Effectiveness of pneumococcal vaccination in adults with common immune-mediated inflammatory diseases in the UK: a case–control study

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Summary

Background People with immune-mediated inflammatory disease are at increased risk of pneumococcal pneumonia. The effectiveness of pneumococcal vaccination in people with immune-mediated inflammatory diseases has not been evaluated. We investigated the effectiveness of pneumococcal vaccination in preventing morbidity and mortality associated with pneumonia in patients with immune-mediated inflammatory diseases.

Methods In this matched case–control study, we used primary-care electronic health record data from the Clinical Practice Research Datalink Gold database in the UK, with linked hospitalisation and mortality data. Adults with incident common immune-mediated inflammatory diseases diagnosed between April 1, 1997, and Dec 31, 2019, were followed up from the first diagnosis date to the occurrence of an outcome or date of last follow-up. Cases (ie, those with an outcome of interest) were age-matched and sex-matched to up to ten contemporaneous controls by use of incidence density sampling. Outcomes were hospitalisation due to pneumonia, death due to pneumonia, or primary-care consultation for lower respiratory tract infection requiring antibiotics. We defined hospital admission for pneumonia using hospital discharge diagnoses, death due to pneumonia using death certification data, and lower respiratory tract infection as present when primary-care consultation and antibiotic prescription occurred on the same date. We used multivariable, unconditional, logistical regression and constructed three models to examine the association between pneumococcal vaccination as an exposure and each of the three outcomes.

Findings The first nested case–control analysis included 12 360 patients (7326 [59·3%] women and 5034 [40·7%] men): 1884 (15·2%) who were hospitalised due to pneumonia and 10 476 (84·8%) who were not admitted to hospital due to pneumonia. The second analysis included 5321 patients (3112 [58·5%] women and 2209 [41·5%] men): 781 (14·7%) who died due to pneumonia and 4540 (85·3%) who were alive on the index date. The third analysis included 54 530 patients (33 605 [61·6%] women and 20 925 [38·4%] men): 10 549 (19·3%) with lower respiratory tract infection treated with antibiotics and 43 981 (80·7%) without infection. In the multivariable analysis, pneumococcal vaccination was negatively associated with hospitalisation due to pneumonia (adjusted odds ratio 0·70 [95% CI 0·60–0·81]), death due to pneumonia (0·60 [0·48–0·76]), and lower respiratory tract infection treated with antibiotics (0·76 [0·72–0·80]).

Interpretation Pneumococcal vaccination is associated with protection against hospitalisation and death due to pneumonia in patients with immune-mediated inflammatory diseases, without apparent residual confounding. However, residual unmeasured confounding cannot be fully excluded in observational research, which includes nested case–control studies. These findings should also be corroborated with data from other countries, given that this study used UK-based data.

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Introduction

Common immune-mediated inflammatory diseases, such as rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory bowel disease, and systemic lupus erythematosus (SLE), affect one in every 30 adults in the UK and are treated with glucocorticoid-sparing immunosuppressive drugs.[1–3] These conditions are associated with an increased risk of infection with *Streptococcus pneumoniae*, the most common cause of community-acquired pneumonia, with rate ratios ranging from 4·0 to 4·4 for pneumococcal pneumonia and from 2·2 to 6·5 for invasive pneumococcal disease.[4–6] Consequently, pneumococcal vaccination is recommended for adults with immune-mediated inflammatory diseases, and the 23-valent pneumococcal polysaccharide vaccine (PPV23) is the main vaccine used globally.[7–9]

The effectiveness of pneumococcal vaccines for clinically relevant outcomes, such as incidence of pneumococcal pneumonia and its complications (eg, death), is not well understood in individuals with immune-mediated inflammatory diseases. To our

Research in context

Evidence before this study

Patients with immune-mediated inflammatory diseases are at an increased risk of pneumococcal pneumonia. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is the most widely used vaccine against pneumococcus globally and is recommended for use in adults in the UK, including this patient group; however, vaccine uptake remains low in patients with immune-mediated inflammatory diseases. Immunosuppression reduces vaccine-induced immunity, including that elicited by PPV23. Whether vaccination against pneumococcus with PPV23 prevents pneumonia and its complications in this patient population is not well understood. This scarcity of evidence is a major barrier to vaccination in people with immune-mediated inflammatory diseases. To identify pre-existing evidence, we searched PubMed, with no language restrictions, for randomised controlled trials and observational studies published between database inception and Dec 21, 2023, using the following terms: (pneumoco* AND vaccin*) AND (effica* OR effective*) AND (trial OR cohort OR case-control) AND (rheumat* OR psoria* OR lupus OR colitis OR Crohn*). We identified one underpowered clinical trial done in Japan in people with rheumatoid arthritis that did not find pneumococcal vaccination to be efficacious in reducing all-cause pneumonia and pneumococcal pneumonia.

Added value of this study

Using a UK-wide cohort of patients with rheumatoid arthritis, spondyloarthritis, inflammatory bowel disease, and systemic lupus erythematosus, we conducted three separate nested case–control studies. The first study included 1884 patients who were hospitalised due to pneumonia and 10 476 patients who were not admitted to hospital with pneumonia; the second included 781 patients who died due to pneumonia and 4540 patients who were alive on the index date; and the third included 10 549 patients who received primary-care consultation for lower respiratory tract infection requiring antibiotics and 43 981 patients without infection. In the multivariable analysis, pneumococcal vaccination was negatively associated with hospitalisation due to pneumonia, death due to pneumonia, and lower respiratory tract infection requiring antibiotics. There was no evidence for waning immunity over time. There was no association between attending a routine wellness check (negative control exposure) and either hospitalisation or death due to pneumonia. Attending a routine wellness check was positively associated with lower respiratory tract infection, suggesting residual confounding.

