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Herpes zoster vaccine and the risk of stroke: a population-based cohort study using linked data from the Clinical Practice Research Datalink

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This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the authors alone. HES APC and ONS death certificate data are Copyright © 2022, and were re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

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ABSTRACT

Background Studies report herpes zoster associated with short-term stroke risk, but it is unclear whether herpes zoster vaccine reduces stroke risk.

Methods We performed cohort studies using Clinical Practice Research Datalink Aurum linked to hospital admission, mortality and deprivation data. We included 678 110 adults aged 70–80 years receiving a live attenuated herpes zoster vaccination between 1 September 2013 and 31 December 2019. We conducted three comparisons to a historical unvaccinated cohort, an active comparator and a self-controlled case series (SCCS). The historical cohort comprised 678 110 matched unvaccinated adults between 2007 and 2012. The active comparator comprised 653 373 adults receiving an influenza vaccination between 2013 and 2019 meeting herpes zoster vaccine eligibility. Cox regression was used to estimate HRs for stroke in the subsequent 5 years adjusted for measured confounders, in the vaccinated compared with comparator cohorts. Secondary outcomes included stroke/transient ischaemic attack and myocardial infarction. The SCCS included incident strokes 12 months before or after herpes zoster vaccination to address healthy vaccinee bias.

Results We recorded 16 281 and 30 430 incident strokes among vaccinated and unvaccinated historical patients, over a median of 2.7 and 5.0 years follow-up, respectively. The adjusted HR for stroke for herpes zoster vaccination compared with unvaccinated historical patients was 0.84 (95% CI 0.82 to 0.86) and to influenza-vaccinated patients was 0.88 (0.85 to 0.89). However, stroke incidence rates were lower in the herpes zoster-vaccinated group prevaccination compared with both comparator cohorts. The SCCS found no association between herpes zoster vaccination and stroke 30–119 days later.

Conclusions Despite our cohort study, with extensive confounder adjustment and an influenza vaccination active comparator, finding herpes zoster vaccination associated with 12%–16% reduced stroke rates, additional analyses suggested this was largely explained by healthy vaccinee bias. Our study illustrates the importance of robust sensitivity analyses and testing the suitability of causal inference tools for observational vaccine studies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Stroke occurs when a blood vessel carrying nutrients and oxygen to a part of the brain becomes blocked by a clot or ruptures; it is the fourth leading cause of death in the UK.

⇒ Reactivation of varicella zoster virus (chickenpox) in adults results in herpes zoster (shingles), particularly in those aged 50 years or older.

⇒ Studies report herpes zoster infection is associated with short-term excess stroke risk.

WHAT THIS STUDY ADDS

⇒ In this large population-based cohort study from 41.2 million patient records, modest stroke risk reductions were associated with receipt of herpes zoster live attenuated vaccine compared with unvaccinated individuals.

⇒ However, sensitivity analysis including a self-controlled case series suggested the protective effect may be largely explained by healthy vaccinee bias.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance of robust sensitivity analyses and testing the suitability of causal inference tools for observational vaccine studies.

INTRODUCTION

Stroke is a non-specific injury to the brain as a result of lack of blood supply (ischaemic) or a ruptured blood vessel (haemorrhagic) and is the fourth leading cause of death in the UK and North America, with an incidence of 37.6 and 50.1 per 100 000 population, respectively.[1 2] Stroke can cause significant disability resulting in an estimated aggregate social annual cost of £26 billion.[3] In addition to well-recognised risk factors for stroke,[4] studies have found associations with positive serology for several pathogens including herpes viruses, such as zoster virus.[5–7]

The varicella zoster virus commonly infects children. After this primary infection, it can lie dormant in the spinal and cranial sensory ganglia. Later in life, it can be reactivated, resulting in herpes zoster (HZ), commonly known as shingles.[8 9] The incidence of HZ was around 3.2–3.7 per 1000 person-years in the UK in the prevaccine era,[10] and was similar in Europe.[11] Incidence rises steeply after the age of 50 years,[12] likely related to a decrease in T-cell immunity with ageing and immunosuppression.[13 14]

Recently, several studies identified transient ischaemic attack (TIA) and stroke as additional neurological complications associated with HZ. By pooling data from nine studies in meta-analysis, we estimated the relative risk for stroke after HZ as 1.78 (95% CI 1.70 to 1.88) in the month following infection, decreasing to 1.20 (95% CI 1.14 to 1.26) for 1 year.[15] In addition, stroke risk increases markedly in the month following HZ ophthalmitis (relative risk 2.05; 95% CI 1.82 to 2.31), and remains elevated for a further year.[16 17] Evidence suggests stronger associations in younger people.[18] Furthermore, studies report moderate and transient increased risks of myocardial infarction (MI) and acute coronary syndrome soon after HZ infection.[19–22]

