The Journal of Rheumatology 2023;xx:xxxxx
doi:10.3899/jrheum.220986
First Release March 1 2023

The Journal of Rheumatology

Incidence of Herpes Zoster in Patients With Rheumatoid Arthritis in the United States: A Retrospective Cohort Study

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ABSTRACT. ***Objective.*** To estimate the incidence of herpes zoster (HZ) in patients with rheumatoid arthritis (RA) compared with the general population in the USA.

Methods. This retrospective, longitudinal cohort study used data from an administrative claims database containing both commercial and Medicare Advantage Part D data, with a data period from October 2015 to February 2020. Patients were aged ≥ 18 years and divided into 2 cohorts: patients with RA and patients without RA. Diagnosis and procedure codes were used to identify HZ cases and calculate incidence rates (IRs) of HZ in the 2 cohorts. Data were stratified by age group (ie, 18-49, 18-29, 30-39, 40-49, 50-64, and ≥ 65 yrs) and RA therapy type. IR ratios (IRRs), adjusted by cohort baseline characteristics, were estimated using generalized linear models to compare the incidence of HZ between cohorts.

Results. The overall IR of HZ was higher in the RA cohort (21.5 per 1000 person-years [PY]; N = 67,650) than in the non-RA cohort (7.6 per 1000 PY; N = 11,401,743). The highest IRs in both cohorts were observed in the age group of ≥ 65 yrs (23.4 and 11.4 per 1000 PY in the RA cohort and non-RA cohort, respectively). The overall adjusted IRR of HZ was 1.93 (95% CI 1.87-1.99, $P < 0.001$) for the RA cohort compared with the non-RA cohort. In the RA cohort, the highest IRs by medication class were observed in patients using corticosteroids and those using Janus kinase inhibitors.

Conclusion. These results highlight the increased incidence of HZ in patients with RA.

Key Indexing Terms: adult, herpes zoster, incidence, rheumatoid arthritis, United States

Herpes zoster (HZ) is a condition caused by reactivation of the varicella-zoster virus, resulting in a painful, blistering rash with a distinctive distribution.[1] Approximately 1 million cases of HZ are diagnosed in the USA annually, which can lead to severe and long-lasting effects on quality of life. Such complications include postherpetic neuralgia, HZ ophthalmicus, and neurological, dermatological, or visceral involvement, all of which may lead to long-term physical impairment.[1-4]

Immunosenescence, or the natural decline in immune function with age, and immunosuppression caused by disease or therapy have both been associated with an increased risk of HZ.[5,6] Rheumatoid arthritis (RA) is an autoimmune disease in which cell-mediated immunity is dampened, leading to a higher susceptibility to infections such as HZ.[5,6] It is estimated that patients with RA have a 2- to 3-fold higher risk of developing HZ compared to those without RA.[7,8] Many patients with RA rely on immunosuppressive therapies, such as glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), biologics, and Janus kinase inhibitors (JAKi) to avoid irreversible joint damage, the use of which can increase the risk of HZ.[5,9,10]

Although it is known that there is a higher incidence of HZ in patients with RA from this study and others, there is a need for up-to-date estimates of disease incidence in the USA, as the most recent estimates are several years old or used data that may not be generalizable to the current US population as a whole.[8,11] Consequently, we aimed to estimate the incidence rates (IRs) of HZ in patients with RA and compare these to patients without RA using a large data source with high generalizability to the broader US population. These results were then further stratified by patient age and therapy type.

METHODS

Data source. This retrospective, longitudinal cohort study used Optum's deidentified Clinformatics® Data Mart (CDM) health administrative claims

GlaxoSmithKline Biologicals SA funded this study (GSK study identifier: VEO-000042) and was involved at all stages of study conduct. GlaxoSmithKline Biologicals SA also funded all costs associated with the development and publication of this manuscript, in accordance with Good Publication Practice 2022 guidelines (https://www.ismpp.org/gpp-2022).

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DS and SP are employees in the GSK group of companies and report holding shares in the GSK group of companies. PTL, DG, WYC, MSD, and FD are employees of Analysis Group Inc., which received funding from the GSK group of companies to conduct the study disclosed in this publication. SM has received grant support for vaccine studies from the GSK group of companies. JRC is a member of the American College of Rheumatology Vaccine Guideline Committee.

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Accepted for publication January 12, 2023.

database, including commercial and Medicare Advantage Part D health plan data, with a data period from October 1, 2015, to February 28, 2020. This database encompasses approximately 15 million to 19 million annual covered lives across all 50 US states.