Implications of all the available evidence

This study found that pneumococcal vaccination prevented hospitalisation and death due to pneumonia in people with common immune-mediated inflammatory diseases, with a protective effect present across various prognostic factors. The extent of protection was similar to that reported in other at-risk populations, such as those in older age. This evidence should be used to promote vaccination in patients with immune-mediated inflammatory diseases. Our findings should be corroborated with data from other countries, given that this study used data from the UK only. Due to a scarcity of evidence on the specific microbial causes of pneumonia, we were unable to ascertain vaccine efficacy on pneumococcal pneumonia.

knowledge, only one randomised placebo-controlled trial has evaluated the efficacy of PPV23 in preventing pneumonia in people with rheumatoid arthritis and it did not show vaccine efficacy, potentially due to low statistical power.[10] However, a retrospective study on the clinical effectiveness of PPV23 in people with rheumatoid arthritis reported a relative risk of 9·7 (95% CI 3·1–38·7) for pneumonia in individuals who were not vaccinated.[11] To date, trials of vaccines in individuals who are immunosuppressed have been short-term, typically reported on serological outcomes only, and showed that the pneumococcal vaccine is immunogenic in people with immune-mediated inflammatory diseases, albeit serological responses in this patient group might be lower than in the general population.[12–14]

A shortage of knowledge about vaccine efficacy and concerns about disease flare underlie vaccine hesitancy in individuals with immune-mediated inflammatory diseases.[15–17] According to the patient and public engagement activity that we conducted to inform the need for this study, it is imperative to provide evidence on the benefits of pneumococcal vaccination in people with immune-mediated inflammatory diseases to improve vaccine uptake. Thus, we aimed to investigate the effectiveness of pneumococcal vaccination in preventing morbidity and mortality associated with respiratory issues in patients with immune-mediated inflammatory diseases. Specifically, we aimed to explore the association between pneumococcal vaccination and hospitalisation due to pneumonia, death due to pneumonia, and primary-care consultation for lower respiratory tract infection requiring antibiotics among individuals with common immune-mediated inflammatory diseases.

Methods

Study design

In this nested case–control study, we used data from the Clinical Practice Research Datalink (CPRD) Gold. The CPRD Gold is an anonymised, longitudinal database of electronic health records for more than 14 million people in the UK. Individuals in this database are representative of the UK population in terms of age, sex, and ethnicity.[18] The CPRD includes information on demographics, lifestyle factors, and diagnoses. Information on diagnoses

are stored as Read codes—a hierarchical, coded thesaurus of clinical terms. Information on primary-care prescriptions and immunisations, including dates of vaccination, is also recorded. The data are enhanced by linkage with records on hospitalisation (Hospital Episode Statistics) and mortality (Office of National Statistics).

Approval for the study was obtained from CPRD Research Data Governance (reference 21_000614). The CPRD has research ethics committee approval for studies that use anonymous data (reference 05/MRE04/87). Practices that contributed data to the CPRD consented to the use of anonymised data for approved research projects and additional consent was not required for each study. The study protocol is available from www.cprd.com (reference 21_000614).

Participants

Adults (aged ≥18 years) who had been diagnosed between April 1, 1997, and Dec 31, 2019, with either rheumatoid arthritis, inflammatory bowel disease, spondyloarthritis (ie, psoriatic arthritis, reactive arthritis, or ankylosing spondylitis), or SLE; who were receiving at least one prescription of either methotrexate, azathioprine, 5-mercaptopurine, sulfasalazine, 5-aminosalicylate, mycophenolate, leflunomide, ciclosporin, tacrolimus, or sirolimus; and who were alive and contributing data to the CPRD during the study period were eligible for inclusion. Patients were required to have a disease-free registration period of at least 1 year in their current general practice surgery before the first date of the diagnosis recorded in the CPRD.

April 1, 1997, was selected as the start date of the study period to coincide with the time that the CPRD commenced this linkage to hospitalisation and mortality data.

Procedures

Pneumococcal vaccination was the exposure of interest. Vaccination was defined with product and Read codes (appendix pp 3–4). In patients who had received at least two vaccinations, the latest record of vaccination before the index date was used to define the vaccination date.[9]

Separate nested case–control studies were conducted for the three outcomes. Patients with incident immune-mediated inflammatory diseases diagnosed at and after age 18 years were followed up from the date of immune-mediated inflammatory diseases diagnosis to the earliest date of outcome, transfer out of the general practice, last data collection from the practice, death, or study end, whichever came first.

Controls were individuals without the outcome of interest during the follow-up period, who were alive and contributing data to the CPRD on the date on which their matched case had an outcome of interest. As many as ten controls were matched to each case for age (±5 years at the index date) and sex by use of incidence density sampling without replacement, whereby the index case was matched to controls drawn from the full-risk set.[19] Controls were allocated an index date corresponding to the outcome date of their matched case. Receipt of pneumococcal vaccination and covariates were ascertained with data before the index date.

We selected the following covariates to minimise confounding: age; sex; practice level Index of Multiple Deprivation (quintiles); BMI (kg/m²); alcohol consumption (none, low, moderate, hazardous, former); smoking status (current, former, or never); Charlson's Comorbidity Index (CCI); immunosuppression (ie, immune-suppressing drugs or glucocorticoid prescription, or both, within 30 days before index date); immune-mediated inflammatory disease type; factors that reflect health-seeking behaviour (ie, influenza vaccination, shingles vaccination, number of primary-care consultations, number of hospital admissions, and number of prescriptions in the 12 months before the index date); and additional risk factors indicating pneumococcal vaccination.[9]

Outcomes

The outcomes were hospitalisation due to pneumonia; death due to pneumonia, recorded as either a primary or contributing cause of death; and primary-care consultation for lower respiratory tract infection requiring antibiotics. The sensitivity analysis considered death due to pneumonia in cases where this was the primary cause of death. Hospitalisation due to pneumonia was defined with ICD codes in the linked Hospital Episode Statistics dataset, and death due to pneumonia was defined with ICD codes in the linked Office of National Statistics dataset (appendix pp 4–5). ICD codes for hospital-acquired pneumonia were not considered to define case status. Lower respiratory tract infection managed in primary care was defined as primary-care consultation for lower respiratory tract infection and antibiotic prescription on the same date.

Statistical analysis

See Online for appendix

We used multivariable, unconditional, logistical regression to assess the association between pneumococcal vaccination as an exposure and each of the three outcomes. Multiple imputation with chained equations was used to impute missing data for smoking status, alcohol consumption, and BMI using the Stata command, *mi impute*. The imputation model included all listed confounders, the exposure, and the case–control indicator.[20] Ten imputations were done because the extent of missing data was modest.

