

Supplemental Materials

Herpes Zoster Vaccine Live and Risk of Stroke Among Medicare Beneficiaries: A Population-Based Cohort Study

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Figure I. Flowchart of Medicare fee-for-service vaccinated and unvaccinated beneficiaries, Medicare 2008–2017 Matched Cohort

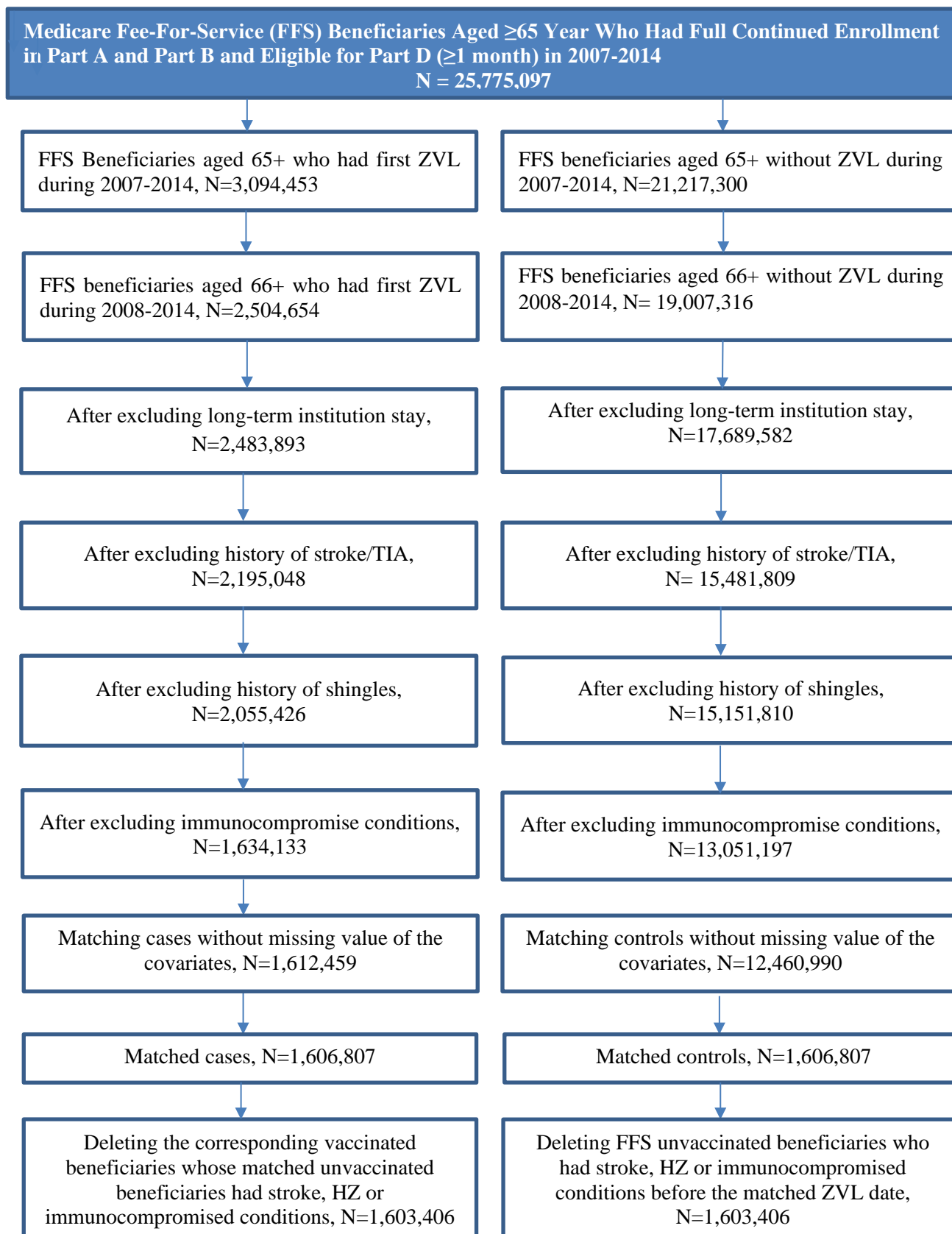


Figure II. Adjusted Hazard Ratio (95% CI) For Risk of 13 Negative Outcomes, Medicare 2008–2017 Matched Cohort

