Title: Predictors and temporal trend of flu vaccination in auto-immune rheumatic diseases in the UK: a nationwide prospective cohort study

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Objectives To [1] examine temporal trend in uptake of seasonal influenza vaccine (SIV) in the UK, [2] explore disease and demographic factors associated with vaccination.

Methods 32,751 people with auto-immune rheumatic diseases (AIRDs) prescribed disease modifying anti-rheumatic drugs (DMARDs) between2006 and 2016 were identified from the Clinical Practice Research Datalink. The proportion vaccinated between 01/September of one year and 31/March of next year was calculated and stratified by age, other indications for vaccination, AIRD type, and number of DMARDs prescribed. Stata and Joinpoint regression programs were used.

Results SIV uptake was high in those aged ≥65 years (82.3% and 80.7% in 2006-07 and 2015-16 respectively). It was significantly lower in other age groups, but improved over time with 51.9% and 61.9% in the 45-64 year age group, and 32.3% and 50.1% in the <45 year age group being vaccinated in 2006-07 and 2015-16 respectively. While 64.9% of the vaccinations in those ≥65 years old occurred by 3rd November, in time to mount a protective immune response before the influenza activity becomes substantial in UK, only 38.9% in the 45-64 year and 26.2% in the <45 year age group without any other reason for vaccination received SIV by this date. Women, those with additional indications for vaccination, on multiple DMARDs and with SLE were more likely to be vaccinated.

Conclusion SIV uptake is low in the under 65s, and the majority of them are not vaccinated in time. Additional effort is required to promote timely uptake of SIV in this population.

Keywords: rheumatoid arthritis, influenza, vaccination, disease modifying anti-rheumatic drugs

Introduction

Autoimmune rheumatic diseases (AIRDs) such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) associate with increased risk of influenza and its complications (1-4). This may be compounded by the use of potent disease modifying anti-rheumatic drugs (DMARDs) and biological agents (5-8). The European League Against Rheumatism and American College of Rheumatology recommend that people with AIRDs receive seasonal influenza vaccine (SIV) before commencing a DMARD, and annually thereafter(9, 10). In the UK, SIV is recommended for people older than 65 years, the immunosuppressed, and those at risk of influenza or its complications (11), while universal vaccination is recommended for adults in the USA (12).

The uptake of SIV in people with RA, the commonest AIRD is suboptimal. For instance, only 23.5% people with RA in the multi-national COMORA cohort received SIV with substantial global variation (range 1-66.2%)(13). Higher self-reported vaccination rates (range 37-77%) were reported in small (n=71-155) hospital based surveys from the UK (14-19). Similar small (n=100-137) single-centre hospital based studies from other European hospitals reported uptakes of 20-48% (20-22). A previous study using data from the Clinical Practise Research Datalink (CPRD) reported that 80% of incident RA cases on DMARDs receive at least one SIV over a mean 5 year period, with 21-31% of the under 65s and 55-76% of those 65 years in age or older receiving all expected vaccinations (23) This and other small single-centre studies mostly include people with RA, and a large study examining the uptake of SIV in a range of AIRDs has not been performed. Similarly, it is not known whether the uptake of SIV is improving, and, if people with AIRDs are vaccinated in

time, i.e. at least two weeks before commencement of influenza activity to allow time for seroconversion.

The overall aim of this study was to determine the uptake of SIV in people with AIRDs treated with DMARDs. The objectives of this study were to examine [1] the temporal trend in SIV uptake between 2006-7 and 2015-16 influenza seasons, [2] the proportion vaccinated in time before the seasonal flu virus circulates in the community, [3] factors associated with receiving SIV, and [4] regional variation in vaccination in people with AIRDs treated with DMARDs.

Methods

Data source: CPRD is a longitudinal database of the UK's general practice (GP) medical records incepted in 1987. In July 2013, 684 general practices were contributing data to CPRD for over 11 million anonymised patients (24). People registered in the CPRD are representative of the UK general population in terms of age, sex and ethnicity. CPRD includes information on demographics, lifestyle factors, diagnoses, medications, results of investigations and examinations, referral to hospitals, and prescribed medications. Diagnoses in CPRD are recorded using Read codes, a coded dictionary of clinical terms. The data undergo thorough quality checks and are of a reliable research standard with a high validity of recorded diagnoses, including a median proportion of cases with a confirmed diagnosis of 89% for 183 different conditions including chronic auto-immune diseases(25). Validation studies also confirm high levels of completeness of clinical, diagnostic and prescription data (25).

This study was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare Regulatory Authority (MHRA) (Reference number: 16_288R).

Study population: Participants having ≥1 Read codes for RA, SLE or spondyloarthropathy (SpA, defined as psoriatic arthritis, reactive arthritis, inflammatory bowel disease associated arthritis, or ankylosing spondylitis) and at least one prescription of methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, mycophenolate mofetil or tacrolimus between 1st April 2006 and 31st March 2016 were included.

Identification of participants: Previously published Read code lists were used to identify people with RA (26, 27). Read code lists to identify participants with SLE, reactive arthritis, inflammatory bowel disease associated arthritis, ankylosing spondylitis or psoriatic arthritis were developed by GN (Post-Doctoral Research Fellow) AA (Rheumatologist) and CDM (General Practitioner). Similarly, product code lists were developed to identify prescriptions of methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, mycophenolate mofetil and tacrolimus.

Study entry: Latest of DMARD prescription date, current registration date, or 1st April 2006.

