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Post-marketing safety surveillance for the recombinant zoster vaccine (Shingrix), vaccine adverse event reporting system, United States, October 2017–April 2024

Yamin Shu [a,1], Wenxin Cheng [b,1], Xucheng He [c], Liu Huang [d], Wei Chen [e,*], Qilin Zhang [f,*]

[a] Department of Pharmacy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[b] Hubei University of Chinese Medicine, Hubei Hospital of Integrated Traditional Chinese and Western Medicine, Wuhan 430015, China
[c] Department of Pharmacy, Pengzhou Second People's Hospital, Pengzhou 611930, China
[d] Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China
[e] Respiratory Medicine Department, Taizhou Affiliated Hospital of Nanjing University of Chinese Medicine, Taizhou 225300, China
[f] Department of Pharmacy, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

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ABSTRACT

Background: Recombinant zoster vaccine (RZV), received its first marketing authorization in October 2017 to prevent herpes zoster and its complications in older adults. The purpose of this study was to provide comprehensively worldwide post-marketing safety information about RZV using data from the Vaccine Adverse Event Reporting System (VAERS).

Methods: We searched for and analyzed adverse event (AE) reports of RZV submitted to U.S. VAERS between October 20, 2017 and April 26, 2024. Descriptive analyses included sex, age, time-to-onset, seriousness, most commonly reported AEs, AE of special interest, and cause of death. The empirical Bayesian data mining was employed to identify potential disproportionalities in reporting.

Results: During the study period, 1,279,596 AE reports for vaccines were received by VAERS after excluding any duplicates, including 66,849 reports specifically related to RZV. Most reports were classified as non-serious (97.3 %). Among reports with age or sex reported, individuals were mainly 50–79 years (71.2 %) and females (63.1 %). The most commonly reported AEs included injection site reactions, pyrexia, chills, headache and fatigue. A total of 86 reports documenting deaths were identified following RZV vaccination. In addition to cardiovascular events and falls, Guillain-Barre syndrome was the most common cause of death. The median TTO for RZV-related AEs was 1 day in all cohort groups over 50 years old.

Conclusion: The safety profile of RZV, based on the large sample post-marketing use, was reassuring and consistent with that observed in clinical trials. Further studies are needed to continue generating real-world safety data and further characterize RZV-AE pairs systematically.

1. Introduction

Herpes zoster (shingles) occurs as a latent reactivation of varicella zoster virus and is typically characterized by painful, blistering vesicular rash. In the general population, the estimated lifetime risk of herpes zoster is about 30 %, with the risk increasing dramatically after age 50 years (Kawai et al., 2014). Herpes zoster complications occur in nearly 25 % of patients with herpes zoster, including postherpetic neuralgia, ophthalmic complications, and cranial and peripheral nerve palsies (Yawn et al., 2007). The most common complication of herpes zoster is postherpetic neuralgia, which can last for months or years and affect more than 30 % of those aged ≥80 years who develop herpes zoster, followed by herpes zoster ophthalmia, which occurs in 10–20 % of herpes zoster patients (Kawai et al., 2014; Tran et al., 2016; Yawn et al., 2013). Both herpes zoster and its complications have a significant impact on patients' quality of life (Johnson et al., 2010). Currently, getting vaccinated is an effective way to prevent herpes zoster and its complications.

* Corresponding authors.
E-mail addresses: chenweitzzyy@sina.com (W. Chen), qilinzhang88@163.com (Q. Zhang).
[1] These authors contributed equally to this work.

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The recombinant zoster vaccine (RZV, Shingrix) was licensed by the U.S. Food and Drug Administration (FDA) in 2017 and recommended as a priority by the Advisory Committee on Immunization Practices shortly thereafter against herpes zoster in immunocompetent adults aged ≥50 years (Dooling et al., 2018; Food and Drug Administration, 2017). It is currently also recommended by the Advisory Committee on Immunization Practices guidelines for immunocompromised adults aged ≥19 years (Anderson et al., 2022). RZV is administered intramuscularly as a 2-dose series with a 2–6 month interval and consists of a recombinant subunit varicella zoster virus glycoprotein E combined with an adjuvant system, $AS01_B$ (Tavares-Da-Silva et al., 2020). Safety data for RZV mainly comes from prelicensure clinical trials, and the commonly reported AEs include fever, injection site pain, and injection site erythema (Cunningham et al., 2016; Lal et al., 2015). Pooled placebo-controlled trial data found an increased risk of local and systemic reactions after taking RZV, with no difference in the risk of other AEs, but lacked statistical potency (López-Fauqued et al., 2019). A systematic literature review involved 1389 relevant records demonstrated that pain at injection site (98.6 %) and fatigue (75.3 %) were the most common AEs of RZV use in immunocompromised 18–49 year old patients (Racine et al., 2020). Additionally, serious adverse events (SAEs) that may be associated with RZV vaccination include pneumonia, febrile neutropenia, immune thrombocytopenic purpura, cutaneous vasculitis, arthralgia, atrial fifibrillation, mucosal inflflammation, Burkitt lymphoma and death (Racine et al., 2020).