We calculated and combined adjusted odds ratios (ORs) and 95% CIs using Rubin's rule across the imputed datasets, with vaccination as the exposure of interest. Three models were constructed. Model 1 included age and sex; model 2 included age, sex, BMI, alcohol consumption, smoking status, Index of Multiple Deprivation, number of primary-care consultations in

the 12 months before the index date, number of hospital admissions in the 12 months before the index date, influenza vaccination in the 12 months before the index date, shingles vaccination in the 12 months before the index date, immune-mediated inflammatory disease type, immunosuppressive drugs, and CCI; and model 3 included all variables in model 2, alongside at-risk conditions (ie, chronic heart disease, diabetes, immunosuppression, chronic liver disease, chronic kidney disease, chronic respiratory disease, and

	Primary-care consultation for lower respiratory tract infection requiring antibiotics		Hospitalisation due to pneumonia		Death due to pneumonia	
	Cases (n=10 549)	Controls (n=43 981)	Cases (n=1884)	Controls (n=10 476)	Cases (n=781)	Controls (n=4540)
Sex						
Male	3952 (37·5%)	16 973 (38·6%)	788 (41·8%)	4246 (40·5%)	338 (43·3%)	1871 (41·2%)
Female	6597 (62·5%)	27 008 (61·4%)	1096 (58·2%)	6230 (59·5%)	443 (56·7%)	2669 (58·8%)
Age, years	55 (16)	54 (16)	63 (15)	60 (15)	71 (11)	69 (11)
BMI, kg/m²	27 (23·6–31·4)	26·3 (23·2–30·1)	26·0 (22·7–30·1)	26·2 (23·2–29·8)	24·4 (21·1–28·2)	26·0 (23·1–29·4)
Data missing	697 (6·6%)	3130 (7·1%)	147 (7·8%)	746 (7·1%)	79 (10·1%)	305 (6·7%)
Charlson Comorbidity Index	1 (0–2)	1 (0–2)	2 (0–3)	1 (0–2)	2 (1–4)	1 (0–3)
Index of Multiple Deprivation	3 (2–5)	3 (2–4)	3 (2–5)	3 (2–4)	3 (2–5)	3 (2–4)
Number of prescriptions*	45 (20–84)	22 (1–57)	66 (32–116)	23 (0–61)	93 (57–153)	39 (1–78)
Number of primary-care consultations*	43 (27–61)	27 (3–48)	54 (35–74)	27 (1–47)	64 (45–86)	33 (9–53)
Number of hospitalisations*	0 (0–0)	0 (0–0)	2 (1–3)	0 (0–1)	2 (1–4)	0 (0–1)
Previous influenza vaccination*	5714 (54·2%)	17 108 (38·9%)	1174 (62·3%)	4484 (42·8%)	508 (65·0%)	2463 (54·3%)
Previous shingles vaccination	101 (1·0%)	490 (1·1%)	28 (1·5%)	137 (1·3%)	8 (1·0%)	46 (1·0%)
Smoking status						
Non-smoker	4490 (42·6%)	21 253 (48·3%)	692 (36·7%)	5073 (48·4%)	306 (39·2%)	2153 (47·4%)
Current smoker	2425 (23·0%)	8574 (19·5%)	380 (20·2%)	1560 (14·9%)	122 (15·6%)	499 (11·0%)
Former smoker	3499 (33·2%)	13 730 (31·2%)	779 (41·3%)	3690 (35·2%)	333 (42·6%)	1833 (40·4%)
Data missing	135 (1·3%)	424 (1·0%)	33 (1·8%)	153 (1·5%)	20 (2·6%)	55 (1·2%)
Alcohol consumption (units per week)						
None	2293 (21·7%)	9427 (21·4%)	495 (26·3%)	2274 (21·7%)	220 (28·2%)	1004 (22·1%)
Low (1–14)	5639 (53·5%)	24 036 (54·6%)	879 (46·7%)	5627 (53·7%)	338 (43·3%)	2466 (54·3%)
Moderate (15–21)	410 (3·9%)	1866 (4·2%)	68 (3·6%)	430 (4·1%)	17 (2·2%)	178 (3·9%)
Hazardous (>21)	600 (5·7%)	2480 (5·6%)	111 (5·9%)	610 (5·8%)	40 (5·1%)	229 (5·0%)
Former	392 (3·7%)	1275 (2·9%)	73 (3·9%)	355 (3·4%)	46 (5·9%)	171 (3·8%)
Data missing	1215 (11·5%)	4897 (11·1%)	258 (13·7%)	1180 (11·3%)	120 (15·4%)	492 (10·8%)
At-risk conditions						
Diabetes	1266 (12·0%)	5084 (11·6%)	321 (17·0%)	1409 (13·4%)	153 (19·6%)	655 (14·4%)
Chronic kidney disease	1129 (10·7%)	6029 (13·7%)	421 (22·3%)	1935 (18·5%)	226 (28·9%)	1105 (24·3%)
Chronic liver disease	63 (0·6%)	337 (0·8%)	23 (1·2%)	80 (0·8%)	12 (1·5%)	30 (0·7%)
Chronic respiratory disease	1282 (12·2%)	3956 (9·0%)	415 (22·0%)	1034 (9·9%)	230 (29·4%)	587 (12·9%)
Chronic heart disease	983 (9·3%)	4135 (9·4%)	373 (19·8%)	1316 (12·6%)	230 (29·4%)	798 (17·6%)
Asplenia	6 (<0·1%)	18 (<0·1%)	<5†	<5†	0	0
Immunosuppression	176 (1·7%)	849 (1·9%)	68 (3·6%)	199 (1·9%)	24 (3·1%)	87 (1·9%)
Glucocorticoid prescription‡	1939 (18·4%)	3135 (7·1%)	339 (18·0%)	699 (6·7%)	177 (22·7%)	415 (9·1%)
Immune-mediated inflammatory disease						
Rheumatoid arthritis	5053 (47·9%)	19 862 (45·2%)	1066 (56·6%)	5174 (49·4%)	504 (64·5%)	2497 (55·0%)
Inflammatory bowel disease	3692 (35·0%)	17 443 (39·7%)	635 (33·7%)	4013 (38·3%)	226 (28·9%)	1619 (35·7%)
Systemic lupus erythematosus	370 (3·5%)	1069 (2·4%)	63 (3·3%)	197 (1·9%)	17 (2·2%)	76 (1·7%)
Spondyloarthritis§	1434 (13·6%)	5607 (12·7%)	120 (6·4%)	1092 (10·4%)	34 (4·4%)	348 (7·7%)
Glucocorticoid-sparing drugs‡						
5-aminosalicylic acid or sulfasalazine	5260 (49·9%)	23 299 (52·9%)	946 (50·2%)	5588 (53·3%)	377 (48·3%)	2402 (52·9%)
Immunosuppressive drugs¶	5289 (50·1%)	20 682 (47·0%)	938 (49·8%)	4888 (46·7%)	404 (51·7%)	2138 (47·1%)

