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Safety profile of recombinant adjuvanted anti-herpes zoster vaccine (RZV) in high-risk groups: Data from active surveillance program. Puglia (Italy), 2021–23

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ABSTRACT

Background: Since 2021 a recombinant adjuvanted anti-Herpes Zoster vaccine(Recombinant Zoster Vaccine, RZV) is offered in Italy to high-risk patients. Few real-life data about RZV safety are available in target populations.

Objectives: This study investigates Adverse Events Following Immunization(AEFIs), baseline disease flare-ups, and Herpes Zoster (HZ) episodes occurring after RZV administration in a heterogeneous population of fragile patients to design its safety profile.

Methods: This is a retrospective population-based study. RZV-vaccinated patients at Bari Policlinico General Hospital vaccination clinic from October 1st, 2021, to March 31st, 2023, were enrolled. Subjects were screened for reason of RZV eligibility and baseline chronic pathologies. AEFIs occurred in the first 7-days post-vaccination period were collected, and baseline disease flare-ups and post-vaccination HZ episodes were assessed via a 3-month follow-up.

Results: Five-hundred-thirty-eight patients were included and total of 1,031 doses were administered. Most patients were vaccinated due to ongoing immunosuppressive therapy(54.65 %); onco-hematological and cardiovascular conditions were the most common chronic baseline pathologies. Out of 1,031 follow-ups, 441 AEFI cases were reported(42.7/100). The most common symptoms were injection site pain/itching(35.60/100), asthenia/malaise(11.44/100), and fever (10.09/100). Four serious AEFIs occurred(0.38/100). Older age, male sex, and history of cardiovascular diseases(OR:0.71; 95CI:0.52-0.98; p-value <0.05) were found to decrease AEFIs risk, while endocrine-metabolic illnesses(OR:1.61; 95CI:1.15-2.26; p-value <0.05) increased it. Twelve patients(2.23 %) reported a flare-up/worsening of their baseline chronic condition within the first three months after vaccination(mean interval 31.75 days, range 0–68 days). Patients with rheumatological illnesses had a higher risk of relapse(OR:16.56; 95CI:3.58-76.56; p-value <0.001), while male sex behaved as a protective factor.

Twelve patients who completed the vaccination cycle(2.43%) had at least one HZ episode by the long-term follow-up.

Conclusions: The study demonstrates RZV safety in a significant number of high-risk patients. Hence, RZV should be actively offered as part of tailored vaccination programs to decrease the burden of HZ in fragile populations.

Abbreviations: HZ, Herpes Zoster; RZV, Recombinant Zoster Vaccine; AEFIs, Adverse Events Following Immunization; ZVL, Zoster Vaccine Live; AIFA, Agenzia Italiana del Farmaco; HIV, Human Immunodeficiency Virus; FDA, Food and Drug Administration; EMA, European Medicines Agency; SmPC, Summary of Product Characteristics; SAEs, Serious Adverse Events; OR, Odds Ratio; WHO, World Health Organization.

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1. Introduction

COVID-19 pandemics raised global awareness of the importance of vaccinating fragile patients – i.e., a heterogeneous population of individuals with underlying chronic medical conditions that increase their risk of infections and severe manifestations, complications, and critical outcomes in case of infectious diseases [1–3]. Notably, incidence of Herpes Zoster (HZ) and its complications was found to be higher among adult patients with hematopoietic cell transplants, cancer, Human Immunodeficiency Virus (HIV), solid organ transplant, a broad array of autoimmune diseases, diabetes, and chronic kidney disease, among others [4–10]. However, high-risk patients could not safely receive the live-attenuated zoster vaccine (ZVL), available since 2006, due to age and/or immune deficiency [11–13].

The public health perspective changed with approval of Recombinant Zoster Vaccine (RZV) by Food and Drug Administration (FDA) in 2017 and European Medicines Agency (EMA) in 2018. RZV is currently approved for the prevention of HZ in adults $\geq$ 50 years and, secondary to a supplement approval, in adults $\geq$ 18 years who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy [14–16].

In line with a Resolution by the Italian Medicines Agency (AIFA), in 2022 the Puglia region, located in South-Eastern Italy, provided a list of high-priority RZV target categories [17,18].

Albeit RZV proved to be safe in pre-marketing trials in both immunocompetent and immunosuppressed adults, few post-marketing data are available up to date as concerns RZV safety in real-life settings. Indeed, the risk of both adverse events following immunization (AEFIs) and possible baseline disease flare-ups in highly vulnerable patients with RZV recommendation has not been deeply analysed so far [19–29].