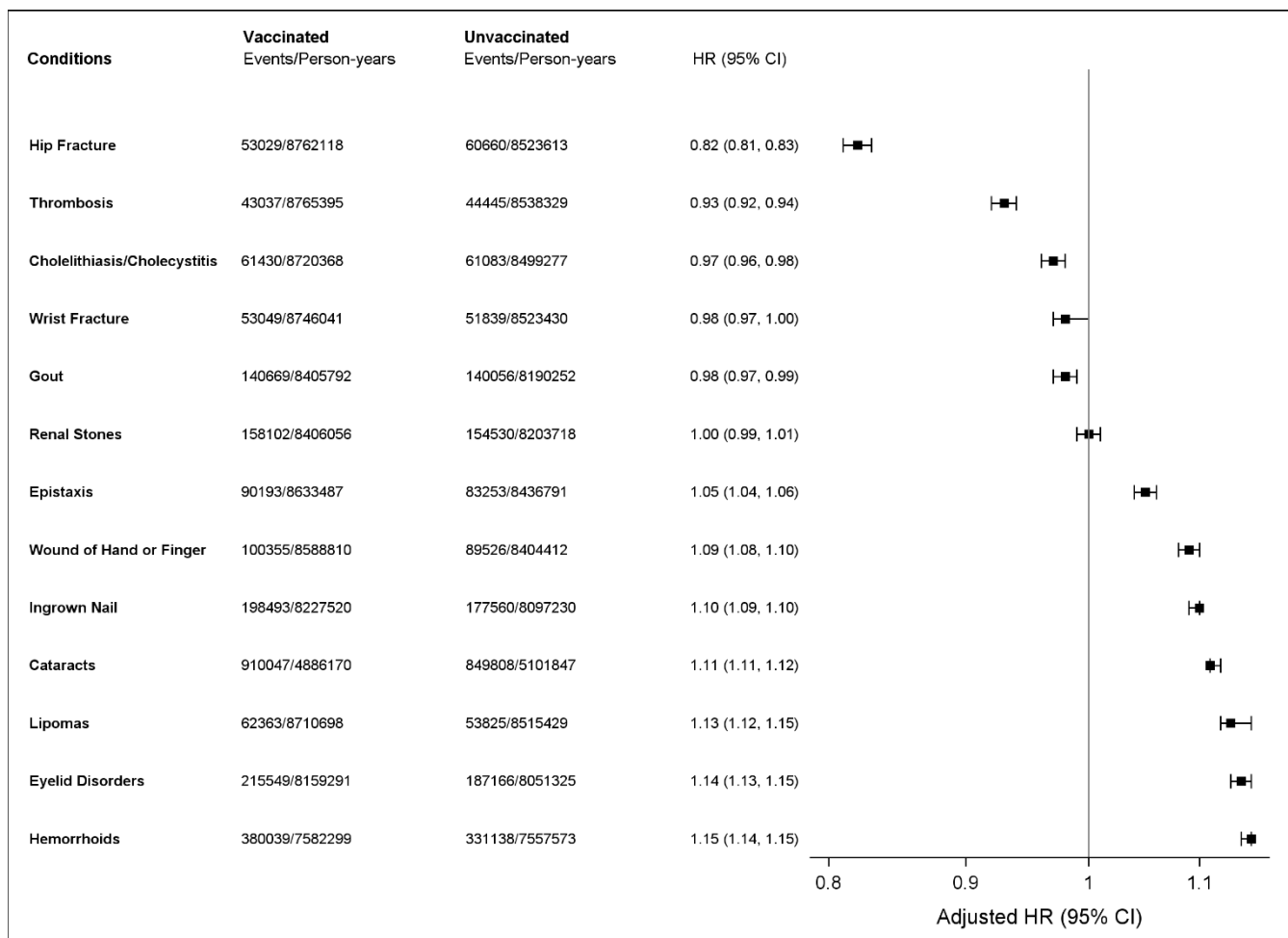


Table I. Zoster Vaccine Live Codes, Medicare 2008–2017 Matched Cohort

		Codes and website link
Zoster Vaccine Live (ZOSTAVAX®)	National Drug Code (NDC)	00006496300 (https://www.hipaaspace.com/medical_billing/coding/national_drug_codes/0006-4963-00)
		00006496301 (https://www.hipaaspace.com/medical_billing/coding/national_drug_codes/0006-4963-00)
		00006496341 (https://www.hipaaspace.com/medical_billing/coding/national_drug_codes/0006-4963-41)
		54868570300 (https://www.bluecrossnc.com/sites/default/files/document/attachment/common/pdfs/2009_MAPD_Vaccine_Claim_Form.pdf)
	Current Procedural Terminology (CPT) code	90736

Table II. ICD-9-CM and ICD-10-CM Codes for Herpes Zoster among Medicare Fee-For-Service Beneficiaries, Medicare 2008–2017 Matched Cohort

Disease	Inclusion criteria	ICD-9-CM codes	Description
Herpes Zoster	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

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

Table III. ICD-9-CM and ICD-10-CM Codes for Immunocompromised Conditions among Medicare Fee-For-Service Beneficiaries, Medicare 2008–2017 Matched Cohort

ICD-10-CM codes	ICD-9-CM codes	Description
	200.xx–208.xx	Leukemia or lymphoma
	042.xx	Human immunodeficiency virus (HIV) infection or AIDS
	238.7	Neoplasm of other lymphatic and hematopoietic tissues
	279.xx	Disorders involving the immune mechanism
	284.xx	Aplastic anemia and other bone marrow failure syndromes
	288.xx	Diseases of white blood cells
	289.89, 289.9	Other diseases of blood and blood-forming organs
	334.8	Other spinocerebellar diseases
	585.xx	Chronic kidney disease
	586.xx	Renal failure
	996.85	Complications of transplanted bone marrow
	200.xx–208.xx	Leukemia or lymphoma

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

Table IV. Covariates Used in Propensity Score Matching, Medicare 2008–2017 Matched Cohort

Covariate	Demographic/Conditions	ICD-9 Diagnosis/Procedure and HCPCS Codes/Sources
Demographic factors	Age	--
	Sex	--
	Race/ethnicity	--
	Year of Cohort Entry	--
	Reason for Entrance into Medicare	--
Socio-economic conditions	Metropolitan Statistical Area (urban/rural status)	--
	Low Income Subsidy (LIS) Status	--
	Household Income by ZIP Code of Residence	Derived from American Community Surveys and matched to the baseline cohort years. United States Census Bureau: https://factfinder.census.gov/faces/nav/jsf/pages/download_center.xhtml#none
Healthcare utilization characteristics	Hospital outpatients visits	--
	Hospital outpatient visits	--
	Home Health visits	--
	Hospital outpatient ER visits	--
	Inpatient ER visits	--
	Ambulatory Surgical Center Events	--
	Medicare Part B physician events	--
	Acute inpatient stays	--
	Other inpatient stays	--
	Flu Vaccine Indicator	HCPCS: 90470, 90655, 90656, 90657, 90658, 90659, 90660, 90661, 90662, 90663, 90724, G0008, G9141, G9142
	Pneumococcal Vaccine Indicator	HCPCS: 90669, 90732, G0009
Frailty characteristics	Home Oxygen	ICD-9: V46.2, 93.96; HCPCS: 99503, 99504, E0424, E0425, E0430, E0431, E0433, E0434, E0435, E0439, E0440, E0441, E0442, E0443, E0444, E0445, E0550, E0560, E1390, E1391, E1392, E1405, E1406, K0671
	Urinary Catheter	ICD-9: 996.64, V53.6, 57.94, 57.95, 96.48, 97.64; HCPCS: 51702, 51703, A4311, A4312, A4313, A4314, A4315, A4316, A4338, A4340, A4344, A4346, A4355
	Walker Use	HCPCS: E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E0154, E0155, E0156, E0157, E0158, E0159, L1520
	Wheelchair Use	ICD-9: E88.43, V46.3, V53.8; HCPCS: 97542, E0192, E0950, E0951, E0952, E0953, E0954, E0955, E0956, E0957, E0958, E0959, E0960, E0961, E0962, E0963, E0964, E0965, E0966, E0967, E0968, E0969, E0971, E0972, E0973, E0974, E0977, E0978, E0981, E0982, E0983, E0984, E0985, E0986, E0990, E0992, E0995, E1002, E1003, E1004, E1005, E1006, E1007, E1008, E1009, E1010, E1011, E1012, E1013, E1014, E1015, E1016, E1017, E1018, E1019, E1020, E1021, E1025, E1026, E1027, E1028, E1029, E1030, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1093, E1100, E1130, E1140, E1150, E1160, E1161, E1170, E1171, E1172, E1180, E1190, E1195, E1200, E1210, E1211, E1212, E1213, E1220, E1221, E1222, E1223, E1224, E1225, E1226, E1227, E1228

