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Influenza and herpes zoster vaccine effectiveness in autoimmune or immune-mediated diseases

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ABSTRACT

Background: Individuals with autoimmune or immune mediated diseases (AID) are more susceptible to infections and often experience worse outcomes if infected, underscoring the importance of vaccination. However, it remains unclear whether vaccine effectiveness (VE) differs between persons with and without AID. Our aim was to compare the effectiveness of influenza and herpes zoster vaccines in both groups, where the AID group consists of individuals with either multiple sclerosis (MS), chronic inflammatory bowel disease (IBD) or chronic inflammatory rheumatic disorders (CIRD).
Methods: We emulated five target trials using claims data from a large German health insurance provider: one for herpes zoster and four for influenza across different seasons. We used 1:1 balanced risk set matching and Cox proportional hazards models with interaction terms between vaccination status and AID status to estimate VE and differences in VE across groups.
Results: For the herpes zoster trial, 169,054 vaccinated individuals were matched to the same number of controls, including 10,994 AID individuals per group. Herpes zoster VE was 68.73 (95% CI 55.75–77.91) in the AID group and 60.30 (55.59–64.52) in the non-AID group (VE ratio: 1.14, 95% CI 0.93–1.30). Across four influenza seasons (2015/2016–2018/2019) between 1403,342 and 1713,064 individuals were included, including between 56,662 and 78,320 AID individuals. Influenza VE varied by outcome, season, and assumptions, but VE ratios remained near one in most analyses (VE ratios: −0.92–3.77), with all CIs including one.
Conclusions: There was no evidence that VE differs meaningfully between individuals with and without AID, conditional on the included confounders. Both vaccines were similarly effective across groups,

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suggesting that VE is not reduced in MS, IBD, or CIRD patients. Further research is necessary to validate these findings for other AID and infections.
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Introduction

Individuals with multiple sclerosis (MS), chronic inflammatory bowel diseases (IBD), chronic inflammatory rheumatic disorders (CIRD) and other autoimmune or immune mediated diseases (AID) are more susceptible to various infectious diseases. [1–4] Two vaccine preventable diseases are influenza and herpes zoster, which can result in severe complications or, in rare cases, death. Individuals with AID are not only more likely to contract these infections, but also more likely to experience worse outcomes. [5,6] This increased susceptibility and associated worse prognosis has been theorized to be caused by the immune-system weakening effects of the disease itself, and the associated immunosuppressive medication. [7,8] The prevention of these infections is therefore of utmost importance in this susceptible population.

The primary way to prevent infectious diseases is vaccination. Accordingly, most national and international clinical practice guidelines strongly recommend influenza and herpes zoster vaccination for individuals with AID. [9–11] Although there has recently been some uptake of both vaccinations in this group, individuals with AID might still be hesitant to get vaccinated. [12–14] One important reason for this hesitancy is that the vaccine effectiveness (VE) in these individuals, compared to individuals without AID, remains unclear. Although a few randomized and observational studies have produced some evidence that the herpes zoster vaccine is safe and effective for different types of immunocompromised individuals [15,16], and for IBD [17–19] and CIRD patients [20–22] specifically, there is much less evidence for MS patients and other types of vaccines, such as influenza vaccines. [23,24] Importantly, none of the studies compared the VE in individuals with and without AID.

The main aim of this paper is therefore to compare the VE of the recombinant herpes zoster vaccine and seasonal influenza vaccines against the development of the associated disease between individuals with and without MS, IBD or CIRD. More specifically, we aim to estimate the effect modification of the VE by AID status.

Study population and methods

Study design

This study was designed according to the target trial framework. [25] In this framework, one first defines a hypothetical randomized study, the results of which are then emulated using the observed data. We performed one target trial emulation to compare the herpes zoster VE in individuals with and without AID, and four separate target trial emulations for four different influenza seasons (2015/2016, 2016/2017, 2017/2018, 2018/2019) to make the same comparison for influenza. For the herpes zoster trial, the inclusion period ranged from December 1, 2018 to December 31, 2021. For each of the influenza trials, it ranged from the first of September of the respective influenza season to May 31 of the following year. These dates were chosen without reference to observed influenza cases. All trials should be considered pragmatic, multi-centre, non-blinded trials. The study is reported according to the RECORD guidelines [26] and is part of the VAC-MAC (German: VACcinierung von MS/Arthritis/Colitis-Patient:innen) project. The study protocol was published prior to the official start of the data analysis. [27] More details on the methodology can be found in that study protocol and the statistical analysis plan contained in the appendix.

Data source and study population

Routinely collected health claims data from the German BARMER health insurance fund, collected between January the 1st 2013 and the December the 31th 2021 were used to perform all trial emulations. In all trials, only individuals aged 18 years or older, with no organ transplantation, cancer or AID other than MS, IBD or CIRD in the previous two years, who were enrolled in the BARMER health insurance fund for at least two years, with interruptions of no more than 5% of the total time, were eligible for inclusion in each study.

Disease groups

Three different diseases were considered for this study: MS, IBD, and CIRD. Individuals with one or more of these diseases were classified as having AID, whereas those without any of these diseases were classified as not having AID. The disease status was determined using different algorithms based on ICD−10 codes and (partially) treatments received by the individuals, guided by previous literature. [27].

Exposures

For the herpes zoster trial, the vaccination strategies that were compared were:

(1) Vaccination against herpes zoster using the recombinant Shingrix vaccine [28], at treatment assignment, with another vaccination after two to six months.
(2) No vaccination at treatment assignment.

For the influenza trial, the strategies were:

(1) A single vaccination against influenza, with any kind of vaccine, at treatment assignment.
(2) No vaccination at treatment assignment.

To determine the timing of vaccination against influenza or herpes zoster, we used standardized reimbursement codes, which include the date of vaccination. Because these codes are directly tied to compensation for physicians, they are expected to be sufficiently accurate. More information on the specific codes is given in the study protocol. [27].

Outcomes

The primary outcome for the herpes zoster trial was a medically attended herpes zoster manifestation, defined by the presence of ICD−10 code B02 in combination with a prescription for antiviral medication. [29] For the influenza trials, the primary outcome was a medically attended influenza infection (MAI),

identified using ICD−10 codes J09, J10 or J11. A secondary outcome was a severe MAI, defined as a MAI associated with hospitalisation or death. [30,31].

