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Review of the initial post-marketing safety surveillance for the recombinant zoster vaccine

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ABSTRACT

Background: The adjuvanted recombinant zoster vaccine (RZV) received its first marketing authorization in October 2017, for prevention of herpes zoster in individuals aged ≥50 years.
Methods: We summarized safety information, following RZV administration, received by GSK via spontaneous adverse event (AE) reports submitted by healthcare providers, vaccine recipients and other reporters. Observed-to-expected (O/E) analyses were performed for selected outcomes: reports of death, Guillain–Barré syndrome and Bell's palsy. Standard case definitions were used to assess individual case reports. Data mining, using proportional reporting ratio and time-to-onset signal detection methods, was employed to identify RZV-AE pairs with disproportionate reporting or unexpected time-to-onset distribution.
Results: Between October 13, 2017 and February 10, 2019, an estimated 9.3 million doses were distributed and GSK received 15,638 spontaneous AE reports involving RZV. Most reports were classified as non-serious (95.3%) and originated from the United States (81.7%), where the majority of doses were distributed. Among reports with age or sex reported, individuals were mainly 50–69-year-olds (62.1%) and female (66.7%). Of all reports, 3,579 (22.9%) described vaccination errors, of which 82.7% were without associated symptoms. Of all vaccination error reports, most described errors of vaccine preparation and reconstitution (29.7%), inappropriate schedule or incomplete course of administration (26.7%), incorrect route of administration (16.4%), and storage errors (12.9%). The most commonly reported symptoms were consistent with the known RZV reactogenicity profile observed in clinical trials, including injection site reactions, pyrexia, chills, fatigue, headache. O/E analyses for selected outcomes and data mining analyses for all reported AEs did not identify any unexpected patterns.
Conclusions: Review of the initial data from the post-marketing safety surveillance showed that the safety profile of RZV is consistent with that previously observed in pre-licensure clinical trials. Other studies are ongoing and planned, to continue generating real-world safety data and further characterize RZV.

1. Introduction

Herpes zoster (HZ), otherwise known as shingles, is typically a painful and debilitating disease that is caused by the reactivation of latent varicella-zoster virus (VZV). Primary VZV infection results in varicella (chickenpox), after which VZV becomes latent in neurons of the dorsal root and cranial nerve ganglia. With increasing age, when immunosenescence starts to manifest or when the

Abbreviations: ACIP, Advisory Committee on Immunization Practices; AE, adverse event; AESI, adverse event of interest; CD, case definition; gE, glycoprotein E; GBS, Guillain–Barré Syndrome; GSKMQ, GSK-customized MedDRA query; HCP, healthcare professional; HZ, herpes zoster; ICH, International Conference on Harmonisation; MedDRA, Medical Dictionary for Regulatory Activities; O/E, observed-to-expected; pIMDs, potential immune-mediated diseases; RZV, recombinant zoster vaccine; SMQ, standardized MedDRA query; TTO, time-to-onset; US, United States; VAERS, Vaccine Adverse Event Reporting System; VZV, varicella-zoster virus; ZVL, live attenuated virus zoster vaccine.

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immune system is impaired, the risk of VZV reactivation, and consequently of developing HZ, rises [1]. Incidence rates of HZ in the general population range from three to five per 1,000 person-years in various countries, and are consistently increasing with age [2]. Of all HZ episodes, 68% occur in adults aged ≥50 years [3]. HZ complications occur in nearly 25% of persons with HZ and become more frequent with age [4]. The most common HZ complication is post-herpetic neuralgia, which develops in around 10–30% of patients with HZ [2,3,5], followed by HZ ophthalmicus, which occurs in 10–20% of HZ patients [2,6–8]. Both HZ and its complications have a substantial impact on the patients' quality-of-life [9], thus reinforcing the need for vaccination to prevent HZ.

Pre-licensure data showed that the adjuvanted recombinant zoster vaccine (RZV; *Shingrix*, GSK) is highly efficacious in preventing HZ in individuals ≥50 years of age and supported a favourable benefit-risk profile of RZV in all age-groups studied [10–12]. RZV received its first marketing authorization for HZ prevention in adults ≥50 years of age in Canada, followed by the United States (US), both in October 2017, and was subsequently licensed in the European Union (March 2018), Japan (April 2018), Australia (July 2018), and China (May 2019).

RZV consists of a recombinant subunit VZV glycoprotein E (gE) combined with an Adjuvant System, $AS01_B$. The truncated gE antigen is provided in a lyophilized form (a white powder) in monodose vials. $AS01_B$ (a liposome-based adjuvant comprising 3-*O*-desacyl-4′-monophosphoryl lipid A, a Toll-like receptor 4 ligand and QS-21, a saponin extracted from the bark of the *Quillaja saponaria* Molina tree) is provided in a liquid form in separate monodose vials (0.5 ml/dose) and is used for reconstitution prior to injection. RZV is administered as a two-dose intramuscular series (two to six months apart) [13].

Based on sales data, an estimated 9.3 million doses of RZV were distributed up to February 2019, of which around 8.4 million in the US only. Continued collection and evaluation of safety data following the introduction of a new vaccine to the general population is pivotal for the early detection and investigation of signals temporally-associated with vaccination.

This article summarizes the post-marketing safety surveillance data involving RZV, reported worldwide to GSK from spontaneous sources during the period October 13, 2017 – February 10, 2019.

2. Methods

An analysis of spontaneous report data involving RZV vaccination extracted from the GSK safety database was conducted for the analytical period October 13, 2017 – February 10, 2019. Spontaneous report data are collated from unsolicited communications describing one or more adverse events (AEs) that occur in patients who were given RZV. These communications (referred to as "spontaneous reports") are either submitted to GSK directly and voluntarily from individual reporters (who may be reporting for themselves or others) via local reception/call centres or are collected by GSK from the scientific literature or the interactive digital media. Attempts for obtaining necessary follow-up information are made to obtain supplementary clinical information needed for the scientific evaluation of the cases. The individual reporters can include healthcare professionals (HCPs), regulatory authorities, consumers and others. All reported AEs are coded using the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities (MedDRA) [14]. One spontaneous report can contain more than one AE, reported by the same individual. AEs are classified as serious if meeting the ICH regulatory definition: any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect in the offspring, or is a medically important event [15].

The review and analyses of spontaneous report data extracted from the GSK safety database (Oracle Argus) and other internal data sources was performed via an in-house Spotfire web application, the Signal Mining and Management (SMM) tool.

Data from external sources were reviewed separately for signal detection purposes, including spontaneous report data from external public safety databases: the US Vaccine Adverse Event Reporting System (VAERS), the Canada Vigilance Adverse Reaction Online Database, and the European Medicines Agency (EMA) EudraVigilance system.

In the SMM tool, quantitative signals for RZV–AE pairs were flagged if there was disproportionate reporting or evidence of an unexpected time-to-onset (TTO) distribution [16,17]. The chosen method for the disproportionality analysis was the stratified proportional reporting ratio (PRR) with a quantitative signal generated when the lower limit of the 95% confidence interval of the stratified PRR is above the threshold of 2 and when at least 3 RZV spontaneous cases were reported. The comparator was restricted to populations ≥50 years of age (the target population) and from countries in which RZV is distributed. A quantitative signal of unexpected temporal relationship for a RZV–AE pair is generated when its TTO distribution within 60 days post-vaccination is significantly different from the same AE reported with comparators or from the reported TTO distribution of other RZV–AE pairs. TTO was calculated from the date of vaccination with any dose of RZV (Day 0) to AE start date, for reports containing available information. The TTO signal detection used a quantitative signal threshold of 1% (p-value < 0.01) on the p-values of both Kolmogorov–Smirnov tests (across products and across events [17]) and there was no restriction to the background (comparator). GSK adopted the safety signal definition of the Council for International Organizations of Medical Sciences-VIII: "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action" [18].