The CDM database consists of enrollment information as well as medical and pharmacy claims data. Medical claims data included International Classification of Diseases and Related Health Problems, 10th revision, Clinical Modification (ICD-10-CM) diagnosis codes and procedure codes, as well as information on the health resource utilization for each specific claim of costs. This included outpatient visits (ie, office visits, consultations, and visits at outpatient facilities, among others), inpatient stays (ie, any claims that came from CDM confinement records), emergency department visits, and other health resources, including skilled nursing facilities, home care services, hospice care, vision, and durable medical equipment use. Pharmacy claims data included the medication dispensed—identified by national drug codes—as well as the number of days of supply, number of refills, and costs. Claims from pharmacy and medical benefits also included the date or dates of service.

As only existing deidentified data were used and no patients were contacted during the course of this study, informed consent was not applicable and Institutional Review Board review was not required. The deidentified data in this study complied with the requirements of the Health Insurance Portability and Accountability Act, and the study was conducted in accordance with the guiding principles of the Declaration of Helsinki.

Study population. Included patients were ≥ 18 years of age and were divided into 2 cohorts based on RA status: a cohort of patients with RA and a non-RA cohort. Patients diagnosed with RA were identified using ICD-10-CM diagnosis codes in medical claims and medication records in pharmacy claims, based on previously validated claims algorithms (Supplementary Tables S1 and S2, available with the online version of this article).[12-15] Diagnosis of RA was defined by at least 2 medical claims associated with RA at least 6 weeks apart and at least 1 prescription for a DMARD for at least 3 months, identified in medical or pharmacy claims, in the year following the first RA diagnosis (Supplementary Table S2). Any patients with RA diagnosis codes were excluded from the non-RA cohort.

Study design. For the cohort of patients with RA, the index date was defined as either the first claim associated with an RA diagnosis or the 6-month mark following the beginning of continuous enrollment, whichever was latest. For the non-RA cohort, the index date was defined as the 6-month mark following the beginning of continuous enrollment.

At least 6 months of continuous enrollment prior to the index date (ie, the baseline period) and at least 18 months of continuous enrollment after the index date were required for both RA and non-RA cohorts. The observation period was defined as the period of time from the index date until the incidence of HZ, HZ vaccination, or the end of data availability (ie, February 28, 2020), whichever occurred first. The full study design is presented in Figure 1.

Patients were excluded from the study if they had at least 1 claim of HZ diagnosis and/or an HZ vaccine administered prior to or on the index date. This was because the current study sought to measure HZ incidence in an unvaccinated population, and vaccination may have acted as an effect modifier.

Study measures: baseline characteristics. Baseline demographics were measured at index. Baseline clinical characteristics of patients were assessed during the 6-month baseline period prior to the index date. Baseline demographics included patient age at index date, sex, geographic location, and insurance type.

Clinical characteristics included the modified Charlson Comorbidity Index (CCI) score,[16] which excludes rheumatologic disease including RA; baseline medications, assessed using pharmacy claims and procedure codes from medical claims; selected immunosuppressive conditions (ie, solid organ transplantation, hematopoietic stem cell transplant, chemotherapy for malignancy, and HIV); and comorbidities potentially associated with HZ, assessed using diagnosis codes. Individuals with these conditions were not excluded from the study in order to preserve the generalizability of this population to that of the broader US population.

Study measures: IRs of HZ. Cases of HZ were identified using ICD-10-CM code B02 occurring on a day not associated with HZ vaccination (Supplementary Table S1, available with the online version of this article), since empirical observations suggest that vaccination might be associated with an HZ diagnosis on the medical claim for administration of the vaccine but may not represent incident disease. IRs of HZ were calculated

