Uptake and safety of pneumococcal vaccination in adults with immune mediated inflammatory diseases: a UK wide observational study

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Abstract

Objective The uptake and safety of pneumococcal vaccination in people with immune mediated inflammatory diseases (IMIDs) is poorly understood. We investigated the UK wide pneumococcal vaccine uptake in adults with IMIDs and explored the association between vaccination and IMID flare.

Methods Adults with IMIDs diagnosed on or before 01/09/2018, prescribed steroid-sparing drugs within the last 12 months and contributing data to the Clinical Practice Research Datalink Gold were included. Vaccine uptake was assessed using a cross-sectional study design. Self-controlled case series (SCCS) analysis investigated the association between pneumococcal vaccination and IMID flare. The SCCS observation period was up to six-month before and after pneumococcal vaccination. This was partitioned into a 14-day pre-vaccination induction, 90-days post-vaccination exposed, and the remaining unexposed periods.

Results We included 32,277 patients, 14,151 with RA, 13,631 with IBD, 3,804 with axial spondyloarthritis and 691 with SLE. Overall, 57% were vaccinated against pneumococcus. Vaccine uptake was lower in those younger than 45 years (32%), with IBD (42%), and without additional indication(s) for vaccination (46%). In the vaccine-safety study, data for 1,067, 935, and 451 vaccinated patients with primary-care consultations for joint pain, AIRD flare and IBD flare respectively were included. Vaccination against pneumococcal pneumonia was not associated with primary-care consultations for joint pain, AIRD flare and IBD flare in the exposed period with incidence rate ratios (95% Confidence Interval) 0.95 (0.83-1.09), 1.05 (0.92-1.19), and 0.83 (0.65-1.06) respectively.
Conclusion Uptake of pneumococcal vaccination in UK patients with IMIDs was suboptimal. Vaccination against pneumococcal disease was not associated with IMID flare.

Keywords: Pneumococcal vaccination, rheumatoid arthritis, psoriatic arthritis, vaccine safety, vaccine uptake.

Key messages
- The uptake of pneumococcal vaccination in people with immune mediated inflammatory diseases is suboptimal.
- Vaccination against pneumococcal disease is safe.
- Pneumococcal vaccination should be actively promoted in people with inflammatory conditions.
Introduction

Immunosuppressed adults with immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE) are at an increased risk of pneumonia and its complications including death (1, 2, 3, 4). Consequently, pneumococcal vaccination is recommended for this at-risk population (5, 6). Despite long-standing recommendations for vaccinating the high risk groups since the year 1992 and the over 65s since the year 2003 (5), the uptake of pneumococcal vaccination in the at-risk populations was suboptimal (7). In a previous study from the UK, the uptake of pneumococcal vaccination among patients with RA was reported to be 50% overall, and 43% in those younger than 65 years in age (8). The uptake of pneumococcal vaccination across a broad range of IMIDs in a UK wide cohort has not been evaluated to the best of our knowledge. Understanding vaccine uptake across a range of conditions is important as the uptake of pneumococcal vaccination in people with IBD was noted to be lower in North America and Europe at 10.3%-38% (9, 10).

Belief that the vaccination could trigger an IMID flare, and cause other IMIDs e.g., vasculitis (11, 12) are key barriers to vaccination (9, 13, 14). The association between pneumococcal vaccination and IMID flare has not been evaluated in an adequately controlled study. There is some evidence from small studies restricted to a few conditions that vaccination against pneumococcal disease does not cause a flare of IMIDs (15, 16). In a systematic review and meta-analysis of pneumococcal vaccine immunogenicity studies in patients with SLE, disease activity did not worsen up to eight weeks after pneumococcal vaccination (17).

