risk ratios and 95% CIs were pooled.

Results: Nine studies were included in the meta-analysis (7 studies investigating anti-rheumatic drug exposures and influenza humoral response, 2 studies investigating pneumococcal vaccine response). Influenza vaccine responses to all subunit strains (H1N1, H3N2, B strain) were preserved with methotrexate and TNF inhibitor drug exposure. Methotrexate but not TNF inhibitor drug exposure was associated with reduced 6B and 23F serotype pneumococcal vaccine response (risk ratio 0.42, 95% CI 0.28 to 0.63) vs. 0.98 (95% CI 0.58 to 1,67)), however limited data were available to draw any firm conclusions. Combination of methotrexate with tocilizumab or tofacitinib was associated with reduced pneumococcal and influenza vaccine responses.

Conclusions: Anti-rheumatic drugs may negatively impact humoral responses to vaccination as evidenced by pneumococcal responses with methotrexate exposure, however they are safe and should not preclude immunisation against vaccine preventable disease. Vaccination should be considered in all RA patients and encouraged as part of routine care. Systematic review registration number: PROSPERO 2016: CRD42016048093.

INTRODUCTION

Rheumatoid arthritis (RA) patients are at an increased risk of infection compared to healthy subjects (1). The is due to a multifactorial complex interaction between inherent immune dysfunction, comorbidity, disease activity and immunosuppression (2). Highly targeted therapies (including Tumour Necrosis Factor inhibitor drugs (TNFi), Rituximab (RTX), Tocilizumab (TOC) and Abatacept (ABA) and most recently Tofacitinib (TOF)) have revolutionised RA management, however the infection risk associated with these drugs is a concern for clinicians and

patients.

British Society for Rheumatology (BSR), European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) guidelines (3, 4) recommend vaccination against vaccine preventable diseases (including influenza and pneumococcal infections). The literature supports the safety of common vaccinations in autoimmune disease and the Swedish EIRA study has reported no increased risk of developing RA following common vaccination (5, 6).

In the U.K., routine vaccination schedules advise annual influenza and single PPV23 vaccination in individuals over the age of 65 or anybody with chronic comorbid illness including pulmonary, cardiac, renal or liver disease. Immunocompromised patients (of any cause) should also be offered vaccination. Historically uptake of vaccination in RA populations has been poor, particularly with pneumococcal vaccination (7, 8). The reasons may include a lack of awareness about the indications for vaccination amongst primary or secondary care providers, concerns pertaining to vaccine safety, efficacy or fear of worsening disease activity.

The seasonal influenza vaccine is an inactivated trivalent subunit vaccine comprised of 3 viral antigens (2 ‘A’ strains, H1N1 and H3N2 and a single ‘B’ strain). The pandemic influenza vaccine (pH1N1) is utilised when necessary. In the U.K., two commercially available pneumococcal vaccines are currently used, a 23-valent polysaccharide vaccine (PPV23) and a 13-valent conjugate vaccine (PCV-13) which superseded a 7-valent conjugate vaccine (PCV-7) in 2010. Vaccine immunogenicity depends upon vaccine type and vaccine strain but post-vaccination antibody (Ab) titres to assess vaccine response are not routinely measured (9).

EULAR guidance recommends that influenza and pneumococcal vaccines should be administered prior to immunosuppression. Vaccination can be

administered during non-biologic disease modifying anti-rheumatic drugs (nbDMARDs) and TNFi treatment but ideally prior to commencing RTX (3). This is because immunosuppression may blunt serological responses to vaccination.

The rationale for undertaking this systematic review of the literature and meta-analysis was to evaluate the impact of immunosuppressive drugs commonly used in RA on humoral immune responses to influenza and pneumococcal vaccination.

MATERIALS AND METHODS

The study was conducted in accordance with the preferred reporting items for systematic reviews and meta- analysis guidelines (10). The systematic review was registered with the international prospective register of systematic reviews (registration number: PROSPERO 2016: CRD42016048093). Ethics board approval was not required for this study.

Search strategy and information sources

The literature was searched systematically by two investigators (S.S. and K.B.) using MEDLINE and EMBASE databases. The vaccines of interest were influenza (seasonal, pH1N1) and pneumococcal (PCV-7, PCV-13, PPV23) vaccines. The search terms were ‘inflammatory arthritis’ or ‘rheumatoid arthritis’ and ‘immunisation’ or ‘vaccination’ or ‘vaccine’ or ‘influenza’ or ‘pneumovax’ or ‘prevenar’.

The search was undertaken in 6th October 2016 and re-run on 12th October 2017 prior to the final analysis to identify further studies that could be retrieved for analysis.

Eligibility criteria and study selection

English language publications of prospective cohort studies and randomised control trials published between 1st January 2000 and 6th October 2016 were

sought. Case reports and conference abstracts were excluded. RA patients aged over 18 years treated with anti-rheumatic drugs who had received influenza and/or pneumococcal vaccines were considered. Alternative diagnoses of inflammatory arthritis were excluded. Drugs exposures studied included methotrexate (MTX), TNFi, RTX, TOC, ABA and TOF. Other nbDMARDs were not studied.

The primary outcome of interest was evidence of seroprotection (SP) as a surrogate measure of vaccine immunogenicity, classified by anti-rheumatic drug exposure. Seroconversion (SC) and/or SR were considered if SP rates were not published or calculable from the data presented. For influenza vaccination, SP was considered as a post-vaccination Ab titre measured by haemagglutination inhibition assay (HI) of ≥ 1:40, SR or SC a 4-fold increase in post vaccine Ab titre. For this study and in the absence of an accepted universal correlate of vaccine protection, a post-vaccination Ab titre of 1 mcg/ml was used as a marker of likely protection following pneumococcal vaccination, SR was defined as ≥2-fold increase in post-vaccine Ab titres. Studies reporting only on geometric mean titres (GMT), opsonisation index (OI) or Ab response rates were excluded. Vaccine response was assessed between 3 and 6-weeks post influenza and pneumococcal vaccination. Healthy controls (HC) or RA subjects not taking anti-rheumatic or immunosuppressive therapies served as the comparator groups.

Titles and abstracts of studies retrieved using the search strategy detailed above and those from additional sources (including reference lists of selected publications) were screened independently (by S.S. and K.B.). The full text of the potential studies for inclusion were retrieved and assessed for eligibility. The full electronic search strategy is available in the supplementary material accompanying this manuscript.

Data collection process and outcomes and quality assessment

Data were extracted independently (by S.S. and K.B.). Disagreements over study eligibility, quality (as assessed using the Newcastle-Ottawa Score (NOS) for cohort studies) or risk of bias were resolved through discussion with a third reviewer (J.G.) where necessary. Details of the assessment of study quality are available in the supplementary material (supplementary Table 1). Data collated included the source (main author, journal, publication date), study design, vaccination intervention, anti-rheumatic drug exposure and patient characteristics (age, disease duration, disease activity, quality of life measures where available). SP, SR and SC rates were documented or calculated from data available.

Data synthesis and statistical analysis

Analyses were performed using Review Manager software version 5.3 (Cochrane Collaboration, Oxford, U.K.). Sensitivity analyses compared vaccine response within immunosuppression class and descriptive analysis was undertaken to assess the effect of vaccine response in patients with RA by drug class. Summary data rather than individual level data were aggregated for quantitative analyses. Summary estimates of response were tabulated and compared using a meta-synthesis approach with forest plots.

RESULTS

Literature search and study characteristics

The initial search strategy yielded 3893 articles for screening which was reduced to 47 after application of filters and screening of titles and abstracts. Nine studies were selected for inclusion (7 influenza (seasonal or pandemic) and 2 pneumococcal vaccine studies). The search strategy is detailed in Figure 1. The

characteristics of studies examining influenza and pneumococcal vaccine immunogenicity are detailed in Tables 1 and 2, forest plots for the risk ratio (RR) of response rates for influenza vaccine strains and pneumococcal serotype responses separated by anti-rheumatic drug exposure (MTX or TNFi) are represented in Figures 2 and 3. All studies included in the meta-analyses were prospective cohort studies. There was good agreement between reviewers on the quality of included studies; all included studies scored between 5 and 7 on the NOS scale (see supplementary material Table 1). It was not possible to evaluate the impact of RTX, ABA, TOC or TOF in meta-analyses either due to an absence HC or comparator groups, unpublished vaccine response rates or limited number of studies available for analysis. These studies are discussed further as part of a narrative review. Studies examining the immunogenicity of pneumococcal vaccine in the context of anti-rheumatic drug exposures have been included in a supplementary material (supplementary Table 2).

Influenza vaccine responses

MTX and influenza vaccination response

Five studies including 787 subjects (350 RA patients, 437 controls) assessed MTX exposure and influenza vaccine humoral responses (11-15). Three studies assessed the response to pH1N1 influenza vaccination, these results were pooled with seasonal influenza H1N1 responses (15-17). MTX exposure was not associated with reduced SP responses to H1N1 (pooled (RR) 0.88 [95% Confidence Interval (CI) 0.69 to 1.11], H3N2 (pooled RR 0.94 95% CI 0.85 to 1.04) or B strain (pooled RR 1.15, 95% CI 0.63 to 2.10).