AEs of interest (AESIs) analyzed here do not imply causal association with RZV vaccination. For RZV, AESIs included potential immune-mediated diseases (pIMDs) [19], and other conditions of interest due to imbalances noted between treatment groups in pre-licensure clinical trials, or conditions of general interest when assessing vaccine safety in the target population (i.e., anaphylaxis, ocular events that might be due to vasculitis or inflammation, seizures/convulsions, acute myocardial ischemia, stroke/cerebrovascular accident, and supraventricular tachyarrhythmias). The groups of AESIs were searched using standardized or customized (in-house) MedDRA (version 21.0) queries (SMQs and GSKMQs, respectively) (Appendix 1). When available, standardized case definitions (CD) from the Brighton Collaboration were applied during reviews to assess the level of diagnostic certainty of AEs [20].

The reactogenicity is a subset of AEs (that occur soon after immunization and are a physical manifestation of the inflammatory response to vaccination), and includes injection-site reactions (pain, redness, swelling) as well as systemic symptoms (fever, myalgia, fatigue, chills headache, malaise or gastrointestinal symptoms such as nausea, vomiting and diarrhea) [21]. We defined severe reactogenicity as symptoms causing quality-of-life impairment, disability or preventing normal daily activities (see search strategy in Appendix 1).

A "confirmed vaccination failure" was defined as the occurrence of HZ clinical symptoms and laboratory confirmation of VZV infec-

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tion (i.e. VZV-positive polymerase chain reaction, culture, immunohistochemical staining, or other tests that strongly suggest VZV infection and which have been performed in the course of a medical evaluation) occurring 30 days or later after full vaccination schedule with RZV. A "suspected vaccination failure" was defined as the occurrence of HZ clinical symptoms suggestive of VZV infection occurring 30 days or later after full vaccination schedule with RZV.

Observed-to-expected (O/E) analyses were performed for mortality (all-cause) and the two most frequently reported pIMDs, GBS and Bell's palsy. Background incidence rates were defined by the number of incident reports of a condition or event occurring naturally in the population, expressed in person-time [22]. These age and country-stratified background estimates were obtained from the literature [23–29], considering populations with similar characteristics to the RZV target population. O/E analyses were performed for the selected events to determine whether the observed number of a reported AE corresponded to the number of events expected to occur within a predefined risk period, under the null hypothesis of no association between vaccination and the event. For all-cause mortality, all reports of death temporally-associated with vaccination were reviewed medically and an O/E analysis was performed considering a risk period of seven days (Day 0–Day 6) after immunization. Time to death was used to assign cases to the risk period of seven days. Cases with unknown time to death were conservatively included in the analysis. For GBS, all reports were reviewed based on Brighton Collaboration diagnostic levels [30], and an O/E analysis was performed considering levels 1 to 4 of diagnosis certainty and a risk period of 42 days (Day 0–Day 41) [30–32]. For Bell's palsy, all reports were reviewed based on Brighton Collaboration diagnostic levels [33] and an O/E analysis was performed considering levels 1 to 4 of diagnosis certainty and a risk period of either seven (Day 0–Day 6) or 30 days (Day 0–Day 29) following vaccination. Reports with an unknown TTO were included in the O/E analyses. For GBS and Bell's palsy, AE onset was used to assign cases to the respective risk windows. Cases with unknown AE onset were conservatively included in the analyses.

The expected number of AEs within a pre-determined risk period was calculated using the following formula: number of expected events (N_e) equals the sum over all age strata of background incidence rate within age stratum (Inc_s), multiplied by the number of doses of vaccine administered within age stratum (Nd_s), multiplied by the pre-determined risk period ($N_e = \sum_s Inc_s \times Nd_s \times Risk\ period$) [22].

3. Results

3.1. Overview of spontaneous adverse event reports

During the analytical period, 9,323,118 doses of RZV were distributed globally and GSK received 15,638 spontaneous reports of individuals documenting 37,697 total AEs (of which 36,539 non-serious and 1,158 serious AEs) following RZV vaccination. Table 1 displays characteristics of the spontaneous reports after RZV vaccination.

A total of 12,770 (81.7%) reports originated from the US, where most RZV doses were distributed. In total, 14,897 (95.3%) reports were non-serious and the remaining 741 (4.7%) reports fulfilled the ICH "serious" criteria, which included nine reports of death.

Among the 6,641 reports where the age was documented, 62.1% were from individuals 50–69 years old and 35.1% from individuals ≥70 years old. The remaining 2.8% were from individuals <50 years old, with reports of vaccination error predominating. Among the 10,539 reports where the sex was documented, 66.7% were female and 33.3% were male.

Table 1
Characteristics of spontaneous RZV reports.

	N	%
Seriousness		
Non-serious	14,897	95.3
Serious[a]	741	4.7
Country		
United States	12,770	81.7
Canada	2,646	16.9
Germany	213	1.4
Belgium	2	0.0
Spain	2	0.0
United Kingdom	2	0.0
Austria	1	0.0
Republic of Korea	1	0.0
Switzerland	1	0.0
Age		
<50 years[b]	186	2.8
50–69 years	4,121	62.1
≥70 years	2,334	35.1
Median age (range)	65 years (4 months[b]–100 years)	
Sex		
Male	3,506	33.3
Female	7,033	66.7
RZV dose		
Dose 1	5,863	37.5
Dose 2	5,504	35.2
Unknown	4,271	27.3
Reporter type		
Health care provider	11,760	75.2
Other	3,878	24.8

RZV, recombinant zoster vaccine; N, number of reports for each category; %, percentage from total number of reports (N = 15,638) for seriousness, country, dose and reporter type and from total number of reports with age/sex documented for sex and age.
Analytical period: October 13, 2017 – February 10, 2019.
[a] Includes hospitalization, prolongation of existing hospitalization, life-threatening illness, permanent disability, congenital anomaly or birth defect, and death.
[b] RZV is not approved for this age group.

HCPs submitted 11,760 reports (75.2%), of which 6,482 (55.1%) were by pharmacists. Of all reports, 148 (0.9%) described co-administration with other vaccine(s) on the same calendar day and no unusual pattern of AEs was observed compared with those reported following RZV alone. The most commonly co-administered vaccines were seasonal influenza, diphtheria-tetanus-pertussis (reduced antigen) and pneumococcal vaccines.

Quantitative signals of the RZV–AE pairs during the analytical period were flagged for common AEs directly or indirectly associated to the vaccine reactogenicity (e.g. injection site reactions, pyrexia, chills, headache, fatigue, etc.), for other adverse reactions listed in RZV local prescribing information leaflets (e.g. urticaria, rash), as well as for some AEs featuring vaccination errors (e.g. incorrect dose or incorrect route of product administration) or those associated to the disease targeted by RZV, i.e. HZ (Appendix 2). The prescribing information leaflet is a document included in the package of any medication, such as the RZV vaccine, that provides information for medical professionals and patients about the medication and its use, including indication, administration, precautions and potential side effects.

3.2. Common adverse events

During the analytical period, the most frequently reported symptoms following RZV vaccination were consistent with the vaccine reactogenicity (Table 2, Fig. 1). Overall, a similar reporting pattern was observed by age (data not shown).

