A Systematic Review and Metaanalysis of Antirheumatic Drugs and Vaccine Immunogenicity in Rheumatoid Arthritis

Sujith Subesinghe, Katie Bechman, Andrew I. Rutherford, David Goldblatt, and James B. Galloway

ABSTRACT. ***Objective.*** Vaccination is a key strategy to reduce infection risk in patients with rheumatoid arthritis (RA) and is advocated in internationally recognized rheumatology society guidelines. The aim was to evaluate to the effect of antirheumatic drugs on influenza and pneumococcal vaccine immunogenicity.

Methods. We conducted a systematic literature review and metaanalysis comparing the humoral response to influenza (pandemic and seasonal trivalent subunit vaccines) and pneumococcal (23-valent pneumococcal polysaccharide vaccine, 7- and 13-valent pneumococcal conjugated vaccines) vaccination in adult patients with RA treated with antirheumatic drugs. Vaccine immunogenicity was assessed by seroprotection rates measured 3 to 6 weeks postimmunization. Risk ratios (RR) and 95% CI were pooled.

Results. Nine studies were included in the metaanalysis (7 studies investigating antirheumatic 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 (MTX) and tumor necrosis factor inhibitor (TNFi) drug exposure. MTX but not TNFi drug exposure was associated with reduced 6B and 23F serotype pneumococcal vaccine response (RR 0.42, 95% CI 0.28–0.63 vs RR 0.98, 95% CI 0.58–1.67); however, limited data were available to draw any firm conclusions. Combination of MTX with tocilizumab or tofacitinib was associated with reduced pneumococcal and influenza vaccine responses.

Conclusion. Antirheumatic drugs may limit humoral responses to vaccination as evidenced by pneumococcal responses with MTX exposure; however, they are safe and should not preclude immunization against vaccine-preventable disease. Vaccination should be considered in all patients with RA and encouraged as part of routine care. (Systematic review registration number: PROSPERO 2016: CRD42016048093.) (J Rheumatol First Release March 15 2018; doi:10.3899/jrheum.170710)

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From the Department of Academic Rheumatology, King's College London, Weston Education Centre; Institute of Child Health, University College London, London, UK.

S. Subesinghe, BSc, MBBS, MSc, MRCP, Clinical Research Fellow and Rheumatology Registrar, Department of Academic Rheumatology, King's College London, Weston Education Centre; K. Bechman, BSc, MBBS, MRCP, Clinical Research Fellow and Rheumatology Registrar, Department of Academic Rheumatology, King's College London, Weston Education Centre; A.I. Rutherford, BSc, MBBS, MSc, MRCP, Clinical Research Fellow and Rheumatology Registrar, Department of Academic Rheumatology, King's College London, Weston Education Centre; D. Goldblatt, MBChB, FRCPCH, FRCP, PhD, Prof, Vaccinology and Immunology, Institute of Child Health, University College London; J.B. Galloway, MBChB, MSc, CHP, FRCP, PhD, FAcadMedEd, Senior Lecturer and Honorary Consultant Rheumatologist, Department of Academic Rheumatology, King's College London, Weston Education Centre.

Address correspondence to S. Subesinghe, Department of Academic Rheumatology, King's College London, Weston Education Centre, Cutcombe Road, Denmark Hill, London SE5 9RJ, UK.
E-mail: ssubesinghe@nhs.net

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Patients with rheumatoid arthritis (RA) are at an increased risk of infection compared to healthy subjects[1]. This is because of a multifactorial complex interaction between inherent immune dysfunction, comorbidity, disease activity, and immunosuppression[2]. Highly targeted therapies [including tumor necrosis factor inhibitor (TNFi) drugs, rituximab (RTX), tocilizumab (TCZ), abatacept (ABA), and most recently tofacitinib (TOF)] have revolutionized RA management; however, the infection risk associated with these drugs is a concern for clinicians and patients.

The British Society for Rheumatology, European League Against Rheumatism (EULAR), and American College of Rheumatology 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 Epidemiological Investigation of Rheumatoid

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Arthritis study has reported no increased risk of developing RA following common vaccination[5,6].

In the United Kingdom, routine vaccination schedules advise annual influenza vaccinations and single 23-valent pneumococcal polysaccharide vaccines (PPV23) in individuals > 65 years 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 among primary or secondary care providers, and concerns pertaining to vaccine safety, efficacy, or the possibility of worsening disease activity.