TNFi and influenza vaccination response

In total, 803 subjects from 7 studies were pooled in the meta-analysis examining TNFi impact on influenza vaccine immunogenicity (304 RA patients, 499 controls) (11-17). Three studies exclusively examined the influence of TNFi exposure on pH1N1 influenza response, these results were combined with seasonal influenza H1N1 responses (15-17). TNFi exposure was not associated with reduced SP responses to H1N1 (pooled RR 0.86, 95% CI 0.72 to 1.04), H3N2 (pooled RR 0.98, 95% CI 0.74 to 1.31) or B strain (pooled RR 1.38, 95% CI 0.70 to 2.72).

RTX and influenza vaccine response

Two studies have described reduced seasonal influenza vaccine responses in RTX treated patients compared to nbDMARD treated patients and HC (18, 19). Arad et al. (18) reported that a longer interval between RTX administration and influenza vaccination was associated with an improved Ab response in contrast to Oren et al. (19) who found no such relationship.

ABA and influenza vaccine response

Ribeiro et al. (20) reported a significantly poorer humoral response to pH1N1 vaccination in ABA treated patients compared to age matched MTX treated patients and HC. Alten et al. described preserved influenza vaccine responses in 296 ABA exposed patients pooling the results from 2 multi-centre, open-label sub-studies (21). In total, 49.5% of patients achieved an appropriate post-vaccine humoral response. Despite vaccine responses not being compared against a comparator group, the authors felt the vaccine responses were preserved.

TOC and influenza vaccine response

Iwamoto et al. (15) reported appropriate humoral responses to pH1N1 vaccination in TOC treated patients compared to HC. However, combination MTX+TOC compared to TOC monotherapy has been associated with a blunted

vaccine response in subjects receiving pH1N1 vaccination (22). Tsuru et al. (23) reported preserved SP rates for all 3 strains of seasonal influenza vaccine in TOC exposed compared to TNFi/nbDMARD treated patients.

TOF and influenza vaccine responses

The data on influenza vaccine response and TOF exposure are limited. Winthrop et al. reported 2 studies investigating humoral responses to trivalent influenza vaccine (24). In both studies, humoral response was considered as a 4 fold increase in at least 2 of 3 influenza antigens, assessed 5 weeks post vaccination. The first study was undertaken in TOF naïve patients randomized 1:1 to TOF 10mg BD or placebo, stratified by MTX exposure. Combination TOF+MTX therapy was associated with poorer influenza humoral response compared to placebo, TOF and MTX monotherapy. In the second study, the effect of temporary withdrawal of TOF compared to continuous therapy was investigated; temporary withdrawal of TOF (1 week pre and post vaccination) had no significant impact on humoral vaccine responses.

Pneumococcal vaccination

MTX and pneumococcal vaccination response

Two studies reporting on 254 subjects (122 RA patients, 132 healthy controls) examining MTX exposure and 6B and 23F pneumococcal serotype responses were included in the meta-analysis (25, 26). From the limited data for the two serotype studies, MTX exposure was associated with a reduced vaccine response compared to HC (pooled RR 0.42, 95% CI 0.28 to 0.63).

TNFi and pneumococcal vaccination response

Two studies reporting on 273 subjects (141 RA patients, 132 healthy controls) assessing 6B and 23F pneumococcal serotype responses with TNFi exposure (25,

26) were included in the meta-analysis. From the limited data, TNFi exposure had no significant negative impact on vaccine response compared to HC, (pooled RR 0.98, 95% CI 0.58 to 1.67).

RTX and pneumococcal vaccine response

Comparing RA patients treated with RTX+MTX (n = 65) with MTX monotherapy (n = 28), Bingham et al. (27) reported that RTX exposed patients had a reduced response to vaccination for each of the 12 PPV23 serotypes tested. The proportions of RTX treated patients with a positive vaccine response (to at least 1, 2, 3, 4, 5, and 6 serotypes) was also decreased compared to MTX monotherapy.

ABA and pneumococcal vaccine response

The data on ABA exposure and humoral vaccine response are conflicting. Migita et al. (28) found significantly decreased Ab response rates for 6B and combined 6B/23F SR rates in ABA exposed patients compared to MTX and RA control groups. In contrast, Alten et al. (21) described preserved SP response to PPV23 vaccination with 55.4% of ABA exposed patients achieving adequate SP response to PPV23 vaccination.

TOC and pneumococcal vaccine response

TOC monotherapy is not associated with impaired PPV23 vaccine response however combination with MTX has been reported to blunt 6B and combined 6B/23F serotype responses (23, 29, 30).

TOF and pneumococcal vaccine response

The data on TOF exposure and pneumococcal vaccine responses are limited; the results of two studies investigating pneumococcal responses in the context of TOF exposure were reported by Winthrop et al. (24). Combination of TOF+MTX was associated with reduced humoral response to PPV23 vaccine compared to placebo,

TOF or MTX monotherapy. Temporary withdrawal of TOF (1 week pre- and post PPV23 vaccination) had little effect on humoral vaccine response compared to continuous therapy.

DISCUSSION

Our meta-analysis found no detrimental effect of MTX therapy on influenza vaccination, but a diminished response to pneumococcal vaccination. There was no observation of an adverse humoral response to influenza or pneumococcal vaccination with TNFi exposure.

Meta-analysis of pneumococcal vaccination responses with immunosuppression exposure was challenging due to the significant heterogeneity in reporting vaccine response; we only considered responses to 6B and 23F serotypes. Despite not being the most prevalent serotypes, bacterial pneumonia associated with 6B and 23F have a high mortality risk (31). We accept that vaccine response may differ across individual pneumococcal vaccine serotypes. Despite achieving a satisfactory response to one serotype, it is not appropriate to assume that vaccine responses for other serotypes will be equal. Vaccine efficacy was defined as achievement of post-vaccination SP Ab titres, however subjects could achieve SP without SR or SC. SP doesn't provide information on vaccine efficacy and we acknowledge alternative methods of reporting vaccine immunogenicity and efficacy, e.g. OI or GMT rises.

Vaccine responses for PCV-7 and PPV23 responses were pooled. PCV-7 however is no longer part of the routine U.K vaccine schedule and was replaced by PCV-13. Both PCV-7 and PCV-13 include 6B and 23F serotypes. Although comparing a conjugated and polysaccharide vaccination may not be appropriate

when considering long term vaccine responses, comparison of vaccine immunogenicity at 3 to 6 weeks post vaccination is similar (32).

Although it was not possible to undertake meta-analysis of the impact of RTX on humoral responses to influenza and pneumococcal vaccination, there are consistent reports in the literature of poorer serological responses to immunisation (19, 27, 33-35). The timing of RTX has also been an important consideration in the assessment of vaccine immunogenicity; a greater interval between RTX administration and vaccination has been associated with an improved vaccine response (18). There were limited data to perform meta-analysis on TOC exposure on vaccine responses compared to healthy controls, although review of the literature suggests there no significant effect on PPV or influenza vaccine immunogenicity (22, 29). Comparatively, ABA has been reported to impair the responses to pH1N1 and PPV23 response (20, 28). TOF in combination with MTX is associated with reduced influenza and pneumococcal vaccine responses. Temporary withdrawal of TOF no significant effect on influenza or PPV vaccine immunogenicity.

EULAR guidelines recommend vaccination against influenza and pneumococcal disease should be undertaken prior to commencement of TNFi or nbDMARD therapy, we accept that in practice this is challenging and may be unrealistic. EULAR guidance (3) also advises vaccination should be undertaken in a period of disease stability however in U.K. practice, biologic drugs (often a trigger to administer vaccinations) are only considered in patients with persistent high disease activity states (DAS28 >5.1). There is limited evidence that vaccine responses are attenuated in RA in patients with high disease activity states. A key clinical decision is determining the best time to vaccination, either before immunosuppressive therapy or in a period of disease stability. Live vaccines are currently contraindicated in the

setting of immunosuppression. If a live vaccine is indicated, vaccination should be administered 2 to 4 weeks prior to immunosuppression, or at least 3 months after stopping nbDMARDs. The Centers for Disease Control and Prevention have provided guidance on the safety of the shingles vaccine in the context of immunosuppression; it is safe to administer the shingles vaccine in patients on nbDMARDs including Azathioprine and MTX but it avoided in patients on biologics and high-dose prednisolone (>20 mg per day) (36).

Only 2 studies included in the meta-analyses reported specifically on the effect of vaccination on disease activity however several confirm no evidence of a detrimental effect on parameters of disease activity post vaccination (13, 17-19, 33, 34, 37-40).

To our knowledge, there has been 1 previous meta-analysis assessing the influence of anti-rheumatic drug therapies on influenza and pneumococcal vaccine responses (41). Of note, there was an alternative methodological approach to analysis and probable access to unpublished data. In Hua's meta-analysis, the definitions and characteristics of treatment exposed and control groups differed, for example when assessing the influence of MTX on pneumococcal vaccine response, the experimental group compared MTX + TNFi exposed patients to TNFi monotherapy rather than HC.

We recognise that biologics are co-prescribed with nbDMARDs including MTX in routine clinical practice. However, by comparing drug therapies with HC groups in our analysis, we felt it would allow better assessment of the impact of drug therapy on vaccine immunogenicity, albeit to the detriment of potential number of studies and subjects that could be included in meta-analysis. Additionally, we have considered newer anti-rheumatic therapies including ABA, TOC and TOF. Our assessment of

MTX exposure negatively impacting pneumococcal vaccine response is congruent with Hua and colleagues, although we did not observe a negative influence of MTX on influenza vaccination.

The NOS was used to assess the risk of bias and grade the quality of included studies. All studies were of ‘satisfactory’ or ‘good’ quality however, there are sources of bias in our meta-analysis that we acknowledge.