Vaccines may offer an opportunity to avoid the downstream neurological consequences of zoster disease. Two vaccines are licenced to prevent HZ: a live, attenuated Oka/Merck HZ vaccine (Zostavax, developed by Merck & Co, licensed in 2006)[23 24] and an adjuvanted subunit zoster recombinant zoster vaccine (Shingrix, developed by GlaxoSmithKline, licensed in 2017).[25 26] The UK introduced an HZ vaccination programme in September 2013 offering Zostavax to those 70 years of age, with a phased catch-up campaign for individuals aged 78–79 years.[27 28] Shringrix vaccine was not recommended for use in the UK until September 2021.[29]

The introduction of the UK programme offers an opportunity to compare vaccinated individuals with an historical comparator group who did not receive the vaccine. We aimed to investigate whether there were fewer incident strokes, TIAs and MI in those receiving Zostavax in England compared with matched patients in previous years before the national zoster vaccination programme. To help address healthy user biases, we also compared an active comparator cohort given an influenza vaccination during 2013–2019 while eligible for the HZ vaccine. Additionally, we conducted a self-controlled case series (SCCS) analysis in HZ vaccinees.

METHODS

Data sources

We used data from patients in England from the Clinical Practice Research Datalink (CPRD) Aurum primary care database, which contains anonymised registration, prescription, diagnoses and referral data. CPRD Aurum includes 41.2 million patient records and is broadly representative of the English population.[30] We also used linked Hospital Episode Statistics Admitted Patient Care (HES APC), Office for National Statistics (ONS) and Index of Multiple Deprivation (IMD) datasets.[31] HES APC data include information on demographics, diagnoses (coded using International Classification of Diseases 10th revision (ICD-10)) and procedures undertaken during hospital admissions.[32] The ONS records death dates and cause of death (ICD-10 coded). IMD combines indicators of housing, employment, income, education and environment at the patient's postal code level.[33]

Cohort study populations

We included patients registered with a contributing general practitioner (GP) in England between 2007 and 2019 when aged 70–80 years. To preserve patient anonymity, CPRD does not release the patient's birth month and day. We allocated each patient's birthday as 1 January, and as such, included patients estimated to be 70–80 years of age to encompass individuals truly aged 70–79 years. Patients were considered exposed when they first received an HZ vaccine between September 2013 and December 2019, aged 70–80 years (this defined their index date). Receipt of the HZ vaccine was determined by the first product code for the vaccine or medical code for vaccine administration, without codes for non-consent, refusal or contraindication on the same day (online supplemental appendix 1 for code list).

For each HZ vaccine-exposed patient, we matched (without replacement) a patient of the same sex and age in 2007–2012. We assigned the HZ vaccine date month and day from the vaccine-exposed patient to the matched, vaccine-unexposed patient to define the index date in this historical cohort.

To address healthy initiator bias and calendar year effects, we also additionally conducted a comparison with an active comparator with an index date defined as the first receipt of the influenza vaccine while eligible for the HZ vaccine in age groups 70–72 or 78–80 years.[34] We hypothesised that unmeasured determinants of vaccination uptake (such as health-seeking behaviour, healthcare access and frailty) would be similar for influenza and zoster vaccination. Our study population was eligible by age for both vaccines which are predominantly delivered by National Health Service primary care.

Patients with a stroke history or <12 months of GP registration before the index date were excluded from all cohorts.

We used the unique HES patient key to remove duplicate patient records in the database. Patients were followed up until the first of the following events: death (as recorded by ONS), leaving the GP practice, 30 days before the last GP practice data collection,[35] 30 days before the first HZ vaccination (in the unvaccinated), 1 March 2020 (due to reduced stroke recording during the COVID-19 pandemic)[36] or 5 years after the index date.

Outcomes

The primary outcome was incident stroke (ischaemic, haemorrhagic or unspecified), defined as the first

diagnosis code for stroke in either CPRD Aurum, HES APC or ONS data.[37] The ICD-10 codes I60–I64 were used to define stroke diagnosis in HES APC and death caused by stroke in ONS.[38] The secondary outcomes were stroke/TIA and MI again detected in either CPRD Aurum, HES APC or ONS and excluded patients with history of the particular outcome.[39] Codes for identifying the outcomes are provided in online supplemental appendix 1.

Covariates

Potential confounders selected included demographic and socioeconomic factors (including ethnicity and deprivation),[40] health behaviours (including smoking status, alcohol abuse, body mass index (BMI) and recent influenza vaccination), comorbidities, components of frailty,[41] healthcare utilisation and medication use associated with either vaccine uptake,[42] vaccine effectiveness[28 43] or stroke risk.[44 45] Our covariate definitions and model variable selection strategy are described in the online supplemental appendix 2 and table 1.

