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REVIEW ARTICLE

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Effectiveness and safety of recombinant zoster vaccine: A review of real-world evidence

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ABSTRACT

The recombinant zoster vaccine (RZV) was licensed in the US for prevention of herpes zoster (HZ) in 2017. We conducted a literature search (January 1, 2017–August 1, 2023) using PubMed, Embase, and Scopus to consolidate the real-world evidence related to RZV. Overall, RZV effectiveness against HZ was high across the studied populations in real-world settings, including adults aged ≥ 50 years and patients aged ≥ 18 years with immunodeficiency or immunosuppression. Effectiveness was higher with two doses versus one dose, especially in elderly people and immunocompromised individuals. The safety profile of RZV was broadly consistent with that established in clinical trials. RZV does not appear to increase the risk of disease flares in patients with immune-mediated diseases. Approximately two-thirds of individuals received a second RZV dose within 2–6 months after the first dose. Collectively, RZV effectiveness against HZ was high, and these real-world studies reaffirm its favorable benefit–risk profile.

PLAIN LANGUAGE SUMMARY

What is the context?

Herpes zoster is a common and painful rash that develops following reactivation of latent (meaning silent or dormant) varicella zoster virus, which is the virus that causes the common childhood illness chickenpox. The recombinant zoster vaccine (RZV) was first approved for the prevention of herpes zoster in the USA and Canada in 2017 and has since been approved in the European Union and various other countries. The approval was based on the results of large clinical trials. Since its launch over 5 years ago, evidence for RZV use in real-world settings has been collected; the benefits of real-world studies include large sample sizes, more diverse populations, and the ability to identify rare side effects.

What is new?

We provide a review of real-world studies, which have shown that RZV is effective across the studied populations, including in adults aged 50 years and above and in patients with immunodeficiencies (i.e., those who have a decreased ability to fight infections or other diseases) or receiving immunosuppressive therapies (treatments that lower the activity of the body's immune system). The safety profile of RZV in real-world studies was generally consistent with that seen in clinical trials.

What is the impact?

These studies show the effectiveness and well-tolerated safety profile of RZV in real-world settings.

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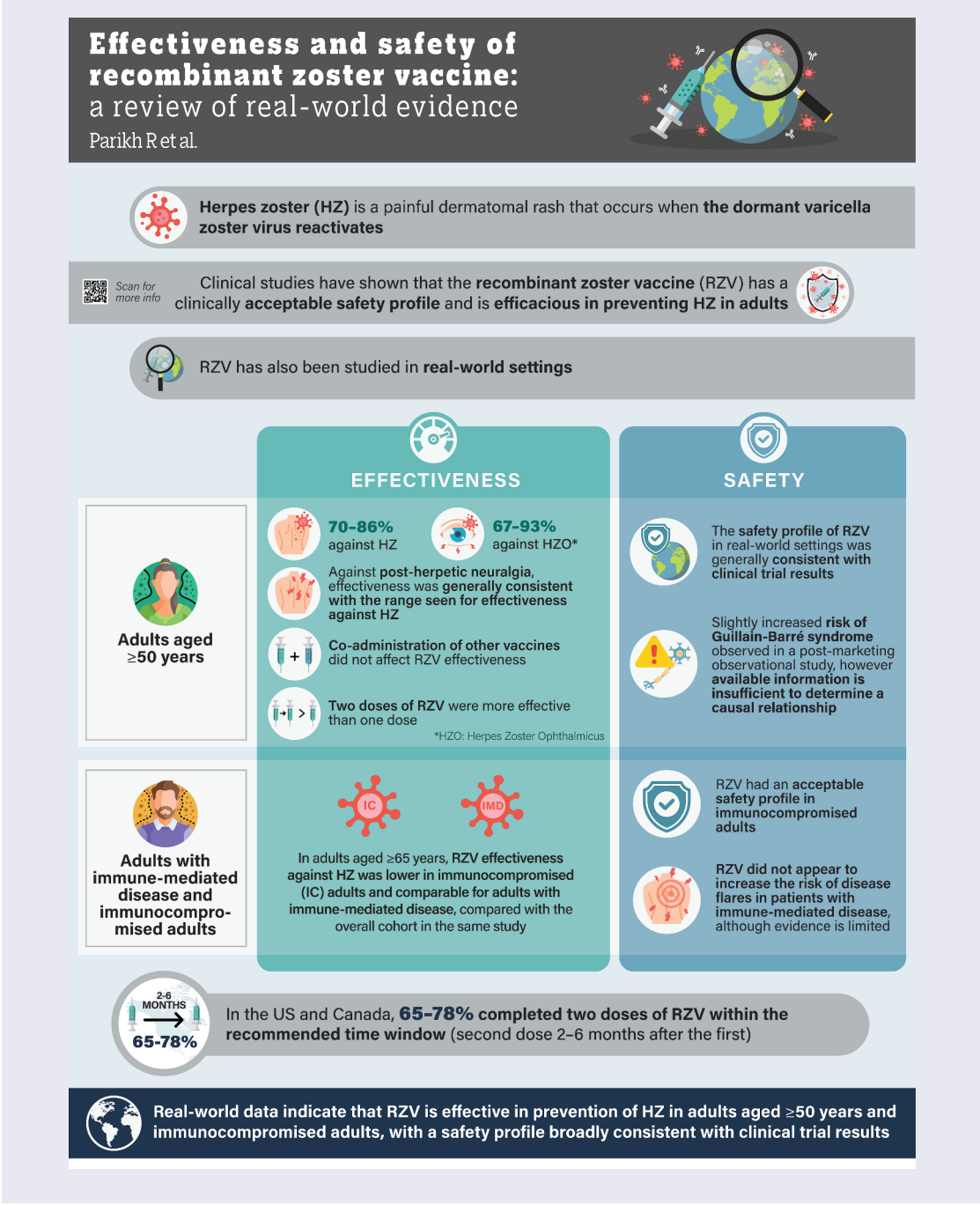

Introduction

Herpes zoster (HZ) is a common, painful, blistering dermatomal rash that arises following reactivation of latent varicella zoster virus (VZV), primarily in people aged ≥ 50 years[1,2] and in immunocompromised individuals.[3–5] HZ, with or without its attendant complications, places a substantial burden on patients and healthcare systems.[1,2,6]

The adjuvanted recombinant zoster vaccine (RZV; Shingrix®, GSK) was first approved in 2017, in Canada and the US, and then in subsequent years in other countries, including the European Union in March 2018.[6–8] Initially, RZV was indicated for HZ prevention in adults aged ≥ 50 years, based on phase III clinical trials (ZOE-50 and ZOE-70) in patients aged ≥ 50 years and ≥ 70 years, respectively.[9,10] These studies demonstrated high vaccine efficacy rates (97.2% [95% confidence interval (CI): 93.7–99.0] in adults aged ≥ 50 years [mean follow-up 3.2 years] and 91.3% [95% CI: 86.8–94.5] in adults aged ≥ 70 years [mean follow-up 3.7 years]), with mild-to-moderate, transient, injection-site and systemic reactions commonly reported.[9,10] Supported by data from several studies in immunocompromised patients,[11–15] the indication was expanded in the European Union in August 2020 to include adults aged ≥ 18 years at increased risk of HZ, and in the US in July 2021 to include adults aged ≥ 18 years at increased risk of HZ because of immunodeficiency or immunosuppression caused by known disease or therapy.[7,8,16]

Collection and analysis of real-world evidence is critical in understanding vaccine effectiveness and safety; indeed, a key advantage of real-world studies is the heterogeneity of the populations involved (i.e., there are few exclusions compared with clinical trials). Further, in several real-world studies, the large sample sizes have enabled the identification of rare adverse events (AEs) and the detection of events to an extent that would not be possible in clinical trials.[2,17] Following the initial approval of RZV, several studies reporting real-world evidence for RZV were published. However, a comprehensive review of these studies is required. The principal aims of this review were, therefore, to identify and summarize studies reporting real-world evidence on the effectiveness and safety of RZV across various adult populations (including, but not limited to, adults aged ≥ 50 years, adults who received prior zoster vaccine live [ZVL] vaccination, and adults aged ≥ 18 years with immunodeficiency or immunosuppression caused by known disease or therapy) and studies investigating completion rates for the recommended two-dose administration regimen of RZV. Due to the broad scope of this review and the resulting heterogeneity in the methodology of the real-world studies, a meta-analysis was not conducted. In parallel, a separate literature review was conducted summarizing the clinical studies of RZV (available at: doi).

Methods

We conducted a targeted literature search of articles published between January 1, 2017, and August 1, 2023, using the Embase, Scopus, and National Library of Medicine PubMed databases. Search terms comprised "recombinant zoster vaccine" and terms related to real-world evidence or other topics of focus for this review ("real world evidence," "post surveillance," "licensure," "observational study," "cohort," "case control study," "case report," "claims," "health records," "experience," "series completion," and "data mining"). Case reports were subsequently excluded, as in all instances the identified publications described three or fewer patients. The studies identified through this literature search were manually reviewed for relevance: the abstracts of identified studies were read in detail and additional papers selected from reference lists of the initially identified papers. Studies were included if they examined the safety or effectiveness of RZV against HZ, post-herpetic neuralgia (PHN), or HZ ophthalmicus (HZO) or of RZV series completion in a real-world setting in adult populations of any age in any country; distinct clinical trials were excluded, as were papers without an English language abstract.

Effectiveness of RZV

In total, seven primary studies[18–24] that examined the real-world effectiveness of RZV in various populations (Table 1) and a meta-analysis[25] of two of these studies[18,19] were identified. Six studies identified HZ based on diagnosis codes from the International Classification of Diseases, ninth or tenth version (ICD-9 or ICD-10),[18–23] and six studies reported the median duration of follow-up, which was approximately 3–24 months in vaccinated groups.[18–23] As the initial indication in the US for RZV was in adults aged ≥ 50 years, which was followed by a recommendation from the Advisory Committee on Immunization Practices in 2017,[7,8,16,26] most studies ($n = 6$)[18–23] focused on RZV use in this age group; however, one study focused on RZV use in adults aged ≥ 65 years.