Study exit: Earliest of transfer out date, date of death, date of last data collection from the participants' GP surgery or 31st March 2016

Cohort building: The study period 1st April 2006 to 31st March 2016 was partitioned into 10 one-year seasonal episodes, beginning on April 1st of one year, and ending on March of the subsequent year. Ten separate cohorts for each influenza season were constructed, comprising people with AIRDs prescribed DMARD(s). Inclusion criteria were age ≥18 years at the start of the cohort, contributing data on the 1st September of that year (start of influenza season) with ≥3-month continuous registration at their current GP surgery prior to this date, and DMARD prescription in this period. The three-month time-lag was to allow the GP surgery time to include patients in any practice level at-risk register for influenza vaccination.

Primary outcome: SIV administration was the primary outcome and was defined using published product and Read code lists . For participants who had more than one entry for SIV administration in an influenza season, the first vaccination record was considered valid. Vaccination status of participants who contributed data to

more than one influenza season returned to unvaccinated on 1st April of the subsequent year. Read codes for pandemic influenza vaccine were excluded as this study focussed on temporal trends in SIV uptake.

Secondary outcome: SIV administration by the 3rd November, i.e. 9 weeks from 1st September. This would allow the individual to mount a protective immune response before mid-November when the influenza virus begins to circulate in the UK (11).

Additional indications for SIV administration: Indications for SIV vary between countries. In the UK, SIV is indicated in those older than 65 years, and in those with chronic respiratory, heart, kidney, liver and neurological diseases, immunosuppression or diabetes as they are at a high risk of influenza and its' complications (11). Therefore, for this study, participants were classified as having an additional indication for vaccination if they were at least 65 years old, or had another at-risk condition that mandates SIV administration apart from DMARD prescription at the start of the influenza season. At-risk conditions were defined using Read code lists developed by Costello *et al*. These encompass chronic respiratory diseases, chronic heart diseases, chronic kidney diseases, chronic liver diseases, chronic neurological diseases, diabetes, immunosuppression, and asplenia (23).

Statistical analyses: The percentage and 95% confidence interval (CI) of participants who received SIV between 1st September of one year and 31st March of the next calendar year (i.e. start and end of influenza season) was calculated. This was stratified by age (<45 years, 45-64 years, ≥65 years), presence of other indication for SIV administration, type of AIRD (RA, SLE or SpA), and number of DMARDs prescribed (1 or >1) at annual-cohort entry. Percentage (95%CI) of vaccinations that occurred by the 3rd November of a year was calculated. The

cumulative weekly uptake of SIV, stratified by age-group and presence of other at-risk conditions was plotted using cumulative frequency curves.

Joinpoint analysis was used to determine the temporal trend in SIV uptake between 2006-07 and 2015-16 influenza seasons. This was stratified for age, AIRD type, and at-risk conditions for vaccination (11). Joinpoint uses Bayesian Information Criterion to generate different numbers of joinpoints indicating points in time where trends in SIV uptake change significantly and to fit separate linear trends in each time segment. Annual percentage changes (APC) for each segment, and the overall APC (i.e. without any model fitted) was calculated.

Poisson regression with robust error variance was used to examine the univariate and multivariate associations between age, sex, AIRD type, at risk conditions for vaccination, number of DMARDs prescribed in the preceding 12-months and receiving the SIV. A unique participant identifier was incorporated as a clustering term in the model (28). Incidence rate ratios (IRR) and 95% CI were calculated. This analysis was repeated using data from participants exposed to methotrexate to avoid confounding due to DMARD potency. The uptake of SIV in each geographic regions of the UK during the 2015/2016 season was calculated. Poisson regression was used to examine the univariate and multivariate association between regions and SIV administration, and adjusted for age, sex, AIRD type, number of DMARDs prescribed, and at-risk conditions for influenza or its complications. Data management and analysis were performed in Stata version 14 (StataCorp, College Station, TX, USA).

Results: Data from 32,751 people with AIRDs prescribed ≥1 DMARDs between 1st April 2006 and 31st March 2016 were included. Their mean (SD) age at study entry was 58.17 (14.65) years and 65.70% were female. The mean (SD) follow-up time was 4.37 (3.17) years. Of those included, 24,826 (75.80%) had RA, 6,671(20.37%) had SpA, and 1,254 (3.83%) had SLE.

The overall uptake of SIV increased by 2.67% (2.0%-3.4%, p<0.01) per year from 2006 to 2013 and remained stable between 2013 and 2015 (Table 1, Figure 1, Table S1). On stratified analysis, the SIV uptake did not increase in the over 65s (Table S1). However, it increased in people aged between 45-64 years, and in those younger than 45 years (Table S1).

Just under half of all vaccinations (49.89%; 95%CI (49.64%-50.14%) occurred by November 3rd, i.e. in time before substantial influenza activity in the UK. The proportion (95% CI) of vaccinations that happened in time was 64.93 (64.57-65.30)% in the over 65s. It was 52.85 (52.01-53.70)% and 38.89 (38.47-39.31)% in those aged 45-64 years with and without another at-risk condition for flu-vaccination respectively, and 33.22 (31.21-35.32)% and 26.18 (25.54-26.84) % in those aged 45 years or younger, with and without another at-risk condition for flu-vaccination respectively (Figure 2). The uptake of SIV was significantly higher in those with an additional indication for vaccination (Figures 3, 4; Table S2, S3).

Increasing age, female sex, presence of other at-risk conditions, and prescription of >1 DMARD were independently associated with SIV administration (Table 2). After adjusting for age, sex, study year, other at-risk conditions, and number of DMARDs prescribed, , SLE was significantly more, and SpA significantly less likely to be associated with vaccination than RA (Table 2). These results remained unchanged when the analysis was restricted to influenza seasons with exposure to methotrexate

at the annual-cohort entry, except for a lack of association between SLE and vaccination status (Table S4).