Given the recognized limitations and observed methodological biases of a single clinical trial in evaluating the safety of RZV, especially in detecting rare, unexpected, and delayed AEs, post-authorization safety surveillance in larger and more heterogeneous populations is of paramount importance for early detection and investigation of signals associated with vaccination. To improve our overall understanding of the safety of RZV, in the United States, the FDA and the Centers for Disease Control and Prevention rely on existing safety systems such as the Vaccine Adverse Event Reporting System (VAERS), a spontaneous safety monitoring system (Shimabukuro et al., 2015). The VAERS database is now widely used to identify pharmacovigilance risk signals of vaccines in real-world clinical settings. The purpose of this study is to summarize the post-marketing safety surveillance data involving RZV reported from VAERS during the period October 20, 2017-April 26, 2024.

2. Methods

2.1. Overview and data source

VAERS is a nationwide spontaneous reporting system, jointly administered by the Centers for Disease Control and Prevention and the U.S. FDA, which conducts post-licensure safety surveillance of vaccines licensed in the United States (Shimabukuro et al., 2015). VAERS receives reports from vaccine manufacturers, healthcare professionals, patients and their caregivers, as well as other individuals who serve as reporters. This study was approved (No. 20220185) by the institutional ethics board of the Union Hospital of Tongji Medical College of Huazhong University of Science and Technology. The data fields in VAERS form encompass the demographic information and medical history on the vaccine recipient, a comprehensive description of symptoms and health outcomes, precise dates of vaccination administration, specific vaccines administered, onset timing of symptoms, concurrent vaccinations and medications, diagnostic laboratory data, recovery status, as well as other pertinent information. The symptoms described in VAERS report using the standard Medical Dictionary for Regulatory Activities (MedDRA), a widely used and accepted internationally standardized medical terminology for AEs or symptoms (Medical Dictionary for Regulatory Activities, 2024). The MedDRA terms are hierarchically categorized, encompassing commonly encountered System Organ Class (SOC) terms and Preferred Terms (PTs), which do not represent confirmed medical diagnoses. A single VAERS report may be assigned one or more PT(s), belonging to one or more SOC(s). For the purpose of facilitating analysis, we align the symptoms reported in different time periods within VAERS to the most recent version of MedDRA 27.0. Multiple reports or symptoms with the same VAERS_ID are consolidated into a single entry, eliminating any duplications (Shimabukuro et al., 2019).

According to Code of Federal Regulations Title 21 Section 600.80 (US Food and Drug Administration, 2024), VAERS reports are classified as serious when any of the following outcomes are associated with the event: death, permanent disability, life-threatening condition, hospitalization, prolonged existing hospitalization, congenital anomaly or birth defect. Vaccine manufacturers bear the responsibility of providing follow-up information regarding serious reports (Shimabukuro et al., 2015; US Food and Drug Administration, 2024).

2.2. Descriptive analysis

We conducted a comprehensive search of the VAERS database to identify reports from the U.S. involving RZV, spanning from October 20, 2017, to April 26, 2024. We performed descriptive analyses on reports based on sex, age (interquartile range, IQR), time-to-onset (TTO) - the interval between vaccination and symptom onset, serious and non-serious status, as well as the most frequently reported PTs. Only usable data were used for specified descriptive analysis, such as removing age missing and TTO error data. The missing or inconsistent reporting of dose numbers in a vaccination series in VAERS precluded the analysis of this information (Hesse et al., 2019). As the total dosage of RZV in the U. S. has not been publicly disclosed, it is currently unfeasible to estimate the crude AE reporting rate for RZV. The data management and analysis were conducted using MYSQL 8.0 and Microsoft EXCEL 2019.

We conducted a comprehensive review of reports and accompanying medical records, when available, for serious reports and anaphylaxis. For serious reports, we have identified the primary incident that triggered the report along with the corresponding MedDRA SOC and PT for this incident. The cause of death was ascertained based on information documented in the autopsy report, death certificate, or medical records.

2.3. Data mining

As a passive surveillance system limited to numerator-only data, VAERS lacks comprehensive information on the total number of vaccinated individuals and the total number experiencing AEs, as well as the incidence of AEs in unvaccinated individuals (Jamieson et al., 2024). The Empirical Bayesian geometric mean (EBGM), an algorithm employed in disproportionality analysis, was utilized to identify potential RZV-AE pairings that exhibited disproportional reporting compared to all other vaccines within the VAERS database (Shimabukuro et al., 2015; Szarfman et al., 2002). During the study period, all VAERS reports (including the vaccine of interest and comparator vaccines) were included in the analysis to assess the EBGM. The statistical signal was determined based on the mathematical criterion of having a one-sided 95 % lower confidence bound of the EBGM (EB05) greater than 2. The analysis of disproportionality serves as a valuable adjunct to clinical reviews and other analyses in identifying AEs that may demonstrate an elevated frequency of association with RZV.

