



Recombinant Zoster Vaccination Among US Veterans Receiving Immunosuppressive Medications

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Introduction

Individuals who are immunocompromised, including those receiving immunosuppressive medications, have an increased risk of herpes zoster and associated complications compared with the general population; those receiving targeted synthetic disease modifying agents (tsDMARDs), such as Janus kinase inhibitors, are at particularly increased risk.^{1,2} In 2017, the Food and Drug Administration (FDA) approved a recombinant zoster vaccine (RZV) for individuals aged 50 years or older. In 2021, the FDA additionally approved RZV for adults aged 18 years and older who are immunocompromised, and the Centers for Disease Control and Prevention and American College of Rheumatology issued updated guidance in 2021 and 2022, respectively.³⁻⁵

However, there is little published evidence regarding RZV vaccination among US adults who are immunocompromised, particularly those younger than 50 years. We assessed RZV receipt among veterans receiving immunosuppressive medications within the Veterans Health Administration (VHA) health care system before and after expanded indications.

Methods

This cross-sectional study was approved by the VA Quality Enhancement Research Initiative and University of California San Francisco institutional review board with a waiver of informed consent as a minimal-risk study. It used nationwide VHA data among veterans at 130 medical facilities prescribed 1 or more immunosuppressive medications for 90 days or more between January 1, 2018, and June 30, 2023. The outcome was the percentage of veterans with 1 or more RZV doses documented during the study period, assessed before the expanded indication (January 2018 to February 2022) and at any time (January 2018 to June 2023). To examine factors associated with RZV receipt at any time, we constructed a multilevel regression model, including age, sex, self-identified race and ethnicity, rurality of residence, visits with more than 1 subspecialty (yes or no), receipt of 1 or more other vaccination at the VA (yes or no), and immunosuppressive medication type, accounting for clustering by facility using generalized estimating equations (eMethods in [Supplement 1](#)). Facility-level performance was reported as the percentage of veterans with 1 or more RZV doses documented among those eligible at any time. Analyses were performed using Stata statistical software version 16 (StataCorp) (eMethods in [Supplement 1](#)). We followed the [STROBE](#) reporting guideline.

Results

We identified 190 162 veterans receiving immunosuppressive medications across 130 facilities during the study period. By the end of the study period, 23 295 veterans (12.3%) were younger than 50 years (characteristics shown in [Table 1](#)).

Among veterans aged 50 years or older, 55 546 of 153 620 individuals (36.2%) had an RZV before the expanded indication and 83 117 of 166 867 individuals (49.8%) had it by mid-2023. Among veterans younger than 50 years, 638 of 22 631 individuals (2.8%) had an RZV before the expanded indication and 3118 of 23 295 individuals (13.4%) had it by mid-2023. Demographic factors associated

+ Supplemental content

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Table 1. Demographic Characteristics of the Study Sample