Thus, this study investigates RZV safety profile in fragile patients requiring RZV due to both a higher risk of HZ than the general population and an incompatibility with ZVL. We studied the distribution, characteristics, and risk factors of all the observed AEFIs via an active surveillance program; baseline disease reactivation and post-vaccination HZ episodes and risk factors were assessed.

2. Methods

2.1. Study setting

This is a retrospective population-based study approved by the Ethics Committee of Bari's Policlinico General Hospital (study id 7813 approved on November 29th, 2023, protocol no. 0103705|05/12/2023 AOUCPG23|COMET|T). For context, care wards within Bari's Policlinico General Hospital refer high-risk patients to the vaccination clinic, which has activated a vaccination offer program tailored to fragile patients. During the first visit, patients of this facility are screened by trained physicians for recommended vaccinations according to their risk group and based on clinical records, drug history and laboratory analyses, when available.

2.2. Participant recruitment

The study population is represented by all the subjects who received at least one dose of RZV at Bari's Policlinico General Hospital's vaccination clinic located in Puglia, South-Eastern Italy, from October 1st, 2021, to March 31st, 2023. RZV was offered actively and free-of-charge to all subjects $\geq$ 18 years suffering from any of the following conditions (only the most prominent was considered):

- Chronic kidney failure or dialysis;
- History of recurrent or severe HZ;
- Candidates for disease-related immune-suppressive therapy;
- Ongoing immunosuppressive therapy;
- Congenital or acquired immunodeficiency;
- Subjects under 50 years of age suffering from diabetes mellitus;
- Subjects under 50 years of age suffering from pneumological or cardiovascular conditions;
- Solid organ transplant candidates and recipients;
- Hematopoietic stem cell transplant candidates and recipients;
- History of splenectomy in the last five years.

RZV-eligible patients were informed about the study and, prior consent to participate, were asked their sex and age and whether they suffered from one or more of the following active chronic diseases (apart from conditions indicating RZV vaccination):

- Rare/genetic diseases;
- Cardiovascular diseases;
- Dermatological diseases;
- Endocrine-metabolic diseases;
- Gastroenterological diseases;
- Ophthalmological and/or ear-nose-throat diseases;
- Onco-haematological diseases;
- Orthopaedical diseases;
- Pneumological diseases;
- Psychiatric/neuropsychiatric disorders;
- Gynaecological diseases;
- Nephrological or urological diseases;
- Neurological diseases;
- Rheumatological diseases;
- Chronic infectious diseases.

Subjects were also asked whether they had ever suffered from HZ and, if so, when.

All patients included in the study population did not receive any other vaccination at the time of RZV administration.

2.3. Data collection

Following first dose administration, patients were provided with a paper-based diary for recording AEFIs occurring until seven days after RZV vaccination and were instructed to fill in the form. The clinical diary included a comprehensive list of AEFIs, gathered into the following categories:

- Local reactions (injection site pain/itching, redness, swelling, induration);
- Systemic reactions (asthenia/malaise, arthromyalgia, lymphadenopathy, skin rash);
- Fever;
- Neurological symptoms (drowsiness/insomnia, headache, irritability/nervousness);
- Gastrointestinal symptoms (nausea/vomit, diarrhoea/abdominal pain);
- Allergic reactions (anaphylaxis, urticaria-like reaction).

For each AEFI, subjects had to specify whether it had resolved within the first week after vaccination or not, if drugs were taken to stop or mitigate AEFIs, and if general practitioner intervention, emergency room access or hospitalization were needed. In case of hospitalization, medical record documentation was requested to the inpatient healthcare facility.

AEFIs were classified as serious and non-serious according to World Health Organization (WHO) guidelines and were entered on the national pharmacovigilance database in accordance with Italian regulation. For serious AEFIs requiring access to healthcare facilities or services, clinical documentation was requested [30–32].

The appointment for the second vaccine dose was scheduled between one and six months after the first, according to the summary of product characteristics (SmPC) and to each patient's medical condition [33].

During the second visit, patients were asked to return the diary and whether they had suffered from HZ during the time lapse between the two appointments. Prior consent, they received the second vaccine dose and a new form identical to the former to detect AEFIs occurring during the following week.

Two phone contacts were scheduled: one after eight days, to gather information from the post-vaccination diary; one at least three months after the second dose (long-term follow-up) to check for HZ episodes or flare-ups/worsening of their main baseline chronic disease. Subjects who refused to complete the vaccination cycle were still called at least three months after the first dose for the long-term follow-up.

A reactivation/worsening of the main chronic disease was defined as a change in the most severe and/or treatment-requiring condition resulting in one of the following:[34–39].