The seasonal influenza vaccine is an inactivated trivalent subunit vaccine comprising 3 viral antigens (2 A strains, H1N1 and H3N2, and a single B strain). The pandemic influenza vaccine (pH1N1) is used when necessary. In the United Kingdom, 2 commercially available pneumococcal vaccines are currently used: a PPV23 and a 13-valent pneumococcal conjugated vaccine (PCV-13), which superseded PCV-7 in 2010. Vaccine immunogenicity depends upon vaccine type and vaccine strain, but postvaccination antibody (Ab) titers to assess vaccine response are not routinely measured[9].

EULAR guidelines recommend that influenza and pneumococcal vaccines should be administered prior to immunosuppression. Vaccination can be administered during nonbiologic disease-modifying antirheumatic drugs (nbDMARD) and TNFi treatment, but ideally prior to commencing RTX[3]. This is because immunosuppression may blunt serological responses (SR) to vaccination.

The rationale for undertaking this systematic review of the literature and metaanalysis was to evaluate the effect 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 metaanalysis 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 2 investigators (SS and KB) 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," "vaccination," "vaccine," "influenza," "pneumovax," or "prevenar." The search was undertaken on October 6, 2016, and rerun on October 12, 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 randomized controlled trials published between January 1, 2000, and October 6, 2016, were sought. Case reports and conference abstracts were excluded. Patients with RA aged > 18 years treated with antirheumatic drugs who had received influenza and/or pneumococcal vaccines were considered. Alternative diagnoses of inflammatory arthritis were excluded. Drug exposures studied included methotrexate (MTX), TNFi, RTX, TCZ, ABA, and TOF. Other nbDMARD were not studied.

The primary outcome of interest was evidence of seroprotection (SP) as a surrogate measure of vaccine immunogenicity, classified by antirheumatic 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 postvaccination Ab titer measured by hemagglutination inhibition assay of ≥ 1:40, and SR or SC as a 4-fold increase in postvaccine Ab titer. For our study and in the absence of an accepted universal correlate of vaccine protection, a postvaccination Ab titer of 1 mcg/ml was used as a marker of likely protection following pneumococcal vaccination; SR was defined as ≥ 2-fold increase in postvaccine Ab titers. Studies reporting only on geometric mean titers (GMT), opsonization index (OI), or Ab response rates were excluded. Vaccine response was assessed between 3 and 6 weeks postinfluenza and pneumococcal vaccination. Healthy controls (HC) or RA subjects not taking antirheumatic 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 SS and KB). The full texts of the potential studies for inclusion were retrieved and assessed for eligibility. The full electronic search strategy is available in the Supplementary Data 1 (available with the online version of this article).

Data collection process and outcomes and quality assessment. Data were extracted independently (by SS and KB). Disagreements over study eligibility, quality [as assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies] or risk of bias were resolved through discussion with a third reviewer (JG) where necessary. Details of the assessment of study quality are available in Supplementary Table 1 (available with the online version of this article). Data collated included the source (main author, journal, publication date), study design, vaccination intervention, antirheumatic 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). 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 metasynthesis 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 Table 1 and Table 2; forest plots for the risk ratio (RR) of response rates for influenza vaccine strains and pneumococcal serotype responses separated by antirheumatic drug exposure (MTX or TNFi) are represented in Figure 2, Figure 3, and Figure 4. All studies included in the metaanalyses were

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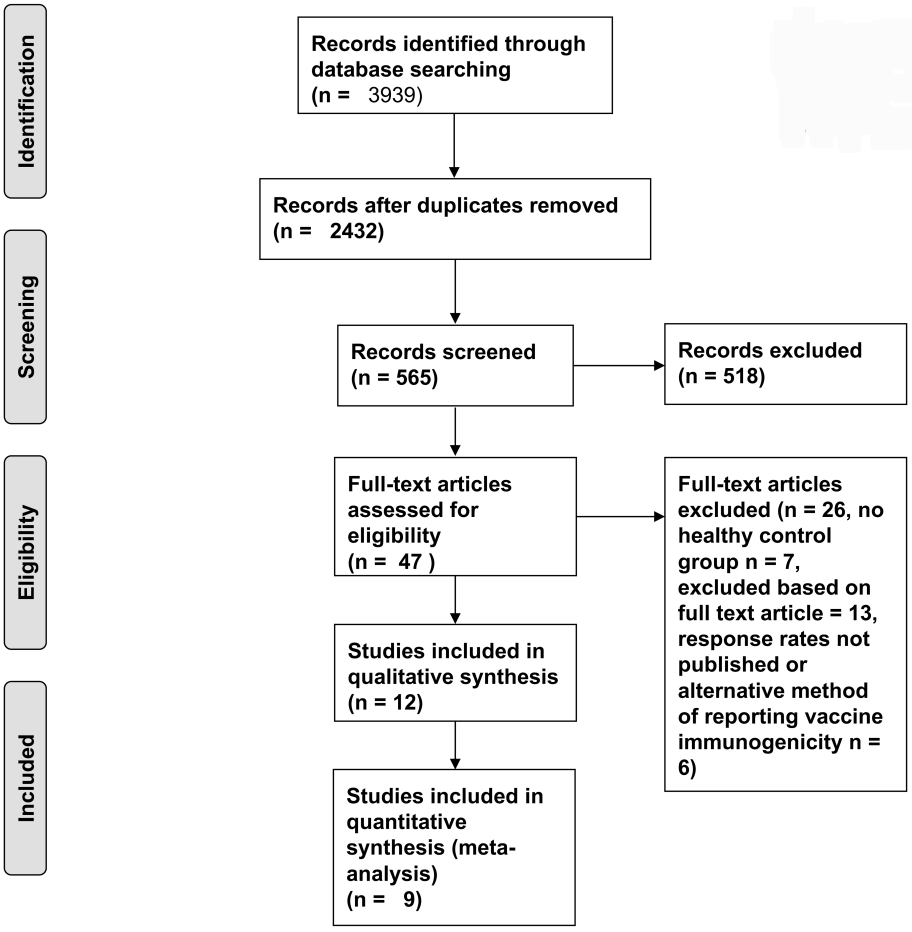

