**Title:** Effectiveness of inactivated influenza vaccine in autoimmune rheumatic diseases treated with disease modifying anti-rheumatic drugs.

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**Running title**: Flu vaccine in rheumatic disease patients

**Abstract**

**Objectives:** The effectivenessof inactivated influenza vaccine (IIV) in people with autoimmune rheumatic disease (AIRDs) is not known. We investigated whether the IIV is effective in preventing respiratory morbidity, mortality, and all-cause mortality in AIRD patients.

**Methods:** Adults with AIRDs treated with disease modifying anti-rheumatic drugs prior to 1st September of each year between 2006-2009, and 2010-2015 were identified from the Clinical Practice Research Datalink. Exposure and outcome data were extracted. Data from multiple seasons were pooled. Propensity score (PS) for vaccination was calculated. Cox-proportional hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, and were [1] adjusted, [2] matched for PS for vaccination.

**Results:** Data for30,788 AIRD patients (65.7% female, 75.5% with RA, 61.1% prescribed methotrexate) contributing 125,034 influenza-cycles were included. Vaccination reduced risk of influenza-like illness (ILI) (aHR 0.70), hospitalization for pneumonia (aHR 0.61) and COPD exacerbations (aHR 0.67), and death due to pneumonia (aHR 0.56) on PS-adjusted analysis in the influenza active periods (IAPs). The associations were of similar magnitude and remained statistically significant on PS-matched analysis except for protection from ILI which became non-significant. Sub-analysis restricted to pre-IAP, IAP and post-IAP did not yield evidence of residual confounding on ILI and death due to pneumonia. Vaccination reduced risk of all-cause mortality, though, IAP restricted analysis demonstrated residual confounding for this outcome.

**Conclusion:** IIV associates with reduced risk of respiratory morbidity and mortality in people with AIRDs. These findings call for active promotion of seasonal influenza vaccination in immunosuppressed people with AIRDs by healthcare professionals.

**Keywords:** Flu vaccine, auto-immune rheumatic diseases, mortality, infection

**Key messages:**

* IIV reduces ILI, hospitalization for pneumonia/COPD exacerbation, and death due to pneumonia in AIRDs.
* IIV reduced all-cause mortality, but, this could be due to residual confounding.
* IIV should be actively promoted in people with AIRDs.

**Introduction** Influenza causes 291,000-650,000 deaths/year globally. It is estimated to cause 3.1 million hospitalized days and 31.4 million outpatient visits, costing 87.1 billion dollars to the USA economy annually (1, 2). Inactivated influenza vaccine (IIV) prevents influenza and its complications, with the degree of protection depending on vaccine match (3, 4). According to the latest Cochrane reviews, IIV prevents influenza and influenza-like illness (ILI) in adults ≥65 years old (risk ratio (RR) 0.42, 0.59 respectively) and in young adults (RR 0.41, 0.84 respectively) (3, 5). It prevents chronic obstructive pulmonary disease (COPD) exacerbation, and lower respiratory tract infection (LRTI) in people with haematological malignancy (6, 7). However, its efficacy remains unproven in asthma, cystic fibrosis and in healthcare workers for preventing influenza among care-home residents (8-10). Although observational studies report that IIV prevents pneumonia, hospitalization, and death, there is a paucity of randomised controlled trial (RCT) evidence for these outcomes (11-13).

Autoimmune rheumatic diseases (AIRDs) such as rheumatoid arthritis (RA), and spondyloarthritis (SpA) associate with increased risk of influenza and its complications, and seasonal-flu vaccination is recommended annually (14, 15). While the magnitude of serological response to IIV has been examined in AIRDs, its effectiveness in preventing patient-centred outcomes such as influenza, pneumonia and death have not been studied (16-18). The only study to evaluate the effectiveness of IIV in the context of immunosuppression had <5% AIRD cases (11). Moreover, there are concerns that methotrexate, the first-choice disease modifying anti-rheumatic drug (DMARD), and rituximab impair the serological response to IIV (16-18). As lack of knowledge about the need for vaccination and vaccine effectiveness (VE) are barriers to vaccination, it is important to examine whether IIV prevents respiratory morbidity and mortality in AIRDs (19, 20). Thus, the objectives of this study were to assess the effectiveness of IIV in preventing ILI, LRTI, pneumonia, COPD exacerbations, and death in immunosuppressed AIRD patients.

**Methods**

*Data source* Data from the Clinical Practice Research Datalink (CPRD) were used. Incepted in 1987, CPRD is a longitudinal anonymised electronic database containing health records of >10 million people UK (21). CPRD participants are representative of the UK population in terms of age, sex, and ethnicity (21). It contains details of diagnoses stored as Read codes, a coded thesaurus of clinical terms, primary-care prescriptions and immunisations. The data are enhanced by linkage with hospitalization (Hospital Episode Statistics (HES)) and mortality records (Office of National Statistics (ONS)). Data on prescription of biologic agents prescribed by hospital-based rheumatologists are not recorded.