In this study we evaluated the uptake and safety of pneumococcal vaccination in UK adults with IMIDs.
Methods

Data source: Data from the Clinical Practice Research Datalink (CPRD) Gold were used in this study. Incepted in the year 1987, CPRD Gold is an anonymised longitudinal database of electronic health records of >14 million people in the UK. CPRD participants are representative of the UK population in terms of age, sex, and ethnicity (18). CPRD includes information on demographics, lifestyle factors, diagnoses stored as Read codes – a coded thesaurus of clinical terms, primary-care prescriptions, and immunisations. Vaccination and date of vaccination are also recorded.

Approval/patient consent This study was approved by Clinical Practice Research Datalink’s Research Data Governance (Reference 21_000614), which has overarching research ethics committee approval for research studies using anonymous data. Practices that contributed data to the Clinical Practice Research Datalink consented to using anonymized patient data for approved research projects and additional consent was not required prior to individual studies (cprd.com).

Study design Cross-sectional and self-controlled case series (SCCS) study designs were used to examine the uptake and safety of pneumococcal vaccination.

Population Adults aged ≥18 years on the 1st September 2018, with at least one primary-care record of an IMID (i.e., rheumatoid arthritis (RA), inflammatory bowel disease (IBD), axial spondyloarthritis (Ax-SpA), systemic lupus erythematosus (SLE)) and with at least one prescription of a steroid sparing drug (i.e., either methotrexate, azathioprine, 6-mercaptopurine, sulfasalazine, 5-aminosalicylates, mycophenolate, leflunomide, ciclosporin, tacrolimus or sirolimus) within the previous 12 months were eligible to be included in this study.
Pneumococcal vaccination  Pneumococcal vaccination was defined using both product codes and Read codes (Supplementary Table S1, available at *Rheumatology* online). Dates of vaccination were extracted from CPRD. Data on vaccination from inception of CPRD in 1987 to 1st September 2018 were considered in the vaccine uptake study. Vaccinations recorded in the CPRD as not administered in primary care e.g., vaccination from hospitals, pharmacy were included in the vaccine uptake study but were excluded from the safety study because the date of administration is not reliably recorded in the CPRD. Similarly in the vaccine safety study we only considered the first vaccination in those with two or more records of vaccination as people that experience an adverse-event with a vaccination are less likely to agree to have a second dose of the vaccine if offered for any clinical indication.

Outcomes

**Vaccine uptake** Vaccination against pneumococcal pneumonia, defined as any pneumococcal vaccination up to 1st September 2018.

**Vaccine safety:**

A. Auto-immune rheumatic disease (AIRD)

[1] Primary care consultation for joint pain. This was defined using Read codes (Supplementary Table S2, available at *Rheumatology* online). Consultations for joint pain within 14 days of each other were considered as part of the same episode.

[2] AIRD flare. This was defined as present when there was a primary-care prescription of oral corticosteroid without another corticosteroid prescription in the preceding sixty days. The patient was also required to not have consulted for an alternate condition that could justify corticosteroid prescription on the same date. For this, all relevant primary care consultations were retrieved and reviewed by AA (General Medicine and Rheumatology expertise) for conditions that might explain the corticosteroid
prescribed and such participants were excluded from the analysis as there was considerable uncertainty whether they experienced IMID flare or another illness (Supplementary Table S3, available at Rheumatology online). The corticosteroid prescription free period used to define consultation for AIRD flare was increased to at least 120 days in a sensitivity analysis as this time-period has been validated for the IBD flare (19) (See below).

[3] RA flare. This was defined as present when there was either a Read code for RA flare or a primary-care prescription of oral corticosteroid without another corticosteroid prescription in the preceding sixty days in patients diagnosed with RA. The patient was also required to not have consulted for an alternate condition that could justify corticosteroid prescription on the same date. This condition was applied following the same procedure as for AIRD flare described above.

B: IBD

[1] IBD flare. This was defined as present when there was primary-care prescription of corticosteroid without another corticosteroid prescription in the preceding 120 days (19). The patient was also required to not have consulted for an alternate condition that could justify corticosteroid prescription on the same date defined as a new primary care prescription of corticosteroid (19).