Figure 1. Flow chart of studies included in the systematic review and metaanalysis.

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 (Supplementary Table 1, available with the online version of this article). It was not possible to evaluate the effect of RTX, ABA, TCZ, or TOF in metaanalyses, either because of an absence of HC or comparator groups, unpublished vaccine response rates, or a 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 antirheumatic drug exposures have been included in Supplementary Table 2 (available with the online version of this article).

MTX and influenza vaccination response. Five studies including 787 subjects (350 RA, 437 HC) assessed MTX exposure and influenza vaccine humoral responses[11,12,15,16,17]. Three studies assessed the response to pH1N1 influenza vaccination; these results were pooled with seasonal influenza H1N1 responses[15,16,17]. MTX exposure was not associated with reduced SP responses to H1N1 (pooled RR 0.88, 95% CI 0.69–1.11), H3N2 (pooled RR 0.94, 95% CI 0.85–1.04; Figure 2), or B strain (pooled RR 1.15, 95% CI 0.63–2.10; Figure 3).

TNFi and influenza vaccination response. In total, 762 subjects from 7 studies were pooled in the metaanalysis examining TNFi effect on influenza vaccine immunogenicity (263 RA, 499 HC)[11–17]. Three studies exclusively examined the influence of TNFi exposure on pH1N1 influenza response; these results were combined with seasonal influenza H1N1 responses[15,16,17]. TNFi exposure was not associated with reduced SP responses to H1N1 (pooled RR 0.86, 95% CI 0.72–1.04; Figure 2), H3N2 (pooled RR 0.98, 95% CI 0.74–1.31), or B strain (pooled RR 1.38, 95% CI 0.70–2.72; Figure 3).

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

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Table 1. Characteristics of the prospective cohort studies examining influenza vaccine immunogenicity included in the metaanalysis.

Author, Yr	N	Vaccine	Outcome	Age, Yrs, Mean (SD)	Women, %	Disease Duration, Yrs, Mean, (SD)	DAS28*, Mean (SD)	HAQ, Mean (Range)	SC, % (95% CI)	SP, % (95% CI)	NOS
MTX											
Franca, *et al*, 2012[16]	RA (25), HC (117)	Pandemic influenza A/H1N1/2009	SP: HI > 1:40, SR: > 4-fold increase from baseline after 3 wks	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,§]	RA (41), HC (14)	Pandemic influenza A1/H1N1/2009	SP: HI > 1:40, SR: > 4-fold increase from baseline after 3 wks	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
Kapetanovic, *et al*, 2007[11]	RA (37), HC (18)	Influenza trivalent subunit vaccine, H1N1/H3N2/B	SP: HI > 1:40, SR: > 4-fold increase from baseline after 4–6 wks	RA median 61.3 (range 20.8–81.4), HC 30.3 (19.2–60.3)	RA (68), HC (74)	Median 7.0 (min 0.9–max 46.9)	Low 53, medium 35, high 12	–	–	RA H1N1 89, H3N2 76, B 95, HC H1N1 78, H3N2 72, B 67	6
Kobie, *et al*, 2011[12]	RA (32), HC (54)	Influenza trivalent subunit vaccine H1N1/H3N2/B	SP: HI > 1:40, SR: > 4-fold increase from baseline after 4 wks	RA 58.4 (12.2), HC 39.8 (13.6)	RA (77), HC (63)	> 3 yrs 60%, < 1 yr 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]	RA (215), HC (234)	Influenza A/H1N1/2009	SP: HI > 1:40, SR: > 4-fold increase from baseline after 3 wks	RA 55.8 (11.5)	RA (87), HC (–)	16.7 (10.4)	Prevaccine 3.66 (1.35), Postvaccine 3.49 (1.36), No significant change	–	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
TNFi											
Franca, *et al*, 2012[16]	RA (41: IFX/ADA 30, ETN 11), HC (117)	Pandemic influenza A/H1N1/2009	SP: HI > 1:40, SR: > 4-fold increase from baseline after 3 wks	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,§]	RA (28: IFX 3, ETN 18, ADA 7), HC (14)	Pandemic influenza A1/H1N1/2009	SP: HI > 1:40, SR: > 4-fold increase from baseline after 3 wks	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]	RA (62: IFX 27, ETN 35), HC (18)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI > 1:40, SR: > 4-fold increase from baseline after 4–6 wks	RA median 53.7 (range 15.1–85.3), HC 30.3 (19.2–60.3)	RA (76), HC (74)	Median 20.8 (min 1.5–max 55.9)	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]	RA (36), HC (54)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI > 1:40, SR: > 4-fold increase from baseline after 4 wks	RA 55.4 (12.3)	RA (82), HC (63)	> 3 yrs 93%, < 1 yr 5%	–	0.71 (0.00–2.22)	–	RA H1N1 97, H3N2 94, B 97, HC H1N1 100, H3N2 100, B 100	6