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More specifically, 4,639 reports described symptoms potentially linked to the vaccine reactogenicity (see search strategy in Appendix 1). This corresponded to a reporting rate of 49.8 reports per 100,000 doses distributed. Of these, 2,849 (61.4%) described injection site reactions, with pain being the most commonly reported (Appendix 3). Most of these reports were non-serious (95.9%), from individuals 60–69 years old (38.9% of reports for which the age was documented) and reported in females (71.3% of reports for which the sex was documented). When described, vaccine reactogenicity symptoms occurred within the first days after vaccination and generally lasted 3–4 days. Overall, the reporting frequency of reactogenicity symptoms was similar in the different age strata, with a tendency to report more injection site reactions in individuals ≥70 years of age, while individuals 50–69 years of age more commonly reported systemic reactogenicity symptoms (data not shown).

Of the 15,638 reports, 805 (5.1%) described symptoms potentially linked to severe reactogenicity (see search strategy in Appendix 1). Most of the 805 reports were non-serious (81.4%), from individuals 60–69 years old (39.3%) and reported in females (74.2% of reports for which the sex was documented). Of these, the most commonly reported AEs were: decreased mobility of the injected arm (1.8 reports per 100,000 doses distributed) and extensive swelling of the injected arm (1.4 reports per 100,000 doses distributed). When described, these events occurred within the first few days after vaccination and generally lasted 3–4 days, although in rare occasions, symptoms persisted for one week or more.

3.3. Vaccination errors

In January 2018, a safety signal was identified due to the high percentage of reports (52% of all reports received worldwide) describing vaccination errors. In the US, the percentage of vaccination errors decreased from 70% in January 2018 to 25% in June 2018 and has since remained stable (ranging between 18% and 30%). In Germany and Canada, the proportion of vaccination errors remained relatively low (around 20%) and stable (Fig. 2).

Of all spontaneous reports, there were 3,579 (22.9%) reports of vaccination errors following RZV. Most of these described more than one error in a single report. An overview of the vaccination error reports by MedDRA high level terms and preferred terms is presented in Appendix 4.

Of all vaccination error reports, 82.7% were without associated symptoms, 17.3% were associated to symptoms (mostly injection site reactions following subcutaneous route of administration). No other unusual pattern of AEs was observed.

Most vaccination errors (N = 1,062; 29.7%) were errors of preparation and reconstitution, followed by inappropriate/incomplete course of administration (N = 956; 26.7%), incorrect route of administration (N = 585; 16.3%), and storage errors (N = 463; 12.9%) (Table 3). Among the errors during vaccine preparation or reconstitution, the most common were due to the administration of the $AS01_B$ adjuvant system only or mixing the RZV lyophilized antigen with a diluent rather than the supplied adjuvant system. Among the reports of inappropriate/incomplete course of administration, the errors described were: a time interval between doses too long, or too short, or incomplete course of vaccination (i.e. only one dose administered). Among the reports of incorrect route of administration, RZV was most commonly given subcutaneously instead of intramuscularly. Among the 463 reports of storage errors, the most common error (N = 215; 46.4%) was storage in the freezer instead of the refrigerator. In addition, among the 463 product storage errors that occurred, 103 (22.2%) were intercepted and the vaccine was not administered, and in the remaining 360 (77.8%) the vaccine was administered.

Table 2
Common adverse events following RZV vaccination.

Symptom[a]	N (%)[b]	Reporting rate per 100,000 doses distributed
Injection site pain	1,699 (10.9)	18.2
Pyrexia	1,658 (10.6)	17.8
Pain in extremity	1,466 (9.4)	15.7
Pain	1,326 (8.5)	14.2
Chills	1,240 (7.9)	13.3
Injection site erythema	1,221 (7.8)	13.1
Fatigue	1,085 (6.9)	11.6
Headache	1,076 (6.9)	11.5
Influenza like illness	866 (5.5)	9.3
Herpes zoster	837 (5.4)	9.0
Myalgia	802 (5.1)	8.6
Injection site swelling	787 (5.0)	8.4
Erythema	649 (4.2)	7.0
Malaise	647 (4.1)	6.9
Nausea	556 (3.6)	6.0
Rash	540 (3.5)	5.8
Injection site warmth	403 (2.6)	4.3
Pruritus	321 (2.1)	3.4
Arthralgia	305 (2.0)	3.3.
Peripheral swelling	299 (1.9)	3.2
Asthenia	246 (1.6)	2.6
Dizziness	244 (1.6)	2.6
Swelling	241 (1.5)	2.6
Injection site pruritus	232 (1.5)	2.5
Feeling abnormal	226 (1.4)	2.4
Injection site rash	201 (1.3)	2.2
Diarrhea	171 (1.1)	1.8
Urticaria	169 (1.1)	1.8
Injected limb mobility decreased	165 (1.1)	1.8

RZV, recombinant zoster vaccine; N, number of reports for each symptom; %, percentage from total number of reports (N = 15,638).
Analytical period: October 13, 2017 – February 10, 2019.
[a] Presented as MedDRA preferred term.
[b] A report may describe more than one symptom. Only reports with a percentage of >1% from the total number of reports are shown.

3.4. Serious reports

A total of 741 (4.7%) reports were serious, including nine reports of death. The most commonly reported symptoms in serious reports were HZ (N = 207; 27.6%), pyrexia (N = 72; 9.6%), pain in extremity (N = 69; 9.2%), and pain (N = 63; 8.4%) (Table 4).

3.5. Fatal reports

A total of nine deaths after receipt of RZV were reported. When described, median age was 84 years (range = 62–100 years). The interval from vaccination to onset of symptoms was described in three reports (6.5 h, 61 and 61 days after unspecified dose of RZV) and the interval from vaccination to death was described in four reports (same day, three days, 61 and 61 days after a dose of RZV).

Of all reports, five lacked sufficient information for adequate medical assessment. Of the remaining four reports, one individual was possibly immunosuppressed with a pre-existing primary membranous nephropathy undergoing treatment with rituximab, and died at an unspecified time after RZV vaccination possibly due to sepsis; two individuals who had cardiac risk factors (including aortic stenosis in one patient and chronic hypertension and diabetes mellitus for the other), died on the same day and three days after RZV vaccination, respectively, and their cause of death was reportedly associated to cardiovascular disease; finally, one individual was diagnosed with GBS, assessed as Brighton Collaboration level 4 [30], at an unspecified time after immunization with the second dose of RZV and an unspecified quadrivalent influenza

