Online supplement to: A Systematic Review and Metaanalysis of Antirheumatic Drugs and Vaccine Immunogenicity in Rheumatoid Arthritis. *The Journal of Rheumatology*. doi:10.3899/jrheum.170710

ONLINE SUPPLEMENTARY DATA

Supplementary Data 1. 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

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 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 Ottawa Scale:

0 – 3 = poor quality study

4 – 6 = satisfactory quality study

7 – 9 = high quality study

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Supplementary Table 1: Quality assessment of studies using the Newcastle Ottawa Scale.

	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.

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 patients responding to each serotype in RTX+MTX group compared to MTX monotherapy	Reduced vaccine response in RTX exposed patients compared to MTX
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 (1.7-5.6)	Post-vaccination Ab responses may be reduced when TOC combined with MTX.

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