

# Recombinant Adjuvanted Zoster Vaccine and Reduced Risk of Coronavirus Disease 2019 Diagnosis and Hospitalization in Older Adults

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**Background.** Some vaccines elicit nonspecific immune responses that may protect against heterologous infections. We evaluated the association between recombinant adjuvanted zoster vaccine (RZV) and coronavirus disease 2019 (COVID-19) outcomes at Kaiser Permanente Southern California.

**Methods.** In a cohort design, adults aged  $\geq 50$  years who received  $\geq 1$  RZV dose before 1 March 2020 were matched 1:2 to unvaccinated individuals and followed until 31 December 2020. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for COVID-19 outcomes were estimated using Cox proportional hazards regression. In a test-negative design, cases had a positive severe acute respiratory syndrome coronavirus 2 test and controls had only negative tests, during 1 March–31 December 2020. Adjusted odds ratios (aORs) and 95% CIs for RZV receipt were estimated using logistic regression.

**Results.** In the cohort design, 149 244 RZV recipients were matched to 298 488 unvaccinated individuals. The aHRs for COVID-19 diagnosis and hospitalization were 0.84 (95% CI, .81–.87) and 0.68 (95% CI, .64–.74), respectively. In the test-negative design, 8.4% of 75 726 test-positive cases and 13.1% of 340 898 test-negative controls had received  $\geq 1$  RZV dose (aOR, 0.84 [95% CI, .81–.86]).

**Conclusions.** RZV vaccination was associated with a 16% lower risk of COVID-19 diagnosis and 32% lower risk of hospitalization. Further study of vaccine-induced nonspecific immunity for potential attenuation of future pandemics is warranted.

**Keywords.** COVID-19; zoster vaccine; trained immunity; nonspecific effects.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) triggered a global pandemic with >270 million infections and >5 million deaths [1]. Despite extraordinarily rapid development of highly efficacious COVID-19 vaccines, nearly 12 months elapsed before vaccine implementation [2], and only 47% of the global population was fully vaccinated as of December 2021 [1].

Traditionally, immune memory consisting of pathogen-specific cellular and humoral responses is the hallmark of the adaptive response. However, a growing body of evidence

suggests that the innate immune system can develop trained immunity, which can ameliorate a broad array of infectious diseases, sometimes for prolonged periods [3–5]. Several studies of bacillus Calmette-Guérin (BCG), measles, oral polio, and influenza vaccines demonstrate the ability of the innate immune system to provide nonspecific protection against heterologous infections [4–6].

Recombinant adjuvanted zoster vaccine (RZV) contains AS01 adjuvant, which elicits an innate immune response and robust cellular and humoral responses [7]. We hypothesized that RZV could induce trained immunity that might reduce SARS-CoV-2 infections in older adults. Therefore, we evaluated the association of RZV receipt with COVID-19 diagnosis and hospitalization.

## METHODS

### Study Setting

We employed matched cohort and test-negative designs in an observational study conducted at Kaiser Permanente Southern California (KPSC), an integrated healthcare system with 15 hospitals, 235 medical offices, and >4.7 million diverse members. KPSC members have strong motivation to seek care within the prepaid system. Recommended no-cost vaccinations

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are proactively offered at any visit, including walk-in visits. Comprehensive electronic health records (EHR) capture all details of patient care, including diagnoses, vaccinations, procedures, laboratory tests, and pharmacy records. Care received outside of KPSC is captured through claims.

During the study period (1 March–31 December 2020), SARS-CoV-2 reverse-transcription polymerase chain reaction testing was primarily conducted on nasopharyngeal/oropharyngeal swabs using the Roche cobas SARS-CoV-2 assay, Aptima SARS-CoV-2 assay, or TaqPath COVID-19 High-Throughput Combo Kit.

### Cohort Design

The cohort design included individuals aged  $\geq 50$  years as of 1 March 2020 with  $\geq 1$  year of prior KPSC membership. Exposures were receipt before a March 2020 of  $\geq 1$  RZV dose, 2 RZV doses  $\geq 4$  weeks apart, or 1 RZV dose only. Outcomes were COVID-19 diagnosis (positive SARS-CoV-2 molecular test or COVID-19 diagnosis code) (Supplementary Table 1) and COVID-19 hospitalization (SARS-CoV-2–positive test during or  $\leq 7$  days before hospitalization, or a COVID-19 diagnosis code during hospitalization). We excluded individuals with COVID-19 outcomes  $\leq 14$  days after RZV receipt.