3. Results

3.1. Descriptive analysis

During the analytic period, a total of 1,279,596 U.S. AE reports for vaccines were received by VAERS after excluding any duplicates. Among these reports, there were 66,849 specifically related to RZV. The detailed information of each dataset is presented in Table 1 and the annual number of reports can be found in Fig. 1, categorized based on

Table 1
Descriptive characteristics of recombinant zoster vaccine reports in all populations for different age groups submitted to the vaccine adverse event reporting system, United States, October 20, 2017–April 26, 2024.

Report characteristic	<50 years Total = 577, n (%)	50–59 years Total = 15,409, n (%)	60–69 years Total = 20,157, n (%)	70–79 years Total = 12,035, n (%)	≥80 years Total = 3321, n (%)	All ages[a] Total = 66,849, n (%)
Sex[b]						
Male	177 (30.7)	4236 (27.5)	5880 (29.2)	3742 (31.1)	1053 (31.7)	18,395 (27.5)
Female	373 (64.6)	11,025 (71.6)	14,050 (69.7)	8159 (67.8)	2241 (67.5)	42,152 (63.1)
Median age[b] (IQR), years	40 (30–46)	55 (52–57)	64 (62–67)	73 (71–76)	83 (81–86)	64 (58–71)
Median TTO[b] (rang), days	0 (0–768)	1 (0–1766)	1 (0–1672)	1 (0–1698)	1 (0–1134)	1 (0–1766)
recombinant zoster vaccine given alone	544 (94.3)	13,815 (89.7)	18,446 (91.5)	11,341 (94.2)	3228 (97.2)	62,712 (93.8)
Seriousness						
Non-serious	567 (98.3)	15,018 (97.5)	19,568 (97.1)	11,570 (96.1)	3158 (95.1)	65,019 (97.3)
Serious, non-death	10 (1.7)	386 (2.5)	570 (2.8)	440 (3.7)	149 (4.5)	1744 (2.6)
Serious, death	0 (0.0)	5 (0.0)	19 (0.1)	25 (0.2)	14 (0.4)	86 (0.1)

IQR: interquartile range, TTO: time-to-onset.
[a] Includes reports missing or unknown age.
[b] Data missing or unknown for sex (6302,9.4 %), age (15,350, 23.0 %) and TTO (20,864, 31.2 %).

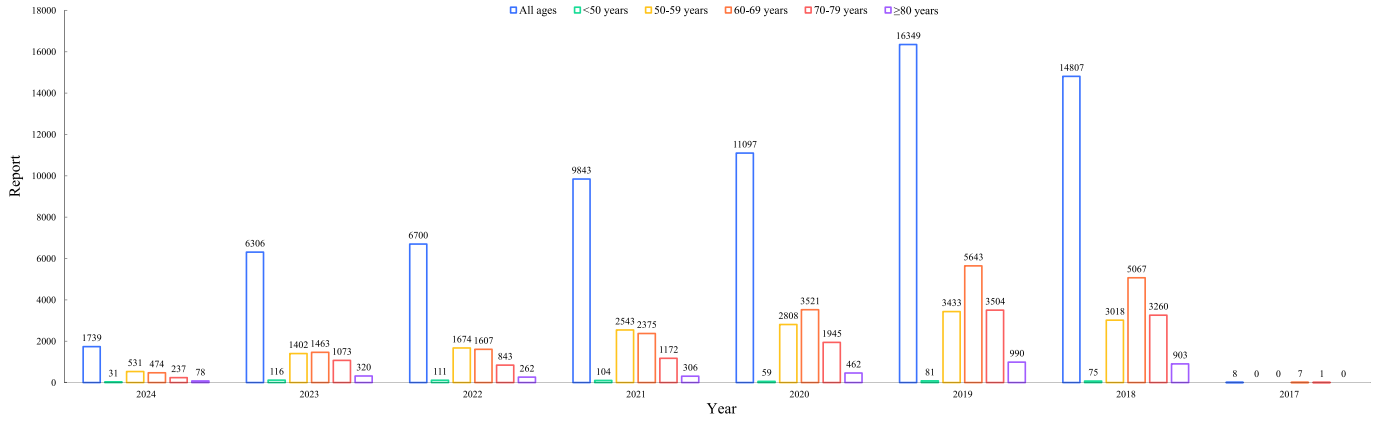

Fig. 1. Number of reports for recombinant zoster vaccine submitted to the vaccine adverse event reporting system by year and age groups in the United States, October 202,017–April 262,024.

