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Haematological abnormalities in new-onset rheumatoid arthritis and risk of common infections: a population-based study

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Abstract

Objectives. To describe the prevalence of haematological abnormalities in individuals with RA at the point of diagnosis in primary care and the associations between haematological abnormalities, vaccinations and subsequent risk of common infections.

Methods. We studied 6591 individuals with newly diagnosed RA between 2004 and 2016 inclusive using the UK Royal College of General Practitioners Research and Surveillance Centre primary care database. The prevalence of haematological abnormalities at diagnosis (anaemia, neutropenia and lymphopenia) was established. Cox proportional hazards models were used to evaluate the association between each haematological abnormality and time to common infections and the influence of vaccination status (influenza and pneumococcal vaccine) on time to common infections in individuals with RA compared with a matched cohort of individuals without RA.

Results. Anaemia was common at RA diagnosis (16.1% of individuals), with neutropenia (0.6%) and lymphopenia (1.4%) less so. Lymphopenia and anaemia were associated with increased infection risk [hazard ratio (HR) 1.18 (95% CI 1.08, 1.29) and HR 1.37 (95% CI 1.08, 1.73), respectively]. There was no evidence of an association between neutropenia and infection risk [HR 0.94 (95% CI 0.60, 1.47)]. Pneumonia was much more common in individuals with early RA compared with controls. Influenza vaccination was associated with reduced risk of influenza-like illness only for individuals with RA [HR 0.58 (95% CI 0.37, 0.90)].

Conclusion. At diagnosis, anaemia and lymphopenia, but not neutropenia, increase the risk of common infections in individuals with RA. Our data support the effectiveness of the influenza vaccination in individuals with RA.

Key words: anaemia, infection, influenza, influenza vaccine, lymphopenia, neutropenia, pneumococcal vaccine, rheumatoid arthritis

Rheumatology key messages

- Anaemia and lymphopenia are associated with increased infection risk in individuals with early rheumatoid arthritis.
- Pneumonia is more common in patients with rheumatoid arthritis compared with those without rheumatoid arthritis.
- Influenza vaccination is associated with a reduced risk of influenza-like illness in patients with rheumatoid arthritis.

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Introduction

The long-term prognosis of RA has improved with the availability of conventional synthetic and later biologic DMARDs [1, 2], coupled with greater monitoring and treatment adjustment to target disease remission. EULAR recommendations suggest the primary target for treatment of RA should be a state of clinical remission, with low disease activity an acceptable therapeutic goal, particularly in patients with a long duration of disease [1].

Haematological abnormalities (including anaemia, neutropenia, and lymphopenia) in RA are common. More than 50% of patients with RA have anaemia [3] and the relationship between anaemia and disease activity is complex; it is logical to assume that the prevalence of anaemia should decline with improved disease control as the underlying cause is often anaemia of chronic disease [4, 5]. Despite this, iron deficiency anaemia and macrocytic anaemia have also been reported [6–9] and may relate to gastrointestinal blood loss, the presence of other autoimmune diseases and iatrogenic causes. DMARD treatment in RA patients has been observed to influence both lymphocyte and neutrophil counts. Furthermore, studies have suggested an increased risk of serious infections with some RA medications, including with anti-TNF therapies [10–13]. Other studies have suggested little or no detectable increase in infectious morbidity or mortality in RA patients with lymphopenia [14, 15]. The effect of lymphocyte and neutrophil counts in early RA on subsequent infection is not well studied and could influence treatment choices.

Due to the increased risk of infection, EULAR guidelines recommend an annual influenza vaccination and a one-off pneumococcal pneumonia vaccination for individuals with RA being treated with immunosuppressive medication [16]. UK guidelines recommend the same strategy for other immunosuppressed individuals [17, 18]. Despite this, vaccination uptake has been shown to be suboptimal for individuals with RA [19, 20], with up to two-thirds of individuals not receiving the influenza vaccine annually post-diagnosis [19]; uptake is especially low in younger age groups [20]. Real-world evidence on the effectiveness of vaccinations on subsequent infection in individuals with RA is lacking.