Covariates

Vaccine uptake Age, sex, type of IMID and presence of additional indication(s) for vaccination as per the UK Health Security Agency (5). Briefly, the additional indications for vaccination included chronic heart diseases, chronic respiratory diseases, chronic kidney diseases, chronic liver diseases, immunosuppression (defined as either solid organ transplant, bone marrow transplant, HIV/AIDS, lymphoma, leukaemia, myeloma, or chemotherapy), diabetes and asplenia. The vaccine uptake study was a
A cross-sectional study that included patients alive on the 1st September 2018. Thus, covariates were ascertained at 01/09/2018.

**Vaccine safety** Season defined in line with the Meteorological Office. According to the Meteorological Office, winter spans from the 1st December to the 28th February of the next year, spring spans from 1st March to 31st May, summer spans from 1st June to 31st August, and autumn spans from 1st September to 31st November.

**Statistical analyses**

**Vaccine uptake** The percentage and 95% CI of the study population alive on 1st September 2018 that were vaccinated was calculated. The proportion vaccinated was stratified according to their age (<45, 45–64, ≥65 years) on the 1st of September 2018, sex, presence of other indications for vaccination, and type of IMID (RA, IBD, SLE, Ax-SpA). Poisson regression with robust standard error was used to examine mutually adjusted associations between pneumococcal vaccination and age group, sex, IMID type and presence of additional at-risk condition for vaccination.

**Vaccine safety** Patients vaccinated against pneumococcal pneumonia and who also consulted their GP for at-least one IMID flare in the six-month period before and the six-month period after vaccination were included in a self-controlled case-series (SCCS) analysis. SCCS is an established study design for assessing vaccine safety. By including patients with both an exposure and an outcome, and undertaking within person comparisons, SCCS analysis removes between person time-fixed confounding, a key confounder in vaccine safety studies. The baseline period extended from the latest of current registration date, first IMID diagnosis date recorded in the CPRD, and 165 days preceding vaccination to 15-days pre-vaccination, and from 90 days post-vaccination to the earliest date of six-months post vaccination, leaving GP surgery, death, or last data collection from the GP surgery. The exposed
period extended from vaccination date to 90 days later and, was further categorised as 0-14 days, 15-30 days, 31-60 days, and 61-90 days (Supplementary Figure S1, available at *Rheumatology* online). The first cut-off was selected at 14-days post-vaccination as it takes two weeks for the serological response and, we hypothesised this period of immune reconstitution would be most likely to associate with disease activity. The 15-day period immediately preceding vaccination was excluded from the baseline period to minimise confounding due to healthy vaccinee effect or due to active promotion of vaccination in those consulting for a disease flare(20).

A Poisson model conditioned on the number of events adjusted for the four UK seasons as categories was fitted to calculate incidence rate ratios (aIRR) and 95% confidence interval (CI) for each exposure period compared to the baseline period. This approach was also followed to assess the association between pneumococcal vaccination and AIRD flare, defined as a ≥4-month gap between corticosteroid prescriptions in people with autoimmune rheumatic diseases during the observation period as a sensitivity analysis.

Data management and analysis were performed in Stata v17, Stata Corp LLC, Texas, USA.
Results

Uptake Data from 32,277 people with IMIDs were included in this study (Figure 1). Their mean age (SD) on 1\textsuperscript{st} of September 2018 was 58 (16) years and 59% were female. 14,151 (43.8%) had RA, 13,631 (42.2%) IBD, 3,804 (11.8%) Ax-SpA, and 691 (2.1%) SLE.