Data are mean (SD), median (IQR), or n (%). *12 months before index date. †Number of participants are suppressed to less than five to comply with the CPRD guidelines. ‡Prescription within 30 days before the index date. §Psoriatic arthritis, ankylosing spondyloarthritis, or reactive arthritis. ¶Methotrexate, leflunomide, azathioprine, ciclosporin, mycophenolate, mercaptopurine, tacrolimus, or sirolimus.

Table: **Demographic and clinical characteristics of patients included in the nested case–control studies**

asplenia [except for the death due to pneumonia outcome]) and treatment (glucocorticoid prescription within 30 days of the index date) that might indicate the need for pneumococcal vaccination. The number of vaccinations received was not included in the model because, in the UK, booster pneumococcal vaccinations are only indicated in people at risk of a rapid reduction in antibody concentration (ie, individuals with splenic dysfunction, asplenia, or chronic kidney disease) and, consequently, those receiving multiple doses might not be more protected against pneumococcal disease.

Exploratory subgroup analyses were conducted according to type of immune-mediated inflammatory disease, age (<65 years *vs* ≥65 years), CCI (below the median *vs* the median or above), and additional indications for pneumococcal vaccination (present *vs* absent). A post-hoc subgroup analysis was done for sex and index year (2011 and before *vs* 2012 and later). A sensitivity analysis was conducted in patients in whom pneumonia was the primary cause of death. A post-hoc sensitivity analysis was conducted for patients treated with any glucocorticoid-sparing immunosuppressive drugs and any methotrexate within 30 days before the index date.

We assessed the extent of unmeasured confounding using E-values, defined as the minimum strength of association that an unmeasured confounder would need to have with both vaccination status and the outcome, conditional on the measured covariates, to cancel the observed association between vaccination status and the outcome of interest. The higher the E-value, the less likely it was that unmeasured confounding could explain the observed exposure–outcome association.[21] Additionally, we used the National Health Service (NHS) wellness check (appendix p 37) as a negative exposure variable to explore the role of unmeasured confounding in the analyses.[22] Data management and analyses were performed in Stata (version 17).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

12 360 patients (7326 [59·3%] women and 5034 [40·7%] men) were included in the analysis that evaluated the association between vaccination and hospitalisation due to pneumonia, of whom 1884 (15·2%) were hospitalised due to pneumonia and 10 476 (84·8%) were not admitted to hospital due to pneumonia (appendix p 2). Compared with controls, patients hospitalised with pneumonia were more likely to be current or former smokers; have been prescribed glucocorticoids; have diabetes, chronic respiratory disease, or chronic heart disease; and have had an influenza vaccination in the previous 12 months (table). Additionally, individuals who had been admitted to hospital due to pneumonia had received more prescriptions and primary-care consultations in the previous 12 months than had controls (table).

5321 patients (3112 [58·5%] women and 2209 [41·5%] men), of whom 781 (14·7%) died due to pneumonia and 4540 (85·3%) were alive on the index date, were included in the analysis that evaluated the association between vaccination and death due to pneumonia (appendix p 2). Among these patients who

	Cases (n [%])	Controls (n [%])	Model 1 (OR [95% CI])	Model 2 (OR [95% CI])	Model 3 (OR [95% CI])
Primary-care consultation for lower respiratory tract infection requiring antibiotics					
Unvaccinated	5299 (50·2)	22 035 (50·1)	1 (ref)	1 (ref)	1 (ref)
Vaccinated	5250 (49·8)	21 946 (49·9)	0·94 (0·90–0·99)	0·73 (0·70–0·77)	0·76 (0·72–0·80)
Hospitalisation due to pneumonia					
Unvaccinated	639 (33·9)	4182 (39·9)	1 (ref)	1 (ref)	1 (ref)
Vaccinated	1245 (66·1)	6294 (60·1)	1·09 (0·98–1·23)	0·71 (0·62–0·82)	0·70 (0·60–0·81)
Death due to pneumonia					
Unvaccinated	200 (25·6)	1168 (25·7)	1 (ref)	1 (ref)	1 (ref)
Vaccinated	581 (74·4)	3372 (74·3)	0·86 (0·72–1·03)	0·64 (0·51–0·81)	0·60 (0·48–0·76)

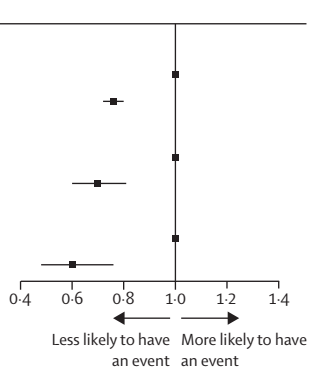

Figure 1: **Effectiveness of pneumococcal vaccination in patients with immune-mediated inflammatory diseases**
Model 1 adjusted for matching variables (age and sex). Model 2 adjusted for age, sex, BMI, alcohol consumption, smoking status, Charlson's Comorbidity Index, number of primary-care consultations and hospital admissions in the 12 months before the index date, influenza vaccination and shingles vaccination in the 12 months before the index date, deprivation score, immune-mediated inflammatory disease type, and corticosteroid-sparing drug prescription within 30 days (immunosuppressive drug *vs* immunomodulatory drug). Model 3 (fully adjusted model) combined model 2 covariates plus at-risk conditions for pneumococcal vaccination (chronic heart disease, diabetes immunosuppression, chronic liver disease, chronic kidney disease, chronic respiratory disease, and asplenia [except for death due to pneumonia]), and treatment (corticosteroid prescription within 30 days of the index date) that might indicate the need for pneumococcal vaccination. OR=odds ratio.