- Need for therapy changes;
- Need for increased dosage of previous therapy;
- Need to add new drugs to existing therapy;
- Worsening of the disease certified by imaging diagnostics and/or biochemical tests;
- Worsening of signs and symptoms certified by a branch physician.

2.4. Statistical analysis

Data collected via the paper-based diary provided were anonymized and computerized via software FileMakerPro®. A database was built on software Microsoft Excel®. Statistical analysis was conducted via StataMP17®.

Continuous quantitative variables were expressed as mean (±standard deviation), discrete quantitative variables as median (interquartile range, IQR), and qualitative variables as percentage (proportion).

AEFIs' reporting rates were calculated as follows:

$$Reporting\ rate = \frac{number\ of\ completed\ clinical\ diaries\ containing\ one\ or\ more\ AEFIs}{total\ number\ of\ completed\ clinical\ diaries} \text{x}100$$

Multivariable logistic regression models were fitted to verify the association between variables. The outcomes were: HZ episodes following the last vaccine dose received; baseline disease worsening/reactivation; occurrence of one or more AEFIs; occurrence of one or more serious adverse events (SAEs). The independent variables used in our models were sex, age, number of baseline chronic diseases, category of baseline chronic diseases, and reason for vaccine recommendation.

For each model, a two-sided p-value <0.05 was considered indicative of statistical significance. In case of significant association between two variables, a Chi2 test was conducted for verification. A two-sided p-value <0.05 was considered indicative of statistical significance for this test as well.

3. Results

During the study period, 558 patients were vaccinated at our clinic, and all accepted to participate. Twenty people (3.58 %) were lost to follow-up, resulting in 538 patients being included in the final study population. Of them, 91.64 % received both vaccine doses (493/538), while 8.36 % (45/538) received one dose only, for a total of 1,031 administered doses.

Our population was made of 257 females (47.77 %) and 281 males (52.23 %). The mean age of the study population was 59.50 ± 13.49 years (range 18–90 years).

The most common reason for RZV vaccination was an ongoing immunosuppressive therapy, reported by 54.65 % of subjects (294/538), followed by programmed or previous solid organ transplant in 15.24 % of patients (82/538). Distribution of RZV eligibility reasons is resumed in Table 1.

Table 1
Distribution of the conditions indicating RZV vaccination.

Reason for vaccine eligibility	N.	% (per 538 subjects) *
Ongoing immunosuppressive therapy	294	54.65
Solid organ transplant candidates and recipients	82	15.24
Haematopoietic stem cell transplant candidates and recipients	41	7.62
Candidates for disease-related immunosuppressive therapy	40	7.43
Congenital or acquired immunodeficiency	29	5.39
History of recurrent or severe HZ	22	4.09
Chronic kidney failure or dialysis	21	3.90
History of splenectomy in the last five years	7	1.30
Subjects under 50 years of age suffering from diabetes mellitus	1	0.19
Subjects under 50 years of age suffering from pneumological or cardiovascular conditions	1	0.19

Only 1.86 % of subjects (10/538) did not report any chronic illnesses; these patients were selected for RZV administration due to history of recurrent or severe HZ. One, two, three, four and five underlying chronic diseases were reported by 49.07 % (264/538), 29.18 % (157/538), 14.13 % (76/538), 4.28 % (23/538) and 1.12 % (6/538) of participants, respectively. Only 0.37 % (2/538) of patients reported six chronic diseases. The median number of baseline illnesses for each subject was 1 (IQR: 1-2), with an average of 1.75 baseline conditions per subject. Among these, onco-haematological and cardiovascular diseases were the most common, affecting 39.03 % (210/538) and 29.74 % (160/538) of patients, respectively. The distribution of reported illnesses is described in Table 2.

During first visit, 23.98 % of subjects (129/538) reported a history of HZ.

Out of 1,031 administered vaccine doses, 441 resulted in one or more AEFIs being reported in the clinical diaries, for an overall adverse reaction reporting rate of 42.77/100 completed follow-ups. AEFIs were reported in 45.17 % (243/538) and 40.16 % (198/493) of post-first and post-second dose diaries, respectively. There was no statistically significant difference between the first and second dose concerning the risk of AEFIs (OR: 0.81; CI95: 0.63-1.05; p-value >0.05).

Table 2
Distribution of reported chronic diseases.

