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Influenza and pneumococcal vaccination in patients with rheumatoid arthritis in comparison with age- and sex-matched controls: results of a claims data analysis

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Abstract The aim of this study was to assess the vaccination status for influenza and pneumonia and the prevalence of hospitalised pneumonia in rheumatoid arthritis (RA) patients and population controls in Germany. Members of a large statutory health insurance fund in Germany who were continuously insured between 2009 and 2013 and had a diagnosis of RA in 2013 were age and sex matched 1:5 to members without RA. Pneumococcal and influenza vaccinations were evaluated with regard to age, sex and region of residence. Logistic regression models were used to determine predictors for influenza vaccination in RA patients. Prevalences of pneumonia that required hospitalisation were compared to regional vaccination rates. The data of 111,482 RA patients and 557,410 matched controls were available for analysis. Compared to controls, RA patients were vaccinated more frequently against influenza (40.8 vs. 32.2 %) and pneumonia (15.0 vs. 10.0 %). Vaccination rates increased with older age and differed between the federal states (highest in East Germany, lowest in South Germany). The region of residence, comorbidities, rheumatologic care and biologic treatment was associated with a higher probability of an influenza vaccination. Prevalences of pneumonia that required hospitalisation were 2–3 times higher in patients compared to controls and tended to be higher in regions with low vaccination rates. The increased pneumonia prevalence in RA patients confirms their status as a risk group. RA patients are vaccinated more frequently than controls, but vaccination rates are still low. The lower pneumonia prevalence in East Germany indicates that vaccination may help to reduce pneumonia in RA.

Keywords Rheumatoid arthritis · Vaccination · Influenza · Pneumonia

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Background

Rheumatoid arthritis (RA) patients are at increased risk for infections [1]. Inflammation, immunosuppressive therapy with biologic disease modifying anti-rheumatic drugs (bDMARDs) and glucocorticoids as well as comorbid conditions independently increases the susceptibility to infections [1–4]. Within the large group of infections, pneumonia and influenza are common in RA patients and seem to be preventable [1, 5, 6]. Vaccination is one of the most effective preventive measures against infectious disease [7]. The European League Against Rheumatism (EULAR) published recommendations for vaccination in RA patients in 2011 [8]. The efficacy and safety of vaccination in RA patients are high enough to recommend vaccination, even if the patients are treated with glucocorticoids or bDMARDs [8]. Only rituximab reduces the humoral response significantly. Therefore, a gap between administration and vaccination is recommended [9, 10]. It has to be kept in mind that the currently available studies are not sufficiently powered [8]. The recommendations of the German Standing Vaccination Committee (STIKO) are in accordance with the EULAR guidelines [11, 12]. Patients older than 60 or suffering from a chronic disease like RA are recommended a seasonal influenza vaccination.

Pneumococcal vaccination is also recommended for these patients. In general, a one-time vaccination seems sufficient, whereas a booster vaccination every 5 years should be taken into consideration in patients with immune deficits [11]. In accordance to this, the German Society of Rheumatology (DGRh) recommends that patients with RA should be re-vaccinated every 5 years [13]. It remains unclear if vaccination is performed sufficiently in routine care. Available data for Germany are limited to two small samples with 301 and 209 patients in rheumatologic care [14, 15].

The aim of this study was to evaluate the current use of influenza and pneumococcal vaccination in RA patients in Germany in primary and specialised care, to identify predictors of vaccination and to assess the prevalence of hospitalised influenza and pneumonia in a large population-based sample.