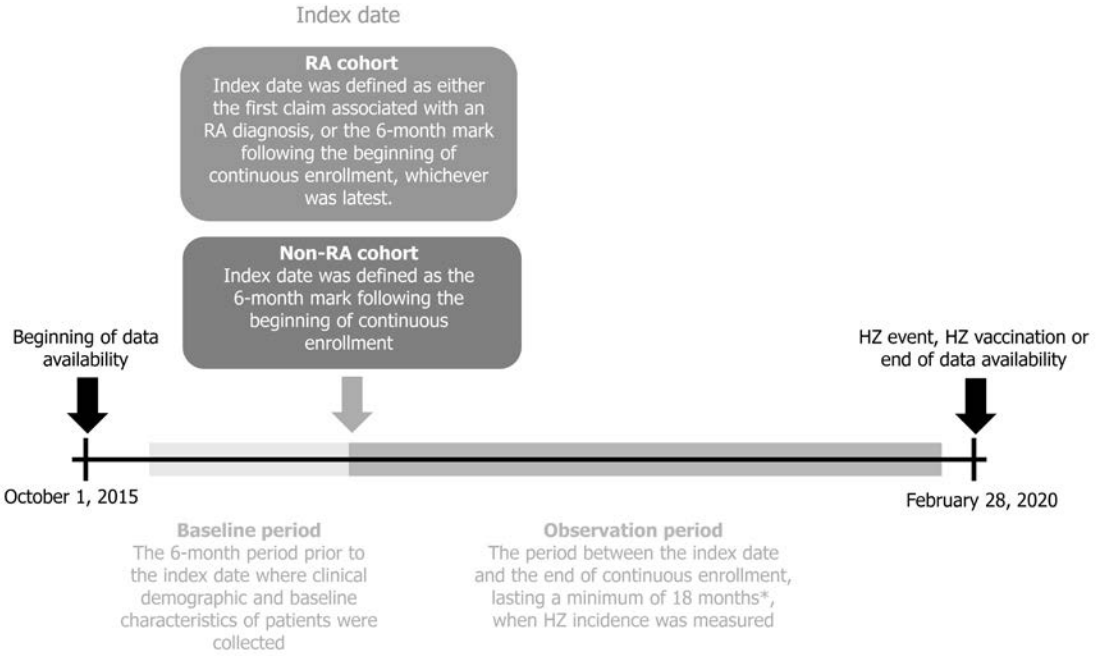


Figure 1. Study design. *This could have ended before 18 months because of the occurrence of an HZ event, HZ vaccination, or the end of data availability (February 28, 2020), whichever occurred first. HZ: herpes zoster; RA: rheumatoid arthritis.

for each cohort by dividing the number of patients with an HZ diagnosis within the observation period by the total patient-months observed. The observation period was from the index date until either the first HZ event, HZ vaccination, or the end of data availability after 18 months; subsequent HZ events were not evaluated. These were then reported per 1000 person-years (PY).

Statistical analysis. All study measures, both baseline and follow-up, were reported using descriptive statistics. All statistical analyses were carried out using the statistical software SAS 9.4, SAS Studio, and SAS Enterprise Guide (SAS Institute). This study was conducted according to a prespecified protocol.

Statistical analysis: baseline characteristics. Comparisons of baseline

Table 1. Baseline characteristics of the RA and non-RA cohorts.

	RA Cohort, N = 67,650	Non-RA Cohort, N = 11,401,743	Standardized Difference[a], %
Age at index date[b], yrs, mean (SD)	64.8 (12.7)	53.5 (19)	70.1
Age group, yrs			
18-49	8442 (12.5)	4,876,669 (42.8)	67.7
18-29	717 (1.1)	1,622,681 (14.2)	49.6
30-39	2189 (3.2)	1,634,663 (14.3)	39.2
40-49	5536 (8.2)	1,619,325 (14.2)	19.1
50-64	21,001 (31)	2,430,250 (21.3)	22.1
≥ 65	38,207 (56.5)	4,094,824 (35.9)	41.2
Sex[c]			
Male	16,150 (23.9)	5,536,259 (48.6)	51.4
Female	51,500 (76.1)	5,865,484 (51.4)	51.4
Geographic region			
South	30,782 (45.5)	4,623,153 (40.5)	10
West	14,930 (22.1)	2,623,531 (23)	2.3
Midwest	15,012 (22.2)	2,665,290 (23.4)	2.8
Northeast	6834 (10.1)	1,249,959 (11)	2.8
Unknown	92 (0.1)	239,810 (2.1)	18.7
Insurance type			
Medicare Advantage	45,123 (66.7)	4,330,304 (38)	57.5
Commercial	22,527 (33.3)	7,071,439 (62)	57.5
Modified CCI[d], mean (SD)	0.7 (1.2)	0.4 (1)	32.8
Select CCI component comorbidities			
Chronic pulmonary disease	12,791 (18.9)	852,452 (7.5)	33.8
Peripheral vascular disease	6121 (9)	457,719 (4)	20.4
Moderate or severe renal disease	6349 (9.4)	474,352 (4.2)	20.8
Select comorbidities potentially associated with HZ			
Total	12,122 (17.9)	227,661 (2)	53.2
Sicca syndrome (ie, Sjögren syndrome)	3365 (5)	11,906 (0.1)	31
Psoriasis	2866 (4.2)	69,136 (0.6)	23.6
RA-related medications at baseline			
NSAIDs	15,918 (23.5)	536,463 (4.7)	54.1
Systemic steroids	21,027 (31.1)	290,782 (2.6)	76.3
DMARDs	49,408 (73)	54,205 (0.5)	150.5
Biologics	18,197 (26.9)	22,354 (0.2)	78
JAKi	1231 (1.8)	27 (0)	19.2
RA management at index date			
DMARDs	26,106 (38.6)	44,327 (0.4)	96.4
Biologics or JAKi with or without DMARDs	13,501 (20)	19,487 (0.2)	65.8
Systemic steroids with or without any of these other medications	21,027 (31.1)	290,782 (2.6)	76.3
NSAIDs only	1751 (2.6)	484,567 (4.2)	9.1