*Ethical approval* ISAC of the MHRA, London (Ref: 16\_288R).

*Study design* Cohort study

*Population* ≥1 Read code for RA, lupus or SpA (defined as either psoriatic arthritis, reactive arthritis, inflammatory bowel disease associated arthritis, or ankylosing spondylitis) in receipt of ≥1 prescription of immunosuppressive DMARDs (methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, mycophenolate mofetil or tacrolimus), registered in GP surgeries validated to meet CPRD data standards, and ≥18 years in age. Participants only ever prescribed the immunomodulatory drug hydroxychloroquine were excluded as IIV is not recommended for hydroxychloroquine prescription in the UK (22).

*Annual cohorts* The study period (01/09/2006-31/08/2016) was partitioned into influenza-cycles of 12 months, beginning on 1st September of one year and ending on 31st August of the subsequent year. Data for the 2009-2010 cycle were excluded due to the use of monovalent pandemic vaccine alongside trivalent IIV, and the almost complete dominance of pandemic influenza A(H1N1)pdm09 in the community.

To be included in a cohort for one influenza-cycle, participants had to be contributing data on the 1st September, with at-least three-month registration at their current GP surgery, and receive a DMARD prescription in this period. The three-month prior registration period was to allow the GP time to incorporate new patients into local at-risk registers and to invite them for vaccination. A sub-set of participants treated with long-term oral corticosteroids, defined as ≥2 corticosteroid prescriptions in this three-month period was constructed for examining VE in those prescribed DMARDs and corticosteroids.

*Exposure:* IIV administration was the exposure of interest. Vaccination and date of vaccination were ascertained using Read codes and event date (23) (Table S1). An individual was defined as exposed (fully-immunised) 14 days after vaccination, in keeping with the typical time taken for mounting a serological response to the IIV (22). Influenza-cycles in which the IIV was recorded in the CPRD as being administered elsewhere e.g. at work, or in community-pharmacies were excluded, as the exact date of vaccination is not available in CPRD.

*Outcomes:*

Primary care consultation for LRTI: Defined as diagnostic Read code for LRTI and antibiotic prescription on the same date without preceding antibiotic prescriptions or Read codes for LRTI within 21 days prior to the eligible LRTI diagnosis date. Published Read code lists were supplemented with additional codes as required (Table S1) (24).

Primary care consultation for ILI: Defined as above using published Read codes supplemented with additional codes as above (Table S1) (25).

Primary care consultation for COPD exacerbation: Defined as either Read code for acute COPD exacerbation, or oral prednisolone and oral antibiotic prescriptions occurring on the same date, with oral prednisolone not prescribed as maintenance treatment in people with COPD (24, 26). Oral prednisolone was considered as maintenance if ≥2 prescriptions were issued within previous 60 days.

Hospitalisation and death including causes: Defined using ICD-10 codes in HES and ONS respectively.

*Follow-up:* In each of the influenza-cycles, participants were followed-up from 1st September until the earliest of outcome date, date of death, date of last data collection, transfer out of the GP-surgery or 31st August of the following year. A participant was defined as having an outcome of interest on the date of first allocation of Read code or ICD-10 code in an influenza-cycle.

IIV is most likely to have an effect on outcomes during periods of influenza virus circulation, and the proportion of ILI and other outcomes attributable to influenza virus activity is greatest. Therefore, we undertook additional analyses, restricting the outcomes to the influenza active period (IAP).

*Propensity score (PS):* As participants at risk of influenza are more likely to be vaccinated, a PS for vaccination was calculated (12).The PS included factors that account for confounding by indication (age, sex, socioeconomic status, smoking status (a dummy category was created for missing smoking data), at-risk conditions i.e. chronic respiratory, heart, kidney, or neurological disease, immunosuppression or diabetes, Charlson comorbidity index (CCI)), and health seeking behaviour (previous pneumococcal and influenza vaccination, and number of primary-care consultations, number of prescribed drugs and number of hospital admissions in the 12 months prior to the 1st September of each year) (12). A separate PS was calculated for each influenza-cycle for every participant using logistic regression, treating vaccination status as the dependent variable.