We aimed to establish the association between haematological abnormalities at disease onset and the risk of common infections in a contemporary RA population. We also set out to determine associations between vaccinations for influenza and pneumococcal pneumonia and the subsequent incidence of influenza and pneumococcal-like infections, respectively.

Methods

Data sources and cohort

The Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database comprises the pseudonymised primary care records of all individuals registered with a network of general practitioner (GP) practices distributed across England and provides a broadly representative sample of the English primary care population [21]. At the time of data extraction for this study, data were available from 164 GP practices with a total population of 1 475 762 people. The RCGP RSC contains information on clinical diagnoses, anthropometric measurements, laboratory tests and prescriptions coded with the Read clinical coding systems. The RCGP is also the primary infectious disease sentinel network for the UK and has been providing weekly infections data since 1964. GP practices within the network are provided with regular feedback on their coding of infectious diseases and therefore the quality of infection recording within the database is high [21, 22]. Study approval was granted by the Research Committee of the RCGP RSC. The study did not require formal ethics board review at a national level as defined using the National Health Service (NHS) Health Research Authority research decision tool (http://www.hra-decisiontools.org.uk/research/).

Infections

Our inclusion criteria specified individuals $\geqslant$18 years of age with a diagnosis of RA after 1 January 2004 and prior to 1 January 2017. The study start date was the date of first RA diagnostic code. RA cases were defined using established criteria [23]. The follow-up period extended to the study end: either 1 January 2017, the date of patient transfer from an included practice, or death.

Vaccinations

We determined the impact of influenza and pneumococcal vaccinations on, respectively, a recorded diagnosis of an influenza-like illness and pneumonia in individuals with RA. A matched cohort analysis was also performed to compare the relative efficacy of influenza and pneumococcal vaccination in individuals with RA compared with those without. For this analysis we included individuals with RA diagnosed after January 2004 but before 1 January 2012. Cases were age- and sex-matched one to one with controls without RA at a GP practice level using nearest-neighbour matching. For this analysis, the start of follow-up was 1 January 2012. This approach enabled comparisons of individuals with and without RA over the same influenza and pneumonia seasons (5 years total follow-up), reducing bias due to differing strains of infective pathogens and variation in vaccination programmes.

The influenza vaccination is typically repeated annually, whereas the pneumococcal vaccination is given only once. Vaccination status at baseline was therefore defined for influenza vaccination to be the presence of any code or prescription for an influenza vaccination in the year before the start of follow-up (1 January 2012). For pneumococcal vaccination it was defined as any code or prescription for a pneumococcal vaccination at any time prior to 1 January 2012.

Definition of haematological abnormalities at baseline, in the 3 years prior to diagnosis and at 3 years post-diagnosis

Haematological abnormalities and other baseline measures were derived by taking the average of up to three

most recent values in the 12 months prior to diagnosis. We evaluated time trends in the proportion of individuals with haematological abnormalities at 1, 2 and 3 years pre-diagnosis using the same definition. The proportion of individuals with RA with haematological abnormalities 3 years post-diagnosis was evaluated in those with sufficient follow-up.

Code lists used to define haematological abnormalities were developed in accordance with published recommendations [24, 25]. Anaemia was defined as a mean haemoglobin <13.5 g/dl (135 g/L) for men or <11.5 g/dl (115 g/L) for women. Neutropenia was defined as a mean total neutrophil count $<1.6 \times 10^9$/L and lymphopenia was defined as a mean total lymphocyte count $<0.75 \times 10^9$/L. Further subdivision by severity was not possible due to low numbers. Baseline medication use was defined as the issuing of a prescription 3 months before to 30 days after diagnosis. This was to allow a period for the transfer of prescribing from secondary care to primary care; the initial prescription is often issued in secondary care with repeat prescriptions issued from primary care.