Methods

Database and identification

This study was performed within the research network PROCLAIR (linking Patient-Reported Outcomes with CLAIms data for health services Research in rheumatology) [16]. Based on claims data of a large German statutory health fund (BARMER GEK), we conducted a cross-sectional study of the years 2009–2013. All members aged 18–99 in 2013 that had been insured continuously between 2009 and 2013 were included in the study. They were considered as RA patients, if they had been diagnosed with M05x or M06x (ICD-10-GM) in at least two quarters of the year 2013. The effect of this case definition on the prevalence of RA in claims data was described elsewhere [16]. A case definition which is based only on the diagnosis is more likely to overestimate the real prevalence than a case definition with diagnostic elements [17, 18]. Therefore, all analyses were repeated in a sensitivity analysis which used the following case definition: diagnosis of M05x or M06x in at least two quarters of 2013 plus at least one claim for a test of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in 2013. This definition was used in a previous analysis and had resulted in the most probably rates for RA [16]. A control group consisting of all insurants without RA diagnosis was matched by age and sex in a ratio of 1 to 5.

The codes of the uniform assessment standard (EBM) 89004, 89111 and 89112 could be used to detect an influenza vaccination in the claims data of 2013. Pneumococcal vaccination was identified with the codes 89014, 89150, 89118, 89119 and 89120 in the years 2009–2013. To ensure that, all valid codes of the study period were known, and every Regional Association of Statutory Health Insurance Physicians (KV) was contacted.

To identify conditions in the claims data, the ICD-10-GM codes were used. The prevalences of pneumonia and influenza that required hospitalisation were determined by the main discharge diagnosis J09, J10 and J11 (influenza) and J13, J15, J16, J17 and J18 (pneumonia) in 2013. J12 (viral pneumonia) and J14 (haemophilus influenza pneumonia) were not included. Pre-existing comorbid conditions were assessed by the corresponding outpatient ICD-10 code. Prescriptions were identified via the anatomical therapeutic chemical classification (ATC). The prescription of biologicals (L01XC02, L04AB, L04AA24, L04AC03 and L04AC07) and DMARDs (L04AA13, L04AD01, L04AX01, L04AX03 and M01C) were assessed in 2013.

Statistical analyses

The vaccination rates of cases and controls were stratified by age and sex. To detect regional variations, we analysed the vaccination coverage both in RA patients and controls depending on federal states. The calendar week of vaccination and the vaccinating physician (rheumatologist, orthopaedist or general practitioner) were assessed. A multivariable logistic regression analysis was conducted to identify predictors for an influenza vaccination in patients with RA. In this analysis, we took into account age, sex, region of residence, pre-existing comorbid conditions, therapy with biologic and synthetic DMARDs, the attending physician (rheumatologist, orthopaedist or general practitioner) and the case status (prevalent or incident). If a RA patient was treated by a rheumatologist at least once a year, the attending physician was classified as rheumatologist. If no rheumatologist, but an orthopaedist was visited at least once a year, he was classified as the attending physician. A RA patient who had no diagnosis in the four quarters of 2012 was defined as incident. The prevalences of pneumonia and influenza that required hospitalisation were investigated for cases and controls. To avoid a healthy user bias, the association of the vaccination rates in the federal states with the pneumonia prevalences was shown on an ecological level (not on an individual basis) [19, 20]. All analyses were performed with SAS 9.2.

Results

Characteristics

More than 6,000,000 adults were insured continuously in the study period of 2009–2013. A total of 111,482 had a diagnosis of RA in two quarters of 2013 (cases). A total of 557,410 age and sex-matched controls were chosen at

random from all other insurants without RA. The mean age was 66.2 years, and the proportion of women was 79.7 %. Pre-existing comorbid conditions were more frequent in RA patients (Table 1).

Influenza and pneumococcal vaccination coverage

The proportion of vaccinated insurants was consistently higher in RA patients than in controls. 40.8 % of RA patients and 31.2 % of the controls were vaccinated against influenza in 2013 (OR 1.51, 95 % CI 1.50–1.52). Pneumococcal vaccination was performed in 15 % of RA patients and in 10 % of the controls (OR 1.57, 95 % CI 1.53–1.60). In our sensitivity analysis with a case definition with diagnostic elements, vaccination rates were comparable (41.2 % for influenza and 15.3 % for pneumonia) and showed the same trends.