*Statistical analyses:* Data for all influenza-cycles from every participant were included in a single dataset. Mean, standard deviation (SD), n (%), and standardised difference (*d*) were used to examine covariate balance between exposed and unexposed. Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) with vaccination as exposure of interest, adjusted for calendar year, and included participant identifier as a clustering term to account for within-person correlation. Adjusted vaccine effectiveness (aVE) was calculated as (1 – aHR) x 100. Different analyses were performed to evaluate the consistency of results across different methods of accounting for propensity for vaccination:

[1] PS-adjusted: Vaccination was a time-varying exposure i.e. the time period from day-14 post-vaccination up to end of the influenza-cycle was defined as exposed, whilst the period before this was classed as unexposed. Participants without a vaccination record in the influenza-cycle were considered unexposed for the entire duration. PS distribution in the vaccinated and unvaccinated groups was visually inspected using a histogram (Fig S1). To account for unexpected treatment effects, influenza cycles in which there was no vaccination in the highest decile of PS, and vaccination in the lowest decile of PS were excluded. Sensitivity and sub-group analyses were performed, restricted to people with RA, excluding influenza-cycles with mild immunosuppressive sulfasalazine prescription alone, stratifying by age, and restricting the analysis to those additionally prescribed corticosteroids. Inverse-probability of treatment weighing (IPTW) using the PS was performed as an additional post-hoc sensitivity analysis because covariate adjustment using PS potentially biases the estimation of marginal and conditional HRs in a time-to-event analysis (27).

[2] PS-matched: A 1:1 matched cohort was constructed using greedy nearest neighbour matching without replacement specifying a maximum calliper width of 0.001. The unexposed participants were allocated a pseudo-exposure date of their matched exposed pair. Standardised difference was used to examine covariate balance between the exposed and unexposed participants. Any covariates for which there was imbalance, defined as *d* >0.10 were included as additional covariates in the model (28). Analyses for VE were stratified for pre-IAP, IAP and post-IAP to assess residual confounding. IAPs were defined as per Public Health England reports using information about rates of consultation for ILI, and isolation of the seasonal influenza virus from virological sentinel surveys. Data management and analysis were performed in Stata v14.

**Results** Data for 30,788 participants, 65.66% female, 75.49% with RA, contributing 125,034 influenza-cycles (87,212 vaccinated) were included (Table S2). During the follow-up period, mean (SD) vaccinations received were 3.78 (2.46), 15,355 (49.87%) received all possible vaccination whereas 8,444 (27.43%) missed >1 potential vaccinations (Table S8). 2,942 participants had COPD and contributed 9,909 influenza-cycles. 17,876 vaccinated influenza-cycles were PS-matched 1:1 to unprotected influenza-cycles. The covariate imbalance between exposed and unexposed influenza-cycles reduced following PS-matching (Table 1).

PS-adjusted analysis: IIV reduced risk of hospitalization for pneumonia, COPD exacerbation, all-cause mortality, and death due to pneumonia (Table 2). On restricting follow-up period to IAPs, IIV reduced risk of primary-care consultations for ILI (Table 3). These associations remained significant on trimming-tails (Tables 2-3).

PS-matched analysis: CCI, diabetes, chronic heart and renal diseases had *d* >0.10 between vaccinated and unvaccinated influenza-cycles, and were included as additional covariates. The results of PS-matched analyses were consistent with PS-adjusted analyses with the exception of lack of statistically significant protective effect on ILI during IAPs (Table 4-5).

There was negative association between vaccination and all-cause mortality in pre-IAP and post-IAP, and between vaccination and hospitalization for pneumonia and COPD exacerbations in post-IAP (Table 6).

Sensitivity analyses: IIV protected from hospitalization for pneumonia, COPD exacerbation, and all-cause and pneumonia related mortality in people with RA; when influenza-cycles exposed to sulfasalazine alone were excluded, and in the over 65s (Tables S3-S5). It reduced the risk of hospitalization for pneumonia and death in influenza-cycles preceded by corticosteroid prescriptions, while there was a trend for reduction in hospitalization for COPD exacerbations (Table S6). The associations remained unchanged on IPTW using PS (Table S7).

**Discussion** This study reports that IIV reduces the risk of ILI by 30%, hospitalisation for pneumonia by 39%, hospitalization for COPD exacerbations by 33%, and death due to pneumonia by 52% in immunosuppressed AIRD patients during IAPs. Similar results were observed when follow-up was extended to the entire influenza-cycle except for absence of protective effect on ILI. This observation provides validity to the findings as the protective effect on ILI is not expected to extend beyond IAP. The protective effect of IIV was present when the analysis was restricted to people with greater immune dysfunction e.g. diagnosed with RA, exposed to corticosteroids, prescribed potent DMARDs, age >65 years. We also observed a protective effect of vaccination on all-cause mortality. However, this is likely to be due to residual confounding as IIV associated with significantly reduced all-cause mortality in the pre-IAP when protection is not expected. Similarly, a negative association between vaccination and hospitalization for pneumonia and COPD exacerbations in the post-IAP, raises the possibility that residual confounding may be present for these outcomes as well. This residual confounding could be due to several reasons such as healthy user bias, and selective non-prescribing to people with poor functional status, short life-expectancy e.g. due to terminal illness, or the hospitalized (29).