distinct age cohorts. A total of 42,152 (63.1 %) reports were attributed to females, while males accounted for 18,395 (27.5 %) reports, with the remaining cases not specifying sex. In the available age data report, the median age was 64 years (IQR: 58–71 years), with a predominant proportion of individuals aged ≥50. Additionally, 68.8 % of the cases reported onset time of AEs, with a median TTO of 1 day (range: 0–1766 days). The distribution of all reports and serious reports by time from vaccination to symptom onset is illustrated in Fig. 2. The administration of RZV as a monotherapy was observed in 62,712 (93.8 %) reports. The most frequently co-administered vaccines included the influenza vaccine, tetanus toxoid, and pneumococcal conjugate vaccine, in accordance with recommendations for immunization schedules targeting older adults. The vast majority of reports, 65,019 (97.3 %), were categorized as non-serious and 1830 (2.7 %) reports were classified as serious, including 86 (0.1 %) deaths. Among all reports, the most commonly reported PTs after vaccination of RZV, included pyrexia 13,661 (20.4 %), pain 12,048 (18.0 %), chills 11,848 (17.7 %), headache 11,371 (17.0 %), injection site pain 10,389 (15.5 %), fatigue 9746 (14.6 %), pain in extremity 9461 (14.2 %), injection site erythema 7741 (11.6 %), myalgia 6404 (9.6 %) and nausea 6345 (9.5 %). The ten most frequently observed PTs in both non-serious and serious reports are presented in Table 2. Consistent patterns were observed in three categories, except for asthenia with 163 cases (8.9 %) and Guillain-Barre syndrome (GBS) with 145 cases (7.9 %) in serious reports (Table 2).

3.2. Serious and death reports

Among serious non-death reports, the majority of reported AEs were categorized under the SOC of nervous system disorders 1148 (65.8 %), with Guillain-Barre syndrome 79 (4.5 %), headache 73 (4.2 %) and dizziness 55 (3.2 %) being the most frequently reported symptoms (Table 3). The second most prevalent SOC was general disorders and administration site conditions, accounting for 1123 (64.4 %). Among these, asthenia 111 (6.4 %), pyrexia 111 (6.4 %), and pain 102 (5.9 %) were the most frequently reported symptoms.

We identified a total of 86 reports documenting deaths following vaccination with RZV in VAERS. Among these reports, we were able to obtain an autopsy report, death certificate, or medical record for 43 cases (Table 3). All death reports occurred in individuals who received RZV as a standalone vaccine, with a median age of 74 years (range: 50–94 years) and a median time from vaccination to death of 1 day (range: 0–238 days). Causes of death are presented in Table 3. The majority of fatalities were attributed to underlying common ailments in elderly individuals, and there is no substantiating evidence within the death reports or accompanying documentation suggesting any involvement or responsibility of RZV in these deaths.

3.3. Anaphylaxis

We have identified a total of 68 anaphylaxis reports (PTs: anaphylactic reaction 60, anaphylactic shock 8, anaphylactoid reaction 1, anaphylactoid shock 0), out of which 14 were classified as severe cases,