Outcomes

The primary outcome was the time to first recorded presentation with a new episode of infection during the study period. The primary outcome comprised an a priori composite of upper respiratory tract infections, bronchitis, influenza-like illness, pneumonia, intestinal infectious diseases, herpes simplex, skin and soft tissue infections, urinary tract infections and genital and perineal infections. The Read codes used to identify infections were taken from the validated indicators used in routine surveillance by the RCGP RSC. The chosen infections were selected principally because they represent the majority of the primary care adult infectious disease burden, include a mixture of viral, bacterial and fungal infections and affect a range of different body systems. They also comprise the key infectious disease monitored as part of the RCGP RSC network and therefore GPs are provided with regular feedback on the coding quality of these conditions. First or new episodes of an infection are coded accordingly in the database, enabling differentiation from chronic infections or follow-up visits for the same episode. For the evaluation of influenza and pneumococcal pneumonia vaccination, the outcomes were time to first recorded presentation with an episode of influenza-like illness and pneumonia over the study period, respectively.

Statistical analyses

Infections

We evaluated differences in baseline characteristics between those with and without haematological abnormalities; all reported *P*-values are two-sided. Event rates were calculated as the number of events divided by the total person-years of follow-up and expressed as the number per 1000 person-years.

Baseline analysis. The influence of each baseline haematological abnormality (anaemia, lymphopenia and neutropenia) on time to first infection was evaluated using separate unadjusted Cox proportional hazards models and a multivariable adjusted Cox model. The multivariable model was adjusted for age, sex, ethnicity and baseline measures of BMI, smoking status, medication use, seropositivity and comorbidities (detailed in Table 1).

Time-varying analysis. To evaluate the influence of haematological abnormalities after diagnosis on risk of infection, we updated the same unadjusted and adjusted Cox models used in the baseline analysis to include haematological measures across follow-up as time-varying covariates. Each haematological abnormality was classified as a time-varying binary exposure: the presence or absence of an abnormality on the most recent full blood count test. In this analysis, individuals were able to transition from one haematological state to another (e.g. neutropenic to non-neutropenic) multiple times during the follow-up period. Haematological results recorded in the 2 weeks prior to an infection were excluded to reduce the likelihood the infection itself influenced the haematological measures.

Vaccinations

We assessed differences in the effectiveness of vaccinations for influenza and pneumococcus among patients with RA and those without RA by comparing incidences of these infections in subgroups who had and had not undergone immunization. Comparisons were made using the χ^2 test. Time to infection by vaccination status was evaluated separately in individuals with and without RA using unadjusted and adjusted Cox models, with adjustment for age, sex, ethnicity, BMI, smoking status, comorbidities likely to influence vaccination status [chronic obstructive pulmonary disease (COPD), asthma, diabetes, chronic kidney disease (CKD)], use of immunosuppressive agents and, in those with RA, the duration of RA and RA autoantibody status. To test for an overall effect of heterogeneity by RA status and vaccination status, we used a likelihood ratio test to compare a model with an RA status and vaccination status interaction term with a nested model without an interaction term. Statistical analyses were performed in R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 6591 individuals were diagnosed with RA, the majority (67%) were female (Table 1). The median follow-up was 2.2 years. At baseline, anaemia was present in 1066 (16.2%) individuals; neutropenia [*n* = 38 (0.6%)] and lymphopenia [*n* = 97 (1.5%)] were less common. The proportion of individuals with anaemia increased in the years prior to diagnosis (5.1% of individuals had anaemia 3 years prior to diagnosis, 6.3% 2 years prior and 8.3% 1 year prior). The proportion with neutropenia and lymphopenia was 0.2-0.4% and 0.4-0.6%, respectively, over the same pre-diagnosis period (Table 2). At 3 years post-diagnosis the proportion of individuals with each haematological abnormality remained similar to at diagnosis (anaemia 15.9%, neutropenia 1.1%, lymphopenia 1.5%; Table 2).