Characteristic	Veterans, No. (%)			P value ^a
	Total (N = 190 162)	Any RZV (n = 86 235)	No RZV (n = 103 927)	
Age, y				
Mean (SD)	67.8 (13.8)	70.6 (10.6)	65.5 (15.5)	
<50	23 295 (12.3)	3118 (3.6)	20 177 (19.4)	<.001
≥50	166 867 (87.7)	83 117 (96.4)	83 750 (80.6)	
Sex				
Female	23 167 (12.2)	9655 (11.2)	13 512 (13.0)	<.001
Male	166 995 (87.8)	76 580 (88.8)	90 415 (87.0)	
Self-identified race				
African American	32 609 (17.1)	13 323 (15.4)	19 286 (18.6)	
Asian	1936 (1)	907 (1.1)	1029 (1.0)	
White	139 744 (73.5)	65 066 (75.5)	74 678 (71.9)	<.001
Other ^b	3485 (1.8)	1546 (1.8)	1939 (1.9)	
Unknown	12 388 (6.5)	5393 (6.3)	6995 (6.7)	
Self-identified ethnicity				
Hispanic	10 964 (5.8)	4733 (5.5)	6231 (6.0)	
Not Hispanic	171 025 (89.9)	77 937 (90.4)	93 088 (89.6)	<.001
Unknown	8173 (4.3)	3565 (4.1)	4608 (4.4)	
Facility region				
Continental	33 352 (17.5)	13 491 (15.6)	19 861 (19.1)	
Midwest	46 064 (24.2)	23 633 (27.4)	22 431 (21.6)	
North Atlantic	42 318 (22.3)	19 983 (23.2)	22 335 (21.5)	<.001
Pacific	31 633 (16.6)	14 769 (17.1)	16 864 (16.2)	
Southeast	36 795 (19.3)	14 359 (16.7)	22 436 (21.6)	
Facility rurality				
Urban	119 698 (62.9)	54 277 (62.9)	65 421 (62.9)	
Rural	69 843 (36.7)	31 789 (36.9)	38 054 (36.6)	<.001
Unknown	621 (0.3)	169 (0.2)	452 (0.4)	
Rheumatic disease^c				
Rheumatoid arthritis	52 665 (27.7)	26 334 (30.5)	26 331 (25.3)	<.001
Other inflammatory arthritis	9402 (4.9)	5066 (5.9)	4336 (4.2)	<.001
Spondylitis	8037 (4.2)	3467 (4.0)	4570 (4.4)	<.001
Systemic lupus erythematosus	7626 (4.0)	3088 (3.6)	4538 (4.4)	<.001
Sarcoidosis	4449 (2.3)	2005 (2.3)	2444 (2.4)	.70
ANCA-associated vasculitis	902 (0.5)	426 (0.5)	476 (0.5)	.26
MCTD	763 (0.4)	327 (0.4)	436 (0.4)	.17
Other	19 867 (10.4)	10 454 (12.1)	9413 (9.1)	<.001
Immunosuppressive medication				
csDMARD monotherapy	71 822 (37.8)	32 388 (37.6)	39 434 (37.9)	
GC monotherapy	37 783 (19.9)	17 783 (20.6)	20 000 (19.2)	
Biologic monotherapy	36 043 (19.0)	14 210 (16.5)	21 833 (21.0)	<.001
Combination of csDMARD, GC, or biologic (no tsDMARDs)	35 995 (18.9)	17 343 (20.1)	18 652 (17.9)	
tsDMARD monotherapy or in combination	8519 (4.5)	4511 (5.2)	4008 (3.9)	
Other vaccination since 2018	178 250 (93.7)	85 660 (99.3)	92 590 (89.1)	<.001
≥1 Subspecialty clinic visit since 2018				
Rheumatology	89 221 (46.9)	43 740 (50.7)	45 481 (43.8)	<.001
Gastroenterology	72 582 (38.2)	35 926 (41.7)	36 656 (35.3)	<.001
Neurology	47 592 (25.0)	23 774 (27.6)	23 818 (22.9)	<.001
Oncology	33 716 (17.7)	15 342 (17.8)	18 374 (17.7)	.53
Visits with >1 specialty since 2018	71 804 (37.8)	36 268 (42.1)	35 536 (34.2)	<.001
No specialty visits since 2018	44 359 (23.3)	17 511 (20.3)	26 848 (25.8)	<.001

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GC, glucocorticoid; MCTD, mixed connective tissue disease; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

^a P values were tested by the t test for continuous variables and χ^2 test for categorical variables.

^b Other race includes American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander.

^c Rheumatic disease diagnoses are not mutually exclusive.

with lower odds of vaccination included male sex, African American and unknown race, and nonurban residence (Table 2). Factors associated with increased odds of vaccination included treatment with tsDMARDs and other measures of increased health care use (Table 2). Across VA facilities, the percentage of veterans with 1 or more RZV doses at any time ranged from 17.7% to 71.1%.

Discussion

To our knowledge, this cross-sectional study is the first study to examine RZV receipt in a large population of adults, including those younger than 50 years, receiving immunosuppressive medications. Overall, less than half of veterans in the US taking chronic immunosuppressive medications received even 1 dose of RZV; for patients younger than 50 years, percentages were much lower. Although vaccination rates among these older veterans at high risk were higher than those in the 2021 National Health Interview Survey (18.6% for US adults aged ≥50 years),⁶ there remains substantial room for improvement.

Table 2. Predictive Margins From GEE Models (N = 190 162)