Adults aged ≥ 50 years

Two large retrospective cohort studies, both of which excluded immunocompromised individuals, investigated the effectiveness of RZV in general populations aged ≥ 50 years.[18,20] These studies included analyses using electronic health record (EHR) data from Kaiser Permanente Hawaii (KPH; $N = 78,356$ individuals included in the study) and from the OptumLabs® (Optum Inc., Cambridge, MA, USA) Data Warehouse (OLDW), which includes claims and EHR data for individuals enrolled in commercial insurance, Medicare Advantage, or Medicare Part D ($N = 4,769,819$ adults included in the study).[18,20] The number of adults who received the recommended two doses of RZV was 11,864 in the KPH study and 173,745 in the OLDW study.[18,20] Compared with unvaccinated individuals, vaccine effectiveness against HZ was reported as 83.5% (95% CI: 74.9–89.2) and 85.5% (95% CI: 83.5–87.3), respectively, in the two studies (Table 1).[18,20]

In addition, a cohort study conducted by the US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) investigated RZV effectiveness in Medicare beneficiaries aged ≥ 65 years.[19] The study, which used information from Medicare Parts A, B, and D (i.e., fee-for-service data), included data from approximately 15.5 million unvaccinated individuals and approximately 1 million individuals who had received two RZV doses. Vaccine effectiveness against HZ was estimated as 70.1% (95% CI: 68.6–71.5) for individuals receiving two doses and was similar regardless of whether individuals received the second dose within 6 months of the first (median time from first to second dose 90 days, vaccine effectiveness 70.0% [95% CI: 68.4–71.5]) or ≥ 6 months after the first dose (median time from first to second dose 230 days, vaccine effectiveness 71.7% [95% CI: 66.1–76.3]).[19] Although some benefit was evident with a second RZV dose given more than 6 months after the first,[19] these findings should be interpreted with caution as the median time from the first to second dose in this group was 7.7 months, and in a previous clinical trial (ZOSTER-026), noninferiority of immune response was not demonstrated for a two-dose, 0- and 12-month, RZV schedule (compared with a two-dose, 0- and 2-month, schedule).[27] A systematic review and meta-analysis[25] combined the data from the study by Izurieta et al.[19] and the OLDW study by Sun et al.[18] Using a random-effects meta-analysis model, the pooled vaccine effectiveness of RZV against HZ in adults aged ≥ 50 years was calculated as 79.2% (95% CI: 57.6 – 89.7).[25] The differences in the study populations of these two studies should be noted. Izurieta et al.[19] used data from adults aged ≥ 65 years, whereas Sun et al.[18] used data from adults aged ≥ 50 years; furthermore, immunocompromised individuals were included in the former study but not in the latter.

Table 1. Overview of real-world evidence investigating the effectiveness of the recombinant zoster vaccine[a].

Publication	Study type/period	Median (IQR) follow-up, months	Population	Sample size	HZ incidence per 100,000 person-years (95% CI)		Adjusted or estimated vaccine effectiveness,[b] % (95% CI)[c]
					Unvaccinated	Vaccinated	
Patients aged ≥ 50 years							
Sun et al. *Vaccine* 2021[20]	Retrospective cohort study using EHR data from Kaiser Permanente Hawaii, USA[d] Jan 2018–Dec 2019	24 (24–24) [vaccinated] 24 (14.1–24.0) [unvaccinated]	Aged ≥ 50 years	RZV – two doses: 11,864 Unvaccinated: 66,492	1063.3 (1006–1122.8)	Two doses: 325.6 (217.4–464.4)[f]	Two doses: 83.5 (74.9–89.2)[f]
			Aged 50–59 years	Vaccinated: 196 PY Unvaccinated: 49,449 PY	944.4 (861.3–1032.7)	Two doses: 0[f]	Two doses: 100[f]
			Aged 60–69 years	Vaccinated: 717 PY Unvaccinated: 42,592 PY	1037.7 (944–1137.5)	Two doses: 557.7 (173.1–1295.3)[f]	Two doses: 67.7 (11.8–88.1)[f]
			Aged 70–79 years	Vaccinated: 4537 PY Unvaccinated: 17,914 PY	1194.6 (1041.6–1361.9)	Two doses: 286.5 (157.6–471.7)[f]	Two doses: 83.3 (70.1–90.7)[f]
			Aged ≥ 80 years	Vaccinated: 2841 PY Unvaccinated: 9764 PY	1536.2 (1303.3–1795.4)	Two doses: 352.0 (176.4–617.3)[f]	Two doses: 86.4 (73.5–93.0)[f]
			Aged ≥ 50 years with prior ZVL vaccination[e]	Vaccinated: 184 PY Unvaccinated: 3695 PY	703.6 (466.6–1009.7)	Two doses: 543.8 (31–2392.2)[f]	Two doses: 61.1 (–124.9–93.3)[f]
			Aged ≥ 50 years with no prior ZVL vaccination[e]	Vaccinated: 8107 PY Unvaccinated: 116,024 PY	1074.8 (1016.2–1135.5)	Two doses: 320.7 (212.7–460.2)[f]	Two doses: 83.9 (75.2–89.5)[f]
			Incidence of HZO	Vaccinated: 8404 PY Unvaccinated: 120,739 PY	72.1 (58.0–88.3)	11.9 (0.7–52.3)[f]	Two doses: 93.3 (48.7–99.1)[f]
Sun et al. *Clin Infect Dis* 2021[18]	Retrospective cohort study using claims and EHR data from OptumLabs Data Warehouse, USA[d] Jan 2018–Dec 2019	7.0 (2.8–13.0) [vaccinated]	Aged ≥ 50 years	RZV – two doses: 173,745 Unvaccinated: 4,596,074	893.1 (886.2–900.0)	Two doses: 258.8 (230.6–289.4)[f]	Two doses: 85.5 (83.5–87.3)
			Aged 50–59 years	Vaccinated: 2019 PY Unvaccinated: 2,252,215 PY	684.8 (674.1–695.7)	Two doses: <544.8 (282.9–933.0)[f,g]	Two doses: 85.6 (53.3–95.6)
			Aged 60–69 years	Vaccinated: 22,934 PY Unvaccinated: 2,040,881 PY	848.9 (836.4–861.7)	Two doses: >148.3 (103.8–203.8)[f,g]	Two doses: 87.7 (82.5–91.4)[f]
			Aged 70–79 years	Vaccinated: 65,423 PY Unvaccinated: 1,926,358 PY	1034.1 (1019.8–1048.5)	Two doses: 246.1 (210.0–286.1)[f]	Two doses: 86.5 (83.9–88.6)[f]
			Aged ≥ 80 years	Vaccinated: 24,750 PY Unvaccinated: 965,456 PY	1191.0 (1169.4–1212.9)	Two doses: 371.7 (300.8–452.9)[f]	Two doses: 80.3 (75.1–84.3)[f]
			Aged ≥ 50 years with prior ZVL vaccination[h]	NR	754.5 (718.4–791.7)	Two doses: 239.4 (142.8–371.8)[f]	Two doses: 84.8 (75.3–90.7)[f]
			Aged ≥ 50 years with no prior ZVL vaccination[h]	NR	908.1 (895.0–921.3)	Two doses: 260.9 (205.9–325.0)[f]	Two doses: 87.1 (83.4–89.9)[f]

(*Continued*)

Table 1. (Continued).

Publication	Study type/period	Median (IQR) follow-up, months	Population	Sample size	HZ incidence per 100,000 person-years (95% CI)		Adjusted or estimated vaccine effectiveness,[b] % (95% CI)[c]
					Unvaccinated	Vaccinated	
Izurieta et al. *Clin Infect Dis* 2021[19]	Cohort study using Medicare claims and enrollment database analysis, USA[d] Nov 2017–Oct 2019	~2.9 (one dose) ~7.1 (two doses)	Aged ≥ 65 years	RZV – one dose: 1,498,275 RZV – two doses: 1,006,446 Unvaccinated: 15,589,546	1032 (1028–1036)	One dose: 450 (431–469) Two doses: 309 (295–323)	One dose: 56.9 (55.0–58.8) Two doses: 70.1 (68.6–71.5)
			Aged 65–79 years	RZV – one dose: 1,222,612 RZV – two doses: 821,731 Unvaccinated: 11,486,608	1010 (1005–1014)	One dose: 429 (408–449) Two doses: 298 (282–313)	One dose: 58.6 (56.5–60.7) Two doses: 70.6 (68.9–72.1)
			Aged ≥ 80 years	RZV – one dose: 275,663 RZV – two doses: 184,715 Unvaccinated: 4,102,938	1103 (1094–1111)	One dose: 538 (491–585) Two doses: 357 (322–391)	One dose: 50.9 (46.2–55.1) Two doses: 68.5 (65.1–71.6)
			Aged ≥ 65 years with prior ZVL within 5 years of RZV	RZV – one dose: 269,852 RZV – two doses: 175,367 Unvaccinated: 2,075,196	852 (842–862)	One dose: 420 (376–463) Two doses: 315 (281–350)	One dose: 51.0 (45.4–56.0) Two doses: 63.0 (58.3–67.2)
			Aged ≥ 65 years with no prior ZVL within 5 years of RZV	RZV – one dose: 1,128,423 RZV – two doses: 831,079 Unvaccinated: 13,514,350	1060 (1056–1064)	One dose: 456 (435–477) Two doses: 307 (292–323)	One dose: 57.6 (55.4–59.6) Two doses: 71.1 (69.5–72.6)
			Aged ≥ 65 years and immunocompromised	RZV – one dose: 60,600 RZV – two doses: 40,442 Unvaccinated: 746,654	1715 (1690–1740)	One dose: 1034 (892–1175) Two doses: 585 (489–681)	One dose: 37.0 (27.4–45.4) Two doses: 64.1 (57.2–69.8)
			Aged ≥ 65 years and not immunocompromised	RZV – one dose: 1,437,675 RZV – two doses: 966,004 Unvaccinated: 14,842,892	1001 (997–1005)	One dose: 424 (406–443) Two doses: 297 (283–311)	One dose: 58.4 (56.4–60.3) Two doses: 70.5 (69.0–72.0)
			Aged ≥ 65 years with autoimmune disease	RZV – one dose: 92,069 RZV – two doses: 61,999 Unvaccinated: 886,123	1489 (1468–1509)	One dose: 625 (535–715) Two doses: 444 (377–512)	One dose: 57.7 (50.9–63.6) Two doses: 68.0 (62.3–72.8)
			Incidence of HZO	RZV – one dose: 487,000 PY RZV – two doses: 618,000 PY Unvaccinated: 25,235,000 PY	77 (75–78)	40 (34–45) 25 (21–29)	One dose: 44.7 (36.0–52.3) Two doses: 66.8 (60.7–72.0)
			Incidence of PHN	RZV – one dose: 295,000 PY RZV – two doses: 240,000 PY Unvaccinated: 19,857,000 PY	99 (97–100)	44 (37–52) 23 (17–29)	One dose: 51.4 (42.0–59.2) Two doses: 76.0 (68.4–81.8)
Bruxvoort et al. *Open Forum Infect Dis* 2022[21]	Retrospective cohort study using EHR data from Kaiser Permanente Southern California, USA[d] Apr 2018–Sept 2019	≥ 12	Aged ≥ 50 years, with or without concomitant vaccination	RZV – two doses, with concomitant vaccine[i]: 12,898 RZV – two doses, without concomitant vaccine[i]: 28,353	NA	Two doses, with concomitant vaccine[i]: 220 (160–300) Two doses, without concomitant vaccine[i]: 340 (290–400)	Adjusted HR: 0.75 (0.53–1.08)[i]
Khan et al. *Clin Gastroenterol Hepatol* 2022[22]	Retrospective cohort study using Veterans Affair Healthcare System data, USA[d] Jan 2018–Oct 2020	NR	Aged 50–60 years, with IBD	RZV – one dose: 358 RZV – two doses: 655 Unvaccinated: 5995	393	One dose: 179 Two doses: 0	One dose: HR for HZ = 0.44 (95% CI: 0.06–3.17) One-dose VE: 56%[j] Two doses: HR for HZ = 0 (95% CI: 0–0) Two-dose VE: 100%[j]
			Aged >60 years, with IBD	RZV – one dose: 1518 RZV – two doses: 4220 Unvaccinated: 20,554	457	One dose: 248 Two doses: 180	One dose: HR for HZ = 0.52 (95% CI: 0.24–1.10) One-dose VE: 48.0%[j] Two doses: HR for HZ = 0.39 (95% CI: 0.19–0.80) Two-dose VE: 61.0%[j]

(*Continued*)

Table 1. (Continued).