We performed both PS-adjusted, IPTW, and PS-matched analyses. The findings of PS-matched analysis were consistent with PS-adjusted and IPTW analysis except for a lack of protective effect on ILI in the IAPs. However, this may be related to a >70% reduction in sample-size on PS-matching.

This large population-based study provides data on the effectiveness of IIV in AIRDs. A previous study only included <5% AIRD cases (11), and a recent smaller study reported 35% VE for hospitalisation due to septicaemia, bacteraemia or viremia; and 38% VE for all-cause mortality with IIV in people with RA (30).

Our estimate of VE against ILI is comparable to those observed in healthy adults (3, 5). VE is lower when ILI, a non-specific outcome with considerable imprecision around diagnosis is the outcome rather than laboratory confirmed influenza. ILI includes infections due to influenza and other respiratory viruses, and, as the IIV only targets the influenza virus, VE is lower for ILI than for laboratory confirmed influenza (3, 5). For example, in a RCT, the VE for lab-confirmed influenza was 50% (1997/8) and 86% (1998/9), but VE for ILI was only 10% and 33% respectively (31). ILI cases presenting to GPs in the UK do not routinely undergo virological investigations and data on laboratory confirmed influenza are not available. Observational studies report greater VE for complications of influenza such as pneumonia (27-45%) and death (38-48%) than for ILI (11-13). Our estimates of VE for pneumonia and death are of similar magnitude.

Primary-care consultation for LRTI was selected as an outcome because bacterial chest-infection is a complication of influenza. However, there was no evidence for protective effect on this outcome. This was unexpected, as, IIV associated negatively with hospitalization and death due to pneumonia. It is possible that risk-averse antibiotic prescription to immunosuppressed people in primary-care contributed. Similarly, our finding of no evidence of VE in those aged <45 years could be due to very-few events in this age-group. However, protective effects of IIV in young adults has been demonstrated (5).

Our study demonstrates that IIV is more effective in AIRDs than in diabetes (32). This may be due to the fact that people with diabetes are at a high risk of influenza and its complications due to underlying immune-dysfunction (33, 34). However, VE in our study was comparable to that in healthy adults >65 years in age (3, 13, 35), despite reports of reduced serological response to IIV in the elderly (36).

The humoral and T-cell responses to IIV is maintained in AIRD patient treated with methotrexate or anti-TNFα agents, however, B-cell depletion therapy results in maintained T-cell responses but lower humoral responses and reduces the serological response to vaccination (16, 37-39). A recent RCT demonstrated greater antibody titres when methotrexate was temporarily discontinued post-vaccination (40). However, 74% and 100% of patients in the intervention arm developed protective titres to the H1N1 and H3N2 viruses (40). Prior to this study, there was no evidence that discontinuing methotrexate would boost serological response to IIV, and, patients in the UK continue methotrexate post-vaccination. Thus, our findings together with the results of previous studies suggest that the serological response in immunosuppressed AIRD patients appears sufficient to offer protection from influenza and its complications.

In this study, 69.8% influenza cycles were in receipt of an IIV. This may be due to financial incentives provided by the government to GPs under the Quality and Outcomes Framework to vaccinate people with co-morbidities e.g. diabetes, asthma, or the elderly. AIRDs are not included in this list of co-morbidities although GPs retain discretion on whom to vaccinate. Consequently, only half of immunosuppressed people with AIRDs younger than 65 years receive the IIV, often quite late in course of the flu-season (23).

The effectiveness of IIV varies according to the circulating influenza strain (4). Although, we could not assess VE by influenza strain, our results are encouraging. The findings of this study, together with the results of our previous study demonstrating the safety of IIV in people with AIRDs provides evidence to promote seasonal-flu vaccination in this population (41).

Ideally, vaccine efficacy should be assessed in RCT, and the challenges in assessing VE using observational data are well known. Nevertheless, there are several strengths of this study, which include a large nationally representative sample, use of combination of diagnostic and prescription codes, and inclusion of broad-spectrum of AIRDs. Studies of VE are biased due to confounding by indication and healthy user bias, but we attempted to account for this using PS for vaccination, and the results of IAP-restricted analysis suggest that our findings are confounded for all-cause mortality, and potentially also for hospitalization for pneumonia and COPD exacerbation for which there was evidence of a protective effect in the post-IAP. In this study, analyses were undertaken in data from all nine influenza-cycles included in a single dataset. This *a priori* approach gave a more powerful analysis and increased precision for less common outcomes. Sensitivity and subgroup analyses confirmed protective effects in presence of greater immunosuppression. Finally, the results were consistent across PS-adjusted, IPTW using PS, and PS-matched analyses, providing internal validity.