Statistical analysis

Cox proportional hazards regression was used to estimate HRs for incident stroke for those vaccinated compared with the two unvaccinated cohorts, both unadjusted and adjusted for selected confounders. We checked the proportional hazards assumption via the scaled Schoenfeld residuals.[46] However, we also report the HR over time, as the vaccine is reported to reach peak effectiveness 42 days postvaccination and remain effective for up to 5 years, although reducing over this period.[28] We adjusted for appropriate parameterisations of calendar time where necessary.[47]

We tested the following prespecified interactions with HZ vaccination: age group (70–72 vs 78–80 years), sex, immunosuppression, history of HZ, antihypertensive use and statin use. We hypothesised weaker associations in older patients, men, immunosuppressed patients and those with recent HZ infection due to possible reductions in vaccine effectiveness.[28 48] In another study, greater protective effects on stroke risk were reported in those taking antihypertensive medications and statins.[48]

Missing data were observed for ethnicity, BMI, systolic blood pressure, IMD and smoking. Since data were unlikely missing at random, we did not perform multiple imputations.[49–52] The primary analysis included a separate missing category for each variable with missing data (and categorised continuous variables). However, we performed sensitivity analyses reporting the complete case analysis and models where we assigned the most common category for each variable with missing data.

To verify our HZ vaccine coding, we also compared the HR for incident HZ diagnoses with those from another study.[28] We performed sensitivity analyses censoring the historical cohort at 1 March 2013 to mirror the reduced follow-up due to censoring at 1 March 2020 in the other cohorts, and restricted to only ages 70–72 and 78–80 years. Stata V.17 was used for data management and statistical analysis.

Additional analyses

To check the suitability of influenza vaccine as an active comparator for controlling healthy initiator bias, we additionally compared the monthly incidence rates of non-fatal stroke in the 9 months before and after the vaccination date.

As this suggested time-fixed residual confounding, we conducted an SCCS analysis to control for time-fixed variables by design (online supplemental eFigure 1).[53] To check the suitability of influenza vaccine as an active comparator for controlling healthy initiator bias, we additionally compared the monthly incidence rates of non-fatal stroke in the 9 months before and after the vaccination date. We mirrored the selection of the three cohorts above but instead excluded patients with a history of stroke 9 months before the index date (rather than by the index date). We estimated the incidence rates of non-fatal stroke (excluding strokes with mortality within 28 days) in the nine 30-day period before and after the index date. As we had only extracted linked hospital data for patients with no stroke history before January 2007 or January before turning 70 years old, we excluded denominator periods before these dates. A base Poisson regression model was used to estimate incidence rates adjusted for cohort, age, sex, month, monthly mean air temperature in England, vaccination month and age×sex interaction. After adding interactions between the cohort and both month and vaccination month, we used Stata's margins command to plot the adjusted incidence rates. We also used the base Poisson regression model to estimate the incidence rate ratios (IRR) in the influenza-vaccinated and historical comparators compared with the HZ-vaccinated cohort 1–9 months before vaccination.

As the above Poisson model tests and plot suggested time-fixed residual confounding, we conducted an SCCS analysis to control for time-fixed variables by design.[53] To allow sufficiently wide periods to adjust for seasonal stroke risk variability,[54] the observation period was 12 months prevaccination and postvaccination (see online supplemental eFigure 1 for additional inclusion criteria). We chose the risk window as the first 1–4 months where the vaccine reaches peak effectiveness. The pre-exposure window is designed to address potential bias from the study outcome (stroke) conditioning the probability of exposure to vaccination.[53] Since stroke is a severe outcome which may impact on vaccination uptake during recovery, we allowed a reasonably long pre-exposure window of 30 days in our study. Conditional Poisson regression was used to estimate IRRs during each of the first 4 months postvaccine compared with baseline (1–12 months prevaccination and 5–12 months postvaccination), adjusted for time-varying monthly age and mean air temperature. We examined the histograms of both time from vaccination to stroke and to end of follow-up,

Table 1 Characteristics of patients receiving herpes zoster vaccination, matched unvaccinated patients and patients receiving an influenza vaccination from CPRD Aurum