Overall uptake of pneumococcal vaccination was 56.5% (95%CI 55.9-57.0%). Pneumococcal vaccinations occurred between 01/01/1992 and 01/09/2018. Vaccination uptake was significantly lower in people with IBD (42.4%, 95% CI (41.6-43.2%)) than in those with AIRDs (66.8%, 95% CI (66.1-67.4%)) with adjusted incidence rate ratio (aIRR) 0.75 (95%CI 0.73-0.76)). Increasing age, female sex and presence of additional at-risk conditions were independently associated with the uptake of pneumococcal vaccination (Table 1). Vaccination uptake was higher in people aged at-least 65 years or with an additional at-risk condition than in those less than 65-years in age and without an additional at-risk condition for vaccination (proportion vaccinated (95% CI); 0.72 (0.72-0.73) and 0.37(0.36-0.38) respectively). On adjusting for gender and type of inflammatory condition, people not considered at additional risk of pneumococcal pneumonia (i.e., age < 65 years and without another at-risk condition) were 46% less likely to get vaccinated than those considered at additional risk of pneumococcal pneumonia (i.e., aged ≥65-year and/or with additional at-risk condition) with aIRR 0.54 (95% CI 0.53-0.56).

Vaccine Safety Data for 1,067, 935, 778 and 451 participants with primary care consultations for joint pain, AIRD flare, RA flare and IBD flare respectively were included. 1,838 participants had either AIRD flare or a primary care consultation for joint pain and of these, 1,412 (76.8%) had RA, 281 (15.3%) had SpA and 145 (7.9%) had SLE. The majority were female (71.6%) and their mean (SD) age was 55 (12)
years. Of the participants with IBD flare, 240 (53.2%) had ulcerative colitis, 160 (35.5%) had Crohn's disease, 51 (11.3%) had IBD without any specific coding for subtype.

Vaccination against pneumococcal pneumonia was not associated with joint pain consultation, AIRD flare or IBD flares respectively in the 90-days post vaccination (Tables 2, 3). The 15-day pre-vaccination period associated with significantly more primary care consultations for joint pain, AIRD flare and IBD flare (Tables 2, 3).

Discussion
This UK wide study has shown that approximately one in two immunosuppressed adults with IMIDs in the UK is vaccinated against pneumococcal pneumonia. This is similar to the vaccine uptake of 54% to 56% reported in people with chronic respiratory disease, chronic kidney disease, and diabetes requiring insulin or oral hypoglycaemic medication (21). The vaccine uptake was even lower at 31.8% in those less than 45-years in age and at 46.4% in IMID patients without an additional indication for vaccination. The vaccine uptake ranged from 42.4% to 69.7% in IBD and RA respectively.

This study did not find an association between pneumococcal vaccination and IMID flare requiring primary-care consultation and/or treatment. An increased risk in flare of underlying disease was observed 15-days pre-vaccination, which could be attributed to opportunistic vaccine promotion to people consulting for an IMID flare resulting in vaccination.

It is difficult to compare our findings on vaccine uptake in IMIDs with those of previous studies, since, to our knowledge, this is the first study to assess pneumococcal vaccination uptake across many inflammatory conditions and to compare uptake between different inflammatory conditions. These low vaccination rates are
concerning given the increased risk of pneumococcal disease in this at-risk population for whom vaccination is recommended and indicates that they would benefit from targeted measures to increase pneumococcal vaccine uptake. We observed substantial variation in vaccination rates across different inflammatory diseases. This may reflect differential advice from different specialties. A 2013 UK primary care study reported 50% pneumococcal vaccine uptake in RA patients which was lower than the 70% pneumococcal vaccine uptake reported in the current study (8). This improvement in pneumococcal vaccination uptake over a 5-year period is remarkable and may be related to clear guidance from the British Society of Rheumatology to offer vaccination against pneumococcal pneumonia in patients with RA (22, 23). Similarly, more and more patients with RA are being treated with potent combination DMARDs and this has resulted in vaccination being promoted more actively in people with this condition (24). Improvement in pneumococcal vaccination uptake in RA patients has also been reported in a multi-centre prospective study of 1,679 patients in Greece (25). In our study patients with IBD had a low vaccine uptake. A similar low pneumococcal vaccine uptake of 38% has been reported from a French online survey of IBD patients (10) while a lower rate of 10.3% was reported from a gastro-enterology clinic in Canada (9). Pneumococcal vaccine uptake was higher in people with Ax-SpA in the current study than has been reported in other countries in Europe. This may be because Ax-SpA patients treated with NSAIDs alone were not included in this study. For comparison, in Switzerland, the pneumococcal vaccine uptake was reported to be 32.5% in an online survey of Ax-SpA patients that was not restricted to patients on immunosuppressive treatment (26). The multinational COMORA study reported higher uptake of pneumococcal vaccine in some countries e.g., France, but lower uptake in
most other countries (27). These questionnaire studies are prone to bias from self-reported vaccination uptake and should be interpreted with caution.