However, this study has several limitations. We merged data from multiple influenza-cycles and provide a single VE estimate for each outcome. However, we accounted for within-person correlations, and report robust standard errors. Penicillamine and gold were excluded from the DMARD list, however, they are rarely prescribed nowadays. Vaccinations occurring outside GP surgery may not be recorded in CPRD resulting in misclassification of vaccinated cycles as unvaccinated. However, this biases the results towards null rather than inflate VE estimates given our findings. Additionally, as data on prescription of biological agents are not recorded in the CPRD, we were unable to assess their impact on VE. However, a proportion of people included in the study are expected to be treated with biologics. Similarly, exclusion of the 2009-2010 flu-season implies that our results cannot be generalized to pandemic influenza. Although we controlled for confounding, unmeasured confounding and healthy user bias could have inflated VE (29). Finally, VE estimates from observational studies does not equate to vaccine efficacy at population level. This is due to covariate imbalance in PS-adjusted analysis that cannot be entirely accounted for by covariate adjustment, and, the fact that PS-matched analysis is restricted to a sample that differs from the entire population. However, it is ethically challenging to justify RCT of vaccination in this at-risk population.

In conclusion, IIV prevents respiratory morbidity and mortality in immunosuppressed AIRD patients. Although the VE estimates reported here may be overestimated for hospitalization and mortality outcomes given the observational study-design, people with AIRDs should be informed of the benefits of vaccination and offered IIV annually.

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**Author Contribution:** AA conceived the idea for the study and all authors planned the study collaboratively. AA, MJG, GN developed the analysis plan, data analysis was undertaken by GN and supervised by MJG and AA. JVT and PM provided influenza specific input and advised on data analysis plan. CDM provided primary care input. AA together with GN wrote the first draft of the manuscript. All authors reviewed the results and critically reviewed the manuscript for intellectual content. All authors approved the final version of the manuscript.

**Conflicts of interest:** C.D.M. 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. J.S.N.-V.-T. is on secondment to the Department of Health and Social Care, England; the views expressed in this manuscript do not represent the official position of the Department of Health and Social Care or any of its agencies. W.Z. has received honoraria from AstraZeneca and Grunenthal and speaker fees from Biobarica and Hisun unrelated to this work. A.A. has received departmental research grants from AstraZeneca and Oxford Immunotech and speaker bureau fees from Menarini and scientific meeting attendance support from Pfizer unrelated to this work. M.D. has attended ad hoc paid advisory boards on osteoarthritis or gout for AstraZeneca, Grunenthal, Mallinckrodt and Roche and is an Investigator in an AstraZeneca funded, investigator-led, non-drug study (the ‘Sons of Gout’ study). P.M. is an employee of Medicines and Healthcare Products Regulatory Agency (MHRA) but MHRA did not play any role in the conduct or reporting of this study. All other authors have declared no conflicts of interest.

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|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Entire cohort | | | PS matched sample | | |
|  | Vaccinated  (n=87,212) | Unvaccinated  (n=37822) | *d*1 | Vaccinated  (n=17,876) | Unvaccinated  (n=17,876) | *d*1 |
| Continuous covariates; mean (SD) |  |  |  |  |  |  |
| Age | 64.13 (12.76) | 55.88 (13.64) | 0.625 | 58.69 (13.39) | 58.06 (13.92) | 0.047 |
| Charlson’s comorbidity index | 1.34 (1.58) | 0.75 (1.23) | 0.415 | 1.16 (1.57) | 0.92 (1.37) | 0.162 |
| Index of Multiple deprivation | 3.12 (1.42) | 3.16 (1.41) | -0.032 | 3.15 (1.41) | 3.16 (1.41) | -0.004 |
| Number of prescriptions± | 3.01 (7.13) | 2.81 (4.88) | 0.034 | 2.95 (9.33) | 2.83 (4.78) | 0.015 |
| Number of consultations± | 19.92 (12.35) | 15.39 (10.91) | 0.389 | 17.24 (11.81) | 17.08 (11.37) | 0.014 |
| Number of hospitalisations± | 0.15 (0.62) | 0.12 (0.57) | 0.040 | 0.19 (0.72) | 0.13 (0.57) | 0.100 |
| Categorical covariates; n (%) |  |  |  |  |  |  |
| Male | 28,495 (32.67) | 13,430 (35.51) | -0.060 | 6,559 ( 36.69) | 5,894 (32.97) | 0.078 |
| Home visit | 709 (0.81) | 186 (0.49) | 0.030 | 180 (1.01) | 95 (0.53) | 0.055 |
| Current smoking | 13,300 (15.25) | 8,656 (22.89) | -0.195 | 4,018 (22.48) | 3,807 (21.30) | 0.029 |
| Previous influenza vaccination | 77,419 (88.77) | 8,787 (23.23) | 1.758 | 8,608 (48.15) | 8,609 (48.16) | -0.0002 |
| Previous pneumococcal vaccination | 62,998 (72.24) | 9,214 (24.36) | 1.092 | 7,520 (42.07) | 7,327 (40.99) | 0.022 |
| Diabetes | 10,509 (12.05) | 1,805 (4.77) | 0.265 | 1,786 (9.99) | 1,197 (6.70) | 0.119 |
| Immunosuppression | 921 (1.06) | 305 (0.81) | 0.026 | 241 (1.35) | 150 (0.84) | 0.049 |
| Chronic kidney disease | 12,854 (14.74) | 2,780 (7.35) | 0.237 | 2,276 (12.73) | 1,634 (9.14) | 0.115 |
| Chronic respiratory disease | 19,121 (21.92) | 5,205 (13.76) | 0.214 | 3,430 (19.19) | 2,986 (16.70) | 0.065 |
| Chronic heart disease | 8,208 (9.41) | 1,292 (3.42) | 0.246 | 1,352 (7.56) | 863 (4.83) | 0.113 |
| Asplenia | 34(0.04) | 26 (0.07) | -0.013 | 11 (0.06) | 7 (0.04) | 0.009 |