The proportion of vaccinated insurants increased with rising age. Whereas the proportion of insurants with influenza vaccination increased continuously, the proportion of insurants with a pneumococcal vaccination had its climax in the 70–79 years old insurants. Overall, the differences in vaccination rates between male and female insurants were minimal, but women were more frequently vaccinated than men in younger age groups, whereas men were vaccinated more often than women in older age groups (Table 2). Significant regional differences were seen in the influenza vaccination in cases and controls. Vaccination rates in East Germany were the highest (cases: 49.0–58.9 %; controls: 40.5–50.9 %), whereas the lowest rates could be registered in South Germany (cases: 25.8–26.5 %; controls: 20.5–21.1 %) (Fig. 1). Regarding pneumococcal vaccination, similar differences were observed. The vaccination rates in East Germany (cases: 14.2–21.7 %; controls: 11.3–16.1 %) were significantly higher than in South Germany (cases: 10.2–12.1 %; controls: 6.6–6.9 %) (Fig. 2).

Table 1 Characteristics of the study population

	Cases		Controls	
	N	%	*N*	%
Age				
18–39	4454	4.0	22,270	4.0
40–49	8626	7.7	43,130	7.7
50–59	19,978	17.9	99,890	17.9
60–69	26,205	23.5	131,025	23.5
70–79	35,747	32.1	178,735	32.1
80+	16,472	14.8	82,360	14.8
Age (mean, SD)	66.2	13.7	66.2	13.7
Sex				
Male	22,670	20.3	113,350	20.3
Female	88,812	79.7	444,060	79.7
All	111,482	100.0	557,410	100.0
Pre-existing comorbid conditions				
Influenza	839	0.8	3349	0.6
Pneumonia	2042	1.8	5729	1.0
Diabetes	23,241	20.8	94,896	17.0
Chronic obstructive pulmonary disease	11,548	10.4	38,266	6.9
Chronic inflammatory bowel disease	2213	2.0	4859	0.9
Chronic artery disease	19,932	17.9	74,042	13.3
Therapy				
Biologicals	8041	7.2	362	0.1
DMARDs	37,885	34.0	3149	0.6

Further analyses on influenza vaccination

The calendar week of the seasonal influenza vaccination and the vaccinating physician were assessed for cases and controls. The week of vaccination did not differ between cases and controls. 95 % of all vaccinated insurants were vaccinated until November ("Appendix Fig. 4"). Differences between the federal states could not be seen.

A total of 93.6 % of the influenza vaccinations in RA patients were performed by the general practitioner and 2.0 % by the rheumatologist. The proportion of RA patients who were vaccinated by the rheumatologist differed between the federal states (from 0.2 % in Mecklenburg-Western Pomerania to 4.9 % in Berlin). Influenza vaccination in controls was performed by the general practitioner in 95.0 %.

A multivariable logistic regression analysis was conducted in RA patients to identify predictors for an influenza vaccination. Besides age, region of residence, specialist care, the presence of comorbid conditions and biologic treatment was associated with a higher possibility for an influenza vaccination (Table 3).

Further analyses on pneumococcal vaccination

A total of 87.9 % of the pneumococcal vaccinations in RA patients were performed by the general practitioner and 6.1 % by the rheumatologist. The proportion of RA patients who were vaccinated by rheumatologists differed considerably between the federal states (from 0.0 % in Bremen to 18.6 % in Saxony-Anhalt). Pneumococcal vaccination in controls was performed by the general practitioner in 93.3 %.