Type of chronic disease	N.	% (per 538 subjects)*
Onco-haematological diseases	210	39.03
Cardiovascular diseases	160	29.74
Rheumatological diseases	155	28.81
Endocrine-metabolic diseases	106	19.70
Nephrological or urological diseases	81	15.06
Neurological diseases	52	9.67
Chronic infectious diseases	49	9.11
Gastroenterological diseases	48	8.92
Pneumological diseases	37	6.88
Orthopaedical diseases	11	2.04
Dermatological diseases	10	1.86
Psychiatric/neuropsychiatric disorders	8	1.49
Ophthalmological and/or ear-nose-throat diseases	7	1.30
Gynaecological diseases	4	0.74
Rare/genetic diseases	3	0.56

* Since patients could report more than one chronic disease, percentages exceed 100%.

Reported AEFIs began within 12 h after vaccination in 52.15 % of cases (230/441), between 12 and 24 h in 31.97 % (141/441), during the first, second, third, fourth and seventh day in 13.15 % (58/441), 0.68 % (3/441), 0.45 % (2/441), 0.23 % (1/441), and 0.45 % (2/441) of cases respectively, with no AEFIs manifesting during either the fifth or sixth day after vaccination. In 0.91 % of cases (4/441), subjects spontaneously described symptoms which started more than seven days after vaccination, with no AEFIs during the week covered by the vaccination diary.

Most AEFIs resolved by the second day after vaccination; 2.49 % of events (11/441) completely resolved within the first 12 h, 11.79 % (52/441) in 12 to 24 h, 18.37 % (81/441) in one day, and 28.35 % (125/441) during the second day, making up for 61.00 % of all reports (269/441). The remaining underwent full resolution by the third, fourth, fifth, sixth, and seventh day after vaccination in 11.34 % (50/441), 6.12 % (27/441), 3.40 % (15/441), 0.45 % (2/441), and 8.39 % (37/441) of cases, respectively. Only 9.30 % of diaries (41/441) highlighted symptoms not resolved by the seventh day after vaccination.

Graph 1 describes changes of AEFI categories over time.

Local reactions were the most common AEFIs' category, observed in 37.44/100 completed follow-ups (386/1,031). Systemic reactions, fever, and neurological symptoms were reported in 13.97 % (144/1,031), 10.09 % (104/1,031), and 4.75 % (49/1,031) of post-vaccination diaries, respectively; gastrointestinal symptoms and allergic reactions were recorded by only 0.97 % (10/1,031) and 0.58 % (6/1,031) of post-vaccination diaries, respectively.

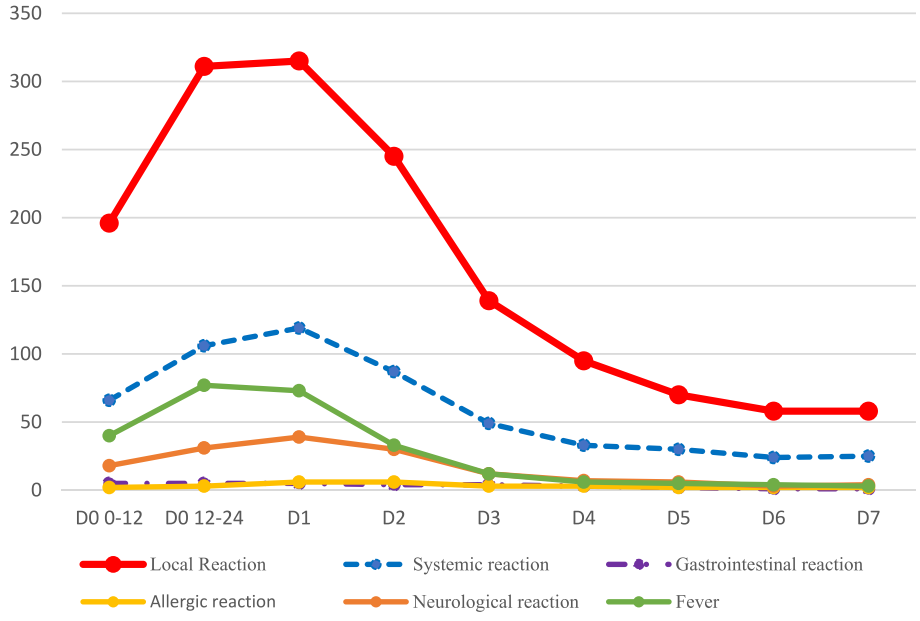
Injection site pain/itching was the most reported symptom (35.60 % of diaries), followed by asthenia/malaise (13.97 %), fever (10.09 %) and injection site redness (8.15 %). No episodes of anaphylaxis were reported, while six cases of urticaria-like reactions were described (0.58 %). In 16 cases (1.55 %), patients reported the need of general practitioner intervention to manage their AEFIs. Table 3 describes the distribution of signs and symptoms characterizing each AEFI report.