Consistent with previous research on factors associated with increased vaccine uptake, female sex, increasing age and other indications for vaccination significantly associated with pneumococcal vaccination (13, 28, 29).

Barriers to vaccination have included the fear that vaccines may trigger an IMID flare (14, 30). This study did not find a significant association between pneumococcal vaccination and flare of the underlying inflammatory disease. Similarly, a systematic review and meta-analysis of pneumococcal vaccine immunogenicity studies in patients with SLE did not find an association between the vaccination and increased disease activity (17). Safety studies in the general population have shown that pneumococcal vaccine is well tolerated (31). Similarly, there was no association between vaccination with the seasonal influenza vaccine and AIRD flare, and no association between vaccination against COVID-19 and AIRD, IBD, and psoriasis flare in previous studies (32, 33, 34, 35). A meta-analysis of prior uncontrolled studies reported a 2% pooled prevalence of IBD flare after vaccination, however, it is not known if the flares were temporally related or coincidental (36).

Strengths of this study included a large nationally representative sample of people with IMIDs in the UK given the almost universal registration with a GP for all UK residents (18). We studied a wide range of IMIDs improving the generalizability of the findings. The use of primary-care prescription and consultation data minimised recall bias on the association between vaccination and disease flares. To improve the validity of our case definition, we used a combination of diagnostic and prescription codes to ascertain people with IMIDs. Additionally, we defined IBD flares according to a validated definition (19) and we undertook a sensitivity analysis for the association...
between pneumococcal vaccination and AIRD flare using a validated IBD flare
definition. Furthermore, to improve the outcome fidelity, we excluded participants with
diagnoses that could potentially explain corticosteroid prescribed on the same date as
the AIRD or IBD flare. Finally, our use of SCCS methodology controlled for between-
person confounding which is a serious problem in observational studies of vaccine
safety.

There are some limitations to our study. Firstly, some vaccinations that were
administered outside of primary-care for example in hospital or at the workplace as for
health care professionals may not have been recorded in the CPRD, reducing
vaccination uptake estimates. This is unlikely to have a significant impact on our
results as vaccination is almost exclusively a general practice activity in the UK. Where
non-primary care administration of the vaccine was recorded, it was excluded from the
vaccine safety study as it is difficult to be sure of the date of vaccination in such
instances. Second, the type of vaccine was not assessed as the vast majority of
vaccinations were with the PPV23 vaccine, which has been universally used in the UK
for risk groups since the year 1992 (5). Third, we were unable to assess the impact of
biologics on vaccine safety because their prescription is not recorded in the CPRD.
We see no reason though to expect more extreme immunologically driven side effects
in these groups given the possibility of less immunogenic response with biologic use
(37). Fourth, data on disease activity and flares managed in hospital or specialist
clinics are not recorded in CPRD. . Fifth, because our definition of AIRD and IBD flare
required consultation and/or prescription, minor flares not needing drug treatment
were not considered as an outcome in the vaccine safety study. It is possible that there
may be an association of vaccination with minor flares that were not ascertained in our
study. However, such effects would be unlikely to greatly discourage vaccination
uptake and it is the more significant flares that we have studied which are of primary concern. Flares managed in hospital or specialist clinics were excluded. Additionally, joint pain was considered as an outcome of interest because it is a common symptom of inflammatory arthritis. However, joint pain might also be caused by another illness such as osteoarthritis reducing the specificity for this outcome.