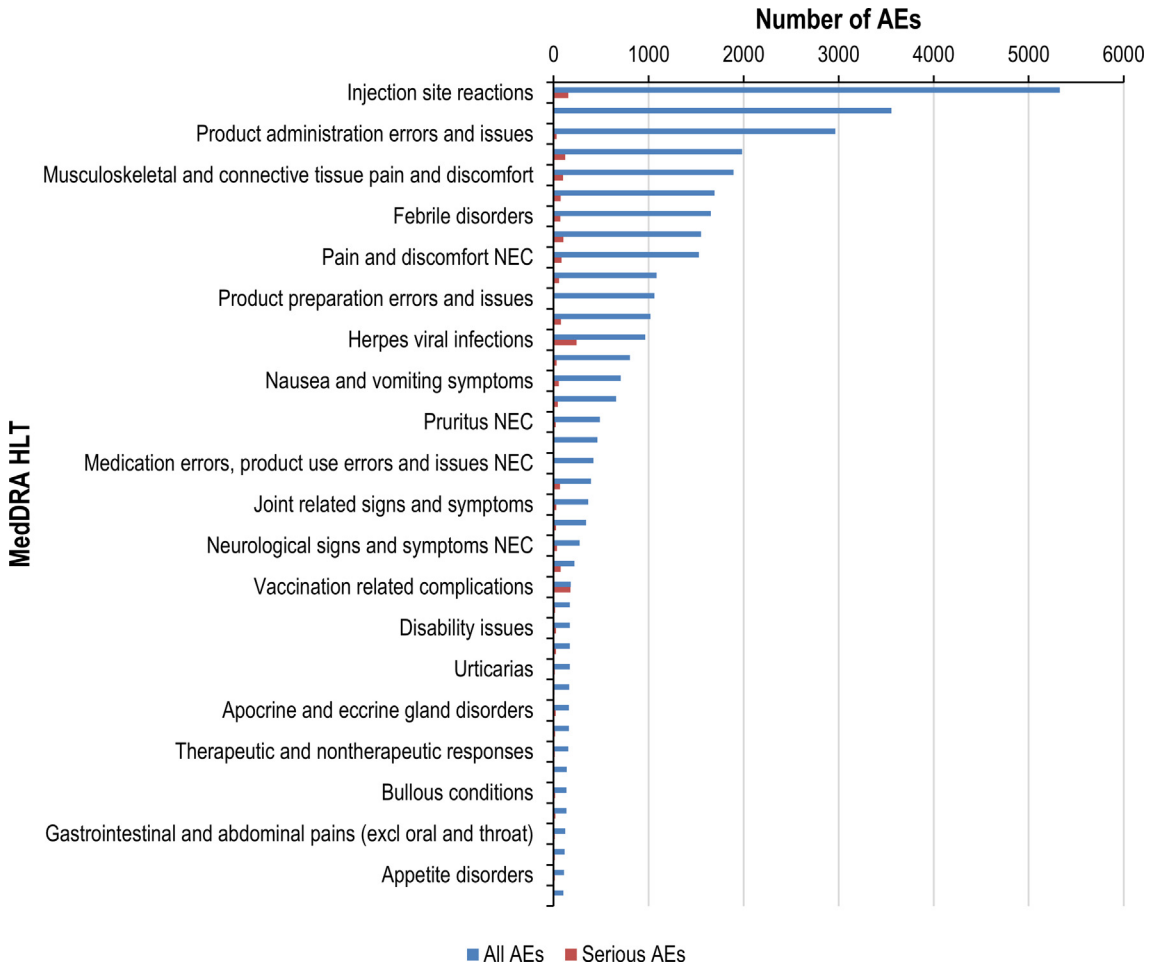

Fig. 1. Common adverse events following RZV vaccination by MedDRA high level term. Footnotes: RZV, recombinant zoster vaccine; AE, adverse event; NEC, not elsewhere classified. Analytical period: October 13, 2017 – February 10, 2019. A report may describe more than one AE. MedDRA High Level Terms (HLTs) contain clinically relevant grouping of AE terms. Only MedDRA HLTs accounting for a number of >100 AEs are shown.

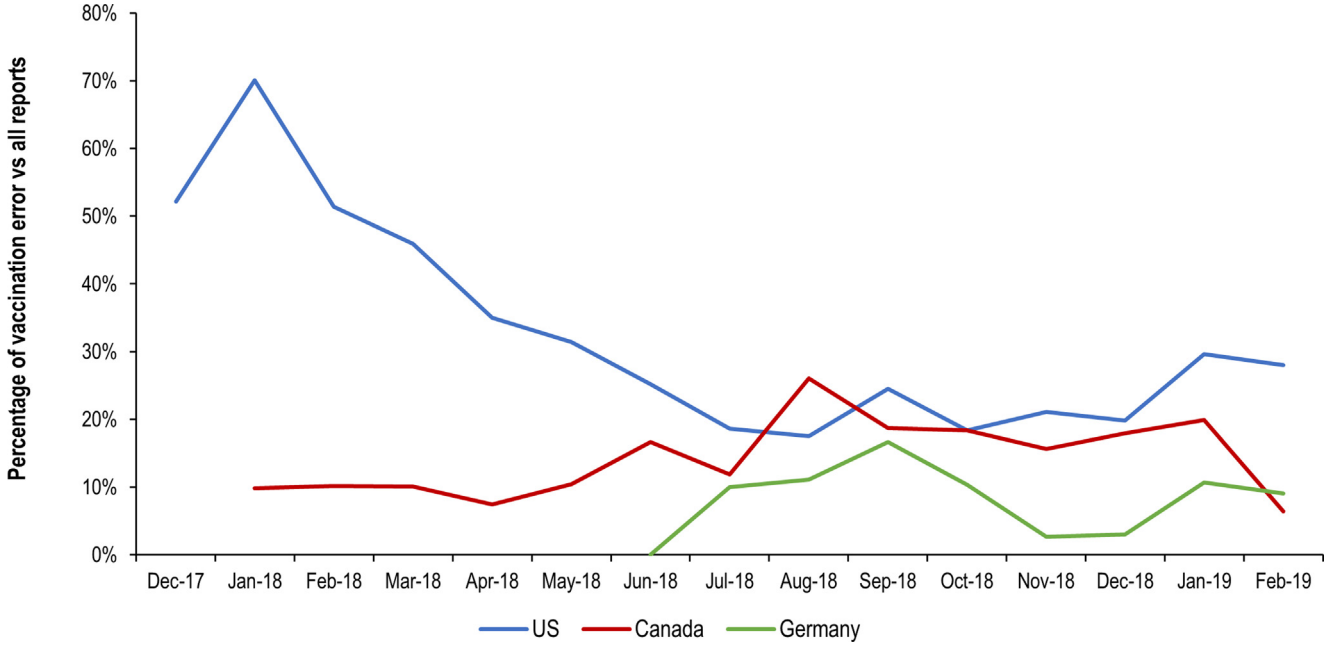

Fig. 2. Evolution of the proportion of vaccination error reports versus all reports following RZV vaccination, by country. Footnotes: RZV, recombinant zoster vaccine. Analytical period: October 13, 2017 – February 10, 2019.

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Table 3
Vaccination errors following RZV vaccination.

Vaccination error[a]	N (%)[b]
Product preparation/reconstitution error	1,062 (29.7)
Inappropriate/incomplete course of administration	956 (26.7)
Incorrect route of administration	585 (16.4)
Product storage error	463 (12.9)
Other error	513 (14.3)

RZV, recombinant zoster vaccine; N, number of vaccination errors for each category; %, percentage from total number of reports of vaccination errors (N = 3,579). Analytical period: October 13, 2017 – February 10, 2019.
[a] Presented as MedDRA customized groups; each group contains multiple MedDRA preferred terms.
[b] A report may describe more than one error.

Table 4
Commonly reported symptoms in serious reports, following RZV vaccination.

Symptom[a]	N (%)[b]	Reporting rate per 100,000 doses distributed
Herpes zoster	207 (27.6)	2.2
Pyrexia	72 (9.6)	0.8
Pain in extremity	69 (9.2)	0.7
Pain	63 (8.4)	0.7
Headache	58 (7.7)	0.6
Fatigue	56 (7.5)	0.6
Injection site pain	51 (6.8)	0.6
Chills	48 (6.4)	0.5
Rash	45 (6.0)	0.5
Erythema	44 (5.9)	0.5
Cellulitis	42 (5.6)	0.5
Nausea	41 (5.5)	0.4
Malaise	39 (5.2)	0.4
Loss of consciousness	35 (4.7)	0.4
Myalgia	34 (4.5)	0.4
Influenza like illness	31 (4.1)	0.3
Injection site erythema	31 (4.1)	0.3
Asthenia	29 (3.9)	0.3
Peripheral swelling	29 (3.9)	0.3
Dizziness	28 (3.7)	0.3
Paresthesia	28 (3.7)	0.3
Ophthalmic herpes zoster	27 (3.6)	0.3
Facial paralysis	25 (3.3)	0.3
Arthralgia	24 (3.2)	0.3
Hypesthesia	23 (3.1)	0.3
Neuropathy peripheral	21 (2.8)	0.2
Hyperhidrosis	20 (2.7)	0.2
Injection site swelling	20 (2.7)	0.2

RZV, recombinant zoster vaccine; N, number of serious reports for each symptom; %, percentage from total number of serious reports (N = 741).
Analytical period: October 13, 2017 – February 10, 2019.
[a] Presented as MedDRA preferred term.
[b] A report may describe more than one symptom. Only reports with a percentage of >2.5% from the total number of reports are shown.

vaccine, and possibly died due to GBS-associated complications one week after diagnosis of this condition.