Characteristic	Herpes zoster-vaccinated cohort (n=678 110)	Historical unvaccinated cohort (n=678 110)	Contemporary cohort with influenza vaccine (n=653 373)
Women	356 308 (52.5%)	356 308 (52.5%)	345 853 (52.9%)
Age, years*	74.0 (4.0)	74.0 (4.0)	73.7 (4.1)
Age 70–72 years	380 656 (56.1%)	380 656 (56.1%)	368 695 (56.4%)
Age 78–80 years	262 658 (38.7%)	262 658 (38.7%)	284 678 (43.6%)
Ethnicity			
White	632 666 (93.3%)	631 797 (93.2%)	607 114 (92.9%)
Asian	22 390 (3.3%)	18 451 (2.7%)	21 794 (3.3%)
Black	9417 (1.4%)	12 917 (1.9%)	10 778 (1.6%)
Other/Mixed	7625 (1.1%)	6658 (1.0%)	7735 (1.2%)
IMD decile (patient level)*	4.8 (2.8)	5.1 (2.8)	4.9 (2.8)
Season (of index date)			
Spring	70 852 (10.4%)	70 852 (10.4%)	1734 (0.3%)
Summer	84 405 (12.4%)	84 405 (12.4%)	2831 (0.4%)
Autumn	403 783 (59.5%)	403 783 (59.5%)	612 424 (93.7%)
Winter	119 070 (17.6%)	119 070 (17.6%)	36 384 (5.6%)
Smoking status			
Non-smoker	205 283 (30.3%)	232 208 (34.2%)	191 592 (29.3%)
Ex-smoker	340 745 (50.2%)	276 518 (40.8%)	325 598 (49.8%)
Current smoker	130 727 (19.3%)	164 890 (24.3%)	135 049 (20.7%)
Alcohol abuse	20 196 (3.0%)	12 695 (1.9%)	21 462 (3.3%)
Body mass index (kg/m^2)*	27.9 (5.2)	27.4 (5.1)	27.8 (5.3)
Systolic blood pressure (mm Hg)*	134.0 (14.1)	137.0 (15.6)	134.1 (14.6)
Requirement for care	40 464 (6.0%)	24 992 (3.7%)	44 528 (6.8%)
Mobility problem/activity restriction/housebound	35 889 (5.3%)	37 390 (5.5%)	41 948 (6.4%)
Medical history in past year			
Fracture	15 576 (2.3%)	13 795 (2.0%)	16 252 (2.5%)
Urinary incontinence	24 355 (3.6%)	19 532 (2.9%)	23 746 (3.6%)
Physician consultations†	16 (5–9)	18 (5–10)	17 (5–10)
Hospital admissions*	0.5 (2.5)	0.6 (3.4)	0.7 (3.6)
Medical history in last 3–5 years			
Herpes zoster (last 3 years)	20 251 (3.0%)	16 536 (2.4%)	17 284 (2.6%)
Time since last influenza vaccination			
≤12 months	622 061 (91.7%)	510 385 (75.3%)	653 373 (100.0%)
13–60 months	26 631 (3.9%)	76 657 (11.3%)	
>60 months	7388 (1.1%)	12 420 (1.8%)	
No record	22 030 (3.2%)	78 648 (11.6%)	
Time since last pneumococcal vaccination			
≤12 months	57 426 (8.5%)	66 486 (9.8%)	54 709 (8.4%)
13–60 months	150 740 (22.2%)	289 274 (42.7%)	165 127 (25.3%)
>60 months	305 426 (45.0%)	110 592 (16.3%)	260 956 (39.9%)
No record	164 508 (24.3%)	211 758 (31.2%)	172 581 (26.4%)
Comorbidities			
Transient ischaemic attack	23 872 (3.5%)	26 901 (4.0%)	23 911 (3.7%)
Brain injury	2215 (0.3%)	1278 (0.2%)	2187 (0.3%)

Continued

Table 1 Continued

Characteristic	Herpes zoster-vaccinated cohort (n=678 110)	Historical unvaccinated cohort (n=678 110)	Contemporary cohort with influenza vaccine (n=653 373)
Dementia	17 002 (2.5%)	13 024 (1.9%)	20 461 (3.1%)
Depression	174 458 (25.7%)	140 446 (20.7%)	176 408 (27.0%)
Epilepsy	39 902 (5.9%)	24 119 (3.6%)	41 203 (6.3%)
Parkinson's disease	7563 (1.1%)	8189 (1.2%)	8699 (1.3%)
Severe mental illness	14 433 (2.1%)	10 517 (1.6%)	15 255 (2.3%)
Coronary heart disease	119 698 (17.7%)	126 767 (18.7%)	121 997 (18.7%)
Heart failure	45 809 (6.8%)	44 425 (6.6%)	49 231 (7.5%)
Atrial fibrillation	73 332 (10.8%)	60 772 (9.0%)	73 463 (11.2%)
Myocardial infarction	75 231 (11.1%)	71 616 (10.6%)	76 375 (11.7%)
Hypertension (treated)	409 543 (60.4%)	397 827 (58.7%)	399 128 (61.1%)
COPD	69 521 (10.3%)	60 802 (9.0%)	73 808 (11.3%)
Diabetes	146 593 (21.6%)	114 537 (16.9%)	145 478 (22.3%)
Inflammatory bowel disease	10 190 (1.5%)	8207 (1.2%)	10 910 (1.7%)
Irritable bowel syndrome	54 710 (8.1%)	37 607 (5.5%)	52 074 (8.0%)
Peripheral arterial disease	31 215 (4.6%)	34 276 (5.1%)	33 262 (5.1%)
Chronic kidney disease	134 831 (19.9%)	127 003 (18.7%)	138 485 (21.2%)
Systemic lupus erythematosus	1994 (0.3%)	1953 (0.3%)	2197 (0.3%)
Rheumatoid arthritis	10 961 (1.6%)	13 898 (2.0%)	18 946 (2.9%)
Immunosuppressive condition	29 754 (4.4%)	27 472 (4.1%)	40 957 (6.3%)
Osteoarthritis	291 293 (43.0%)	242 320 (35.7%)	275 480 (42.2%)
Prescriptions in last 90 days			
Anticoagulant	55 590 (8.2%)	36 102 (5.3%)	54 691 (8.4%)
Antiplatelet	143 735 (21.2%)	187 459 (27.6%)	145 936 (22.3%)
Antipsychotic	14 811 (2.2%)	19 238 (2.8%)	16 640 (2.5%)
Benzodiazepine	27 999 (4.1%)	40 074 (5.9%)	31 594 (4.8%)
Cardiac glycoside	9771 (1.4%)	15 505 (2.3%)	11 134 (1.7%)
Lipid regulating medication	341 107 (50.3%)	281 008 (41.4%)	322 901 (49.4%)
Opioid	112 639 (16.6%)	124 584 (18.4%)	119 166 (18.2%)