The Centers for Medicare and Medicaid (CMS) Chronic Condition Warehouse (CCW) Conditions		Centers for Medicare & Medicaid Services: https://www2.ccwdata.org/web/guest/condition-categories Accessed October 30, 2019.
	Acute Myocardial Infarction	--
	Congestive Heart Failure	--
	Atrial Fibrillation	--
	Alzheimer's Disease and Related Disorders or Senile Dementia	--
	Anemia	--
	Anxiety Disorders	--
	Asthma	--
	Chronic Kidney Disease	--
	Chronic Obstructive Pulmonary Disease and Bronchiectasis	--
	Colorectal Cancer	--
	Depressive disorders	--
	Diabetes	--
	Hyperlipidemia	--
	Hypertension	--
	Ischemic Heart Disease	--
	Lung Cancer	--
	Liver disease	--
	Obesity	--
	Peripheral Vascular Disease	--
	Tobacco Use	--
CMS Hierarchical Condition Category (CMS-HCC) risk score		Centers for Medicare & Medicaid Services. Risk adjustment—2019 Model Software/ICD-10 Mappings. 2018: https://www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Risk-Adjustors-Items/RiskModel2019.html Accessed October 30, 2019.
Use of medications		
	Antihypertensive medication	Yes/No
	Statins	Yes/No
Charlson Comorbidity Index		Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130-1139

Table V. ICD-9-CM and ICD-10-CM Codes for Stroke, Acute Ischemic Stroke and Hemorrhagic Stroke among Medicare Fee-For-Service Beneficiaries, Medicare 2008–2017 Matched Cohort

Disease		ICD-9-CM or ICD-10-CM Codes*
All stroke	ICD-9-CM codes	34660, 34661, 34662, 34663, 430, 431, 4320, 4321, 4329, 43301, 43311, 43321, 43331, 43381, 43391, 4340, 43400, 43401, 4341, 43410, 43411, 4349, 43490, 43491, 436, 4330, 43300, 4331, 43310, 4332, 43320, 4333, 43330, 4338, 43380, 4339, 43390, 4370, 4371, 4373, 4374, 4375, 4376, 4377, 4378, 4379, 438, 4380, 43810, 43811, 43812, 43813, 43814, 43819, 43820, 43821, 43822, 43830, 43831, 43832, 43840, 43841 43842, 43850, 43851, 43852, 43853, 4386, 4387, 43881, 43882, 43883, 43884, 43885, 43889, 4389
	ICD-10-CM codes	I60, I61, I62, I63, I64, I65, I66, I67, I68, I69
Acute ischemic stroke	ICD-9-CM codes	43301, 43311, 43321, 43331, 43381, 43391, 43400, 43401, 43411, 43491, 436
	ICD-10-CM codes	I63, I66, I6789
Hemorrhagic stroke	ICD-9-CM codes	430, 431
	ICD-10-CM codes	I60, I61

* ICD-9-CM was used from 2008 to September 30, 2015, and ICD-10-CM was used from October 1, 2015 to December 31, 2017 to identify the Medicare beneficiaries with stroke.

Table VI. ICD-9-CM and ICD-10-CM Codes for 13 Negative Control Outcomes for Sensitivity Analysis, Medicare 2008–2017 Matched Cohort

Negative Control Outcomes*	ICD-9 Diagnosis Codes	ICD-10 Diagnosis Codes
Lipomas	214.1, 214.8, 214.9	D17.1, D17.20, D17.21, D17.22, D17.23, D17.24, D17.30, D17.39, D17.72, D17.79, D17.9
Gout	274.0, 274.9	M10.9
Eyelid Disorders	373.00, 373.2, 373.11	H01.001, H01.002, H01.003, H01.004, H01.005, H01.006, H01.00A, H01.00B, H01.009, H00.11, H00.12, H00.13, H00.14, H00.15, H00.16, H00.19, H00.011, H00.012, H00.013, H00.014, H00.015, H00.016, H00.019,
Thrombosis	451.9, 453.8, 453.9	I80.9, I82.91
Hemorrhoids	455.0, 455.2, 455.3, 455.6	K64.0, K64.1, K64.2, K64.3, K64.4, K64.8, K64.9
Renal Stones	592.0, 592.9, 788.0	N13.2, N20.0, N20.2, N20.9, N13.9, N22, N23
Ingrown Nail	703.0	L60.0
Epistaxis	784.7	R04.0
Wound of Hand or Finger	882.0, 883.0, 883.1, 883.2	S61.001A, S61.002A, S61.009A, S61.011A, S61.012A, S61.019A, S61.021A, S61.022A, S61.029A, S61.031A, S61.032A, S61.039A, S61.041A, S61.042A, S61.049A, S61.051A, S61.052A, S61.059A, S61.101A, S61.102A, S61.109A, S61.111A, S61.112A, S61.119A, S61.121A, S61.122A, S61.129A, S61.131A, S61.132A, S61.139A, S61.141A, S61.142A, S61.149A, S61.151A, S61.152A, S61.159A, S61.200A, S61.201A, S61.202A, S61.203A, S61.204A, S61.205A, S61.206A, S61.207A, S61.208A, S61.209A, S61.210A, S61.211A, S61.212A, S61.213A, S61.214A, S61.215A, S61.216A, S61.217A, S61.218A, S61.219A, S61.220A, S61.221A, S61.222A, S61.223A, S61.224A, S61.225A, S61.226A, S61.227A, S61.228A, S61.229A, S61.230A, S61.231A, S61.232A, S61.233A, S61.234A, S61.235A, S61.236A, S61.237A, S61.238A, S61.239A, S61.240A, S61.241A, S61.242A, S61.243A, S61.244A, S61.245A, S61.246A, S61.247A, S61.248A, S61.249A, S61.250A, S61.251A, S61.252A, S61.253A, S61.254A, S61.255A, S61.256A, S61.257A, S61.258A, S61.259A, S61.300A, S61.301A, S61.302A, S61.303A, S61.304A, S61.305A, S61.306A, S61.307A, S61.308A, S61.309A, S61.310A, S61.311A, S61.312A, S61.313A, S61.314A, S61.315A, S61.316A, S61.317A, S61.318A, S61.319A, S61.320A, S61.321A, S61.322A, S61.323A, S61.324A, S61.325A, S61.326A, S61.327A, S61.328A, S61.329A, S61.330A, S61.331A, S61.332A, S61.333A, S61.334A, S61.335A, S61.336A, S61.337A, S61.338A, S61.339A, S61.340A, S61.341A, S61.342A, S61.343A, S61.344A, S61.345A, S61.346A, S61.347A, S61.348A, S61.349A, S61.350A, S61.351A, S61.352A, S61.353A, S61.354A, S61.355A, S61.356A, S61.357A, S61.358A, S61.359A, S61.401A, S61.402A, S61.409A, S61.411A, S61.412A, S61.419A, S61.431A, S61.432A,