The O/E analysis was performed for all-cause mortality considering a risk period of seven days following vaccination and was found to be below the expected range, possibly indicating a very high underreporting of this outcome (Fig. 3, Appendix 5).

3.6. Potential immune-mediated diseases

A total of 105 reports (from 104 individuals) encompassing 114 pIMDs (see search strategy in Appendix 1) were received during the analytical period. This corresponded to a reporting rate of 1.1 reports per 100,000 doses distributed. The reported events were distributed over a range of body systems and disease categories (Table 5). There was no evidence for disproportionate reporting of any of these events.

Seventy-three (69.5%) reports were received from the US, 30 (28.6%) from Canada and two (1.9%) from Germany. The age ranged between 50 and 95 years. All reports with documented TTO occurred within 60 days post-vaccination (Fig. 4), and more than half occurred within 1 week after vaccination.

Of all spontaneous reports, 179 reports concerned individuals who had reported a pre-existing pIMD in the medical history and who also reported an AE after vaccination with RZV. Seventeen of these patients reportedly had apparent flares of the pre-existing disease after vaccination, most common of which were rheumatoid arthritis or polymyalgia rheumatica. All these episodes lacked sufficient clinical information for adequate medical assessment.

O/E analyses were performed for GBS and Bell's palsy (the two most frequently reported pIMDs). For GBS, the O/E analyses of reports, assessed as Brighton Collaboration level 1 to 4 of diagnostic certainty and considering a risk period of 42 days following vaccination, were found to be below the expected number considering several scenarios of underreporting and background incidence rates (Fig. 5A). For Bell's palsy, the O/E analyses of reports, assessed as Brighton Collaboration level 1–4 of diagnostic certainty and considering a risk period of seven or 30 days following vaccination, were found to be below the expected number considering several scenarios of underreporting and background incidence rates and for both risk periods (Fig. 5B and C, Appendices 6 and 7).

3.7. Herpes zoster, including herpes zoster-like rash and complications

A total of 865 spontaneous reports documented 837 HZ events and 50 HZ-related complications. The 50 HZ-related complications were: HZ ophthalmicus (N = 25; 0.3 reports per 100,000 doses distributed), post-herpetic neuralgia (N = 21; 0.2 reports per 100,000 doses distributed), two reports of HZ with neurological infection for which limited information was available for assessment, and two reports of HZ oticus (one of which lacked sufficient information for assessment and for the other the clinical picture was not compatible with Ramsay Hunt syndrome). Laboratory confirmation of VZV infection (i.e. VZV-positive polymerase chain reaction, culture, immunohistochemical staining, or other tests) was typically not reported.

Of the 865 case reports of HZ or HZ-related complications, 178 met the criteria for a suspected or confirmed vaccination failure (see search strategy in Appendix 1 and definitions in Section 2).

Of these, 176 reports (1.9 reports per 100,000 doses distributed) were considered as "suspected vaccination failure" and two reports (0.02 reports per 100,000 doses distributed) were confirmed vaccination failure. Most suspected or confirmed vaccination failure reports were from Canada (68.5%) and from a non-medically confirmed source, which could explain the lack of information. The outcome was unknown or not reported in 177 reports.

3.8. Other events of medical interest

The evaluation using the SMQ anaphylaxis (see narrow search in Appendix 1) retrieved a total of 10 reports of anaphylaxis (MedDRA PTs: Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction). Of these, two were assessed as possibly vaccine-related and Brighton Collaboration for anaphylaxis CD level 2 [34], corresponding to a reporting rate of 0.02 reports per 100,000 doses distributed.

Reports of other events of medical interest following RZV vaccination, such as ocular events that might be due to vasculitis or inflammation, seizures/convulsions, acute myocardial ischemia, stroke/cerebrovascular accident, or supraventricular tachyarrhythmias (see search strategy in Appendix 1; data not shown), were infrequent and accounted for <0.1% of the total reports. There was no evidence for disproportionate reporting of these events.

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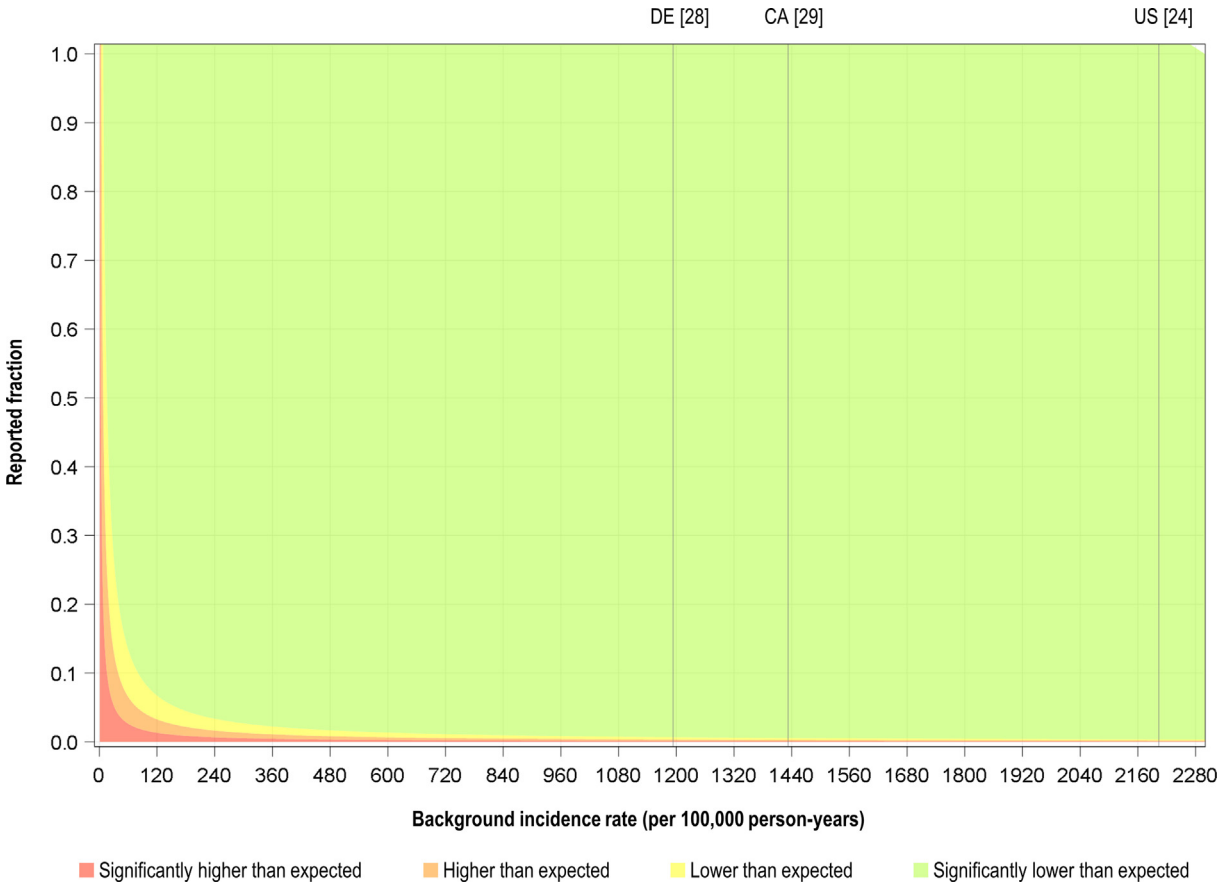