Four serious adverse events (SAEs) were reported, with a reporting rate of 0.38 serious events/100 completed follow-ups. SAEs included two cases of hyperpyrexia (highest temperature 40°C) occurring in two patients under immunosuppressive treatment due to rheumatologic and onco-hematologic conditions, respectively; both cases subsided with paracetamol until complete resolution in five and seven days after onset, respectively. As for the remaining SAEs, there was one case of a self-described severe local reaction with injection site redness, swelling and pain in a rheumatologic patient under immunosuppressive therapy; the patient required emergency room access and was dismissed in few hours with a prescription of anti-histaminic drugs, with referred complete resolution in few weeks. The last SAE occurred in an onco-hematologic patient with a history of spontaneous pneumothorax and under immunosuppressive therapy, who experienced a significant and worsening dyspnea starting within 12h after vaccination; the event required emergency room access and subsequent hospital admission; during hospitalization, oxygen therapy was started, with referred recommendation of ongoing oxygen therapy. Therefore, only two vaccine administrations were followed by emergency room access (0.19%), one requiring hospitalization (hospitalization rate: 0.10%).

Table 3
Distribution of signs and symptoms, as single events and by belonging category.

AEFIs by belonging category and single events	Number of reports	Reporting rate/1,031 diaries (per 100 completed follow-ups)*
Local reaction	386	37.44
• Injection site pain/itching	367	35.60
• Injection site redness	84	8.15
• Injection site swelling	76	7.37
• Injection site induration	23	2.23
Systemic reaction	144	13.97
• Asthenia/malaise	118	11.44
• Arthromyalgia	59	5.72
• Lymphadenopathy	5	0.48
• Skin rash	11	1.07
Fever	104	10.09
Neurological symptoms	49	4.75
• Headache	45	4.36
• Drowsiness/insomnia	8	0.78
• Irritability/nervousness	3	0.29
Gastrointestinal symptoms	10	0.97
• Nausea/vomit	7	0.68
• Diarrhea/abdominal pain	5	0.48
Allergic reactions	6	0.58
• Urticaria-like reaction	6	0.58
• Anaphylaxis	..	..
Others	15	1.45

* Since patients were able to report more than one symptom, and categories include reports containing at least one of the belonging symptoms, sums do not match.



Graph 1. Changes over time of signs and symptoms, by category.

Table 4
Flare-up and worsening of baseline disease, by classification criteria and time of occurrence.

Flare-up definition criteria	Number of flare-ups < 3 months postvaccination	Number of flare-ups > 3 months postvaccination
Need for therapy changes.	2	2
Need for increased dosage of previous therapy.	2	1
Need to add new drugs to existing therapy.	1	..
Worsening of the disease certified by imaging diagnostics and/or biochemical tests.	2	1
Worsening of signs and symptoms certified by a branch physician	5 (one due to dose adjustment of previous therapy secondary to side effects)	1 (due to voluntary therapy withdrawal)

Following causality assessment, the first three SAEs described were deemed to have a consistent causal association with RZV administration (reporting rate: 0.29%), while the last was not.

At the long-term follow-up, 3.16% of patients (17/538) reported a flare-up/worsening of their baseline chronic condition. In detail, 12 subjects (2.23%) reported a disease flare-up occurring during the first three months after vaccination (mean interval 31.75 days, range 0–68 days); in detail, eight subjects belonged to the rheumatologic, two to the hematologic, and two to the neurologic patient group. The remaining five subjects (belonging to the rheumatologic patient group) experienced a worsening after this checkpoint. Table 4 shows the distribution of flare-ups based on defining criteria, with occurrences within and after the three-month follow-up interval.

As regards the 12 patients who experienced a baseline disease reactivation within three months after vaccination, one case was attributed by the branch physician to dose adjustment of pre-existing therapy due to therapy-related side effects occurred before vaccination; three cases completely resolved within about two weeks with or without therapy; the remaining cases were managed and treated by branch physicians leading to overall improvement or at least clinical stabilization of patient conditions without further deterioration.

Considering only subjects who received both vaccine doses, 1.83 % (9/493) developed HZ during the time lapse between administrations, while 2.43 % (12/493) had at least one HZ episode after completing the vaccination cycle by the long-term follow-up. Of these 12 patients, five were vaccinated due to history of recurrent or severe HZ, five belonged to the onco-hematologic, and two to the rheumatologic patient group. As for timing, two patients developed HZ less than seven days after the second dose, while the others at least three weeks after. Six subjects with a history of HZ reported less severe forms compared to previous episodes, or mild episodes with rapid remission. Two subjects stated that they did not require anti-herpetic treatment due to mild symptoms. None of the 45 subjects who only received the first RZV dose reported suffering from HZ thereafter.