Table 1. Continued.

Author, Yr	N	Vaccine	Outcome	Age, Yrs, Mean (SD)	Women, %	Disease Duration,	DAS28*, Mean (SD)	HAQ, Mean (Range)	SC, % (95% CI)	SP, % (95% CI)	NOS
Kubota, *et al*, 2007[14]	RA (27: ETN 11, IFX 16), HC (52)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI > 1:40, SR: > 4-fold increase from baseline after 4–6 wks	RA 55.7 (12.6), HC 55.9 (9.82)	–	–	–	–	–	RA H1N1 44.4, H3N2 44.4, B 29.6, HC H1N1 17.3, H3N2 25, B 9.6	6
Ribeiro, *et al*, 2011[17]	RA (47: IFX 20, ADA 16, ETN 11), HC (234)	Pandemic influenza A/H1N1/2009	SP: HI > 1:40, SR: > 4-fold increase from baseline after 3 wks	RA 55.8 (11.5)	RA (87), HC (–)	16.7 (10.4)	Prevaccine: 3.66 (1.35), postvaccine: 3.49 (1.36); no significant change	–	RA 51.0 (45.0–57.0), HC 76.9 (71.0–82.2)	RA 67.4 (53.7–81.1), HC 82.9 (77.5–87.5)	7
Salemi, *et al*, 2010[13]	RA (22: n = unknown IFX, ADA, ETN), HC (10)	Influenza trivalent subunit H1N1/H3N2/B	SP: HI > 1:40, SR: > 4-fold increase from baseline after 30 d	RA 53 (3)	RA (82), HC (–)	–	2.47 (0.2), no significant change at 30 days	–	RA 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

* DAS28 prevaccination scores are quoted unless stated otherwise. ** Includes patients with RA taking nbDMARD, including non-MTX users; §Additional data supplied on request by the author. DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; NOS: Newcastle-Ottawa Scale; RA: rheumatoid arthritis; HC: healthy controls; SC: seroconversion; SP: seroprotection; SR: serological response; TNFi: tumor necrosis factor inhibitor; IFX: infliximab; ADA: adalimumab; ETN: etanercept; MTX: methotrexate; HI: hemagglutination inhibition assay; nbDMARD: nonbiological disease-modifying antirheumatic drugs.

a significantly worse humoral response to pH1N1 vaccination in ABA-treated patients compared to age-matched MTX-treated patients, and Alten, *et al* described preserved influenza vaccine responses in 296 ABA-exposed patients, pooling the results from 2 multicenter, open-label substudies[21]. In total, 49.5% of patients achieved an appropriate postvaccine humoral response. Despite vaccine responses not being compared against a comparator group, the authors concluded that the vaccine responses were preserved.

TCZ and influenza vaccine response. Iwamoto, *et al*[15] reported appropriate humoral responses to pH1N1 vaccination in TCZ-treated patients compared to HC. However, combination MTX + TCZ compared to TCZ 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 TCZ-exposed patients 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 postvaccination. The first study was undertaken in TOF-naive patients randomized 1:1 to TOF 10 mg bid or placebo, stratified by MTX exposure. Combination TOF + MTX therapy was associated with worse 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 wk pre- and postvaccination) had no significant effect on humoral vaccine responses.

