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

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**Word count:** Manuscript: 3301

**Abstract**

**Objectives**

To describe the prevalence of haematological abnormalities in individuals with rheumatoid arthritis (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 6,591 individuals with newly diagnosed RA between 2004 and 2016 inclusive using the UK Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) primary care database. The prevalence of haematological abnormalities at diagnosis (anaemia, neutropenia and lymphopenia) was established. Cox proportional hazards models were used to evaluate i) the association between each haematological abnormality and time to common infections; ii) 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), neutropenia (0.6%) and lymphopenia (1.4%) less so. Lymphopenia and anaemia were associated with increased infection risk (respective hazard ratios (HR) 1.18 (95%CI 1.08-1.29); HR 1.37 (95%CI 1.08-1.73)). 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**

Rheumatoid arthritis; Anaemia; Lymphopenia; Neutropenia; Infection; Influenza; Influenza Vaccine; Pneumococcal Vaccine

**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 was associated with reduced risk of influenza-like illness in patients with rheumatoid arthritis.

The long-term prognosis of rheumatoid arthritis (RA) has improved with the availability of conventional synthetic and later biologic disease modifying antirheumatic drugs (DMARDs),(1, 2) coupled with greater monitoring and treatment adjustment to target disease remission. European League Against Rheumatism (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. Over 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. DMARDs 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-tumour necrosis factor (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, respectively, subsequent incidence of influenza and pneumococcal-like infections.

**MATERIALS AND 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 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 a weekly infections data return 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)

*Infections*

Our inclusion criteria specified individuals aged 18 years and older with a diagnosis of RA after January 1, 2004 and prior to January 1, 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 January 1, 2017, or 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 with RA after January 2004 but before January 1, 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 January 1, 2012. This approach enabled comparisons of individuals with and without RA over the same influenza and pneumonia seasons (five 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 (January 1, 2012). For pneumococcal vaccination it was defined as any code or prescription for a pneumococcal vaccination at any time prior to January 1, 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 of <13.5g/dl (135g/L) for men or <11.5g/dl (115g/L) for women. Neutropenia was defined as a mean total neutrophil count of <1.6×109/L and lymphopenia was defined as a mean total lymphocyte count < 0.75×109/L. Further subdivision by severity was not possible due to low numbers. Baseline medication use was defined as the issuing of a prescription three 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 as 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, respectively, time to first recorded presentation with an episode of influenza-like illness or pneumonia over the study period.

**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 two 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 immunisation. Comparisons were made using the χ2 tests. 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 (COPD, asthma, diabetes, 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 a 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.

**Ethics**

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 NHS Health Research Authority research decision tool (http://www.hra-decisiontools.org.uk/research/).

**RESULTS**

6591 individuals were diagnosed with RA, the majority (67%) were female (Table 1). Median follow-up was 2.2 years. At baseline anaemia was present in 1066 (16.2%); 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 (4.5% of individuals had anaemia 3 years prior to diagnosis, 5.6% 2 years prior, and 7.5% 1 year prior). The proportion with neutropenia and lymphopenia ranged from, respectively, 0.4-0.6% and 0.2-0.4% 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).

***Baseline patient characteristics differ by haematological status***

Baseline characteristics of the study population, overall and by haematological abnormality, are shown in Table 1 and Appendix Tables 1-3. 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, whilst 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 associated for baseline neutropenia. For a breakdown of infection types see Appendix Table 4.

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 (IQR 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 3,699 individuals with a diagnosis of RA before January 1st 2012, and all were matched with controls (Appendix 5). 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 individual 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 amongst 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)). Amongst 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 (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 amongst 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 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 and colleagues found infection risks were increased by 45% (Hazard ratio 1.45 (95%CI 0.86;2.43) in the presence of lymphopenia and by 76% (Hazard ratio 0.76 (95%CI 0.42-7.37)with neutropenia in a population-based cohort from Minnesota in the United States. The wide confidence intervals reported, and the different settings and infections considered (Crowson et al. considered only serious infections requiring hospitalisation or intravenous antibiotics), limit direct comparison of our results with this previous study. (26)

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 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 noteworthy that in fully adjusted analyses, influenza vaccination offered a protective effect in individuals with RA but not in matched patients.

Strengths of the study include the use of primary care data from a nationally representative sample of England.(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 healthcare 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, however, was mitigated 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 amongst 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 increased risk of common infection. This suggests haematological markers may be clinically useful to identify individuals who may 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 individuals with RA, and support the effectiveness of the influenza vaccination in people with RA.