Prevalence of pneumonia and influenza that required hospitalisation

The prevalence of pneumonia that required hospitalisation was determined in patients and controls. A total of

Table 2 Proportion of vaccinated insurants by age and sex

Characteristics	Influenza vaccination in RA patients in %	Influenza vaccination in controls in %	Pneumococcal vaccination in RA patients in %	Pneumococcal vaccination in controls in %
18–39				
Male	9.6	3.6	5.6	0.7
Female	13.7	5.9	5.9	0.6
All	12.9	5.4	5.8	0.6
40–49				
Male	17.9	6.7	5.6	1.2
Female	20.4	9.4	7.2	1.1
All	20.0	8.9	6.9	1.2
50–59				
Male	23.9	12.8	7.8	2.3
Female	26.5	14.8	8.2	2.2
All	26.0	14.4	8.1	2.2
60–69				
Male	40.1	28.3	17.1	10.9
Female	40.9	29.9	18.2	11.8
All	40.7	29.6	17.9	11.6
70–79				
Male	55.1	47.1	19.3	15.2
Female	51.8	44.8	19.6	15.0
All	52.5	45.3	19.6	15.0
≥80				
Male	56.0	51.8	17.3	14.7
Female	51.3	47.6	14.9	12.6
All	52.3	48.5	15.4	13.0
All				
Male	41.8	32.8	15.0	10.3
Female	40.6	32.0	15.0	9.9
All	40.8	32.1	15.0	10.0

3038 insurants (0.46 %) with a hospital stay due to pneumonia could be identified. The inpatient pneumonia prevalence was higher in RA patients (0.66 %) than in controls (0.41 %) and tended to be higher in regions with low vaccination rates (Fig. 3). The number of hospital stays due to influenza was only 21 and therefore too low for further regional analyses.

Discussion

In a large claims data cohort, current vaccination rates in German RA patients could be assessed. Our study calculated overall vaccination rates of 15.0 % (pneumonia) and 40.8 % (influenza). Two studies have examined the vaccination coverage of subgroups in Germany [14, 15]. COMORA studied the vaccination coverage in 3920 RA patients, among them 209 German patients [15]. The proportion of patients with a pneumococcal vaccination in the last 5 years in the German COMORA patients was 18.8 %. A total of 41.6 % were vaccinated against influenza in the last 12 months. Although our proportion of pneumococcal vaccination is slightly lower, the results are comparable. Our analysis showed that RA patients in Germany had a higher chance to get an influenza vaccination if they were treated by rheumatologists. Because only RA patients in rheumatologic care were included in COMORA, our study confirms this vaccination coverage. The proportion of vaccinated RA patients was, both in COMORA and PROCLAIR, considerably lower than in the second study, where 301 patients were included in a single centre and the reported vaccination rates were between 20.2 and 39.0 % (pneumococcal) and 59.3 and 69.2 % (influenza) for different treatment arms [14]. The higher rates may be explained by higher vaccination awareness in the hospital or within the region. A recent study on influenza and pneumococcal vaccination in patients with RA under immunosuppressive therapy in the United Kingdom (UK) showed considerably