Table 1: Covariate balance before and after propensity score (PS) matching

1Standardised difference; ± In previous 12 months

Table 2: Inactivated influenza vaccine effectiveness in people with AIRDs using follow-up data from the entire influenza-cycle: propensity score adjusted analysis

| **Outcomes** | **Vaccinated** | **Event rate (95% CI)/ 1,000 person-years** | **Unadjusted HR (95% CI)** | **Adjusted HR1**  **(95% CI)** | **Adjusted HR2 (95% CI)** | **Adjusted VE3**  **% (95% CI)** |
| --- | --- | --- | --- | --- | --- | --- |
| Primary care consultation for LRTI requiring antibiotics | No | 78.02 (75.59 to 80.53) | 1.00 | 1.00 | 1.00 | - |
| Yes | 100.97 (98.53 to 103.46) | 1.41(1.34 to 1.49) | 1.07 (1.01 to 1.13) | 1.04 (0.97 to 1.11) | -4 (-11 to 3) |
| Primary care consultation for ILI | No | 6.96 (6.27 to 7.73) | 1.00 | 1.00 | 1.00 | - |
| Yes | 7.09 (6.48 to 7.75) | 0.91(0.78 to 1.06) | 0.91 (0.74 to 1.12) | 0.89 (0.70 to 1.13) | -11 (-13 to 30) |
| Primary care consultation for COPD exacerbation | No | 240.89 (222.47 to 260.84) | 1.00 | 1.00 | 1.00 | - |
| Yes | 275.45 (262.09 to 289.48) | 1.09 (0.94 to 1.27) | 0.96 (0.83 to 1.12) | 0.93 (0.79 to 1.10) | 7 (-21 to 10) |
| Hospitalisation for pneumonia | No | 17.03 (15.59 to 18.60) | 1.00 | **1.00** | **1.00** | - |
| Yes | 20.37 (18.98 to 21.86 | 1.29 (1.12 to 1.48) | **0.59 (0.51 to 0.69)** | **0.69 (0.58 to 0.83)** | **31 (17 to 42)** |
| Hospitalisation for COPD exacerbation | No | 109.42 (93.85 to 127.58) | 1.00 | **1.00** | **1.00** | **-** |
| Yes | 88.74 (79.46 to 99.10) | 0.78 (0.57 to 1.05) | **0.59 (0.44-0.80)** | **0.65 (0.46 to 0.93)** | **35 (7 to 54)** |
| All cause death | No | 18.75 (17.59 to 19.99) | 1.00 | **1.00** | **1.00** | **-** |
| Yes | 21.77 (20.69 to 22.91) | 1.10 (1.00 to 1.20) | **0.52 (0.47 to 0.59)** | **0.66 (0.57 to 0.75)** | **34 (25 to 43)** |
| Deaths due to pneumonia | No | 5.33 (4.56 to 6.24) | 1.00 | **1.00** | **1.00** | **-** |
| Yes | 5.74 (5.03 to 6.56) | 1.08 (0.85 to 1.35) | **0.47 (0.35 to 0.63)** | **0.67 (0.47 to 0.96)** | **33 (53 to 4)** |

1 **Model 1**: Adjusted for propensity score for IIV and year. **2Model 2:** Adjusted for propensity score for IIV and year with PS trimmed tails 3VE: Vaccine effectiveness from Model 2.

