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Effect of herpes zoster vaccine and antiviral treatment on risk of ischemic stroke

Quanhe Yang, PhD, **Mary G. George, MD, MSPH**, **Anping Chang, MS, MPH**, **Xin Tong, MPH**, **Robert Merritt, MS**, **Yuling Hong, MD, PhD**

Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA.

Abstract

Objective—To determine whether increased risk of acute ischemic stroke (AIS) following herpes zoster (HZ) might be modified by the status of zoster vaccine live (ZVL) vaccination and antiviral treatment following HZ.

Methods—We included 87,405 Medicare fee-for-service beneficiaries aged ≥66 years diagnosed with HZ and AIS from 2008 to 2017. We used a self-controlled case series design to examine the association between HZ and AIS, and estimated incidence rate ratios (IRRs) by comparing incidence of AIS in risk periods vs control periods. To examine effect modification by ZVL and antiviral treatment, beneficiaries were classified into 4 mutually exclusive groups: (1) no vaccination and no antiviral treatment; (2) vaccination only; (3) antiviral treatment only; and (4) both vaccination and antiviral treatment. We tested for interaction to examine changes in IRRs across 4 groups.

Results—Among 87,405 beneficiaries with HZ and AIS, 22.0%, 2.0%, 70.1%, and 5.8% were in groups 1 to 4, respectively. IRRs in 0–14, 15–30, 31–90, and 91–180 days following HZ were 1.89 (95% confidence interval [CI], 1.77–2.02), 1.58 (95% CI, 1.47–1.69), 1.36 (95% CI, 1.31–1.42), and 1.19 (95% CI, 1.15–1.23), respectively. There was no evidence of effect modification by ZVL and antiviral treatment on AIS ($p = 0.067$ for interaction). The pattern of association between HZ and risk for AIS was largely consistent across age group, sex, and race.

Conclusions—Risk of AIS increased significantly following HZ, and this increased risk was not modified by ZVL and antiviral treatment. Our findings suggest the importance of following recommended HZ vaccination in prevention of HZ and HZ-associated AIS.

Stroke is the 5th leading cause of death and causes serious long-term disability, with an estimated annual cost of $33.9 billion in 2015 in the United States.[1] Accumulating evidence shows the importance of infectious causes of stroke.[2–4] Herpes zoster (HZ), also known as shingles, is caused by reactivation of latent varicella-zoster virus infection generally acquired at young ages. Studies have suggested that HZ infection is associated with an increased risk of stroke, especially ischemic stroke.[4–6] Almost 1 in 3 people in the United

Correspondence Dr. Yang qay0@cdc.gov.

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States will develop HZ during their lifetime, with an estimated 1 million HZ cases each year (cdc.gov/shingles/about/overview.html). More than half of individuals who developed HZ were aged 60 years or older.[7,8] In 2006, the Advisory Committee on Immunization Practices (ACIP) recommended routine zoster vaccine live (ZVL) (Zostavax, a one-dose HZ live-attenuated vaccine manufactured by Merck & Co., Inc.) for preventing HZ for all persons aged >60 years,[9] and in 2017, ACIP recommended a new HZ vaccine (Shingrix, manufactured by GlaxoSmithKline, a 2-dose, adjuvant, recombinant HZ vaccine [RZV]) for people aged 50 years and older.[10] ZVL coverage increased continuously since 2006 and 33.0% of adults received ZVL in 2016.[10] For patients with HZ, antiviral therapy is recommended.[11]

While many studies examined the association between HZ and risk for stroke, a few studies also examined if the risk of stroke after HZ might be modified by status of ZVL and antiviral treatment, with inconsistent findings. For example, some suggested that there was no difference in risk of stroke between patients with or without ZVL,[12] others suggested that antiviral treatment was associated with reduced risk of stroke,[13,14] and other studies suggested no difference in risk of stroke with antiviral treatment following HZ.[15,16] To our knowledge, no study simultaneously examined the effect of ZVL and antiviral treatment on risk of acute ischemic stroke (AIS); the present study examined these effects among adults ≥66 years of age who enrolled in a Medicare fee-for-service (FFS) program from 2008 to 2017 in the United States.

Methods

Standard protocol approvals, registrations, and patient consents

The Centers for Disease Control and Prevention Human Subjects Coordinator determined that this study did not require review for human subjects protections because the data did not contain personal identifiers and were not originally collected specifically for this study. Therefore, the requirement of informed consent was waived.

Data source and study population

This population-based study utilized Medicare's Enrollment Databases to generate study cohort and FFS Medicare Parts A (hospitalization), B (office-based care), and D (prescription drug coverage) claims data, and Medicare Provider Analysis and Review (MEDPAR) data to examine the association between HZ and risk of AIS from 2008 to 2017. We used the following procedures and definitions to select the final analytical cohort: (1) identified all Medicare FFS beneficiaries aged 65 years or older with at least 12 months continuous enrollment in Medicare Part A and B and eligible for Part D (≥1 month) during 2007–2017; (2) identified all diagnosed AIS among FFS beneficiaries during 2007–2017, including multiple admissions; (3) identified all diagnosed HZ among FFS beneficiaries during 2007–2017, including multiple admissions; (4) used ≥12 months lookback period of time to identify incident HZ (lookback period where no HZ codes were billed), and the length of lookback time varied by the years of Medicare enrollment, for example, 12 months for beneficiaries 66 years of age (Medicare eligible at age 65 years), 24 months for age 67 years, and so on. Among FFS beneficiaries with multiple admissions and/or