Our review was potentially subject to outcome reporting bias. We only included studies reporting on post-vaccine Ab titres (rather than OI or GMT responses) as it was the most commonly reported method of assessing vaccine response. Literature review identified several studies that could not be included due to the heterogeneity in study design or differing methods of reporting vaccine efficacy, particularly those reporting on pneumococcal vaccine immunogenicity. Several studies reported on Ab response rates, GMT rises or OI without providing numerical data on response rates for SP, SR or SC. However, the conclusions drawn from each study agreed with our findings and provided further evidence that TNFi do not significantly diminish the response to pneumococcal or influenza vaccines (33, 38, 39, 42-46).

We included 2 studies from a single centre analysing vaccine responses of 2 pneumococcal serotypes (6B and 23F), thus the generalizability of our conclusions is limited. A strength is that both studies were methodologically similar and good quality with low risk of bias. There was a relative paucity of data examining newer biologic agents including RTX, ABA, TOC and TOF compared to TNFi drugs, this may be a result of publication bias.

Adjustment for confounding factors including age and smoking status or significant comorbidity which could impact on vaccine immunogenicity was not

possible. Control groups were not necessarily age matched to the RA cohorts. Older subjects are have a higher risk of serious infection and attenuated vaccine responses to vaccination, a consequence of immunosenescence (44, 47). Smoking may reduce pneumococcal vaccine responses in RA patients treated with MTX (48), however this was poorly reported in studies included. Most studies examined established RA cohorts (evidenced by RA disease duration prior to vaccination). It is uncertain whether longer disease duration (and potentially historically more immunosuppressive exposures) impacts upon vaccine response; this was outside the scope of this study.

Seasonal and pandemic influenza vaccination utilise strains that vary each season depending on the most virulent predicted strains. Although vaccine responses were broadly categorised by A or B strain responses for the meta-analysis, there may have been variation in the immunogenicity of each vaccine between studies, this was not possible to correct for.

Co-prescription of MTX with a biologic is recommended to maximise efficacy and reduce drug immunogenicity. We aimed to compare TNFi monotherapy to a HC group to prevent aberrancies due to MTX exposure. Concerning influenza vaccine responses with TNFi exposure, 3 studies included patients taking TNFi with concomitant MTX (12, 15, 16). Excluding these studies increased the heterogeneity but not RR interpretation. Three of the 4 other studies included in the meta-analysis did not explicitly comment if TNFi exposed patients were taking concurrent MTX (13, 14, 17). Additionally, the studies included different TNFi drugs. We assumed that TNFi exposure had similar class effects irrespective of whether they were a monoclonal antibody or fusion receptor protein.

Our meta-analysis and systematic review suggests that MTX exposure diminishes humoral responses to pneumococcal but not influenza vaccination. TNFi therapy does not negatively impact influenza or pneumococcal vaccine responses. Immunosuppression should not preclude vaccination against immune preventable disease. Vaccination is safe and well tolerated and should be encouraged as part of routine clinical care. Increasing the awareness and uptake of vaccinations in RA patients will require collaborative approaches between primary and secondary care.

REFERENCES

1. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287-93

2. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294-300

3. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2010;70:414-22

4. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthrit Care Res 2015;68:1-25

5. Rahier JF, Moutschen M, Van Gompel A, Van Ranst M, Louis E, Segaert S, et al. Vaccinations in patients with immune-mediated inflammatory diseases. Rheumatology 2010;49:1815-27

6. Bengtsson C, Kapetanovic MC, Kallberg H, Sverdrup B, Nordmark B, Klareskog L, et al. Common vaccinations among adults do not increase the risk of

developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis 2010;69:1831-3

7. Costello R, Winthrop KL, Pye SR, Brown B, Dixon WG. Influenza and Pneumococcal Vaccination Uptake in Patients with Rheumatoid Arthritis Treated with Immunosuppressive Therapy in the UK: A Retrospective Cohort Study Using Data from the Clinical Practice Research Datalink. PLoS One 2016;11:e0153848

8. Subesinghe S, Rutherford AI, Ibrahim F, Harris H, Galloway J. A large two-centre study in to rates of influenza and pneumococcal vaccination and infection burden in rheumatoid arthritis in the UK. BMC Musculoskelet Disord 2016;17 (1) (no pagination)

9. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. Virus Research 2004;103:133-8

10. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systems Review 4:1

11. Kapetanovic MC, Saxne T, Nilsson JA, Geborek P. Influenza vaccination as model for testing immune modulation induced by anti-TNF and methotrexate therapy in rheumatoid arthritis patients. Rheumatology 2007;46:608-11

12. Kobie JJ, Zheng B, Bryk P, Barnes M, Ritchlin CT, Tabechian DA, et al. Decreased influenza-specific B cell responses in rheumatoid arthritis patients treated with anti-tumor necrosis factor. Arthritis Res Ther 2011;13:R209

13. Salemi S, Picchianti-Diamanti A, Germano V, Donatelli I, Di Martino A, Facchini M, et al. Influenza vaccine administration in rheumatoid arthritis patients under treatment with TNFalpha blockers: Safety and immunogenicity. Clin Immunol 2010;134:113-20

14. Kubota T, Nii T, Nanki T, Kohsaka H, Harigai M, Komano Y, et al. Anti-tumor necrosis factor therapy does not diminish the immune response to influenza vaccine in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2007;17:531-3

15. Iwamoto M, Homma S, Onishi S, Kamata Y, Nagatani K, Yamagata Z, et al. Low level of seroconversion after a novel influenza A/H1N1/2009 vaccination in Japanese patients with rheumatoid arthritis in the 2009 season. Rheumatol Int 2012;32:3691-4

16. Franca ILA, Ribeiro ACM, Aikawa NE, Saad CGS, Moraes JCB, Goldstein-schainberg C, et al. Tnf blockers show distinct patterns of immune response to the pandemic influenza a h1n1 vaccine in inflammatory arthritis patients. Rheumatology 2012;51:2091-8

17. Ribeiro ACM, Guedes LKN, Moraes JCB, Saad CGS, Aikawa NE, Calich AL, et al. Reduced seroprotection after pandemic H1N1 influenza adjuvant-free vaccination in patients with rheumatoid arthritis: Implications for clinical practice. Ann Rheum Dis 2011;70:2144-7

18. Arad U, Tzadok S, Amir S, Mandelboim M, Mendelson E, Wigler I, et al. The cellular immune response to influenza vaccination is preserved in rheumatoid arthritis patients treated with rituximab. Vaccine 2011;29:1643-8

19. Oren S, Mandelboim M, Braun-Moscovici Y, Paran D, Ablin J, Litinsky I, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann Rheum Dis 2008;67:937-41

20. Ribeiro AC, Laurindo IM, Guedes LK, Saad CG, Moraes JC, Silva CA, et al. Abatacept and reduced immune response to pandemic 2009 influenza A/H1N1 vaccination in patients with rheumatoid arthritis. Arthrit Care Res 2013;65:476-80

21. Alten R, Bingham CO, Cohen SB, Curtis JR, Kelly S, Wong D, et al. Antibody response to pneumococcal and influenza vaccination in patients with rheumatoid arthritis receiving abatacept. BMC Musculoskelet Disord 2016;17 (1) (no pagination)

22. Mori S, Ueki Y, Hirakata N, Oribe M, Hidaka T, Oishi K. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. Ann Rheum Dis 2012;71:2006-10

23. Tsuru T, Terao K, Murakami M, Matsutani T, Suzaki M, Amamoto T, et al. Immune response to influenza vaccine and pneumococcal polysaccharide vaccine under IL-6 signal inhibition therapy with tocilizumab. Mod Rheumatol 2014;24:511-6

24. Winthrop KL, Silverfield J, Racewicz A, Neal J, Lee EB, Hrycaj P, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. Ann Rheum Dis 2016;75:687-95

25. Kapetanovic MC, Saxne T, Sjoholm A, Truedsson L, Jonsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. Rheumatology 2006;45:106-11

26. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L, Saxne T, Geborek P. Antibody response is reduced following vaccination with 7-valent conjugate pneumococcal vaccine in adult methotrexate-treated patients with established arthritis, but not those treated with tumor necrosis factor inhibitors. Arthritis Rheum 2011;63:3723-32

27. Bingham ICO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: Results from a controlled clinical trial. Arthritis Rheum 2010;62:64-74

28. Migita K, Akeda Y, Akazawa M, Tohma S, Hirano F, Ideguchi H, et al. Effect of abatacept on the immunogenicity of 23-valent pneumococcal polysaccharide vaccination (PPSV23) in rheumatoid arthritis patients. Arthritis Res Ther 2015;17:357

29. Mori S, Ueki Y, Akeda Y, Hirakata N, Oribe M, Shiohira Y, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. Ann Rheum Dis 2013;72:1362-6

30. Bingham CO, Rizzo W, Kivitz A, Hassanali A, Upmanyu R, Klearman M. Humoral immune response to vaccines in patients with rheumatoid arthritis treated with tocilizumab: Results of a randomised controlled trial (VISARA). Ann Rheum Dis 2015;74:818-22

31. Lujan M, Gallego M, Belmonte Y, Fontanals D, Valles J, Lisboa T, et al. Influence of pneumococcal serotype group on outcome in adults with bacteraemic pneumonia. Eur Respir J 2010;36:1073-9

32. Kapetanovic MC, Roseman C, Jonsson G, Truedsson L. Heptavalent pneumococcal conjugate vaccine elicits similar antibody response as standard 23-valent polysaccharide vaccine in adult patients with RA treated with immunomodulating drugs. Clin Rheumatol 2011;30:1555-61