Publication	Study type/period	Median (IQR) follow-up, months	Population	Sample size	HZ incidence per 100,000 person-years (95% CI)		Adjusted or estimated vaccine effectiveness,[b] % (95% CI)[c]
					Unvaccinated	Vaccinated	
Lu et al. *Ophthalmol* 2021[23]	Retrospective, observational cohort study using the OptumLabs Data Warehouse, USA[d] Jan 2018–Dec 2019	730 days (730–730) [vaccinated]	Aged ≥ 50 years	RZV – two doses: 177,289 Unvaccinated: 4,665,290 Vaccinated: 117,517 PY Unvaccinated: 7,374,053 PY	76.7 (95% CI: 74.7–78.7)	25.5 (95% CI: 17.4–35.8)	VE against HZO: 89.1% (95% CI: 82.9–93.0)
Patients aged ≥ 18 years undergoing HSCT							
Baumrin et al. *Blood Adv* 2021[24]	Single-center prospective observational cohort study at Dana–Farber Cancer Institute, USA Dec 2018–Jun 2020	8.6 (5.7–11.5) [total vaccinated cohort]	Allogeneic HSCT recipients aged ≥ 18 years, 9–24 months after transplant	RZV – at least one dose: 158 RZV – two doses: 150	NA	At least one dose: 3669 Two doses only: 2834 HZ incidence was 4/157 in patients receiving at least dose and 3/144 in patients receiving two doses	NA

[a]Excluding case reports.
[b]Adjusted or estimated VE; for full details of the statistical methodology used, please refer to the relevant original study.
[c]Unless stated otherwise.
[d]HZ diagnosed according to International Classification of Diseases, 9th or 10th version (ICD-9 or ICD-10).
[e]Prior ZVL within 1 year of the index date, which was defined as the date on which both of the following were met: 1) the patient reached age ≥ 50 years in 2018 or 2019, and met age eligibility criteria for RZV; 2) the patient had at least 365 days of continuous enrollment in the Kaiser Permanente Hawaii database prior to becoming age-eligible for the RZV vaccine.
[f]All patients received two doses; patients receiving a single dose were excluded.
[g]The analysis reported these values using < or > symbols for reasons of patient privacy.
[h]Prior ZVL within 5 years of the index date, which was defined as the date on which both of the following were met: 1) the patient reached age 50 years in 2018 or 2019, and met age eligibility criteria for RZV; 2) the patient had at least 365 days of continuous enrollment in the OptumLabs Data Warehouse.
[i]Concomitant vaccination defined as any other vaccine received on the same day as either the first or second dose of RZV (most common types were influenza vaccines [65.9%] and pneumococcal vaccines [20.2%]). After adjusting for clinical and demographic covariates, the difference between the group with vs. without concomitant vaccination was not statistically significant (adjusted hazard ratio 0.75 [95% CI: 0.53–1.08]).
[j]VE calculated as (1 – HR) * 100%.
CI, confidence interval; EHR, electronic health record; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; HZO, herpes zoster ophthalmicus; IBD, inflammatory bowel disease; IQR, interquartile range; NA, not applicable; NR, not reported; PHN, post-herpetic neuralgia; PY, person-years; RZV, recombinant zoster vaccine; VE, vaccine effectiveness; ZVL, zoster vaccine live.

Overall, vaccine effectiveness appeared lower in the Izurieta et al. study (70.1%; 95% CI: 68.6–71.5)[19] than in pivotal clinical trials[9] and other studies in individuals aged ≥ 50 years included in the KPH and OLDW databases (vaccine effectiveness: 83.5% [95% CI: 74.9–89.2] and 85.5% [95% CI: 83.5–87.3], respectively).[18,20] Among the three real-world studies, lower vaccine effectiveness in the Izurieta et al. study[19] compared with the other two studies[18,20] could perhaps be attributed to the older age of the population (≥ 65 years vs. ≥ 50 years) and non-exclusion of immunocompromised individuals. In addition, key potential contributors to effectiveness – efficacy differences (in the three real-world studies vs. pivotal clinical trials) included ascertainment factors linked to healthcare pursuit, diagnosis, coding (such as differential outcome misclassification and false-positive cases), residual confounding factors due to unbalanced cohorts and a less restrictive eligibility criteria allowing for a wider and more heterogeneous group of patients with comorbid or underlying conditions to be included in the real-world studies.[28] Moreover, HZ case identification varied in real-world studies (primarily by ICD codes) compared with pivotal trials (primarily polymerase chain reaction confirmation) which can impact the specificity of HZ case identification and resultant efficacy/effectiveness.[9,10,19] HZO has been reported in 10–20% of HZ cases,[1,29] and several real-world studies have assessed the effectiveness of RZV in preventing HZO (Table 1).[19,20,23] Among KPH members aged ≥ 50 years, RZV vaccine effectiveness after two doses was 93.3% (95% CI: 48.7–99.1) for preventing HZO.[20] In addition, in an analysis of OLDW data for adults aged ≥ 50 years, two doses of RZV had a vaccine effectiveness of 89.1% (95% CI: 82.9–93.0) for HZO.[23] Further, the Medicare fee-for-service beneficiary analysis previously discussed reported that two RZV doses were associated with a vaccine effectiveness of 66.8% (95% CI: 60.7–72.0) for HZO in adults aged ≥ 65 years.[19] Within each of these studies, results suggested that RZV had comparable efficacy in preventing both HZ and HZO.

PHN is the most common complication of HZ, seen in 10–34% of cases,[30] with a greater incidence in individuals aged ≥ 60 years and in patients with immunosuppression.[3–5,31] In the previously mentioned analysis of Medicare beneficiaries aged ≥ 65 years, RZV effectiveness in preventing PHN (within 90–180 days of HZ onset) was 76.0% (95% CI: 68.4–81.8) for two doses of RZV compared with the unvaccinated cohort (Table 1).[19] Effectiveness against PHN was consistent with effectiveness against HZ (70.1% [95% CI: 68.6–71.5]) in the same analysis.[19]

Analysis of age subgroups

The effectiveness of RZV was explored in distinct age subgroups in three of the cohort studies (Table 1).[18–20] Two of the studies reported generally consistent RZV effectiveness across studied age groups,[19,20] in line with efficacy findings in analyses of the pivotal clinical trials.[9,10] The OLDW real-world evidence study suggested slightly lower efficacy in patients aged ≥ 80 years, but vaccine effectiveness remained high in this subgroup (80.3% [95% CI: 75.1–84.3]).[18] Collectively, these results support the real-world effectiveness of RZV in adults aged ≥ 50 years.

Adults with prior zoster vaccine live vaccination

The three cohort studies described above also investigated RZV effectiveness in individuals who had received prior ZVL, either within the prior year or within the prior 5 years.[18–20] Among participants who received two RZV doses, HZ incidence rates appeared to be similar regardless of whether participants had received ZVL in the prior 5 years (Table 1), thus indicating the benefit of revaccination with RZV against HZ, in spite of previous ZVL vaccination.[18,19] Izurieta et al.[19] reported RZV effectiveness of 63.0% (95% CI: 58.3–67.2) within 5 years of ZVL receipt, and the corresponding value reported by Sun et al.,[18] based on OLDW data, was 84.8% (95% CI: 75.3–90.7). The abovementioned meta-analysis of these two studies suggested that RZV was 75.5% (95% CI: 41.5 – 89.7) effective in preventing HZ in participants who had received ZVL within the prior 5 years.[25] Based on KPH data, Sun et al.[20] reported RZV effectiveness of 61.1% (95% CI: −124.9–93.3) within 1 year of ZVL receipt. The very wide CIs in that report demonstrate the uncertainty in the estimate, as might be expected given the small sample size.[20] Indeed, results of the KPH study should be interpreted cautiously, as the number of participants who received two doses of RZV following ZVL was very small ($n = 296$), providing only 184 person-years (PY) of follow-up data and further limiting the ability to accurately evaluate vaccine effectiveness; although the incidence of HZ was similarly low in patients who received RZV versus those who did not (543.8 [95% CI: 31.0–2392.2] vs. 703.6 [95% CI: 466.6–1009.7] per 100,000 PY), only 3,695 PY of follow-up data were available for RZV-unvaccinated individuals (Table 1).[20] The potential for unmeasured confounding may also have influenced this result, which is not unexpected as individuals who received RZV soon after ZVL may have been at increased risk of developing HZ. Furthermore, when interpreting vaccine effectiveness in individuals who have previously received ZVL, it should be noted that these patients will likely have some protection from their previous ZVL vaccination, which can impact the effectiveness of RZV. Overall, available real-world data indicate that there is clinical benefit of revaccination against HZ with RZV in patients previously vaccinated with ZVL.

Adults with immune-mediated diseases

Patients with autoimmune disease often receive immunosuppressive medication, which increases their risk of HZ. The effectiveness of RZV in patients with autoimmune diseases was investigated by Izurieta et al. in Medicare beneficiaries aged ≥ 65 years.[19] Autoimmune diseases included conditions such as multiple sclerosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus, and ulcerative colitis.[19] RZV effectiveness was 68.0% (95% CI: 62.3–72.8) in patients with autoimmune diseases, which was similar to the effectiveness in the overall cohort in this analysis (70.1% [95% CI: 68.6–71.5]) (Table 1).[19] Although Izurieta et al. did not include patients with Crohn's disease in the autoimmune disease subgroup,[19] other studies have assessed vaccine effectiveness in patients with inflammatory bowel disease (IBD), including a retrospective cohort study using Veterans Affairs Healthcare System data from patients with IBD. This study

reported RZV vaccine effectiveness of 100% (95% CI: 100–100) after two doses in patients with IBD aged 50–60 years, and 61% (95% CI: 20–81) after two doses in patients aged >60 years; however, the sample size for the two-dose vaccinated group was small for those aged 50–60 years (715 PY of follow-up; Table 1).[22] Although a pooled *post hoc* analysis of patients with immune-mediated diseases in the ZOE-50 and ZOE-70 clinical trials reported higher RZV efficacy in this subgroup (90.5% [95% CI: 73.5–97.5]), these trials excluded immunosuppressed patients.[32] Overall, these real-world findings support the effectiveness of RZV in patients with immune-mediated diseases.