		S61.439A, S61.451A, S61.452A, S61.459A, S66.529A
Cataracts	366.10, 366.14, 366.16, 366.17, 366.19	H25.041, H25.042, H25.043, H25.049, H25.10, H25.11, H25.12, H25.13, H25.811, H25.812, H25.813, H25.819, H25.89, H25.9
Cholelithiasis and Cholecystitis	574.00, 574.10, 575.10	K80.00, K80.10, K80.12, K80.18, K81.9
Wrist Fracture	813.05, 813.23, 813.41, 813.42, 813.44, 813.81	S52.121A, S52.122A, S52.123A, S52.124A, S52.125A, S52.126A, S52.209A, S52.309A, S52.501A, S52.502A, S52.509A, S52.511A, S52.512A, S52.513A, S52.514A, S52.515A, S52.516A, S52.531A, S52.532A, S52.539A, S52.541A, S52.542A, S52.549A, S52.551A, S52.552A, S52.559A, S52.561A, S52.562A, S52.569A, S52.571A, S52.572A, S52.579A, S52.591A, S52.592A, S52.599A, S52.609A, S52.90XA, S52.91XA, S52.92XA, S59.201A, S59.202A, S59.209A, S59.211A, S59.212A, S59.219A, S59.221A, S59.222A, S59.229A, S59.231A, S59.232A, S59.239A, S59.241A, S59.242A, S59.249A, S59.291A, S59.292A, S59.299A
Hip Fracture	820.00, 820.01, 820.02, 820.03, 820.8, 820.9, 820.09, 820.10, 820.11, 820.12, 820.13, 820.19	S72.001A, S72.001B, S72.001C, S72.002A, S72.002B, S72.002C, S72.009A, S72.009B, S72.009C, S72.011A, S72.011B, S72.011C, S72.012A, S72.012B, S72.012C, S72.019A, S72.019B, S72.019C, S72.021A, S72.021B, S72.021C, S72.022A, S72.022B, S72.022C, S72.023A, S72.023B, S72.023C, S72.024A, S72.024B, S72.024C, S72.025A, S72.025B, S72.025C, S72.026A, S72.026B, S72.026C, S72.031A, S72.031B, S72.031C, S72.032A, S72.032B, S72.032C, S72.033A, S72.033B, S72.033C, S72.034A, S72.034B, S72.034C, S72.035A, S72.035B, S72.035C, S72.036A, S72.036B, S72.036C, S72.041A, S72.041B, S72.041C, S72.042A, S72.042B, S72.042C, S72.043A, S72.043B, S72.043C, S72.044A, S72.044B, S72.044C, S72.045A, S72.045B, S72.045C, S72.046A, S72.046B, S72.046C, S72.051A, S72.051B, S72.051C, S72.052A, S72.052B, S72.052C, S72.059A, S72.059B, S72.059C, S72.061A, S72.061B, S72.061C, S72.062A,

		S72.062B, S72.062C, S72.063A, S72.063B, S72.063C, S72.064A, S72.064B, S72.064C, S72.065A, S72.065B, S72.065C, S72.066A, S72.066B, S72.066C, S72.091A, S72.091B, S72.091C, S72.092A, S72.092B, S72.092C, S72.099A, S72.099B, S72.099C, S79.001A, S79.002A, S79.009A, S79.011A, S79.012A, S79.019A, S79.091A, S79.092A, S79.099A
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*Conditions were defined by using all diagnosis positions in Medicare Part A, Part B, and non-institutional settings.

Table VII. Characteristics of Original Cohort Medicare Fee-For-Service Beneficiaries Aged 66 Years or Older Compared to ZVL Vaccinated Beneficiaries, 2008–2017 Medicare Cohort

Characteristics	Number of original cohort FFS beneficiaries	Mean / % (95% CI)	Number of vaccinated FFS beneficiaries	Vaccinated mean / % (95% CI)	Number of matched unvaccinated FFS beneficiaries	Unvaccinated mean / % (95% CI)	Standardized differences between original and vaccinated FFS beneficiaries / %*	Standardized differences between vaccinated and matched unvaccinated FFS beneficiaries / %*
All	12,691,959		1,603,406		1,603,406			
Age, mean		73.8 (73.8-73.8)		73.4 (73.4–73.5)		73.4 (73.4–73.5)	-0.045	0.000
Age group (%)								
66–74 years	8,033,965	63.3 (63.3-63.3)	1,065,678	66.5 (66.3–66.6)	1,065,678	66.5 (66.3–66.6)	0.066	0.000
75–84 years	3,370,704	26.6 (26.5-26.6)	452,242	28.2 (28.1–28.3)	452,242	28.2 (28.1–28.3)	0.038	0.001
≥85 years	1,287,290	10.1 (10.1-10.2)	85,486	5.33 (5.30–5.37)	85,486	5.33 (5.30–5.37)	-0.182	0.001
Sex (%)								
Men	5,022,738	39.6 (39.5-39.6)	597,294	37.3 (37.2–37.3)	597,294	37.3 (37.2–37.3)		
Women	7,669,221	60.4 (60.4-60.5)	1,006,112	62.7 (62.6–62.9)	1,006,112	62.7 (62.6–62.9)	0.048	0.000
Ethnicity								
Non-Hispanic white	10,185,599	80.3 (80.2-80.3)	1,438,674	89.7 (89.6–89.9)	1,438,674	89.7 (89.6–89.9)	0.268	0.000
Non-Hispanic black	1,066,826	8.41 (8.39-8.42)	36,681	2.29 (2.26–2.31)	36,681	2.29 (2.26–2.31)	-0.275	0.000
Hispanic	875,082	6.89 (6.88-6.91)	44,898	2.8 (2.77–2.83)	44,898	2.8 (2.77–2.83)	-0.192	0.000
Other	564,452	4.45 (4.44-4.46)	83,176	5.19 (5.15–5.22)	83,176	5.19 (5.15–5.22)	0.035	0.000