Table 3: Inactivated influenza vaccine effectiveness in people with AIRDs using data restricted to influenza-active periods: propensity score adjusted analysis

| **Outcomes** | **Vaccinated** | **Event rate (95% CI)/**  **1,000 person-years** | **Unadjusted HR**  **(95% CI)** | **Adjusted HR1**  **(95% CI)** | **Adjusted HR2**  **(95% CI)** | **Adjusted VE3**  **% (95% CI)** |
| --- | --- | --- | --- | --- | --- | --- |
| Primary care consultation for LRTI requiring antibiotics | No | 86.17 (82.53 to 89.96) | 1.00 | 1.00 | 1.00 | - |
| Yes | 114.43 (111.30 to 117.65) | 1.38 (1.30 to 1.46) | 1.05 (0.98 to 1.13) | 1.04 (0.96 to 1.13) | -4 (-13 to 4) |
| Primary care consultation for ILI | No | 9.23 (8.12 to 10.51) | 1.00 | 1.00 | 1.00 | - |
| Yes | 7.99 (7.21 to 8.85) | 0.85 (0.72 to 1.01) | **0.75 (0.60 to 0.95)** | **0.70 (0.54 to 0.92)** | **30 (8 to 46)** |
| Primary care consultation for COPD exacerbation | No | 275.20 (244.47 to 309.80) | 1.00 | 1.00 | 1.00 | - |
| Yes | 271.62 (255.84 to 288.37) | 0.98 (0.83 to 1.15) | 0.89 (0.74 to 1.06) | 0.87 (0.72 to 1.05) | 13 (-5 to 28) |
| Hospitalisation for pneumonia | No | 17.51 (15.46 to 19.82) | 1.00 | 1.00 | 1.00 | - |
| Yes | 22.15 (20.41 to 24.04) | 1.25 (1.07 to 1.46) | **0.54 (0.45 to 0.64)** | **0.61 (0.50 to 0.75)** | **39 (25 to 50)** |
| Hospitalisation for COPD exacerbation | No | 122.17 (96.97 to 153.91) | 1.00 | 1.00 | 1.00 | **-** |
| Yes | 98.52 (86.82 to 111.81) | 0.74 (0.53 to 1.03) | **0.58 (0.42 to 0.82)** | **0.67 (0.46 to 0.99)** | **33 (1 to 54)** |
| All cause death | No | 21.82 (20.06 to 23.74) | 1.00 | 1.00 | 1.00 | **-** |
| Yes | 22.23 (20.91 to 23.64) | 1.02 (0.91 to 1.13) | **0.47 (0.41 to 0.54)** | **0.56 (0.48 to 0.65)** | **44 (35 to 52)** |
| Deaths due to pneumonia | No | 6.44 (5.13 to 7.90) | 1.00 | 1.00 | 1.00 | **-** |
| Yes | 6 (5.13 to 7.02) | 0.94 (0.72 to 1.22) | **0.37 (0.27 to 0.51)** | **0.48 (0.33 to 0.71)** | **52 (29 to 67)** |

Table 4: Inactivated influenza vaccine effectiveness in people with AIRDs using follow-up data from the entire influenza-cycle: propensity score matched analysis

| **Outcomes** | **Vaccinated** | **Event rate (95% CI)/ 1,000 person-years** | **Model 1**  **HR (95% CI)1** | **Model 2**  **HR (95% CI)2** | **Adjusted VE %**  **(95% CI)2** |
| --- | --- | --- | --- | --- | --- |
| Primary care consultation for LRTI requiring antibiotics | No | 78.36 (73.40 to 83.66) | 1.00 | 1.00 | - |
| Yes | 92.41 (87.30 to 97.82) | 1.18 (1.08 to 1.29) | 1.11 (1.02 to 1.22) | -11 (-2 to -22) |
| Primary care consultation for ILI | No | 8.41 (6.92 to 10.22) | 1.00 | 1.00 | - |
| Yes | 8.05 (6.67 to 9.71) | 0.97 (0.74 to 1.27) | 0.91 (0.69 to 1.22) | 9 (-22 to 31) |
| Primary care consultation for COPD exacerbation | No | 268.07 (224.64 to 319.88) | 1.00 | 1.00 | - |
| Yes | 275.42 (242.56 to 312.73) | 1.02 (0.82 to 1.27) | 1.03 (0.82 to 1.29) | -3 (-29 to 18) |
| Hospitalisation for pneumonia | No | 25.44 (21.91 to 29.54) | 1.00 | 1.00 | **-** |
| Yes | 15.81 (13.21 to 18.93) | **0.62 (0.49 to 0.78)** | **0.50 (0.39 to 0.63)** | **50 (37 to 61)** |
| Hospitalisation for COPD exacerbation | No | 154.37 (115.26 to 206.75) | 1.00 | 1.00 | **-** |
| Yes | 78.80 (58.44 to 106.26) | **0.50 (0.34 to 0.75)** | **0.46 (0.31 to 0.70)** | **54 (30 to 69)** |
| All cause death | No | 32.22 (29.17 to 35.59) | 1.00 | 1.00 | **-** |
| Yes | 18.94 (16.76 to 21.40) | **0.59 (0.50 to 0.69)** | **0.45 (0.38 to 0.53)** | **55 (47 to 62)** |
| Deaths due to pneumonia | No | 9.10 (7.09 to 11.67) | 1.00 | 1.00 | **-** |
| Yes | 4.88 (3.54 to 6.74) | **0.54 (0.36 to 0.81)** | **0.43 (0.29 to 0.66)** | **57 (34 to 71)** |

1 Adjusted for year and including patient ID as a clustering term. 2 As in model 1, and, additionally adjusted for age, Charlson comorbidity index, diabetes, chronic heart disease and chronic kidney disease.