Values are numbers (percentages) unless stated otherwise.
*Mean (SD).
†Median (IQR).
COPD, chronic obstructive pulmonary disease; IMD, Index of Multiple Deprivation.

and also performed a sensitivity analysis restricted to non-fatal strokes, and where the risk window was extended to months 1–6.

Patient and public involvement

Patients were not involved in this study.

RESULTS

Our analysis included 678 110 patients receiving an HZ vaccination from 2013 to 2019. These were matched to 678 110 unvaccinated patients in the historical comparator (from 2007 to 2012), and additionally compared with 653 373 patients in the active comparator receiving an influenza vaccination between 2013 and 2019 (online supplemental eFigure 2).

Of the HZ-vaccinated patients, 356 308 (53%) were women and the mean (SD) age was 74.0 (4.0) years. Patient characteristics were similar by cohort (table 1), except slightly fewer comorbidities in the HZ-vaccinated cohort and greater mobility and care needs in the influenza-vaccinated cohort.

Stroke incidence

We recorded 16 281 incident strokes during a median of 2.7 (IQR 1.4–4.4) years follow-up in the HZ-vaccinated cohort. Incident strokes in the historical and influenza-vaccinated cohorts were 30 430 and 11 124 during a

Table 2 Incidence rates and crude and adjusted HRs for herpes zoster vaccination and stroke compared with historical unvaccinated patients and with patients receiving an influenza vaccination

Cohort	No. strokes	Follow-up (per 1000 PY)	Incidence rate (per 1000 PY)	HR (95% CI)	
				Unadjusted	Adjusted*
Comparison with historical cohort					
Historical unvaccinated	30430	2870.7	10.6	1.00	1.00
Herpes zoster vaccinated	16281	1937.6	8.4	0.83 (0.81 to 0.84)	0.84 (0.82 to 0.86)
Comparison with contemporary active comparator (with influenza vaccine)					
Influenza vaccinated	11124	1103.9	10.1	1.00	1.00
Herpes zoster vaccinated	16281	1937.6	8.4	0.81 (0.79 to 0.83)	0.88 (0.85 to 0.90)

All HRs have p<0.01.
*Adjusted for age, age^2, region and all variables listed in table 1 (as described in online supplemental appendix 2).
PY, person-years.

median of 5.0 (IQR 4.2–5.0) and 1.0 (IQR 0.4–2.4) years follow-up, respectively (table 2). The adjusted HR comparing the vaccinated and unvaccinated historical cohort for overall stroke was 0.84 (95% CI 0.82 to 0.86), whereas it was 0.88 (95% CI 0.85 to 0.90) compared with the influenza-vaccinated cohort.

We recorded 32171 incident ischaemic strokes and 12509 incident haemorrhagic strokes within the three cohorts. We observed similar associations for administration of HZ vaccine and risk of ischaemic stroke compared with both comparator cohorts as we did for overall stroke (online supplemental eTable 1). Whereas fewer haemorrhagic strokes occurred in the HZ-vaccinated cohort compared with the influenza vaccinees (HR 0.88, 95% CI 0.83 to 0.93), there was a similar rate of haemorrhagic strokes compared with the historical unvaccinated comparator (HR 0.97, 95% CI 0.93 to 1.02).

There were no statistically significant interactions between stroke risk and the prespecified patient factors (online supplemental eTable 2). There was very limited evidence of associations with stroke waning over time since vaccination in the influenza-vaccinated cohort (p=0.12 for linear trend), but none for the historical comparison (p=0.22) (table 3). The associations between HZ vaccine receipt and incident HZ were strongest 43–90 days postvaccination, in line with peak vaccine effectiveness, and subsequently waned slowly over time (online supplemental eTable 3), as expected.[28]

Missing data, described in online supplemental appendix 5, were infrequent except for BMI and systolic blood pressure (online supplemental eTable 4) and study findings were robust to our approach to handling the missing data (online supplemental eTable 5). Findings were also similar when censoring follow-up at 1 March 2013 in the historical cohort (online supplemental eTable 6) or restricting to patients aged 70–72 and 78–80 years (online supplemental eTable 7).