Multivariable logistic regression models fitted for the risk of AEFIs showed age to be inversely associated with the risk of AEFIs (OR: 0.97; 95CI: 0.96–0.98; p-value <0.001), as well as male sex (OR vs. female sex: 0.72; 95CI: 0.54–0.95; p <0.05) and a history of cardiovascular disease (OR: 0.71; 95CI: 0.52–0.98; p-value <0.05). Contrarily, endocrine-metabolic illnesses were associated with a higher risk of AEFIs (OR: 1.61; 95CI: 1.15–2.26; p-value <0.05). All other categories of chronic illness, as well as the number of chronic diseases affecting the subject, did not significantly modify the risk of AEFIs (p >0.05). No regression model could be fitted for SAEs, as their number was too low for statistical significance purposes.

When multivariable logistic regression model were fitted for the risk of baseline disease flare-up/worsening, a significantly higher risk was identified for subjects suffering from rheumatological illnesses (OR: 16.56; 95CI: 3.58–76.56; p-value <0.001). On the other hand, males were shown to have a significantly lower risk of baseline disease flare-up/worsening than females (OR vs. females: 0.17; 95CI: 0.05–0.59; p-value <0.05).

As regards the risk of HZ after a two-dose vaccination cycle, despite the low number of observations, patients with onco-haematological conditions were shown to have a significantly lower risk of HZ episodes following complete vaccination (OR: 0.10; 95CI: 0.02–0.48; p-value <0.05), as well as patients with rheumatological disease (OR: 0.05; 95CI: 0.01–0.34; p-value <0.05), and patients with a higher number of baseline health conditions (OR: 0.31; 95CI: 0.11–0.82; p-value <0.05). Male patients (OR vs. females: 0.26; 95CI: 0.07–0.99; p-value <0.05) were less exposed to HZ episodes after vaccination, too.

4. Discussion

Real-life data about Recombinant Zoster Vaccine (RZV) are very limited in terms of vaccine safety and effectiveness, due to recent licensure and introduction in clinical practice. Both pre- and post-marketing evidence is scarce in those patients who are recommended to receive RZV due to baseline conditions that increase their risk of developing HZ but make them incompatible with ZVL. Indeed, while several small pre- and post-marketing studies provided reassuring preliminary results about RZV safety in patients with selected immunocompromising conditions due to disease or therapy, robust evidence is still lacking and thus further investigation to guide daily practice and provide insights into AEFIs, underlying disease flare-up, and HZ recurrency in this heterogeneous patient population is warranted [27,28,32,40].

Therefore, the present study investigated such aspects in a relevant number of fragile patients (n = 538), with a wide array of baseline diseases and conditions and a broad age range (18–90 years, median age 61), thereby providing an extensive view on this varied population.

As regards RZV safety, the overall adverse reaction reporting rate was 42.77 % (441/1,031) during the seven days post-vaccination period. Available literature data are uneven across different study populations. For example, overall AEFIs reporting rate in active surveillance studies ranged from 84.4 % of RZV recipients in the ZOE-50 pre-marketing trial, to 8.7 % in a population of rheumatologic patients. The lower incidence of AEFIs in our population compared to the ZOE-50 trial might be related to the effects of immunosuppression due to therapy or disease [24,41,42].

On the other hand, the lower AEFIs rate in passive surveillance studies (ranging from 0.136 % to 12.7 %) is coherent with the tendency of passive surveillance to underreport known outcomes, especially if common, mild, and transient [43,44].

Most of the collected AEFIs in our study population were local, with a reporting rate of 37.44/100 completed diaries; the most common local AEFI was injection site pain/itching (35.60 %), followed by redness (8.15 %) and swelling (7.37 %). Albeit with different percentages, local reactions (especially injection site pain) had already been recognised as the most common AEFIs in both immunocompetent and immunosuppressed patients [23,44].

Systemic reactions were the second most common AEFIs in our sample (reporting rate 13.97/100 completed diaries), with asthenia/malaise leading the list (11.44 % of total diaries), followed by arthromyalgia, (5.72 % of diaries). This result is coherent with previous findings, which recognized these as the most common systemic AEFIs, despite overall higher reporting rates.' The same concept can be applied to fever (found in 10.09 % of diaries), widely reported in passive surveillance studies as well [31,45,46].

Our study showed that male sex was associated with a lower risk of AEFIs (OR vs. female sex: 0.72; 95CI: 0.54–0.95; p <0.05). This finding is consistent with previous data about RZV and other vaccines as well, as

women were found to report more AEFIs compared to males, possibly due to biological or behavioural factors. Moreover, we found that there was an inverse relationship between age and risk of AEFIs (OR: 0.97; 95CI: 0.96–0.98; p-value <0.001), as previously demonstrated on immunocompetent patients [43,47,48].