Data are in n (%) unless otherwise indicated. [a] For continuous variables, the standardized difference was calculated by dividing the absolute difference in means by the pooled SD of both groups. The pooled SD was the square root of the average of the squared SDs. For categorical variables with 2 levels, the standardized difference was calculated using the following expression: $|P_1 - P_2| / \sqrt{(p\ (1 - p))}$, where $p = (P_1 + P_2) / 2$. P_1 was the respective proportion of participants in the RA+/HZ+ cohort, and P_2 was the respective proportion of participants in the respective RA+/HZ− cohort. [b] To ensure deidentification, patients' dates of birth were never earlier than 1930 in the data source; therefore, the maximum patient age as of the index date is 89 years. [c] A patient with unknown sex was imputed as female sex. [d] The modified CCI was computed according to the updated version of the Charlson methods[16]; the "rheumatic disease" comorbidity was removed from the CCI as it contains RA, which was one of the study exposure measures, and several other conditions already captured under the comorbidities potentially associated with HZ. CCI: Charlson Comorbidity Index; DMARD: disease-modifying antirheumatic drug; HZ: herpes zoster; JAKi: Janus kinase inhibitors; NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis.

demographic and clinical characteristics for both cohorts were conducted using standardized differences. The full formula used for calculation of these standardized differences can be found in the footnotes of Table 1. Standardized differences of 20%, 50%, and 80% were considered small, medium, and large differences, respectively.[17]

Statistical analysis: IRs of HZ. IRs of HZ were measured overall and stratified by patient age at index date for each cohort (ie, 18-49, 18-29, 30-39, 40-49, 50-64, and ≥ 65 yrs). Additionally, the IRs of HZ of patients with RA aged < 50 years were compared to those of patients without RA aged ≥ 50 years. IRs of HZ were also stratified by RA therapy type for the RA cohort, which was divided into the following categories: DMARDs alone or no treatment, biologics with or without DMARDs, JAKi with or without DMARDs, and systemic steroids with or without other medications. Use of DMARDs alone or no treatment was assessed within 30 days prior to or on the event date or censor. Use of biologic medications with or without DMARDs was assessed 3 months immediately prior to the event or censor. Use of rituximab or rituximab-abbs/rituximab-pvvr was assessed 6 months immediately prior to the event or censor. Use of JAKi with or without DMARDs was assessed 3 months immediately prior to the event or censor. Use of systemic steroids with or without any other medications was assessed 3 months immediately prior to the event or censor.

Propensity scores were calculated using logistic regression, with RA status as the dependent variable and relevant baseline characteristics as predictors in the model. Relevant baseline characteristics were based on assessment of their clinical relevance or standardized differences suggesting imbalance across cohorts (Supplementary Table S3, available with the online version of this article). These propensity scores, in the form of a continuous variable, were used as covariates, along with individual component variables, to adjust Poisson regressions that were used to estimate adjusted IR ratios (IRRs) of HZ between RA and non-RA cohorts in a doubly robust approach. This approach has been previously demonstrated to perform well in each case tested, maintaining precision in effect estimates.[18] Adjusted IRRs were also stratified by patient age group for each cohort.

RESULTS

Patient demographics and baseline characteristics. Of 32,157,116 patients in the database during the study period with any records, 116,518 had an RA diagnosis using the operational definition described above. After applying all study eligibility criteria, the final study sample included 67,650 patients in the RA cohort and 11,401,743 patients in the non-RA cohort (Supplementary Figure S1, available with the online version of this article).

The baseline characteristics of both cohorts are presented in Table 1. The mean age of patients in the RA cohort was higher than that in the non-RA cohort (64.8 [SD 12.7] yrs vs 53.5 [SD 19.0] yrs; standardized difference 70.1%). This aligned with the most common type of insurance seen in each cohort, which was Medicare Advantage (usually applicable for individuals aged ≥ 65 yrs) for the RA cohort (66.7%) and commercial for the non-RA cohort (62%). The majority of patients in the RA cohort were female (76.1%), whereas a more even distribution was seen in the non-RA cohort (51.4% female).

Notably, the RA cohort had a higher comorbidity burden as measured by the mean modified CCI (0.7 [SD 1.2] vs 0.4 [SD 1.0]; standardized difference 32.8%). In particular, among the comorbidity categories measured by the CCI, the RA cohort had higher rates of chronic pulmonary disease (18.9% vs 7.5%; standardized difference 33.8%), peripheral vascular disease (9% vs 4%; standardized difference 20.4%), and moderate or severe renal disease (9.4% vs 4.2%; standardized difference 20.8%). In addition to this, the RA cohort also had a higher rate of comorbidities associated with HZ compared with the non-RA cohort (17.9% vs 2%; standardized difference 53.2%). This included Sicca syndrome (5% vs 0.1%; standardized difference 31%) and psoriasis (4.2% vs 0.6%; standardized difference 23.6%).