33. Gabay C, Bel M, Combescure C, Ribi C, Meier S, Posfay-Barbe K, 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;63:1486-96

34. Van Assen S, Holvast A, Benne CA, Posthumus MD, Van Leeuwen MA, Voskuyl AE, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. Arthritis Rheum 2010;62:75-81

35. Gelinck LBS, Teng YKO, Rimmelzwaan GF, Van Den Bemt BJF, Kroon FP, Van Laar JM. Poor serological responses upon influenza vaccination in patients with rheumatoid arthritis treated with rituximab [4]. Ann Rheum Dis 2007;66:1402-3

36. Subesinghe S, Whittaker M, Galloway J. Mitigating infection risk with immunotherapy for rheumatoid arthritis. Int J Clin Rheumtol 2015;10:177-93

37. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al. Protective effect of A/H1N1 vaccination in immune-mediated disease-a prospectively controlled vaccination study. Rheumatology 2012;51:695-700

38. Fomin I, Caspi D, Levy V, Varsano N, Shalev Y, Paran D, et al. Vaccination against influenza in rheumatoid arthritis: The effect of disease modifying drugs, including TNFalpha blockers. Ann Rheum Dis 2006;65:191-4

39. Elkayam O, Bashkin A, Mandelboim M, Litinsky I, Comaheshter D, Levartovsky D, et al. The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum 2010;39:442-7

40. Elkayam O, Paran D, Caspi D, Litinsky I, Yaron M, Charboneau D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. Clin Infect Dis 2002;34:147-53

41. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor alpha, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: A systematic review and meta-analysis. Arthrit Care Res 2014;66:1016-26

42. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol 2007;34:272-9

43. Kivitz AJ, Schechtman J, Texter M, Fichtner A, De Longueville M, Chartash EK. Vaccine responses in patients with rheumatoid arthritis treated with certolizumab pegol: Results from a single-blind randomized phase IV trial. J Rheumatol 2014;41:648-57

44. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wagner CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. J Rheumatol 2007;34:952-7

45. Elkayam O, Caspi D, Reitblatt T, Charboneau D, Rubins JB. The Effect of Tumor Necrosis Factor Blockade on the Response to Pneumococcal Vaccination in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis. Semin Arthritis Rheum 2004;33:283-8

46. Gelinck LBS, Van Der Bijl AE, Beyer WEP, Visser LG, Huizinga TWJ, Van Hogezand RA, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis 2008;67:713-6

47. Weinberger B, Herndler-Brandstetter D, Schwanninger A, Weiskopf D, Grubeck-Loebenstein B. Biology of immune responses to vaccines in elderly persons. Clin Infect Dis 2008;46:1078-84

48. Roseman C, Truedsson L, Kapetanovic MC. The effect of smoking and alcohol consumption on markers of systemic inflammation, immunoglobulin levels and immune response following pneumococcal vaccination in patients with arthritis. Arthritis Res Ther 2012;14:R170

Figure Legends

Figure 1: Flow chart of studies included in the systematic review and meta-analysis

Figure 2: Forest plots for the risk ratios of response rates for influenza vaccine serotypes between rheumatoid arthritis patients receiving anti-tumour necrosis factor drugs or methotrexate and healthy controls

Legend: 95% CI = 95% Confidence Interval; M-H = Mantel-Haenszel; MTX = Methotrexate; TNFi = Tumour Necrosis Factor inhibitor Drug

Figure 3: Forest plot for the risk ratios of response rates for pneumococcal vaccine (combined 6B and 23F serotype responses) between rheumatoid arthritis patients receiving methotrexate or anti-tumour necrosis factor drugs and healthy controls

Legend: 95% CI = 95% Confidence Interval; M-H = Mantel-Haenszel; MTX = Methotrexate; TNFi = Tumour Necrosis Factor inhibitor Drug

Table 1: Characteristics of the studies examining influenza vaccine immunogenicity included in the meta-analysis

Author, Year (ref)	Study design	Number of Subjects (n)	Vaccine	Outcome	Age, years (SD)	% Women	Disease duration, years (SD)	DAS28 score (SD)	HAQ score	Seroconversion % (95% CI)	Seroprotection % (95% CI)	NOS score
MTX												
Franca et al. 2012 (16)	**Prospective cohort study**	RA MTX (25), HC (117)	Pandemic Influenza A/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA 46.5 (10.6), HC 44.3 (12.4)	RA 67, HC 79	15.6 (10.4)	-	-	RA 56.0 (36.5, 75.5), HC 74.3 (66.4, 82.3)	RA 56.0 (36.5 - 75.5), HC 78.6 (71.2 - 86.1)	7
Iwamoto et al. 2012 (15) §	Prospective cohort study	RA MTX (41), HC (14)	Pandemic Influenza A1/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3	RA median 67 (range 29-90)	RA 98, HC -	-	-	-	RA 58.5 (44.1 – 71.9) ** HC 64.3	RA 60.4 (46 – 73.6) **, HC 71.4	5

				weeks								
Kapetanovic et al. 2007 (11)	Prospective cohort study	RA MTX (37), HC (18)	Influenza trivalent subunit vaccine, H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4-6 weeks	RA 61.3 (20.8-81.4) HC 30.3 (19.2-60.3)	RA 68, HC 74	Median 7.0 (min 0.9– max 46.9	Pre Vaccine DAS28, low 53, med 35, high12	-	-	RA H1N1 89%, H3N2 76%, B 95%, HC H1N1 78%, H3N2 72%, B 67%	6
Kobie et al. 2011 (12)	Prospective cohort study	RA MTX (70), HC (97)	Influenza trivalent subunit vaccine H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4 weeks	RA 58.4 (12.2) HC 39.8 (13.6)	RA 77, HC 63	>3years 60%, <1 year 17%	-	0.71 (0.00-2.22)	-	RA H1N1 88%, H3N2 94%, B 97%, HC H1N1 100%, H3N2 100%, B 100%	6
Ribeiro et al. 2011 (17)	Prospective cohort study	RA MTX (215), HC (234)	Influenza A/H1N1/2009	SP: HI >1:40 SR: >4-fold increase	RA 55.8 (11.5)	RA 87, HC -	16.7 (10.4)	Pre Vaccine 3.66 (1.35), Post	-	RA 46.3 (39.6 - 53.0) HC: 76.9 (71.0 - 82.2)	RA 53.2(46.6 - 59.9), HC 82.9 (77.5 - 87.5)	7

				from baseline after 3 weeks				Vaccine 3.49 (1.36) No significant change				
TNFI												
Franca et al. 2012 (16)	Prospective cohort study	RA (41) (IFX/ADA 30, 11 ETA), HC (117	Pandemic Influenza A/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA 45.1 (11.8) HC 44.3 (12.4)	RA 60, HC 79	18.4 (10.1)	-	-	RA 65.9 (51.3, 80.4) HC 74.3 (66.4, 82.3)	RA 65.9 (51.3-80.4), HC 78.6 (71.2- 86.1)	7
Iwamoto et al. 2012 (15) §	Prospective cohort study	RA (28) IFX 3, ETA 18, ADA 7), HC (14)	Pandemic Influenza A1/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA median 64.5 (range 29-78)	RA 100, HC -	-	-	-	RA 38.9 (23.1 – 56.5) * HC 64.3	RA 47.2 (30.4 – 64.5) *, HC 71.4	5

Kapetanovic et al. 2007 (11)	Prospective cohort study	RA TNFi (62) (IFX 27, ETA 35), HC (18)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4-6 weeks	RA median 53.7 (15.1-85.3) HC 30.3 (19.2-60.3)	RA 76, HC 74	Median 20.8 (min 1.5- max 55.9)	Pre Vaccine DAS28, low 49%, medium 41%, high 10%	-	-	RA H1N1 58%, H3N2 74%, B 87%, HC H1N1 78%, H3N2 72%, B 67%	6
Kobie et al. 2011 (12)	Prospective cohort study	RA: TNF (61) (ETA 35, IFX 17, ADA 9), HC (97)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 4 weeks	RA 55.4 (12.3)	RA 82, HC 63	>3 years 93%, <1year 5%	-	0.71 (0.00-2.22)	-	RA H1N1 97% H3N2 94% B 97%, HC H1N1 100%, H3N2 100%, B 100%	6
Kubota et al. 2007 (14)	Prospective cohort study	RA TNFi (27) (ETA 11/IFX 16)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase	RA 55.7 (12.6) HC 55.9 (9.82)	-	-	-	-	-	RA H1N1 44.4%, H3N2 44.4%, B 29.6%, HC H1N1 17.3%,	6

		HC (52)		from baseline after 4-6weeks							H3N2 25%, B 9.6%	
Ribeiro et al. 2011(17)	Prospective cohort study	RA: TNF (47) (20 IFX, 16 ADA, 11 ETA), HC (234)	Pandemic Influenza A/H1N1/2009	SP: HI >1:40 SR: >4-fold increase from baseline after 3 weeks	RA 55.8 (11.5)	RA 87, HC -	16.7 (10.4)	Pre Vaccine: 3.66 (1.35) Post Vaccine: 3.49 (1.36) No significant change	-	RA: 51.0(45.0 to 57.0) HC: 76.9(71.0 to 82.2)	RA 67.4 (53.7-81.1), HC 82.9 (77.5-87.5)	7
Salemi et al 2010 (13)	Prospective cohort study	RA TNFi (28) (n = unknown IFX, ADA, ETA), HC (20)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI >1:40 SR: >4-fold increase from baseline after 30 days	RA 53 (3)	RA 82, HC -	-	2.47 (0.2), no significant change at 30 days	-	RA TNF H1N1 45%/H3N2 35%/B 15% HC: H1N1 50%/H3N2 60%/B 20%	RA H1N1 68%, H3N2 75%, B 50%, HC H1N1 90%, H3N2 80%, B 40%	5