died, pneumonia was reported as the primary cause of death in 649 (83·1%) cases. Compared with controls, patients who died of pneumonia were more likely to be current smokers; have had an influenza vaccination in the previous 12 months; have rheumatoid arthritis, chronic heart disease, chronic respiratory disease, chronic kidney disease, or diabetes; have been prescribed glucocorticoids in the preceding 30 days; and have received more prescriptions and primary-care consultations in the previous 12 months (table).

54 530 patients (33 605 [61·6%] women and 20 925 [38·4%] men) were included in the analysis that evaluated the association between vaccination and primary-care consultation for lower respiratory tract infection requiring antibiotics, of whom 10 549 (19·3%) were diagnosed with a lower respiratory tract infection and 43 981 (80·7%) had no infection (appendix p 2).

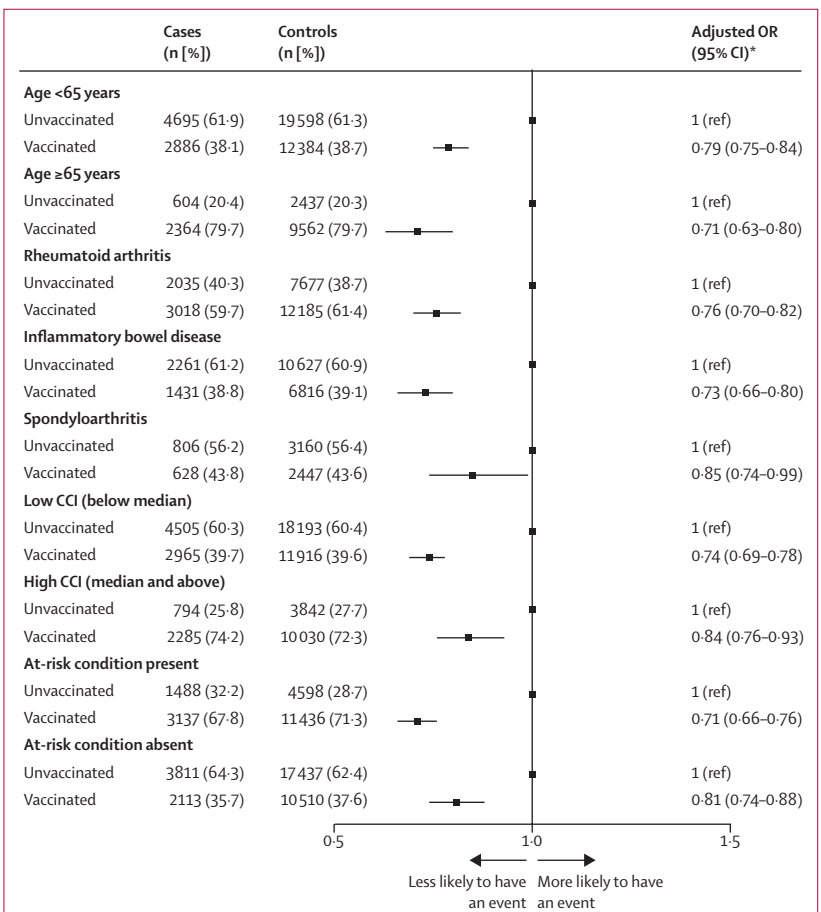

Figure 2: **Subgroup analysis of the association between pneumococcal vaccine and primary-care consultation for lower respiratory tract infection requiring antibiotics**

CCI=Charlson's Comorbidity Index. OR=odds ratio. *Adjusted for age, sex, BMI, alcohol consumption, smoking status, CCI, number of primary-care consultations and hospital admissions in the 12 months before the index date, influenza vaccination and shingles vaccination in the 12 months before the index date, deprivation score, immune-mediated inflammatory disease type, glucocorticoid-sparing drug prescription within 30 days (immunosuppressive drug *vs* immunomodulatory drug), chronic heart disease, diabetes, immunosuppression, chronic liver disease, chronic kidney disease, chronic respiratory disease, asplenia (except for death due to pneumonia), and glucocorticoid prescription within 30 days of the index date.

Compared with controls without lower respiratory tract infection, the proportion of individuals with a diagnosis of chronic respiratory disease, glucocorticoid prescription within the previous 30 days, and vaccination against influenza was higher among patients with a lower respiratory tract infection (table). Additionally, patients with a lower respiratory tract infection had received more prescriptions and primary-care consultations in the previous 12 months than had controls (table). In all three nested case–control studies, there was no appreciable difference in either moderate or heavy alcohol consumption between cases and controls.

Pneumococcal vaccinations occurred both before and after the diagnosis of an immune-mediated inflammatory disease was recorded in the CPRD (appendix p 38). In the multivariate analysis, pneumococcal vaccination was associated with significantly lower odds of hospitalisation due to pneumonia (adjusted OR 0·70 [95% CI 0·60–0·81]), death due to pneumonia (0·60 [0·48–0·76]), and primary-care consultation for lower respiratory tract infection requiring antibiotics (0·76 [0·72–0·80]; figure 1). In the sensitivity analysis, pneumococcal vaccination was associated with significantly lower odds of death due to pneumonia in cases where pneumonia was recorded as the primary cause of death (adjusted OR 0·65 [95% CI 0·51–0·83]). Among people whose data were included in the nested case–control studies, 567 (4·6%) of 12 360 patients who were included in the analysis of the association between pneumococcal vaccination and hospitalisation due to pneumonia, 52 (1·0%) of 5321 patients who were included in the analysis of the association between pneumococcal vaccination and death due to pneumonia, and 2099 (3·9%) of 54 530 patients who were included in the analysis of the association between pneumococcal vaccination lower respiratory tract infection had received more than one pneumococcal vaccination. The results were unchanged after excluding the data from these individuals (appendix p 39). There were only 97 hospitalisations with details of the causative organism recorded in the Hospital Episode Statistics dataset; therefore, pneumococcal pneumonia could not be analysed separately as an outcome.

