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ORIGINAL RESEARCH

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Safety profile and medium- to long-term protection of the Recombinant Zoster Vaccine (RZV) in a cohort of high-risk patients: real-world data from a General Hospital in Southern Italy, 2021–2025

Pasquale Stefanizzi [a], Lorenza Moscara[a], Claudia Palmieri[a], Andrea Martinelli[b], Antonio Di Lorenzo[a], Chiara Scaltrito[a], Petra Buonvino[a], Francesca Oliveto[a], Giovanna Pice[a], Laura Marchisella[a], Giuseppe Spinelli[c] and Silvio Tafuri [a,d]

[a]Interdisciplinary Department of Medicine, University of Bari Aldo Moro, Bari, Italy; [b]Local Health Authority of Bari, Bari, Italy; [c]Control Room Unit, Bari Polyclinic General Hospital, Bari, Italy; [d]Alternate Member Management Board ECDC

ABSTRACT

Introduction: Recombinant Zoster Vaccine (RZV) is recommended for Herpes Zoster (HZ) prevention in high-risk patients over 18 years of age.

Research design and methods: This is a prospective population-based study conducted over a three-year period in a Southern Italian General Hospital. The study population was represented by RZV recipients with diverse chronic comorbidities. Adverse Events Following Immunization (AEFIs), baseline disease flares and post-vaccination HZ episodes were evaluated through sequential follow-ups conducted 7 days, 3 months, and 3–38 months post-vaccination, respectively.

Results: Study population included 787 RZV recipients, mostly affected by onco-hematological, cardiovascular and rheumatological disorders. The AEFIs reporting rate was 44.15%. The most frequent symptoms were injection site pain/itching (37.19%), asthenia/malaise (12.74%) and fever (10.30%). Three serious AEFIs with consistent causal association with vaccination were recorded (0.22%), all of which underwent full recovery. Sixteen patients (2.37%) experienced a baseline condition flare-up within 3 months (mean interval 33.88 ± 24.88 days). Multiple baseline disorders (OR:1.97; 95% CI:1.37–2.83; p-value < 0.001) and rheumatological conditions (OR:11.67; 95%CI:2.00–68.27; p-value < 0.01) increased flare risk, while male sex decreased it. Twenty-six vaccinees manifested HZ post-vaccination (cumulative incidence rate 5.05/100,000 person-days), with particularly increased incidence in patients with recurrent/severe HZ history (IRR:14.35; 95%CI:5.64–34.04; p-value < 0.001).

Conclusion: The study demonstrates RZV safety and HZ protection in vulnerable patients, consistently with available evidence.

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Recombinant zoster vaccine; Adverse events following immunization; underlying disease flares; HZ protection; vulnerable patients; Immunocompromising conditions

1. Introduction

Herpes zoster (HZ), or shingles, is a painful and disabling disease that may manifest across a spectrum of clinical manifestations, sometimes severe and associated with substantial morbidity, loss of productivity, and diminished quality of life [1,2]. Neurological complications are the most frequently reported HZ sequelae, with postherpetic neuralgia (PHN) being the most common [3]. Other complications (e.g. ocular, cutaneous, and visceral) occur with progressively lower frequencies [4]. Furthermore, HZ has a significantly high risk of recurrence, particularly among elderly and immunocompromised populations [5].

A Recombinant Zoster Vaccine (RZV), containing recombinant VZV glycoprotein E and the AS01B adjuvant system, was first approved for the prevention of HZ in the United States (US) [6] and Canada [7] in 2017 and in 2018 by the European Medicines Agency (EMA) [8]. The Italian Medicines Agency (AIFA) followed with vaccine authorization on 4 June 2018 [9], but the product became available for use in Italy only in mid-2021 [10]. The introduction of this vaccine marked a radical advancement in Public Health strategies, representing an opportunity to protect at-risk patients from HZ. Indeed, RZV can be administered from the age of 18 years in individuals at increased risk of HZ due to immunodeficiency or immunosuppression [11]. However, prior to RZV approval, such high-risk patients lacked vaccine prophylaxis options, as the live-attenuated zoster vaccine (ZVL), available since 2006 [12], was contraindicated due to age restrictions and/or immune deficiency [13,14]. Indeed, ZVL administration to patients with even low-grade immunosuppression may result in viral dissemination and death, as demonstrated by post-marketing data [15].