>1 HZ occurrence as identified in step 3, we selected first HZ occurrence as the index case and the date of diagnosed HZ as index date; (5) used the same procedures to identify the incident AIS and its index date as we used for incident HZ and its index date; and (6) merged incident HZ and AIS data as identified in steps 4 and 5 to create the final analytical cohort. Because of ≥12 months lookback period, our final cohort included FFS beneficiaries aged ≥66 years or older (Medicare eligible at age 65 years) with diagnosed incident HZ and AIS from 2008 to 2017 (2007 served as look-back time). During 2007–2017, there were 210,197,235 FFS beneficiaries aged 65 years or older, among which there were 1,242,801 and 1,574,739 incident AIS and HZ among FFS beneficiaries aged 66 years or older from 2008 to 2017, respectively. Among FFS beneficiaries with incident AIS and HZ, we identified 87,405 beneficiaries who had both incident AIS and HZ during 2008–2017 (figure 1).

Exposure, vaccination and antiviral treatment, and outcome

The exposure variable was HZ, and the index date of HZ for each FFS beneficiary was identified in the inpatient and outpatient claims data from January 1, 2008, to December 31, 2017. National Drug Code data from the Medicare Part D events data and Current Procedural Terminology code from inpatient and outpatient claims data were used to identify the status of ZVL,[12] and beneficiaries were classified as vaccinated if the date of ZVL was before the index date of HZ. The antiviral treatment status was determined by prescription of antiviral medications ±7 days from the index date of HZ based on Medicare Part D data, and the ±7 days criteria were used to accommodate the difference in reporting dates of HZ diagnosis and antiviral treatment in Medicare data.[17] The antiviral medications included acyclovir, famciclovir, and valacyclovir (table 1).[16] Beneficiaries who had ZVL before the index date of HZ were defined as having ZVL. Beneficiaries who received antiviral treatment ±7 days from index date of HZ were defined as having HZ antiviral treatment. To examine the possible effect modification by ZVL and antiviral treatment on risk for AIS, beneficiaries were classified into 4 mutually exclusive groups based on the status of ZVL and antiviral treatment: (1) no vaccination and no antiviral treatment (n = 19,250); (2) vaccination only (n = 1,769); (3) antiviral treatment only (n = 61,298); and (4) with both vaccination and antiviral treatment (n = 5,088).

We used MEDPAR files to identify AIS, the outcome of interest. The MEDPAR files contained inpatient hospital and skilled nursing facility stay records for all Medicare beneficiaries, and we used the primary diagnosis codes (ICD-9-CM for 2007–2015 and ICD-10-CM for last quarter of 2015 and 2016–2017) to identify beneficiaries with AIS. If the beneficiaries had a diagnosis of stroke (any type, including TIA) based on the Chronic Conditions Warehouse definition used by Centers for Medicare and Medicaid Services (CMS) (ccwdata.org/web/guest/condition-categories) that occurred >30 days before the index date of AIS, they were classified as having history of stroke. Table 2 provides the ICD-9-CM and ICD-10-CM codes for HZ and AIS, respectively.

Statistical analysis

We calculated the mean age (±SD) and distribution of age group, sex, race, and AIS with and without history of stroke by 4 ZVL and antiviral treatment groups. We used

self-controlled case series (SCCS) study design to estimate incidence rate ratio (IRR) and 95% confidence interval (CI) for risk of AIS following exposure to HZ. As shown in figure 2, the SCCS study design is based on within-person comparisons (self-matched) after exposure during an observation period subdivided into risk and control periods, and this method implicitly controls for all fixed confounders during the period of study.[18] The null hypothesis, IRR = 1.0, implies that AIS event rates remained constant during the entire observation period of time and were not affected by HZ. An IRR >1.0 or <1.0 implies an increased or reduced risk of AIS following HZ. The start of the observation period was January 1, 2008, and for those beneficiaries who enrolled after January 1, 2008, it was the January 1 of the first enrollment year. The end of the observation period was December 31, 2017, or the date of death for those who died before December 31, 2017. We used the National Death Index linked to Medicare data to determine the date of death until December 31, 2016, and date of death in beneficiary file in 2017. We categorized the baseline risk after HZ into 4 periods: 0–14, 15–30, 31–90, and 91–180 days. The findings of other studies suggested that the elevated risk of stroke after HZ gradually returned to the baseline (IRR ≈ 1.0) within 1 year.[12,14] One of 2 key assumptions of SCCS design is that the occurrence of events (AIS in our case) does not influence the length of observation period.[19] Among beneficiaries with AIS, 39% of them (n = 34,119) died before the end of the observation period. Thus, the assumption of event being independent of observation period was violated (due to increased mortality after AIS), so we used the modified SCCS method that takes into account the event dependent observation period of time.[19–21] We conducted a test for interaction in the modified SCCS model to examine whether the IRRs for risk of AIS changed significantly across 4 groups classified by status of ZVL and antiviral treatment based on the likelihood ratio tests.[18,21] To correct for multiple hypothesis testing, we calculated the false discovery rate (FDR) and denoted significance by an FDR threshold of 5%, and reported the FDR-adjusted p value for interaction.[22] Beneficiaries with and without history of stroke might have different risk profiles,[23,24] so we also presented results by status of history of stroke (first vs recurrent stroke). The IRRs were adjusted for age as a categorical variable of 5-year age group from 66 to ≥95 years of age.