Recipients of  $\geq 1$  RZV dose were matched 1:2 with RZV unvaccinated individuals by age (50–59, 60–69, 70–79, and  $\geq 80$  years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian, and other/unknown), and zip code. Individuals were followed from 1 March to 31 December 2020 or until occurrence of COVID-19 outcomes, membership termination, death, or RZV receipt for unvaccinated individuals.

We identified clinical characteristics in the year before 1 March 2020, including body mass index (BMI) and smoking status, healthcare utilization (number of outpatient visits, emergency department [ED] visits, hospitalizations), frailty [8], comorbidities (cardiovascular disease, diabetes, hypertension, pulmonary disease, renal disease, cancer, autoimmune disease using *International Classification of Diseases, Tenth Revision [ICD-10]* codes [9], and HIV using the KPSC HIV registry), other vaccinations (influenza, pneumococcal, and Tdap [tetanus, diphtheria, and acellular pertussis]), and medical center area.

For each RZV exposure, we compared characteristics of RZV vaccinated and unvaccinated individuals with absolute standardized difference (ASD) and included characteristics with ASD  $> 0.1$  in multivariable analyses. We calculated incidence rates for COVID-19 outcomes by dividing the number of COVID-19 outcomes by the total number of person-years, and we used the Kaplan–Meier method to estimate cumulative incidence. Finally, we used Cox proportional hazards regression to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for COVID-19 outcomes comparing RZV vaccinated

and unvaccinated individuals. To further control for healthcare-seeking behavior (eg, healthy vaccinee effects) and potential effect modification by receipt of other vaccines, we conducted sensitivity analyses among a subset of RZV vaccinated ( $\geq 1$  dose) and unvaccinated individuals who had received influenza vaccine but no other vaccines in the year before 1 March 2020.

### Test-Negative Design

The test-negative design included individuals tested for SARS-CoV-2 during 1 March–31 December 2020, who had  $\geq 1$  year of prior membership and were aged  $\geq 50$  years. Test-positive cases were defined as the first positive test for individuals with any positive tests, and test-negative controls were defined as the first negative test for individuals with only negative tests. Separate analyses were conducted defining the exposure as receipt  $\geq 14$  days before the SARS-CoV-2 test of  $\geq 1$  RZV dose or of 2 RZV doses  $\geq 4$  weeks apart.

We described characteristics of test-positive cases and test-negative controls in the year before their SARS-CoV-2 test date, using similar methods as for the cohort design. We used logistic regression to estimate adjusted odds ratios (aORs) and 95% CIs comparing odds of RZV vaccination among test-positive cases and test-negative controls. We also conducted analyses stratifying the RZV exposure by time from most recent RZV dose to SARS-CoV-2 test (15 days to  $< 1$  month, 1 to  $< 6$  months, 6 months to  $< 1$  year, and  $\geq 1$  year).

The KPSC Institutional Review Board approved the study, waiving the requirement of informed consent.

## RESULTS

### Cohort Design

The cohort design with  $\geq 1$  RZV dose as the exposure included 149 244 RZV vaccinated and 298 488 matched unvaccinated individuals (Table 1). Overall, 16.2% were aged 50–59 years and 12.8% were aged  $\geq 80$  years, 57.8% were female, and 54.1% were non-Hispanic White. Recipients of  $\geq 1$  RZV dose had fewer missing data on BMI (2.6% vs 13.2% of unvaccinated individuals, ASD = 0.41) and on smoking (2.7% vs 12.7%, ASD = 0.39), and had more prior-year outpatient visits (39.1% vs 28.8% with  $\geq 11$  visits, ASD = 0.49). They more commonly had hypertension (49.0% vs 43.9%, ASD = 0.10) and had received other vaccinations in the prior year (93.6% vs 73.3%, ASD = 0.57). Other characteristics, including the number of ED visits and hospitalizations, frailty, other comorbidities in the prior year, and medical center area, were well-balanced.