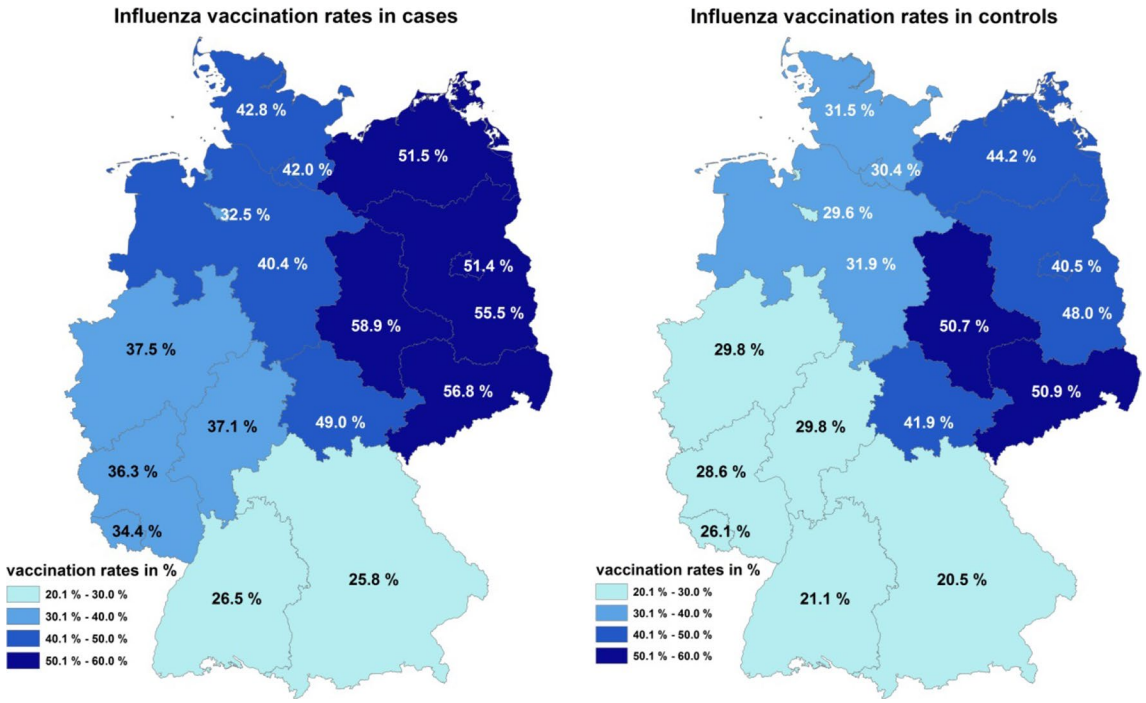

Fig. 1 Influenza vaccination rates in RA patients and controls

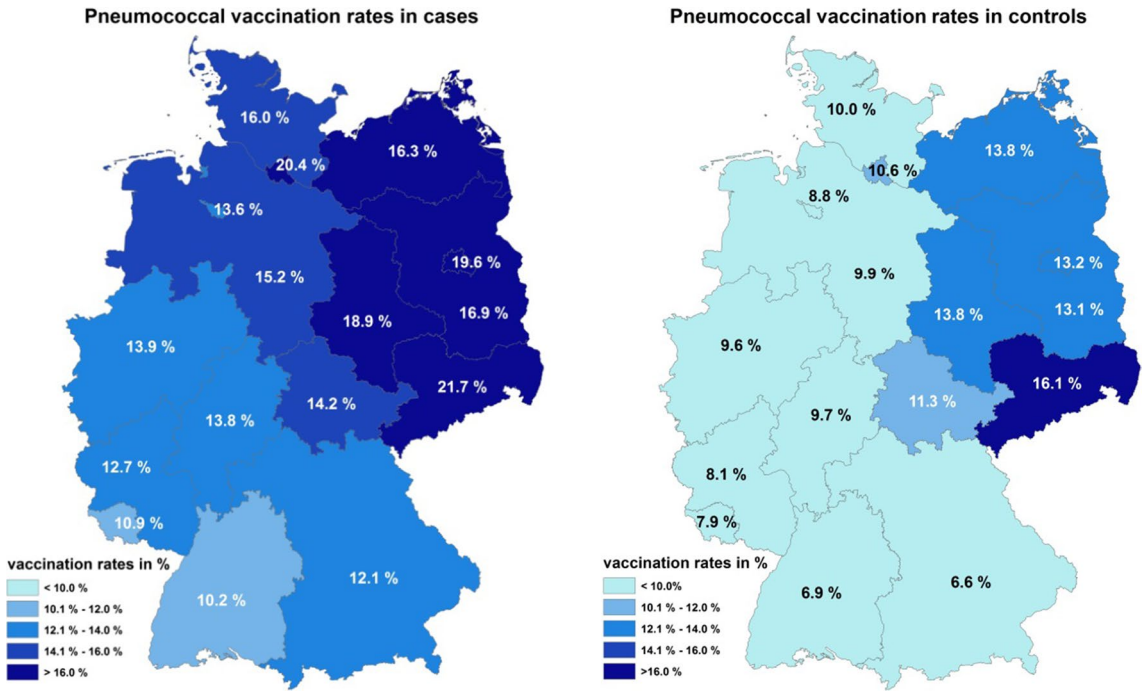

Fig. 2 Pneumococcal vaccination rates in RA patients and controls

higher vaccination coverage. 80 % patients received at least one influenza vaccination, and 50 % patients received a pneumococcal vaccination during the follow-up of 5 years [21]. The higher rate compared to the present data could be explained by the fact that Costello et al. included only patients with immunosuppressive medication.