IRs of HZ by age group. The total number of HZ cases was 3934 in the RA cohort and 248,046 in the non-RA cohort. The total follow-up time was 182,800 PY in the RA cohort and 32,528,570 PY in the non-RA cohort (Figure 2).

Overall, the IR of HZ was higher in the RA cohort than in the non-RA cohort (21.5 vs 7.6 per 1000 PY). When stratified by age group, the IR of HZ was also consistently higher in the RA cohort compared with the non-RA cohort. The highest IRs of HZ in both cohorts were observed in the ≥ 65 years age group (23.4 and 11.4 per 1000 PY, respectively). The lowest IRs of HZ in both cohorts were seen in the 18- to 29-years age group (5.4 and 2.1 per 1000 PY, respectively). Notably, patients with RA aged < 50 years had a higher IR of HZ than patients without RA aged ≥ 50 years (15.0 vs 10.3 per 1000 PY). All stratum-specific unadjusted IRs and IRRs are presented in Figure 2.

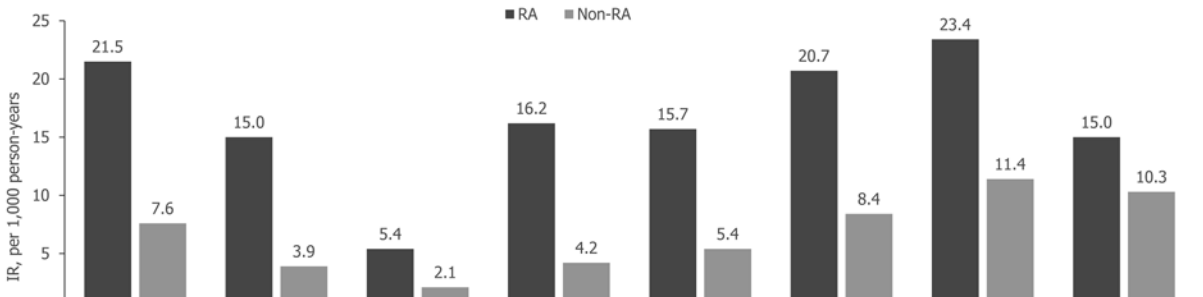
When comparing the incidence of HZ between cohorts using adjusted IRRs, the RA cohort had a significantly higher rate of HZ compared with the non-RA cohort (adjusted IRR 1.93, 95% CI 1.87-1.99; $P < 0.001$). When stratified by age, the adjusted IRRs also indicated a significantly higher rate of HZ among the RA cohort compared with the non-RA cohort for most age groups ($P < 0.001$), with the exception of the 18- to 29-years age group (adjusted IRR 1.47, 95% CI 0.79-2.74; $P = 0.23$). Notably, the adjusted IRRs were highest in the 30- to 39-years age group (adjusted IRR 2.59, 95% CI 2.10-3.18; $P < 0.001$), whereas lower adjusted IRRs were observed with increasing age groups. Further, patients with RA who were aged < 50 years had a significantly higher rate of HZ than patients without RA who were aged ≥ 50 years (adjusted IRR 1.34, 95% CI 1.20-1.49; $P < 0.001$; Figure 3).

IRs of HZ by therapy type. When stratifying the RA cohort by therapy type, the IR of HZ was highest among patients receiving systemic steroids with or without other medications (27.7 per 1000 PY). This was followed by patients receiving JAKi (24.8 per 1000 PY) and patients receiving biologics (20.8 per 1000 PY). The IR of HZ per 1000 PY in the RA cohort was lowest in patients treated with conventional DMARDs alone or receiving no treatment (16.2 per 1000 PY; Figure 4).

DISCUSSION

This retrospective database analysis aimed to provide new insights into the incidence of HZ in patients with RA in the USA, relative to the general population.

The current study used up-to-date data from a large data source that is representative of the commercially insured and Medicare Advantage–insured US population. Before this study, the most recent estimates of HZ incidence in RA had been calculated several years ago and used data sources that were not always generalizable to the entire US population. For example, an estimate by Veetil et al[8] was based on data from up until 2008,