Geographic variation in SIV uptake was assessed in the latest flu season. In the 2015/2016 influenza season, the uptake of SIV ranged between 62.58% in London to 77.74% in Scotland (Table S5). Using Poisson regression adjusted for age, sex, and at-risk condition for flu vaccination, a statistically significant increased SIV uptake was observed in Northern Ireland (aIRR (95%CI) 1.16 (1.03-1.30) and Scotland (aIRR 1.15 (1.05-1.27) compared with the South West of England (Table S5). The South West of England was used as the reference as this region had the median SIV uptake among all regions of the UK,

Discussion This nationwide primary-care study of SIV uptake over 10 years in people with AIRDs treated with DMARDs demonstrates an increase in uptake of SIV driven by improving uptake in people aged under 65 years. However, despite this, the uptake of SIV in individuals younger than 45 years, and in those aged between 45-64 years without an at risk condition for vaccination remained significantly lower than the recommended 75% target of flu vaccination coverage for people with at-risk conditions(29-31). Additionally, most flu vaccinations in the under 65s did not occur in time i.e., 2 weeks before the flu virus begins to circulate.

It is not possible to compare these findings to those of previous studies, since, to our knowledge, this is the first study to assess temporal trend in uptake of SIV among AIRDs and to compare uptake between different AIRDs. However, when compared to the national flu vaccination rates in England, the vaccine uptake in the under 65s in our study was higher in the year 2006-07 (national SIV uptake: 42.10% vs. SIV uptake in study: 44.80%) and improved further (in the year 2014-15 national SIV uptake: 50.30% vs. SIV uptake in study: 63.73%) (11). A similar trend was observed for vaccine uptake in the over 65s, with 73.9% and 71.0% people in England receiving SIV in 2006-07 and 2015-16 respectively, compared to 82.3% and 80.7% in our study for the same years. The trend towards a reduction in vaccine uptake in the 2015/16 influenza season observed in this study was mirrored in the nationwide data (11).

The trend of increasing SIV uptake may be explained by greater public awareness, national campaigns, recommendations (9, 10), and efforts of rheumatology multi-disciplinary teams in educating people with AIRDs and their GPs about the need of SIV(14-17). There was a substantial increase in SIV administration in the 2010-11 and 2011-12 flu seasons, especially in the under 65 age group which could be

related to the pandemic flu in the year 2009-10 which increased awareness of flu vaccination.

We observed that the uptake of SIV in those without an additional reason for vaccination has improved over the ten-year period, but is still significantly lower than the uptake in those 65 years or older or with other at-risk conditions (11) This accords with results of previous smaller studies (13-16, 18-23, 32), and may reflect the fact that immunosuppressive DMARDs for which seasonal flu vaccination is indicated is left to individual doctors' clinical judgement which may result in differential vaccine access (11). Thus, more needs to be done to improve SIV uptake in this age group. As flu vaccinations occur in primary care, there is a need to educate people with AIRDs younger than 65 years in age, as well as their GPs about the risks of influenza and its complications in the immunosuppressed(16, 32). Such interventions are likely to increase SIV uptake, as people with AIRDs cite lack of awareness about increased risk of influenza, need for influenza vaccination, and not being offered the vaccine as reasons for not being vaccinated (14-16, 18-20, 22, 32, 33). Strategies to improve flu-vaccination uptake include face-to-face patient education or provision of written educational materials (Odds Ratio (OR)s 1.11-3.33), and financial incentives (OR 2.22) or reminders (ORs 2.03-3.03) directed at healthcare professionals (HCPs) (34). Interestingly, educational outreach/feedback directed at HCPs did not improve uptake of SIV (OR (95%CI) 0.77 (0.72-0.81), whereas improving vaccine access with home visits or free vaccinations did improve the uptake (ORs 1.30-1.98)(34). Other factors such as having a lead HCP responsible for flu-vaccination in a GP surgery, robust IT-systems to identify people at risk of flu and its complications, reminding HCPs about SIV, and sending personal

invitations and reminders, including telephone reminders to patients, associated with improved SIV uptake in a survey of 795 GP surgeries across England (35).

The ideal time for influenza vaccination in the UK is between September and early November, allowing 2 weeks for the immune response to be achieved before influenza activity becomes significant (11). Our results, however, reveal delayed uptake of vaccination, especially in the under 65s and in those without another at-risk condition for receiving SIV. This is contrary to the findings of a claims database study from Germany in which 95% participants who received SIV did so by November(4). Thus, people with AIRDs and their GPs should be especially reminded about SIV in autumn months. (35)

The uptake of SIV was significantly higher in people aged 65 years and over, and was more than the target for vaccination coverage set by the Department of Health, European Council, and the World Health Organisation. This may be driven by the Quality and Outcome Framework which provides financial incentives to GP surgeries for administering flu vaccination to people aged 65 years and over since the 1999-2000 influenza season. It resulted in a substantial increase in vaccination rates within one year (36). Other factors such as a high burden of co-morbidities, and availability of time may also have contributed. A previous study from Germany also demonstrated increasing SIV uptake with increasing age(4).

Our study revealed variations in the uptake of influenza vaccination according to AIRD type, with lower uptake in SpA. This was present on sensitivity analysis, restricting to influenza seasons in which a methotrexate prescription was issued. This suggests that greater effort should be employed to improve vaccination rates in

people with SpA, who are predominantly male and less likely to seek preventive measures.