In the outpatient setting in Germany, ICD−10 codes are recorded for billing quarters only and thereby often lack exact diagnosis dates. Therefore, when no inpatient diagnosis was available, we used a standardised algorithm to assign event dates based on recorded time intervals of diagnosis, associated prescriptions, and work incapacity certificates as outlined in the study protocol. [27] If this algorithm was unable to identify a specific date, the middle of the time interval was used. The impact of these definitions on the results was studied using several sensitivity analyses, as described further below.

Confounders

The following variables were used to adjust for confounding in all analyses: age, sex, calendar time, region (first two letters of German postal codes), number of general practitioner (GP) visits and number of total physician visits in the year before study entry, presence of a pneumococcal vaccination and participation in a voluntary medical check-up in the last two years before study entry, the (modified) Charlson comorbidity index [32], number of distinct inpatient hospital stays in the last two years before study entry, the current official level of care, and a classification of medical treatments of an individual into three categories of severity in regards to immunosuppressive effect. [27,33].

In the herpes zoster analyses, we additionally adjusted for the previous presence of a chickenpox infection and for whether an individual has experienced a medically attended herpes zoster manifestation in the last six months before study entry. The former does not capture most actual chickenpox infections, because childhood is usually not included in the available time-frame. [27] For the influenza VE analysis, we additionally adjusted for prior influenza vaccination and for MAI in the previous influenza season. All confounders were identified using a causal directed acyclic graph. [27].

Statistical analysis

We used a two-stage strategy to adjust for confounding in all analyses. First, we performed balanced risk set matching [34] to generate a matched cohort for each trial, whereby each eligible individual receiving their first vaccination was matched 1:1 to an, as of this date, unvaccinated individual based on exact values of age (in years), sex, region and MS, IBD, and CIRD status. The matching date served as time zero for all subsequent analyses. [35].

Characteristics of the matched populations were described using summary statistics, stratified by both vaccination and AID status. For the influenza trials, the four separate datasets were pooled into one dataset for descriptive purposes.

Cox proportional hazards models, with the time to the first occurrence of the outcome as dependent variable, were then calculated, separately for each trial. The confounders, the AID and vaccination status were used as independent variables, with an interaction term between AID and vaccination. The primary analysis followed the per-protocol approach, in which individuals were censored whenever they deviated from their “assigned” treatment strategy. For example, if an individual used as control later received a vaccination, he or she gets censored at that time. In case of such unplanned vaccination, the matched pair of the individual was additionally censored at the same point in time, to avoid artificially induced dependent censoring. [35] AID status specific VEs and their ratios were calculated from the resulting hazard ratios, as (1 - hazard ratio) * 100. For influenza, VE ratios were pooled across seasons using inverse variance weighted meta-analyses.

Sensitivity analyses

We conducted multiple sensitivity analyses to assess the robustness of our findings. For the influenza analyses, the first three sensitivity analyses consisted of:

(1) Using the first day of the ICD−10 code based time interval as the outcome diagnosis date when no exact date was identified (Sens1)
(2) Using the last day of the interval (Sens2)
(3) Using only laboratory-confirmed influenza cases (Sens3).

For the herpes zoster analyses, sensitivity analyses 1–3 expanded the outcome definition to include all herpes zoster ICD−10 diagnosis, regardless of antiviral treatment. Diagnosis dates were assigned using the same logic as for influenza, varying the date of diagnosis for uncertain cases: first date (Sens1), middle date (Sens2) and last date (Sens3).

Sensitivity analyses 4 and 5 were applied for both influenza and herpes zoster trials:

(4) In Sens4 an additional covariate, indicating whether a medication category change occurred within 14 days after vaccination, was included in the Cox models. This sensitivity analysis is used to quantify the potential effects of a pre-planned medication change, which is unmeasured in the data but may act as a confounder.
(5) In Sens5 we randomly removed 10% of all vaccinations to quantify the potential impact of misclassification.

Finally, we conducted a negative control outcome analysis (NCO) to assess residual confounding. [36] We repeated the main analysis using urinary tract infection as the outcome, which we defined as the presence of an N39.0 ICD−10 code in combination with antibiotic treatment, following prior literature. [37] Since this outcome is not caused by the respective vaccinations, but is likely subject to the same confounding structure, deviation from a null association would suggest the presence of residual confounding. [37,38].

Results

During the herpes zoster trial period, 8583,220 individuals were insured at BARMER. Of these, 332,434 (3.87%) received at least one herpes zoster vaccination during that timeframe. After excluding individuals who never met the inclusion criteria, 209,408 potentially eligible vaccination records remained. Among these, 169,054 met all inclusion criteria at the vaccination date and were successfully matched to currently unvaccinated individual, resulting in a final dataset of 338,108 individuals. Only 493 eligible vaccinated individuals could not be matched. This matched dataset contains 316,120 (93.5%) individuals without AID and 21,988 (6.5%) individuals with AID (MS=1720; IBD=17,380; CIRD=2704; Multiple disease groups (Multi) = 184). A flowchart describing the selection process is given in Fig. 1.

For the influenza trials, 7839,336; 8621,174; 8497,766 and 8326,191 individuals were insured during the 2015/2016, 2016/2017, 2017/2018 and 2018/2019 influenza seasons respectively. After applying the inclusion criteria and matching in the same way as above, a total of 745,187; 704,430; 701,671 and 856,532 individuals were successfully matched to the same amount of at baseline unvaccinated controls. 28,331; 29,343; 31,366 and 39,160 of these were individuals with AID, respectively. Flowcharts for