Legend: § additional data supplied on request by the author; RA = Rheumatoid arthritis; HC = Healthy Control; TNFi = Tumour Necrosis Factor inhibitor drug; IFX = Infliximab; ADA = Adalimumab; ETA = Etanercept; MTX = Methotrexate; HI = haemagglutination inhibition assay; SP = Seroprotection; SR = Seroresponse; * DAS28 = Disease Activity Score in 28 joints, scores pre vaccination are

quoted unless stated otherwise; HAQ = Health Assessment Questionnaire; 95% CI = 95% Confidence Interval; - = data not provided; Disease duration = mean disease duration unless otherwise stated; ** includes RA patients on non-biological DMARDs including non-MTX users; NOS = Newcastle Ottowa Score

Table 2: Characteristics of the studies examining pneumococcal vaccine immunogenicity included in the meta-analysis

Author, Year (ref)	Study Design	Number of Subjects (n)	Vaccine Intervention	Outcome	Age, years (SD)	% Women (SD)	Disease duration years (SD)	DAS28 score (SD)	HAQ	SC % (95% CI)	SP % (95% CI)	NOS score
MTX												
Kapetanovic et al. 2006 (25)	Prospective cohort study	RA MTX (37), HC (47)	PPV-23	2-fold increase in post-vaccination titres for 6B and 23F serotypes, 4-6 weeks post vaccination	RA 61.3 (20.8-81.4) HC 30.3 (19.2-60.3)	RA:68 HC: 74	Median 7.0 (minimum 0.9 - maximum 46.9)	Pre Vaccine DAS28, low 53% medium 35%, high 12%	-	-	RA 13.5 HC 38.2	5
Kapetanovic et al. 2011 (26)	Prospective cohort study	RA MTX (85), HC (86)	PCV-7	2-fold increase in post-vaccination titres for 6B and 23F serotypes, 4-6 weeks post	RA 61.5 (14) HC 51.6 (12)	RA 78.8 HC: 45	RA 11.4 (10) HC 12.7 (12)	RA 3.7 (1.2)	0.7 (0.6)	-	RA 21.2 HC 47.7	6

				vaccination								
TNFi												
Kapetanovic et al. 2006 (25)	Prospective cohort study	RA TNFi (62) (IFX 27/ETA 35) HC (47)	PPV-23	2-fold increase in post-vaccination titres for 6B and 23F serotypes, 4-6 weeks post vaccination	RA median 53.7 (15.1-85.3), HC median 30.3 (19.2-60.3)	RA: 76 HC: 74	Median 20.8 (1.5 - 55.9)	Pre Vaccine DAS28, low 49%, medium 41%, high 10%	-	-	RA 50 HC 38.2	5
Kapetanovic et al. 2011 (26)	Prospective cohort study	RA TNFi (79) (TNFi not specified) HC (85)	PCV-7	2-fold increase in post-vaccination titres for 6B and 23F serotypes, 4-6 weeks post vaccination	RA 59.8 (14), HC 51.6 (12)	RA TNF: 87 HC: 45	RA 20.6 (11) HC 12.7 (12)	RA 3.9 (1.1)	1.2 (0.7)	-	RA 36.7 HC 47.7	6

Legend: RA = Rheumatoid arthritis; HC = Healthy Control; TNFi = Tumour Necrosis Factor inhibitor drug; IFX = Infliximab; ADA = Adalimumab; ETA = Etanercept; MTX = Methotrexate; HI = haemagglutination inhibition assay; * DAS28 = Disease Activity Score in 28 joints, scores pre-vaccination are quoted unless stated otherwise; HAQ = Health Assessment Questionnaire; 95% CI =

95% Confidence Interval; - = data not provided; PPV23: Pneumococcal polysaccharide vaccine; PCV-7: Conjugate pneumococcal vaccine; Disease duration = mean disease duration unless otherwise stated; Age = mean age unless otherwise stated, NOS score = Newcastle Ottowa Score

Figure 1: Flow chart of studies included in the systematic review and meta-analysis

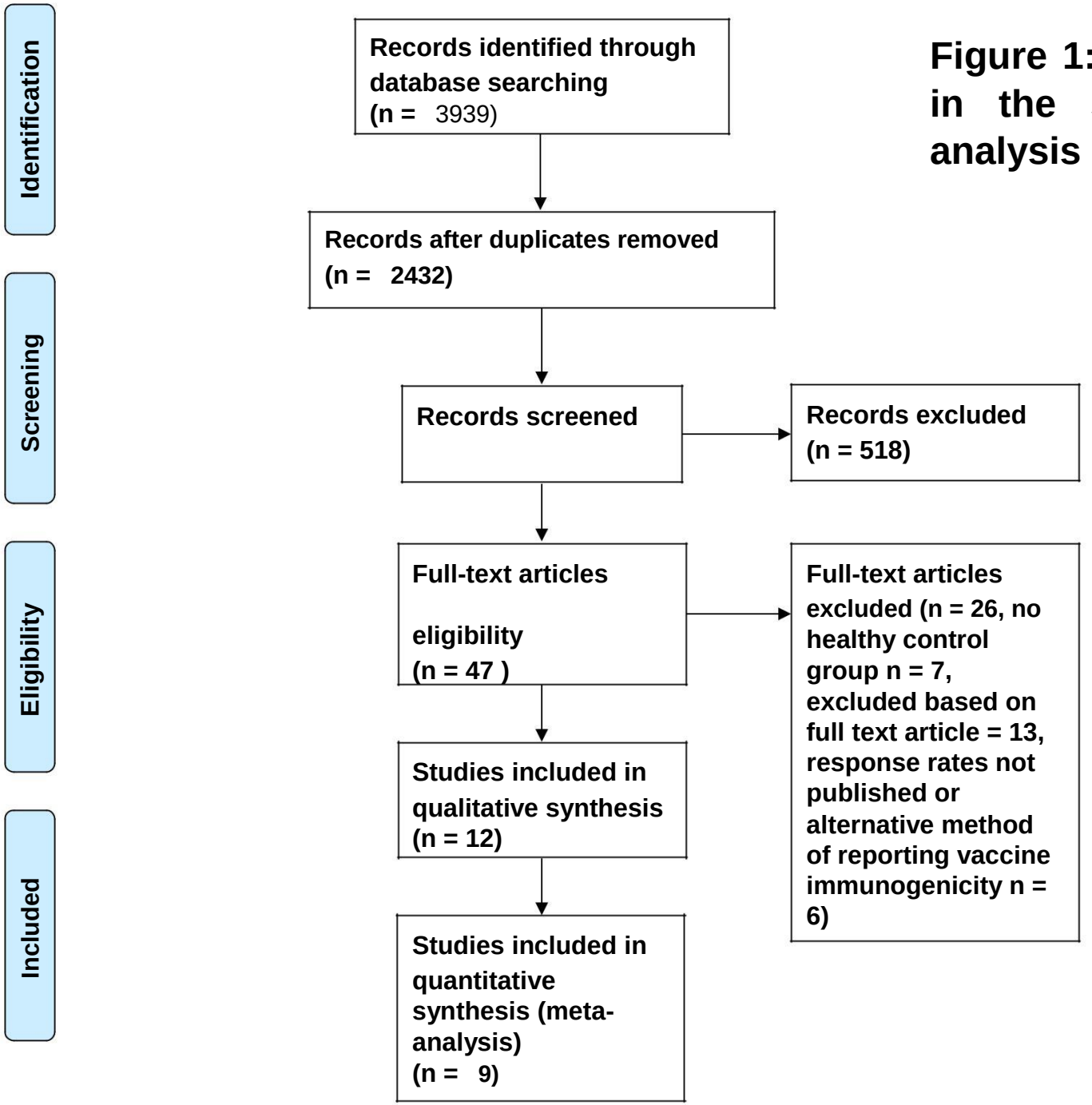
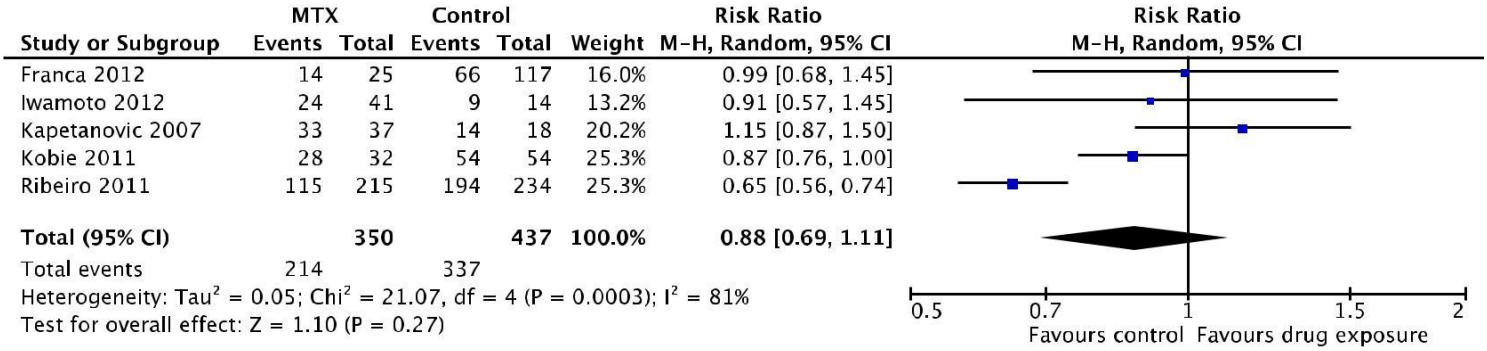
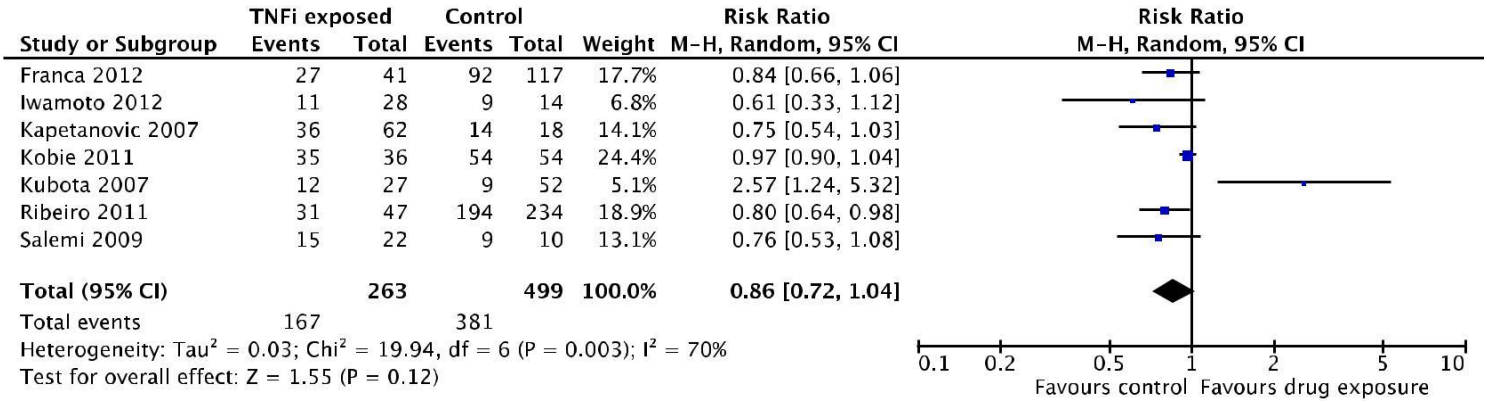