In the subgroup analyses, pneumococcal vaccination was associated with reduced risk of primary-care consultation for lower respiratory tract infection requiring antibiotics, regardless of age, type of immune-mediated inflammatory disease, CCI, and additional indications for vaccination (figure 2). Similarly, vaccination was associated with reduced risk of hospitalisation and death due to pneumonia across age, comorbidity, and immune-mediated inflammatory disease type, except for people with spondyloarthritis, inflammatory bowel disease, or a high CCI, in whom the effect was not significant (figures 3, 4). Compared with being unvaccinated, hospitalisation due pneumonia was negatively associated with vaccination within 5 years of

the index date (adjusted OR 0·82 [95% CI 0·69–0·97]) and 5 years before this date (0·62 [0·53–0·73]). Similarly, death due to pneumonia was negatively associated with vaccination within 5 years of the index date (0·70 [0·53–0·92]) and 5 years before this date (0·55 [0·43–0·71]). However, evidence for an association between lower respiratory tract infection and vaccination within 5 years of or at least 5 years before the index date was inconsistent (0·96 [0·90–1·02] and 0·61 [0·57–0·65]). Similar vaccine effectiveness was observed when the data analysed were restricted to individuals prescribed any glucocorticoid-sparing immunosuppressive drug and those prescribed methotrexate within the 30 days preceding the index date (appendix p 40). Vaccine effectiveness was similar when the analyses were stratified by sex and the calendar year in which an outcome was reported (appendix p 40).

No patient was vaccinated on the index date. Ten (0·1%) of 12 360 patients who were included in the analysis of the association between pneumococcal vaccination and hospitalisation due to pneumonia, 11 (0·2%) of 5321 patients who were included in the analysis of the association between pneumococcal vaccination and death due to pneumonia, and 50 (0·1%) of 54 530 patients who were included in the analysis of the association between pneumococcal vaccination and lower respiratory tract infection were vaccinated within 14 days of the index date. The results did not change when data were analysed excluding the data from these individuals (data not shown). Similarly, the results were unchanged in the complete-case analysis (appendix p 41).

The E-value for the association between pneumococcal vaccination and hospitalisation for pneumonia was 2·21, death due to pneumonia was 1·96, and primary-care consultation for lower respiratory tract infection requiring antibiotics was 1·81. There was no association between the NHS wellness check (negative exposure) and hospitalisation for pneumonia (adjusted OR 0·92 [95% CI 0·74–1·15]) or death due to pneumonia (0·90 [0·63–1·29]). A positive association was observed between the NHS wellness check and lower respiratory tract infection (1·13 [1·03–1·23]).

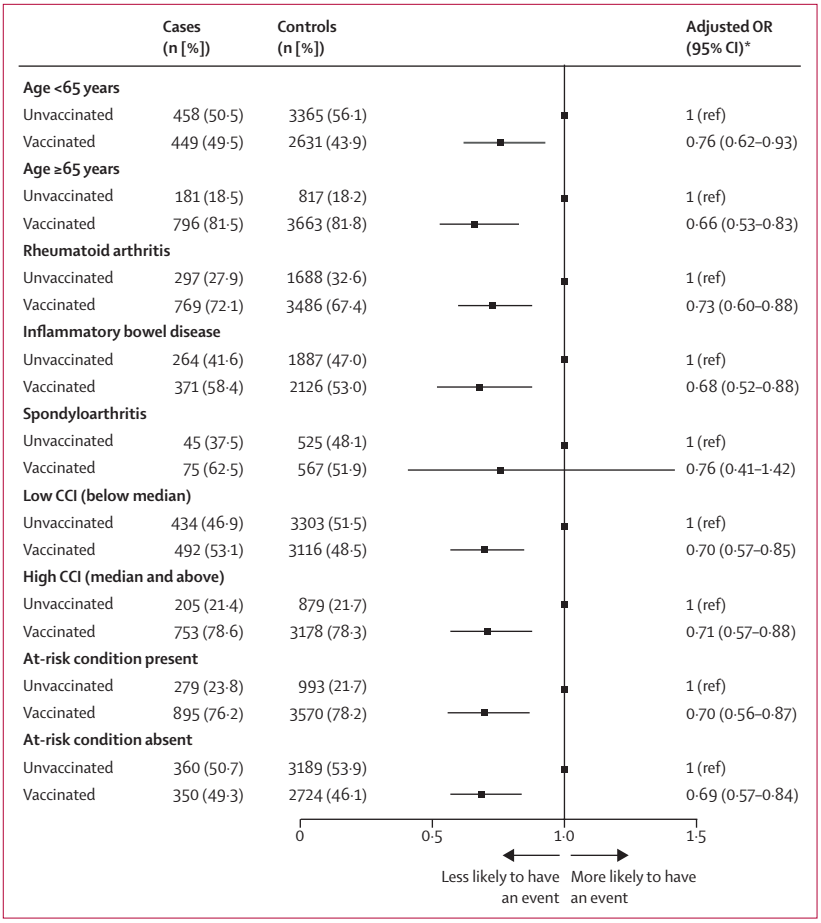

Figure 3: **Subgroup analysis of the association between pneumococcal vaccine and hospitalisation due to pneumonia**

CCI=Charlson's Comorbidity Index. OR=odds ratio. *Adjusted for age, sex, BMI, alcohol consumption, smoking status, CCI, number of primary-care consultations and hospital admissions in the 12 months before the index date, influenza vaccination and shingles vaccination in the 12 months before the index date, deprivation score, immune-mediated inflammatory disease type, glucocorticoid-sparing drug prescription within 30 days (immunosuppressive drug *vs* immunomodulatory drug), chronic heart disease, diabetes, immunosuppression, chronic liver disease, chronic kidney disease, chronic respiratory disease, asplenia (except for death due to pneumonia), and glucocorticoid prescription within 30 days of the index date.