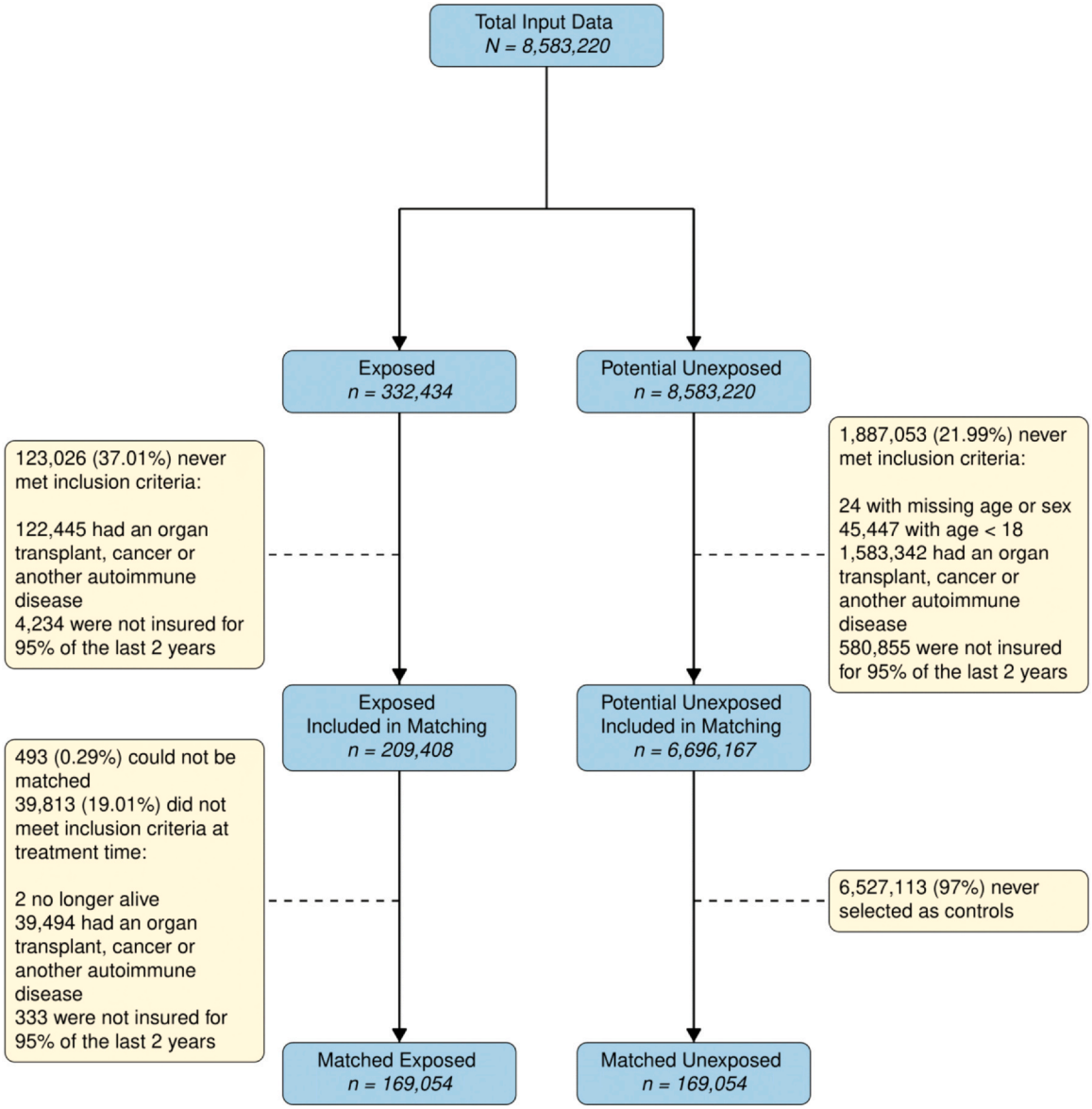

Fig. 1. Flowchart displaying the inclusion process of the herpes zoster trial emulation. "Exposed" refers to individuals who received at least one inactivated herpes zoster vaccination during the study period. "Potential Unexposed" refers to all individuals who could have received the vaccination at some point in time during the study period (including individuals who were indeed later vaccinated). Note that the "Potential Unexposed Included in Matching" is only a summary measure of the true time-dependent number of available controls. Because of the time-dependency of the inclusion criteria, 2187,435 (32.66%) of these did not fulfil the inclusion criteria at some point during the study duration. Percentages shown in beige boxes are calculated relative to the total number in the preceding blue box. The two individuals excluded due to no longer being alive at the day of matching died on the same day as they were vaccinated.

each influenza season, as well as a comparison of the observed vaccination rates with officially released vaccination rates, are provided in the online supplement.

Table 1 displays the baseline characteristics of the matched population in the herpes zoster trial, stratified by vaccination and AID status. Table 2 shows corresponding characteristics for the pooled influenza cohorts. All trials included mostly older patients, with a higher proportion of women than men. The AID group had more physician visits, GP visits and inpatient stays then the non-AID group, irrespective of vaccination. Similarly, the vaccinated groups had more contacts with both physicians in general and GP in particular. Previously vaccinated or infected individuals were more likely to get vaccinated again in all trials.

Fig. 2 displays both the AID group specific per-protocol VE estimates and the corresponding VE ratios for herpes zoster vaccination. In the main analysis, the VE was 68.73 (95% CI 55.75–77.91) in the AID group and 60.30 (55.59–64.52) in the non-AID group, yielding a VE ratio of 1.14 (0.93–1.30). This indicates no substantial difference in VE between the groups. Using all ICD−10 herpes zoster diagnoses as events (Sens1-Sens3) resulted in considerably lower values for the VE in both groups, suggesting that this alternative definition is affected by misclassification. Nevertheless, the absolute difference between the VEs remained mostly consistent to the main analysis. Additionally, the results of both Sens4 and Sens5 were almost identical to the results of the main analysis, indicating that neither the additional adjustment variable nor 10% randomly misclassified herpes zoster vaccinations have a substantial impact on the results. The associated NCO analysis showed only minimal deviations from the null effect (VE AID: −5.47, 95% CI: −9.98 to

Table 1
Baseline values in the matched data for the herpes zoster VE trial.