Table 3 Results of a multivariable logistic regression model to identify predictors for an influenza vaccination

	OR	95 % CI	
Age			
40–49 versus 18–39	1.66	1.50	1.85
50–59 versus 18–39	2.25	2.05	2.48
60–69 versus 18–39	4.38	3.99	4.81
70–79 versus 18–39	6.97	6.36	7.65
≥80 versus 18–39	8.19	7.44	9.02
Sex			
Male versus female	1.02	0.98	1.05
Region			
North versus south	2.13	2.04	2.23
West versus south	1.77	1.70	1.84
East versus south	3.64	3.50	3.80
Case			
Prevalent versus incident	1.19	1.14	1.25
Physician			
Orthopaedist versus general practitioner	1.23	1.19	1.28
Rheumatologist versus general practitioner	1.25	1.21	1.29
Pre-exisitng comorbid conditions			
Influenza[a]	1.19	1.02	1.38
Pneumonia[a]	1.09	0.99	1.20
Diabetes[a]	1.25	1.21	1.29
Chronic obstructive pulmonary disease[a]	1.29	1.23	1.34
Chronic inflammatory bowel disease[a]	1.11	1.01	1.22
Coronary artery disease[a]	1.20	1.16	1.24
Therapy			
Biologicals[b]	1.15	1.10	1.22
DMARDs[b]	1.18	1.14	1.22

[a] Reference = no disease, [b] reference = no prescription

The results of the present study show that, compared to the vaccination coverage in the general population of Germany, patients with RA were vaccinated more frequently, but overall, the rates are still low. Other claims data analyses showed an overall vaccination rate for influenza of 21 % in 2006/07 [22]. As the general population is younger than our controls, the slightly higher vaccination rate of our controls is plausible (32.1 %). A further claims data study from Germany analysed pneumococcal vaccination between July 2008 and June 2009 in all insurants. The vaccination rate was 1.9 % in 1 year and comparable to pneumococcal vaccination rate of 5 years in our controls (10.0 %) [23].

The data of the present study revealed that RA patients are vaccinated more frequently than controls, especially if they do not meet the generally recommended age criterion or if additional risk factors are present. These results indicate that the current recommendation to vaccinate patients at increased risk seems to be implemented at least in part in routine care and that the adherence to this recommendation is higher in specialised rheumatologic care. As the German Standing Vaccination Committee recommends standard vaccination against pneumococcal infections and influenza from age 60 onwards and for all persons with an increased health risk, vaccination coverage in RA patients raised with rising age and with increasing numbers of pre-existing conditions. Previous studies also reported that persons with a higher age or pre-existing conditions had higher vaccination rates [22].

Regional variations in vaccination coverage were seen in our study in RA patients as well as in the controls. Vaccination coverage is known to be highest in East Germany, which can be explained by a historic vaccination policy in the German Democratic Republic [22, 24]. The lowest vaccination rates were consistently seen in South Germany. Historically, there is an anti-vaccination lobby in Germany which is connected to homoeopathy and anthroposophy [25]. About 3–5 % of the population is radically against any vaccination, and about 30 % is sceptical. This tradition is stronger in the two southern German states which may contribute to their generally lower vaccination rates [26].

Predictors for an influenza vaccination were analysed in our cohort. In COMORA, older age, the use of biologicals and the presence of comorbidities were reported predictors for vaccination [15]. These factors were also associated with a higher vaccination rate in our study. In addition, rheumatologic care and the region of residence were associated with higher rates. It is of interest that the region of residence had a higher influence on the influenza vaccination than the presence of comorbidities, rheumatologic care or biologic treatment.