Discussion

This large, nested case–control study found that pneumococcal vaccine was associated with reduced risk of hospitalisation due to pneumonia, death due to pneumonia, and primary-care consultation for lower respiratory tract infection requiring antibiotics in people with common immune-mediated inflammatory diseases in the UK. This effect was observed in individuals who had been prescribed glucocorticoid-sparing immunosuppressive drugs, methotrexate, or glucocorticoids, and was present regardless of comorbidity burden, age, sex, and type of immune-mediated inflammatory disease; however, it was weaker in people with inflammatory bowel disease or spondyloarthritis, or both. There was no evidence of waning of immunity over time. These findings are supported by immunogenicity studies, which have shown that the humoral response to PPV23 was present in people with inflammatory conditions treated with immunosuppressive drugs; however, serological titres were lower for strains such as the 6B and 23F serotypes, and in the context of B-cell-depleting therapy.[12,13]

To our knowledge, this is the first study to show the clinical effectiveness of PPV23 in patients with various common immune-mediated inflammatory diseases. Few studies have considered vaccine effectiveness in patients with either individual immune-mediated inflammatory diseases or groups of similar immune-mediated inflammatory diseases, and have reported variable magnitudes of protection.[11,23,24] These studies

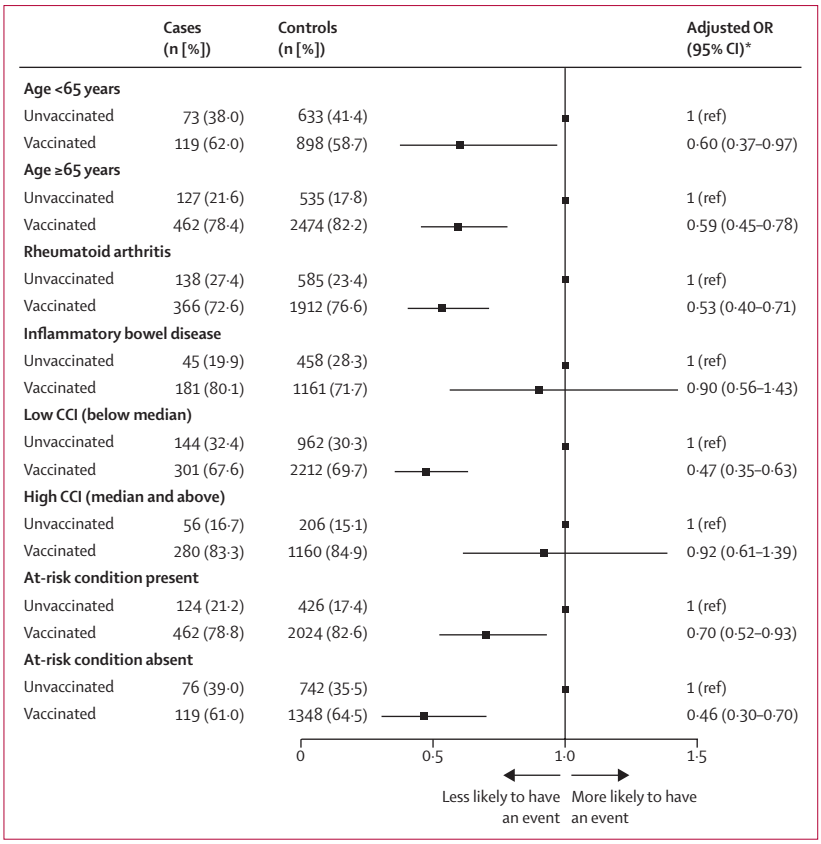

Figure 4: **Subgroup analysis of the association between pneumococcal vaccine and death due to pneumonia**
CCI=Charlson's Comorbidity Index. OR=odds ratio. *Adjusted for age, sex, BMI, alcohol consumption, smoking status, CCI, number of primary-care consultations and hospital admissions in the 12 months before the index date, influenza vaccination and shingles vaccination in the 12 months before the index date, deprivation score, immune-mediated inflammatory disease type, glucocorticoid-sparing drug prescription within 30 days (immunosuppressive drug *vs* immunomodulatory drug), chronic heart disease, diabetes, immunosuppression, chronic liver disease, chronic kidney disease, chronic respiratory disease, asplenia (except for death due to pneumonia), and glucocorticoid prescription within 30 days of the index date.

mainly assessed the effectiveness of pneumococcal conjugated vaccines (PCVs) and not that of a single-dose PPV23 vaccine, which is commonly used in routine vaccinations among adults in the UK and across many countries globally.[9] In a 2023 study from Sweden, PCV7 reduced the risk of pneumonia and serious infections in people with inflammatory arthritis by 53%.[24] Among US veterans with inflammatory bowel disease, vaccination with PPV23 in combination with PCV13 was found to reduce the risk of severe pneumococcal disease (HR 0·17 [95% CI 0·14–0·22]); however, this effect was not observed with PPV23 alone (1·10 [0·99–0·21]).[23] Similarly, receipt of an additional dose of PPV23 reduced the risk of severe pneumococcal disease in individuals with inflammatory bowel disease (0·80 [0·67–0·95]).[23] Among patients with rheumatoid arthritis treated with methotrexate, patients vaccinated with PPV23 were found to have median antibody concentrations that were 1·9 times as high as those in unvaccinated patients.[11] Additionally, unvaccinated individuals were 9·7 times (95% CI 3·1–38·7) more likely to develop pneumonia over a 10-year period than were vaccinated patients.[11] However, a double-blind randomised trial on the clinical efficacy of PPV23 in preventing pneumonia in patients with rheumatoid arthritis did not show vaccine efficacy, potentially due to low statistical power.[25]

Our estimates of vaccine effectiveness against pneumonia are similar to findings from general population studies.[26,27] In a Cochrane meta-analysis, PPV23 protected against all-cause pneumonia in the general population by 29% (95% CI 3–48).[26] Similarly, in observational studies, pneumococcal vaccination was associated with a reduced risk of pneumococcal community-acquired pneumonia (HR 0·49 [95% CI 0·29–0·84]),[27] all-cause community-acquired pneumonia (0·75 [0·58–0·98]) in individuals aged 60 years or older,[27] and hospitalisation due to pneumonia (0·74 [0·59–0·92]) in individuals aged 65 years or older.[28]

Our study found that pneumococcal vaccination was protective against morbidity and mortality due to pneumonia among patients with common immune-mediated inflammatory diseases, irrespective of age and comorbidity burden. Previous studies in people aged 65 years and older reported similar findings of protection against invasive pneumococcal disease, ranging from 23% to 56%.[29–31] However, in patients with some conditions, such as diabetes and HIV, PPV23 has been shown to have reduced effectiveness.[32,33] In our study, protection against death due to pneumonia conferred by vaccination in patients with a high comorbidity burden was not significant, although this finding could be due to the occurrence of few events. The protective effect against hospitalisation due to pneumonia in people with a high comorbidity burden with high event numbers was significant.