We performed analyses in subgroups defined according to age group (66–74 years, 75–84 years, and ≥85 years), sex, and race (non-Hispanic white, non-Hispanic black, Hispanics, and others). For analyses stratified by demographics, we combined the 4 vaccination and antiviral groups since there was no evidence of effect modification in risk for AIS and to increase the sample size for stable estimates. We evaluated the presence of interaction in these subgroups. SAS version 9.4 (SAS Institute, Cary, NC) was used for analysis, and R package SCCS was used for SCCS analyses.[21]

Data availability

Medicare data are available from CMS, Department of Health and Human Services, for any qualified investigator.

Results

Description of Medicare beneficiaries

Among 87,405 beneficiaries included in the study, the mean age ±SD was 80.0 ± 7.5 years, 19,250 (22.0%) did not receive ZVL and did not have antiviral treatment, 1,769 (2.0%) had ZVL only, 61,298 (70.1%) received antiviral treatment only, and 5,088 (5.8%) had both vaccine and antiviral treatment (table 3). ZVL coverage increased with age and the median time from ZVL to the index date of HZ was 33 months (interquartile range, 15–56). The antiviral treatment decreased with age, 57,806 (66.1%) of beneficiaries were women, and there were no difference in ZVL and receiving antiviral treatment between men and women. Non-Hispanic black and Hispanic beneficiaries were less likely to receive ZVL or to receive both ZVL and antiviral treatment as compared to non-Hispanic white or other participants, but more likely to receive antiviral treatment after HZ. Among all cases, 59,294 (68%) had no prior history of stroke (table 3).

IRR for AIS

The IRRs for AIS in 0–14, 15–30, 31–90, and 91–180 days following HZ were 1.89 (95% CI, 1.77–2.02), 1.58 (95% CI, 1.47–1.69), 1.36 (95% CI, 1.31–1.42), and 1.19 (95% CI, 1.15–1.23), respectively. There was no evidence of effect modification by the status of ZVL and antiviral treatment (FDR-adjusted $p = 0.067$ for interaction) (table 4). The pattern of null effect modification was similar among beneficiaries diagnosed with or without history of stroke (FDR-adjusted $p = 0.171$ and 0.097 for interaction, respectively [table 4]). The pattern of association between HZ and risk for AIS was largely consistent across demographic subgroups (table 5). However, the risk of stroke in 31–90 days following HZ were significantly higher among men compared to women (1.50 [95% CI, 1.40–1.60] vs 1.30 [95% CI, 1.23–1.36]) and was significantly higher among Hispanic patients in 90–180 days following HZ compared to other racial groups (table 5).

Discussion

Our findings from this large Medicare cohort study using SCCS design suggested that the risk of AIS increased significantly in the first 6 months following HZ. The risk was highest within the first 2 weeks following HZ and reduced gradually over time, consistent with the findings of previous studies.[4–6] The pattern of association was consistent among beneficiaries with and without history of stroke. To our knowledge, this is the first study to examine simultaneously the effect modification by the status of ZVL and antiviral treatment following HZ on risk of AIS. Our results provided no evidence of such modification on risk of AIS after HZ. It appears that having HZ vaccine before symptoms of HZ appear might be the most effective way to prevent HZ-associated stroke risk. It is worth noting that only a small fraction of beneficiaries (5.8%) among this Medicare cohort received recommended ZVL and were treated with antiviral medications after HZ.[9]

Previous findings of effect modification by ZVL or antiviral treatment were inconsistent. Minassian et al.[12] studied Medicare beneficiaries ≥65 years of age with HZ diagnosis and either an ischemic stroke or myocardial infarction between 2006 and 2011, and found no

evidence of difference in IRRs for ischemic stroke between vaccinated and unvaccinated beneficiaries. Two studies suggested that antiviral treatment following HZ was associated with reduced risk of stroke.[13,14] One of these studies included patients with autoimmune disease.[13] Two matched cohort studies from Taiwan and Denmark suggested that antiviral treatment of HZ had no effect on the incidence of stroke.[15,16] The Denmark study used antiviral treatment following HZ to identify the patients with HZ and compared patients with HZ with those without HZ.[16] Both studies were subject to the effects of uncontrolled confounders. Differences in study designs, sample size, patients studied (e.g., patients with autoimmune disease), and definition of stroke included in the study (ischemic or hemorrhagic stroke or TIA) might contribute to the inconsistent findings. Our study included a large number of Medicare beneficiaries diagnosed with AIS, and with an adequate number to classify beneficiaries into 4 mutually exclusive groups based on status of ZVL and antiviral treatment. Both ZVL and antiviral treatment are proven to reduce the severity of HZ.[9,11] Our findings indicated that reducing the HZ severity by these means has no impact on AIS risk and the elevated risk of AIS after HZ might be independent of ZVL history and antiviral treatments after HZ.