Incidence rates per 1000 person-years of COVID-19 diagnosis and hospitalization were 48.82 (95% CI, 47.60–50.08) and 8.69 (95% CI, 8.18–9.23), respectively, among RZV recipients ( $\geq 1$  dose), and 55.01 (95% CI, 54.07–55.96) and 11.59 (95% CI, 11.17–12.03), respectively, among unvaccinated individuals (Table 2). In Kaplan–Meier analyses, cumulative incidences of COVID-19 diagnosis and hospitalization were lower among

**Table 1. Baseline Characteristics of the Recombinant Zoster Vaccine (≥1 Dose) Vaccinated and Unvaccinated Cohorts**

Characteristic	Vaccinated (n = 149 244)	Unvaccinated (n = 298 488)	Absolute Standardized Difference <sup>a</sup>
Age at index date, y			NA <sup>b</sup>
50–59	24 169 (16.2)	48 338 (16.2)	
60–69	56 047 (37.6)	112 094 (37.6)	
70–79	49 986 (33.5)	99 972 (33.5)	
≥80	19 042 (12.8)	38 084 (12.8)	
Sex			NA <sup>b</sup>
Female	86 206 (57.8)	172 412 (57.8)	
Male	63 038 (42.2)	126 076 (42.2)	
Race/ethnicity			NA <sup>b</sup>
Non-Hispanic White	80 743 (54.1)	161 486 (54.1)	
Non-Hispanic Black	8411 (5.6)	16 822 (5.6)	
Hispanic	30 376 (20.4)	60 752 (20.4)	
Non-Hispanic Asian	24 434 (16.4)	48 868 (16.4)	
Other/unknown	5280 (3.5)	10 560 (3.5)	
Body mass index, kg/m <sup>2c</sup>			0.41
<18.5	1925 (1.3)	4418 (1.5)	
18.5–24.9	45 482 (30.5)	76 156 (25.5)	
25.0–29.9	54 387 (36.4)	93 932 (31.5)	
30.0–34.9	27 736 (18.6)	52 216 (17.5)	
35.0–39.9	10 398 (7.0)	20 911 (7.0)	
40.0–44.9	3647 (2.4)	7511 (2.5)	
≥45.0	1734 (1.2)	3993 (1.3)	
Unknown	3935 (2.6)	39 351 (13.2)	
Smoking <sup>c</sup>			0.39
No	111 269 (74.6)	194 333 (65.1)	
Yes	34 016 (22.8)	66 278 (22.2)	
Unknown	3959 (2.7)	37 877 (12.7)	
No. of outpatient visits <sup>d</sup>			0.49
0	862 (0.6)	26 145 (8.8)	
1–4	33 628 (22.5)	95 907 (32.1)	
5–10	56 401 (37.8)	90 503 (30.3)	
≥11	58 353 (39.1)	85 933 (28.8)	
No. of ED visits <sup>d</sup>			0.05
0	121 729 (81.6)	238 943 (80.1)	
1	19 135 (12.8)	39 466 (13.2)	
≥2	8380 (5.6)	20 079 (6.7)	
No. of hospitalizations <sup>d</sup>			0.01
0	130 826 (87.7)	261 940 (87.8)	
1	11 291 (7.6)	22 608 (7.6)	
≥2	7127 (4.8)	13 940 (4.7)	
Frailty (top quartile) <sup>d</sup>	37 951 (25.4)	73 969 (24.8)	0.01
Baseline comorbidities <sup>d</sup>			
Cardiovascular disease	45 251 (30.3)	81 069 (27.2)	0.07
Diabetes	34 703 (23.3)	69 237 (23.2)	0.00
Hypertension	73 201 (49.0)	131 033 (43.9)	0.10
Pulmonary disease	23 628 (15.8)	41 768 (14.0)	0.05
Renal disease	18 965 (12.7)	37 487 (12.6)	0.00
Cancer	8484 (5.7)	17 322 (5.8)	0.01
HIV	1201 (0.8)	818 (0.3)	0.07
Autoimmune disease	7566 (5.1)	13 681 (4.6)	0.02
Other vaccinations <sup>d</sup>	139 723 (93.6)	218 851 (73.3)	0.57
Influenza vaccine	136 984 (98.0)	211 906 (96.8)	
PCV13/PPSV23	17 920 (12.8)	25 737 (11.8)	
Tdap	13 806 (9.9)	17 254 (7.9)	

Data are presented as No. (%) unless otherwise indicated. Medical center area is not shown. There were no significant differences in the distribution of the vaccinated and unvaccinated individuals across the 19 medical center areas.