Low-income subsidy (%)								
Yes	3,366,105	26.5 (26.5-26.5)	210,903	13.2 (13.1–13.2)	210,903	13.2 (13.1–13.2)		
No	9,325,854	73.5 (73.4-73.5)	1,392,503	86.8 (86.7–87.0)	1,392,503	86.8 (86.7–87.0)	0.347	0.007
Antihypertensive Use Status (%)								
Yes	8,589,566	67.7 (67.6-67.7)	1,140,006	71.1 (71.0–71.2)	1,140,006	71.1 (71.0–71.2)		
No	4,102,393	32.3 (32.3-32.4)	463,400	28.9 (28.8–29.0)	463,400	28.9 (28.8–29.0)	-0.072	0.002
Statin Use Status (%)								
Yes	5,426,896	42.8 (42.7-42.8)	861,495	53.7 (53.6–53.8)	861,495	53.7 (53.6–53.8)		
No	7,265,063	57.2 (57.2-57.3)	741,911	46.3 (46.2–46.4)	741,911	46.3 (46.2–46.4)	-0.226	0.002
Hypertension (%)								
Yes	9,474,206	74.6 (74.6-74.7)	1,229,895	76.7 (76.6-76.8)	1,235,521	77.1 (76.9-77.2)		
No	3,217,753	25.4 (25.3-25.4)	373,511	23.3 (23.2-23.4)	367,885	22.9 (22.9-23.0)	0.048	-0.008
Diabetes (%)								
Yes	3,898,495	30.7 (30.7-30.7)	444,188	27.7 (27.6-27.8)	450,911	28.1 (28.0- 8.2)		
No	8,793,464	69.3 (69.2-69.3)	1,159,218	72.3 (72.2-72.4)	1,152,495	71.9 (71.8-72.0)	-0.066	-0.009
Hyperlipidemia (%)								
Yes	8,766,136	69.1 (69.0-69.1)	1,292,510	80.6 (80.5-80.8)	1,298,061	81.0(80.8- 81.1)		
No	3,925,823	30.9 (30.9-31.0)	310,896	19.4 (19.3-19.5)	305,345	19.0 (19.0-19.1)	0.268	-0.009

Ischemic heart disease (%)								
Yes	5,056,928	39.8 (39.8-39.9)	590392	36.8 (36.7-36.9)	595,861	37.2 (37.2-37.3)		
No	7,635,031	60.2 (60.1-60.2)	1,013,014	63.2 (63.2- 63.3)	1,007,545	62.8 (62.7-63.0)	-0.062	-0.007
Congestive heart failure (%)								
Yes	2,546,631	20.1 (20.0-20.1)	213,046	13.3 (13.2-13.3)	212,439	13.3 (13.2-13.3)		
No	10,145,328	79.9 (79.9-80.0)	1,390,360	86.7 (86.6-86.9)	1,390,967	86.8 (86.6-86.9)	-0.183	0.001
Atrial fibrillation (%)								
Yes	1,338,221	10.5 (10.5-10.6)	154,610	9.6 (9.6-9.7)	152,203	9.5 (9.5- 9.5)	-0.030	0.005
No	11,353,738	89.5 (89.4-89.5)	1,448,796	90.4 (90.2- 90.5)	1,451,203	90.5 (90.4-90.7)		
Obesity (%)								
Yes	709,943	5.6 (5.6-5.6)	96,179	6.0 (6.0-6.0)	94,047	5.9 (5.8-5.9)		
No	11,982,016	94.4 (94.4-94.5)	1,507,227	94.0 (93.9-94.2)	1,509,359	94.1 (94.0-94.3)	0.017	0.006
Tobacco use (%)								
Yes	623,659	4.9 (4.9-4.9)	49,053	3.1 (3.0-3.1)	48,930	3.1 (3.0-3.1)		
No	12,068,300	95.1 (95.0-95.1)	1,554,353	96.9 (96.8-97.1)	1,554,476	96.9 (96.8-97.1)	-0.095	0.000
Charlson Comorbidity Index (%)								
0	4,227,715	33.3 (33.3-33.3)	606,806	37.8 (37.8–37.9)	606,806	37.8 (37.8–37.9)	0.087	0.008

1	2,926,369	23.1 (23.0-23.1)	413,712	25.8 (25.7–25.9)	413,712	25.8 (25.7–25.9)	0.052	0.012
2	1,963,717	15.5 (15.5-15.5)	257,532	16.1 (16.0–16.1)	257,532	16.1 (16.0–16.1)	0.017	0.001
3	1,413,695	11.1 (11.1-11.2)	167,496	10.4 (10.4–10.5)	167,496	10.4 (10.4–10.5)	0.020	0.002
4+	4,227,715	33.3 (33.3-33.3)	157,781	9.84 (9.79–9.89)	157,781	9.84 (9.79–9.89)	0.186	0.026

Abbreviations: CI, confidence interval; FFS, fee-for-service; ZVL, zoster vaccine live.

*Standardized differences were the differences in means or proportions between original cohort and vaccinated FFS beneficiaries and between vaccinated and unvaccinated FFS beneficiaries divided by standard errors where differences <0.10 were considered negligible.

Table VIII. Incidence Rates and Adjusted Hazard Ratio (95% CI) For Risk of Stroke by ZVL Status and Selected Covariates, Medicare 2008–2017 Matched Cohort