Table 1 Baseline characteristics at diagnosis for individuals with RA by haematological abnormality

Characteristics	Overall ($n = 6591$)	Anaemia ($n = 1066$)	*P*-value[a]	Neutropenia ($n = 38$)	*P*-value[b]	Lymphopenia ($n = 97$)	*P*-value[c]
Age, mean (S.D.), years	58.7 (15.5)	63.9 (15.6)	<0.001	59.8 (13.2)	0.64	64.0 (15.3)	0.001
Sex, male, *n* (%)	2142 (32.5)	556 (52.2)	<0.001	16 (42.1)	0.27	32 (33.0)	1.00
Ethnicity, *n* (%)			<0.001		<0.001		0.542
White	4883 (74.1)	740 (69.4)		17 (44.7)		74 (76.3)	
Asian	255 (3.9)	65 (6.1)		3 (7.9)		2 (2.1)	
Black	128 (1.9)	26 (2.4)		11 (28.9)		0 (0.0)	
Mixed	26 (0.4)	7 (0.7)		0 (0.0)		0 (0.0)	
Other	36 (0.5)	4 (0.5)		0 (0.0)		0 (0.0)	
Missing	1263 (19.2)	224 (21)		7 (18.4)		21 (21.6)	
Smoking status, *n* (%)			<0.001		0.016		0.196
Never	1853 (28.1)	294 (27.6)		12 (31.6)		32 (33.0)	
Current	1348 (20.5)	167 (15.7)		5 (13.2)		15 (15.5)	
Former	2968 (45.0)	528 (49.5)		14 (36.8)		40 (41.2)	
Missing	422 (6.4)	77 (7.2)		7 (18.4)		10 (10.3)	
BMI, mean (S.D.), kg/m^2[d]	27.7 (6.0)	27.2 (6.3)	0.010	26.7 (4.8)	0.349	26.1 (6.4)	0.008
Comorbidities, *n* (%)							
Atrial fibrillation	237 (3.6)	61 (5.7)	<0.001	1 (2.6)	1.000	5 (5.2)	0.578
Hypertension	2063 (31.3)	441 (41.4)	<0.001	15 (39.5)	0.361	33 (34.0)	0.637
Myocardial infarction	202 (3.1)	59 (5.5)	<0.001	0	0.530	5 (5.2)	0.365
Stroke	254 (3.9)	82 (7.7)	<0.001	3 (7.9)	0.381	5 (5.2)	0.686
Heart failure	108 (1.6)	37 (3.5)	<0.001	0	0.875	1 (1.0)	0.943
CKD Stages III–V	618 (9.4)	177 (16.6)	<0.001	4 (10.5)	1.000	12 (12.4)	0.399
Diabetes	735 (11.2)	187 (17.5)	<0.001	3 (7.9)	0.703	14 (14.4)	0.383
COPD	466 (7.1)	79 (7.4)	0.683	1 (2.6)	0.451	11 (11.3)	0.146
Asthma	1118 (17.0)	179 (16.8)	0.906	4 (10.5)	0.399	14 (14.4)	0.594
Malignancy	369 (5.6)	75 (7.0)	0.031	2 (5.3)	1.000	3 (3.1)	0.390
Metastatic cancer	62 (0.9)	17 (1.6)	0.025	0	1.000	2 (2.1)	0.534
Depression	1855 (28.1)	234 (22.0)	<0.001	7 (18.4)	0.248	21 (21.6)	0.187
Haematological/lab values, mean (S.D.)							
Haemoglobin (g/L)[d]	13.2 (1.5)	11.6 (1.4)	<0.001	12.7 (1.8)	0.020	12.2 (1.7)	<0.001
Neutrophil count (10^9/L)[d]	4.7 (2.6)	5.0 (2.5)	<0.001	1.3 (0.4)	<0.001	4.5 (2.7)	0.483
Lymphocyte count (10^9/L)[d]	2.0 (1.0)	1.7 (0.8)	<0.001	1.6 (0.6)	0.008	0.6 (0.2)	<0.001
Seropositive[e]	1791 (27)	269 (25)	0.129	13 (34)	0.427	21 (22)	0.264
Medications, *n* (%)							
NSAIDs	1962 (29.8)	314 (29.5)	0.836	10 (26.3)	0.773	21 (21.6)	0.099
Glucocorticoids	2001 (30.4)	433 (40.6)	<0.001	7 (18.4)	0.153	58 (59.8)	<0.001
Methotrexate	992 (15.1)	197 (18.5)	0.001	5 (13.2)	0.921	22 (22.7)	0.048
Other csDMARDs	1263 (19.2)	260 (24.4)	<0.001	6 (15.8)	0.747	42 (43.3)	<0.001
bDMARDs	19 (0.3)	2 (0.2)	0.721	0 (0.0)	1.000	1 (1.0)	0.674