Figure 2: Forest plots for the risk ratios of response rates for influenza vaccine serotypes between rheumatoid arthritis patients receiving anti-tumour necrosis factor drugs or methotrexate and healthy controls

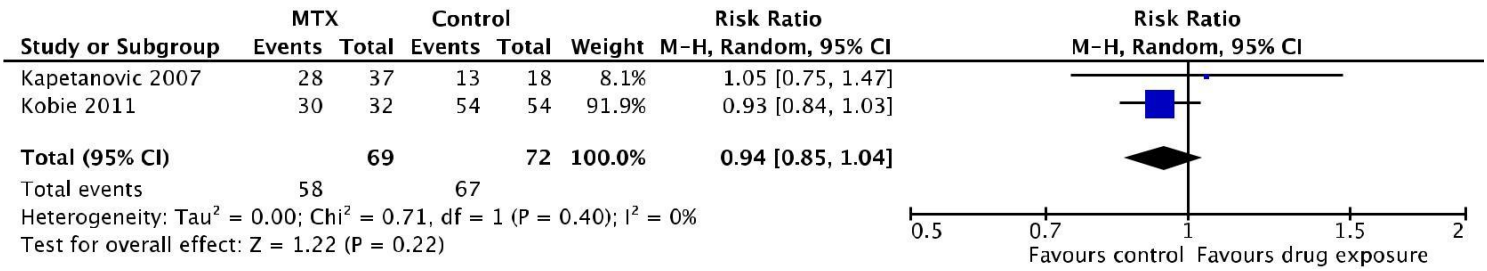
(a) Treatment with MTX and H1N1 strain responses (including pandemic and seasonal H1N1 pooled)



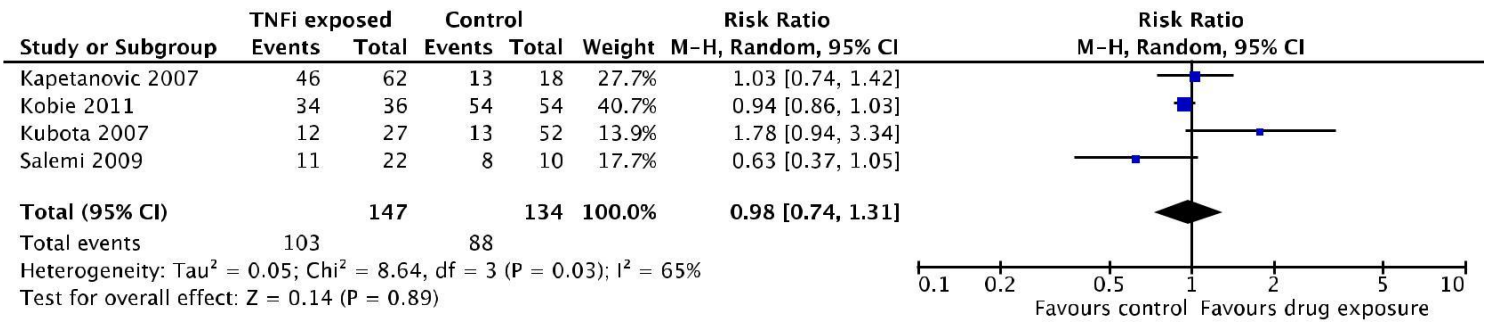
(b) Treatment with TNFi and H1N1 strain responses (including pandemic and seasonal H1N1 pooled)



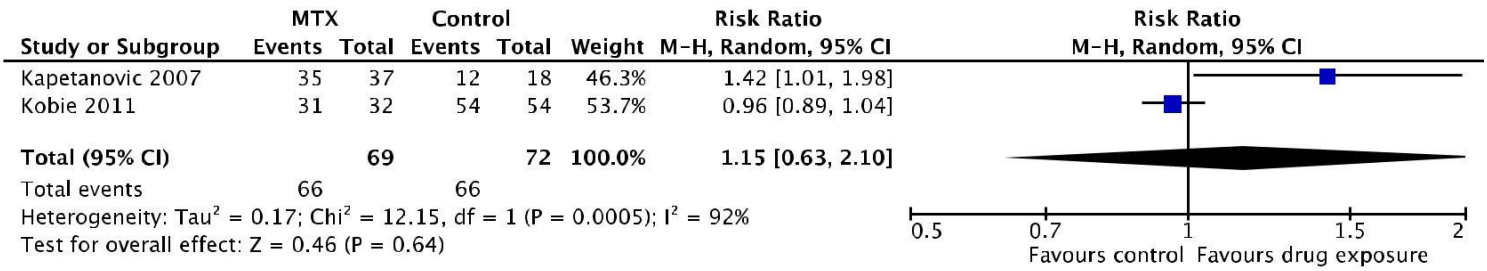
(c) Treatment with MTX and H3N2 strain responses



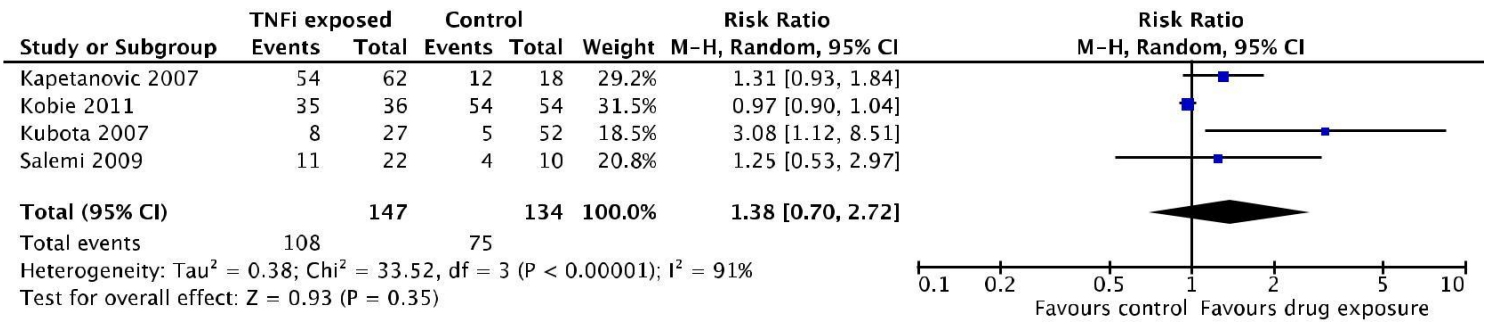
(d) Treatment with TNFi and H3N2 strain responses