Our results suggested that the risk of AIS in 31–90 days following HZ was higher among men compared to women (IRR 1.50 [95% CI, 1.40–1.60] vs 1.30 [95% CI, 1.23–1.36]). HZ incidence was generally higher in women than in men, as observed in previous studies,[6,25,26] but the reasons for the observed higher risk for stroke in 31–90 days among men compared to women were unclear; however, this difference in risk of AIS has limited clinical significance in prevention of AIS following HZ. In addition, the pattern of association between HZ and risk of AIS following HZ among Hispanic patients appeared to be different compared to that of other racial groups. The risk for AIS among Hispanic patients was consistently higher from within 2 weeks to 91–180 days following HZ, especially in 91–180 days (IRR 1.45 [95% CI, 1.25–1.67]); the significant likelihood ratio test for interaction by status of ZVL and antiviral treatment was mainly driven by this difference in IRR in 91–180 days following HZ. We are not aware of any publication on racial differences in effects of HZ on risk of AIS. Other studies suggested that Hispanic patients were significantly less likely to seek health care after HZ,[27] and there were racial disparities in general health care utilizations among older US adults that might contribute to the persistent risk of AIS following HZ among Hispanic patients.[28]

HZ infection involves viral invasion of the arterial walls, and can lead to granulomatous and necrotizing vasculitis.[29] Possible biological explanation for the association between HZ and stroke is the HZ viral ability to replicate in cerebral arteries where the infection is spread along the nerve fibers to the blood vessels with subsequent inflammation leading to pathologic vascular remodeling and increased risk of stroke.[30,31] This mechanism might provide partial explanation for the null effect modification by ZVL, for example, after the reactivation of HZ, its viral ability to replicate in cerebral arteries, and the associated inflammation responses might not be altered by ZVL status. In addition, the recipients of ZVL had a 51% overall reduction in HZ and the vaccine efficacy reduced significantly by age from 64% (95% CI, 56% to 71%) for 60–69 years, 41% (95% CI, 28% to 52%) for 70–79 years, to 18% (95% CI, −29 to 48%) among persons ≥80 years of age (merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf). The mean age of the beneficiaries in

our study was 80.0 years, which might also contribute to the null effect of ZVL on risk for AIS. However, this might not explain the null effect of antiviral treatment following HZ, and reasons for the null effect of antiviral treatment on risk for stroke remain unclear. The main goal of treatment after HZ among elderly patients is the reduction or elimination of pain. Three antiviral drugs (acyclovir, famciclovir, and valacyclovir) are guanosine analogs that are phosphorylated by viral thymidine kinase and cellular kinases to a triphosphate form that inhibits varicella-zoster virus DNA polymerase.[32] However, we cannot rule out the findings by chance or effect of other factors such as the differences in seeking health care for HZ by age, sex, race, ethnicity, and HZ severity, and further studies are needed to elucidate the possible mechanisms underlying null effect of ZVL and antiviral treatment, and racial and sex differences in HZ-related risk for AIS. Our study of a large national cohort of Medicare beneficiaries had adequate numbers to classify all beneficiaries into mutually exclusive groups to examine the effect modification of ZVL and antiviral treatment following HZ on risk of AIS. As each individual treats himself or herself as the control (within-individual comparison) under the SCCS study design, only individuals who had HZ and AIS were included, therefore all fixed confounding effects were eliminated.

Our study had several limitations. First, HZ diagnosis was based on administrative data and was not able to be verified. Other studies have combined ICD-9 codes and antiviral treatment in Medicare data to identify HZ cases,[12,13] and had a positive predicted value >85% for HZ.[13] In order to examine effect modification by antiviral treatment, we used ICD-9-CM and ICD-10-CM codes to identify HZ and misclassification is possible. However, when we restricted our analysis to the beneficiaries identified by combined ICD-9-CM and ICD-10CM codes and antiviral treatment, the pattern of association remained unchanged (IRRs in 0–14, 15–30, 31–90, and 91–180 days following HZ were 1.87 [95% CI, 1.73–2.02], 1.63 [95% CI, 1.51–1.77], 1.33 [95% CI, 1.27–1.40], and 1.18 [95% CI, 1.14–1.23], respectively). Second, Zostavax, a live and attenuated vaccine, was the only vaccine that was approved by the Food and Drug Administration for preventing HZ for all persons aged >60 years during the study period.[9] The usual age of eligibility for Medicare is 65 years, and if beneficiaries had ZVL before age 65 years, this information was not captured in Medicare data. The efficacy of ZVL is higher among adults aged 60–65 compared to older age groups, and misclassification resulting from missing information for adults aged 60–65 years might affect our results. This is an important limitation, and further study is needed to clarify its effect on risk of AIS. In 2017, ACIP recommended RZV (Shingrix) for people ≥50 years of age with higher efficacy for prevention of HZ, and its possible effect on AIS following HZ remains to be determined.[10] Third, similar to ZVL vaccination, if beneficiaries had any stroke before age 65 years, this information was not available in Medicare data and some recurrent stroke could be classified as first stroke. Fourth, dose and duration of antiviral therapy for HZ varied between patients, and this information was not available in Medicare; further study is needed to examine their effect on risk of stroke following HZ. Fifth, another study suggested that there were moderate differences in seeking care for HZ by age, sex, race/ethnicity, and HZ severity.[27] Medicare data might miss those who did not seek for care after HZ. Sixth, the efficacy of ZVL declines over time, and the median time of ZVL to HZ was 33 months (ranging from 1 to 130 months with an interquartile range 15–56). In our study, we have limited sample size for

a detailed analysis of timing of ZVL on risk of AIS. Seventh, the AIS diagnosis was based on ICD-9-CM and ICD-10-CM codes from the Medicare claims data and was not verified in this study, and this could also lead to misclassification. However, other studies validated the selected diagnostic codes for AIS with relatively high positive predictive values.[33,34] Finally, other studies suggested stronger association between HZ ophthalmicus and risk of stroke.[4,15] The sample size for HZ ophthalmicus from the Medicare data is limited to examine the effect modification by ZVL and antiviral treatment.