**Funding:** This work was supported by Pfizer UK.

**Acknowledgements**

CM is funded by the National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Health Research and Care West Midlands, the NIHR School for Primary Care Research and a NIHR Research Professorship in General Practice (NIHR-RP-2014-04-026); the views expressed in this manuscript are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. CDB and KR are supported by the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre.

Medical writing and statistical support was provided by John Dennis at Momentum Data and was funded by Pfizer. We acknowledge additional medical writing and statistical support from Andrew McGovern and Jack Brownrigg (Momentum Data), and project management support from Filipa Ferreira (University of Surrey).

**Conflicts of interest:** KR has received research funding from Abbvie and Pfizer and honoraria / consultancy fees from Lilly, BMS, UCB, Pfizer, Janssen and Roche Chugai. JG has received honoraria and/or sponsorship for conferences from Abbvie, Celgene, Janssen, Pfizer, and UCB. KK and JR are employees of Pfizer. All other authors declare no conflicts of interest.

**REFERENCES**

1. Shourt CA, Crowson CS, Gabriel SE, Matteson EL. Orthopedic surgery among patients with rheumatoid arthritis 1980–2007: a population-based study focused on surgery rates, sex, and mortality. The Journal of rheumatology. 2012;39(3):481-5.

2. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Annals of the rheumatic diseases. 2009;68(7):1100-4.

3. Wilson A, Yu H-T, Goodnough LT, Nissenson AR. Prevalence and outcomes of anemia in rheumatoid arthritis: a systematic review of the literature. The American journal of medicine. 2004;116(7):50-7.

4. Pincus T, O'Dell JR, Kremer JM. Combination therapy with multiple disease-modifying antirheumatic drugs in rheumatoid arthritis: a preventive strategy. Annals of internal medicine. 1999;131(10):768-74.

5. Kay J, Bryant S, Cravets M, McCabe D. FRI0002 Il-1 receptor antagonist (il-1ra) treatment is associated with improvement of anaemia in rheumatoid arthritis. BMJ Publishing Group Ltd; 2001.

6. Porter D, Sturrock R, Capell H. The use of serum ferritin estimation in the investigation of anaemia in patients with rheumatoid arthritis. Clinical and experimental rheumatology. 1994;12(2):179-82.

7. Vreugdenhil G, Swaak A. Anaemia in rheumatoid arthritis: pathogenesis, diagnosis and treatment. Rheumatology international. 1990;9(6):243-57.

8. Peeters H, Jongen-Lavrencic M, Raja A, Ramdin H, Vreugdenhil G, Breedveld F, et al. Course and characteristics of anaemia in patients with rheumatoid arthritis of recent onset. Annals of the rheumatic diseases. 1996;55(3):162.

9. Vreugdenhil G, Wognum A, Van Eijk H, Swaak A. Anaemia in rheumatoid arthritis: the role of iron, vitamin B12, and folic acid deficiency, and erythropoietin responsiveness. Annals of the rheumatic diseases. 1990;49(2):93.

10. Kroesen S, Widmer A, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti‐TNF‐α therapy. Rheumatology. 2003;42(5):617-21.

11. Gómez‐Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active‐surveillance report. Arthritis & Rheumatology. 2003;48(8):2122-7.

12. Wallis R, Broder M, Wong J, Hanson M, Beenhouwer D. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clinical Infectious Diseases. 2004;38(9):1261-5.

13. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. Jama. 2006;295(19):2275-85.

14. Lorenzi AR, Clarke AM, Wooldridge T, Waldmann H, Hale G, Symmons D, et al. Morbidity and mortality in rheumatoid arthritis patients with prolonged therapy‐induced lymphopenia: Twelve‐year outcomes. Arthritis & Rheumatology. 2008;58(2):370-5.

15. Isaacs JD, Greer S, Sharma S, Symmons D, Smith M, Johnston J, et al. Morbidity and mortality in rheumatoid arthritis patients with prolonged and profound therapy‐induced lymphopenia. Arthritis & Rheumatology. 2001;44(9):1998-2008.

16. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Annals of the Rheumatic Diseases. 2011;70(3):414-22.

17. Pneumococcal: the green book, chapter 25. In: England PH, editor. 2013.

18. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2013;1(3):208-19.