Thus, the question rose whether higher regional vaccination rates were also associated with a lower rate of pneumonias. Indeed, the pneumonia prevalence tended to be lower in areas with a higher vaccination rate. This seems plausible because vaccination is one of the most effective measures for preventing infectious disease. Overall, the prevalence of hospitalised cases of pneumonia was rather low. Taking into account the mean age of the cases and controls, a higher prevalence of pneumonia could have been expected when considering commonly used risk indexes [27–29]. Furthermore, the ecological analysis can only display a trend, and the analysis of an effect of vaccination on an individual level is troublesome as it is known that vaccinated people are more healthy than the general population [20, 30]. Hmamouchi et al. [15] identified that a lower disease activity of RA was a predictor of vaccination, so we assume that a healthy user effect would bias the results on an individual level.

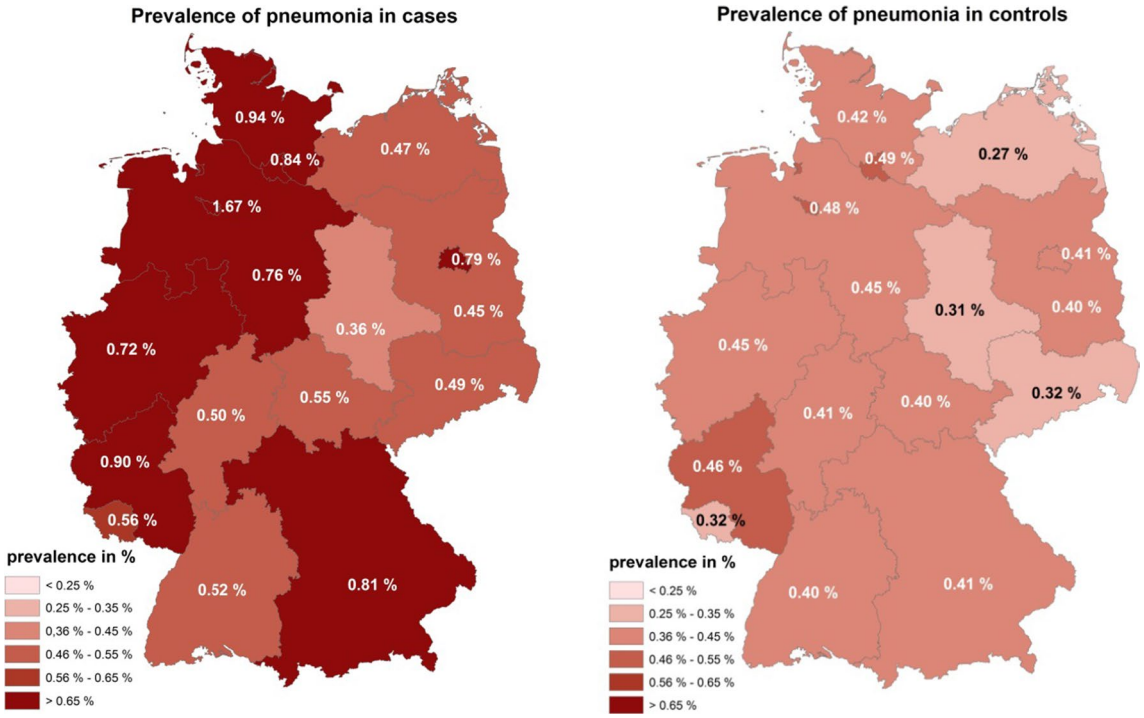

Fig. 3 Prevalence of hospitalised pneumonia in RA patients and controls

Overall, the vaccination rates need to be improved, but the implementation may not always be easy to perform. A regional prospective analysis reported that 66 % of all patients whom a rheumatologist had recommended vaccination did not receive this preventive measure. Furthermore, the vaccination status was often incomplete [31]. Besides difficulties in the implementation or missing recommendations, the patients' attitude towards vaccination should be considered. Michel et al. [32] reported that one-third of patients were afraid of side effects and were not sufficiently aware of their increased infection risk.