Risk of AIS increased significantly following HZ, and this increased risk was not modified by ZVL and antiviral treatment. Our findings underscore the importance of following HZ vaccination recommendations in order to prevent HZ and HZ-associated AIS.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

APPENDIX

Appendix

Appendix Authors

Name	Location	Contribution
Quanhe Yang, PhD	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA	Designed and conceptualized study, conducted statistical analysis, drafted the manuscript for intellectual content
Mary G. George, MD, MSPH	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA	Interpreted the data, revised the manuscript for intellectual content
Anping Chang, MPH	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA	Generated the analytical datasets
Xin Tong, MPH	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA	Validated and generated analytical datasets
Robert Merritt, MS	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA	Interpreted the data, revised the manuscript for intellectual content
Yuling Hong, MD, PhD	Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention, Atlanta, GA	Interpreted the data, revised the manuscript for intellectual content

Glossary

ACIP	Advisory Committee on Immunization Practices

AIS	acute ischemic stroke
CI	confidence interval
CMS	Centers for Medicare and Medicaid Services
FFS	fee-for-service
HZ	herpes zoster
ICD-9-CM	International Classification of Diseases, 9th revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th revision, Clinical Modification
IRR	incidence rate ratio
MEDPAR	Medicare Provider Analysis and Review
RZV	recombinant herpes zoster vaccine
SCCS	self-controlled case series
ZVL	zoster vaccine live

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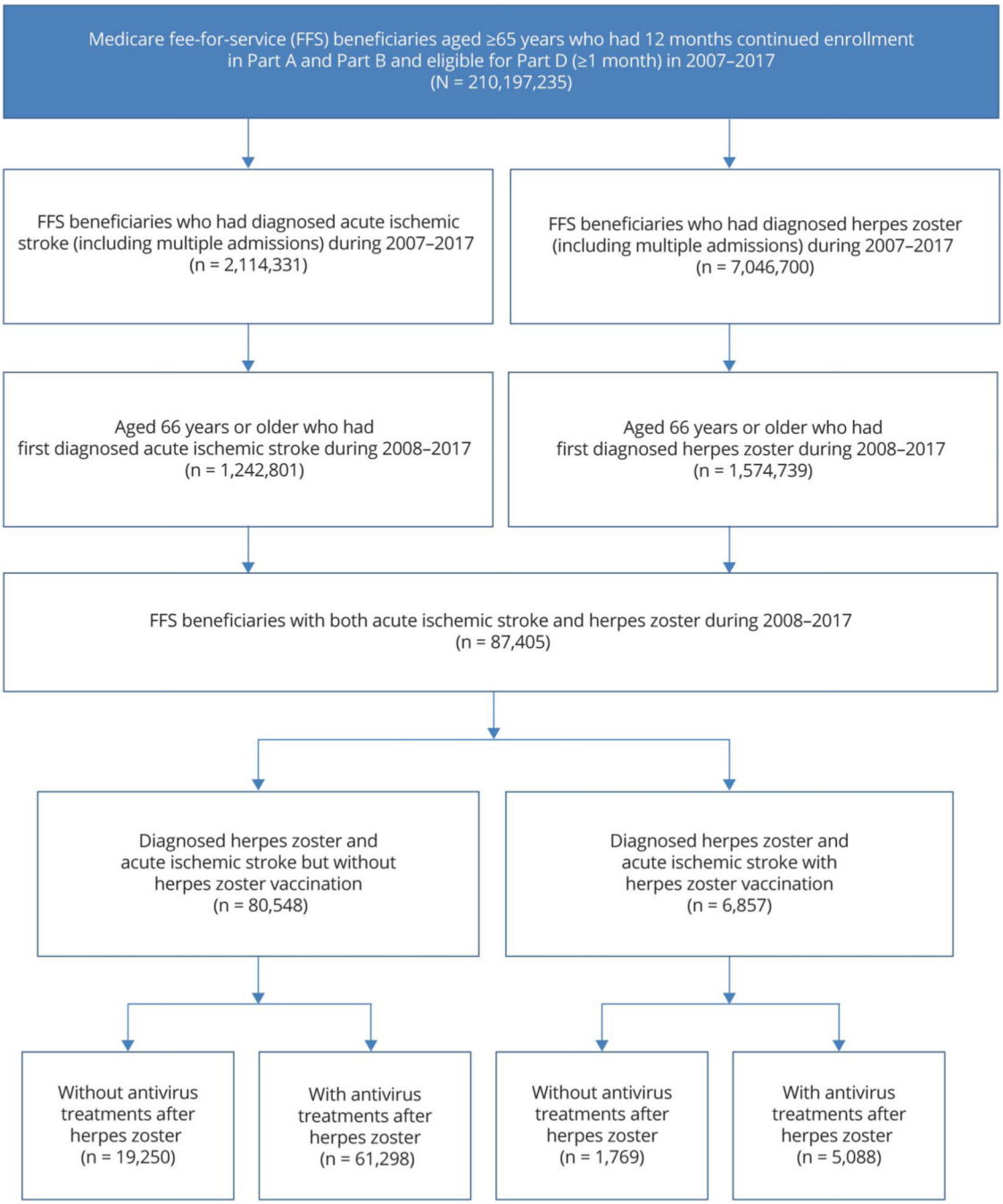

Figure 1.