Immunocompromised adults

In clinical trials, RZV vaccine efficacy was reported as 68.2% (95% CI: 55.6–77.5) in immunocompromised adults aged ≥ 18 years undergoing autologous hematopoietic stem cell transplantation (HSCT)[11] and 87.2% (95% CI: 44.3–98.6) in a *post hoc* analysis in patients with hematologic malignancies.[15] In real-world settings, a single-center, prospective, observational, cohort study in allogeneic HSCT recipients aged ≥ 18 years reported an HZ incidence of 37.3 per 1000 PY in patients who received at least one RZV dose, and 28.3 per 1000 PY in patients who received two doses (Table 1).[24] Although this study lacked an unvaccinated comparator group, the authors noted that the rates of HZ breakthrough with two RZV doses were low compared with historic controls.[24] Moreover, in the phase III, randomized, placebo-controlled study of RZV referenced above, in a total of 1846 patients aged ≥ 18 years who had undergone recent autologous HSCT, the incidence of HZ in the modified total vaccinated cohort (patients who received two vaccine doses and did not develop HZ within 1 month of the second dose) was 30.0 per 1000 PY for RZV and 94.3 per 1000 PY for placebo (incidence rate ratio 0.32 [95% CI: 0.22–0.44]; vaccine efficacy 68.2% [95% CI: 55.6–77.5]);[11] thus, in immunocompromised adults, real-world data[24] appear to be consistent with clinical trial data.[11]

The Medicare beneficiary analysis referred to earlier investigated RZV effectiveness in a subgroup of patients considered to be immunocompromised.[19] This subgroup included patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome, hematologic or solid malignancies, immune deficiencies, transplants and related conditions, and rheumatologic and inflammatory conditions, as well as those undergoing dialysis or with intermediate conditions (defined as conditions viewed unlikely to be immunocompromising but included for optional use by users seeking to be as inclusive as possible). RZV effectiveness after two doses was only slightly lower in immunocompromised versus immunocompetent patients (Table 1).[19]

Adults receiving concomitant vaccination

Real-world data have also been used to investigate the effects of concomitant administration of other vaccines alongside RZV. In a retrospective cohort study using EHR data from Kaiser Permanente Southern California (KPSC), the HZ incidence in adults aged ≥ 50 years who received RZV with concomitant vaccination was not higher than in adults who received RZV without concomitant vaccination, suggesting that vaccine effectiveness was not impacted by concomitant vaccination (HZ incidence 2.2 vs. 3.4 per 1000 PY).[21] In this study, concomitant vaccination was defined as any other vaccine received on the same day as either the first or second dose of RZV, with influenza vaccines (65.9% of participants) and pneumococcal vaccines (20.2% of participants) most commonly received.[21] The hazard ratio, adjusted for clinical and demographic variables, was 0.75 (95% CI: 0.53–1.08) for individuals who received RZV with rather than without concomitant vaccination (Table 1). These data complement prior clinical trial evidence indicating that the immune responses of RZV and influenza vaccine are not impacted by co-administration.[33]

One versus two doses

In pivotal efficacy studies in older adults and immunocompromised individuals, RZV was administered as a two-dose vaccine.[9–11] Two studies were identified that explored RZV effectiveness after one or two doses.[19,22] In both studies, the two-dose versus one-dose regimen was consistently associated with greater effectiveness across all studied subgroups (Table 1).[19,22] The lower effectiveness of one dose was more pronounced with increasing age and in immunocompromised patients; vaccine effectiveness against PHN was 51.4% (95% CI: 42.0–59.2) for one dose of RZV and 76.0% (95% CI: 68.4–81.8) for two doses of RZV.[19] These findings underscore the importance of completing the two-dose series.

Real-world safety of RZV vaccination

Besides safety evaluation in clinical trials, the safety of RZV vaccination has been extensively studied in regulatory- and manufacturer-led, post-licensure surveillance studies[6,34,35] and other studies.[24,36–48] These studies focused on RZV safety in specific populations and explored key areas of interest, such as the incidence of Guillain–Barré syndrome (GBS).[6,36,46–48]

Adults aged ≥ 50 years

An initial post-licensure safety surveillance report for RZV was conducted by the FDA and CDC using data obtained from October 2017 through June 2018 from the Vaccine Adverse Event Reporting System (VAERS), which collates reports from healthcare providers, vaccine manufacturers, and the public.[34] This study encompassed the first 8 months of RZV use in the USA, during which approximately 3.2 million RZV doses were distributed. At the time of the analysis, RZV was licensed for use only in adults aged ≥ 50 years, although a small proportion of the AEs reported (0.6%) were in adults aged <50 years. Overall, the reporting rate was 136 per 100,000 RZV doses distributed, with pyrexia, injection-site pain, and injection-site erythema the most common; the reported signs or symptoms were similar regardless of whether RZV was administered alone or combined with other vaccines. Vaccination errors accounted for 5% of reports, with most such instances (62%) related to administration errors (e.g., subcutaneous rather than intramuscular administration). Serious AEs were rare (4 per 100,000 doses), and overall, the safety profile of RZV was consistent with clinical trial results. The authors concluded

that these initial data were reassuring and suggested that healthcare providers should counsel patients to expect self-limiting local adverse reactions, to encourage completion of the two-dose RZV regimen.[34]

The manufacturer of RZV (GSK) subsequently published an analysis of worldwide safety data from the GSK safety database, which included spontaneous reports of AEs, received either directly or via indirect routes (e.g., the scientific literature), in individuals given RZV.[6] Compared with the VAERS study, the manufacturer-led analysis included a longer monitoring period (October 2017 through February 2019), during which approximately 9.3 million doses of RZV were distributed. Where age was known, almost all reports (97.2%) were from adults aged ≥ 50 years. In total, 15,638 reports were received: symptoms related to vaccine reactogenicity (e.g., injection-site reactions, pyrexia, chills, fatigue, etc.) were most common, with a reporting rate of approximately 50 reports per 100,000 doses distributed; such symptoms typically lasted 3–4 days after vaccination. Most reports were non-serious (95%); among serious reports, the most common events were HZ (28% of reports), pyrexia (10%), pain in an extremity (9%), and pain (8%). Overall, 5.1% described symptoms potentially linked to severe reactogenicity (e.g., decreased mobility of injected arm or extensive swelling of the injected arm); when described, these events occurred within the first few days after vaccination and generally lasted 3–4 days, although in rare cases, symptoms persisted for one week or more. A total of 865 case reports listed 837 HZ events and 50 HZ-related complications; generally, laboratory corroboration of HZV (i.e., HZV-positive polymerase chain reaction, culture, immunohistochemical staining, or other testing) was not reported. In total, 22.9% of reports outlined vaccination errors, which included product preparation or reconstitution errors (29.7%), inappropriate or incomplete course of administration (26.7%), incorrect administration route (16.4%), and storage inconsistencies (12.9%); most reports of vaccination errors were not accompanied by symptoms (82.7%). Observed-to-expected analyses for certain outcomes (i.e., total mortality, and the two most commonly reported potential immune-mediated diseases, GBS and Bell's palsy) and data-mining analyses for all reported AEs did not reveal any unanticipated patterns. Overall, the manufacturer-led analysis demonstrated that the safety profile of RZV was consistent with that observed in clinical trials conducted prior to licensing.[6]

Following reports in Germany of vesicular and bullous cutaneous eruptions (compatible with HZ rash) occurring in temporal association with RZV vaccination, GSK conducted a focused analysis of the worldwide safety database referred to above to investigate the incidence of events suggestive of HZ or non-HZ vesicular and bullous cutaneous eruptions.[35] At the time of this analysis, approximately 2.5 years of reporting data were available, and over 32 million RZV doses had been distributed. In total, 2423 reports describing HZ or HZ complications were identified, of which 645 described possible lack of efficacy. The reporting rate of vaccination failure was low (2.0 cases per 100,000 RZV doses distributed) and in line with the high efficacy of RZV in adults aged ≥ 50 years demonstrated in clinical trials.[9,10] A total of 1928 reports met criteria for possible VZV reactivation (HZ or HZ complications with an onset within 30 days post vaccination). An observed-to-expected analysis demonstrated that, generally, the observed incidence of those cases was below the background incidence in the general population. Additionally, 810 reports of non-HZ vesicular and bullous cutaneous eruptions were identified. These included injection-site rashes, attributed to the vaccine's reactogenicity, and non-injection-site hypersensitivity rashes, in a population (older adults) that has a higher prevalence of, and susceptibility for, dermatologic disorders in general[35] and for hypersensitivity rashes including vesicular, blistering, or pustular rashes as clinical manifestations. Discussion of potential underlying pathophysiologic mechanisms (immune exhaustion or cytokine-mediated reactivation) supported the medical review of the reports retrieved and did not raise safety concerns.[35]

In contrast to the abovementioned studies analyzing passive reports submitted to the regulators and the manufacturer, another study conducted active post-licensure surveillance with proactive capture and rapid analysis of the EHR data from the CDC Vaccine Safety Datalink (VSD) framework.[48] This approach allowed for near–real-time sequential monitoring to overcome issues, such as underreporting, that are linked to passive report databases. The prospective cohort study followed individuals aged ≥ 50 years enrolled in seven VSD-data –contributing healthcare systems in the US from January 2018, when RZV was introduced among this population, through December 2019. Within that period, a total of 647,833 RZV doses were administered. Primary outcomes evaluated included acute myocardial infarction, stroke, supraventricular tachycardia, polymyalgia rheumatica, convulsions, Bell's palsy, optic ischemic neuropathy, giant cell arteritis, anaphylaxis, and GBS. Secondary outcomes included systemic and local reactions occurring within 1–7 days, as well as gout, myocarditis, pericarditis, and several eye-related diseases, diagnosed within 1–42 days. ZVL recipients (2013–2017) served as historical controls for primary outcomes, whereas non-RZV vaccine recipients who had an annual well-person visit in 2018−2019 served as controls for both primary and secondary outcomes. No sustained increased risk was reported for any primary outcomes. An increase was reported for four secondary outcomes, including increased risk of reactions (systemic reactions, adjusted relative risk [aRR] = 1.17 [95% CI: 1.10 – 1.24]; local reactions, aRR = 2.75 [95% CI: 2.14 – 3.54]; combined "any reaction" group, aRR = 1.27 [95% CI: 1.20 – 1.34]), and a slight increase in gout (aRR = 1.08 [95% CI: 1.08 – 1.14]).[48]

The safety of RZV vaccination was also assessed in a data-mining study using IBM® MarketScan® (IBM Corp., Armonk, NY, USA) data from commercially insured people in the USA; the data covered the administration of approximately 1 million RZV doses in adults aged ≥ 50 years, from January 2018 through May 2020.[36] The analysis assessed whether various health outcomes were associated with RZV vaccination, through evaluation of temporal clustering of outcomes identified via ICD-10 Clinical Modification (ICD-10-CM) codes. In the first few days after vaccination, clustering of ICD-10-CM codes relating to the following were identified: unspecified AEs, complications, or reactions to immunization or other medical substances or care; fever; unspecified allergy; syncope and collapse; cellulitis; myalgia; and dizziness and giddiness.