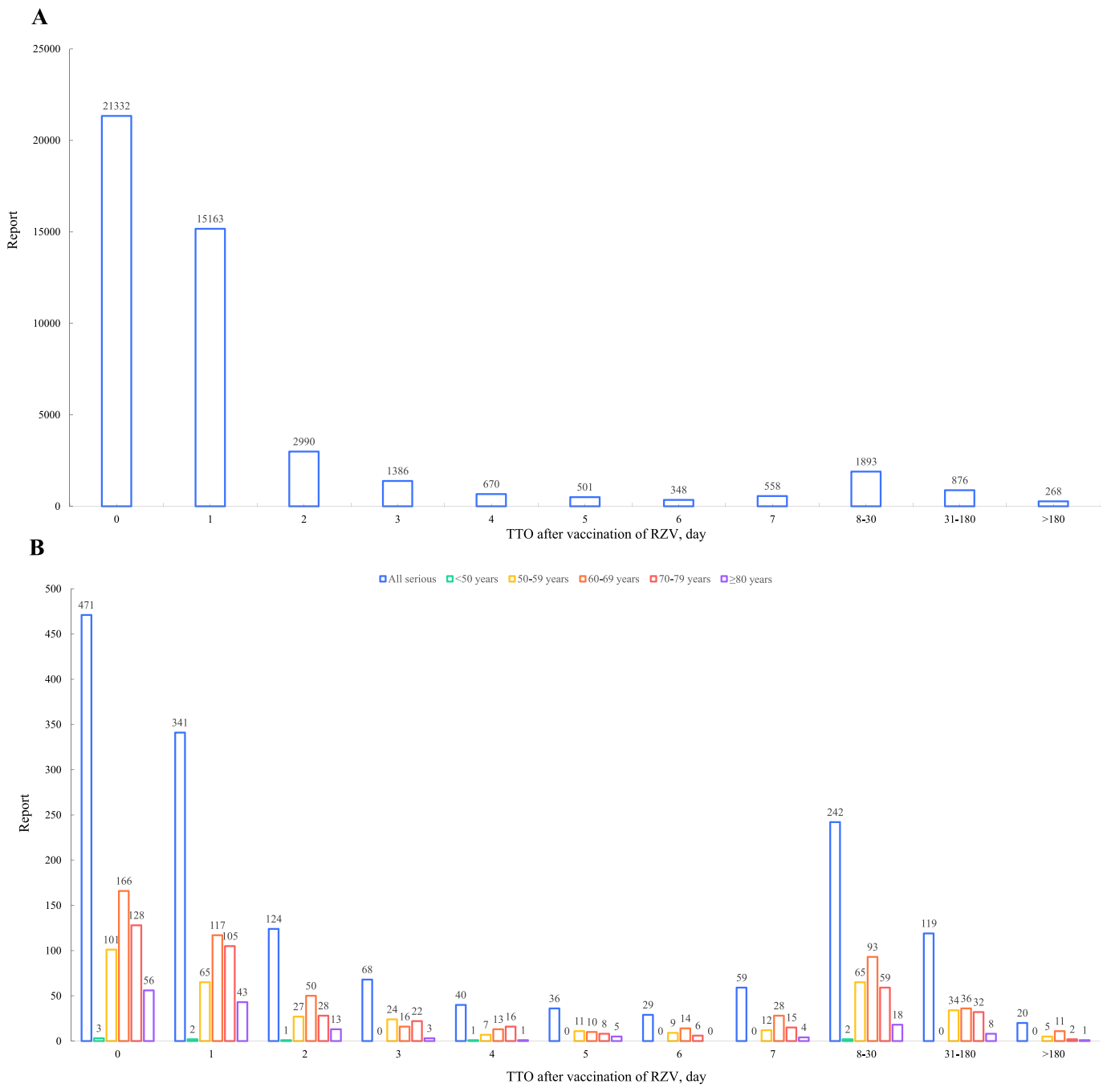

Fig. 2. Number of available reports for time-to-onset after vaccination of recombinant zoster vaccine from the vaccine adverse event reporting system, United States, October 202,017–April 262,024. (A) Time-to-onset of all reports; (B) Time-to-onset of serious reports by age group.

but none resulting in a fatal outcome. Among the 45 reports with documented onset intervals, symptoms were observed on the same day as vaccination in 30 cases. The median age of affected individuals was 63.5 years (range: 50–82 years). About 19 reports indicated a probable or potential alternative trigger for anaphylaxis, encompassing various factors such as food, drugs, and vaccines. The majority of reports documented anaphylaxis occurring after administration of RZV as a standalone vaccine, while only 3 reports provided information on the outcome following receipt of multiple vaccines.

3.4. Data mining

The application of data mining revealed a significant increase in disproportional reporting for 55 PTs (EB05 > 2), belonging to 11 primary SOCs, following vaccination with RZV, as presented in Table 4. The majority of disproportionately reported terms described local reactions commonly reported after vaccines, eye disorders, skin disorders, herpes zoster and complications. Revealing a disproportional reporting of an AE does not necessarily indicate a causal relationship, yet it can serve as a crucial threshold for conducting further assessment on the occurrence.

4. Discussion

While pre-licensing clinical trials can assess the safety of vaccines, it is essential to continue to monitor the vaccine's real-world safety profile

Table 2
Most commonly reported preferred term after vaccination with recombinant zoster vaccine in all populations, reports submitted to the vaccine adverse event reporting system, United States, October 202,017–April 262,024.

All reports preferred term	n (%)	Non-serious reports preferred term	n (%)	Serious reports preferred term	n (%)
Pyrexia	13,661 (20.4)	Pyrexia	13,382 (20.6)	Pyrexia	279 (15.3)
Pain	12,048 (18.0)	Pain	11,784 (18.1)	Pain	264 (14.4)
Chills	11,848 (17.7)	Chills	11,676 (18.0)	Pain in extremity	258 (14.1)
Headache	11,371 (17.0)	Headache	11,198 (17.2)	Fatigue	173 (9.5)
Injection site pain	10,389 (15.5)	Injection site pain	10,236 (15.7)	Headache	173 (9.5)
Fatigue	9746 (14.6)	Fatigue	9573 (14.7)	Chills	172 (9.4)
Pain in extremity	9461 (14.2)	Pain in extremity	9203 (14.2)	Asthenia[a]	163 (8.9)
Injection site erythema	7741 (11.6)	Injection site erythema	7692 (11.8)	Injection site pain	153 (8.4)
Myalgia	6404 (9.6)	Myalgia	6315 (9.7)	Nausea	151 (8.3)
Nausea	6345 (9.5)	Nausea	6194 (9.5)	Guillain-Barre syndrome[a]	145 (7.9)