(e) Treatment with MTX and B strain responses



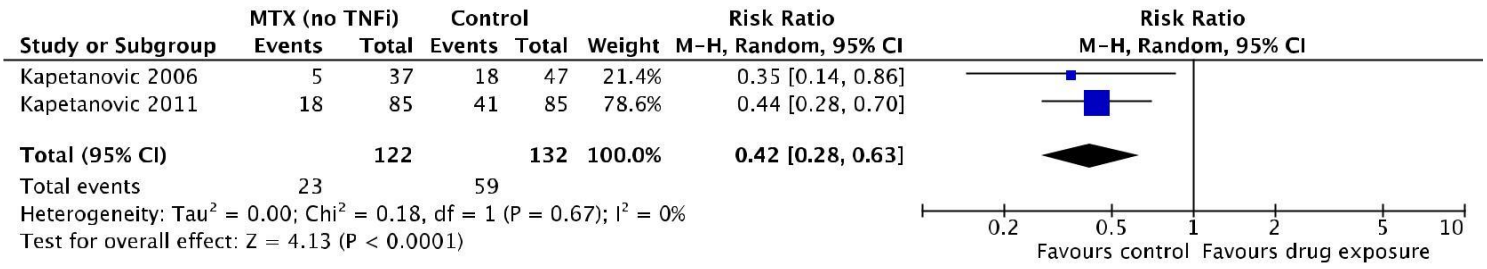
(f) Treatment with TNFi and B strain responses



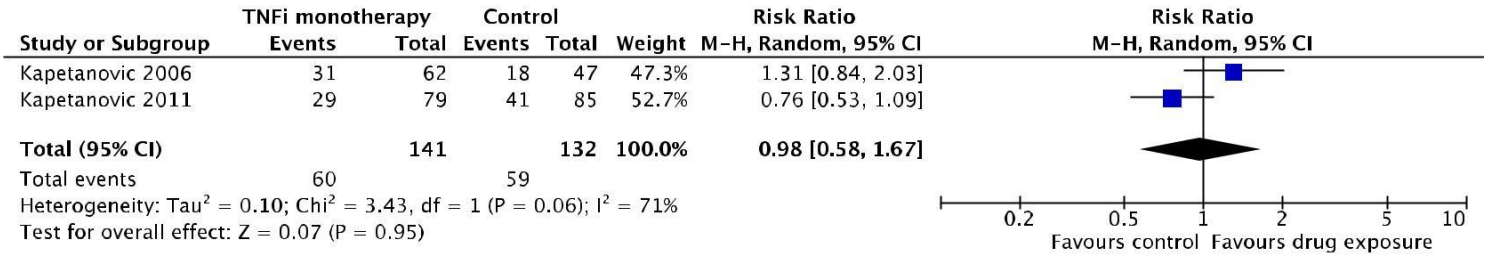
Legend: 95% CI = 95% Confidence Interval; M-H = Mantel-Haenszel; MTX = Methotrexate; TNFi = Tumour Necrosis Factor inhibitor Drug

Figure 3: Forest plot for the risk ratios of response rates for pneumococcal vaccine (combined 6B and 23F serotype responses) between rheumatoid arthritis patients receiving methotrexate or anti-tumour necrosis factor drugs and healthy controls

(a) Treatment with MTX and pneumococcal 6B/23F serotype responses



(b) Treatment with TNFi and pneumococcal 6B/23F serotype responses



Legend: 95% CI = 95% Confidence Interval; M-H = Mantel-Haenszel; MTX = Methotrexate; TNFi = Tumour Necrosis Factor inhibitor Drug

Supplementary Table 1: Quality assessment of studies using the Newcastle Ottowa Score

	Selection			Comparability		Outcome				
Study	**Representativeness of the exposed cohort**	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur?**	**Adequacy of follow up of cohorts**	**Total NOS score**	**Comment**
Franca 2012 (16)	1	1	1	1	0	1	1	1	7	RA and control cohorts not aged matched. Control population from hospital population.
Iwamoto 2012 (15)	1	0	0	0	0	1	1	1	5	Method of recruitment of RA or control cohorts not discussed. Demographic data for comparability of cohorts not presented. Previous vaccination status not documented.
Kapetanovic 2006 (25)	1	0	1	0	0	1	1	1	5	RA and control cohorts were not aged matched. Controls were selected from healthy hospital controls. Previous vaccination status not documented.
Kapetanovic 2007 (11)	1	0	1	0	1	1	1	1	6	RA and control cohorts not aged matched. Controls were selected from healthy hospital controls. Previous vaccination status not documented.
Kapetanovic 2011 (26)	1	0	1	1	0	1	1	1	6	RA and control cohorts not aged matched.
Kobie 2011 (12)	1	0	1	1	0	1	1	1	6	RA and control cohorts not aged matched.

Kubota 2007 (14)	1	0	0	1	1	1	1	1	6	No information of how control cohort were recruited.
Ribeiro 2011 (17)	1	1	1	1	0	1	1	1	7	RA and control cohorts not aged matched.
Salemi 2009 (13)	1	0	0	1	0	1	1	1	5	No data presented comparing ages of two cohorts.

COHORT STUDIES

Selection (4 points in total)

Representativeness of the exposed cohort (1 point)

Yes if:

- rheumatoid arthritis (RA) diagnosis confirmed by American College of Rheumatology (ACR) 1987/2010 criteria.
- details on selection process of the RA cohort, e.g. randomly selected from a hospital clinic, or invited via postal-invitation to participate in the study

No if:

- RA patients do not fulfil ACR RA diagnostic criteria
- details on the method of recruitment of RA patients not presented

Selection of the non-exposed cohort (1 point)

Yes if:

- RA patients serving as healthy cohorts were stated to not have any immunosuppressive exposure prior to vaccination
- the healthy control cohort were randomly selected from the local population

No if:

- the control cohort were drawn from a hospital workers only
- the control drawn from a different source and not from the same community
- there was no description of the derivation of the non-exposed cohort

Ascertainment of exposure (1 point)

Yes if:

- it was documented that no recent vaccination against influenza (within the same vaccination season) and/or pneumococcal vaccine (within 5 years) had been performed
- details were from a secure record (e.g. medical records)

No if:

- there was no description of pre-vaccination antibody titres or no evidence of exclusion criteria including previous vaccination history

Demonstration that outcome of interest was not present at start of study (1 point)

Yes if:

- pre-vaccine titres were checked pre-immunisation and details provided on to calculate number/proportion of patients who achieved seroprotection, seroconversion or seroresponse

No if

- there was no history of vaccination within 12 months for influenza vaccination or 5 years for pneumococcal vaccination

Comparability (2 points)

Yes if:

- RA and control cohorts were age matched
- RA and control cohorts were age and sex matched
- The RA population serving as a control cohort, matched for disease duration

No if:

- Cohorts not age matched

Outcome (3 points)

Assessment of outcome (1 point)

Yes if:

- The percentages of achieving seroprotection or seroconversion calculable from data presented
- Blinded analysis of post-vaccination titres

No if:

- No data presented for post vaccination titres

Was follow-up long enough for outcomes to occur (1 point)

Yes if:

- 3-6 week follow up period for post-vaccination titres to assess seroprotection or seroconversion

No if:

- Follow up period outside set time frame

Adequacy of follow up of cohorts (1 point)

Yes if:

- Complete follow up - all subjects accounted for or >80% subject follow up rate

No if:

- Follow up rates unable to be calculated or data not presented

Interpretation of Newcastle Ottowa Scale score:
0 – 3 = poor quality study
4 – 6 = satisfactory quality study
7 – 9 = high quality study

Supplementary Table 2: Studies examining pneumococcal vaccine responses with different anti-rheumatic drug exposures

Author, Year [Reference]	Subjects (n)	Vaccine	Outcome	Mean Age, years (SD)	Female n (%)	Disease duration, years (SD)	DAS28 score (SD)	HAQ score (SD)	Vaccine response	Comments
Kapetanovic et al. 2006 (25)	RA (149, 62 TNFi monotherapy, 50 TNFi + MTX, 37 MTX monotherapy) HC (47)	PPV23	≥ 2-fold or higher increase in 6b and 23f serotype Ab concentration, 4 to 6-weeks post vaccination	Median age: TNFi monotherapy 53.7 TNF+MTX 52.8 MTX monotherapy 61.3 HC 30.3	TNFi (76) TNFi + MTX (70) MTX (68) HC (74)	TNFi 20.8 TNFi + MTX 10.8 MTX 7.0 HC -	% of patients with Low/Intermediate/High DAS28 at time of vaccination: TNFi: 49/41/10 TNF+MTX: 50/44/6 MTX: 53/35/12	-	% of patients with adequate vaccine response: TNFi 50%, TNFi + MTX 32%, MTX 13.5%, HC 38.2%	MTX associated with a reduced response to PPV23 vaccination, no effect of TNFi on vaccine response
Visvanathan et al. 2007 (44)	RA (70, 20 IFX 3mg/kg + MTX, 36 IFX 6mg/kg + MTX, 14 Placebo + MTX)	PPV23	≥ 2-fold increase at least 6 vaccine serotypes compared to pre-vaccine levels	Median age: IFX 3mg/kg: 52 IFX 6mg/kg 50 Placebo 50	IFX 3mg/kg: (65) IFX 6mg/kg: (66.7) Placebo (78.6)	-	-	-	>80% of patients in each group responded to 1≥ serotypes, 20-25% responded to 6≥ different serotypes	No impact of MTX exposure on vaccine responses