	AID Unvaccinated (N = 10,994)	AID Vaccinated (N = 10,994)	Non-AID Unvaccinated (N = 158,060)	Non-AID Vaccinated (N = 158,060)
Age (years)				
Mean (SD)	69.33 (8.72)	69.33 (8.72)	70.94 (7.89)	70.94 (7.89)
Range	20.00–98.00	20.00–98.00	29.00–102.00	29.00–102.00
No. (%) Male	2564 (23.3)	2564 (23.3)	53027 (33.5)	53027 (33.5)
Disease group (No. (%))				
None	0 (0.0)	0 (0.0)	158060 (100.0)	158060 (100.0)
MS	860 (7.8)	860 (7.8)	0 (0.0)	0 (0.0)
IBD	1352 (12.3)	1352 (12.3)	0 (0.0)	0 (0.0)
CIRD	8690 (79.0)	8690 (79.0)	0 (0.0)	0 (0.0)
Multi[a]	92 (0.8)	92 (0.8)	0 (0.0)	0 (0.0)
Number of physician visits in the previous year				
Mean (SD)	25.92 (17.39)	30.81 (17.19)	17.08 (14.65)	21.93 (14.67)
Range[b]	0.00–407.00	0.00–392.00	0.00–413.00	0.00–472.00
Number of GP visits in the previous year				
Mean (SD)	11.93 (8.68)	13.03 (7.97)	8.94 (7.82)	10.57 (6.87)
Range[b]	0.00–141.00	0.00–91.00	0.00–366.00	0.00–156.00
Number of inpatient stay in the previous two years				
Mean (SD)	0.78 (1.41)	0.77 (1.31)	0.50 (1.11)	0.49 (1.02)
Range	0.00–24.00	0.00–16.00	0.00–41.00	0.00–30.00
No. (%) Health check-up in the previous two years	4026 (36.6)	4889 (44.5)	53788 (34.0)	73997 (46.8)
No. (%) Pneumococcal vaccination in the previous two years	1803 (16.4)	4171 (37.9)	20260 (12.8)	53943 (34.1)
No. (%) Herpes zoster manifestation in the previous six months	74 (0.7)	210 (1.9)	733 (0.5)	2959 (1.9)
Charlson comorbidity index (No. (%))				
0	4058 (36.9)	3816 (34.7)	72594 (45.9)	62423 (39.5)
1	2606 (23.7)	2661 (24.2)	35972 (22.8)	39281 (24.9)
2	1592 (14.5)	1726 (15.7)	18297 (11.6)	21060 (13.3)
3	1075 (9.8)	1225 (11.1)	12829 (8.1)	14639 (9.3)
4	664 (6.0)	672 (6.1)	7692 (4.9)	8976 (5.7)
> = 5	999 (9.1)	894 (8.1)	10676 (6.8)	11681 (7.4)
Official level of care (No. (%))				
0	9305 (84.6)	9824 (89.4)	143303 (90.7)	149526 (94.6)
1	261 (2.4)	241 (2.2)	2324 (1.5)	1984 (1.3)
2	709 (6.4)	599 (5.4)	5984 (3.8)	4176 (2.6)
3	449 (4.1)	258 (2.3)	3810 (2.4)	1724 (1.1)
4	196 (1.8)	59 (0.5)	1769 (1.1)	510 (0.3)
5	74 (0.7)	13 (0.1)	870 (0.6)	140 (0.1)
No. (%) ever had chickenpox (in available data)	12 (0.1)	13 (0.1)	70 (0.0)	136 (0.1)
Medication category (No. (%))				
1 (no immune-suppressive effect)	7819 (71.1)	6710 (61.0)	155212 (98.2)	154649 (97.8)
2 (small to moderate immune-suppressive effect)	2794 (25.4)	3818 (34.7)	1126 (0.7)	1418 (0.9)
3 (strong immune-suppressive effect)	381 (3.5)	466 (4.2)	1722 (1.1)	1993 (1.3)

Abbreviations: GP, General practitioner; AID, Individual with either multiple sclerosis (MS), chronic inflammatory bowel disease (IBD) or chronic inflammatory rheumatic disease (CIRD); SD, standard deviation.
[a] The "Multi" category in the disease group variable refers to individuals who belong to at least two of the three considered disease groups MS / IBD / CIRD
[b] Visits to different physicians are counted as separate visits, making it possible to observe more than 366 visits for some rare individuals.

−1.15; VE Non-AID: 3.08 95% CI: −10.13–14.70), suggesting a possible slight underestimation of the VE in the non-AID group and a slight overestimation of the VE in the AID group, although the 95% CI for the latter does include null, and the 95% CI for the VE ratio (−0.56, 95% CI: −6.49–2.11) also includes one.

The group specific VE for all influenza trials and both the primary and secondary outcome are shown in Table 3. VE estimates in the main analysis varied substantially by season and outcome. For MAI, VE ranged from −18.16 (95% CI: −24.74–11.93) to 5.35 (95% CI: 1.49–9.07) in the non-AID group, and from −1.50 (95% CI: −23.18–16.37) to 9.30 (95% CI: −11.29–26.08) in the AID group. These modest or negative estimates are likely, at least partially, the result of outcome misclassification. In Sens3, where only laboratory-confirmed influenza cases were considered, the VE estimates are much higher across all trials. Similarly, VE estimates for severe MAI were also higher overall, ranging from 8.72 (95% CI: −40.60–40.74) to 28.58 (95% CI: 16.45–38.95) in the non-AID group and from −23.45 (95% CI: −238.73–54.94) to 23.33 (95% CI: −49.17–60.60) in the AID group. The negative control outcome analysis produced VE estimates consistently below the null, ranging from −12.35 to −6.36 in the non-AID group, and from −12.06–0.81 in the AID group, suggesting the presence of residual confounding, likely leading to an underestimation of VE in both groups.

Fig. 3 shows the ratios of the VE estimates for both MAI and severe MAI, pooled over all trials. In the main analysis, the VE ratio

Table 2
Baseline values in the matched data for the influenza VE trials, pooled into one dataset.