MTX and pneumococcal vaccination response. Two studies reporting on 254 subjects (122 patients with RA, 132 HC) examining MTX exposure and 6B and 23F pneumococcal serotype responses were included in the metaanalysis[25,26]. From the limited data for the 2 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; Figure 4).

TNFi and pneumococcal vaccination response. Two studies reporting on 273 subjects (141 RA and 132 HC) assessing 6B and 23F pneumococcal serotype responses with TNFi exposure[25,26] were included in the metaanalysis. From the limited data, TNFi exposure had no significant detriment to vaccine response compared to HC (pooled RR 0.98, 95% CI 0.58–1.67; Figure 4).

RTX and pneumococcal vaccine response. Comparing patients with RA treated with RTX + MTX (n = 65) to MTX monotherapy (n = 28), Bingham, *et al*[27] reported that RTX-exposed patients had a reduced response to vaccination

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Table 2. Characteristics of the prospective cohort studies examining pneumococcal vaccine immunogenicity included in the metaanalysis.

Author, Yr	No. Subjects	Vaccine Intervention	Outcome	Age, Yrs, Mean (SD)	Women, %	Disease Duration, Yrs, Mean (SD)	DAS28*, Mean (SD)	HAQ, Mean (SD)	SC, % (95% CI)	SP, % (95% CI)	NOS
MTX											
Kapetanovic, *et al*, 2006[25]	RA (37), HC (47)	PPV23	2-fold increase in postvaccination titers for 6B and 23F serotypes, 4–6 wks postvaccination	RA median 61.3 (range 20.8–81.4), HC 30.3 (19.2–60.3)	RA (68), HC (74)	Median 7.0 (min 0.9–max 46.9)	Prevaccine DAS28, low 53%, medium 35%, high 12%	–	–	RA 13.5, HC 38.2	5
Kapetanovic, *et al*, 2011[26]	RA (85), HC (85)	PCV-7	2-fold increase in postvaccination titers for 6B and 23F serotypes, 4–6 wks postvaccination	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
TNFi											
Kapetanovic, *et al*, 2006[25]	RA TNFi (62: IFX 27, ETN 35), HC (47)	PPV23	2–fold increase in postvaccination titers for 6B and 23F serotypes, 4–6 weeks postvaccination	RA median 53.7 (range 15.1–85.3), HC 30.3 (19.2–60.3)	RA (76), HC (74)	Median 20.8 (1.5–55.9)	Prevaccine DAS28, low 49%, medium 41%, high 10%	–	–	RA 50, HC 38.2	5
Kapetanovic, *et al*, 2011[26]	RA (79: TNFi not specified), HC (85)	PCV-7	2-fold increase in postvaccination titers for 6B and 23F serotypes, 4–6 weeks postvaccination	RA 59.8 (14), HC 51.6 (12)	RA (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

* DAS28 prevaccination scores are quoted unless stated otherwise. RA: rheumatoid arthritis; HC: healthy controls; TNFi: tumor necrosis factor inhibitor; IFX: infliximab; ADA: adalimumab; ETN: etanercept; MTX: methotrexate; HI: hemagglutination inhibition assay; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; PPV23: 23-valent pneumococcal polysaccharide vaccine; PCV-7: 7-valent pneumococcal conjugated vaccine; NOS: Newcastle Ottawa Scale; SC: seroconversion; SP: seroprotection.

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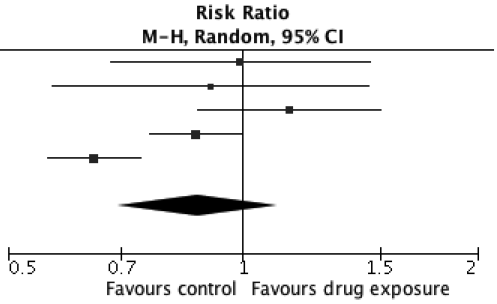
(A) Treatment with MTX and H1N1 strain responses (including pandemic and seasonal H1N1 pooled)

Study or Subgroup	MTX Events	MTX Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Franca 2012	14	25	66	117	16.0%	0.99 [0.68, 1.45]
Iwamoto 2012	24	41	9	14	13.2%	0.91 [0.57, 1.45]
Kapetanovic 2007	33	37	14	18	20.2%	1.15 [0.87, 1.50]
Kobie 2011	28	32	54	54	25.3%	0.87 [0.76, 1.00]
Ribeiro 2011	115	215	194	234	25.3%	0.65 [0.56, 0.74]
Total (95% CI)		**350**		**437**	**100.0%**	**0.88 [0.69, 1.11]**
Total events	214		337			