Table 3 Adjusted HRs for HZ vaccination and stroke by year of follow-up, compared with historical unvaccinated patients and with patients receiving an influenza vaccination

Cohort	Adjusted* HR (95% CI), according to time since index date						
	0–42 days	43–90 days	91–180 days	181–365 days	>1–2 years	>2–3 years	>3–5 years
Comparison with historical cohort							
Historical unvaccinated	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HZ vaccine	0.84 (0.73 to 0.95)	0.77 (0.68 to 0.87)†	0.87 (0.79 to 0.95)†	0.88 (0.83 to 0.94)†	0.85 (0.81 to 0.89)†	0.85 (0.81 to 0.89)†	0.82 (0.79 to 0.85)†
Comparison with contemporary active comparator (with influenza vaccine)							
Influenza vaccinated	1.00	1.00	1.00	1.00	1.00	1.00	1.00
HZ vaccine	0.89 (0.77 to 1.02)	0.88 (0.78 to 1.00)	0.90 (0.82 to 0.98)	0.89 (0.83 to 0.95)†	0.88 (0.85 to 0.91)†	0.88 (0.83 to 0.94)†	0.91 (0.87 to 0.96)†

*Adjusted for age, age^2, region and all variables listed in table 1 (as described in online supplemental appendix 2).
†P<0.01.
HZ, herpes zoster.

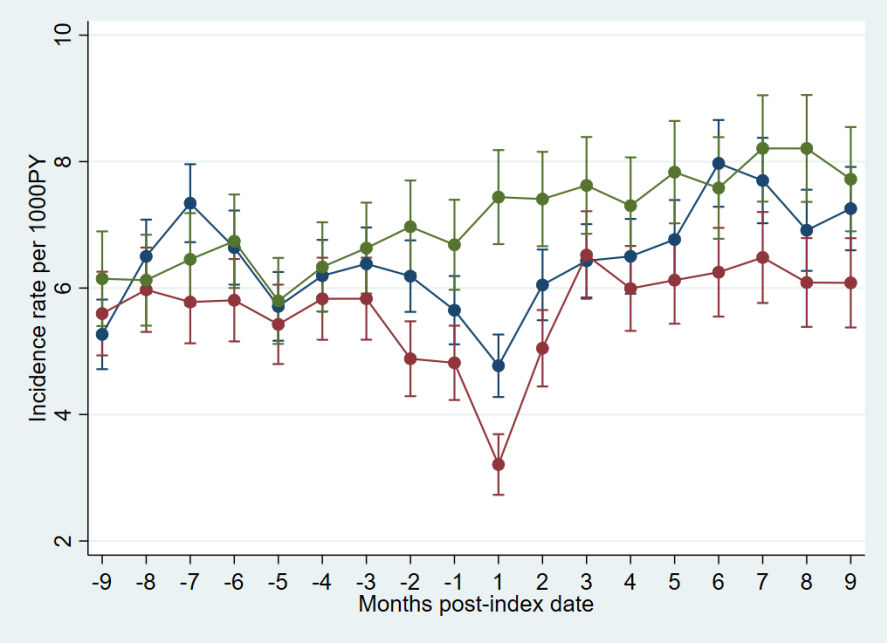

Figure 1 Adjusted* non-fatal stroke incidence rate in the 9 months prevaccination and postvaccination for herpes zoster vaccine, influenza vaccine (when eligible for the herpes zoster vaccine) and in an herpes zoster unvaccinated matched historical cohort. *Adjusted for age, sex, age×sex interaction, monthly mean air temperature in England and index month. Red=herpes zoster-vaccinated cohort, blue=active comparator influenza-vaccinated cohort, green=historical comparator unvaccinated cohort.

Secondary outcomes

We also observed HZ vaccination associated with fewer strokes/TIA, with HRs (95% CI) of 0.86 (0.85 to 0.88) and 0.91 (0.89 to 0.93) compared with the historical unvaccinated and influenza-vaccinated cohorts (online supplemental eTable 8). Similarly, HZ vaccination was associated with fewer MIs, with HRs (95% CI) of 0.92 (0.87 to 0.97) and 0.87 (0.84 to 0.90) compared with the historical unvaccinated and influenza-vaccinated cohorts (online supplemental eTable 9).