	AID Unvaccinated (N = 128,200)[a]	AID Vaccinated (N = 128,200)[a]	Non-AID Unvaccinated (N = 2879,620)[a]	Non-AID Vaccinated (N = 2879,620)[a]
Age (years)				
Mean (SD)	66.43 (13.60)	66.43 (13.60)	66.73 (15.44)	66.73 (15.44)
Range	18.00–100.00	18.00–100.00	18.00–107.00	18.00–107.00
Male	32658 (25.5%)	32658 (25.5%)	1051223 (36.5%)	1051223 (36.5%)
Disease group				
None	0 (0.0%)	0 (0.0%)	2879620 (100.0%)	2879620 (100.0%)
MS	13187 (10.3%)	13187 (10.3%)	0 (0.0%)	0 (0.0%)
IBD	17340 (13.5%)	17340 (13.5%)	0 (0.0%)	0 (0.0%)
CIRD	97073 (75.7%)	97073 (75.7%)	0 (0.0%)	0 (0.0%)
Multi[b]	600 (0.5%)	600 (0.5%)	0 (0.0%)	0 (0.0%)
Number of physician visits in the previous year				
Mean (SD)	26.33 (17.58)	30.99 (18.46)	16.42 (15.19)	22.02 (16.81)
Range[c]	0.00–437.00	0.00–445.00	0.00–543.00	0.00–587.00
Number of GP visits in the previous year				
Mean (SD)	12.01 (9.62)	13.88 (10.00)	8.41 (8.59)	11.17 (9.79)
Range[c]	0.00–366.00	0.00–247.00	0.00–387.00	0.00–401.00
Number of inpatient stays in the previous two years				
Mean (SD)	0.91 (1.59)	0.99 (1.63)	0.54 (1.18)	0.64 (1.31)
Range	0.00–33.00	0.00–29.00	0.00–303.00	0.00–310.00
Health check-up in the previous two years	64640 (50.4%)	73389 (57.2%)	1279336 (44.4%)	1614542 (56.1%)
Pneumococcal vaccination in the previous two years	8049 (6.3%)	15819 (12.3%)	124296 (4.3%)	276161 (9.6%)
Influenza infection in the previous influenza season	1298 (1.0%)	1605 (1.3%)	22577 (0.8%)	31818 (1.1%)
Charlson comorbidity index				
0	51485 (40.2%)	43469 (33.9%)	1469076 (51.0%)	1097165 (38.1%)
1	30158 (23.5%)	31595 (24.6%)	615191 (21.4%)	725422 (25.2%)
2	17574 (13.7%)	18954 (14.8%)	295118 (10.2%)	371299 (12.9%)
3	11362 (8.9%)	13005 (10.1%)	199593 (6.9%)	265748 (9.2%)
4	7192 (5.6%)	8594 (6.7%)	126529 (4.4%)	172902 (6.0%)
> = 5	10429 (8.1%)	12583 (9.8%)	174113 (6.0%)	247084 (8.6%)
Official level of care				
0	112044 (87.4%)	110886 (86.5%)	2636676 (91.6%)	2581885 (89.7%)
1	921 (0.7%)	915 (0.7%)	11850 (0.4%)	12279 (0.4%)
2	6738 (5.3%)	6814 (5.3%)	94129 (3.3%)	106696 (3.7%)
3	5322 (4.2%)	5605 (4.4%)	77120 (2.7%)	93071 (3.2%)
4	2378 (1.9%)	2842 (2.2%)	41753 (1.4%)	58898 (2.0%)
5	797 (0.6%)	1138 (0.9%)	18092 (0.6%)	26791 (0.9%)
Medication category				
1 (no immuno-suppressive effect)	90020 (70.2%)	82776 (64.6%)	2829240 (98.3%)	2810150 (97.6%)
2 (small to moderate immuno-suppressive effect)	32974 (25.7%)	39673 (30.9%)	22146 (0.8%)	30339 (1.1%)
3 (strong immuno-suppressive effect)	5206 (4.1%)	5751 (4.5%)	28234 (1.0%)	39131 (1.4%)
Influenza vaccination in the previous influenza season	21534 (16.8%)	48505 (37.8%)	382428 (13.3%)	1047263 (36.4%)

Abbreviations: GP, General practitioner; AID, Individual with either multiple sclerosis (MS), chronic inflammatory bowel disease (IBD) or chronic inflammatory rheumatic disease (CIRD); SD, standard deviation.
[a] Since individuals are eligible to be included in more than one of the four trial emulations, the shown value of N does not refer to the total number of unique individuals
[b] The "Multi" category in the disease group variable refers to individuals who belong to at least two of the three considered disease groups MS / IBD / CIRD
[c] Visits to different physicians are counted as separate visits, making it possible to observe more than 366 visits for some rare individuals.

was −0.16 (95% CI: −1.32–1.01) for MAI and 0.69 (95% CI: −1.08–2.47) for severe cases, again indicating no substantial differences in VE. As in the herpes zoster analyses, this result is stable over all performed sensitivity analyses, with all 95% Cis including one. The NCO analysis also yielded a VE ratio with a CI including one: 0.54 (95% CI: 0.00–1.09), indicating no difference in the amount of residual confounding present in the AID group-specific VE estimates.

Additional results, such as the stratified numbers of person years and events, comparisons of matched and unmatched individuals, intention-to-treat based, descriptive tables for each influenza trial, influenza trial-specific VE ratios, MS, IBD and CIRD specific VE estimates and weighting based sensitivity analyses, are provided in the online supplement.

Discussion

In this large, population-based study we emulated multiple target trials using German claims data, to compare the VE of herpes