Flowchart of Medicare fee-for-service beneficiaries with herpes zoster and acute ischemic stroke 2008–2017

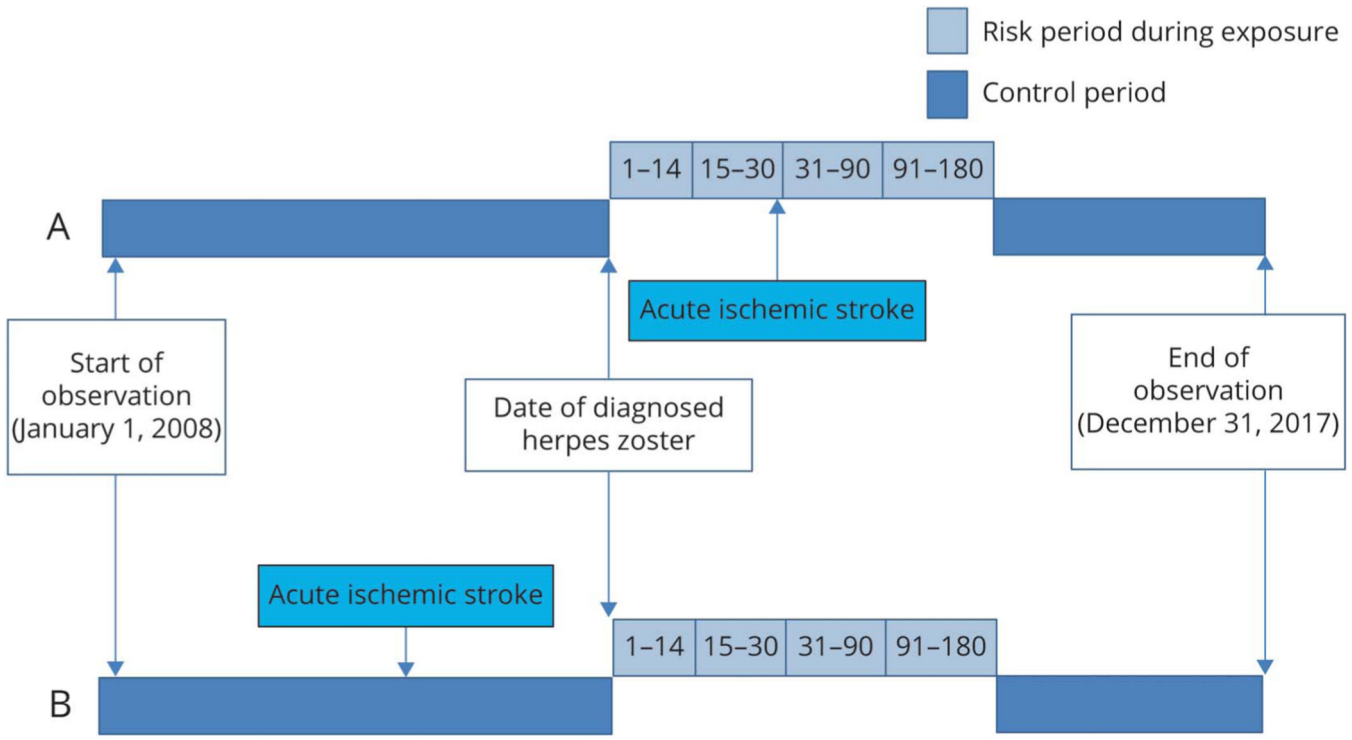

Figure 2.

Graphic representation of self-controlled case series study design

(A) A patient who had acute ischemic stroke in the risk period during exposure. (B) A patient who had acute ischemic stroke during the control period.

Table1

Zoster vaccine live codes and antiviral treatment medications, Medicare fee-for-service beneficiaries 2008–2017

	Code	Codes and website link
Zoster vaccine live (Zostavax)	National Drug Code	00006496300 (hipaaspace.com/medical_billing/coding/national.drug.codes/00064963-00)
		00006496301 (hipaaspace.com/medical_billing/coding/national.drug.codes/00064963-00)
		00006496341 (hipaaspace.com/medical_billing/coding/national.drug.codes/00064963-41)
		54868570300 (bluecrossnc.com/sites/default/files/document/attachment/common/pdfs/2009_MAPD_Vaccine_Claim_Form.pdf)
	Current Procedural Terminology code	90,736
Antiviral treatment medications for herpes zoster	Acyclovir Famciclovir Valacyclovir	CMS Chronic Conditions Data Warehouse (CCW)–Codebook Medicare Part D Event (PDE)/Drug Characteristics File Version 1.1 (January 2019) (ccwdata.org/web/guest/data-dictionaries)

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Table 2

ICD-9-CM and ICD-10-CM codes for herpes zoster and acute ischemic stroke, Medicare fee-for-service beneficiaries 2008–2017