[a] Not observed in either the all reports or the non-serious reports in the most commonly reported preferred term after vaccination of recombinant zoster vaccine.

in the post-licensure setting, especially for rare or less frequent AEs not observed during clinical trials. One of the primary sources of safety information for newly approved vaccines is routine post-marketing surveillance of spontaneously reported AEs. To our knowledge, this study is the first analysis to comprehensively evaluate the post-marketing safety of RZV using the latest VAERS data to investigate the potential link between RZV and its AEs. In our data, the AEs of RZV occurred more commonly in population aged ≥50 years and females (63.1 %), which was corresponding to the results of a post-marketing safety surveillance on RZV reporting that the individuals were mainly 50–69 years (62.1 %) and female (66.7 %) (Tavares-Da-Silva et al., 2020). The majority of the reported AEs of RZV (97.3 %) were non-serious and were generally consistent with the known vaccine safety observed in pre-licensing clinical research (Leroux-Roels et al., 2012; López-Fauqued et al., 2019). These AEs are usually low grade in intensity, self-limited and short in duration, and generally do not require medical intervention.

It was reported that injection site reactions were commonly reported for herps zoster vaccines, whereas systemic reactions including pyrexia and chills were commonly reported for RZV (Racine et al., 2020). According to the disproportionality analysis, the majority of reported AEs after vaccination of RZV include pyrexia (n = 13,661, 20.4 %), chills (n = 11,848, 17.7 %), headache (n = 11,371, 17.0 %) and injection site pain (n = 10,389, 15.5 %). In addition, fatigue, injection site extremity, injection site erythema, myalgia and nausea were also the most common general AEs, as reported in the RZV label (Food and Drug Administration, 2017). Some studies have shown that healthcare professionals make a decision not to give a second dose of RZV after observing local or systemic reactions. In clinical trials, about 17 % of RZV recipients had grade 3 adverse reactions (Cunningham et al., 2016; Lal et al., 2015). But these symptoms are self-limited and can be resolved within a few days. Since the effectiveness of a single dose of RZV has not been confirmed, health care providers may advise them to continue vaccination.

Although cardiovascular events were associated with wild-type varicella zoster virus infection, no significant increase in risk was found after varicella zoster virus infection (Minassian et al., 2015).

Table 3
Diagnostic categories of serious reports of recombinant zoster vaccine in system organ class level and causes of death for reports of death following recombinant zoster vaccine in all populations from the vaccine adverse event reporting system, United States, October 202,017–April 262,024.

Serious, non-death reports		Serious, death reports	
MedDRA SOC[a]	n (%)	Cause of death[b]	n (%)
Nervous system disorders	1148 (65.8)	Heart disease	21 (48.8)
General disorders and administration site conditions	1123 (64.4)	Fall	3 (7.0)
Investigations	881 (50.5)	Chest pain	2 (4.7)
Musculoskeletal and connective tissue disorders	778 (44.6)	Guillain-Barre syndrome	2 (4.7)
Skin and subcutaneous tissue disorders	557 (31.9)	Immune-mediated adverse reaction	2 (4.7)
Injury, poisoning and procedural complications	531 (30.5)	Shingles	2 (4.7)
Cardiac disorders	442 (25.3)	Stroke	2 (4.7)
Infections and infestations	428 (24.5)	Pulmonary failure	1 (2.3)
Psychiatric disorders	423 (24.3)	Difficulty breathing	1 (2.3)
Immune system disorders	414 (23.7)	Double pneumonia	1 (2.3)
Vascular disorders	406 (23.3)	Intracranial bleed	1 (2.3)
Gastrointestinal disorders	385 (22.1)	Parkinson's Disease	1 (2.3)
Respiratory, thoracic and mediastinal disorders	329 (18.9)	Possible drug interaction	1 (2.3)
Surgical and medical procedures	228 (13.1)	Respiratory failure	1 (2.3)
Social circumstances	152 (8.7)	Seizure	1 (2.3)
Eye disorders	140 (8.0)	Severe stomach upset	1 (2.3)
Metabolism and nutrition disorders	130 (7.5)		
Ear and labyrinth disorders	114 (6.5)		
Renal and urinary disorders	87 (5.0)		
Blood and lymphatic system disorders	56 (3.2)		
Neoplasms benign, malignant and unspecified	25 (1.4)		
Endocrine disorders	24 (1.4)		
Reproductive system and breast disorders	22 (1.3)		
Hepatobiliary disorders	19 (1.1)		
Product issues	7 (0.4)		
Congenital, familial and genetic disorders	1 (0.1)		
Pregnancy, puerperium and perinatal conditions	1 (0.1)		

MedDRA: medical dictionary for regulatory activities, SOC: system organ class.
[a] A report may have one or more assigned preferred terms and a preferred term may correspond to multiple SOCs.
[b] Among the 86 reports documenting death subsequent to recombinant zoster vaccine administration, 43 reports provided adequate information from a death certificate, autopsy report, or medical record to validate the occurrence of mortality and ascertain its underlying cause.