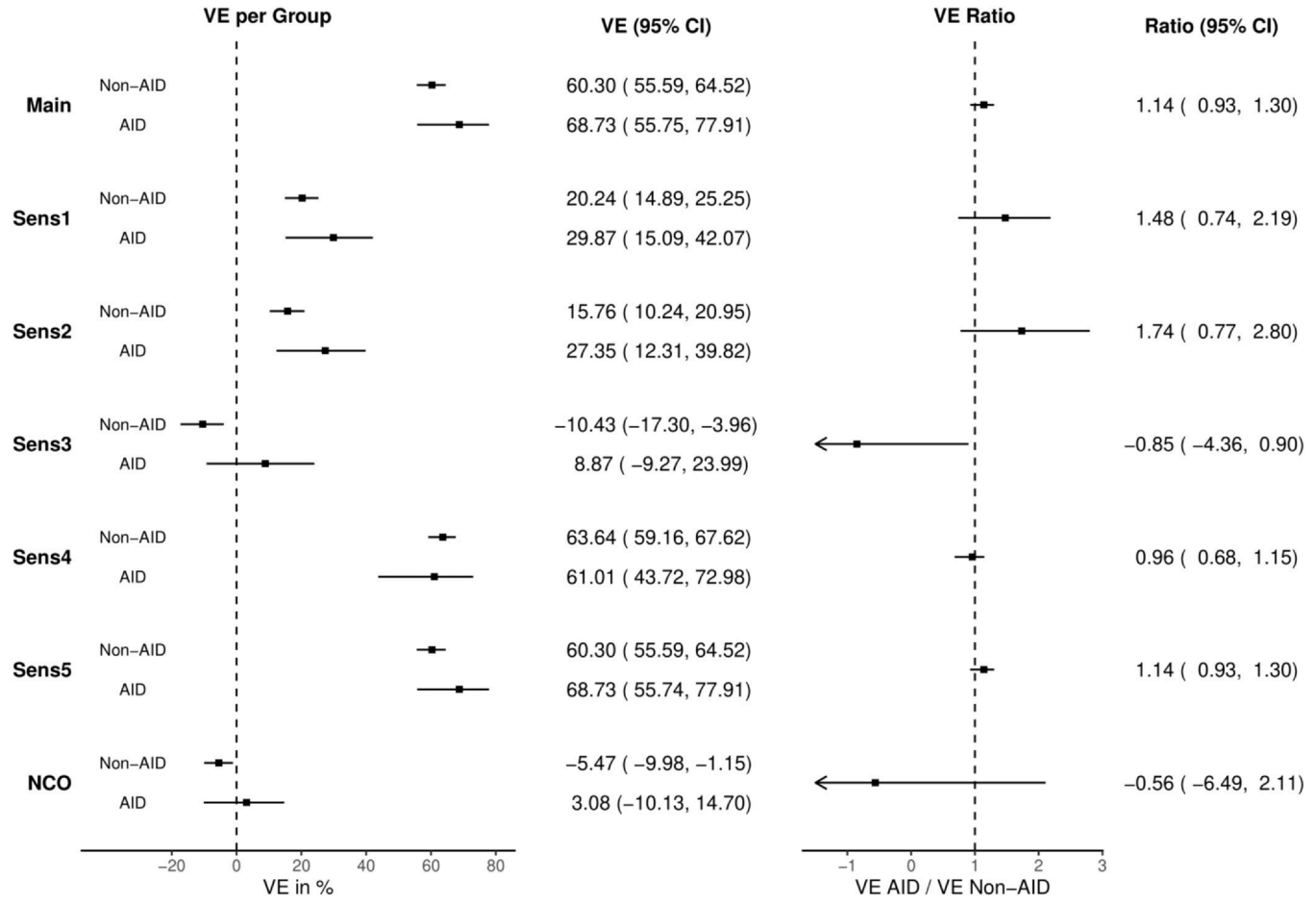

Fig. 2. Vaccine effectiveness (VE) of the inactivated herpes zoster vaccination against herpes zoster manifestation for individuals with and without autoimmune diseases (AID vs. Non-AID) and the ratio of these two values, as estimated in the main analysis, the five sensitivity analyses (Sens1-Sens5) and the negative control outcome analysis (NCO). Point estimates and 95% confidence intervals (CI) were estimated using separate multivariable Cox proportional hazards models, including all relevant confounders. 95% CI for the ratio were obtained using the Monte-Carlo method with 100,000 simulation draws.

zoster and influenza vaccines in individuals with and without MS, IBD, or CIRD. Across both vaccine types, we found no evidence of a meaningful reduction in VE among individuals with MS, IBD, or CIRD compared to those without AID, within strata of the considered confounders. These findings provide reassuring evidence that the presence of MS, IBD, or CIRD alone does not compromise VE.

Our results are consistent with and extend previous immunogenicity and observational VE studies, which generally found acceptable levels of VE for individuals with AID, but were limited to single disease cohorts, lacked control groups without AID, or were conducted outside of routine care settings. [17,18,20–24,39] To the best of our knowledge, this is the first real-world study directly comparing VE across AID and non-AID groups using a formal, pre-planned, target trial emulation approach. Importantly, our findings remained consistent across multiple sensitivity analyses, including alternative outcome definitions, adjustment for possibly pre-planned post-vaccination treatment changes and misclassification of the vaccination status.

The observed VE for herpes zoster vaccination was high in both groups, which is consistent with existing observational studies of the general population [29] and of individuals with AID in routine care settings. [17,20,29] For influenza vaccines, VE estimates were modest or even negative, depending heavily on the considered outcomes, assumptions, and influenza season. This is particularly true for general MAI, which likely captures a high proportion of non-specific respiratory infections, against which the influenza vaccine offers no protection. Notably, VE estimates were substantially higher when considering only laboratory-confirmed or severe cases. These patterns underscore the inherent limitations of using claims data to identify the presence of infectious diseases without standardized diagnosis criteria and emphasise the importance of sensitivity analyses.

Although a multi-stage strategy was employed to deal with confounding, residual confounding remains a potential concern. Our NCO analysis using urinary tract infection did suggest small degrees of residual bias, which might partially explain the low VE estimates in the influenza analyses. This residual confounding likely reflects unmeasured differences in healthcare-seeking behaviour or general susceptibility to infectious diseases. [33] However, the direction of this bias suggests that the true VE was underestimated in both groups, rather than being differentially biased by AID status. Another possible explanation for the underestimation of influenza VE is misclassification of influenza vaccination status. [40] However, as shown in a sensitivity analysis, even 10% random misclassification does not substantially change the results. Although this sensitivity analysis assumes that misclassification is independent of the outcome and considered confounders, which is likely not true in reality, it shows the robustness of balanced risk set matching against misclassification. The very large number of potential controls makes it very unlikely that individuals who were vaccinated are included in the matched control group. It is therefore unlikely that this is the reason for the underestimation.

Table 3
Person years, number of events and vaccine effectiveness values for all influenza trials.