[a]*P*-value for differences when compared with those without anaemia.
[b]*P*-value for differences when compared with those without neutropenia.
[c]*P*-value for differences when compared with those without lymphopenia.
[d]Missing baseline data: BMI, $n = 520$ (8%); haemoglobin, $n = 499$ (8%); neutrophils, $n = 530$ (8%); lymphocytes, $n = 526$ (8%).
[e]Based on RF or anti-CCP antibody (%). bDMARDs, biological DMARDs; csDMARDs, conventional synthetic DMARDs.

Baseline patient characteristics differ by haematological status

Baseline characteristics of the study population, overall and by haematological abnormality, are shown in Table 1 and Supplementary Table S1–3, available at *Rheumatology* online. Individuals with anaemia and lymphopenia were older than the study population as a whole. Individuals with anaemia were more likely to be male and had greater comorbidity, while individuals with neutropenia were more likely to be of black ethnicity.

Anaemia and lymphopenia are associated with an increased risk of infection

Crude rates of infection among individuals with baseline anaemia, neutropenia and lymphopenia were 181.2, 151.8 and 256.4 per 1000 person-years, respectively, compared with 172.0 per 1000 person-years among individuals without haematological abnormality. Baseline anaemia and lymphopenia were associated with an increased risk of infection in both unadjusted and adjusted analyses (Table 3). There was no evidence of an association for

Table 2 The proportion of individuals with RA with recorded haematological abnormalities before, at and after diagnosis

Abnormality	3 years pre-diagnosis ($n = 5,535$)	2 years pre-diagnosis ($n = 5,731$)	1 year pre-diagnosis ($n = 5,901$)	At diagnosis RA (n=6,591)	3 years post-diagnosis ($n = 4646$)
Anaemia	284 (5.1%)	361 (6.3%)	488 (8.3%)	1066 (16.1%)	739 (15.9%)
Neutropenia	14 (0.2%)	19 (0.3%)	25 (0.4%)	38 (0.6%)	56 (1.1%)
Lymphopenia	25 (0.4%)	25 (0.4%)	38 (0.6%)	97 (1.4%)	75 (1.5%)

Table 3 Adjusted HRs of infections by the presence or absence of haematological abnormality at baseline

Abnormality	No haematological abnormality ($n = 5499$)	Anaemia ($n = 1066$)	Neutropenia ($n = 38$)	Lymphopenia ($n = 97$)
Infection events, *n* (%)	3506 (53.2)	658 (61.7)	19 (50.0)	73 (75.3)
Exposure time, person-years	20 384	3631	125	285
Event rate per 1000 person-years, median (IQR)	172.0 (166.4–177.8)	181.2 (167.7–195.6)	151.8 (91.4–237.0)	256.4 (201.0–322.4)
Unadjusted HR (95% CI)	Reference	1.09 (1.00, 1.18)	0.90 (0.54, 1.41)	1.49 (1.18, 1.88)
Adjusted HR (95% CI)[a]	Reference	1.19 (1.08, 1.30)	1.06 (0.67, 1.67)	1.41 (1.11, 1.79)