Fig. 3. All-cause mortality: Heat map of the observed-to-expected (O/E) analyses conclusions considering different scenarios of mortality rate and reported fraction. Footnotes: DE, German mortality rate adjusted by age to the German RZV exposed population [28]; CA, Canadian mortality rate adjusted by age to the Canadian RZV exposed population [29]; US, United States mortality rate adjusted by age to the RZV exposed population in the United States [24]. Risk period: 7 days; doses distributed: 9,323,118; observed cases: 7. Analytical period: October 13, 2017 – February 10, 2019. Note: This figure represents a visual framework which enables independent reviewers to draw their conclusions by making their own assumptions about two sources of uncertainty. The background incidence rate and the underreporting were considered the two major sources of uncertainty. Therefore, different scenarios of spontaneous reports, regardless of the causality, among those actually occurring within the risk period, labelled "Reported fraction" and different background incidence rates, in a range chosen to include all incidence rate references, were used to perform the O/E analyses and to determine if the observed number of reports was: (i) significantly higher than expected (expected below the lower limit of the Poisson exact 95% confidence interval computed from the observed reports); (ii) higher than expected; (iii) lower than expected; (iv) significantly lower than expected (expected above the upper limit of the Poisson exact 95% confidence interval computed from the observed reports).

4. Discussion

While pre-licensure clinical trials assess the vaccine's safety profile, continued monitoring of the vaccine's real-world safety profile in the post-licensure setting is essential. One of the main sources of safety information for newly approved vaccines (as for any medication) is the routine post-marketing surveillance of AEs reported spontaneously. These AEs, while temporally-associated with the product's use, may not necessarily be causally associated with it [35]. One of the strengths of the passive safety surveillance is the rapid collection of data following real-world use of the product in the general population, including individuals with concurrent illnesses treated with concomitant medications or high-risk individuals for whom pre-licensure clinical trial data is typically limited, as well as rare or less frequent events not observed in pre-licensure clinical trials. Limitations of post-marketing passive surveillance that relies on spontaneous reports include reporting bias (which can be due to country-specific reporting environment, influences of media, or length of time the product has been on the market), underreporting, missing information such as lack of denominator data, misclassification or incorrect information, and the absence of an adequate comparator group [36]. The clinical information provided by the reporter is often limited and may preclude the interpretation of the report. These passive reporting systems are most suited at detecting events that may have a short latency period; however, they likely capture events that are commonly occurring in the general population and not necessarily associated with vaccine exposure.

The review of the initial post-marketing safety surveillance of RZV is reassuring and appears consistent with safety findings reported in pre-licensure clinical trials, including the pivotal trials [10–12,37]. The majority (95.3%) of the AEs reported were non-serious and generally consistent with the known reactogenicity profile of the vaccine observed in pre-licensure clinical studies [12] and the kinetics of the inflammatory response induced by RZV in animal studies [38]. These reactions associated to the vaccine reactogenicity occurring in close temporal assotiation to vaccination are expected as common, generally low grade in intensity, self-limiting and of short duration, and generally do not require medical intervention.

As anticipated, the observed quantitative signals of the RZV–AE pairs were either for reactions already recognized in the RZV local prescribing information leaflets (including those linked to the vaccine reactogenicity and hypersensitivity reactions) or for certain vaccination error types.

The O/E analyses performed for mortality (all-cause) and the two most frequently reported pIMDs, GBS and Bell's palsy, following RZV did not suggest a greater frequency of these outcomes

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Table 5
Potential immune-mediated diseases following RZV vaccination.

Potential immune-mediated disease	N (%)[a]	Country of occurrence	Diagnostic certainty[b]	Reporting rate per 100,000 doses distributed
Bell's palsy/paresis	25 (23.8)	18 US, 7 CA	BC level 1: 1 report BC level 3: 1 report BC level 4: 17 reports BC level 5 (not idiopathic palsy): 6 reports	0.27
GBS	17 (16.2)	14 US, 3 CA	BC level 2: 2 reports BC level 4: 14 reports BC level 5: 1 report, final diagnosis was consistent with idiopathic progressive polyneuropathy	0.18
Polymyalgia rheumatica	6 (5.7)	3 US, 3 CA	Insufficient data for assessment 3 reported apparent flare (2 occurrences in one individual after dose 1 and 2)	0.06
Uveitis	5 (4.8)	4 US, 1 CA	Insufficient data for assessment	0.05
Rheumatoid arthritis	5 (4.8)	4 CA, 1 US	4 reported apparent rheumatoid arthritis flare-(one co-reported with GBS). In 2 of these, the very short onset (within a day) suggests that symptoms could have been confounded by the vaccine reactogenicity 1 new onset of rheumatoid arthritis confounded by vaccine co-administration	0.05
Vasculitis group	5 (4.8)	4 US, 1 CA	2 reports of cutaneous vasculitis (urticarial): BC levels 2 and 4, respectively 1 report of Henoch–Schönlein purpura: BC level 4, with possible alternative cause 1 report of microscopic polyangiitis, with insufficient data for assessment 1 report of vasculitis, possibly cerebral, with insufficient data for assessment	0.05
Psoriasis	4 (3.8)	3 CA, 1 US	Insufficient data for assessment: 4 reports 2 reported apparent flare	0.04
Systemic lupus erythematosus	3 (2.9)	3 US	BC level 4: 3 reports 1 reported apparent flare. The very short onset and resolution of symptoms (within 2 days after vaccination) suggests that symptoms could have been confounded by the vaccine reactogenicity	0.03
SJS	3 (2.9)	3 US	The event description, evolution and treatment (ambulatory) did not seem to be compatible with SJS: 2 reports Insufficient data for assessment: 1 report	0.03
Colitis ulcerative	3 (2.9)	3 US	Insufficient data for assessment: 3 reports 1 reported apparent flare	0.03
Pemphigoid & Pemphigus	3 (2.9)	2 US, 1 CA	Insufficient data for assessment: 2 reports Alternative cause: 1 report (event recurred with drugs used after cataract surgery)	0.03
Gout	3 (2.9)	1 US, 2 CA	Insufficient data for assessment: 3 reports 1 reported apparent flare	0.03
Neuritis	3 (2.9)	2 US, 1 CA	Insufficient data for assessment: 2 reports. Alternative cause: 1 report (secondary to the ear infection)	0.03
Myasthenia gravis / ocular myasthenia	2 (1.9)	2 US	Both reported apparent flares. Insufficient data for assessment: 2 reports	0.02
Spondylitis	2 (1.9)	1 US, 1 CA	Insufficient data for assessment: 2 reports	0.02
Multiple sclerosis relapse	2 (1.9)	1 CA, 1 DE	Both reported multiple sclerosis relapse 1 and 7 days post-vaccination Alternative cause: 1 report (patient discontinued treatment 1 month earlier)	0.02
Optic ischemic neuropathy	2 (1.9)	2 US	Both reported as non-arteritic Insufficient data for assessment: 1 report Alternative cause: 1 report (retinal artery and vein occlusion)	0.02
Lichen planus & lichen planopilaris	2 (1.9)	1 CA, 1 US	Insufficient data for assessment: 2 reports	0.02
Anosmia	1 (1.0)	1 CA	Secondary to Influenza-like symptoms, not a pIMD	0.01
Cranial nerve (Trigeminal) disorder	1 (1.0)	1 US	Insufficient data for assessment	0.01
IIIrd nerve paralysis	1 (1.0)	1 US	Alternative cause (elderly pacient with hypertension)	0.01
Optic neuritis	1 (1.0)	1 US	Insufficient data for assessment	0.01
Erythema multiforme	1 (1.0)	1 CA	Insufficient data for assessment	0.01
Erythema nodosum	1 (1.0)	1 US	Insufficient data for assessment	0.01
Autoimmune hepatitis	1 (1.0)	1 US	Insufficient data for assessment	0.01
Immune thrombocytopenic purpura	1 (1.0)	1 US	Insufficient data for assessment	0.01
Crohn's disease	1 (1.0)	1 US	Insufficient data for assessment	0.01
Mixed connective tissue disease	1 (1.0)	1 US	Reported apparent flare. The very short onset (within a day) suggests that symptoms could have been confounded by the vaccine reactogenicity	0.01