There are several caveats to our study. Firstly, some flu vaccinations may have been administered in a hospital or at work-place e.g. HCPs. This is unlikely to have a significant impact as SIV is administered predominantly in primary care in the UK, and Read codes that indicate SIV administration outside the GP surgery i.e. in a hospital, place of work, or privately were included in the code list. Moreover, we excluded small vessel vasculitis because of the rarity of its recording in the CPRD (37). Similarly, given their extremely rare use in modern rheumatology practice, we excluded penicillamine and gold prescriptions. Finally, the data on prescription of biological agents is not recorded in the CPRD, and for this reason we cannot compare SIV uptake in those prescribed biological and conventional DMARDs. However, a previous German study did not report higher SIV uptake in people on biological DMARDs compared to conventional DMARDs(4).

There are several strengths of this study which include a large nationally representative sample size, use of a combination of diagnostic Read codes and DMARD prescriptions to identify immunosuppressed people with AIRDs, inclusion of a broad spectrum of AIRDs, and a longitudinal observation period of 10 years. Use of primary care prescription and consultation data minimises the risk of recall bias associated with questionnaire surveys.

In summary, this study demonstrates improving but still low uptake of SIV in people with AIRDs younger than 65 years. Similarly, the majority of people in this age group are vaccinated after the seasonal flu virus begins to circulate. Thus, rheumatologists

and GPs should particularly educate younger people with AIRDs about the need for timely annual seasonal flu vaccination.

Key messages:

- Uptake of seasonal influenza vaccine is low in the absence of additional indications for vaccination.
- Most vaccinations do not occur in time before the flu virus begins to circulate.
- Young age seems to be an important barrier to seasonal influenza vaccination.

Competing Interests Professor Mallen 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. Professor Nguyen-Van-Tam is on secondment to the Department of Health, England. The views expressed in this manuscript do not represent the official position of the Department of Health. Professor Zhang has received honorariums from AstraZeneca and Grunenthal and speaker fees from Biobarica and Hisun unrelated to this work. Dr. Abhishek has received departmental research grants from AstraZeneca and Oxford Immunotech and speaker bureau fees from Menarini unrelated to this work. Professor Doherty has attended ad hoc advisory boards on osteoarthritis or gout for AstraZeneca, Grunenthal, Mallinckrodt and Roche. Professor Doherty is an Investigator in an AstraZeneca funded, investigator-led, non-drug study (the “Sons of Gout” study). Dr. Myles 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.

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Table 1: Total population and percentage (95%CI) administered seasonal influenza vaccine± between 2006 and 2016

Year	Overall	Age ≥65 year	Age 45-64 year at risk condition present	Age 45-64 year at risk condition absent	Age <45 year at risk condition present	Age <45 year at risk condition absent
2006/7	13,805 61.52 (60.71-62.33)	5,658 82.33 (81.31-83.30)	1,054 69.07 (66.21-71.79)	5,078 48.39 (47.01-49.76)	192 46.35 (39.40-53.45)	1,823 30.77 (28.70-32.93)
2007/8	14,663 62.11(61.32-62.89)	6,073 81.67 (80.68-82.63)	1,168 69.43 (66.73-72.01)	5,355 49.23 (47.89-50.56)	191 46.07(39.11-53.19)	1,876 32.62 (30.54-34.78)
2008/9	15,377 64.04 (63.28-64.80)	6,468 81.79 (80.83-82.71)	1,288 71.12 (68.58-73.53)	5,849 51.76 (50.43-53.08)	209 48.33 (41.61-55.11)	1,923 36.40 (34.28-38.58)
2009/10	15,904 64.60 (63.85-65.34)	6,775 80.80 (79.84-81.72)	1,378 69.38 (66.89-71.76)	5,572 53.02 (51.70-54.32)	218 49.08 (42.49-55.71)	1,961 39.93 (37.78-42.12)
2010/11	17,013 67.10 (66.39-67.80)	7,170 81.72 (80.80-82.59)	1,475 73.02 (70.69-75.22)	6,029 57.62 (56.37-58.86)	236 58.05 (51.64-64.20)	2,103 41.32 (39.23-43.44)
2011/12	16,430 71.23 (70.53-71.92)	7,229 82.99 (82.10-83.83)	1,447 76.36 (74.11-78.48)	5,643 62.77 (61.50-64.02)	219 56.62 (49.96-63.05)	1,892 49.31(47.06-51.57)
2012/13	16,563 72.30 (71.61-72.78)	7,409 83.53 (82.67-84.36)	1,489 78.84 (76.70-80.85)	5,587 63.24 (61.96-64.49)	224 61.61 (55.06-67.76)	1,854 50.76 (48.48-53.03)
2013/14	15,879 72.35 (71.65-73.04)	7,236 84.41 (83.56-85.23)	1,571 76.38 (74.22-78.42)	5,140 62.24 (60.90-63.55)	223 60.09 (53.51-66.33)	1,709 49.62 (47.25-51.99)
2014/15	14,593 72.41 (71.68-73.13)	6,784 82.40 (81.47-83.29)	1,373 77.57 (75.28-79.70)	4,786 63.66 (62.29-65.02)	178 57.87 (50.47-64.92)	1,472 51.77 (49.21-54.31)
2015/16	12,252 69.38 (68.55-70.19)	5,717 80.74 (79.70-81.74)	1,114 72.26 (69.56-74.81)	4,049 59.08 (57.55-60.58)	135 60.00(51.49-67.94)	1,237 48.99 (46.21-51.78)

± Vaccination period taken as from 1st September to 31st March.