[a]Adjusted for age, sex, ethnicity (white/missing or non-white), baseline measures of other haematological measures, BMI category (<18.5 underweight, 18.5–24.9 normal weight, 25.0–29.9 overweight, 30.0–34.9 class I obesity, 35.0–39.9 class II obesity, ⩾40.0 class III obesity, missing), smoking status (never, current, former, missing), seropositivity (presence of RF or anti-CCP antibodies), medication use and comorbidities (see Table1). IQR, interquartile range.

baseline neutropenia. For a breakdown of infection types see Supplementary Table S4, available at *Rheumatology* online.

Incorporating haematological measures throughout follow-up identified many more individuals with at least one test indicating haematological abnormality (anaemia 34% of individuals, neutropenia 4%, lymphopenia 9%) compared with the assessment of baseline haematological measures. The median number of test measures per individual was 6 (interquartile range 2–18). Consistent with the analysis of baseline measures, anaemia and lymphopenia were associated with an increased risk of infection (Table 4).

Vaccination

We identified 3699 individuals with a diagnosis of RA before 1 January 2012 and all were matched with controls (Supplementary Table S5, available at *Rheumatology* online). During a follow-up of 31 660 person-years, 168 influenza-like illness and 150 pneumonia events were recorded. Table 5 shows the infection rates and risk of infection associated with vaccination status among individuals with and without RA.

Pneumonia. A higher proportion of individuals with RA were vaccinated against pneumococcal pneumonia compared with individuals without RA (16% *vs* 12%, $P < 0.001$; Table 5). Event rates for pneumonia in both the vaccinated and non-vaccinated group (7.7 and 6.9 per 1000-person years, respectively) exceeded those among individuals without RA (5.9 and 2.1 per 1000-person years, respectively). Pneumococcal vaccination was associated with an increased risk of pneumonia in those without RA, but we found no evidence of an association among individuals with RA (test for RA: vaccination status interaction in multivariable model $P = 0.14$).

Influenza. A higher proportion of individuals with RA were vaccinated against influenza compared with individuals without RA (64% *vs* 48%, $P < 0.001$; Table 5). Among the non-vaccinated, the event rate for influenza-like illness among individuals with RA was slightly increased compared with individuals without RA (Table 5). Vaccination was associated with a reduction in influenza-like illness in those with RA [hazard ratio (HR) 0.59 (95% CI 0.36, 0.98)], but there was no evidence of an association in those without RA [HR 0.95 (95% CI 0.55, 1.64)] (test for RA: vaccination status interaction in multivariable model $P = 0.24$).

Discussion

This study provides the most comprehensive evaluation to date of the association between haematological abnormalities at disease onset and risk of common infection among individuals with RA. Anaemia and lymphopenia, but not neutropenia, at and after diagnosis were associated with an increased risk of infection. Our study provides important real-world evidence that the influenza vaccine is effective in people with RA. We also found individuals with RA had higher rates of pneumonia when compared with matched individuals and provide the first

Table 4 HRs of infections by time-varying haematological abnormality status across study follow-up

Status	Anaemia	Neutropenia	Lymphopenia
Individuals with at least one episode across follow-up, *n*	2220	259	562
Unadjusted HR (95% CI)	1.13 (1.04, 1.24)	1.10 (0.74, 1.63)	1.46 (1.17, 1.81)
Adjusted HR (95% CI)[a]	1.21 (1.10, 1.33)	1.19 (0.80, 1.76)	1.39 (1.12, 1.73)

HRs represent the increase in the risk of infections associated with the presence of each haematological abnormality at any time during study follow-up compared with the absence of the haematological abnormality in the total study population with RA ($n = 6591$; infection events, $n = 3506$).
[a]Adjusted for age, sex, ethnicity (white/missing or non-white), baseline measures of other haematological measures, BMI category (<18.5 underweight, 18.5–24.9 normal weight, 25.0–29.9 overweight, 30.0–34.9 class I obesity, 35.0–39.9 class II obesity, ⩾40.0 class III obesity, missing), smoking status (never, current, former, missing), seropositivity (presence of RF or anti-CCP antibodies), medication use and comorbidities (see Table1).