However, deaths due to heart disease (n = 21, 48.8 %) and stroke (n = 2, 4.7 %) have been reported to VAERS. One study observed a higher relative incidence of myocardial infarction between 43- and 84-days after vaccination (Totterdell et al., 2020). Of note, it is possible that some deaths in these populations were caused by cardiovascular events, whether or not they were vaccinated. Moreover, other post-marketing study has not found an increased risk of cardiovascular and cerebrovascular events after herpes zoster vaccine (Tseng et al., 2012). This study may not have enough evidence to prove that these cardiovascular

Table 4
MedDRA preferred terms with a significant disproportionality score grouped by system organ class for reports of recombinant zoster vaccine in all populations from the vaccine adverse event reporting system, United States, October 202,017–April 262,024.

MedDRA system organ class	MedDRA preferred term	n	EBGM (EBGM 05)
Eye disorders	Eyelid rash	36	3.2 (2.2)
	Keratitis	16	5.1 (2.9)
	Corneal oedema	11	7.8 (3.6)
	Keratic precipitates	4	12.8 (2.3)
Gastrointestinal disorders	Abdominal discomfort	1243	2.7 (2.6)
General disorders and administration site conditions	Injection site pain	10,389	2.7 (2.6)
	Injection site erythema	7741	2.6 (2.6)
	Injection site swelling	5500	2.3 (2.2)
	Influenza like illness	3798	4.2 (4.0)
	Injection site warmth	2986	2.2 (2.1)
	Injected limb mobility decreased	933	2.8 (2.6)
	Vaccine positive rechallenge	595	3.7 (3.4)
	Injection site inflammation	305	2.7 (2.4)
	Local reaction	252	2.7 (2.4)
	Injection site discolouration	202	2.8 (2.4)
	Extensive swelling of vaccinated limb	180	11.6 (9.2)
	Injection site vesicles	168	2.9 (2.5)
	Adverse drug reaction	106	2.6 (2.1)
	Injection site irritation	90	2.7 (2.2)
	Injection site scab	37	2.9 (2.1)
	Injection site streaking	33	3.5 (2.4)
	Administration site swelling	24	4.8 (3.0)
	Injection site macule	14	3.8 (2.1)
	Injection site exfoliation	13	7.8 (3.8)
	Administration site warmth	10	5.0 (2.5)
Infections and infestations	Herpes zoster	3962	3.3 (3.2)
	Oral herpes	329	3.2 (2.8)
	Ophthalmic herpes zoster	149	4.6 (3.8)
	Rash pustular	107	4.9 (4.0)
	Varicella	95	5.4 (4.3)
	Herpes simplex	70	3.1 (2.4)
	Herpes virus infection	58	3.0 (2.3)
	Pustule	51	3.1 (2.3)
	Genital herpes	49	4.7 (3.4)
	Herpes ophthalmic	18	4.9 (2.8)
Injury, poisoning and procedural complications	Corneal abrasion	8	4.8 (2.2)
	Eschar	5	6.8 (2.3)
Investigations	CSF white blood cell count negative	20	3.7 (2.3)
	Herpes simplex test positive	15	3.7 (2.1)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	736	4.3 (4.0)
	Musculoskeletal disorder	125	2.7 (2.3)
Nervous system disorders	Neuralgia	536	2.4 (2.2)
	Hyperaesthesia	195	3.3 (2.9)
	Post herpetic neuralgia	129	3.0 (2.5)
Psychiatric disorders	Middle insomnia	204	6.4 (5.4)
	Poor quality sleep	164	2.7 (2.3)
Renal and urinary disorders	Nocturia	20	4.1 (2.5)
Skin and subcutaneous tissue disorders	Erythema	4824	2.1 (2.0)
	Blister	1025	3.4 (3.1)
	Rash vesicular	662	2.8 (2.6)
	Pain of skin	291	2.3 (2.0)
	Scab	213	3.9 (3.4)
	Skin ulcer	73	3.9 (3.0)
	Blister rupture	23	3.4 (2.2)
	Transient acantholytic dermatosis	9	5.9 (2.7)

MedDRA: medical dictionary for regulatory activities, EBGM: empirical bayesian geometric mean; EBGM05, the lower limit of 95 % CI of EBGM.

deaths were attributed to RZV. Further clinical studies and investigations may provide greater support for identifying and validating cardiovascular and cerebrovascular outcome events.