These associations were considered to reflect the known safety profile of RZV and the outcomes typically reported after injected vaccinations.[36] A subsequent publication by the same authors applied a modified statistical approach using the same database and including a similar number of RZV doses.[47] This study employed a sequential analysis using the tree-based scan statistic to identify AEs in days 1–28 versus 29–56 following RZV vaccination. Statistically significant signals emerged only for unspecified AEs or complications in days 1–28; the majority (90% of unique cases within signals) were reported within the first week following vaccination. Based on previous case-by-case investigations of similar signals, the authors speculated that most of the cases might relate to nonserious AEs, such as injection-site reactions, headache, fever, and fatigue.[47]

A retrospective cohort study using EHR data from KPSC reported the incidence of various reactions in over 30,000 adults aged ≥ 50 years receiving at least one dose of RZV.[37] Among these adults, very few experienced medically attended local reactions 1–7 days after the first dose (0.2% in adults receiving only one dose, or two doses), medically attended systemic reactions (approximately 0.5%), or medically attended pain (approximately 0.3%); these events did not influence whether individuals completed the two-dose series.[37]

Overall, the abovementioned reports in adults aged ≥ 50 years indicate that the real-world safety profile of RZV is consistent with that seen in clinical studies and with that described in the Prescribing Information for RZV.[7,8] A summary of these studies is provided in Table 2. The incidence of GBS in the abovementioned studies is discussed in a later section of this article.

Immunocompromised adults aged ≥ 18 years

In clinical trials, an acceptable safety profile for RZV was shown in patients aged ≥ 18 years undergoing autologous HSCT,[11] people living with HIV,[12] patients with solid[13] or hematologic[15] malignancies, and patients after renal transplantation.[14]

Data from two real-world, single-center, US studies[24,38] (Table 2) complement the clinical trial findings. Baumrin et al.[24] conducted a small, prospective, observational study exploring the safety of RZV in 158 allogeneic HSCT recipients aged ≥ 18 years who received RZV 9–24 months after transplantation at the Dana–Farber Cancer Institute (Boston, MA, USA); most of these patients received other vaccines co-administered with RZV. AEs were reported by 92.1% of patients, including injection-site AEs (87.3% of patients), most commonly pain. Serious AEs were reported in two patients (1.3%). Four of 157 (2.5%) patients experienced an episode of HZ; one case (0.6%, 1/109 PYs) was fatal, presenting as disseminated vesicular rash, pneumonitis, and hepatitis in a cord blood recipient. There was no difference in the incidence of graft-versus-host disease, disease relapse, or death in patients receiving RZV versus historic controls. The authors concluded that RZV had an acceptable safety profile and was well tolerated in allogeneic HSCT recipients.[24] Barghash et al.[38] conducted a small, retrospective study at Mount Sinai Hospital (New York, NY, USA) in 65 immunosuppressed adults who had previously received a heart transplant and received RZV between September 2018 and June 2020. Chart reviews identified AEs in 35.4% of patients after the first RZV dose and in 28.3% after the second dose; the AEs were typically injection-site reactions (29.2% and 28.2% of patients after first and second RZV dose, respectively). The authors reported no evidence of increased allograft rejection after the vaccinations.[38]

Adults with immune-mediated diseases

RZV safety has also been investigated in real-world studies in patients with immune-mediated diseases, many of whom were receiving immunosuppressive therapies, as summarized below and in Table 3. Besides AE incidence, these studies investigated the theoretical concern that vaccination could be associated with an increased risk of disease flares due to vaccine adjuvants.[39,40]

A self-controlled risk interval study was conducted using claims data from IBM MarketScan and Centers for Medicare & Medicaid Services (Baltimore, MD, USA) databases (2018–2019).[41] The self-controlled risk interval design was selected to investigate whether a temporal association exists between RZV administration and disease flares in older adults with immune-mediated inflammatory diseases. The IBM MarketScan database included patients for whom outpatient pharmaceutical claims were available; patients were covered by employer-sponsored insurance each year from US states. The Centers for Medicare & Medicaid Services database included patients with enrollment in Medicare Parts A (hospital insurance), B (outpatient medical insurance), and D (prescription drug coverage). The study investigated the incidence of disease flares among patients aged ≥ 50 years with immune-mediated inflammatory diseases who received at least one RZV dose. The study population was stratified across databases according to age, such that 7207 adults aged 50–64 years with employer-sponsored insurance coverage were included from the MarketScan database and 72,468 Medicare fee-for-service beneficiaries aged ≥ 65 years were included from the Medicare database. Patients had various diseases; the most common included rheumatoid arthritis, psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease, and systemic lupus erythematosus. No increase in the risk of flares was identified in the self-controlled case-series analysis: that is, the incidence of flares was similar during a control period (98–140 days) prior to vaccination and during follow-up (1–42 days) post vaccination. In patients aged ≥ 65 years, 12% had flares after the first RZV dose, and 11% after the second dose, compared with 13% who experienced flares during the period prior to vaccination; in patients aged 50–64 years, 9% developed flares in the period following the first or second doses of RZV, compared with 10% during the period prior to vaccination (Table 3).[41]

Two studies specifically investigated RZV safety in patients with IBD, primarily focusing on the incidence of disease flares.[39,42] A retrospective cohort study, using data from the Veterans Affairs Healthcare System for patients aged ≥ 50 years with IBD, explored the incidence of disease flares (by chart review) in patients receiving RZV ($N = 1677$) compared with matched, unvaccinated patients.[42] No difference was

Table 2. Overview of real-world evidence investigating the incidence of selected adverse events[a] after administration of the recombinant zoster vaccine.

				Safety data[a]	
Publication	Study type/period	Population	Sample	Outcome	Results
Adults aged ≥ 50 years[b]					
Hesse et al. *MMWR Morb Mortal Wkly* 2019[34]	Retrospective analysis of VAERS data Oct 2017–Jun 2018	US population	~3.2 million RZV doses	Total reports of AEs, *N* (%) *n* per 100,000 doses distributed Serious AEs, *n* (%) Fever, *n* (%) Injection-site pain, *n* (%) Injection-site erythema, *n* (%)	4381 (100.0) 136 130 (3.0) 1034 (23.6) 985 (22.5) 880 (20.1)
Tavares-Da-Silva et al. *Vaccine* 2020[6]	Retrospective analysis of the GSK safety database Oct 2017–Feb 2019	Worldwide population	9,323,118 RZV doses	Total reports of AEs, *N* (%) *n* per 100,000 doses distributed Serious AEs, *n* (%) Fever, *n* (%) Injection-site reactions, *n* (%) Injection-site pain, *n* (%)	15,638 (100) 167.7 741 (4.7) 1658 (10.6) 2849 (61.4) 1699 (10.9)
Nelson et al. *Am J Epidemiol* 2023[48]	Prospective analysis of VSD data Jan 2018–Dec 2019	US adults ≥ 50 years enrolled in 7 VSD-data-contributing healthcare systems	End-of-surveillance analysis: RZV recipients: *n* = 647,307 first and second doses; "well-visit" comparators:[c] n = 1,086,206	Diagnoses consistent with systemic reactions: RZV group, *n* (rate per 10,000 doses[d]) RZV vs "well-visit" group, aRR[d] (95% CI) Diagnoses consistent with local reactions: RZV group, *n* (rate per 10,000 doses[d]) RZV vs "well-visit" group, aRR[d] (95% CI) Any adverse reaction diagnosis: RZV group, *n* (rate per 10,000 doses[d]) RZV vs "well-visit" group, aRR[d] (95% CI) Urgent or emergency healthcare visit for any reason RZV group, *n* (rate per 10,000 doses[d]) RZV vs "well-visit" group, aRR[d] (95% CI)	 2202 (31.49) 1.17 (1.10–1.24) 202 (2.69) 2.75 (2.14–3.54) 2497 (35.63) 1.27 (1.20–1.34) 2541 (36.93) 1.01 (0.96–1.07)
Pirrotta et al. *Drug Saf* 2021[35]	Retrospective analysis of the GSK safety database Oct 2017–Apr 2020	Worldwide population	32,597,779 RZV doses	Reports of AEs suggestive of HZ or HZ complications, *n* Reports of possible VZV reactivation,[e] *n* Reports of vaccination failure, *n* Unique reports of AEs suggestive of other vesicular and bullous cutaneous eruptions (non-HZ), *n* Injection-site eruptions, *n* Non-injection-site eruptions, *n*	2423 1928 645 810 74 557
Yih et al. *Am J Epidemiol* 2022[36]	Retrospective analysis of the IBM MarketScan database Jan 2018–May 2020	Commercially insured US adults aged ≥ 50 years	1,014,329 RZV doses	ICD-10 Diagnosis Description (post-vaccination risk window detected): Dizziness and giddiness (days 1–8) Poisoning by, adverse effect of, and underdosing of diuretics and other and unspecified drugs, medicaments, and biological substances (days 1–4)[f] Fever of other and unknown origin (days 1–2) Syncope and collapse (days 1–3) Fever, unspecified (days 1–2) Adverse effects of other vaccines and biological substances (days 1–3)[f]	Cases, *n* in 56-day follow-up; *n* in risk window (excess cases per 100,000 doses) 1448; 251 (7.8) 187; 68 (5.9) 973; 82 (5.1) 908; 74 (4.5) 40; 33 (3.2)
Yih et al. *Am J Epidemiol* 2023[47]	Retrospective analysis of the IBM MarketScan database Jan 2018–May 2020	Commercially insured US adults aged ≥ 50 years	999,876 RZV doses	ICD-10 Diagnosis Description[f] (days 1–28 post vaccination) Adverse effect of other vaccines and biological substances Other complications following immunization, not classified elsewhere Poisoning by, adverse effect of, and underdosing of viral vaccines Adverse effect of other viral vaccines	Cases, *n* (attributable risk per 100,000 doses): 37 (3.7) 27 (2.6) 24 (2.4) 23 (2.3)

(*Continued*)

Table 2. (Continued).