following vaccination compared to the expected range in this population [23,25–27,39–43]. However, the conclusions that can be drawn from the O/E analyses are hindered by limitations inherent to the spontaneous safety data reporting. Other potential limitations are the uncertainties related to the true risk period (i.e. exact time period of increased vaccine-associated risk is generally unknown) and the relevance of the background incidence rates for the exposed population (calculated from a targeted population unexposed to RZV), and the number of doses actually administered by age strata.

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Table 5 (*continued*)

Potential immune-mediated disease	N (%)[a]	Country of occurrence	Diagnostic certainty[b]	Reporting rate per 100,000 doses distributed
Dermatomyositis	1 (1.0)	1 US	Co-reported with systemic lupus erythematosus	0.01
Arthritis reactive	1 (1.0)	1 DE	Insufficient data for assessment.	0.01
Noninfective encephalitis	1 (1.0)	1 US	Insufficient data for assessment	0.01
Myelitis transverse	1 (1.0)	1 US	BC level 4	0.01

RZV, recombinant zoster vaccine; pIMD, potential immune-mediated disease; GBS, Guillain–Barré syndrome; BC, Brighton Collaboration; US, United States; CA, Canada; DE, Germany; SJS, Stevens-Johnson syndrome; N, number of pIMD reports for each category; %, percentage from the total number of pIMD reports (N = 105).
Analytical period: October 13, 2017 – February 10, 2019.

[a] A report may describe more than one pIMD.

[b] BC definitions were available for GBS [30], Bell's palsy [33], encephalitis-myelitis [54], Systemic Lupus Erythematosus [55], cutaneous vasculitis [56], and IgA vasculitis (Henoch-Schönlein) [57]; reports were categorized as level 1–3 (meets the case definition), level 4 (insufficient evidence to meet the case definition) and level 5 (diagnosis excluded).

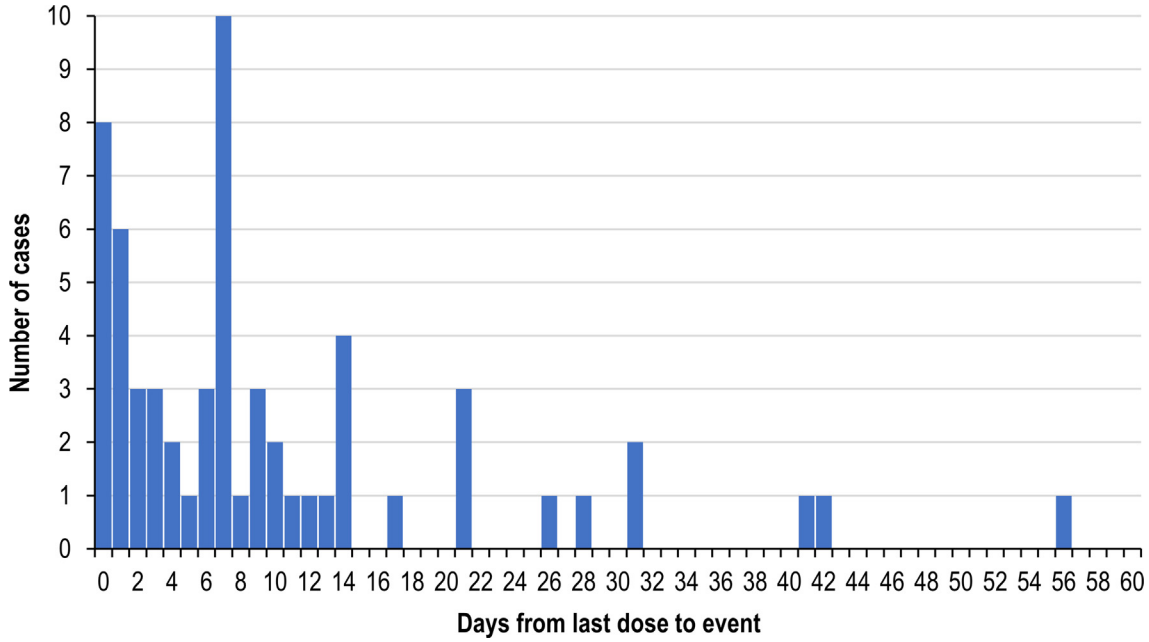

Fig. 4. Time-to-onset for pIMD reports following vaccination with any dose of RZV. Footnotes: pIMDs, potential immune-mediated diseases; RZV, recombinant zoster vaccine. Analytical period: October 13, 2017 – February 10, 2019. Note: Time-to-onset data (symptom onset after RZV vaccination) was available for 60 out of 114 pIMDs.

The US Centers for Disease Control and Prevention conducted descriptive analyses of reports to the VAERS involving RZV for the period October 20, 2017 to June 30, 2018 and concluded that no AEs reported for RZV were disproportionate to AE reporting patterns observed for other vaccines in the VAERS database [44]. At the US Advisory Committee on Immunization Practices (ACIP) meeting on February 28, 2019, the Committee presented data regarding a "preliminary statistical signal" for GBS after RZV in a sequential analysis of data from the Vaccine Safety Datalink [45]. This was based on a small number of reports (four) after administration of approximately 106,000 doses of RZV. Upon chart review, two cases were determined to be historical, one was a valid case in the risk interval, and one case was valid with a questionable onset risk interval. An update was presented at the ACIP meeting on June 26, 2019 and the Committee noted that the preliminary data were insufficient to conclude that a safety problem exists for GBS, but further evaluation and continued monitoring were warranted [46].

Our evaluation of the pIMDs, were overall consistent with CDC and ACIP analyses described above and the reporting patterns observed for other vaccines in the GSK database. The reported pIMDs may represent temporally-associated events, occurring as background incidence in the general population [44]. While the time needed for an exposure to initiate an autoimmune/immune-mediated process leading to a clinically observable illness is generally unknown, we consider that an interval of more than 5–7 days would possibly be needed [19], therefore the short TTO ($\leq$7 days) observed for most pIMDs following vaccination argues against a possible association with vaccination.