Table 5: Inactivated influenza vaccine effectiveness in people with AIRDs using follow-up data from influenza-active periods: propensity score matched analysis

| **Outcomes** | **Vaccinated** | **Event rate (95% CI)/ 1,000 person-years** | **Model 1**  **HR (95% CI)1** | **Model 2**  **HR (95% CI) 2** | **Adjusted VE**  **% (95% CI)2** |
| --- | --- | --- | --- | --- | --- |
| Primary care consultation for LRTI requiring antibiotics | No | 89.45 (83.09 to 96.31) | 1 | 1 | - |
| Yes | 101.81 (95.38 to 108.69) | 1.14 (1.03 to 1.26) | 1.08 (0.98 to 1.20) | -8 (-20 to 2) |
| Primary care consultation for ILI | No | 10.61 (8.59 to 13.11) | 1 | 1 | - |
| Yes | 8.67 (6.95 to 10.80) | 0.83 (0.61 to 1.12) | 0.79 (0.57 to 1.08) | 21 (-8 to 43) |
| Primary care consultation for COPD exacerbation | No | 283.66 (232.23 to 346.47) | 1 | 1 | - |
| Yes | 273.01 (234.91 to 317.30) | 0.95 (0.74 to 1.22) | 0.97 (0.75 to 1.25) | 3 (-25 to 25) |
| Hospitalisation for pneumonia | No | 27.95 (23.50 to 33.23) | 1 |  | **-** |
| Yes | 18.14 (14.79 to 22.26) | **0.64 (0.49 to 0.84)** | **0.52 (0.39 to 0.69)** | **48 (31 to 61)** |
| Hospitalisation for COPD exacerbation | No | 161.41 (114.75 to 227.04) | 1 | 1 | **-** |
| Yes | 85.03 (60.13 to 120.23) | **0.52 (0.32 to 0.82)** | **0.50 (0.30 to 0.78)** | **50 (22 to 70)** |
| All cause death | No | 36.25 (32.34 to 40.63) | 1 | 1 | **-** |
| Yes | 18.80 (16.19 to 21.83) | **0.52 (0.43 to 0.63)** | **0.41 (0.33 to 0.50)** | **59 (50 to 67)** |
| Deaths due to pneumonia | No | 11.51 (9.00 to 15.07) | 1 | **1** | **-** |
| Yes | 5.11 (3.48 to 7.50) | **0.44 (0.28 to 0.71)** | **0.37 (0.23 to 0.59)** | **63 (41 to 77)** |

1 Adjusted for year and including patient ID as a clustering term. **2**As in model 1, and, additionally adjusted for age, Charlson comorbidity index, diabetes, chronic heart and chronic kidney disease.

Table 6: Inactivated influenza vaccine effectiveness in people with AIRDs in the pre-influenza, influenza and post-influenza-active periods: propensity score matched analysis

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **Adjusted HR (95% CI)\*** | | |
|  | **Pre-IAP** | **IAP** | **Post-IAP** |
| Primary care consultation for LRTI requiring antibiotics | 1.24 (0.55 to 2.81) | 1.08 (0.98 to 1.20) | 1.19 (0.98 to 1.44) |
| Primary care consultation for ILI | 3.02 (0.32 to 28.22) | 0.79 (0.57 to 1.08) | 1.49 (0.71 to 3.16) |
| Primary care consultation for COPD exacerbation | 1.20 (0.29 to 5) | 0.97 (0.75 to 1.25) | 1.46 (0.89 to 2.38) |
| Hospitalisation for pneumonia | 0.19 (0.02 to 1.66) | 0.52 (0.39 to 0.69) | 0.50 (0.30 to 0.83) |
| Hospitalisation for COPD exacerbation | -/- | 0.50 (0.30 to 0.78) | 0.51 (0.25 to 1.05) |
| All cause death | 0.11 (0.02 to 0.57) | 0.41 (0.33 to 0.50) | 0.67 (0.48 to 0.93) |
| Deaths due to pneumonia | -/- | 0.37 (0.23 to 0.59) | 0.88 (0.33 to 2.35) |

**\***Adjusted for year, age, Charlson comorbidity index, diabetes, chronic heart disease and chronic kidney disease and including patient ID as a clustering term (Model 2). -/- No outcomes.