Publication	Study type/period	Population	Sample	Safety data[a] Outcome	Results
Ackerson et al. *Vaccine* 2021[37]	Retrospective cohort study Apr–Nov 2018	Kaiser Permanente Southern California members aged ≥ 50 years	31,120 individuals who received at least one RZV dose: *n* = 10,222 first dose only *n* = 20,898 second dose completed	Days 1–7 after first RZV dose: Medically attended local reactions First dose only group, *n* (%) Second dose completed group, *n* (%) Medically attended systemic reactions First dose only group, *n* (%) Second dose completed group, *n* (%) Medically attended pain First dose only group, *n* (%) Second dose completed group, *n* (%)	 21 (0.2) 32 (0.2) 55 (0.5) 85 (0.4) 32 (0.3) 50 (0.2)
Immunocompromised adults aged ≥ 18 years					
Baumrin et al. *Blood Adv* 2021[24]	Prospective cohort study Dec 2018–Jun 2020	Allogeneic hematopoietic cell transplantation recipients	158 patients who received at least one RZV dose[g]	Days 1–7 after vaccination:[h] All solicited AEs Any grade, *n/N* (%) Grade 3, *n/N* (%) Injection-site AEs Any grade, *n/N* (%) Grade 3, *n/N* (%) Pain Any grade, *n/N* (%) Grade 3, *n/N* (%) Days 1–30 after vaccination:[h] All unsolicited AEs, *n/N* (%) Related to trial intervention, *n/N* (%) Serious AEs, *n/N* (%)	 139/151 (92.1) 49/151 (32.5) 131/150 (87.3) 28/150 (18.7) 129/150 (86.0) 24/150 (16.0) 11/150 (7.3) 6/150 (4.0) 2/150 (1.3)
Barghash et al. *J Heart Lung Transplant* 2020[38]	Retrospective cohort study Sep 2018–Jun 2020	Heart transplant recipients	65 patients who received at least one RZV dose: *n* = 65 first dose *n* = 46 second dose	All AEs After first dose, *n* (%) After second dose, *n* (%) Injection-site reactions After first dose, *n* (%) After second dose, *n* (%) Fever After first dose, *n* (%) After second dose, *n* (%) Gastrointestinal side effects After first dose, *n* (%) After second dose, *n* (%) Headache After first dose, *n* (%) After second dose, *n* (%)	 23 (35.4) 13 (28.3) 19 (29.2) 13 (28.3) 1 (1.5) 1 (2.2) 1 (1.5) 0 (0) 1 (1.5) 0 (0)

[a]The safety data listed for each study are not exhaustive; a selection of key outcomes is presented.
[b]The vast majority of cases involved individuals aged ≥ 50 years, as this was the age group for which RZV was indicated at the time of the data collection. In some studies, nevertheless, a small fraction of cases came from individuals aged <50 years.
[c]Individuals who had not received RZV, had an annual well-person healthcare visit during the RZV uptake period, and had been vaccinated against influenza during the year before their visit.
[d]Propensity-score –adjusted for age, sex, study site, a dermatology visit, an optometry visit, and prior zoster vaccine live vaccination.
[e]When considering an RF of 75%, the observed number of possible VZV reactivations was lower than the expected number in all countries. The observed number of possible VZV reactivations was higher than the expected number for RFs of <10% for worldwide and the USA, <56% for Canada, and <53% for Germany. The RF is the proportion of possible VZV reactivations reported among all those events that actually occurred in the vaccinated general population within the risk period, regardless of the causality.
[f]The authors noted that previous studies examining similar nonspecific post-vaccination signals case by case using similar methodology found that the majority of the cases experienced conditions such as injection-site reactions, fever, fatigue, and headache.
[g]The majority of the participants had co-administered vaccines (94% at first RZV dose, 84% at second RZV dose).
[h]The data are reported as *n/N*. The total *N* varied, as participants with missing symptom diaries for the first or second RZV dose were removed unless a grade 3 event was reported.
AE, adverse event; aRR, adjusted relative risk; CI, confidence interval; HZ, herpes zoster; RF, reported fraction; RZV, recombinant zoster vaccine; US, United States; VAERS, Vaccine Adverse Event Reporting System; VSD, Vaccine Safety Datalink; VZV, varicella zoster virus.

Table 3. Overview of real-world evidence investigating the incidence of adverse events and disease flares after administration of the recombinant zoster vaccine in patients with immune-mediated diseases.

Publication	Study type/period	Follow-up	Population	Sample size	Principal underlying conditions, *n* (%)	Concomitant medication, *n* (%)	Flare incidence[a]	AE incidence[a,b]
Gupta et al. *J Clin Rheumatol* 2022[45]	Medical records review Jan 2018–Mar 2020	3 months	Adults with rheumatic disease	RZV – one dose: 31 RZV – two doses: 34	RA, 20 (31) Polymyalgia rheumatica, 11 (17) Sjögren syndrome, 6 (9) SLE, 5 (8) PsA, 5 (8) Scleroderma, 4 (6) IBD arthropathy, 3 (5) AS, 2 (3) Other, 8 (15)	Biologic DMARD, 16 (24.6) Nonbiologic DMARD, 29 (44.6) No DMARD, 20 (30.8)	Baseline period: *n* = 8 (12.3%) After RZV: *n* = 3 (9.2%)	Minor, systemic AEs: *n* = 4 (6.2%)
Venerito et al. *Int J Mol Sci* 2023[49]	Prospective study at the RA clinic of a tertiary center Feb–Jun 2022	3 months	Patients with RA on JAK inhibitors or biologic DMARD who received two doses of RZV	JAK inhibitors: *n* = 26 Biologic DMARD: *n* = 26	RA, 52 (100)	JAK inhibitors, 26 (50) Biologic DMARD, 26 (50)	After RZV: *n* = 0	Local site reactions *n* = 45 (86.5%) Most frequent systemic AEs: fatigue (*n* = 13, 25%); fever (*n* = 11, 21.2%); headache (*n* = 11, 21.2%) No serious AEs
Khan et al. *J Crohns Colitis* 2022[42]	Retrospective cohort study using Veterans Affairs Healthcare System data Study period NR	90 days	Patients with IBD	RZV – 1677 Unvaccinated matched controls –1677	IBD, 1677 (100)	Mesalamine, 1450 (86) Anti-TNF agents, 109 (7) Thiopurines, 105 (6) Anti-TNF and thiopurines, 6 (<1) Vedolizumab, 7 (<1)	Cumulative 90-day incidence of IBD flare: 1.2% (vaccinated) vs. 1.0% (unvaccinated); *p* = 0.503	NR
Lenfant et al. *Rheumatology (Oxford)* 2021[43]	Single-center review of electronic medical records Feb 2018–Mar 2020	Median 36 weeks	Adults with (*n* = 359) or without (*n* = 263) IMID	RZV – one dose: 146 RZV – two doses: 476	RA, 88 (25)[c] Vasculitis, 50 (14)[c] PMR, 29 (8)[c] Gout, 28 (8)[c] SLE, 24 (7)[c]	Non-biologic DMARD, 176 (49) Glucocorticoids, 125 (35) Biologic DMARD, 68 (19) Other biologics, 47 (13)	In the IMID subgroup[d] *n* = 59/359 (16.4%): RA, 21/88 (24%) Vasculitis, 5/50 (10%) PMR, 5/29 (17%) Gout, 5/28 (18%) SLE, 4/24 (17%)	In the entire population, *n* = 54 (8.7%): most frequently, injection-site reactions (*n* = 19, 3%); general fatigue (*n* = 12, 2%); myalgia (*n* = 12; 2%); and fever (*n* = 6; 1%)

(*Continued*)

Table 3. (Continued).

Publication	Study type/period	Follow-up	Population	Sample size	Principal underlying conditions, *n* (%)	Concomitant medication, *n* (%)	Flare incidence[a]	AE incidence[a,b]
Leung et al. *Arthritis Rheumatol* 2022[41e]	SCCS analysis of medical claims data from the IBM MarketScan (patients aged 50–64 years; 2017–2019) and Centers for Medicare and Medicaid Services Medicare (patients aged ≥ 65 years; 2017–2020) databases	≥ 6 months	Aged ≥ 50 years, with IMID	At least one RZV dose: MarketScan, *n* = 7207; Medicare, *n* = 72,468	Marketscan: RA, 3415 (47.4) PsO, 1039 (14.4) PsA, 992 (13.8) IBD, 1477 (20.5) UC, 916 (12.7) CD, 594 (8.2) SLE, 507 (7.0) AxSpA, 216 (3.0) AS, 166 (2.3) Medicaid: RA, 45,851 (63.3) IBD, 12,679 (17.5) UC, 7416 (10.2) PsA, 6678 (9.2) PsO, 5993 (8.3) CD, 5384 (7.4) SLE, 4205 (5.8) AxSpA, 86 (<1) AS, 72 (<1)	NR	At least one RZV dose: risk window – MarketScan 9%, Medicare 11–12%; control window – MarketScan 10%, Medicare 13%[f]	NR
Raza et al. *South Med J* 2022[44]	Single-center, retrospective study 2018	4.78 months after second vaccine	Patients with rheumatic disease who received two doses of RZV	*N* = 47	RA, 36 (76.6) SLE, 5 (10.6) Fibromyalgia, 3 (6.4) Vasculitis, 2 (4.2) Sjögren syndrome, 2 (4.2)	Conventional DMARD, 28 (59) Biologic/targeted DMARD, 23 (49) Both conventional and biologic/targeted DMARD, 12 (25)	Four events of disease flare occurred at subsequent post-vaccination follow-up visits	Mild AEs: 6.4%
Satyam et al. *Dig Dis Sci* 2020[39]	Prospective, observational study at tertiary IBD referral center Feb 2018–Jul 2019	Median (IQR) 207 days (169–304.5) days	Patients with IBD	At least one RZV dose: *n* = 67	UC, *n* = 28 CD, *n* = 39	Prednisone, 7 (10.4) Immunomodulator (6-mercaptopurine, azathioprine, or methotrexate), 11 (16.4) Anti-TNF inhibitor, 9 (13.4) Vedolizumab, 15 (22.4) Ustekinumab, 9 (13.4) Tofacitinib, 3 (4.5)	1/67 (1.5%)	Local AEs: 74.6% Systemic AEs: 56.7%

(*Continued*)

Table 3. (Continued).