Stroke incidence rates before and after vaccination

The HZ-vaccinated cohort had a consistently lower incidence of stroke in the 9 months pre-index and post-index date than both comparator cohorts (figure 1), suggesting a time-fixed healthy vaccinee bias. The adjusted IRR for non-fatal stroke in the 1–9 months period prevaccine was 0.87 (95% CI 0.82 to 0.92) and 0.88 (0.83 to 0.93) for HZ vaccinees compared with influenza vaccinees and the matched historical comparator, respectively. We often observed slightly increased stroke rates postvaccination, which could be attributed to patient ageing, seasonal effects (vaccines mainly received during autumn mean the postvaccine period is mainly during colder months)[54] or immortal time bias prevaccine (where patients need to survive and remain with their GP poststroke to receive the vaccine).

The SCCS analysis included 6797 patients with incident stroke. Strokes occurred fairly uniformly across the 24-month study period, except for fewer events just before vaccination (online supplemental eFigure 3). The SCCS analysis found no association between HZ vaccination and stroke in the 30–119 days postvaccination, with adjusted IRRs (95% CI) of 1.08 (0.97 to 1.21), 0.95 (0.84 to 1.07) and 1.00 (0.89 to 1.12) for the 30–59, 60–89 and 90–119 days postvaccination, compared with baseline (table 4). As expected, there were fewer strokes 30 days prevaccine (IRR of 0.47, 95% CI 0.40 to 0.56). There was also no evidence of decreased stroke risks up to 6 months post vaccination (online supplemental eTable 10). Fatal strokes truncated the observable follow-up time (online supplemental eFigure 4), however findings were similar when restricted to non-fatal stroke (online supplemental eTable 11).

DISCUSSION

Our cohort study observed 12%–16% fewer strokes in the population aged 70–79 years receiving the HZ live vaccine, using influenza vaccination as an active comparator, and adjusting for a wide range of confounders at baseline to control for measured confounders. Consistent findings were found for ischaemic stroke, TIA/stroke and MI outcomes; however, associations were weaker for haemorrhagic stroke. Associations did not vary significantly by patient characteristics examined. There was very limited evidence of associations weakening over time, alongside vaccine effectiveness waning.[28] However, sensitivity analysis found baseline differences in stroke risk between zoster-vaccinated individuals and comparators, despite using influenza vaccination as an active comparator, and the association between zoster vaccination and stroke did not remain in SCCS analysis which controls by design for time-fixed individual-level confounders.

Table 4 IRRs for stroke in risk periods following herpes zoster vaccination from the self-controlled case series analysis

Period postvaccine, days	No. of strokes	Unadjusted IRR	95% CI	Adjusted IRR*	95% CI
Baseline†	5401	1.00		1.00	
−30 to −1	140	0.46	0.39 to 0.55	0.47	0.40 to 0.56
0 to 29	279	0.93	0.82 to 1.04	0.91	0.80 to 1.02
30 to 59	343	1.15	1.03 to 1.28	1.08	0.97 to 1.21
60 to 89	307	1.04	0.93 to 1.17	0.95	0.84 to 1.07
90 to 119	327	1.12	1.00 to 1.26	1.00	0.89 to 1.12

*Adjusted for time-varying monthly age and mean air temperature in England.
†Baseline defined as the period −31 to −365 days before vaccination and 120 to 365 days postvaccination.
IRR, incidence rate ratio.

A cohort study compared US Medicare fee-for-service beneficiaries who received Zostavax with propensity score-matched unvaccinated beneficiaries for a median of 5.1 years.[48] They reported adjusted HRs (95% CI) of 0.84 (0.83 to 0.85) for all strokes, 0.83 (0.82 to 0.84) for acute ischaemic stroke and 0.88 (0.85 to 0.91) for haemorrhagic stroke. These findings mirror our cohort study results, likely due to similar confounder adjustments. However, the researchers were unable to account for smoking and alcohol abuse, which we could in our analysis. While they reported stronger associations with stroke among younger beneficiaries, we found little evidence for this in our study, although our patient age range was relatively narrow. A study of US veterans also reported decreased stroke rates among those with HZ vaccination history in subgroup analysis restricted to the 30-day post-HZ infection.[55] These studies did not, however, report findings from an SCCS analysis or examine stroke rates prevaccine.

There are several possible mechanisms for a causal relationship between HZ vaccination and decreased stroke risk. First via direct protection against HZ virus, a known risk factor for stroke, by blocking its effects in the central nervous system.[56] Other possible mechanisms include excessive inflammation, triggering vasculopathy[57] and viral infections increasing sympathetic activity, restricting blood flow and rupturing coronary plaques, resulting in strokes.[56 57]

Indirect protection may lower stroke risk through non-specific vaccine effects, reduction in pro-inflammatory cytokines and subsequent damage related to inflammation.[58] Live attenuated vaccines, such as measles, BCG and oral polio vaccines, have shown larger mortality reductions then predicted through prevention of the vaccine-targeted disease.[59–63] These benefits are suspected due to reprogramming of the innate immune response, leading to enhanced function or trained innate immunity, through epigenetic reprogramming, emergency granulopoiesis and heterologous T-cell immunity.[64–67]