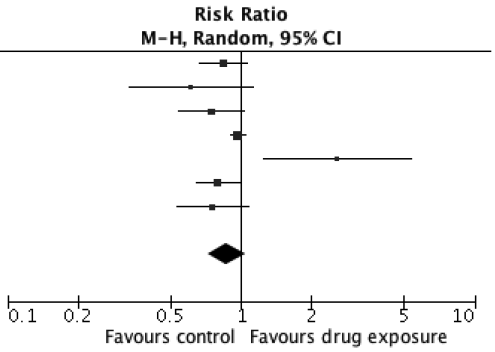
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 21.07$, df = 4 (P = 0.0003); $I^2 = 81\%$
Test for overall effect: Z = 1.10 (P = 0.27)



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

Study or Subgroup	TNFi exposed Events	TNFi exposed Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Franca 2012	27	41	92	117	17.7%	0.84 [0.66, 1.06]
Iwamoto 2012	11	28	9	14	6.8%	0.61 [0.33, 1.12]
Kapetanovic 2007	36	62	14	18	14.1%	0.75 [0.54, 1.03]
Kobie 2011	35	36	54	54	24.4%	0.97 [0.90, 1.04]
Kubota 2007	12	27	9	52	5.1%	2.57 [1.24, 5.32]
Ribeiro 2011	31	47	194	234	18.9%	0.80 [0.64, 0.98]
Salemi 2009	15	22	9	10	13.1%	0.76 [0.53, 1.08]
Total (95% CI)		**263**		**499**	**100.0%**	**0.86 [0.72, 1.04]**
Total events	167		381			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 19.94$, df = 6 (P = 0.003); $I^2 = 70\%$
Test for overall effect: Z = 1.55 (P = 0.12)



(C) Treatment with MTX and H3N2 strain responses

Study or Subgroup	MTX Events	MTX Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Kapetanovic 2007	28	37	13	18	8.1%	1.05 [0.75, 1.47]
Kobie 2011	30	32	54	54	91.9%	0.93 [0.84, 1.03]
Total (95% CI)		**69**		**72**	**100.0%**	**0.94 [0.85, 1.04]**
Total events	58		67			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.71$, df = 1 (P = 0.40); $I^2 = 0\%$
Test for overall effect: Z = 1.22 (P = 0.22)

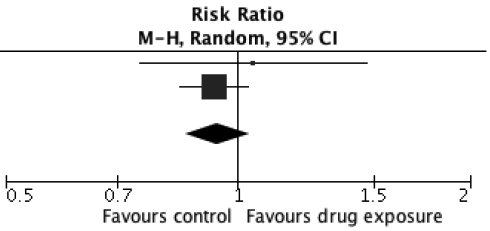


Figure 2. Forest plots for the risk ratios of response rates for influenza vaccine serotypes between patients with rheumatoid arthritis receiving anti-tumor necrosis factor drugs or MTX, and HC. HC: healthy controls; M-H: Mantel-Haenszel test; MTX: methotrexate; TNFi: tumor necrosis factor inhibitor.

for each of the 12 PPV23 serotypes tested. The proportions of RTX-treated patients with a positive vaccine response (≥ 1, 2, 3, 4, 5, and 6 serotypes) were 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.

TCZ and pneumococcal vaccine response. TCZ 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].

TCZ and pneumococcal vaccine response. The data on TCZ exposure and pneumococcal vaccine responses are limited; the results of 2 studies investigating pneumococcal responses in the context of TOF exposure were reported by Winthrop, *et al*[24]. Combination TOF + MTX was associated with reduced humoral response to PPV23 vaccine compared to placebo, TOF, or MTX monotherapy. Temporary withdrawal of TOF (1 wk pre- and post-PPV23 vaccination) had little