In conclusion, this study provides recent UK-wide population evidence that the uptake of pneumococcal vaccination in people with IMIDs is suboptimal particularly in patients with IBD, those younger than 65 years in age, and in those without another indication for vaccination. It also demonstrated that pneumococcal vaccination does not associate with flare of the underlying IMIDs. These data should be used to promote pneumococcal vaccination in this at-risk population.
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**Disclosure statement** A.A. has received personal fees from UpToDate (royalty), Springer (royalty), Cadilla Pharmaceuticals (lecture fees), NGM Bio (consulting), and Limbic (consulting) unrelated to this work. CDM is Director of the NIHR School for Primary Care Research. Keele University has received research funding for CDM from NIHR, MRC, Versus Arthritis and BMS. JSN-V-T was seconded to the Department of Health and Social Care (DHSC) from October 2017 to March 2022. Since March 2022 he has received personal fees from CSL Seqirus (lectures, writing and consulting), AstraZeneca (lecture) and Sanofi Pasteur (lectures and speaking) all of whom manufacture influenza vaccines. He has consulted for Moderna Therapeutics who are developing influenza vaccines. He has performed consultancy for MSD, which manufactures PPV23, in spring 2023 but unrelated to PPV23. The views expressed in this manuscript are those of its authors and not necessarily those of DHSC or any other entity mentioned above. The other authors have no conflict of interest to declare.

**Author contribution** The study was conceived by Prof Abhishek. All authors were involved in the design of the study. The analysis was carried out by Dr Nakafero. All authors edited the first and all subsequent drafts and approved the final draft for submission.

**Data sharing statement** Data used in the study are from the Clinical Practice Research Datalink (CPRD). Due to CPRD licencing rules, we are unable to share data used in this study with third parties. The data used in this study may be obtained directly from the CPRD. Study protocol is available from [www.cprd.com](http://www.cprd.com).
References


Table 1: Uptake and risk factors of pneumococcal vaccination in immune mediated inflammatory diseases (n=32,277)

<table>
<thead>
<tr>
<th>Vaccination uptake</th>
<th>Incidence rate ratios (IRR) and 95% confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number</td>
</tr>
<tr>
<td>Overall</td>
<td>32,277</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>7,190</td>
</tr>
<tr>
<td>45-64</td>
<td>13,045</td>
</tr>
<tr>
<td>≥65</td>
<td>12,042</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13,231</td>
</tr>
<tr>
<td>Female</td>
<td>19,046</td>
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<tr>
<td>Additional clinical risk group(s)</td>
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</tr>
<tr>
<td>Absent</td>
<td>19,643</td>
</tr>
<tr>
<td>Present</td>
<td>12,634</td>
</tr>
<tr>
<td>Inflammatory condition</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>14,151</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>13,631</td>
</tr>
<tr>
<td>Systemic Lupus</td>
<td>691</td>
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<tr>
<td>Erythematous</td>
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<tr>
<td>Axial spondyloarthitis*</td>
<td>3,804</td>
</tr>
</tbody>
</table>

*Psoriatic arthritis, reactive arthritis, and ankylosing spondylitis
Table 2: The association between pneumococcal vaccination and consultation for autoimmune rheumatic disease (AIRD) flare, rheumatoid arthritis (RA) flare, joint pain, and inflammatory bowel disease (IBD) flare