19. Costello R, Winthrop KL, Pye SR, Brown B, Dixon WG. Influenza and Pneumococcal Vaccination Uptake in Patients with Rheumatoid Arthritis Treated with Immunosuppressive Therapy in the UK: A Retrospective Cohort Study Using Data from the Clinical Practice Research Datalink. PLOS ONE. 2016;11(4):e0153848.

20. Nakafero G, Grainge MJ, Myles PR, Mallen CD, Zhang W, Doherty M, et al. Predictors and temporal trend of flu vaccination in auto-immune rheumatic diseases in the UK: a nationwide prospective cohort study. Rheumatology (Oxford). 2018;57(10):1726-34.

21. Correa A, Hinton W, McGovern A, van Vlymen J, Yonova I, Jones S, et al. Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) sentinel network: a cohort profile. BMJ open. 2016;6(4):e011092.

22. de Lusignan S, Correa A, Smith GE, Yonova I, Pebody R, Ferreira F, et al. RCGP Research and Surveillance Centre: 50 years’ surveillance of influenza, infections, and respiratory conditions. British Journal of General Practice. 2017;67(663):440-1.

23. Muller S, Hider SL, Raza K, Stack RJ, Hayward RA, Mallen CD. An algorithm to identify rheumatoid arthritis in primary care: a Clinical Practice Research Datalink study. BMJ open. 2015;5(12):e009309.

24. Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. Pharmacoepidemiology and drug safety. 2009;18(8):704-7.

25. de Lusignan S, Liaw S-T, Michalakidis G, Jones S. Defining datasets and creating data dictionaries for quality improvement and research in chronic disease using routinely collected data: an ontology-driven approach. Journal of Innovation in Health Informatics. 2011;19(3):127-34.

26. Crowson CS, Hoganson DD, Fitz‐Gibbon PD, Matteson EL. Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. Arthritis & Rheumatology. 2012;64(9):2847-55.

27. Lim A, Gaffney K, Scott D. Methotrexate-induced pancytopenia: serious and under-reported? Our experience of 25 cases in 5 years. Rheumatology. 2005;44(8):1051-5.

28. Hastings R, Ding T, Butt S, Gadsby K, Zhang W, Moots RJ, et al. Neutropenia in patients receiving anti–tumor necrosis factor therapy. Arthritis care & research. 2010;62(6):764-9.

29. Remschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. BMC infectious diseases. 2015;15(1):429.

30. McDonald HI, Thomas SL, Millett ER, Quint J, Nitsch D. Do influenza and pneumococcal vaccines prevent community-acquired respiratory infections among older people with diabetes and does this vary by chronic kidney disease? A cohort study using electronic health records. BMJ Open Diabetes Research and Care. 2017;5(1):e000332.

31. Remschmidt C, Wichmann O, Harder T. Vaccines for the prevention of seasonal influenza in patients with diabetes: systematic review and meta-analysis. BMC medicine. 2015;13(1):53.

32. Curtis JR, Xie F, Chen L, Muntner P, Grijalva CG, Spettell C, et al. Use of a disease risk score to compare serious infections associated with anti–tumor necrosis factor therapy among high- versus lower-risk rheumatoid arthritis patients. Arthritis Care & Research. 2012;64(10):1480-9.

33. Zink A, Manger B, Kaufmann J, Eisterhues C, Krause A, Listing J, et al. Evaluation of the RABBIT Risk Score for serious infections. Annals of the Rheumatic Diseases. 2014;73(9):1673-6.

34. Nguyen MTT, Lindegaard H, Hendricks O, Jørgensen CS, Kantsø B, Friis-Møller N. Initial Serological Response after Prime-boost Pneumococcal Vaccination in Rheumatoid Arthritis Patients: Results of a Randomized Controlled Trial. The Journal of Rheumatology. 2017:jrheum.161407.

**TABLES**

**Table 1. Baseline characteristics at diagnosis for individuals with RA by haematological abnormality.** Values are mean (percentage) unless stated otherwise.BMI = body mass index, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, NSAIDs = non-steroidal anti-inflammatory drugs, csDMARDs = conventional synthetic disease-modifying antirheumatic drugs, bDMARDs = biological disease-modifying antirheumatic drugs.