Variable	Unadjusted predictive margin (95% CI)	P value	Adjusted predictive margin (95% CI) ^a	P value
Age, y				
<50 (reference)	13.4 (12.9-13.8)	NA	13.5 (12.5-14.6)	NA
≥50	49.8 (49.6-50.1)	<.001	48.8 (47.2-50.4)	<.001
Sex				
Female (reference)	41.7 (41.0-42.3)	NA	47.9 (46.2-49.5)	NA
Male	45.9 (45.6-46.1)	<.001	44.2 (42.7-45.8)	<.001
Self-identified race				
Asian	46.8 (44.6-49.1)	.80	51.7 (48.6-54.8)	<.001
African American	40.9 (40.3-41.4)	<.001	42.1 (40.4-43.7)	<.001
White (reference)	46.6 (46.3-46.8)	NA	45.2 (43.7-46.7)	NA
Other ^b	44.4 (42.7-46.0)	.01	44.3 (41.7-46.9)	.33
Unknown	43.5 (42.7-44.4)	<.001	43.6 (41.9-45.3)	.002
Self-identified ethnicity				
Hispanic (reference)	43.2 (42.2-44.1)	NA	46.5 (44.6-48.4)	NA
Not Hispanic	45.6 (45.3-45.8)	<.001	44.5 (42.9-46.0)	.001
Unknown	43.6 (42.5-44.7)	.53	45.0 (43.2-46.8)	.08
Rurality of residence				
Urban (reference)	45.3 (45.1-45.6)	NA	45.0 (43.5-46.5)	NA
Rural	45.5 (45.1-45.9)	.47	44.1 (42.4-45.7)	.004
Unknown	27.2 (23.7-30.7)	<.001	26.8 (19.5-34.1)	<.001
Visits with >1 specialty since 2018				
No (reference)	42.2 (41.9-42.5)	NA	42.3 (40.8-43.8)	NA
Yes	50.5 (50.1-50.9)	<.001	48.4 (46.7-50.0)	<.001
Medications				
csDMARD monotherapy (reference)	45.1 (44.7-45.5)	NA	43.6 (42.1-45.1)	NA
GC monotherapy	47.1 (46.6-47.6)	<.001	44.1 (42.3-46.0)	.19
Biologic monotherapy	39.4 (38.9-39.9)	<.001	43.6 (42.0-45.1)	.92
Combination of csDMARD, GC, or biologic (no tsDMARDs)	48.2 (47.7-48.7)	<.001	46.5 (44.8-48.1)	<.001
tsDMARD monotherapy or in combination	53.0 (51.9-54.0)	<.001	51.8 (49.7-53.9)	<.001
Other vaccination since 2018				
No (reference)	4.8 (4.4-5.2)	NA	5.6 (4.9-6.4)	NA
Yes	48.1 (47.8-48.3)	<.001	47.0 (45.4-48.6)	<.001

Abbreviations: csDMARD, conventional synthetic disease-modifying antirheumatic drug; GC, glucocorticoid; GEE, generalized estimating equation; NA, not applicable; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

^a Model adjusted for all variables shown in the table.

^b Other race includes American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander.

This study may not be generalizable to nonveteran populations or non-US countries. Limitations also include difficulty with capture of vaccinations not administered within the VHA system, which may result in an underestimate of the percentage of patients vaccinated. Future work to improve RZV vaccination in patients at high risk should focus on creating informatics tools to identify individuals at high risk and standardizing vaccination guidelines across subspecialties.

ARTICLE INFORMATION

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Author Contributions: Dr Schmajuk had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPLEMENT 1.**eMethods.****eReferences.****SUPPLEMENT 2.****Data Sharing Statement**

Supplemental Online Content

Abada S, Li J, Tarasovsky G, et al. Recombinant zoster vaccination among US veterans receiving immunosuppressive medications. *JAMA Netw Open*. 2024;7(10):e2439945. doi:10.1001/jamanetworkopen.2024.39945

eMethods.

eReferences.

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Data source and study design

This cross-sectional study used nationwide VHA Corporate Data Warehouse (CDW) data. The VHA is a national healthcare system serving United States military veterans and is a subdivision within the U.S. Department of Veterans Affairs (VA). The VHA healthcare system is the largest integrated healthcare delivery system in the United States, with more than 9 million living enrollees. This analysis was conducted as part of a quality improvement project funded by the VA's Quality Enhancement Research Initiative (QUERI).

Study population and study period

The study included all patients at 130 medical facilities who were prescribed at least one immunosuppressive medication for at least 90 days between 1/1/2018 and 6/30/2023 by a VA clinician. Immunosuppressive medications of interest were based on the American College of Rheumatology (ACR) 2022 vaccination guidelines, and included conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs; azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate mofetil, mycophenolic acid, sulfasalazine, tacrolimus, and voclosporin), biologics and any available biosimilars (abatacept, adalimumab, anakinra, anifrolumab, belimumab, certolizumab, canakinumab, etanercept, denosumab, golimumab, guselkumab, infliximab, ixekizumab, obinutuzumab, ocrelizumab, risankizumab, rituximab, rilonacept, sarilumab, secukinumab, tocilizumab, tildrakizumab, and ustekinumab), targeted synthetic (ts) DMARDs (apremilast,

baricitinib, filgotinib, tofacitinib, and upadacitinib), and oral glucocorticoids (GCs; prednisone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, and prednisolone) at dose of ≥ 10 mg daily prednisone equivalents.¹ This glucocorticoid dose threshold was chosen based on existing literature which has identified a consistently increased risk of HZ with ≥ 10 mg daily prednisone equivalents.^{2–6} Patients age < 18 years were excluded.