Table 2: Disease and demographic characteristics associated with seasonal influenza vaccine administration

	Crude IRR (95% CI)	Adjusted IRR (95% CI) *
Age (years)		
<45	1	1
45-64	1.35 (1.32-1.39)	1.33 (1.29-1.36)
≥65	1.81 (1.77-1.86)	1.73 (1.68-1.77)
Sex		
Male	1	1
Female	1.04 (1.03-1.06)	1.03 (1.02-1.05)
AIRD type		
Rheumatoid arthritis	1	1
Systemic lupus erythematosus	0.92 (0.88-0.95)	1.06 (1.02-1.10)
Seronegative spondyloarthropathy	0.81 (0.80-0.83)	0.93 (0.92-0.95)
Number of DMARDs		
1	1	1
≥2	1.07 (1.05-1.09)	1.08 (1.07-1.10)
Other influenza at-risk conditions		
Absent	1	1
Present	1.23 (1.22-1.25)	1.12 (1.11-1.13)

*adjusted for study year and other variables in the table

Figure legends

Figure 1: Percentage of people with autoimmune rheumatic diseases on disease modifying anti-rheumatic drugs vaccinated in each flu season from 2006 to 2016.

Figure 2: Weekly cumulative seasonal influenza vaccine uptake between the 1st September and 31st March in all influenza seasons. Overall vaccine uptake was significantly higher in the over 65s ($p<0.001$) and, 45-64 ($p<0.001$) year age group with another at-risk condition for vaccination than the 45-64 year age group without another at-risk condition for vaccination (reference group). The latter had statistically similar vaccination rates as people <45 years in age with another at-risk condition for vaccination ($p=0.267$), while those younger than 45 years without another at-risk condition for vaccination had significantly lower vaccination uptake than the reference group ($p<0.001$).

Figure 3: Percentage of people with autoimmune rheumatic diseases (AIRD) on disease modifying anti-rheumatic drugs vaccinated in each flu season from 2006 to 2016 according to individual AIRD.

Figure 4: Percentage of people with autoimmune rheumatic diseases (AIRD) on disease modifying anti-rheumatic drugs vaccinated in each flu season from 2006 to 2016 according to number of different types of DMARDs at the start of flu season.

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Figure 1: Percentage of people with autoimmune rheumatic diseases on disease modifying anti-rheumatic drugs vaccinated in each flu season from 2006 to 2016.

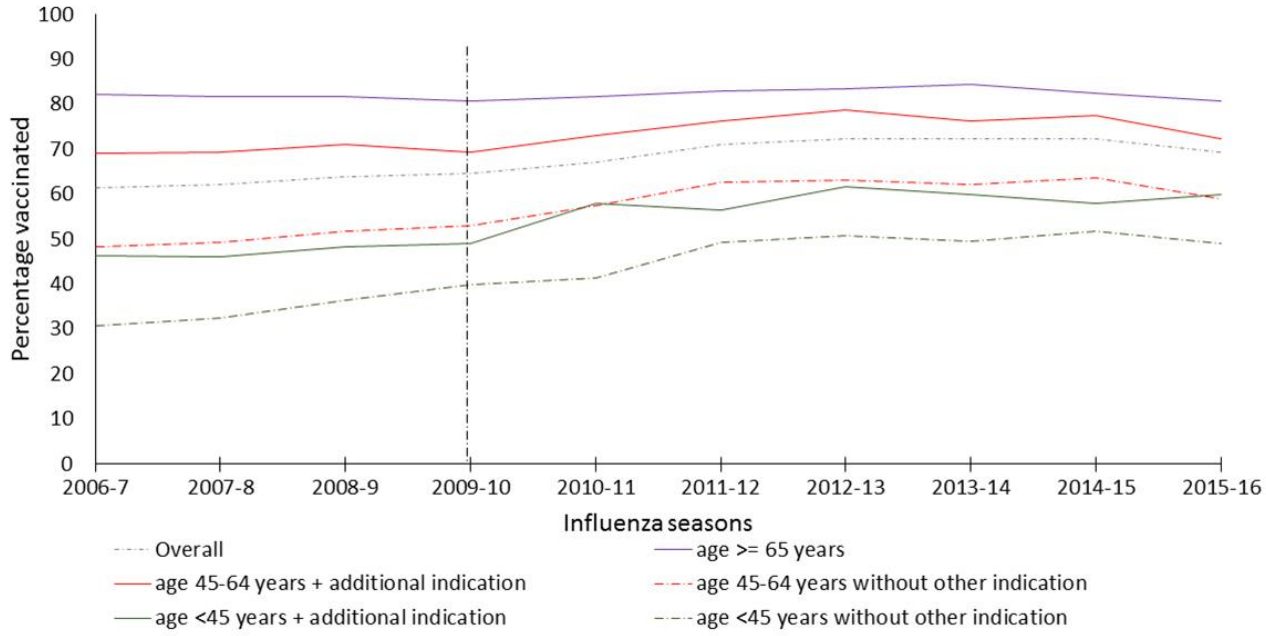


Figure 2: Weekly cumulative seasonal influenza vaccine uptake between the 1st September and 31st March in all influenza seasons.