Characteristics	All Stroke			Acute Ischemic Stroke			Hemorrhagic Stroke		
	ZVL status			ZVL status			ZVL status		
	Unvaccinated	Vaccinated	<i>P</i> -value*	Unvaccinated	Vaccinated	<i>P</i> -value*	Unvaccinated	Vaccinated	<i>P</i> -value*
Age group									
66–74 years									
Stroke events (person-years)†	35352 (5590626)	29543 (5707036)		24339 (5608309)	19761 (5724002)		3495 (5667971)	3019 (5773718)	
Incidence rate per 1,000 person-years (95% CI)	6.32 (6.32-6.33)	5.18 (5.17-5.18)	<.001	4.34 (4.34-4.34)	3.45 (3.45-3.45)	<.001	0.62 (0.62-0.62)	0.52 (0.52-0.52)	<.001
HR (95% CI)	1.0	0.82 (0.80-0.83)	<.001	1.0	0.79 (0.78-0.81)	<.001	1.0	0.84 (0.80-0.89)	<.001
Fully adjusted HR (95% CI)‡	1.0	0.81 (0.80-0.82)	<.001	1.0	0.79 (0.78-0.81)	<.001	1.0	0.84 (0.80-0.88)	<.001
75–84 years									
Stroke events (person-years)†	29420 (2506599)	26892 (2600891)		20542 (2518185)	18572 (2612739)		3047 (2561759)	2920 (2654895)	
Incidence rate per 1,000 person-years (95% CI)	11.7 (11.7-11.7)	10.3 (10.3-10.3)		8.16 (8.15-8.16)	7.11 (7.11-7.11)		1.19 (1.19-1.19)	1.1 (1.1- 1.1)	
HR (95% CI)	1.0	0.88 (0.86-0.89)		1.0	0.87 (0.85-0.88)		1.0	0.92 (0.87-0.97)	0.001
Fully adjusted HR (95% CI)‡	1.0	0.86 (0.85-0.87)		1.0	0.85 (0.84-0.87)		1.0	0.90 (0.86-0.95)	<.001
≥85 years									
Stroke events (person-years)†	8251 (420096)	8200 (447404)		5595 (422168.8)	5621 (449751.6)		734 (430604)	788 (459079)	
Incidence rate per 1,000 person-years (95% CI)	19.6 (19.6-19.7)	18.3 (18.3-18.3)		13.3 (13.2-13.3)	12.5 (12.5-12.5)		1.7 (1.70-1.71)	1.72 (1.71-1.72)	
HR (95% CI)	1.0	0.93 (0.90-0.95)	<.001	1.0	0.94 (0.90-0.97)	0.001	1.0	1.0 (0.91-1.11)	0.925
Fully adjusted HR (95% CI)‡	1.0	0.91 (0.88-0.93)	<.001	1.0	0.92 (0.88-0.95)	<.001	1.0	0.99 (0.89-1.09)	0.822
Sex									
Men									
Stroke events (person-years)†	28201 (3065929)	25409 (3155094)		19294 (3078378)	17039 (3167752)		2586 (3123192)	2539 (3208971)	
Incidence rate per 1,000 person-years (95% CI)	9.2 (9.19- 9.2)	8.05 (8.05-8.06)		6.27 (6.26-6.27)	5.38 (5.38-5.38)		0.83 (0.83-0.83)	0.79 (0.79-0.79)	
HR (95% CI)	1.0	0.87 (0.86-0.89)	<.001	1.0	0.86 (0.84-0.87)	<.001	1.0	0.95 (0.90-1.01)	0.078
Fully adjusted HR (95% CI)‡	1.0	0.85 (0.84-0.87)	<.001	1.0	0.84 (0.82-0.86)	<.001	1.0	0.93 (0.88-0.98)	0.009

Women									
Stroke events (person-years)†	44822 (5451393)	39226 (5600237)		31182 (5470285)	26915 (5618741)		4690 (5537142)	4188 (5678722)	
Incidence rate per 1,000 person-years (95% CI)	8.22 (8.22-8.22)	7.00 (7.00-7.01)		5.7 (5.7- 5.7)	4.79 (4.79-4.79)		0.85 (0.85-0.85)	0.74 (0.74-0.74)	
HR (95% CI)	1.0	0.85 (0.84-0.86)	<.001	1.0	0.84 (0.82-0.85)	<.001	1.0	0.87 (0.83- 0.9)	<.001
Fully adjusted HR (95% CI)‡	1.0	0.83 (0.82-0.84)	<.001	1.0	0.82 (0.81-0.83)	<.001	1.0	0.85 (0.81-0.88)	<.001
Race/ethnicity									
Non-Hispanic white									
Stroke events (person-years)†	66214 (7677004)	58719 (7897863)		45924 (7704926)	40100 (7925679)		6400 (7807727)	5963 (8019079)	
Incidence rate per 1,000 person-years (95% CI)	8.62 (8.62-8.63)	7.43 (7.43-7.44)		5.96 (5.96-5.96)	5.06 (5.06-5.06)		0.82 (0.82-0.82)	0.74 (0.74-0.74)	
HR (95% CI)	1	0.86 (0.85-0.87)	<.001	1	0.85 (0.84-0.86)	<.001	1	0.9 (0.87-0.94)	<.001
Fully adjusted HR (95% CI)‡	1	0.84 (0.83-0.85)	<.001	1	0.83 (0.82-0.84)	<.001	1	0.88 (0.85-0.92)	<.001
Non-Hispanic black									
Stroke events (person-years)†	1661 (169661)	1408 (172226)		1179 (170275)	972 (172831)		155 (172523)	147 (174770)	
Incidence rate per 1,000 person-years (95% CI)	9.79 (9.78-9.81)	8.18 (8.16-8.19)		6.92 (6.91-6.94)	5.62 (5.61-5.64)		0.90 (0.89- 0.9)	0.84 (0.84-0.85)	
HR (95% CI)	1	0.83 (0.78-0.89)	<.001	1	0.81 (0.75-0.88)	<.001	1	0.94 (0.75-1.17)	0.5604
Fully adjusted HR (95% CI)‡	1	0.80 (0.74-0.86)	<.001	1	0.78 (0.71-0.85)	<.001	1	0.92 (0.73-1.15)	0.4501
Hispanic									
Stroke events (person-years)†	1639 (220706)	1555 (223460)		1087 (221557)	1021 (224336)		200 (223675)	186 (226358)	
Incidence rate per 1,000 person-years (95% CI)	7.43 (7.41-7.44)	6.96 (6.95-6.97)		4.91 (4.90-4.92)	4.55 (4.54-4.56)		0.89 (0.89- 0.9)	0.82 (0.82-0.83)	
HR (95% CI)	1	0.94 (0.87-1.00)	0.060	1	0.93 (0.85-1.01)	0.081	1	0.92 (0.75-1.12)	0.399
Fully adjusted HR (95% CI)‡	1	0.89 (0.83-0.95)	0.001	1	0.88 (0.81-0.96)	0.003	1	0.91 (0.74-1.11)	0.338
Other									
Stroke events (person-years)†	3509 (449951)	2953 (461783)		2286 (451906)	1861 (463646)		521 (456409)	431 (467486)	
Incidence rate per 1,000 person-years (95% CI)	7.80 (7.79-7.81)	6.39 (6.39- 6.4)		5.06 (5.05-5.07)	4.01 (4.01-4.02)		1.14 (1.14-1.14)	0.92 (0.92-0.92)	