There remained evidence of considerable healthy vaccinee bias when comparing stroke incidence among zoster vaccinees with influenza vaccinees as an active comparator, and this analysis produced similar results to an unvaccinated general population comparator. The UK shingles vaccine programme was designed to enable co-administration of shingles and influenza vaccines and our study population were eligible for both vaccines. Healthy initiator bias may arise through confounding by indication,[34] and individuals with underlying conditions known to be risk factors for influenza (many of which are risk factors for stroke) were expected to be more likely to receive influenza vaccination. However, adjusting for influenza vaccine and stroke risk factors, comorbidities and mobility issues made minimal difference to the results.[68] Healthy initiator bias may also arise when treatment is channelled away from frail or otherwise high-risk individuals.[34] Although we adjusted for components of the electronic frailty index,[41] this is only a proxy, and residual confounding by frailty may partly explain this finding. Our results suggest the determinants of influenza and HZ vaccine uptake are too different for influenza vaccine to be effective as an active comparator for HZ vaccination. There is evidence that individuals most at risk of shingles in the UK (eg, care home residents) are least likely to receive zoster vaccine.[40] Healthcare access is also critical to vaccine uptake,[69] and there is considerable variation between GP practices in how vaccine programmes are administered.[70] The impact of comorbidities on vaccine uptake may also differ between the vaccines, particularly as live-attenuated zoster vaccine is contraindicated in immunosuppression.[27] Practice-level vaccination efforts might also more effectively address access barriers for influenza than for zoster vaccination, due to incentivisation of influenza vaccination in the Quality Outcomes Framework.[71] Finally, vaccine confidence is vaccine-specific, and so one uptake of one vaccine does not necessarily reflect the health beliefs of another.[72]

Strengths of this study include using a large population-representative primary care database linked to hospital admission data, allowing adjustment for a wide range of potential confounders. Furthermore, we used two comparator groups to evaluate the effect size and found comparable results. Possible misclassification in the recording of vaccination events in CPRD was limited due to strong effects on reduced HZ risk observed replicating

previous findings and vaccine uptake rates similar to levels reported nationally.[28 73] Recording of stroke was improved through linkage to hospital admission and mortality data.[74] There is debate on whether to include ICD-10 code I62 'other non-traumatic intracranial haemorrhage' in the definition of haemorrhagic stroke hospital admissions, hence we may have overestimated haemorrhagic stroke by including it.[75 76] Our study was strengthened via extensive sensitivity analyses to check for and investigate residual confounding and healthy vaccinee bias. Possible residual confounding by frailty was reduced through adjustment for the main components of the electronic frailty index.[41] Small misclassifications of exact age (and thus vaccine eligibility) were possible due to CPRD not releasing birth dates, but this is not expected to impact findings. Our study only evaluated the effect of live attenuated HZ vaccine on stroke risk, and further research is needed to investigate the effect of the recombinant vaccine on stroke and cardiovascular events.[77]

Cohort studies on vaccine safety produced important evidence during the COVID-19 pandemic.[78] However, healthy vaccinee bias is a well-recognised problem in observational vaccine studies.[34] Causal inference methods offer much promise in addressing this, and plausible causal inference tools (such as active comparators) need to be tested for suitability. The graph of incidence rates before and after vaccination was valuable in detecting residual confounding. Despite small risks of immortal time bias in the prevaccine periods, we would recommend comparing prevaccine incidence rates for non-fatal events in vaccine safety and effectiveness cohort studies where data are available. The SCCS makes comparisons within individuals, so it intrinsically accounts for time-invariant confounding, whereas cohort studies are prone to this confounding by making comparisons between individuals.[53] The SCCS is particularly valuable for vaccine studies, for which it was originally developed, due to examining the temporal association between accurately timed transient exposures and events. SCCS is best suited for short-term acute events, but even for hypothesised long-term effects, it is worth examining whether the effect starts occurring soon after vaccination.

An 'active comparator' of influenza vaccine did not enable a head-to-head comparison with zoster vaccination, despite both vaccines sharing the same delivery method and age eligibility criteria and extensive adjustments being made for health conditions recognised as risk factors for influenza and frailty components.[41 68] Our study highlights the importance of taking a triangulation approach using multiple study designs such as the SCCS.[79]

CONCLUSION

In cohort studies, we observed reduced incidence of stroke in people vaccinated against HZ compared with unvaccinated individuals, with extensive adjustment for confounding and use of an active comparator of influenza vaccination. However, sensitivity analysis examining outcomes from pre-exposure periods to account for time-fixed confounding, suggested this may be largely explained by healthy vaccinee bias. Our study illustrates the importance of robust sensitivity analyses and testing the suitability of causal inference tools for observational vaccine studies. Nevertheless, vaccine uptake should continue to be encouraged due to the benefits of the zoster vaccine on zoster prevention.

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