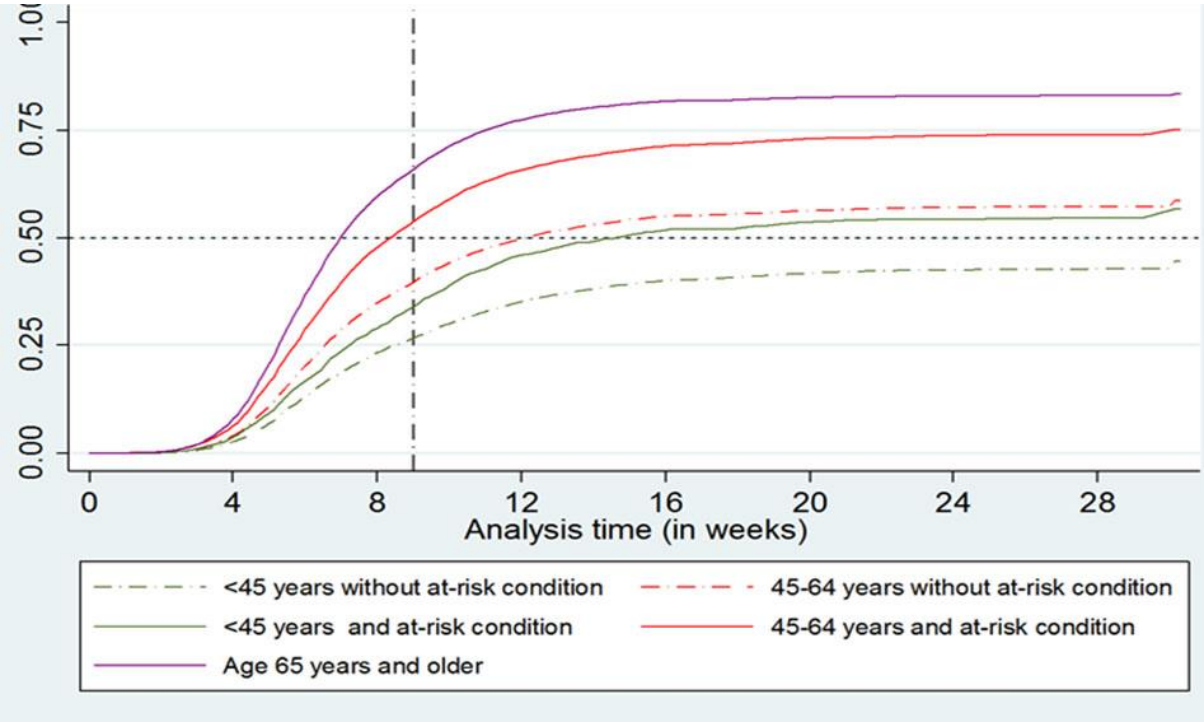


Figure 3: Percentage of people with AIRDs on DMARDs vaccinated in each flu season from 2006 to 2016 according to individual AIRD.

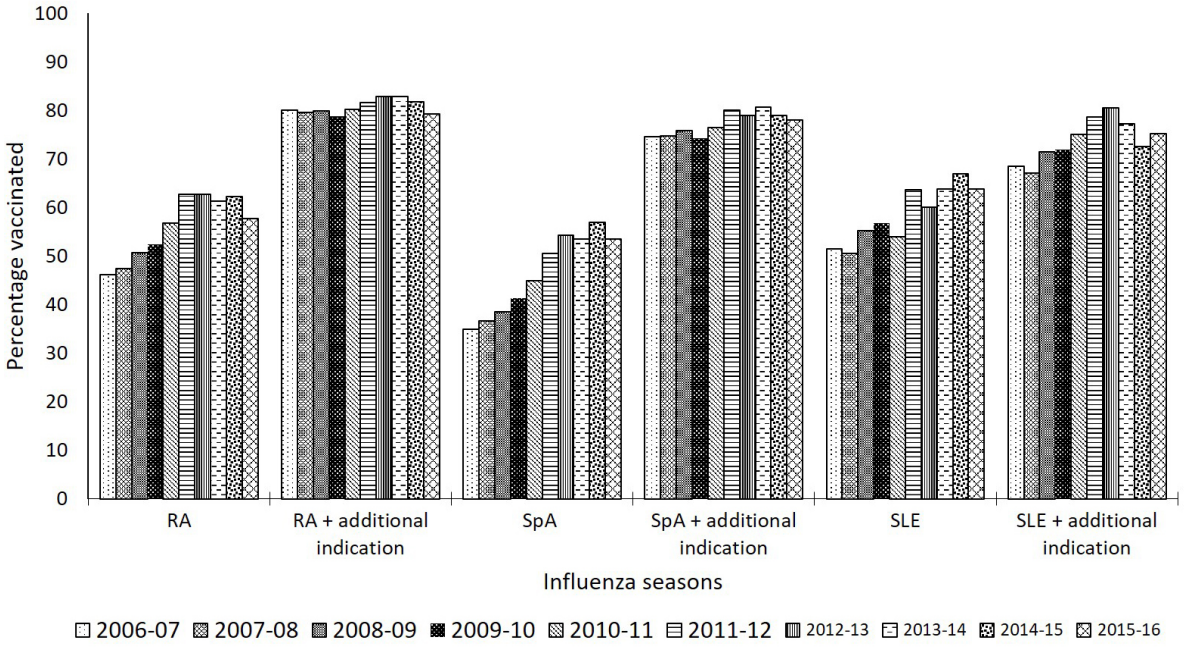
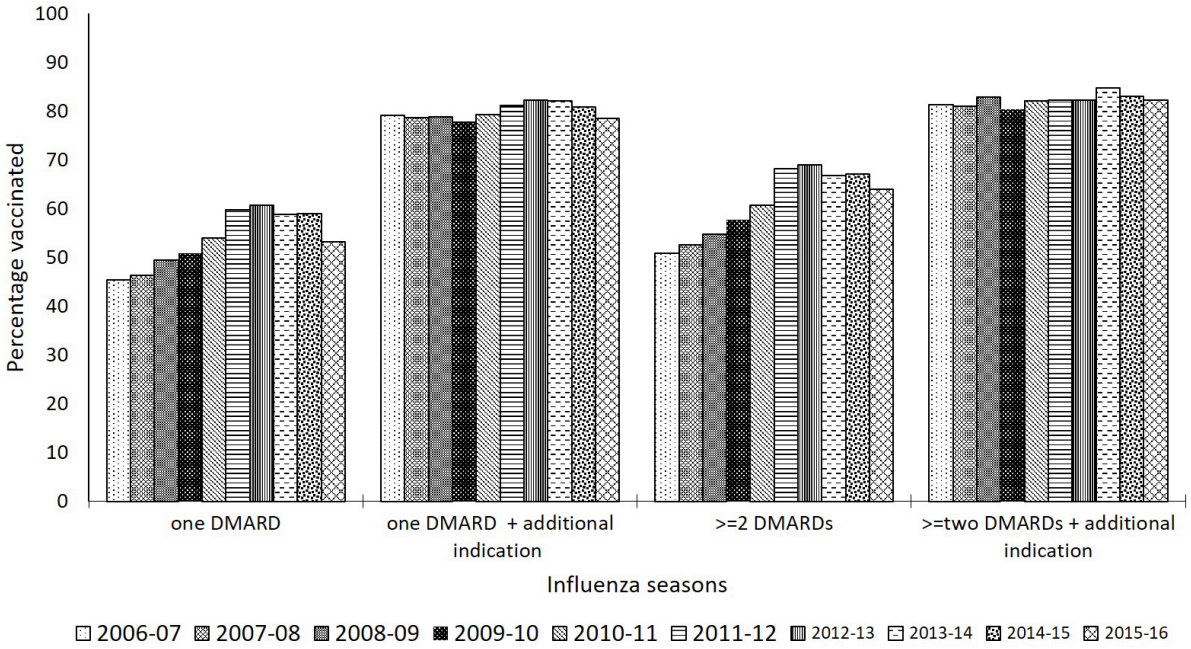