Focusing on RZV safety and efficacy, since its first approval over 5 years ago, encouraging evidence from systematic reviews and meta-analyses of randomized controlled trials (RCT) has been collected [16–21]. However, real-world data remain limited, particularly regarding long-term protection against HZ episodes [22–25], while these would be crucial to

CONTACT Pasquale Stefanizzi pasquale.stefanizzi@uniba.it Interdisciplinary Department of Medicine, University of Bari Aldo Moro, G. Cesare Square 11, Bari 70124, Italy

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confirm safety and effectiveness of novel vaccines like RZV in target populations [26].

Within the Bari's Policlinico General Hospital, one of the largest hospitals in Southern Italy, a Vaccination Clinic operates in collaboration with care units to deliver customized immunization programs for vulnerable patients, based on their clinical conditions and risk category. This clinical setting represented an optimal environment to implement a post-marketing active surveillance program to investigate RZV safety profile and the occurrence of post-vaccination HZ episodes in a medically diverse cohort of frail patients.

2. Methods

This is a prospective observational population-based study approved by the Ethics Committee of Bari's Policlinico General Hospital. Study has been conducted from 26 August 2021, through 2 January 2025.

Subjects ≥18 years who accessed the Bari Policlinico General Hospital Vaccination Clinic were screened for RZV eligibility. In line with official recommendations [27], eligibility criteria included:

- Chronic kidney failure or dialysis;
- History of recurrent or severe HZ;
- Candidates for immune-suppressive therapy;
- Receiving immunosuppressive therapy;
- Congenital or acquired immunodeficiency;
- Diabetes mellitus;
- 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.

During their initial visit, eligible patients were offered enrollment in an active surveillance post-vaccination follow-up program through serial telephone interviews to monitor outcomes of interest over time.

All those who provided their informed consent to participate to the study were included in the study population. For each enrolled patient, the following data were recorded: age, sex, reason for vaccine eligibility (only the most prominent per patient), chronic diseases (categorized in rare/genetic, cardiovascular, dermatological, endocrine-metabolic, gastroenterological, ophthalmological and/or ear-nose-throat, onco-hematological, orthopedical, pneumological, psychiatric/neuropsychiatric, gynecological, nephrological-urological, neurological, rheumatological, and chronic infectious diseases). Participants were also asked about any prior history of HZ, including the timing of episodes, and whether they experienced recurrent HZ events (i.e. at least 2 pre-vaccination episodes). In addition, previous HZ vaccination history with ZVL was investigated. All enrolled patients did not receive any other vaccination at the time of RZV administration.

An appointment for the second vaccine dose was scheduled one-to-six months after the first, according to patients' therapeutic needs [28]. Following each dose, patients received a paper diary containing a list of solicited adverse events following immunization (AEFIs) to document any reactions during the week following RZV administration.

Solicited AEFIs were subsequently organized into categories, i.e.:

- Local reactions (injection site pain/itching, redness, swelling, induration);
- Systemic reactions (asthenia/malaise, arthromyalgia, lymphadenopathy, skin rash);
- Fever (> 37°C/ > 98,6°F)
- Neurological symptoms (drowsiness/insomnia, headache, irritability/nervousness);
- Gastrointestinal symptoms (nausea/vomit, diarrhea/abdominal pain);
- Allergic reactions (anaphylaxis, urticaria-like reaction).

The diary also included a blank field where patients could report unsolicited AEFIs. For each AEFI, participants had to document time of resolution, event-related use of medications, and need for medical interventions (including general practitioner consultation, emergency room visit, hospitalization). In hospitalization cases, medical documentation from the inpatient healthcare facility was requested.