	Overall		Age 18–49		Age 18–29		Age 30–39		Age 40–49		Age 50–64		Age 65+		Age <50 RA vs ≥50 non-RA*	
Unadjusted IRR; 95% CI, p value	**2.82**; 2.73–2.91, p<0.001		**3.81**; 3.43–4.24, p<0.001		**2.55**; 1.37–4.74, p=0.003		**3.88**; 3.17–4.76, p<0.001		**2.89**; 2.54–3.28, p<0.001		**2.46**; 2.32–2.60, p<0.001		**2.05**; 1.97–2.14, p<0.001		**1.45**; 1.31–1.62, p<0.001	
Number of patients	67,650	11,401,743	8,442	4,876,669	717	1,622,681	2,189	1,634,663	5,536	1,619,325	21,001	2,430,250	38,207	4,094,824	8,442	6,525,074
Total cases of HZ, n	3,934	248,046	343	54,031	10	9,357	94	19,198	239	25,476	1,154	57,484	2,437	136,531	343	194,015
Total follow-up time, person-years	182,800	32,528,570	22,863	13,717,134	1,855	4,429,621	5,806	4,605,601	15,203	4,681,912	55,800	6,824,799	104,136	11,986,637	22,863	18,811,436
Mean observation period, months ± SD	32.4 ± 11.8	34.2 ± 11.2	32.5 ± 10.6	33.8 ± 10.5	31.0 ± 9.8	32.8 ± 10.2	31.8 ± 10.5	33.8 ± 10.5	33.0 ± 10.7	34.7 ± 10.7	31.9 ± 11.6	33.7 ± 11.4	32.7 ± 12.1	35.1 ± 11.7	NR	NR

Figure 2. IRs and unadjusted IRRs of HZ stratified by age. Data labels above bars show IRs of HZ. IRRs represent the ratio of HZ case IRs in the RA vs non-RA cohort. Patients were followed from the index date until HZ diagnosis or censored at receipt of HZ vaccine or end of data availability, whichever occurred first. IRs were calculated by dividing the number of incident HZ events during the observation period by the patient-time observed and was reported on a per 1000 person-years basis. Adjusted IRRs are reported in Figure 3. * These data show the IRs and unadjusted IRRs for patients with RA aged < 50 years vs patients without RA aged ≥ 50 years; the multivariable model used a Poisson distribution and adjusted for the propensity score and its component covariates (ie, sex, region of residence, insurance type, CCI, comorbidities associated with HZ, immunosuppressive conditions, and use of NSAIDs as of the index date). CCI: Charlson Comorbidity Index; HZ: herpes zoster; IR: incidence rate; IRR: IR ratio; NR: not reported; NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis.

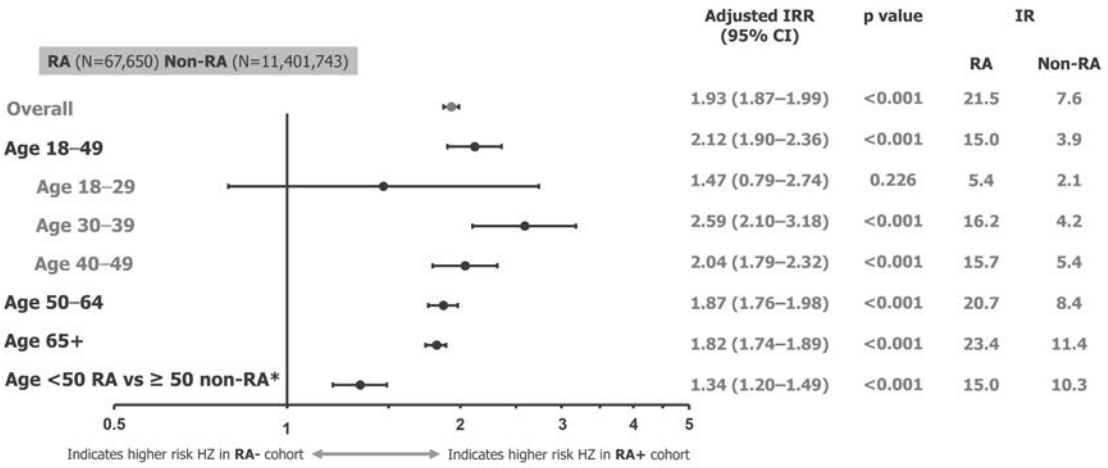
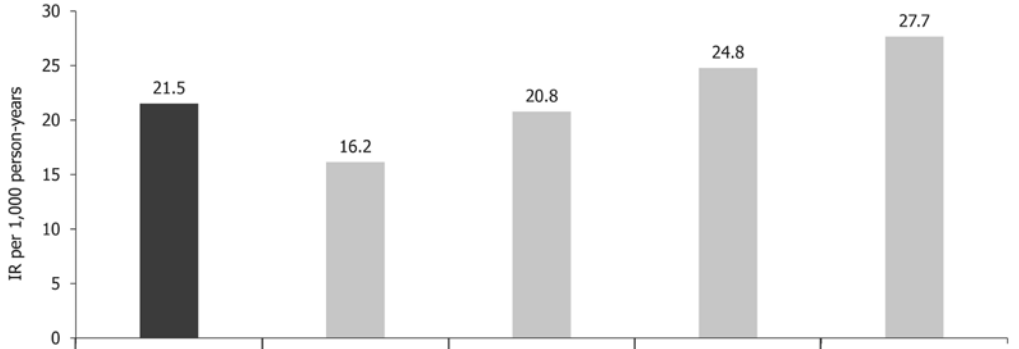