Although not evaluated in the multivariate analysis in our study, glucocorticoid prescription within the previous 30 days was two to three times more common in patients diagnosed with lower respiratory tract infection, hospitalised due to pneumonia, or who died due to pneumonia than in age-matched and sex-matched controls. This finding is consistent with previous reports of an association between glucocorticoid prescription and hospitalisation due to pneumonia,[34] suggesting that these patients should be prioritised in primary care to receive pneumococcal vaccination.

The main strength of our study is the use of data from a nationally representative dataset that originated during routine care of patients in the NHS. Health care in the NHS is free at the point of delivery for all UK residents. We included patients with various common immune-mediated inflammatory diseases that were treated with glucocorticoid-sparing immunosuppressive drugs, thereby indicating pneumococcal vaccination in the UK. The abovementioned factors increase the generalisability of our findings. We used primary-care records of both immune-mediated inflammatory disease diagnoses and

prescriptions of immunosuppressive drugs to define our population, hence improving the internal validity of our findings. We also assessed outcomes of clinical importance—namely, hospitalisation due to pneumonia, death due to pneumonia, and primary-care consultation for lower respiratory tract infection requiring treatment with antibiotics. In the UK, hospital discharge summaries include information on reasons for hospitalisation and are completed by doctors. Similarly, death certification is completed by doctors. Both hospital discharge diagnoses and causes of death are regarded as having high validity. Primary-care consultation for lower respiratory tract infection requiring antibiotics was selected as an outcome because these infections can include community-acquired pneumonia. However, this outcome is non-specific and should be interpreted with caution. It is possible that lower respiratory tract infection was a misdiagnosed viral illness, for which patients were prescribed antibiotics due to risk-averse prescribing for those with immunosuppression. This possibility was reflected in the association between the negative control exposure (ie, the routine NHS wellness check) and lower respiratory tract infection, and the low E-value.

Our study has several limitations. Although the outcomes studied were clinically relevant, they included hospitalisation and death due to all-cause pneumonia. Therefore, these outcomes are not specific to *Streptococcus pneumoniae*, which the pneumococcal vaccine is designed to protect against.[9] Additionally, PPV23 is the only vaccine recommended for use in adults in the UK, making it difficult to assess other vaccine types using this dataset. People vaccinated in settings other than primary care were not included in this study because the actual date of their vaccination could not be established. However, these individuals comprise a small proportion of vaccinated individuals in the UK, given that most vaccinations are administered in primary-care settings where PPV23 is reimbursed by the state. We were unable to assess the effect of biologics on vaccine effectiveness because data on prescriptions of biological agents are not recorded in the CPRD. These missing data are likely to be a particular issue for patients with axial spondyloarthritis, who are often only ever treated with biological monotherapy. Nevertheless, some patients in our study would have been treated with biologics. We could not separately investigate vaccine effectiveness in people with less common immune-mediated inflammatory diseases, such as SLE, because of the small sample size. We did not include patients with vasculitis, polymyalgia rheumatica, or rare connective tissue diseases, such as systemic sclerosis and polymyositis, and our findings should not be extrapolated to these patient groups. Despite controlling for confounding, unmeasured confounding and healthy user bias might have inflated vaccine effectiveness (particularly against lower respiratory tract infection), but it is ethically challenging to support a randomised controlled trial of vaccination in this at-risk patient population. Additionally, we assumed the data to be missing at random and did not conduct any sensitivity analyses to assess the validity of these assumptions. It is possible that variables outside of our imputation model could have explained the patterns of missing data, in which case data would be missing not at random. Our results were similar to those from a complete-case analysis, which provides a degree of reassurance. Furthermore, many patients could not be matched to controls, which might have contributed to the absence of a significant negative association between vaccination and hospitalisation and death due to pneumonia within some subgroups in the stratified analyses.

In conclusion, pneumococcal vaccination prevents morbidity and mortality associated with pneumonia in people with common immune-mediated inflammatory diseases. These findings should be used to promote pneumococcal vaccination in this at-risk patient group. Given that this study used data from the UK only, these findings should be corroborated with data from other countries.

Contributors

AA conceptualised the study. All authors were involved in study methodology. AA and GN were responsible for project administration and resources. AA, GN, and MJG contributed to software. AA, MJG, JSNV-T, TC, and CDM supervised the study. AA validated the study. GN developed the figures. AA and GN wrote the original draft. All authors wrote, reviewed, and edited the manuscript. GN and AA directly accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AA reports personal fees from UpToDate (royalty), Cadilla Pharmaceuticals (lecture fees), and Limbic (consulting), unrelated to this work. CDM is Director of the National Institute for Health and Care Research (NIHR) School for Primary Care Research. Keele University has received research funding for CDM from the NIHR and the Medical Research Council. JSNV-T was seconded to the UK Department of Health and Social Care from October, 2017, to March, 2022. He performed a one-off consultancy for MSD, which manufactures PPV23, in May, 2023. All other authors declare no competing interests. The views expressed in this manuscript are those of its authors and not necessarily those of the NIHR, the Department of Health and Social Care, or any other entity mentioned above.

Data sharing

Data used in the study are from the CPRD (www.cprd.com). Due to CPRD licencing rules, we are unable to share the data used in this study with third parties. The data used in this study may be obtained directly from the CPRD.

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