|  | **Overall**  **(n=6591)** | **Anaemia**  **(n=1066)** | **p valuea** | **Neutropenia (n=38)** | **p valueb** | **Lymphopenia (n=97)** | **p valuec** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Age, years (Mean (SD))** | 58.7 (15.5) | 63.9 (15.6) | <0.001 | 59.8 (13.2) | 0.64 | 64.0 (15.3) | 0.001 |
| **Male sex** | 2142 (32.5) | 556 (52.2) | <0.001 | 16 (42.1) | 0.27 | 32 (33.0) | 1.00 |
| **Ethnicity** |  |  | <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** |  |  | <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, kg/m2 (Mean (SD)) d** | 27.7 (6.0) | 27.2 (6.3) | 0.010 | 26.7 (4.8) | 0.349 | 26.1 (6.4) | 0.008 |
| **Comorbidities** |  |  |  |  |  |  |  |
| 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 (SD)** |  |  |  |  |  |  |  |
| 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 (109/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 (109/L)d | 2.0 (1.0) | 1.7 (0.8) | <0.001 | 1.6 (0.6) | 0.008 | 0.6 (0.2) | <0.001 |
| Seropositivee | 1791 (27) | 269 (25) | 0.129 | 13 (34) | 0.427 | 21 (22) | 0.264 |
| **Medications** |  |  |  |  |  |  |  |
| 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 csDMARD | 1263 (19.2) | 260 (24.4) | <0.001 | 6 (15.8) | 0.747 | 42 (43.3) | <0.001 |
| bDMARD | 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 for differences when compared with those without neutropenia, c 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 Rheumatoid Factor or anti cyclic-citrullinated peptide [CCP] antibody(%)

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

|  | **3 years pre-diagnosis**  **(n=6,591)** | **2 years pre-diagnosis**  **(n=6,591)** | **1 year pre-diagnosis**  **(n=6,591)** | **At diagnosis of RA (n=6,591)** | **3 years post diagnosis (n=4646)** |
| --- | --- | --- | --- | --- | --- |
| **Anaemia** | 296 (4.5%) | 372 (5.6%) | 497 (7.5%) | 1066 (16.1%) | 739 (15.9%) |
| **Neutropenia** | 15 (0.2%) | 19 (0.3%) | 25 (0.4%) | 38 (0.6%) | 56 (1.1%) |
| **Lymphopenia** | 27 (0.4%) | 27 (0.4%) | 39 (0.6%) | 97 (1.4%) | 75 (1.5%) |

**Table 3. Adjusted hazard ratios of infections by presence or absence of haematological abnormality at baseline**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **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) | 20384 | 3631 | 125 | 285 |
| Event rate per 1000 person-years | 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 hazard ratio (95% CI) | Reference | 1.09 (1.00-1.18) | 0.90 (0.54-1.41) | 1.49 (1.18-1.88) |
| Adjusted hazard ratio (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), and 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 rheumatoid factor or anti citrullinated protein [CCP] antibodies), medication use and comorbidities (see Table 1).

**Table 4. Hazard ratios of infections by time-varying haematological abnormality status across study follow-up.** Hazard ratios represent the increase in the risk of infections associated with the presence of each haematological abnormality at any time during study follow-up, compared to the absence of the haematological abnormality, in total study population with RA (n=6591; number of infection events 3506)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Anaemia** | **Neutropenia** | **Lymphopenia** |
| Number of individuals with at least one episode across follow-up | 2,220 | 259 | 562 |
| Unadjusted hazard ratio (95% CI) | 1.13 (1.04-1.24) | 1.10 (0.74-1.63) | 1.46 (1.17-1.81) |
| Adjusted hazard ratio (95% CI)a | 1.21 (1.10-1.33) | 1.19 (0.80-1.76) | 1.39 (1.12-1.73) |

a adjusted for age, sex, ethnicity (white/missing or non-white), and 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 rheumatoid factor or anti citrullinated protein [CCP] antibodies), medication use and comorbidities (see Table 1).

**Table 5. Hazard ratios of infection outcomes by vaccination status**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **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) | 14401 | 2032 | 12780 | 2601 |
| Event rate per 1000 person-years | 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 hazard ratio (95% CI) | Reference | 2.84 (1.45-5.54) | Reference | 1.12 (0.69-1.82) |
| Adjusted hazard ratio (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 | 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 hazard ratio (95% CI) | Reference | 0.65 (0.42-0.99) | Reference | 0.58 (0.37-0.90) |
| Adjusted hazard ratio (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, and CKD), use of immunosuppressive agents and in those with RA the duration of RA, and seropositivity (presence of rheumatoid factor or anti citrullinated protein [CCP] antibodies).