Figure 3. Comparison of HZ incidence in RA vs non-RA cohorts stratified by age. IRRs were calculated using the PROC GENMOD procedure for generalized linear models assuming a Poisson distribution and log link, accounting for the propensity score of being diagnosed with RA and relevant baseline characteristics. Baseline characteristics included as control covariates in these models were patient age, sex, region, type of insurance, CCI, any comorbidity potentially associated with HZ, any additional immunosuppressive condition, and RA management (through medication use) prior to index date. *These data show the adjusted IRRs for patients with RA aged < 50 years vs patients without RA aged ≥ 50 years; the multivariable model used a Poisson distribution and adjusted for the propensity score and its component covariates (ie, sex, region of residence, insurance type, CCI, comorbidities associated with HZ, immunosuppressive conditions, and use of NSAIDs as of the index date). CCI: Charlson Comorbidity Index; HZ: herpes zoster; IRR: incidence rate ratio; NSAID: nonsteroidal antiinflammatory drug; RA: rheumatoid arthritis.



	Overall	DMARDs alone or no treatment	Biologics with or without DMARDs	JAK inhibitors with or without DMARDs	Systemic steroids with or without any other medications
Number of patients	67,650	27,557	10,294	1,262	27,408
Total cases of HZ, n	3,934	1,223	576	87	2,011
Total follow-up time, person-years	182,800	75,710	27,718	3,510	72,673
Mean observation period, months ± SD	32.4 ± 11.8	33.0 ± 11.6	32.3 ± 11.5	33.4 ± 11.1	31.8 ± 12.1

Figure 4. IR of HZ in the RA cohort stratified by therapy type. Therapy type was assessed prior to the incident HZ event, HZ vaccination, or end of data availability. Data labels above bars show IRs. IR was calculated by dividing the number of incident HZ events during the observation period by the patient-time observed and was reported on a per 1000 person-years basis. Patients were followed from the index date until HZ diagnosis or censored at receipt of HZ vaccine or end of data availability, whichever occurred first. Attribution of medication was hierarchical based on the categories presented in this figure from left to right. DMARD: disease-modifying antirheumatic drug; HZ: herpes zoster; IR: incidence rate; JAK: Janus kinase; RA: rheumatoid arthritis.

included a smaller patient sample, and only included data from Olmsted County, Minnesota. Another study by Yun et al[11] used a large and generalizable data source comparable to the one used in this study; however, the latest data used in that study were from 2010, and the RA cohort was slightly smaller than the one observed in the current study (ie, approximately 50,600 vs 67,600 patients).

This study found the overall IR of HZ to be nearly twice as high in patients with RA than in the general population after adjusting for differences in patient baseline characteristics (unadjusted IRs of 21.5 and 7.6 per 1000 PY, respectively; adjusted IRR of 1.93), highlighting the significant burden of HZ in patients with RA. This increased incidence may be a result of the RA-related and immunosuppressive-related declining cell-mediated immunity that these patients experience, leaving them more susceptible to developing HZ.[5] These findings are supported by previous studies that also found a higher incidence of HZ in patients with RA.[5,6,8,11,19]

Notably, our study found higher IRs of HZ in patients with RA than did some previous studies that were carried out in the USA.[5] For example, a study using MarketScan data from 2005 to 2009 found the overall IR of HZ in patients with RA to be 12.2 per 1000 PY,[5] as compared with 21.5 per 1000 PY in our study. This difference may be due to the older average age of patients (64.8 years for patients with RA in our study vs 52.7 years for patients with RA in the alternate study) and an increased proportion of patients using immunosuppressive treatments for RA in this study. However, the population in the current study—using data from 2015 to 2020—reflects present trends, with increasing proportions of older individuals in the population and use of immunosuppressive drugs.[20] The higher IRs of HZ observed during the more recent time frame of this study make these findings an important contribution to the literature and allow for establishing the burden of illness nationally. Additionally, future studies could use these analyses to estimate the number of patients with RA who need to be vaccinated in order to prevent 1 case of HZ.