As concerns SAEs, four were reported in the 1,031 completed diaries (0.38/100 completed diaries). SAEs included two cases of hyperpyrexia (highest temperature 40 °C); one case of a self-described severe local reaction with injection site redness, swelling and pain, which required emergency room access and dismission in few hours with a prescription of anti-histaminic drugs and referred complete resolution; and one case of significant and worsening dyspnoea requiring emergency room access and subsequent hospitalization, with referred recommendation of long-term oxygen therapy. Actually, only the first three SAEs were considered to have a consistent causal association to vaccination by the investigator (0.29 %), and all underwent complete resolution.

Our results about SAEs were consistent with previous active surveillance studies, which demonstrated comparable rates in both immunocompetent (1.13 %, with 0.01 % ascribed to vaccination) and immunocompromised patients (ranging from no SAEs related to vaccination to 0.18 %) [19,22–24,49].

To our knowledge, this was the first post-licensure study to consider the possible role of reasons for RZV eligibility and a wide array of underlying chronic pathologies in the risk of AEFIs, underlying disease reactivation, and post-vaccination HZ episodes. While none of the RZV eligibility reasons was shown to be significantly associated with any of the above outcomes, some of the patient's chronic pathologies were. Preliminary data showed that RZV safety was not affected by type or number of patient's medical conditions present at enrolment [50]. The real-world data collected in our population of fragile patients confirmed that number of comorbidities did not affect the risk of AEFIs, but certain chronic pathologies per se could. Indeed, we found that a history of cardiovascular disease had a protective role on AEFIs risk, while the opposite was true for endocrine-metabolic illnesses; the latter result seems to be in line with previous evidence of a higher AEFIs' reporting rate among diabetic COVID-19 vaccine recipients compared to vaccinated non-diabetic patients. All other chronic illness, instead, were not significantly associated with the risk of AEFIs (p >0.05). The effect of chronic underlying diseases on SAEs risk could not be investigated due to the low number of SAEs reported [51].

To our knowledge, few studies have evaluated the risk of baseline disease reactivation in fragile patients receiving RZV or other vaccines [41,43,52–54].

In our study population, 3.16 % of patients (17/538) reported a flare-up/worsening of their baseline chronic condition at the long-term follow-up (at least three months after the last received dose). In detail, 12 subjects (2.23 %) reported a disease flare-up occurring during the first three months after vaccination (eight belonging to the rheumatologic, two to the hematologic, and two to the neurologic patient group), while five subjects (belonging to the rheumatologic patient group) experienced a worsening in their conditions after this checkpoint.

This result cannot be directly compared with data from previous studies, which have always focused on a single patient group at a time (e.g., rheumatologic patients). Considering rheumatologic patients only, our rates of disease flare-up in the first three months (5.16 %, 8/155) are consistent with previous findings, ranging from 6.7 % to 16 % (albeit 31 % of the latter occurred in temporal relation to treatment change) in different studies [41,43].

Indeed, our analysis confirmed that rheumatologic patients have an increased risk of disease reactivation. However, increasing the patient sample is needed to clarify the actual risk of disease flare-up/worsening in these patients. Therefore, in our opinion, this potentially alarming result should not discourage RZV vaccination in rheumatologic patients but raise medical awareness of an issue that deserves further investigation.

Conversely, male sex had a protective role on the risk of baseline disease flare-up, but this could be related to the effect of rheumatologic baseline pathology on the risk of disease reactivation, as 73.55 % of the rheumatologic patients were females, thereby potentially influencing the result.

Although this study was not designed to evaluate RZV effectiveness in fragile patients, referred HZ episodes were collected at the follow-up at least three months after the last dose received. Incident HZ occurred in 12/493 patients (2.43 %) who completed the vaccination cycle. This rate is consistent with previous findings in chronically immunosuppressed adults across different medical conditions and treatments (ranging from 0.74 % to 1.54 %) [19,32]. Differences in the adopted definition of HZ episode (i.e., referred or confirmed by PCR) may explain the slight variability in HZ rate.

In our population, two patients referred HZ less than seven days after the second dose; six subjects with a history of HZ reported less severe forms compared to previous episodes, or mild episodes with rapid remission; two subjects stated they did not require anti-herpetic treatment due to mild symptoms, while the rest were successfully treated with antiviral therapy.