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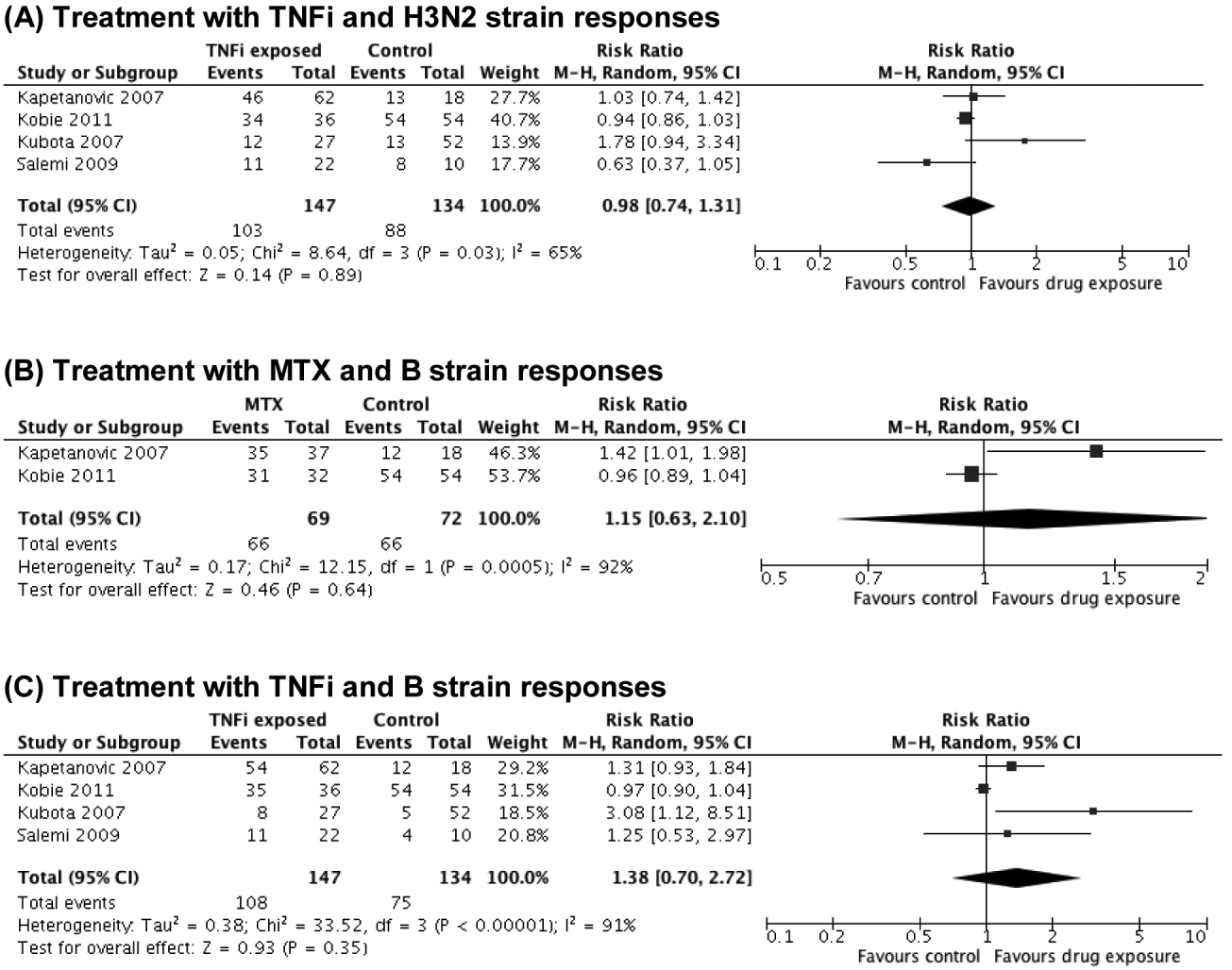

Figure 3. Forest plots for the RR of response rates for influenza vaccine serotypes between patients with rheumatoid arthritis receiving TNFi or MTX, and HC. HC: healthy controls; M-H: Mantel-Haenszel test; MTX: methotrexate; TNFi: tumor necrosis factor inhibitor; RR: risk ratio.

effect on humoral vaccine response compared to continuous therapy.

DISCUSSION

Our metaanalysis 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.

Metaanalysis of pneumococcal vaccination responses with immunosuppression exposure was challenging because of the significant heterogeneity in reporting vaccine response; we only considered responses to 6B and 23F serotypes. Despite not being the most prevalent serotypes, cases of 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 1 serotype, it is not appropriate to assume that vaccine responses for other serotypes will be equal. Vaccine efficacy was defined as achievement of postvaccination SP Ab titers; however, subjects could achieve SP without SR or SC. SP does not 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 UK 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 longterm vaccine responses, comparison of vaccine immunogenicity at 3 to 6 weeks postvaccination is similar[32].

Although it was not possible to undertake metaanalysis of

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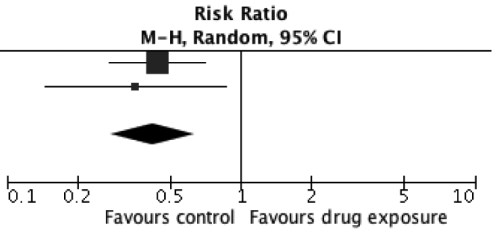
(A) Treatment with MTX and pneumococcal 6B/23F serotype responses

Study or Subgroup	MTX (no TNFi) Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kapetanovic 2011	18	85	41	85	78.6%	0.44 [0.28, 0.70]
Kapetanovic 2006	5	37	18	47	21.4%	0.35 [0.14, 0.86]
Total (95% CI)		**122**		**132**	**100.0%**	**0.42 [0.28, 0.63]**
Total events	23		59			