The observed reporting rates of vaccination errors were not unexpected. Vaccination errors are events that might reflect incorrect use of the product and the monitoring of these spontaneous reports offers a mechanism to introduce corrective strategies. Prior experiences with other vaccines indicate that vaccination errors are highest in the period shortly after launch [47]. Vaccination errors occurring during the RZV surveillance were mainly related to reconstitution and administration of only one component, as previously observed for other vaccines requiring reconstitution [48]. Errors related to inappropriate/incorrect route of administration and storage conditions were also frequently reported in this post-marketing surveillance. These errors may have reflected the lack of familiarity of HCPs with the RZV specificities during the early phase post-licensure and the 10 years of practice with the live attenuated virus zoster vaccine (ZVL; *Zostavax*, Merck) in the US, which is reconstituted prior to subcutaneous

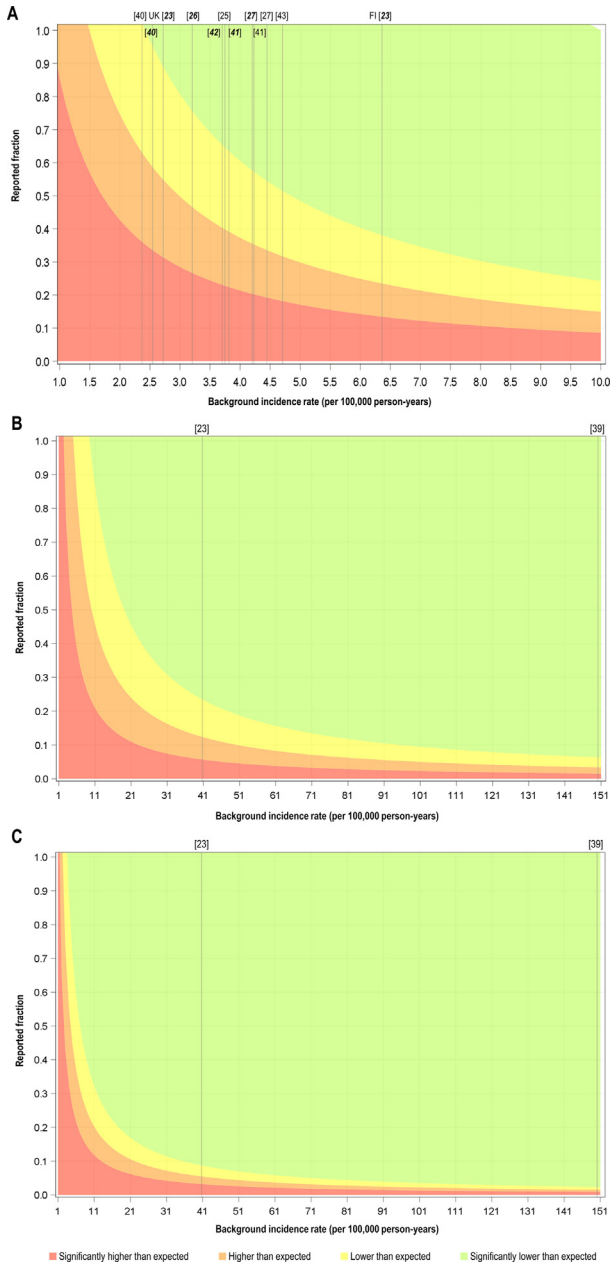

Fig. 5. GBS (A) and Bell's palsy (B, C): Heat map of the observed-to-expected (O/E) analyses conclusions considering different scenarios of incidence rates and reported fraction. Footnotes: GBS, Guillain–Barré syndrome; FI, Finalnd; UK, United Kingdom. Risk period: 42 days (panel A) (GBS), 7 (panel B) and 30 (panel C) days (Bell's palsy); doses distributed: 9,323,118; observed cases: 16 (GBS Brighton Collaboration levels 1–4, for a risk period of 42 days), 9 and 17 (Bell's palsy Brighton Collaboration levels 1–4, for a risk period of 7 and 30 days, respectively). Analytical period: October 13, 2017 – February 10, 2019. Note: Vertical lines indicate incidence rates adjusted by age to the RZV exposed population for GBS [23,25–27,40–43] and Bell's palsy [23,39]. Bolded references indicate incidence rates adjusted by age and sex. These figures represent a visual framework which enables independent reviewers to draw their conclusions by making their own assumptions about two sources of uncertainty. The background incidence rate and the underreporting were considered the two major sources of uncertainty. Therefore, different scenarios of spontaneous reports, regardless of the causality, among those actually occurring within the risk period, labelled "Reported fraction" and different background incidence rates, in a range chosen to include all incidence rate references, were used to perform the O/E analyses and to determine if the observed number of reports was: (i) significantly higher than expected (expected below the lower limit of the Poisson exact 95% confidence interval computed from the observed reports); (ii) higher than expected; (iii) lower than expected; (iv) significantly lower than expected (expected above the upper limit of the Poisson exact 95% confidence interval computed from the observed reports).

administration by injecting the provided diluent into a vial containing the lyophilized component [49]. A similar conclusion was previously drawn from early VAERS data on vaccine administration errors during the first four months following licensure of RZV in the US [50]. Several measures – such as distribution of educational materials on proper product handling, dosing and administration, highlighting the vaccine presentation and reconstitution step in local prescribing information leaflets and engagement with the Centers for Disease Control and Prevention to highlight the differences between preparation of ZVL and RZV – were proposed in the ACIP recommendations for use of HZ vaccine [51,52]. Because the error rates seem to be declining with time in the US, these measures were considered sufficient to address the issue. Limitations of these reports include the generally inconsistent data quality and completeness, that many errors might go completely unnoticed or not reported and that some might not be true vaccination errors (e.g. delays in immunization due to supply shortages classified as "Inappropriate Schedule" errors). It is worth noting that RZV demand exceeded supply during the observation time and reports of inappropriate/incomplete course of administration may have been due to the supply shortages that have occurred for RZV during the same period; however, in most cases the reason for these errors was not provided.

The frequency of suspected or confirmed vaccination failure was very low and the majority (68.5%) of these reports were from Canada. It is worth noting that in March 2018, the RZV Facebook page in Canada [53] turned on the capability to comment and following this, an increase in these AEs reported by patients/consumers having limited clinical data for diagnosis ascertainment was observed. Reports of HZ, HZ-like rash or HZ complications accounted for 5.5% of the overall number of reports, with most occurring in persons not fully vaccinated. Therefore one may assume that most have been due to reactivations of wild-type VZV infections, anticipated to occur in the target population, althought data from spontaneous reporting systems cannot be used to draw conclusions in this regard.

The occurrence of other AEs of interest in the target population, as well as serious AEs, were rare after RZV immunization, and have not suggested any safety concern.

5. Conclusions

RZV was licensed in several countries more than one year ago. The safety profile of the vaccine will continue to be monitored in ongoing clinical trials and post-marketing passive and active safety surveillance. Despite the knowpost-marketing passive surveillance that relies on spontaneous AE reports, these data provide important safety information allowing ongoing evaluation of reported AEs following RZV immunization in the general population ≥50 years of age. The present review, based on post-marketing data, is reassuring and reinforces the clinically acceptable safety profile of RZV, previously established in clinical settings.

6. Trademark statement

Shingrix is a trademark of the GSK group of companies. *Zostavax* is a trademark of Merck Sharp& Dohme Corp.

7. Data sharing statement

Information on GSK's data sharing commitments and requesting access to anonymized individual participant data and associated documents can be found at www.clinicalstudydatarequest.com.

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Declaration of Competing Interest

All authors are employees of the GSK group of companies. LVH was an employee of the GSK group of companies at the time of the work. OM, FTDS and LVH own restricted shares from the GSK group of companies.

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Authors' contribution

Conceptualization, FTDS, MMC, OM, LVH, and JUS; Methodology, FTDS, MMC, OM, LVH, and JUS; Formal Analysis, FTDS, MMC, LVH, JUS, CH, CD, MLF, and OM; Investigation, FTDS, MMC, LVH, JUS, CH, CD, MLF, and OM; Writing – Original Draft, FTDS; Writing – Review & Editing, FTDS, MMC, LVH, JUS, CH, CD, MLF, and OM; Visualization,FTDS, MMC, LVH, and OM; Supervision, FTDS and JUS.

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Appendix A. Supplementary material

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