Kaine et al. 2007 (42)	RA (218, 109 Placebo ± MTX, 109 ADA ± MTX)	PPV23	≥ 2-fold titre increase in ≥ 3 of 5 vaccine serotypes and protective Ab titres ≥1.6 mcg/ml, 4-weeks post vaccination. Serotypes 9V, 14, 18C, 19F, and 23F	51.7 ± 11.66	Placebo 82 (75.2), ADA 84 (84.8), Overall 166 (79.8)	-	-	-	% of patients achieving a ≥ 2-fold increase in ≥ 3 of 5 pneumococcal Ab titres: ADA 37.4%, Placebo 40.4%. % of patients achieving protective Ab titres >1.6mcg/ml in ≥ 3 of 5 antigens) 4 weeks post vaccination: ADA 85.9%, Placebo 81.7%	No impact of TNFi exposure on vaccine responses
Bingham et al. 2010 (27)	RA (93, RTX+MTX 65, MTX 28)	PPV23	≥2-fold increase or an increase of 1 mcg/ml from pre-vaccination level. 12 pneumococcal serotype responses assessed	RTX + MTX 49.7 (9.6) MTX 49.7 (10.5)	RTX + MTX 51 (75), MTX 25 (78)	-	RTX +MTX 6.2 (1.1) MTX -	-	Decreased responses to PPV23 RTX+MTX 57% of subjects had a 2-fold rise in Ab titre response to >1 serotype, compared with 82% of MTX monotherapy patients. Lower proportions of	Reduced vaccine response in RTX exposed patients compared to MTX

									patients responding to each serotype in RTX+MTX group compared to MTX monotherapy	
Kapetanovic et al. 2011 (32)	RA (253, MTX 85, TNF+MTX 89, TNF 79) SpA/HC (85)	PCV-7	ARR ≥ 2, 4 to 6-weeks post-vaccination, serotypes 6b and 23f	MTX 61.5 (14) TNFi + MTX 60.1 (10) TNFi 59.8 (14) SpA/HC 51.6 (12)	MTX: 67 (78.8) TNFi + MTX 69 (77.5) TNFi 69 (87.3) SpA/HC 39 (45.3)	MTX 11.4 (10) TNFi + MTX 16.2 (12) TNFi 20.6 (11) SpA/HC 12.7 (12)	MTX 3.7 (1.2) TNFi + MTX 3.4 (1.2) TNFi 3.9 (1.1) SpA/HC 3.0 (1.1)	MTX 0.7 (0.6) TNFi + MTX 0.9 (0.7) TNFi 1.2 (0.7) SpA/HC 0.5 (0.5)	Number (%) of subjects achieving ≥ 2-fold increase in pre-vaccination Ab levels MTX 18 (21.2), TNFi + MTX 14 (15.7), TNFi 29 (36.7), SpA/HC 41 (47.7)	MTX associated with a reduced response to PCV-7, no effect of TNFi therapy on vaccine response
Mori et al. 2012 (29)	RA (190, MTX 62, TOC + MTX 54, TOC 50, Control 24)	PPV23	≥2-fold in IgG concentrations or ≥10-fold or more increase in opsonisation indices	MTX 68.3, TOC + MTX 65.1, TOC 68.3, Control 69.2	MTX 51 (82.3), TOC + MTX 50 (92.6), TOC 43 (86), Control 19 (79.2)	MTX 10.0, TOC + MTX 9.1, TOC 12.5, Control 11.3	-	-	Fold increases 6b/23f (SD) MTX 1.5 (1.1-3.0)/ 2.6 (1.4-4.1 TOC + MTX 1.6 (1.2-1.9)/ 2.9 (1.0-6.9), TOC 2.8 (1.4-4.4)/ 3.4 (1.5-6.8), Control 1.8 (1.3-3.7)/ 3.5	Post-vaccination Ab responses may be reduced when TOC combined with MTX.

									(1.7-5.6)	
Kivitz et al. 2014 (43)	RA (207, Placebo +/- MTX 110, CZP+/- MTX 107)	PPV23	≥ 2-fold increase in ≥ 3 of 6 pneumococcal antigens at 6 weeks, serotypes: 6b, 9v, 14, 18c, 19f, 23f	Placebo 52.7 (11.1), CZP 53.1 (11.8)	Placebo (76.3), CZP (83.6)	Placebo 7.9 (8.4), CZP 7.4 (8.1)	Placebo 5.5 (0.9), CZP 5.5 (1.0)	-	Adequate response in patients with/without protective titres at baseline: Placebo 58.2%/62.5%, CZP 53.3%/54.5%	No significant effect of TNFi exposure on vaccine response.
Tsuru et al. 2014 (23)	RA (21, TOC)	PPV23	≥2-fold increase in Ab titres in at least 6 of 12 measured serotypes	54	17 (81)	9.0	-	-	100% patients achieved adequate sero-response	No comparator group in study.
Bingham et al, 2015 (30)	RA (74, TOC + MTX 50, MTX 24)	PPV23	≥2-foldincrease or an increase of 1 mcg/ml from pre-vaccination level, to ≥6/12 serotypes	TOC + MTX 51.1 (8.9), MTX 51.4 (9.5)	TOC+MTX 41 (75.9), MTX 22 (81.5)	TOC+MTX 13.2 (11.5), MTX 8.4 (7.0)	-	-	Proportions of responders to ≥6 of 12 anti-pneumococcal antibody serotypes: TOC + MTX 60%, MTX 70.8%	No significant effect of TOC exposure on vaccine response, however individual serotype responses may vary.

Migita et al. 2015 (28)	RA (111, RA control 35, MTX 55, ABA 21)	PPV23	≥2-fold increase in IgG concentrations of 6b or 23f serotypes	RA control 70.5 (10.8), MTX 63.8 (11.5), ABA 59.8 (12.0)	RA control 23 (65.7), MTX 44 (80), ABA 17 (81)	RA control 11.7 (12.5), MTX 14.1 (10.9), ABA 13.5 (11.2)	RA control 2.79 (1.17), MTX 2.61 (0.98), ABA 2.48 (1.31)	-	Fold increase in GMT 6b (95%CI)/23f (95% CI) RA control 2.38 (1.41 - 5.62)/3.36(1.85 to 9.42), MTX 1.75(1.15-3.11)/ 2.00(1.27 to 5.48), ABA 1.41(0.87-3.09)/ 2.45 (1.23-7.44)	Reduced responses in ABA and MTX exposed patients compared to RA control group.
Alten et al. 2016 (21)	RA (125, 115 ABA + MTX, 10 ABA)	PPV23	≥2-fold increase in post-vaccination titers to ≥3 of 5 antigens and protective Ab levels of ≥1.6 mcg/mL to ≥3 of 5 antigens. Serotypes measured 9V, 14, 18C, 19F, 23F	45.7 (13.8)	107 (85.6)	-	5.0 (1.9)	1.4 (0.8)	83.9 % demonstrated protective Ab levels following PPV23 vaccination.	No comparator group in study.

Winthrop et al. 2016 (24)	RA (200, TOF + MTX 57, TOF 45, MTX 55, placebo 43)	PPV23	2-fold increase in post-vaccination titers to ≥6 of 12 antigens, 5-weeks post-vaccination. Serotypes measured 1,3,4,5,6B,7F,14,19A, 19F, 23F, 18C)	RA (TOF exposed) 53 RA (placebo or MTX monotherapy) 53	RA (TOF exposed) 75 (73.5) RA (placebo or MTX monotherapy) 79 (80.6)	-	RA (TOF exposed) 6.03 (1.05) RA (placebo or MTX monotherapy) 5.78 (1.10)	-	TOF overall 46/102 (45.1%) demonstrated appropriate vaccine response. In TOF non-exposed patients, response rate was higher 67/98 (68.4%). Achievement of appropriate PPV23 vaccine response stratified by MTX use at baseline: TOF + MTX 18/57 (31.6%), TOF monotherapy 28/45 (62.2%). MTX monotherapy 34/55 (61.8%) demonstrated appropriate vaccine response compared to 33/43 (76.7%) in the placebo group.	TOF exposure, particularly in combination with MTX is associated with reduced humoral response to PPV23 vaccination. Temporary withdrawal of TOF has no benefit on vaccine response compared to continuous therapy.

Legend: n: number, SD: standard deviation, DAS28: Disease Activity Score of 28 joints, HAQ: Health Assessment Questionnaire, RA: rheumatoid arthritis, HC: Healthy Controls, SpA: Spondyloarthropathy, MTX: methotrexate, TNFi: Tumour Necrosis Factor inhibitor drug, PPV23: pneumovax vaccine, PCV-7: 7 conjugate pneumococcal vaccine, PCV-13: 13 conjugate pneumococcal vaccine, Ab: antibody, ARR: antibody response ratio (i.e., ratio of post to pre-vaccination antibody levels), DMARD: Disease Modifying Anti-Rheumatic Drug, RTX: Rituximab, ABA: Abatacept, TOC: Tocilizumab, IFX: infliximab, CZP: Certolizumab pegol, ADA: Adalimumab, ETA: Etanercept, TOF: Tofacitinib

A Systematic Review and Meta-Analysis of Anti-Rheumatic Drugs and Vaccine Immunogenicity in Rheumatoid Arthritis

Supplementary material – Literature Search Strategy

Initial search undertaken 6th October 2016, repeated 12th October 2017

Databases:

1. EMBASE 1974 – 2017 Week 41
2. Ovid MEDLINE ® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE ® Daily and Ovid MEDLINE ® 1946 – Present

Literature Search Strategy

1. inflammatory arthritis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
2. rheumatoid arthritis.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
3. immunisation.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
4. vaccination.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
5. vaccine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
6. influenza.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
7. influenza vaccine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
8. pneumovax.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]

9. pneumococcal vaccine.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
10. prevenar.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, nm, kf, px, rx, an, ui, sy]
11. 1 or 2
12. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
13. 11 and 12
14. remove duplicates from 13
15. limit 14 to english language
16. limit 15 to human
17. limit 16 to yr="2000 -Current