HR (95% CI)	1	0.82 (0.78-0.86)	<.001	1	0.79 (0.74-0.84)	<.001	1	0.81 (0.71-0.91)	0.001
Fully adjusted HR (95% CI)‡	1	0.78 (0.75-0.82)	<.001	1	0.76 (0.71-0.81)	<.001	1	0.78 (0.69-0.89)	<0.001
Low-income subsidy									
Yes									
Stroke events (person-years)†	11001 (1039335)	9775 (1051955)		7651 (1043641)	6693 (1056314)		1100 (1059258)	964 (1070593)	
Incidence rate per 1,000 person-years (95% CI)	10.6 (10.6-10.6)	9.29 (9.29- 9.3)		7.33 (7.33-7.34)	6.34 (6.33-6.34)		1.04 (1.04-1.04)	0.90 (0.9- 0.9)	
HR (95% CI)	1	0.88 (0.85- 0.9)	<.001	1	0.86 (0.84-0.89)	<.001	1	0.86 (0.79-0.94)	0.001
Fully adjusted HR (95% CI)‡	1	0.85 (0.82-0.87)	<.001	1	0.84 (0.81-0.87)	<.001	1	0.83 (0.76- 0.9)	<.001
No									
Stroke events (person-years)†	62022 (7477986)	54860 (7703376)		42825 (7505022)	37261 (7730179)		6176 (7601076)	5763 (7817099)	
Incidence rate per 1,000 person-years (95% CI)	8.29 (8.29- 8.3)	7.12 (7.12-7.12)		5.71 (5.7-5.71)	4.82 (4.82-4.82)		0.81 (0.81-0.81)	0.74 (0.74-0.74)	
HR (95% CI)	1	0.85 (0.85-0.86)	<.001	1	0.84 (0.83-0.85)	<.001	1	0.90 (0.87-0.94)	<.001
Fully adjusted HR (95% CI) ^c	1	0.84 (0.83-0.85)	<.001	1	0.83 (0.82-0.84)	<.001	1	0.89 (0.86-0.92)	<.001
Antihypertensive Use									
Yes									
Stroke events (person-years)†	57864 (5973987)	52114 (6132430)		40341 (5997975)	35869 (6156226)		5401 (6088038)	5037 (6239872)	
Incidence rate per 1,000 person-years (95% CI)	9.69 (9.68-9.69)	8.50 (8.5- 8.5)		6.73 (6.72-6.73)	5.83 (5.82-5.83)		0.89 (0.89-0.89)	0.81 (0.81-0.81)	
HR (95% CI)	1	0.87 (0.86-0.88)	<.001	1	0.86 (0.85-0.88)	<.001	1	0.91 (0.87-0.94)	<.001
Fully adjusted HR (95% CI)‡	1	0.85 (0.84-0.86)	<.001	1	0.84 (0.83-0.86)	<.001	1	0.88 (0.85-0.91)	<.001
No									
Stroke events (person-years)†	15159 (2543335)	12521 (2622901)		10135 (2550688)	8085 (2630267)		1875 (2572296)	1690 (2647821)	
Incidence rate per 1,000 person-years (95% CI)	5.96 (5.96-5.96)	4.77 (4.77-4.78)		3.97 (3.97-3.98)	3.07 (3.07-3.08)		0.73 (0.73-0.73)	0.64 (0.64-0.64)	
HR (95% CI)	1	0.8 (0.78-0.82)	<.001	1	0.77 (0.75-0.79)	<.001	1	0.87 (0.82-0.93)	<.001
Fully adjusted HR (95% CI)‡	1	0.8 (0.78-0.82)	<.001	1	0.78 (0.76- 0.8)	<.001	1	0.88 (0.82-0.94)	<.001

Statins Use									
Yes									
Stroke events (person-years)†	40329 (4566665)	36412 (4690315)		27947 (4584295)	24922 (4707821)		3795 (4649084)	3547 (4768389)	
Incidence rate per 1,000 person-years (95% CI)	8.83 (8.83-8.83)	7.76 (7.76-7.77)		6.10 (6.09- 6.1)	5.29 (5.29- 5.3)		0.82 (0.82-0.82)	0.74 (0.74-0.74)	.
HR (95% CI)	1	0.88 (0.86-0.89)	<.001	1	0.87 (0.85-0.88)	<.001	1	0.91 (0.87-0.95)	<.001
Fully adjusted HR (95% CI)‡	1	0.86 (0.85-0.87)	<.001	1	0.85 (0.83-0.86)	<.001	1	0.89 (0.85-0.93)	<.001
No									
Stroke events (person-years)†	32694 (3950657)	28223 (4065016)		22529 (3964368)	19032 (4078672)		3481 (4011250)	3180 (4119303)	
Incidence rate per 1,000 person-years (95% CI)	8.28 (8.27-8.28)	6.94 (6.94-6.95)		5.68 (5.68-5.69)	4.67 (4.66-4.67)		0.87 (0.87-0.87)	0.77 (0.77-0.77)	.
HR (95% CI)	1	0.83 (0.82-0.85)	<.001	1	0.82 (0.8-0.83)	<.001	1	0.89 (0.84-0.93)	<.001
Fully adjusted HR (95% CI)‡	1	0.82 (0.81-0.83)	<.001	1	0.81 (0.79-0.82)	<.001	1	0.87 (0.83-0.91)	<.001
Charlson Comorbidity Index									
0									
Stroke events (person-years)†	20169 (3381964)	16470 (3418549)		13821 (3391217)	11041 (3427206)		2313 (3419416)	2037 (3450422)	
Incidence rate per 1,000 person-years (95% CI)	5.96 (5.96-5.97)	4.82 (4.82-4.82)		4.08 (4.07-4.08)	3.22 (3.22-3.22)		0.68 (0.68-0.68)	0.59 (0.59-0.59)	
HR (95% CI)	1	0.80 (0.79-0.82)	<.001	1	0.79 (0.77-0.81)	<.001	1	0.87 (0.82-0.92)	<.001
Fully adjusted HR (95% CI)‡	1	0.81 (0.8-0.83)	<.001	1	0.80 (0.78-0.82)	<.001	1	0.88 (0.83-0.93)	<.001
1									
Stroke events (person-years)†	18447 (2205649)	15746 (2222012)		15746 (2213652)	15746 (2229883)		15746 (2241558)	15746 (2253817)	
Incidence rate per 1,000 person-years (95% CI)	8.36 (8.36-8.37)	7.09 (7.08-7.09)		5.71 (5.71-5.72)	4.76 (4.76-4.77)		0.83 (0.83-0.83)	0.74 (0.74-0.74)	
HR (95% CI)	1	0.84 (0.82-0.86)	<.001	1	0.83 (0.81-0.85)	<.001	1	0.89 (0.83-0.95)	<.001
Fully adjusted HR (95% CI)‡	1	0.83 (0.82-0.85)	<.001	1	0.82 (0.80-0.84)	<.001	1	0.87 (0.81-0.93)	<.001
2									
Stroke events (person-years)†	13287 (1352746)	11908 (1399169)		9204 (1358601)	8119 (1404774)		1277 (1380069)	1158 (1424311)	