Publication	Study type/period	Follow-up	Population	Sample size	Principal underlying conditions, *n* (%)	Concomitant medication, *n* (%)	Flare incidence[a]	AE incidence[a,b]
Stevens et al. *ACR Open Rheumatol* 2020[40]	Retrospective chart review at a rheumatology outpatient center Feb 2018–Feb 2019	Mean (range): 13.2 (1.0–50.0) weeks	Patients with RA or other SRD	At least one RZV dose: *n* = 403	RA, *n* = 239 (59.3) SRD, *n* = 164 (40.7) PsA, *n* = 28 (6.9) SLE, *n* = 16 (3.9) Spondylitis, *n* = 12 (2.9) Sjögren syndrome, *n* = 12 (2.9) Giant cell arteritis, *n* = 8 (1.9) Other, *n* = 88 (21.8)	Any immunosuppressant, *n* = 316 (78.4) MTX, *n* = 143 (35.5) Prednisone, *n* = 106 (26.3) Tofacitinib, *n* = 52 (12.9) TNF inhibitor, *n* = 105 (26.1) Other biologic, *n* = 49 (12.2) Other immunosuppressant, *n* = 49 (12.2)	After first RZV dose: 23 (5.7%) After second RZV dose: 5 (2.3%) After both RZV doses: 1 (0.2%)	Mild AEs: *n* = 51 (12.7%) After first RZV dose: 43 (10.7%) After second RZV dose: 12 (5.4%) After both RZV doses: *n* = 4 (<1%)

[a]Unless otherwise stated, *n* = number of patients.
[b]After RZV.
[c]Underlying conditions in the IMID subgroup.
[d]Multivariable analysis revealed that glucocorticoid use at the time of RZV dosing was the only factor significantly associated with flares (odds ratio 2.31; 95% CI: 1.30–4.10; $p = .004$).
[e]Flare rate for each IMID can be found in Leung et al. *Arthritis Rheumatol* 2022.[41]
[f]For specific values for flare incidence according to IMID, the reader is referred to the original Leung et al. paper.[41]
AE, adverse event; AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; CD, Crohn's disease; DMARD, disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; JAK, Janus kinase; MTX, methotrexate; NR, not recorded; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; pts, patients; PsO, psoriasis; RA, rheumatoid arthritis; RZV, recombinant zoster vaccine; SCCS, self-controlled case series; SLE, systemic lupus erythematosus; SRD, systemic rheumatic disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

found in the incidence of IBD flares within 90 days after vaccination between the RZV and unvaccinated groups: flares were reported in 1.2% versus 1.0% of patients, respectively (Table 3).[42] A prospective, observational, single-center study at Boston Medical Center (Boston, MA, USA) investigated the safety of RZV in 67 patients with IBD who received at least one RZV dose.[39] Two-thirds of patients were immunosuppressed. Eleven patients (16.4%) were on an immunomodulator (6-mercaptopurine, azathioprine, or methotrexate), 9 (13.4%) were on a tumor necrosis factor inhibitor, 15 (22.4%) were on vedolizumab, 9 (13.4%) were on ustekinumab, and 3 (4.5%) were on tofacitinib. Rates of injection-site reactions were considered similar to those in the general population (Table 3). A disease flare was reported in only one patient in this study, and the authors concluded that the study suggests that rates of IBD flare are not increased by RZV administration.[39] However, the study was uncontrolled and without a comparator group.

Besides studies in IBD populations, several studies explored RZV safety in patients with rheumatologic disorders.[40,43–45,49] Although these studies were uncontrolled and without a comparator arm, they nonetheless highlight real-world experience with RZV. The incidence of disease flares with RZV vaccination was investigated in a single-center study, conducted at the rheumatology outpatient center at Brigham and Women's Hospital (Boston, MA, USA), in 403 patients with rheumatoid arthritis or other systemic rheumatic diseases who were vaccinated between February 2018 and February 2019.[40] Most patients (78.4%) were receiving immunosuppressive medications. AEs were reported in 12.7% of patients, most commonly injection-site reactions; all AEs were mild and were consistent with the known safety profile of RZV. Disease flares 12 weeks post vaccination were identified in 6.7% of patients; all flares were mild and responded to treatment with glucocorticoids without requiring changes in immunosuppressive therapy (Table 3). The authors noted that the incidence of flares was lower than the background incidence in a previous analysis conducted at the same institution prior to the availability of RZV.[40,50]

A retrospective study, using EHR data from the Cleveland Clinic Rheumatology Department (Cleveland, OH, USA), investigated the safety of RZV in patients aged ≥ 18 years who received at least one dose of RZV from February 2018 to March 2020.[43] In the total rheumatology clinic population studied who received at least one dose of RZV ($N = 622$), 8.7% of patients reported AEs following RZV vaccination, most commonly local reactions. Among the total of 622 patients, 359 had immune-mediated inflammatory diseases, most frequently rheumatoid arthritis (25% of patients). Disease flares following RZV vaccination were reported in 16% of the 359 patients; 31% of the flares were related to a change in treatment, and 25% of patients with flares required alteration of immunosuppressive therapy. Multivariable analysis revealed that flares were significantly more likely (odds ratio 2.31; $p = .004$) in patients using glucocorticoids at the time of RZV administration. As short-term glucocorticoid therapy is typically used to control active disease, the authors suggested that it may be prudent to delay RZV vaccination until low disease activity is achieved. However, the study lacked a comparator group, so a definitive causal link between RZV vaccination and disease flares could not be confirmed.[43]

Two small, single-center studies explored the safety of RZV in rheumatology patients, most of whom were receiving disease-modifying antirheumatic drugs.[44,45] In the first study ($N = 47$), three (6.4%) patients self-reported AEs after RZV vaccination but all were mild; four patients (8.5%) had disease flares at subsequent follow-up, but these flares were not reported immediately after vaccination and were considered likely related to the natural disease course and not to RZV vaccination.[44] In the second study ($N = 65$), self-reported AEs after vaccination occurred in four (6.2%) patients, but none were severe; the incidence of disease flares was 5.6 per 100 PY in the pre-vaccination baseline period, compared with 2.1 per 100 PY in the post-vaccination follow-up period.[45] A third small study followed rheumatology patients receiving Janus kinase inhibitors or one of the biologic agents rituximab and abatacept at the rheumatoid arthritis clinic of a tertiary center in Italy.[49] A total of 52 patients, aged 18–85 years, received two RZV doses 1 month apart and were followed up for AE detection for 7 days after immunization. No flares were detected within the total duration of the study (3 months' follow-up). Injection-site reactions, such as swelling and redness, were reported by 86.5% of patients, and fatigue was the most reported systemic AE (25%).[49]

Collectively, these studies suggest that RZV is well tolerated in real-world clinical practice in patients with immune-mediated diseases, including those receiving concomitant immunosuppressive therapy. Although evidence is limited and it is difficult to compare these studies directly (as the definition of disease flare may vary between studies and flare cases may not have been chart reviewed), RZV does not appear to increase the risk of disease flares. Additional research on this topic is required.

Guillain–barré syndrome

Individuals who develop HZ have an elevated risk of also developing GBS,[51] and studies have evaluated the potential risk of GBS following RZV. In the GSK safety database analysis discussed earlier, 17 cases of GBS were reported, representing a reporting rate of 0.18 per 100,000 RZV doses distributed.[6] The authors evaluated this reporting rate further using an observed-to-expected analysis and found that the observed number of cases of GBS following RZV was not greater than expected in the patient population.[6]

A data-mining study using IBM MarketScan data for commercially insured people in the USA aged ≥ 50 years, and including approximately 1 million RZV doses administered from January 2018 through May 2020, found no association between RZV and GBS.[36] Nine cases of GBS were identified in this sample, of which four, after further review, were considered likely not true new-onset GBS cases.[36] Subsequently, a sequential data-mining analysis of this database by the same authors reported no signals for GBS on days 8–21 following RZV vaccination.[47]

Initial post-licensure safety surveillance by the CDC using the VSD database identified an elevated incidence of GBS

following RZV.[46] Subsequently, a US FDA- and CDC-led analysis of the Medicare claims database investigated the incidence of GBS following RZV vaccination in adults aged ≥ 65 years (1,318,004 doses in 849,397 patients), using data up to February 2020.[46] In this self-controlled case series, the authors identified an increased risk of GBS in the risk versus control window (relative risk 2.84; 95% CI: 1.53–5.27; $p = .001$); that is, a small excess of approximately 3 cases per million RZV doses during the 42-day period following vaccination in the Medicare population.[46] A self-controlled case-series analysis of data from two US claims databases suggested a confounding effect of HZ episodes on the potential causal association between RZV vaccination and the risk of GBS.[52] Nonetheless, the RZV label was updated, with the FDA noting a potentially increased risk of GBS following RZV vaccination in post-marketing reports while also acknowledging that the available evidence was insufficient to establish a causal relationship.[8,53]

In an active post-licensure study using data from the VSD framework, a preliminary signal for GBS was observed in RZV recipients compared with historical ZVL recipients (aRR = 5.25; $p = .02$) but waned over time (aRR = 1.24; $p > .05$).[48] Following chart review, the aRR for confirmed GBS in RZV recipients versus historical ZVL recipients ranged from 1.04 (95% CI: 0.14−7.74) to 1.56 (95% CI: 0.18−18.62).[48]

Overall, GBS following RZV administration is a rare event. Some post-marketing data suggest a potentially increased risk of GBS. However, collective evidence is insufficient to determine a causal association between RZV and GBS; even if it is confirmed, this relatively low risk is to be balanced with the health benefits of RZV vaccination.[54]

Two-dose RZV series completion rates

Overall, 14 real-world studies investigated completion rates for the RZV two-dose series (Table 4).[19,38,39,41,45,55–63] These studies were all conducted in the US, with the exception of a single study in Canada.[57] Although most of the studies did not report mean or median times to two-dose RZV completion, five studies reported these times as approximately 86–140 days (Table 4).[38,41,59,61,62] Importantly, the recommended RZV dosage schedule comprises a second dose administered 2–6 months after the first (or 1–2 months later for individuals who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule).[8]

In general population studies conducted in adults aged ≥ 50 years, two-dose completion rates within 2–6 months of the first dose ranged from 65% to 78%.[19,38,55–58,62,63] Completion rates assessed over longer periods (up to 24 months after the first dose) ranged from 67% to 89.5% (Table 4).[19,37,55–58,62,63] In studies assessing completion rates at multiple time points, completion rates tended to increase with increased duration of follow-up, as expected (Table 4).[19,55–58,62,63] In special populations, such as those with immune-mediated inflammatory disorders, completion rates were broadly similar to those in the general population (Table 4).[38,39,41,45,60]

In the US, a large retrospective pharmacy and medical claims analysis extracted data from the IQVIA LRx Longitudinal Pharmacy and Dx Medical Claims Databases. Annually, the LRx database includes almost 4 billion adjudicated electronic prescription claims, and monthly, the Dx database includes approximately 1 billion non-adjudicated claims for professional fees from >870,000 practitioners.[56] Overall, data were collated for >7 million adults aged ≥ 50 years with an RZV claim between October 1, 2017, and September 30, 2019; a total of 1,225,088 individuals had data available for 12 months after the index date. The RZV second-dose completion rate was 70.4% at 6 months and 81.8% at 12 months, median time to the second dose was 4.08–5.13 months, and adherence to receiving the second dose 2–6 months after the first dose was 67.6%.[56] Another large retrospective US study using the IQVIA PharMetrics Plus and IBM MarketScan databases for adults aged 50–64 years reported similar completion rates[62] (Table 4). Moreover, Fix et al. retrospectively analyzed data from January 2018 through December 2019 using the IBM MarketScan database.[63] In a cohort of over 4.5 million enrollees aged 50–64 years, 89.5% of the individuals who received a first RZV dose completed the two-dose series. Among those who received both doses, 88.6% did so within the recommended 2–6 months.[63] A cohort study conducted by the US FDA and CDC investigated RZV effectiveness among Medicare beneficiaries aged ≥ 65 years.[19] The study included data from approximately 15.5 million unvaccinated individuals and approximately 1 million individuals who had received two RZV doses, among whom the second RZV dose was given by 6 months after the first dose in 78% of individuals and by 12 months in 86% of individuals.[19]