All the enrolled patients were recalled by Vaccination Clinic operators at least a week after each dose to collect data recorded in the post-vaccination diary. For patients referring ongoing AEFIs during the first follow-up, resolution, persistence, or potential worsening of the reported signs/symptoms were assessed during the subsequent follow-ups. AEFIs were classified as serious/non-serious according to World Health Organization (WHO) guidelines and EMA's Important Medical Events (IME) list [29,30]. For serious AEFIs requiring access to healthcare services, clinical documentation was requested. For the recorded serious adverse events, causality assessment was conducted using the WHO algorithm [29]. Collected AEFIs' were subsequently registered into the Italian Drug Authority's (AIFA) National Pharmacovigilance Network database in accordance with Italian regulation [31].

During the outpatient visit scheduled for the administration of the second RZV dose, patients were asked about any HZ episodes occurred between the first and second dose. Both HZ episodes experienced before vaccination and between the two doses were classified and analyzed as HZ events occurring prior to the completion of the vaccination cycle.

Subsequently, each patient received a follow-up call at least three months after completing the vaccination course to identify any potential occurrences of HZ episodes and flares/worsening of their main baseline chronic disease. This was defined as a change in the most severe and/or treatment-requiring chronic underlying condition, resulting in one of the following [32–37]:

- 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.

As for safety evaluation, only patients who completed the two-dose RZV series and all the three scheduled safety follow-ups (i.e. at least a week after dose 1, at least a week after dose 2, at least 3 months after completing the vaccination cycle) were included in the analysis.

Between 23 July 2024, and 2 January 2025, all enrolled patients received a telephone call to investigate the occurrence of HZ episodes in the medium- to long-term post-vaccination period. Patients who missed the initial call were contacted on multiple occasions. However, as for the evaluation of the duration of protection against HZ episodes following vaccination, all the patients who completed a valid follow-up at least 3 months after the second RZV dose were included in the analysis.

Overall, the study has been conducted between August 2021 and January 2025, considering both the period during which each enrolled patient received the RZV vaccination cycle and the follow-up period thereafter.

2.1. Statistical analysis

Data collected during the serial follow-up telephone calls 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).

The outcomes of the analysis were:

- AEFIs after RZV administration (outcome 1);
- worsening/flare-up of baseline disease (outcome 2);
- HZ episodes following completion of the vaccination course (outcome 3).

Concerning outcome 1, AEFIs' reporting rates (RR) were calculated as number of completed clinical diaries containing at least one AEFIs divided by the total number of completed clinical diaries, finally multiplied by 100. Moreover, outcomes 1 and 2 were investigated via a series of three multivariable logistic regression models, using the subject's diseases' categories, the overall number of diagnosed conditions and the main reasons for RZV eligibility as independent variables, respectively. All three models investigated sex and age as confounders. In relation to outcome 3, the onset of HZ episodes after immunization was evaluated by calculating their incidence rate and their cumulative incidence rate during follow-up. Kaplan-Meyer's curve was used to describe the progressive depletion of subjects free from post-vaccination HZ episodes from the study population. Finally, cumulative incidence rate ratios (IRR) were calculated between males and females, for history of HZ before completing the RZV course, for subject's diseases' categories and eligibility criteria and for subjects with and without conditions associated with an immunocompromised state (selecting the following RZV eligibility reasons, i.e. 'Chronic kidney failure or dialysis,' 'Candidates for disease-related immune-suppressive therapy,' 'Ongoing immunosuppressive therapy,' 'Congenital or acquired immunodeficiency,' 'Solid organ transplant candidates and recipients,' 'Hematopoietic stem cell transplant candidates and recipients'). For all statistical tests, significance was set at p-value < 0.05.