Table 5 HRs of infection outcomes by vaccination status

Outcome	No RA ($n = 3699$)		RA ($n = 3699$)	
	Not vaccinated	Vaccinated	Not vaccinated	Vaccinated
Pneumonia vaccinations, *n* (%)	3239 (88)	460 (12)	3093 (84)	606 (16)
Pneumonia events, *n* (%)	30 (1)	12 (3)	88 (3)	20 (3)
Exposure time, person-years	14 401	2032	12 780	2601
Event rate per 1000 person-years, median (IQR)	2.1 (1.4–3.0)	5.9 (3.1–10.3)	6.9 (5.5–8.5)	7.7 (4.7–11.9)
Unadjusted HR (95% CI)	Reference	2.84 (1.45, 5.54)	Reference	1.12 (0.69, 1.82)
Adjusted HR (95% CI)[a]	Reference	2.03 (1.00, 4.11)	Reference	0.90 (0.55, 1.48)
Influenza vaccinations, *n* (%)	1920 (52)	1779 (48)	1348 (36)	2351 (64)
Influenza-like illness events, *n* (%)	57 (3)	34 (2)	35 (3)	42 (2)
Exposure time, person-years	8484	7842	4951	10383
Event rate per 1000 person-years, median (IQR)	6.7 (5.1–8.7)	4.3 (3.0–6.1)	7.1 (4.9–9.8)	4.0 (2.9–5.5)
Unadjusted HR (95% CI)	Reference	0.65 (0.42, 0.99)	Reference	0.58 (0.37, 0.90)
Adjusted HR (95% CI)[a]	Reference	0.95 (0.55, 1.64)	Reference	0.59 (0.36, 0.98)

[a]Adjusted for age, sex, ethnicity (white/missing or non-white), BMI category (<18.5 underweight, 18.5–24.9 normal weight, 25.0–29.9 overweight, 30.0–34.9 class I obesity, 35.0–39.9 class II obesity, ⩾40.0 class III obesity, missing), smoking status (never, current, former, missing), comorbidities (COPD, asthma, diabetes, CKD), use of immunosuppressive agents and, in those with RA, the duration of RA and seropositivity (presence of RF or anti-CCP antibodies.

data to suggest the efficacy of the pneumococcal vaccine may differ in individuals with and without RA.

In this study we used a large primary care database and considered a broad range of common infections presenting to primary care physicians, meaning we provide information on more than six times as many individuals with RA and five times as many infection events as the only previous population-based study to evaluate the impact of haematological abnormalities on infection risks [26]. In the previous study, Crowson *et al.* [26] found infection risks were increased by 45% [HR 1.45 (95% CI 0.86, 2.43)] in the presence of lymphopenia and by 76% [HR 1.76 (95% CI 0.42, 7.37)] with neutropenia in a population-based cohort from Minnesota in the USA. The wide CIs reported and the different settings and infections considered (Crowson *et al.* [26] considered only serious infections requiring hospitalization or intravenous antibiotics), limit direct comparison of our results with this previous study.

Although we found no evidence that the presence of neutropenia was associated with an increase in infections, few individuals had neutropenia, limiting the power of our study. Our findings do not imply that neutropenia induced in some patients receiving DMARDs is benign, given previous studies [27, 28]. The high prevalence of anaemia in individuals with RA is in keeping with previous studies [19], but further studies are required to establish whether proactive anaemia management may be beneficial in early RA in the context of infection risk.