Abbreviations: ED, emergency department; HIV, human immunodeficiency virus; NA, not applicable; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; Tdap, tetanus, diphtheria, acellular pertussis vaccine.

<sup>a</sup>Potential confounders were determined by absolute standardized difference >0.1.

<sup>b</sup>Not applicable for matching variable.

<sup>c</sup>Most recent in the 365 days prior to 1 March 2020.

<sup>d</sup>In the 365 days prior to 1 March 2020.

**Table 2. Incidence Rates and Hazard Ratios of Coronavirus Disease 2019 Diagnosis and Hospitalization Among Recombinant Zoster Vaccinated Versus Unvaccinated Individuals**

No. of Doses	Vaccinated			Unvaccinated			Hazard Ratio (95% CI)	
	No. of Cases	No. of PY	Incidence per 1000 PY (95% CI)	No. of Cases	No. of PY	Incidence per 1000 PY (95% CI)	Unadjusted	Adjusted <sup>a</sup>
≥1 RZV dose	(n = 149 244)			(n = 298 488)				
COVID-19 diagnosis	5951	121 887.27	48.82 (47.60–50.08)	13 028	236 826.63	55.01 (54.07–55.96)	0.86 (.84–.89)	0.84 (.81–.87)
COVID-19 hospitalization	1066	122 689.85	8.69 (8.18–9.23)	2765	238 530.10	11.59 (11.17–12.03)	0.73 (.68–.79)	0.68 (.64–.74)
2 RZV doses	(n = 94 895)			(n = 189 790)				
COVID-19 diagnosis	3403	77 714.97	43.79 (42.34–45.28)	7689	150 668.58	51.03 (49.90–52.19)	0.83 (.80–.87)	0.81 (.77–.84)
COVID-19 hospitalization	612	78 164.05	7.83 (7.23–8.48)	1676	151 656.50	11.05 (10.53–11.59)	0.69 (.63–.76)	0.64 (.58–.70)
1 RZV dose only	(n = 54 349)			(n = 108 698)				
COVID-19 diagnosis	2548	44 172.30	57.68 (55.49–59.97)	5339	86 158.05	61.97 (60.33–63.65)	0.92 (.88–.97)	0.86 (.82–.91)
COVID-19 hospitalization	454	44 525.79	10.20 (9.30–11.18)	1089	86 873.60	12.54 (11.81–13.30)	0.81 (.73–.91)	0.76 (.68–.86)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; PY, person-years; RZV, recombinant zoster vaccine.

<sup>a</sup>Adjusted for covariates: body mass index, smoking, number of outpatient visits, hypertension (model for ≥1 RZV dose and 1 RZV dose only), and other vaccinations.

RZV recipients (≥1 dose) compared to their unvaccinated matches (Figure 1). In fully adjusted analyses, RZV recipients (≥1 dose) had a 16% lower rate of COVID-19 diagnosis (aHR, 0.84 [95% CI, .81–.87]) and a 32% lower rate of COVID-19 hospitalization (aHR, 0.68 [95% CI, .64–.74]) compared to unvaccinated individuals (Table 2).

In sensitivity analyses among individuals who had received influenza vaccine but no other vaccines, we observed similar results (Table 3); RZV recipients (≥1 dose) had a 17% lower rate of COVID-19 diagnosis (aHR, 0.83 [95% CI, .78–.89]) and a 32% lower rate of COVID-19 hospitalization (aHR, 0.68 [95% CI, .59–.78]).

The cohort design with 2 RZV doses as the exposure included 94 895 RZV vaccinated and 189 790 matched unvaccinated individuals; recipients of 2 RZV doses had a 19% lower rate of COVID-19 diagnosis (aHR, 0.81 [95% CI, .77–.84]) and 36% lower rate of COVID-19 hospitalization (aHR, 0.64 [95% CI, .58–.70]) (Table 2). Results of the cohort design with 1 RZV dose only as the exposure were similar, but less pronounced than analyses of the other exposures (Table 2).