This study also investigated the incidence of HZ stratified by age groups. The results show that the incidence of HZ increased with age in both the RA and non-RA cohorts and was particularly high in patients 65 years of age or older. This is consistent with findings in the literature that also report on the increased incidence of HZ in older patients.[6,19,21] For example, in a previous population-based administrative claims database study in the USA, the IRs of HZ stratified by age were comparable to the rates observed in the non-RA cohort of this study; the IRs also increased with age, with patients aged 15 to 29 years having lower IRs (1.4 per 1000 PY) and patients aged 70 to 79 years having one of the highest IRs (9.5 per 1000 PY).[21]

When the cohorts were compared, the adjusted IRRs of HZ stratified by age showed significantly higher rates of HZ in the RA cohort across all age groups, with the exception of the 18- to 29-years age group. The highest adjusted IRR of HZ was observed in the 30- to 39-years age group, with the difference in HZ rates between cohorts attenuating over successive age groups. Additionally, younger patients with RA (< 50 years) had significantly higher rates of HZ than older patients without RA (≥ 50 years). This suggests that patients with RA are at a higher

relative risk of HZ at a younger age than their non-RA counterparts and older patients without RA.

There have been reports in the literature of certain immunosuppressive medications, such as systemic corticosteroids and JAKi, causing higher risk of HZ in patients with RA.[7,22-24] One study estimated the risk of HZ to be 59% higher in patients using systemic steroids, increasing with higher cumulative doses,[22] and another demonstrated a dose-dependent association between corticosteroid usage and HZ risk.[25] Here, we saw the highest incidence of HZ in patients using systemic steroids, with or without other medications (27.7 per 1000 PY). The incidence of HZ in this study was also particularly high in patients using JAKi, with or without other conventional DMARDs (24.8 per 1000 PY). JAKi have a wider pleiotropic biological effect than other RA medications, such as conventional DMARDs and biologics. This is because JAKi are able to suppress multiple cytokine signaling pathways simultaneously, as opposed to biologics, which act on a single cytokine or receptor; this may explain the trends seen in this study.[23,26] Additionally, it has been demonstrated that JAKi are able to broadly inhibit interferons, a family of cytokines required in the innate immune response to viruses, which increases the risk of HZ.[27,28]

Although this study used a large data source, included recent data, and implemented a robust statistical analysis, there were several limitations. First, although this study used diagnosis codes that were used previously by other researchers to define HZ cases, it is possible that some HZ cases may not have been identified or some cases may not have been true cases of HZ.[29,30] Second, although this study adjusted for differences in clinical and demographic characteristics that could confound the relationship with risk of HZ and RA, the data used did not have detailed clinical information, which limits the precision and accuracy with which patient characteristics could be measured and adjusted for.

This study also only recorded the RA medications that patients were using 3 to 6 months prior to the HZ event or at the end of follow-up in the case where patients were censored; therefore, this study did not account for medications and treatment patterns over a long period of time. However, despite this limitation, the findings of this study align well with previous evidence on the rate of HZ in patients with RA by medication class. Further, this analysis did not examine the effects of the calendar year. However, the patient index year could only occur in 2016, 2017, or 2018, and there was little imbalance between the cohorts; thus, it was unlikely to have meaningfully affected the results. Finally, given the mean follow-up time—32.4 months for the RA cohort and 34.2 months for the non-RA cohort—and that age was recorded at index date, patients may have moved into a higher age category by the time they experienced an incident case of HZ.

Overall, these results demonstrate that patients with RA have a higher relative risk of HZ at a younger age compared to the general population. In July 2021, the US Food and Drug Administration expanded the recombinant zoster vaccine (RZV) indication to include adults 18 years or older who are or will be at increased risk of HZ because of immunodeficiency or immunosuppression caused by disease or therapy.[31] In October 2021, the Advisory Committee on Immunization Practices recommended RZV for the prevention of HZ and related complications in immunodeficient or immunosuppressed adults aged 19 years or older.[31] Further, the Centers for Disease Control and Prevention has noted in clinical guidance that this recommendation can apply to patients with autoimmune and inflammatory conditions.[32]

In conclusion, the results of this study show that incidence of HZ was higher in patients with RA compared to those without RA. This risk increased with age, with the highest incidence observed in patients 65 years or older. Additionally, when comparing the cohorts by age group, the RA cohort had a higher risk of HZ across age groups compared with patients without RA, particularly among younger age groups, such as the 30- to 39-years age group. When stratified by RA therapy type, the highest HZ incidence was found in patients using systemic steroids with or without other medications and JAKi with or without DMARDs.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are not publicly available as they are part of Optum's CDM health administrative claims database.

ACKNOWLEDGMENT

The authors acknowledge Alexandra Enrique and Azeem Banatwala from Analysis Group Inc. for statistical programming/analysis during the study, and Ingrid Leal, GSK, USA, for publication management. The authors also thank Costello Medical for editorial assistance and publication coordination, on behalf of GSK, and acknowledge Megan Thomas, Costello Medical, UK, for medical writing and editorial assistance based on the authors' input and direction.

PLAIN LANGUAGE SUMMARY

A plain language summary of this article (text or graphical) is included as online supplementary material.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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