Disease	Inclusion criteria	CD-CM codes	Description
Herpes zoster		ICD-9-CM codes	
	Including	053.00	Herpes zoster with meningitis
		053.10	Herpes zoster with unspecified nervous system complication
		053.14	Herpes zoster myelitis
		053.19	Herpes zoster with other nervous system complications
		053.20	Herpes zoster dermatitis of eyelid
		053.21	Herpes zoster keratoconjunctivitis
		053.22	Herpes zoster iridocyclitis
		053.29	Herpes zoster with other ophthalmic complications
		053.71	Otitis externa due to herpes zoster
		053.79	Herpes zoster with other specified complications
		053.8	Herpes zoster with unspecified complication
		053.9	Herpes zoster without complication
	Excluding	053.12	Postherpetic trigeminal neuralgia
		053.13	Postherpetic polyneuropathy
		ICD-10-CM codes	
	Including	B02	Zoster
	Excluding	B0222	Zoster with other nervous system involvement
		B0223	Zoster ocular disease
Acute ischemic stroke		ICD-9-CM codes	
		433.01	Occlusion and stenosis of basilar artery with cerebral infarction
		433.11	Occlusion and stenosis of carotid artery with cerebral infarction
		433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
		433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
		433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
		433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
		434.01	Cerebral thrombosis with cerebral infarction

Disease	Inclusion criteria	CD-CM codes	Description
		434.11	Cerebral embolism with cerebral infarction
		434.91	Cerebral artery occlusion unspecified with cerebral infarction
		436	Acute but ill-defined cerebrovascular disease
		ICD-10-CM codes	
		I63	Cerebral infarction
		I66	Occlusion and stenosis of cerebral arteries
		I6789	Other cerebrovascular disease

Abbreviations: ICD-9-CM = *International Classification of Diseases, 9th revision*; ICD-10-CM = *International Classification of Diseases, 10th revision*.

Table 3

Characteristics of Medicare fee-for-service (FFS) beneficiaries aged ≥66 years with diagnosed herpes zoster (HZ) and acute ischemic stroke by status of zoster vaccine live (ZVL) and antiviral treatment, Medicare 2008–2017

			Status of ZVL and antiviral treatment			
Characteristics	**Medicare FFS beneficiaries, n**	**Total**	**No vaccination and no antiviral treatment**	**Vaccination only[a]**	**Antiviral treatment only**	**Vaccination and antiviral treatment[a]**
All, n (%)	87,405	100	19,250 (22.0)	1,769 (2.0)	61,298 (70.1)	5,088 (5.8)
Age, y, mean ± SD		80.0 ± 7.5	80.5 ± 7.7	79.9 ± 6.9	79.8 ± 7.5	80.4 ± 6.8
Age group, y, n (%)						
66–74	25,523	100	5,283 (20.7)	485 (1.9)	18,527 (72.6)	1,228 (4.8)
75–84	38,139	100	8,158 (21.4)	826 (2.2)	26,650 (69.9)	2,505 (6.6)
≥85	23,743	100	5,809 (24.5)	458 (1.9)	16,121 (67.9)	1,355 (5.7)
Sex, n (%)						
Men	29,599	100	6,455 (21.8)	626 (2.1)	20,766 (70.2)	1,752 (5.9)
Women	57,806	100	12,795 (22.1)	1,143 (2.0)	40,532 (70.1)	3,336 (5.8)
Race, n (%)						
Non-Hispanic white	75,364	100	16,252 (21.6)	1,592 (2.1)	52,839 (70.1)	4,681 (6.2)
Non-Hispanic black	4,933	100	1,315 (26.7)	31 (0.6)	3,508 (71.1)	79 (1.6)
Hispanics	4,107	100	1,010 (24.6)	45 (1.1)	2,957 (72.0)	95 (2.3)
Other	3,001	100	673 (22.4)	101 (3.4)	1,994 (66.4)	233 (7.8)
Without history of stroke, n (%)	59,294	100	12,639 (21.3)	1,237 (2.1)	41,768 (70.4)	3,650 (6.2)
With history of stroke, n (%)	28,111	100	6,611 (23.5)	532 (1.9)	19,530 (69.5)	1,438 (5.1)

[a]The median month from ZVL to the index date of HZ was 33 (ranging from 1 to 130 months with an interquartile range 15–56).

Table 4

Incidence rate ratio (95% confidence interval) of acute ischemic stroke (AIS) among Medicare fee-for-service beneficiaries diagnosed with herpes zoster (HZ), Medicare 2008–2017