#### Test-Negative Design

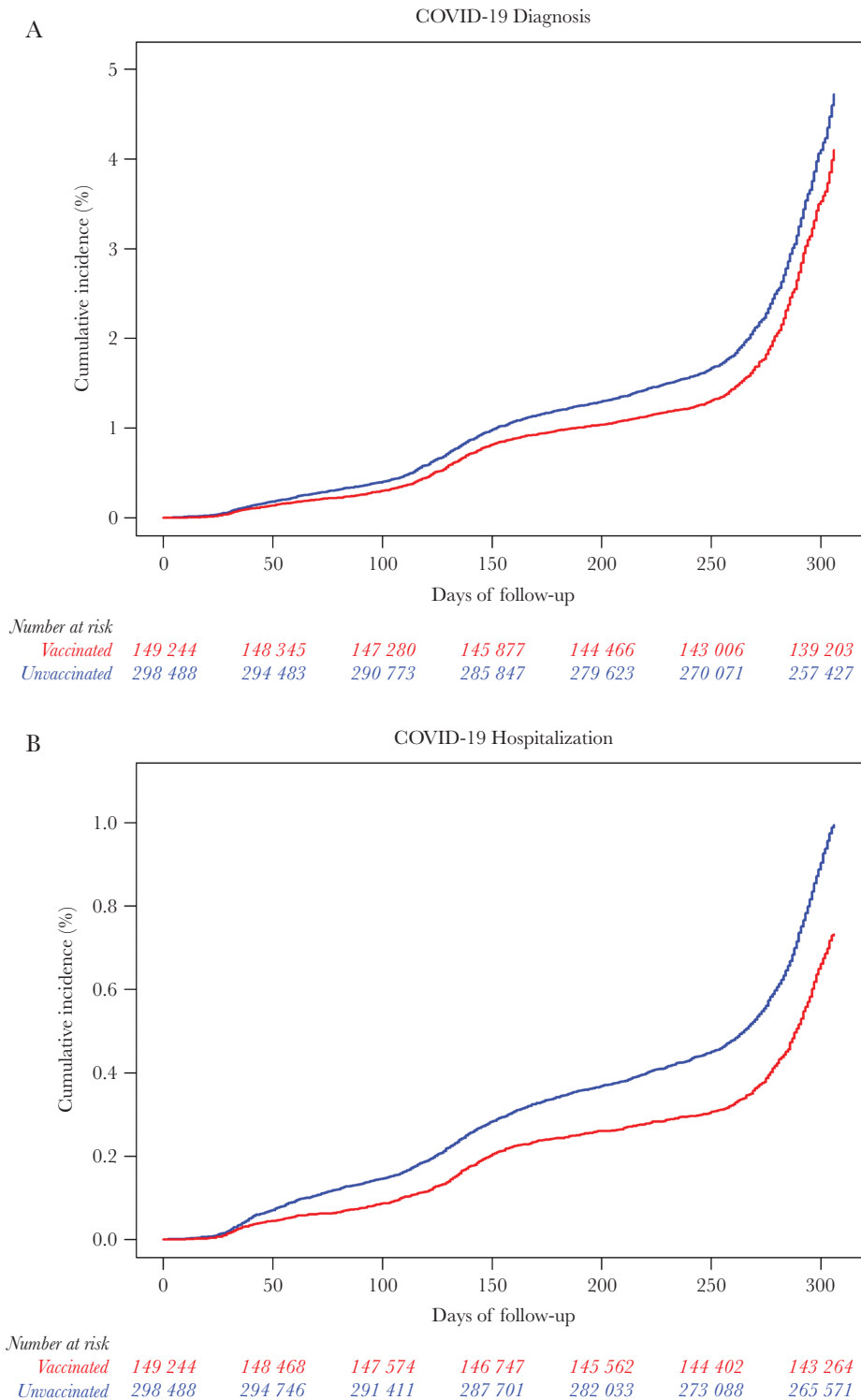
The test-negative design included 75 726 test-positive COVID-19 cases and 340 898 test-negative controls (Supplementary Table 2). Cases were younger than controls (49.0% vs 36.1% aged 50–59 years, ASD = 0.31) and less often non-Hispanic White (25.2% vs 43.4%, ASD = 0.50). A higher proportion of cases were obese, and a lower proportion of cases were smokers as compared to controls. Cases also had fewer outpatient and ED visits in the prior year than controls (16.3% vs 27.8% with