Figure 4: Percentage of people with AIRDs on DMARDs vaccinated in each flu season from 2006 to 2016 according to number of different types of DMARDs.

Age group	At risk conditions	Significant joinpoints	Start	End	APC	Lower 95% CI	Upper 95% CI	P-value
Overall		2013-14	2006	2013	2.7^	2.0	3.4	<0.01
			2013	2015	-2.7	-7.7	2.5	0.20
≥65 years*		none	2006	2015	0.1	-0.2	0.5	0.40
45-64 years	+	2011-12	2006	2011	6.1^	3.7	8.6	<0.01
			2011	2015	-0.3	-3.2	2.7	0.80
45-64 years	-	none	2006	2015	1.3^	0.1	2.6	<0.01



Supplementary material

Table S1: Annual percentage change in seasonal influenza vaccine uptake 2006-2016

<45 years	+	2012-13	2006	2012	8.8^	6.2	11.4	<0.01
			2012	2015	-0.2	-4.6	4.5	0.90
<45 years	-	2012-13	2006	2012	5.4^	2.4	8.5	<0.01
			2012	2015	-1.5	-8.7	6.3	0.60

*People aged 65 years or greater in the UK are offered influenza vaccination regardless of comorbidities. ^Indicates that the annual Percent change (APC) is significantly different from zero at the alpha=0.05 level

Table S2: Administration of seasonal influenza vaccine according to autoimmune rheumatic disease type

Year	RA additional indication –ve	SLE additional indication -ve	SpA additional indication –ve	RA additional indication +ve	SLE additional indication +ve	SpA additional indication +ve
2006/7	4,998	301	1,602	6,132	152	620
	46.08(44.70-47.46)	51.50 (45.84-57.11)	34.96 (32.66-37.33)	80.06 (79.04-81.04)	68.42 (60.59-75.33)	74.52 (70.93-77.80)
2007/8	5,176	317	1,738	6,568	164	700
	47.39(46.03-48.75)	50.47(44.98-55.96)	36.54(34.30-38.83)	79.57(78.57-80.53)	67.07(59.50-73.85)	74.71(71.36-77.80)
2008/9	5,226	326	1,860	6,987	175	803
	50.63 (49.27-51.99)	55.21(49.77-60.54)	38.44(36.25-40.68)	79.78 (78.82-80.70)	71.43 (64.28-77.65)	75.72 (72.63-78.56)
2009/10	5,228	331	1,974	7,299	181	891
	52.31 (50.96-53.67)	56.80 (51.39-62.04)	41.24 (39.08-43.42)	78.71 (77.75-79.63)	71.82 (64.82-77.91)	74.30 (71.32-77.06)
2010/11	5,578	374	2,180	7,648	200	1,033
	56.72 (55.42-58.02)	54.01 (48.93-59.01)	44.82 (42.74-46.91)	80.19 (79.28-81.07)	75.00 (68.52-80.53)	76.48 (73.79-78.97)
2011/12	5,126	319	2,090	7,617	201	1,077
	62.76 (61.43-64.07)	63.64 (58.20-68.74)	50.48 (48.33-52.62)	81.52 (80.63-82.37)	78.61 (72.38-83.75)	79.94 (77.44-82.23)
2012/13	4,965	310	2,166	7,790	220	1,112
	62.69 (61.34-64.03)	60 (54.43-65.32)	54.25 (52.14-56.34)	82.76 (81.90-83.58)	80.45 (74.67-85.18)	78.87 (76.37-81.17)
2013/14	4,569	271	2,009	7,678	215	1,137
	61.28 (59.86-62.69)	63.84 (57.93-69.35)	53.46 (51.27-55.63)	82.82 (81.96-83.65)	77.21 (71.11-82.34)	80.65 (78.25-82.85)
2014/15	4,168	257	1,833	7,016	197	1,122
	62.24 (60.75-63.70)	66.93 (60.93-72.42)	56.90 (54.62-59.15)	81.67 (80.75-82.56)	72.59 (65.93-78.38)	78.88 (76.39-81.17)
2015/16	3,463	229	1,594	5,857	161	948
	57.75 (56.10-59.39)	63.76 (57.31-69.74)	53.45 (50.99-55.89)	79.24 (78.18-80.26)	75.16 (67.88-81.24)	78.06 (75.31-80.58)

RA: Rheumatoid arthritis; SLE- Systemic Lupus Erythematosus; SpA-Spondyloarthropathy.