Analysis	Trial	Group	Medically Attended Influenza			Severe Medically Attended Influenza		
			Person Years[a]	Events[a]	VE [95% CI][a]	Person Years[a]	Events[a]	VE [95% CI][a]
Main	2015/2016	AID	26,150	310	1.36, [−23.98, 21.52]	26,242	6	2.02, [−410.44, 81.19]
		Non-AID	697,169	6497	−18.16, [−24.74, −11.93]	699,249	98	8.72, [−40.60, 40.74]
	2016/2017	AID	26,490	388	9.30, [−11.29, 26.08]	26,616	16	−23.54, [−238.73, 54.94]
		Non-AID	642,176	7515	−10.15 [−15.76, −4.81]	644,555	375	7.46, [−14.93, 25.48]
	2017/2018	AID	28,809	617	5.79, [−10.81, 19.90]	28,972	53	17.33, [−44.45, 52.69]
		Non-AID	642,102	11,863	5.35, [1.49, 9.07]	645,349	768	28.58, [16.45, 38.95]
	2018/2019	AID	34,759	437	−1.50, [−23.18, 16.37]	34,880	37	23.33, [−49.17, 60.60]
		Non-AID	767,605	7902	−0.40, [−5.37, 4.34]	769,886	633	20.29, [5.45, 32.80]
Sens1	2015/2016	AID	26,152	296	3.62, [−21.77, 23.72]	26,242	6	2.02, [−410.43, 81.19]
		Non-AID	697,224	6287	−13.90, [−20.33, −7.81]	699,249	98	8.73, [−40.60, 40.75]
	2016/2017	AID	26,497	375	12.02, [−8.32, 28.55]	26,616	16	−23.70, [−239.22, 54.89]
		Non-AID	642,217	7302	−5.84, [−11.31, −0.64]	644,554	373	7.23, [−15.28, 25.35]
	2017/2018	AID	28,807	609	10.66, [−5.20, 24.12]	28,972	53	17.57, [−44.05, 52.83]
		Non-AID	642,063	11,672	6.94, [3.11, 10.63]	645,350	765	28.66, [16.51, 39.04]
	2018/2019	AID	34,759	417	0.46, [−21.33, 18.33]	34,880	37	23.43, [−48.99, 60.65]
		Non-AID	767,634	7669	−0.19, [−5.23, 4.60]	769,886	631	19.80, [4.84, 32.41]
Sens2	2015/2016	AID	26,140	324	−20.46, [−50.82, 3.79]	26,242	6	9.02, [−372.20, 82.47]
		Non-AID	696,970	6857	−40.15, [−47.79, −32.91]	699,249	106	18.72, [−23.33, 46.43]
	2016/2017	AID	26,484	411	−6.24, [−29.71, 12.98]	26,616	16	−22.93, [−236.95, 55.15]
		Non-AID	642,067	7793	−23.96, [−30.18, −18.04]	644,554	381	6.86, [−15.46, 24.86]
	2017/2018	AID	28,805	643	−3.67, [−21.56, 11.59]	28,972	54	13.65, [−50.03, 50.30]
		Non-AID	642,019	12,173	−2.86, [−7.00, 1.11]	645,349	782	26.97, [14.71, 37.46]
	2018/2019	AID	34,748	454	−14.09, [−38.09, 5.74]	34,880	37	23.18, [−49.46, 60.51]
		Non-AID	767,432	8201	−14.99, [−20.59, −9.64]	769,886	639	18.94, [3.94, 31.59]
Sens3[b]	2015/2016	AID	26,352	27	−34.33, [−196.10, 39.06]	NA	NA	NA
		Non-AID	702,535	533	1.85, [−18.44, 18.67]	NA	NA	NA
	2016/2017	AID	26,701	46	8.62, [−65.59, 49.58]	NA	NA	NA
		Non-AID	646,644	957	0.07, [−14.80, 13.02]	NA	NA	NA
	2017/2018	AID	29,055	118	16.12, [−21.63, 42.16]	NA	NA	NA
		Non-AID	647,424	2158	22.44, [14.75, 29.43]	NA	NA	NA
	2018/2019	AID	34,982	76	28.71, [−13.38, 55.18]	NA	NA	NA
		Non-AID	772,428	1403	24.22, [14.94, 32.48]	NA	NA	NA
Sens4	2015/2016	AID	24,036	279	−20.22, [−53.16, 5.64]	24,119	8	70.39, [−54.78, 94.34]
		Non-AID	630,849	5875	−19.35, [−25.94, −13.11]	632,734	93	21.12, [−20.33, 48.29]
	2016/2017	AID	24,337	352	−3.88, [−28.86, 16.25]	24,449	18	7.65, [−138.22, 64.20]
		Non-AID	581,676	6845	−9.79, [−15.60, −4.28]	583,837	356	19.63, [−0.37, 35.64]
	2017/2018	AID	26,369	575	4.93, [−12.47, 19.65]	26,519	45	1.92, [−79.32, 46.36]
		Non-AID	581,203	10,934	9.22, [5.39, 12.89]	584,181	713	30.43, [18.31, 40.76]
	2018/2019	AID	32,120	390	−14.50, [−40.68, 6.81]	32,231	34	18.03, [−63.88, 59.00]
		Non-AID	696,955	7261	1.45, [−3.61, 6.26]	699,078	601	23.99, [9.62, 36.07]
Sens5	2015/2016	AID	26,150	310	1.39, [−23.95, 21.54]	26,242	6	1.95, [−410.83, 81.18]
		Non-AID	697,169	6497	−18.11, [−24.69, −11.89]	699,249	98	8.69, [−40.66, 40.72]
	2016/2017	AID	26,490	388	9.47, [−11.08, 26.22]	26,616	16	−23.54, [−238.73, 54.94]
		Non-AID	642,176	7515	−10.06, [−15.67, −4.73]	644,555	375	7.42, [−14.97, 25.46]
	2017/2018	AID	28,809	617	5.73, [−10.88, 19.85]	28,972	53	17.38, [−44.37, 52.72]
		Non-AID	642,102	11,863	5.40, [1.54, 9.12]	645,349	768	28.57, [16.43, 38.94]
	2018/2019	AID	34,759	437	−1.47, [−23.14, 16.39]	34,880	37	23.34, [−49.15, 60.60]
		Non-AID	767,605	7902	−0.31, [−5.27, 4.43]	769,886	633	20.32, [5.48, 32.82]
NCO[c]	2015/2016	AID	25,634	2005	0.81, [−8.57, 9.38]	25,634	2005	0.81, [−8.57, 9.38]
		Non-AID	688,941	34,037	−7.65, [−10.19, −5.17]	688,941	34,037	−7.65, [−10.19, −5.17]
	2016/2017	AID	26,022	2036	−12.06, [−22.66, −2.38]	26,022	2036	−12.06, [−22.66, −2.38]
		Non-AID	635,339	31,730	−6.36, [−8.92, −3.85]	635,339	31,730	−6.36, [−8.92, −3.85]
	2017/2018	AID	28,348	2099	−8.54, [−18.63, 0.69]	28,348	2099	−8.54, [−18.63, 0.69]
		Non-AID	636,148	31,539	−7.09, [−9.72, −4.52]	636,148	31,539	−7.09, [−9.72, −4.52]
	2018/2019	AID	34,203	2449	−4.65, [−13.63, 3.62]	34,203	2449	−4.65, [−13.63, 3.62]
		Non-AID	759,601	35,980	−12.35, [−14.92, −9.84]	759,601	35,980	−12.35, [−14.92, −9.84]

Abbreviations: AID, Individual with either multiple sclerosis (MS), chronic inflammatory bowel disease (IBD) or chronic inflammatory rheumatic disease (CIRD); SD, standard deviation; VE, vaccine effectiveness; CI, confidence interval; NCO, negative control outcome analysis.

[a] Both person years and events are crude values, calculated using the matched data. The VEs and associated 95% CIs were derived from separate multivariable Cox proportional hazards models, including the relevant confounders.

[b] Sensitivity analysis 3 (Sens3) was not performed for the severe medically attended influenza, because severe cases are a lot less likely to be misclassified and due to the already low number of events in this analysis.

[c] The NCO analysis does not differ between moderate and severe cases and thus has identical values.

Our study has several strengths, including a large and representative population, matching on key confounders, and extensive sensitivity analyses. Nevertheless, some limitations must be acknowledged. First, not all confounders are directly observable using only claims data, limiting the possibilities for confounder adjustment. Secondly, although our algorithms for the identification of outcome and vaccination status were used in previous studies [27], misclassification cannot be ruled out. Finally, the study only covered three AID groups and two vaccine types. It is possible that our results do not generalise completely to other settings.