≥11 outpatient visits, ASD = 0.36; and 6.5% vs 9.4% with ≥2 ED visits, ASD = 0.14), were less frail (17.8% vs 26.6%, ASD = 0.21), less commonly had chronic comorbidities, and less commonly had received other vaccinations in the prior year (68.3% vs 76.7%, ASD = 0.19). There were also significant differences between cases and controls in test month and medical center area.

Of cases and controls, respectively, 8.4% and 13.1% had received ≥1 RZV dose, 5.4% and 9.2% had received 2 RZV doses, and 91.6% and 86.9% were RZV unvaccinated (Table 4). The aORs comparing cases and controls were 0.84 (95% CI, .81–.86) for RZV vaccinated (≥1 dose) individuals vs unvaccinated individuals and 0.82 (95% CI, .79–.85) for RZV vaccinated (2 doses) individuals vs unvaccinated individuals. The aORs did not vary substantially by time since RZV vaccination.

#### DISCUSSION

This large study, spanning the first year of the COVID-19 pandemic, provides evidence that RZV receipt may have reduced the burden of COVID-19 in adults aged ≥50 years prior to the availability of COVID-19 vaccine. In a cohort analysis, after adjusting for potential confounders including other vaccinations, the risk of COVID-19 diagnosis was reduced by 16% among RZV recipients (≥1 dose) compared to unvaccinated individuals, an association that was similar and did not vary by time since most recent RZV dose in the test-negative analysis. Furthermore, the risk of hospitalization with COVID-19 was reduced by 32% among RZV recipients (≥1 dose) compared to unvaccinated individuals.



**Figure 1.** Cumulative incidence estimates of coronavirus disease 2019 (COVID-19) diagnosis (A) and hospitalization (B) by recombinant zoster vaccine ( $\geq 1$  dose) vaccination status.

A similar reduction in risk of COVID-19 infection and severe disease has been reported following receipt of influenza vaccine in some, but not all, studies [10]. In our study, among individuals who received influenza vaccine but no other vaccines, we

found that RZV receipt was still associated with a similar reduction in risk of COVID-19 diagnosis and hospitalization, suggesting that influenza vaccination or healthy vaccinee bias had minimal impact on our findings.

**Table 3. Incidence Rates and Hazard Ratios of Coronavirus Disease 2019 Diagnosis and Hospitalization Among Recombinant Zoster Vaccinated ( $\geq 1$  Dose) Versus Unvaccinated Individuals, Among a Subset of Individuals Who Received Influenza Vaccination but no Other Vaccinations in the Year Prior to 1 March 2020**

Outcome	Vaccinated (n = 37 513)			Unvaccinated (n = 75 026)			Hazard Ratio (95% CI)	
	No. of Cases	No. of PY	Incidence per 1000 PY (95% CI)	No. of Cases	No. of PY	Incidence per 1000 PY (95% CI)	Unadjusted	Adjusted <sup>a</sup>
COVID-19 diagnosis	1356	30 677.70	44.20 (41.91–46.62)	3070	59 409.98	51.67 (49.88–53.54)	0.84 (.79–.90)	0.83 (.78–.89)
COVID-19 hospitalization	290	30 850.43	9.40 (8.38–10.55)	816	59 765.63	13.65 (12.75–14.62)	0.68 (.59–.78)	0.68 (.59–.78)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; PY, person-years.

<sup>a</sup>Adjusted for covariates: body mass index, smoking, number of outpatient visits, and hypertension.

While the mechanism for the reduced risk of heterologous infections following receipt of certain immune stimuli is not yet clear, it is thought that exposure to such stimuli, including some vaccines, induces epigenetic and functional changes in innate immune cells that generate trained innate immunity [4, 5, 11]. This trained innate immune response is linked to early cytokine responses that can lead to enhanced reactivity to subsequent heterologous infections, including SARS-CoV-2 [12, 13]. Induction of an innate immune response may control viral replication early in the course of infection, reducing the risk of severe disease [3, 6, 12]. This may be particularly important for viral infections such as SARS-CoV-2, which attenuate the host innate immune response, increasing viral replication, disease severity, and viral transmission [14]. Similarly, innate immunity has been found to play an important role in the control of coronavirus infection in animal reservoirs and may contribute to the reduced severity of COVID-19 disease observed in children [15].