In Canada, data on RZV use were retrospectively collected from the IQVIA LRx Longitudinal Prescription Database, which includes patient-level data for >70% of prescriptions dispensed at approximately 6000 Canadian retail pharmacies.[57] The RZV second-dose completion rate was 65.0% within 2–6 months of the first dose and 74.9% within 2–12 months of the first dose. However, the authors mentioned the potential for some immunizations not to be recorded in the pharmacy-based database: that is, in some regions, nurses can immunize patients without a prescription, and some patients may purchase prescriptions at sources other than retail pharmacies or receive drugs during hospital inpatient stays. Thus, the recorded completion rates in the database may have underestimated the actual completion rates in the real-life setting, although this is unlikely to have been a major difference.[57]

The abovementioned real-world data suggest that two-dose RZV completion rates are generally high. However, up to one-fifth of vaccinees do not receive a second dose and up to one-third of individuals may not receive the second RZV dose within the 2- to 6-month period after the first dose, as recommended for healthy adults aged 50 years and above.[8,19,55,56,62,63] As explained previously, in the study conducted by the US FDA and CDC investigating RZV effectiveness among Medicare beneficiaries aged ≥ 65 years,[19] effectiveness with two doses was higher than with one dose; although effectiveness remained comparable for individuals who received their second dose beyond 6 months, as the median time from the first to second dose was 230 days, this should be interpreted with caution given the findings in ZOSTER-026.[27]

Table 4. Overview of real-world evidence investigating series completion rate for the recombinant zoster vaccine[a].

Publication	Study type/period	Population	Two-dose series completion rate
Patients aged ≥ 50 years			
Patterson et al. *Hum Vaccin Immunother* 2021[55b] and Patterson et al. *J Am Pharm Assoc* 2022[56c]	Retrospective study of IQVIA prescription claims and medical claims datasets, USA Oct 2017–Sep 2019	Aged ≥ 50 years (*N* = 7,097,441)	Second dose within 60 days: 3%[55] Second dose within 90 days: 36%[55] Second dose within 2–6 months: 67.6%[56] Second dose within 6 months: 70.4%[56] Second dose within 12 months: 81.8%[56]
McGirr et al. *Vaccine* 2021[57]	Retrospective study of IQVIA prescription database, Canada Jan 2017–May 2019	Aged ≥ 50 years (6-months' follow-up: *N* = 155,747; 12-months' follow-up: *N* = 55,524)	*6-month follow-up cohort*: Second dose within 2–6 months: 65.0% *12-month follow-up cohort*: Second dose within 2–6 months: 66.8% Second dose within 2–12 months: 74.9%
Izurieta et al. *Clin Infect Dis* 2021[19]	Cohort study using Medicare claims and enrollment database analysis, USA Nov 2017–Oct 2019	Aged ≥ 65 years (*N* = 1,006,446)	Second dose within 6 months: 78% Second dose within 12 months: 86%
LaMori et al. *Vaccine* 2022[58]	Retrospective study using EHR data from Optum Clinformatics Data Mart, USA Apr 2017–Mar 2021	Aged ≥ 50 years (*N* = 726,352)	Second dose within 2–6 months: 71.8% Second dose within 6 months: 72.3% Second dose within 24 months: 86.2%
Leung et al. *Vaccine* 2022[62]	Retrospective study of IQVIA PharMetrics Plus and IBM MarketScan databases, USA Apr 2017–Dec 2021	Aged 50–64 years (IQVIA 6-month follow-up: *N* = 1,106,956; MarketScan 6-month follow-up: *N* = 788,831; IQVIA 12-month follow-up: *N* = 868,619; MarketScan 12-month follow-up: *N* = 594,987)[d]	IQVIA 6-month follow-up cohort: 67% (median dose interval: 89 days) MarketScan 6-month follow-up cohort: 71% (median dose interval: 90 days) IQVIA 12-month follow-up cohort: 78% MarketScan 12-month follow-up cohort: 82%
Gatwood et al. *Am J Prev Med* 2022[59]	Prospective quality improvement program conducted at a US pharmacy chain Nov 2018–2021	Aged ≥ 50 years (*N* = 113,441)	Without clinical nudge: 71.9% (mean days to completion: 109.8)[e] With clinical nudge: 75.2% (mean days to completion: 93.3)[e]
Gatwood et al. *Vaccine* 2023[61f]	Prospective quality improvement program conducted at a US pharmacy chain Jan 2019–Mar 2020	Aged ≥ 50 years (*N* = 220,966)	*Prior to text messaging[g] being launched:*[h] 83.9% (mean days to completion: 88.6) *After text messaging being launched*: With text message: 88.3% (mean days to completion: 86.2) Without text message: 85.3% (mean days to completion: 94.4)
Ackerson et al. *Vaccine* 2021[37]	Retrospective cohort study using EHR data from Kaiser Permanente Southern California, USA Apr 2018–Nov 2018	Aged ≥ 50 years (*N* = 31,120)	Second dose within 9 months: 67.2%
Fix et al. *Vaccine* 2023[63]	Retrospective cohort study of IBM MarketScan database, USA Jan 2018–Dec 2019	Aged 50–64 years (*N* = 4,678,729)	Second dose within 6 months: 88.6% (average dose interval: 3.7 months) Second dose within study period: 89.5%

(*Continued*)

Table 4. (Continued).

Publication	Study type/period	Population	Two-dose series completion rate
Special patient populations			
Gupta et al. *J Clin Rheumatol* 2022[45]	Medical records review using University of Texas Southwestern Medical Center EHR data, USA Jan 2018–Mar 2020	Aged ≥ 18 years with established rheumatic disease (N = 65)	52.3%[a]
Leung et al. *Arthritis Rheumatol* 2022[41]	Self-controlled case-series analysis using claims data from IBM MarketScan, USA (2017–2019) and Centers for Medicare and Medicaid Services Medicare databases, USA (2017–2020)	Aged ≥ 50 years with immune-mediated inflammatory disorders (N = 216,199)	Aged 50–64 years: 76.6% (median dose interval: 100 days) Aged ≥ 65 years: 85.4% (median dose interval: 98 days)
Satyam et al. *Dig Dis Sci* 2020[39]	Prospective, observational, single-center study at Boston Medical Center, USA Feb 2018–Jul 2019	Patients with IBD (N = 67)	82%[a]
Barghash et al. *J Heart Lung Transplant* 2020[38]	Retrospective single-center study, USA Sept 2018–June 2020	Adults who had previously received a heart transplant (N = 65)	70.8% (average dose interval: 4.6 months)
Porter et al. *J Am Pharm Assoc* 2021[60]	Retrospective cohort study in an HIV/infectious disease clinic Jul 2018–Dec 2018	HIV-positive patients aged ≥ 50 years, without immunocompromise (N = 119) Pharmacist-directed pilot program (n = 35) Usual HZ education (n = 84)	Pharmacist-driven RZV administration program: 66% (p < .001 vs. standard care) Standard care: 23%

[a]No timescale reported.
[b]Paper described the same study as in footnote c and evaluated cumulative RZV uptake, second-dose completion levels, and adherence to dosing recommendations in the US.
[c]Paper evaluated completion rates and adherence in the overall US adult population aged ≥ 50 years and in subpopulations of interest (e.g., immunocompromised individuals, African Americans), and evaluated factors affecting completion rates and adherence.
[d]Some individuals were included in both the 6-month and 12-month cohorts, but the cohorts do not completely overlap because of different enrollment requirements described in the study.
[e]Clinical nudge consisted of an alert triggered ≥ 8 weeks after the initial RZV dose and a prompt to proactively contact such patients. The alert appeared in the pharmacy electronic dashboard each time eligible patients visited the pharmacy until either the second dose was given or 6 months after the first dose had passed.
[f]Paper described the second phase of the program first implemented in November 2018 and described in Gatwood et al. *Am J Prev Med* 2022.[59] The second phase included additional initiatives (text messaging) that were launched on September 18, 2019.
[g]Patients received a text message ≥ 8 weeks after the initial RZV dose in addition to the clinical nudge described in footnote e. Messages were sent once monthly until either the second dose was given or 6 months after the first dose had passed.
[h]With clinical nudge in place, as described in footnote e.
EHR, electronic health record; HIV, human immunodeficiency virus; HZ, herpes zoster; IBD, inflammatory bowel disease; RZV, recombinant zoster vaccine.

Collectively, available data suggest that there is a need to ensure that patients receive two doses of RZV within the recommended schedule.

Beyond counseling and standard follow-up, several real-world studies explored potential strategies to improve adherence.[59–61,64] For example, pharmacist-driven RZV administration programs were suggested to increase completion rates versus standard provider-directed RZV education.[60] Using alerts within pharmacy electronic databases to prompt pharmacists to engage with individuals requiring a second dose of RZV was also reported to improve completion rates and shorten the time to completion.[59] The addition of a patient-facing nudge via text messaging achieved further benefits.[61] Finally, receiving a pharmacist phone call was reported to significantly increase the likelihood of individuals returning for a second RZV dose.[64]

Conclusions and future directions

The real-world evidence summarized in this review complements and supports the clinical trial data previously accrued for RZV. Overall, RZV effectiveness against HZ was high across the studied populations in real-world settings, including in adults aged ≥ 50 years and in patients aged ≥ 18 years at increased risk of HZ because of immunodeficiency or immunosuppression.[18,19,21–24] Besides the high RZV efficacy in phase III clinical trials,[9–11] the real-world effectiveness results for RZV are reassuring, as these results were obtained in a more heterogeneous population. Further, the safety profile of RZV in post-licensing surveillance database analyses and other real-world safety studies was broadly consistent with the safety profile of RZV established in clinical trials.[6,24,34–49] Collectively, these real-world studies reaffirm the favorable benefit–risk profile of the vaccine.

The real-world studies reported in this review also highlight areas requiring further attention. Most of the studies were conducted in adults aged ≥ 50 years, and in the US, RZV only recently (mid-2021) gained approval for use in adults aged ≥ 18 years with immunodeficiency or immunosuppression due to disease or therapy.[8,16] Therefore, a need exists for further real-world evidence for RZV in adults aged ≥ 18 years, with increased focus on effectiveness and safety in at-risk populations (e.g., people living with HIV, people with autoimmune diseases), the concurrent use of specific immunosuppressive therapies, and longer-term follow-up for the assessment of RZV effectiveness. Strategies to increase RZV two-dose completion rates could be another future focus for healthcare providers. In addition, there is a current paucity of real-world evidence from outside the USA. Data from other countries may help enhance understanding of the clinical profile of RZV in diverse populations.

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Data availability statement

The data summarized in this review are from published articles and are publicly available.

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