		Status of zoster vaccine live (ZVL) and antiviral treatment			
AIS and risk period	**Total**	**No vaccination and no antiviral treatment**	**Vaccination only**	**Antiviral treatment only**	**Vaccination and antiviral treatment**
Total AIS [a]					
AIS, n (%)	87,405 (100)	19,250 (22.0)	1,769 (2.0)	61,298 (70.1)	5,088 (5.8)
1–14 days	1.89 (1.77–2.02)	2.08 (1.83–2.36)	1.66 (1.01–2.74)	1.91 (1.76–2.07)	1.39 (0.99–1.95)
15–30 days	1.58 (1.47–1.69)	1.51 (1.31–1.74)	1.47 (0.86–2.49)	1.68 (1.55–1.83)	1.10 (0.77–1.59)
31–90 days	1.36 (1.31–1.42)	1.49 (1.37–1.61)	1.30 (0.97–1.74)	1.33 (1.26–1.39)	1.50 (1.28–1.77)
91–180 days	1.19 (1.15–1.23)	1.22 (1.13–1.31)	1.33 (1.04–1.70)	1.19 (1.14–1.25)	1.09 (0.93–1.28)
Without history of stroke only [b]					
AIS, n (%)	59,294 (100)	12,639 (21.3)	1,237 (2.1)	41,768 (70.4)	3,650 (6.2)
1–14 days	1.87 (1.72–2.03)	1.99 (1.70–2.34)	1.78 (1.00–3.16)	1.90 (1.72–2.10)	1.10 (0.71–1.72)
15–30 days	1.62 (1.49–1.77)	1.53 (1.28–1.83)	1.64 (0.91–2.99)	1.71 (1.55–1.90)	0.98 (0.62–1.54)
31–90 days	1.38 (1.32–1.45)	1.47 (1.34–1.63)	1.15 (0.79–1.67)	1.36 (1.28–1.44)	1.42 (1.17–1.72)
91–180 days	1.20 (1.15–1.25)	1.24 (1.13–1.36)	1.09 (0.79–1.50)	1.20 (1.14–1.27)	1.03 (0.85–1.24)
With history of stroke only [c]					
AIS, n (%)	28,111 (100)	6,611 (23.5)	532 (1.9)	19,530 (69.5)	1,438 (5.1)
1–14 days	1.97 (1.76–2.20)	2.21 (1.81–2.71)	1.42 (0.53–3.85)	1.90 (1.65–2.18)	1.87 (1.10–3.17)
15–30 days	1.52 (1.34–1.71)	1.47 (1.16–1.87)	1.03 (0.33–3.22)	1.57 (1.36–1.82)	1.22 (0.65–2.28)

AIS and risk period	Total	Status of zoster vaccine live (ZVL) and antiviral treatment			
		No vaccination and no antiviral treatment	Vaccination only	Antiviral treatment only	Vaccination and antiviral treatment
31–90 days	1.32 (1.23–1.42)	1.50 (1.32–1.71)	1.62 (1.00–2.60)	1.24 (1.14–1.35)	1.45 (1.07–1.96)
91–180 days	1.18 (1.11–1.26)	1.18 (1.04–1.34)	1.95 (1.34–2.83)	1.17 (1.08–1.26)	1.07 (0.80–1.43)

[a]False discovery rate–adjusted *p* value = 0.067 for interaction between HZ and the status of ZVL and antiviral treatment after HZ based on likelihood ratio test.

[b]False discovery rate–adjusted *p* value = 0.097 for interaction between HZ and status of ZVL and antiviral treatment after HZ on risk of AIS based on likelihood ratio test.

[c]False discovery rate–adjusted *p* value = 0.171 for interaction between HZ and status of ZVL and antiviral treatment after HZ on risk of AIS among beneficiaries with history of stroke based on likelihood ratio test.

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Table5

Incidence rate ratio (95% confidence interval [CI]) for acute ischemic stroke (AIS) among Medicare fee-for-service beneficiaries diagnosed with herpes zoster (HZ) by selected characteristics, Medicare 2008–2017

		Incidence rate ratio (95% CI) after HZ			
Characteristics	**AIS, n**	**0–14 days**	**15–30 days**	**31–90 days**	**91–180 days**
Age group, y [a]					
66–74	25,523	2.01 (1.77–2.28)	1.64 (1.43–1.87)	1.43 (1.32–1.54)	1.28 (1.20–1.37)
75–84	38,139	1.81 (1.63–2.01)	1.42 (1.27–1.60)	1.34 (1.26–1.42)	1.11 (1.05–1.18)
≥85	23,743	1.75 (1.56–1.97)	1.57 (1.39–1.76)	1.21 (1.13–1.31)	1.12 (1.05–1.20)
Sex [b]					
Men	29,599	1.75 (1.55–1.97)	1.64 (1.45–1.85)	1.50 (1.40–1.60)	1.23 (1.16–1.31)
Women	57,806	1.99 (1.84–2.16)	1.57 (1.44–1.71)	1.30 (1.23–1.36)	1.18 (1.13–1.23)
Race [c]					
Non-Hispanic white	75,364	1.84 (1.71–1.97)	1.60 (1.48–1.72)	1.40 (1.34–1.46)	1.20 (1.15–1.25)
Non-Hispanic black	4,923	2.31 (1.82–2.94)	1.70 (1.30–2.24)	1.18 (1.00–1.41)	1.05 (0.90–1.23)
Hispanic	4,107	2.43 (1.86–3.17)	1.40 (1.00–1.96)	1.22 (1.00–1.48)	1.45 (1.25–1.69)
Other	3,001	2.08 (1.47–2.94)	1.36 (0.91–2.05)	1.08 (0.85–1.37)	0.95 (0.77–1.17)

[a] False discovery rate–adjusted *p* value = 0.067 for interaction between HZ and age group on risk for AIS based on likelihood ratio test.

[b] False discovery rate–adjusted *p* value = 0.012 for interaction between HZ and sex on risk for AIS based on likelihood ratio test.

[c] False discovery rate–adjusted *p* value = 0.008 for interaction between HZ and race on risk for AIS based on likelihood ratio test.