Uptake of both influenza and pneumococcus vaccine prior to diagnosis was greater among individuals with RA compared with matched controls without RA. In the case of influenza, after adjustment for a range of patient characteristics and comorbidities that have previously been shown to be associated with infection risk [26], an approach designed to reduce the possibility of confounding by indication [29], we also observed a protective effect of vaccination in individuals with RA. In individuals without

RA, there was no evidence that vaccination was associated with a reduced risk of influenza.

We found no evidence of a protective effect for the pneumococcus vaccine in patients with RA. This may relate to a lack of specificity of the infection outcome, as primary care coding does not allow for identification of microbiologically confirmed pneumococcal pneumonia. As a result clinical codes likely cover both true pneumococcal pneumonia and the majority of pneumonias that are caused by pneumococcal strains or other pathogens not covered by the vaccine. The positive association between pneumococcal vaccination and pneumonia events we observed in the non-RA cohort may be explained by a further common bias evaluating vaccine efficacy in routine data; if patients at higher risk of pneumonia are more likely to be vaccinated, higher infection rates may be seen among vaccinated individuals than non-vaccinated individuals, and an underestimation of vaccine effectiveness will be made [30]. Such bias may also explain the apparent lack of efficacy of the influenza vaccine in people without RA. Identification and elimination of confounding by indication is difficult [31], and our results highlight the potential limitations of vaccine efficacy studies using routine observational data. Despite these limitations, it is should be noted that in fully adjusted analyses, influenza vaccination offered a protective effect in individuals with RA but not in matched patients.

The strengths of the study include the use of primary care data from a nationally representative sample of the UK [21]. The RCGP RSC network is the principle infections surveillance network in the UK and provides regular feedback about the quality of infection recording and reporting to constituent practices. The infection incidence data are therefore the highest quality available using routine health care records.

Limitations of the study include the fact that data are observational and therefore the possibility of residual confounding as an explanation of our findings cannot be excluded, despite attempts to reduce it through the use of a matched cohort design and by adjustment for likely measured confounders. In particular, there remains a potential diagnostic bias if individuals with RA are more likely to visit their general practitioner compared with individuals without RA, in particular at times of infection or infection-like symptoms. Despite the use of a matched design for the vaccination analysis there remained differences in baseline factors between the RA and non-RA populations, with individuals with RA having higher levels of, in particular, smoking, COPD, asthma and CKD. Although these factors and other relevant clinical variables, including medication use, were adjusted for in multivariable analysis, unmeasured differences unrelated to the presence or absence of RA are a potential explanation of the differences in vaccine efficacy we observed. In common with other studies using primary care records, our study relied on the use of comprehensive code lists, against which all variables were defined. This limitation was mitigated, however, by the use of a validated approach for case ascertainment and defining variables [24, 25]. A further limitation is that our definition of RA was based on primary rather than specialist care records, and results may not be applicable to dissimilar populations.

Future work

Our results demonstrate robust associations between haematological markers and risk of common infections. Further study of the clinical utility of these markers in contemporary real-world RA populations would be of considerable interest. This could involve interrogation of hospital admissions data to evaluate associations with more serious infection events. An evaluation of whether existing risk scores for infection can be improved through inclusion of haematological abnormality markers and thereby help guide clinical management would be of particular interest [32, 33]. Given the apparent effectiveness of influenza vaccination in individuals with RA we demonstrated in this study, further studies to explore rates of annual flu vaccine uptake among people with RA and reasons for remaining unvaccinated would be of interest to encourage improvement in vaccination rates. Further studies, ideally evaluating confirmed pneumococcal disease, are required to determine the efficacy of pneumococcal vaccination in individuals with RA and examine how efficacy is modified by RA therapy [34].

Conclusions

Anaemia and lymphopenia in individuals with RA are independently associated with an increased risk of common infection. This suggests haematological markers may be clinically useful to identify individuals who might benefit from targeted counselling to stress the importance of early presentation if symptoms of infection develop. Our data show a higher rate of pneumococcal-like illness in individuals with RA and support the effectiveness of the influenza vaccination in people with RA.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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