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk period (days)</th>
<th>Events (n)</th>
<th>Person-time (days)</th>
<th>IRR (95%CI)</th>
<th>Adjusted IRR (95%CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>AIRD flare</td>
<td>Baseline</td>
<td>1,048</td>
<td>373,886</td>
<td>1</td>
<td>1</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>15 days pre-</td>
<td>96</td>
<td>22,656</td>
<td>1.50</td>
<td>1.52</td>
<td>*</td>
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<tr>
<td></td>
<td>vaccination</td>
<td></td>
<td></td>
<td>(1.22,1.85)</td>
<td>(1.23,1.88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post vaccination</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0 - 90 days</td>
<td>391</td>
<td>138,045</td>
<td>0.99</td>
<td>1.05</td>
<td>0.514</td>
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<tr>
<td></td>
<td>0 - 14 days</td>
<td>63</td>
<td>22,914</td>
<td>0.97</td>
<td>0.99</td>
<td>0.953</td>
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<tr>
<td></td>
<td>15 - 30 days</td>
<td>51</td>
<td>22,985</td>
<td>0.78</td>
<td>0.80</td>
<td>0.133</td>
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<tr>
<td></td>
<td>31 - 60 days</td>
<td>128</td>
<td>46,033</td>
<td>0.97</td>
<td>1.04</td>
<td>0.681</td>
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<td></td>
<td>61 - 90 days</td>
<td>149</td>
<td>46,113</td>
<td>1.13</td>
<td>1.20</td>
<td>0.050</td>
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<tr>
<td>RA flare</td>
<td>Baseline</td>
<td>856</td>
<td>30,5713</td>
<td>1</td>
<td>1</td>
<td>*</td>
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<tr>
<td></td>
<td>15 days pre-</td>
<td>77</td>
<td>18,521</td>
<td>1.48</td>
<td>1.50</td>
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<tr>
<td></td>
<td>vaccination</td>
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<td></td>
<td>(1.17,1.87)</td>
<td>(1.18,1.89)</td>
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<td></td>
<td>Post vaccination</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0 - 90 days</td>
<td>321</td>
<td>11,3087</td>
<td>0.99</td>
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<td>0.430</td>
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<tr>
<td></td>
<td>0 - 14 days</td>
<td>54</td>
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<td>1.01</td>
<td>1.04</td>
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<tr>
<td></td>
<td>15 - 30 days</td>
<td>42</td>
<td>18,835</td>
<td>0.78</td>
<td>0.81</td>
<td>0.184</td>
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<td>107</td>
<td>37,710</td>
<td>0.99</td>
<td>1.08</td>
<td>0.488</td>
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<tr>
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<td>61 - 90 days</td>
<td>118</td>
<td>37,773</td>
<td>1.09</td>
<td>1.17</td>
<td>0.124</td>
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<tr>
<td>Joint pain</td>
<td>Baseline</td>
<td>956</td>
<td>33,1904</td>
<td>1</td>
<td>1</td>
<td>*</td>
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<td></td>
<td>15 days pre-</td>
<td>80</td>
<td>20,153</td>
<td>1.38</td>
<td>1.38</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>vaccination</td>
<td></td>
<td></td>
<td>(1.09,1.73)</td>
<td>(1.20,1.74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 - 90 days</td>
<td>341</td>
<td>122,959</td>
<td>0.94</td>
<td>0.95</td>
<td>0.434</td>
</tr>
<tr>
<td></td>
<td>0 - 14 days</td>
<td>60</td>
<td>20,371</td>
<td>1.01</td>
<td>1.02</td>
<td>0.859</td>
</tr>
<tr>
<td></td>
<td>15 - 30 days</td>
<td>46</td>
<td>20,469</td>
<td>0.77</td>
<td>0.78</td>
<td>0.107</td>
</tr>
<tr>
<td></td>
<td>31 - 60 days</td>
<td>99</td>
<td>41,020</td>
<td>0.82</td>
<td>0.85</td>
<td>0.143</td>
</tr>
<tr>
<td></td>
<td>61 - 90 days</td>
<td>136</td>
<td>41,099</td>
<td>1.12</td>
<td>1.16</td>
<td>0.129</td>
</tr>
<tr>
<td>IBD flare</td>
<td>Baseline</td>
<td>338</td>
<td>125,190</td>
<td>1</td>
<td>1</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>15 days pre-</td>
<td>35</td>
<td>7,485</td>
<td>1.72</td>
<td>1.79</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>vaccination</td>
<td></td>
<td></td>
<td>(1.22,2.44)</td>
<td>(1.26,2.55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 - 90 days</td>
<td>126</td>
<td>44,906</td>
<td>1.03</td>
<td>0.83</td>
<td>0.143</td>
</tr>
<tr>
<td></td>
<td>0 - 14 days</td>
<td>18</td>
<td>7,485</td>
<td>0.89</td>
<td>0.89</td>
<td>0.629</td>
</tr>
<tr>
<td></td>
<td>15 - 30 days</td>
<td>16</td>
<td>7,485</td>
<td>0.79</td>
<td>0.75 (0.45, 1.25)</td>
<td>0.271</td>
</tr>
<tr>
<td></td>
<td>31 - 60 days</td>
<td>53</td>
<td>14,970</td>
<td>1.30</td>
<td>1.07</td>
<td>0.666</td>
</tr>
</tbody>
</table>
Table 3. The association between pneumococcal vaccination and autoimmune rheumatic disease (AIRD) flare*: Sensitivity analysis