Our study found a durable reduction in the risk of COVID-19 diagnosis following receipt of RZV vaccine, consistent with the durable protection against heterologous infections provided by trained immunity [6]. It is possible that the AS01 adjuvant in RZV, which activates innate immune responses, may be

associated with the reduced risk of COVID-19 diagnosis and hospitalization observed in this study [7, 16, 17]. Our findings support the concept of trained immunity-based vaccines, possibly injectable adjuvant systems or existing vaccines such as BCG, measles, oral polio or influenza vaccine, to potentially mitigate serious infections in future pandemics until specific vaccines become available [18].

Our study had several strengths and limitations. Despite comprehensive EHR data on demographic and clinical characteristics, vaccinations, and COVID-19 outcomes from a large, diverse cohort of adults aged  $\geq 50$  years, there may have been some residual confounding. RZV vaccinated and unvaccinated individuals may have differed with respect to health status, healthcare-seeking behavior, mask use, social distancing, and other factors that might, in part, explain the observed differences in risk of COVID-19 diagnosis and hospitalization. However, to reduce potential confounding, we used a cohort design, matching RZV recipients with unvaccinated individuals on age, sex, race/ethnicity, and zip code, and adjusting for healthcare utilization, other vaccinations, and comorbidities. Furthermore, to further reduce potential healthcare-seeking bias, we performed a cohort analysis among a subset of individuals with influenza vaccine receipt, with similar results. We

**Table 4. Odds Ratio of Recombinant Zoster Vaccination Among Severe Acute Respiratory Syndrome Coronavirus 2 Test-Positive Cases Versus Test-Negative Controls**

Exposure	Test Positive (n = 75 726)		Test Negative (n = 340 898)		Odds Ratio (95% CI)	
	No.	(%)	No.	(%)	Unadjusted	Adjusted <sup>a</sup>
RZV ( $\geq 1$ dose) vaccinated	6392	(8.4)	44 786	(13.1)	0.61 (.59–.63)	0.84 (.81–.86)
15 days to <1 month <sup>b</sup>	302	(0.4)	1810	(0.5)	0.71 (.63–.81)	0.79 (.69–.90)
1 to <6 months	1703	(2.3)	10 643	(3.1)	0.68 (.65–.72)	0.87 (.82–.92)
6 months to <1 year	1697	(2.2)	14 606	(4.3)	0.50 (.47–.52)	0.83 (.78–.87)
$\geq 1$ year	2690	(3.6)	17 727	(5.2)	0.65 (.62–.68)	0.82 (.79–.86)
RZV (2 doses) vaccinated	4108	(5.4)	31 359	(9.2)	0.56 (.54–.58)	0.82 (.79–.85)
RZV unvaccinated	69 334	(91.6)	296 112	(86.9)	NA	NA

Abbreviation: CI, confidence interval; NA, not applicable; RZV, recombinant zoster vaccine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup>Adjusted for the following covariates: age, sex, race/ethnicity, calendar time, body mass index, smoking, number of outpatient visits, number of emergency department visits, frailty, cardiovascular disease, hypertension, pulmonary disease, renal disease, cancer, other vaccinations, and medical center area.

<sup>b</sup>Time since most recent RZV vaccination.

also used a test-negative design, which may be less confounded by healthcare-seeking behavior than the cohort design [19]. We observed similar results using both designs, supporting the validity of the results. In addition, some members may have received RZV outside of KPSC; however, such misclassification was likely minimal, because members received vaccines at KPSC without charge, and providers were required to document previous receipt of vaccines at all encounters. In conclusion, RZV recipients aged  $\geq 50$  years had a reduced risk of COVID-19 diagnosis and hospitalization compared to unvaccinated individuals, suggesting that RZV may elicit durable innate immune responses that could offer heterologous protection against COVID-19. Further study of vaccine-elicited trained innate immunity for potential attenuation of future pandemics is warranted.

### Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

### Notes

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