Strengths and limitations

The claims data did not allow us to study the reasons for non-vaccination. It remains unclear if the physician did not recommend a vaccination or if the patient refused it. A French study reported that the main reason for non-vaccination was the absence of recommendation from the treating physician [33]. In the present study, only insurants of one German statutory health fund were analysed. Differences in demographic factors and morbidity between the funds limit the extrapolation of the results to the German population in general [34]. The main strength of this study is the large sample size with more than 100,000 RA patients, which enabled a nationwide analysis and further evaluation with regard to region, treatment and the treating physician.

Conclusion

RA patients are vaccinated more frequently against influenza and pneumonia than controls, but the German vaccination rates are still low. Differences in vaccination rates between federal states and between primary and specialist care indicate that preventive measures should focus on a broader implementation of the current recommendations, in particular because RA patients remain a risk group for pneumonia.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval Although no ethical approval is required for the analysis of claims data, an ethics vote for PROCLAIR study, which also includes surveys of patients identified via claims data, was obtained from the Ethics Committee of the Charité University Medicine, Berlin in 2015 (EA1/051/15). This claims data analysis does not contain personal information. In this case, an informed consent is not necessary in Germany.

Appendix

See Fig. 4.

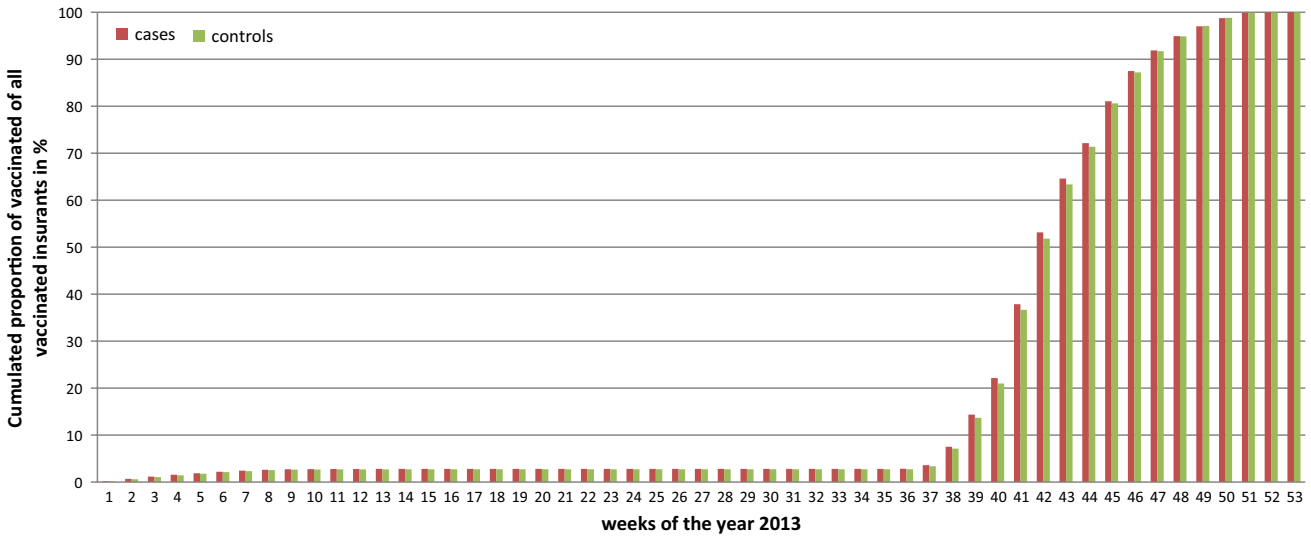

Fig. 4 Week of influenza vaccination in RA patients and controls ("Appendix")

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