Counterintuitive as it may seem, patients with a higher number of baseline health conditions were less exposed to HZ episodes after vaccination. However, some extremely frail patients e.g., onco-hematologic patients after hematopoietic stem cell transplant, receive prophylactic antiviral therapy as a standard of care and could be recommended by their branch physician to continue prophylaxis even after vaccination until vaccine-elicited protection against HZ is achieved. Interestingly, we found onco-hematologic chronic illnesses behaved as strong protective factors for HZ episodes following complete vaccination, thereby providing grounds to this theory, even if assessment of ongoing therapy in the study population was not performed [55].

Rheumatologic chronic pathologies were associated with a lower risk of HZ recurrencies as well; this finding supports RZV recommendation in rheumatologic patients despite the immune-activating activity of RZV might increase the risk of disease flare-ups in this category.

Thus, RZV vaccination seemed to protect our group of fragile patients from HZ, particularly from severe forms. Of course, due to the relatively short follow-up period, patients need to be monitored over time to assess ongoing protection.

The strengths of our study include the use of active surveillance systems for appropriate safety signal detection and the enrolment of a varied population of fragile patients, encompassing a broad range of diseases and age groups. No selection bias occurred during population enrolment, as all the subjects who received at least one RZV dose in the study period were included, with 96.42 % of them completing the long term follow up (538/558). The number of participants (n = 538) and administered doses/completed diaries (n = 1,031) was thus relevant, especially considering the lack of robust post-marketing data in fragile patients with RZV recommendation. Lastly, all the patients included in the study population did not receive any other vaccination at the time of RZV administration, thereby avoiding a confounding factor.

The study also has limitations. First, the number of enrolled patients was inadequate to produce evidence of uncommon and rare AEFIs, and to provide findings with a strong statistical significance about specific patient subgroups; expanding the patient sample and stratifying patients by baseline chronic diseases could increase statistical significance of the results and assess the role of the variables in the outcomes of interest, especially those with the rarest occurrence.

In addition, as regards AEFIs recording, collected data are based on patients' reports during the scheduled phone contacts, without performing any medical assessment.

Moreover, the study did not include a cohort of unvaccinated patients to compare the rate of baseline disease flare-ups in vaccine recipients vs. nonrecipients; thus, adding a matched control group of unvaccinated participants from studies conducted before vaccine approval (a placebo control group could create ethical concerns) would be useful to evaluate the risk of baseline disease flare-up after

vaccination. Furthermore, a retrospective analysis of patient's medical records for a given period before vaccination could describe baseline disease activity before RZV administration, as disease course could be unstable even before vaccination. Indeed, a previous study concluded that RZV vaccination did not determine a change in flare incidence or disease activity in rheumatologic patients compared to a pre-vaccination baseline period [26].

Additionally, we did not investigate the possible role of ongoing pharmacological therapies on the outcomes of interest, especially in the context of chronic pathologies that showed significant results in terms of AEFIs (cardiovascular, endocrine-metabolic), disease flare-up (rheumatologic), and post-vaccination HZ episodes (rheumatologic, onco-hematologic). Further investigation is warranted, as previous literature showed controversial results about frequency of postvaccination AEFIs or disease activity based on received therapy [26,27].

Lastly, a longer follow-up would provide long-term results of both post-vaccination HZ episodes and disease activity.

Thus, the present study demonstrates the safety and overall benefits of RZV in a significance number of fragile patients belonging to different categories. Therefore, in our opinion, RZV should be promoted and actively offered to these patients as part of tailored vaccination programs. This requires interaction with medical specialists and healthcare authorities to safely decrease the burden of HZ in fragile populations. Immunizations strategies targeting subjects at risk and organizational and educational strategies targeting healthcare providers and patients have to be implemented to reduce hesitancy and improve RZV vaccination coverage [56–61].

Ethical statement

The study was approved by the Ethics Committee of Bari's Policlinico General Hospital (study id 7813 approved on November 29th, 2023, protocol no. 0103705|05/12/2023 AOUCPG23|COMET|T). The study follows the principles of the World Medical Association.

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CRediT authorship contribution statement

Pasquale Stefanizzi: Conceptualization, Methodology, Writing – Original Draft, Writing – Reviewing and Editing Supervision. **Lorenza Moscara:** Investigation, Writing – Reviewing and Editing. **Claudia Palmieri:** Investigation, Writing – Original Draft. **Andrea Martinelli:** Formal analysis. **Antonio Di Lorenzo:** Formal analysis. **Vincenzo Venerito:** Writing – Original Draft. **Cinzia Annatea Germinario:** Methodology. **Silvio Tafuri:** Conceptualization, Methodology, Supervision.

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.

Data availability

Data will be made available on request.

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