<table>
<thead>
<tr>
<th>Risk period (days)</th>
<th>Events (n)</th>
<th>Person-time (days)</th>
<th>IRR (95%CI)</th>
<th>Adjusted IRR (95%CI) *</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>225</td>
<td>86,797</td>
<td>1</td>
<td>1</td>
<td>-/-</td>
</tr>
<tr>
<td>15 days pre-vaccination</td>
<td>24</td>
<td>5,204</td>
<td>1.78 (1.17,2.71)</td>
<td>1.94 (1.26,2.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>Post vaccination intervals</td>
<td>0 - 90 days</td>
<td>105</td>
<td>31,817</td>
<td>1.25 (0.99,1.58)</td>
<td>1.21 (0.92,1.58)</td>
</tr>
<tr>
<td></td>
<td>0 - 14 days</td>
<td>18</td>
<td>5,204</td>
<td>1.30 (0.80,2.10)</td>
<td>1.41 (0.87,2.29)</td>
</tr>
<tr>
<td></td>
<td>15 - 30 days</td>
<td>13</td>
<td>5,299</td>
<td>0.93 (0.53,1.63)</td>
<td>0.99 (0.56,1.74)</td>
</tr>
<tr>
<td></td>
<td>31 - 60 days</td>
<td>36</td>
<td>10,620</td>
<td>1.28 (0.90,1.82)</td>
<td>1.29 (0.89,1.87)</td>
</tr>
<tr>
<td></td>
<td>61 - 90 days</td>
<td>38</td>
<td>10,620</td>
<td>1.35 (0.96,1.91)</td>
<td>1.34 (0.93,1.94)</td>
</tr>
</tbody>
</table>

*adjusted for season; †AIRD flare defined as a ≥4-month gap between steroid prescriptions in people with autoimmune rheumatic diseases (AIRDs) during the observation period. The baseline period extended from the latest of current registration date, first disease diagnosis date recorded in the CPRD, and six-months preceding vaccination to 15-days pre-vaccination, and from 90 days post-vaccination to the earliest date of six-months post vaccination, leaving GP surgery, death, or last data collection from the GP surgery.
Figure 1: Participant selection criteria

Patients with inflammatory conditions alive and contributing data to CPRD Gold on 1st September 2018
n=53,169

Excluded n= 20,892
20,569: Patients without at least one prescription of immune suppressing drug in 12 months preceding 1st September 2018.
323: aged <18 years on 1st September 2018.

Included in the study
n=32,277

CPRD: Clinical Practice Research Datalink.