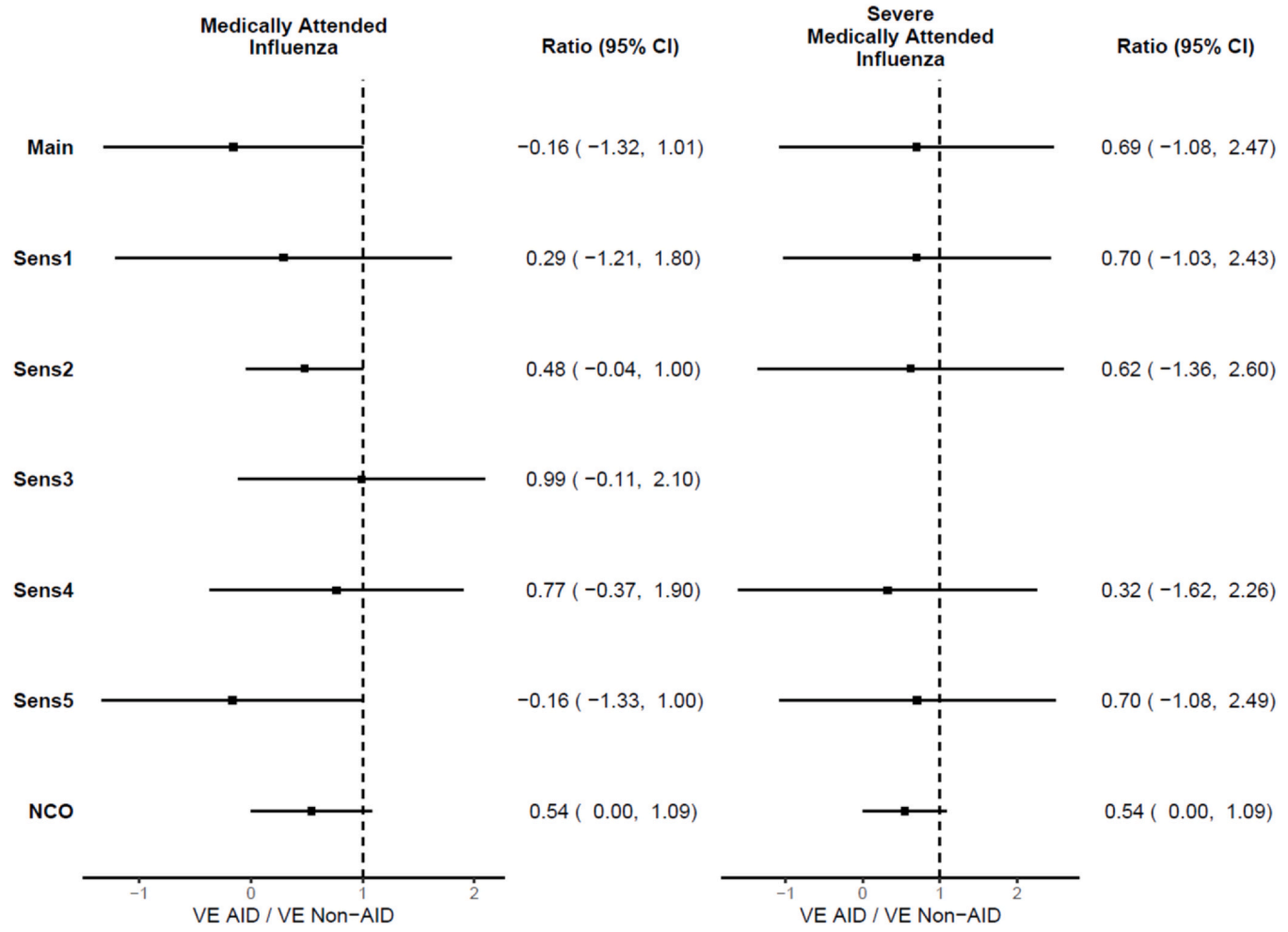

Fig. 3. Ratios of the influenza vaccine effectiveness (VE) of individuals with autoimmune diseases (AID) vs. individuals without autoimmune diseases (Non-AID), and associated 95% confidence intervals (CI), against medically attended influenza and severe medically attended influenza, pooled over all four performed trials using inverse variance weighted meta-analyses. The 95% CI for the pooled values were calculated using a normal approximation based on the 95% CI of the trial-specific estimates. The values are shown for the main analysis, the five sensitivity analyses (Sens1-Sens5), and the negative control outcome analysis (NCO). Sensitivity analysis 3 (Sens3) was not performed for the severe medically attended influenza, because severe cases are a lot less likely to be misclassified. The NCO analysis does not differ between moderate and severe cases and is thus identical.

Conclusions

In conclusion, this study provides robust evidence that the effectiveness of herpes zoster or influenza vaccination is not substantially diminished in the presence of MS, IBD or CIRD. These findings support current recommendations for timely vaccinations in AID individuals [9–11], particularly before initiating immunosuppressive therapies. Further studies should explore vaccine timing in regard to such therapies, and real-world VE for other infectious diseases, such as pneumococcal infections or Covid−19, in this susceptible population.

List of abbreviations

AID: autoimmune or immune-mediated disease; CIRD: chronic inflammatory rheumatic diseases; GP: general practitioner; IBD: chronic inflammatory bowel diseases; ICD−10: international classification of diseases 10; MAI: medically attended influenza infection; MS: multiple sclerosis; NCO: negative control outcome; VAC-MAC: VACcinierung von MS/Arthritis/Colitis-Patient:innen; VE: vaccine effectiveness.

CRediT authorship contribution statement

KH, IM, HCV, NT, UK, AS were involved in the funding acquisition for this study. TO, KH, IM, and NT were involved in project administration. RD, JB, KM, MT, and NT contributed to the methodological and statistical considerations of the study. RD and HVDS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. RD, HVDS, JB, KM, MT, IM, UM, JS, CH, KR, DS, AS, NT, and CT helped to provide and prepare the required data, and thus also had full access to and verified the data. RD, HVDS, JB, KM, MT, TO, TG, SST, DS, AS, UK, MZ, HCV, ICO, CG, RL, AST, AF, KR, IM, KH, and NT contributed to the formal definitions of the disease groups, outcomes and confounders. RD wrote the statistical analysis plan and performed the statistical analysis. RD wrote the first draft of the manuscript. All authors contributed to the formulation of the study questions and associated target trials, the writing of the study protocol and the final manuscript, and were involved in the decision to submit the manuscript.

Ethics approval

No ethical approval was needed for this study, because only already existing anonymized health claims data was analysed.

Statement regarding the use of AI

ChatGPT version 4.5 was partially used to edit the manuscript texts for better readability. AI was not used for any parts of the analysis or interpretation of the findings. All outputs were carefully reviewed and revised by the authors, who take full responsibility for the final content of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2026.103296.

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