Incidence rate per 1,000 person-years (95% CI)	9.82 (9.82-9.83)	8.51 (8.51-8.52)		6.77 (6.77-6.78)	5.78 (5.78-5.78)		0.93 (0.92-0.93)	0.81 (0.81-0.81)	
HR (95% CI)	1	0.86 (0.84-0.88)	<.001	1	0.85 (0.83-0.88)	<.001	1	0.88 (0.81-0.95)	0.001
Fully adjusted HR (95% CI) [‡]	1	0.86 (0.83-0.88)	<.001	1	0.84 (0.82-0.87)	<.001	1	0.86 (0.79-0.93)	<.001
3									
Stroke events (person-years) [†]	9961 (853009)	8909 (887050)		6940 (857020.3)	6174 (891041)		870 (872935)	819 (905950)	
Incidence rate per 1,000 person-years (95% CI)	11.7 (11.7-11.7)	10.0 (10.0-10.0)		8.10 (8.09- 8.1)	6.93 (6.92-6.93)		1.00 (0.99-10.)	0.90 (0.9-0.91)	
HR (95% CI)	1	0.86 (0.83-0.88)	<.001	1	0.85 (0.83-0.88)	<.001	1	0.90 (0.82-0.99)	0.038
Fully adjusted HR (95% CI) [‡]	1	0.84 (0.82-0.87)	<.001	1	0.84 (0.81-0.87)	<.001	1	0.88 (0.8-0.97)	0.009
≥4									
Stroke events (person-years) [‡]	11159 (723954)	11602 (828550)		7862 (728173)	7997 (833588.2)		951 (746355)	1043 (853193)	
Incidence rate per 1,000 person-years (95% CI)	15.4 (15.4-15.4)	14.0 (14.0-14.0)		10.8 (10.8-10.8)	9.59 (9.59- 9.6)		1.27 (1.27-1.28)	1.22 (1.22-1.22)	
HR (95% CI)	1.0	0.91 (0.88-0.93)	<.001	1.0	0.89 (0.86-0.92)	<.001	1.0	0.96 (0.88-1.05)	0.354
Fully adjusted HR (95% CI) [‡]	1.0	0.88 (0.85- 0.9)	<.001	1.0	0.86 (0.83-0.89)	<.001	1.0	0.92 (0.84-1.01)	0.071

Abbreviations: CI, confidence interval; HR, hazard ratio; ZVL, zoster vaccine live.

**P*-value for difference in risk of stroke between beneficiaries who received ZVL and matched controls; all tests were two-tailed.

[†]Stroke events included both fatal and nonfatal incident events.

[‡]In addition to propensity score matching, adjusted for all matching variables to control for potential residual confounding.

Table IX. Comparison of Incidence Rates and Hazard Ratio (95% CI) of 13 Negative Control Outcomes Between Vaccinated and Unvaccinated FFS Beneficiaries, Medicare 2008–2017 Matched Cohort

Negative control outcomes	Received ZVL (n=1,603,406)		Matched controls (n=1,603,406)		Hazard ratio (95% CI)*
	Number of cases (person-years)	Incidence rate (95% CI)	Number of cases (person-years)	Incidence rate (95% CI)	
Lipomas	62363 (8710698)	7.16 (7.16-7.16)	53825 (8515429)	6.32 (6.32-6.32)	1.13 (1.12-1.15)
Gout	140669 (8405792)	16.7 (16.7-16.7)	140056 (8190252)	17.1 (17.1-17.1)	0.98 (0.97-0.99)
Eyelid Disorders	215549 (8159291)	26.4 (26.4-26.4)	187166 (8051325)	23.2 (23.2-23.2)	1.14 (1.13-1.15)
Thrombosis	43037 (8765395)	4.91 (4.91-4.91)	44445 (8538329)	5.21 (5.20-5.21)	0.93 (0.92-0.94)
Hemorrhoids	380039 (7582299)	50.1 (50.1-50.1)	331138 (7557573)	43.8 (43.8-43.8)	1.15 (1.14-1.15)
Renal Stones	158102 (8406056)	18.8 (18.8-18.8)	154530 (8203718)	18.8 (18.8-18.8)	1.00 (0.99-1.00)
Ingrown Nail	198493 (8227520)	24.1 (24.1-24.1)	177560 (8097230)	21.9 (21.9-21.9)	1.10 (1.09-1.10)
Epistaxis	90193 (8633487)	10.4 (10.4-10.4)	83253 (8436791)	9.87 (9.87-9.87)	1.05 (1.04-1.06)
Wound of Hand or Finger	100355 (8588810)	11.7 (11.7-11.7)	89526 (8404412)	10.7 (10.7-10.7)	1.09 (1.08-1.10)
Cataracts	910047 (4886170)	186 (186.0-186.1)	849808 (5101847)	167 (167.0- 167.0)	1.11 (1.11-1.12)
Cholelithiasis and Cholecystitis	61430 (8720368)	7.04 (7.04-7.05)	61083 (8499277)	7.19 (7.19-7.19)	0.97 (0.96-0.98)
Wrist Fracture	53049 (8746041)	6.07 (6.06-6.07)	51839 (8523430)	6.08 (6.08-6.08)	0.98 (0.97-1.00)
Hip Fracture	53029 (8762118)	6.05 (6.05-6.05)	60660 (8523613)	7.12 (7.11-7.12)	0.82 (0.81-0.83)

Abbreviations: CI, confidence interval; ZVL, zoster vaccine live.

*In addition to propensity score matching, adjusted for all matching variables to control for potential residual confounding.