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)



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

Study or Subgroup	TNFi monotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kapetanovic 2006	31	62	18	47	47.3%	1.31 [0.84, 2.03]
Kapetanovic 2011	29	79	41	85	52.7%	0.76 [0.53, 1.09]
Total (95% CI)		**141**		**132**	**100.0%**	**0.98 [0.58, 1.67]**
Total events	60		59			

Heterogeneity: Tau² = 0.10; Chi² = 3.43, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 0.07 (P = 0.95)

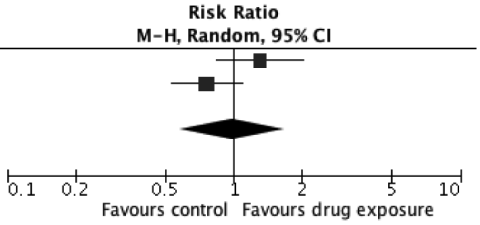


Figure 4. Forest plot for the risk ratios of response rates for pneumococcal vaccine (combined 6B and 23F serotype responses) between patients with rheumatoid arthritis receiving MTX or TNFi, and healthy controls. M-H: Mantel-Haenszel test; MTX: methotrexate; TNFi: tumor necrosis factor inhibitor.

the effect of RTX on humoral responses to influenza and pneumococcal vaccination, there are consistent reports in the literature of worse serological responses to immunization[19,27,33,34,35]. 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 metaanalysis on TCZ exposure on vaccine responses compared to HC, although review of the literature suggests there was no significant effect on PPV or influenza vaccine immunogenicity[22,29]. Comparatively, ABA has been reported to impair the responses to pH1N1 and PPV23[20,28]. TOF in combination with MTX is associated with reduced influenza and pneumococcal vaccine responses. Temporary withdrawal of TOF had no significant effect on influenza or PPV vaccine immunogenicity.

EULAR guidelines recommend that 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 guidelines[3] also advise vaccination should be undertaken in a period of disease stability; however, in UK practice, biologic drugs (often a trigger to administer vaccinations) are only considered in patients with persistent high disease activity states (28-joint count Disease Activity Score > 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 for 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 nbDMARD. 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 taking nbDMARD, including azathioprine and MTX, but it should be avoided in patients taking biologics and high-dose prednisolone (> 20 mg/d)[36].

Only 2 studies included in the metaanalyses reported specifically on the effect of vaccination on disease activity; however, several confirm no evidence of a detrimental effect on variables of disease activity postvaccination[13,17–19,33,34,37–40].

To our knowledge, there has been 1 previous metaanalysis assessing the influence of antirheumatic 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 the metaanalysis by Hua, *et al*[41], 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-plus TNFi-exposed patients to TNFi monotherapy rather than HC.

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We recognize that biologics are co-prescribed with nbDMARD (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 effect of drug therapy on vaccine immunogenicity, albeit to the detriment of the potential number of studies and subjects that could be included in metaanalysis. Additionally, we have considered newer antirheumatic therapies, including ABA, TCZ, and TOF. Our assessment of MTX exposure impairing pneumococcal vaccine response is congruent with Hua, *et al*[41], 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 metaanalysis that we acknowledge.

Our review was potentially subject to outcome reporting bias. We included only studies reporting on postvaccine Ab titers (rather than OI or GMT responses) because it was the most commonly reported method of assessing vaccine response. Literature review identified several studies that could not be included because of 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 center analyzing 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, TCZ, 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 affect vaccine immunogenicity, was not possible. Control groups were not necessarily age-matched to the RA cohorts. Older subjects 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 patients with RA treated with MTX[48]; however, this was poorly reported in the 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) affect vaccine response; this was outside the scope of our study.

Seasonal and pandemic influenza vaccinations use strains that vary each season depending on the most virulent predicted strains. Although vaccine responses were broadly categorized by A or B strain responses for the metaanalysis, there may have been variations 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 maximize efficacy and reduce drug immunogenicity. We aimed to compare TNFi monotherapy to an HC group to prevent aberrations resulting from 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 metaanalysis did not explicitly comment on whether 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 metaanalysis and systematic review suggest that MTX exposure diminishes humoral responses to pneumococcal but not influenza vaccination. TNFi therapy does not impair influenza or pneumococcal vaccine responses. Immunosuppression should not preclude vaccination against immune-preventable disease. Vaccination is safe, well-tolerated and should be encouraged as part of routine clinical care. Increasing the awareness and uptake of vaccinations in patients with RA will require collaborative approaches between primary and secondary care.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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