Among the various adverse outcome events reported after immunization, neurological AEs are among the most serious and difficult to evaluate. In our study, GBS (n = 145) was a serious outcome AE, including 2 death. GBS is a rare, immune-mediated polyneuropathy that causes muscle weakness and paralysis. GBS has been tentatively associated with numerous vaccines, and in rare cases, an association with a specific vaccine appears to have been demonstrated based on biological or epidemiological evidence (Sejvar et al., 2011). A case series cohort study using two large national data sources in the US showed a statistically significant increased risk of GBS during the 42 days following RZV vaccination (Anderson et al., 2021). This study also found an estimated 3 cases of GBS per million vaccinations administered in adults aged ≥65 years. Another study also reported an increased risk of GBS following RZV, with a rate ratio of 6.3 (95 % CI, 1.8–21.9) for those 18–64 years and 4.1 (95 % CI, 1.9–8.7) for those ≥65 years (Chohan and Chohan, 2022). Despite the extensive sample size of the Vaccine Safety Datalink study, uncertainty persists regarding potential associations with GBS due to the limited number of confirmed GBS cases observed (Janusz et al., 2022; Nelson, 2020). Similarly, our disproportionality analysis did not detect a significant signal for GBS. In March 2021, the FDA placed a black box warning on RZV regarding the possible risk of acquiring GBS. Patients and clinicians should be aware of the risk of GBS, while considering the benefits of avoiding herpes zoster and its complications through an efficacious vaccine (Goud et al., 2021). In our study, among the 137 GBS reports, the time of symptom onset following vaccination was documented, with a median TTO of 8 days (IQR: 2–15 days), and 2 of the reports involved the combined use of COVID-19 vaccine.

Typically, AEs associated with vaccine reactogenicity occurred within the first few days after vaccination and generally lasted 3–4 days (Tavares-Da-Silva et al., 2020). In clinical trials, the median duration of all-grade general symptoms was 3.5 days or less in the RZV group (Dagnew et al., 2019). A postlicensure safety surveillance for RZV using electronic health record data showed systemic and local reactions occurred within 1–7 days, while cardiovascular events and several eye-related diseases were diagnosed within 1–42 days (Nelson et al., 2023). Another 10 year review of post-marketing safety of herpes zoster vaccine live demonstrated that the median TTO of injection-site reactions and central nervous system experiences were 2 days, while herpes zoster and herpes zoster-like rash were reported within 2–6 weeks postvaccination (Willis et al., 2017). The current study suggested that the TTO for RZV-related AEs was 1 day in all groups over 50 years old. The median TTO of post-marketing surveillance was consistent with clinical trials and previous studies.

Similar to other spontaneous public health reporting systems, VAERS exhibits certain limitations. First, the issues of reporting bias, underestimation, inconsistent data quality, diagnostic uncertainty of events, and completeness arise due to the voluntary nature of reporting. Second, although some AEs reported to VAERS may be attributed to the vaccine of interest, others could be linked to an underlying disease or condition, concurrent medications or other vaccines, or simply occur coincidentally shortly after vaccination. Third, due to the absence of denominator data and an unvaccinated comparison group in VAERS data, it is not

feasible to calculate and compare AE rates between vaccinated and unvaccinated individuals, thus precluding determination of any potential association between vaccination and increased risk of AEs. Fourth, with the exception of unambiguous biologically plausible cases (such as pain and redness at the injection site), it is insufficient to consider the mere quantity of reports as conclusive evidence for establishing a causal association between a vaccine and an AE. Despite its limitations, VAERS can often promptly identify preliminary signals or warnings of vaccine safety issues and facilitate further investigation in conjunction with other data sources such as epidemiologic studies and controlled trials.

5. Conclusion

Our pharmacovigilance study systematically explored and quantified the safety profile of RZV and obtained new safety information about RZV. AEs of RZV occurred more commonly in population aged ≥50 years and females, and the majority of the reported AEs were non-serious. In addition to cardiovascular events and falls, Guillain-Barre syndrome was the most common cause of death after RZV vaccination. The median TTO for RZV-related AEs was 1 day in all cohort groups over 50 years old. The current study, based on post-marketing data, is reassuring and reinforces the clinically acceptable safety profile of RZV.

Ethics approval and consent participate

This study was approved (No. 20220185) by the institutional ethics board of the Union Hospital of Tongji Medical College of Huazhong University of Science and Technology.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

Yamin Shu: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Wenxin Cheng:** Writing – original draft, Validation, Resources, Investigation. **Xucheng He:** Writing – original draft, Software, Methodology, Formal analysis. **Liu Huang:** Writing – review & editing, Supervision. **Wei Chen:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Qilin Zhang:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Data availability

All the data generated or analyzed during this study are included in this published article. The database used in this study is publicly available in website of https://vaers.hhs.gov/data/datasets.html.

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