Table S3: Administration of seasonal influenza vaccine stratified by number of prescribed DMARDs

Year	1 DMARD, no additional indications	>1 DMARD, no additional indications	1 DMARD and additional indications	>1 DMARD and additional indications
2006/7	5,985	916	6,156	748
	42.64(41.39-43.90)	50.87(47.63-54.10)	79.06(78.03-80.06)	81.28(78.32-83.92)
2007/8	6,255	976	6,560	872
	43.73(42.50-44.96)	52.56(49.42-55.68)	78.55(77.54-79.53)	80.96(78.22-83.44)
2008/9	6,342	1,070	7,006	959
	46.61 (45.38-47.84)	54.67 (51.67-57.64)	78.69 (77.71-79.63)	82.79 (80.27-85.06)
2009/10	6,401	1,132	7,300	1,071
	48.18 (46.96-49.41)	57.69 (54.78-60.54)	77.75 (76.78-78.69)	80.39 (77.90-82.66)
2010/11	6,853	1,279	7,725	1,156
	52.05 (50.87-53.23)	60.67 (57.96-63.32)	79.28 (78.36-80.16)	82.09 (79.77-84.20)
2011/12	6,379	1,156	7,745	1,150
	57.81 (56.60-59.02)	68.08 (65.33-70.71)	81.11 (80.22-81.97)	82.26 (79.94-84.36)
2012/13	6,336	1,105	7,960	1,162
	58.60 (57.38-59.81)	68.87 (66.07-71.53)	82.24 (81.38-83.06)	82.19 (79.88-84.28)
2013/14	5,826	1,023	7,878	1,152
	57.74 (56.47-59.00)	66.76 (63.82-69.59)	82.08 (81.21-82.91)	84.72 (82.53-86.69)
2014/15	5,359	899	7,258	1,077
	59.82 (58.50-61.13)	67.07 (63.93-70.07)	80.79 (79.87-81.68)	83.01 (80.64-85.14)
2015/16	4,554	732	6,092	874
	55.56 (54.11-56.99)	63.93 (60.38-67.34)	78.51 (77.46-79.53)	82.27 (79.59-84.66)

Table S4: Disease and demographic characteristics associated with seasonal influenza vaccine administration in patients using methotrexate

Characteristic	Crude IRR (95% CI)	Adjusted IRR (95% CI)*
Age (years)		
<45	1	1
45-64	1.26 (1.23-1.30)	1.24 (1.21-1.28)
≥65	1.59 (1.54-1.63)	1.53 (1.49-1.57)
Sex		
Male	1	1
Female	1.03 (1.01-1.04)	1.03 (1.01-1.04)
AIRD type		
Rheumatoid arthritis	1	1
Systemic lupus erythematosus	0.92 (0.86-0.98)	1.02 (0.95-1.08)
Seronegative spondyloarthropathy	0.87 (0.85-0.87)	0.96 (0.94-0.98)
Number of DMARDs		
1	1	1
>1	1.02 (1.00-1.03)	1.03 (1.02-1.05)
Other influenza at-risk condition		
Absent	1	1
Present	1.18 (1.16-1.19)	1.09 (1.08-1.10)

IRR; Incident rate ratio

*adjusted for study year and other variables in the table

Table S5: Vaccinated with seasonal influenza vaccine in the 2015/16 influenza season stratified by geographic region.

Region	Percentage (95% CI)	Crude IRR (95% CI)	Adjusted IRR (95% CI) ≠
South West[§]	68.77 (65.42-71.94)	1	1
North West England	69.27 (66.45-71.96)	1.01 (0.90-1.13)	1.00 (0.89-1.11)
Yorkshire and Humber	72.64 (63.35-80.31)	1.06 (0.83-1.34)	1.04 (0.82-1.32)
West Midlands	64.19 (60.95-67.30)	0.93 (0.83-1.05)	0.95 (0.84-1.07)
East Midlands	-	-	-
East England	65.28 (60.80-69.51)	0.95 (0.82-1.09)	0.95 (0.83-1.00)
South Central	66.49 (64.10-68.81)	0.97 (0.87-1.07)	0.99 (0.89-1.10)
London	62.58 (59.20-65.84)	0.91 (0.81-1.03)	0.92 (0.82-1.04)
South East Coast	66.02 (63.69-68.27)	0.96 (0.87-1.06)	0.96 (0.87-1.07)
Northern Ireland	76.53 (73.53-79.29)	1.11 (0.99-1.25)	1.16 (1.03-1.30)
Scotland	77.74 (75.91-79.46)	1.13 (1.03-1.25)	1.15 (1.05-1.27)
Wales	68.59 (66.49-70.62)	1.00 (0.90-1.10)	1.01 (0.91-1.11)
North East England	70.97 (60.91-79.32)	1.03 (0.78-1.33)	1.00 (0.77-1.29)

§ Region with a median vaccinated population
≠ adjusted for age at start of vaccination period, sex and presence of one or more risk condition for influenza vaccination at start of vaccination period.
Statistical significance determined at $p<0.05$
- No data from the East Midlands region.