Outcomes

RZV documentation data was extracted from both vaccination tables and “health factors” which are structured fields available at each facility that capture additional RZV records (e.g., “Shingrix outside site”).⁷ RZV was defined using CVX codes 187 (“zoster recombinant”) during the study period or 188 (“zoster vaccine, unspecified formulation”) documented after 1/1/2021 (when the live-attenuated zoster vaccine was no longer available in the United States). CVX codes indicate the product used in a vaccination and are maintained by the Centers for Disease Control and Prevention. The outcome of interest was the percentage of veterans in the study population who had any RZV (at least 1 dose). The percentage with any RZV before the expanded indication (1/1/2018 – 2/28/2022) was calculated as the number of veterans who had any RZV documented during that time divided by the number of veterans who were prescribed ≥ 1 immunosuppressive medication for over 90 days during the same period AND ≥ 50 years old by 8/31/2021. We required veterans to be at least 50 years old 6 months prior to the end of the time window in order to allow time for them to have an encounter during which they could be vaccinated. The percentage with any RZV documented over the entire study period was calculated similarly but without the age restriction: the number of veterans with any

RZV documented during the entire study period (1/1/2018 – 6/30/2023) divided by the number of veterans with ≥ 1 immunosuppressive medication for over 90 days during the same period.

We aggregated individual patient data to the facility level, expressed as the percentage of veterans in the study population at that facility who had at least 1 dose of RZV documented at any time. Since patients who received the live-attenuated vaccine are still recommended to receive two doses of RZV, live-attenuated vaccination status was not included in the study analysis.

Patient characteristics

Patient characteristics included in this study were age, gender, self-identified race (African American, Asian, White, other, and unknown) and self-identified ethnicity (Hispanic, not Hispanic, and unknown) as recorded in the EHR, Veteran rurality based on residential address (urban, rural, or unknown), visits to specific VHA specialty clinics during the study period (Rheumatology, Gastroenterology, Neurology, Oncology; more than one specialty clinic visit, and none), other vaccinations received at the VHA during the study period (including influenza, pneumococcal, etc.; yes/no), and rheumatic condition (rheumatoid arthritis, other inflammatory arthritis, spondylitis, systemic lupus erythematosus, sarcoidosis, ANCA-associated vasculitis, or mixed connective tissue disease (MCTD)) based on the presence of at least one ICD-10 code for these conditions.⁸ “Other” race included individuals self-identified as American Indian or Alaska Native, as well as individuals self-identified as Native Hawaiian or Other Pacific Islander. Self-identified race and ethnicity were assessed in this study to identify possible

disparities in RZV receipt among self-identified groups; knowledge of such disparities could help identify specific subgroup needs and assist with the design of interventions for those subgroups. Rheumatic conditions were not mutually exclusive.

Facility characteristics

Facility-level covariates included geographical region (Midwest, North Atlantic, Continental, Southeast, Pacific) and complexity (High, Medium, Low). Facility complexity was assigned by the VHA based on a variety of factors (morbidity of patient population, presence of clinical services such as intensive care unit and surgical operating rooms, administrative complexity, and presence of graduate medical education programs).⁹

Statistical analysis

Descriptive statistics were used to examine patient and practice characteristics according to the RZV documentation status. Bivariate analyses were completed by chi-square tests for categorical variables and t-tests for continuous variables.

To examine factors associated with RZV documentation at any time, we constructed a multi-level regression model that included age, gender, race, ethnicity, rurality of residence, visits with >1 subspecialty during the study period (yes/no), receipt of at least one other vaccination at the VA during the study period (yes/no), and medication type (csDMARD monotherapy, GCs monotherapy, combinations of csDMARD – GCs – biologics (other combination without

tsDMARDs), and tsDMARD monotherapy or in combination (any tsDMARDs)), accounting for clustering by practice using generalized estimating equations (GEE). Multicollinearity was examined using the variance inflation factor.

Facility-level performance at any time was reported as the percentage of patients with at least one dose of RZV documented among all those eligible within a given facility using median and interquartile ranges. Facilities with fewer than 20 patients were excluded from the facility-level analysis. For all models, model output parameters were used to produce predicted probabilities and 95% confidence intervals. A 2-sided P value $<.05$ was considered statistically significant.

Analyses were performed using Stata 16 (StataCorp. 2017. College Station, TX: StataCorp LLC).

This work was approved by the VA Quality Enhancement Research Initiative (QUERI; IRB 15-18358). We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cross-sectional studies (see Supplement 1).

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Data Sharing Statement

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Data

Data available: No

Additional Information

Explanation for why data not available: VHA data is only available to approved VHA investigators.