3. Results

3.1. Population characteristics

A total of 831 subjects were enrolled, with 44 not completing any of the scheduled follow-ups. Thus, 787 patients, enrolled between 26 August 2021, and 25 August 2023, were included in the final study population (response rate 94.71%).

Female patients represented 47.78% (376/787) of the sample. The average age of enrolled subjects was 59.04 ± 13.89 years.

The most common reason for RZV eligibility was an ongoing immunosuppressive therapy, reported by 50.44% of subjects (397/787), followed by programmed or previous solid organ transplant in 12.07% of patients (95/787) and candidate status to immunosuppressive therapy in 11.82% of cases (93/787). Distribution of RZV eligibility reasons across the whole patient sample is resumed in Supplementary Table S1.

Only 1.65% of subjects (13/787) did not report any chronic illnesses; these patients were eligible for RZV administration due to either history of recurrent/severe HZ or splenectomy following trauma. The average number of baseline illnesses was 1.76 (±1.01) per subject (range 0–6, median 1, IQR 1–2). The distribution of patients according to the number of reported chronic diseases is depicted in Supplementary Graph S1. Among these, the most reported categories were onco-hematological (40.91%), cardiovascular (28.97%) and rheumatological diseases (25.79%). The distribution of patients based on underlying disease categories is summarized in Supplementary Table S2.

Furthermore, for 192/787 patients (24.40%), at least a previous HZ episode prior to the completion of the vaccination cycle was recorded. None of the patients had previously received the live-attenuated zoster vaccine (ZVL).

Safety analysis about AEFIs and baseline disease flares (outcomes 1 and 2) was conducted on a subpopulation of 675 subjects (85.77%), for whom all safety follow-ups could be completed. The distribution of chronic diseases and eligibility reasons of the safety subpopulation is provided in Supplementary Tables S3 and S4, respectively.

3.2. Adverse events following immunization (outcome 1)

Out of 1,350 administered doses (two per patient), 596 resulted in one or more AEFIs being reported, for an overall adverse reaction reporting rate (RR) of 44.15/100 completed follow-ups.

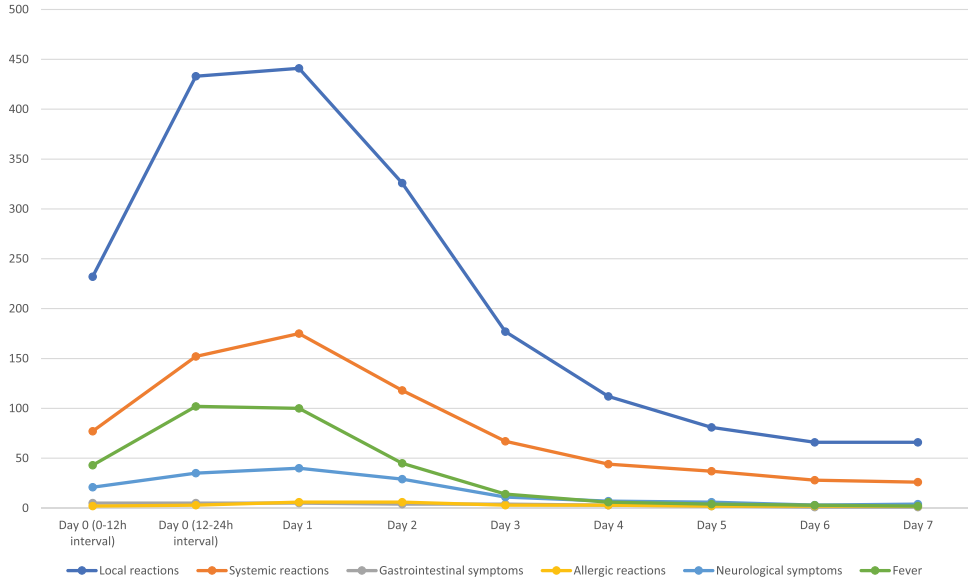
Most AEFIs began within 24 hours after vaccination (84.56%, 504/596). Approximately 3 out of 4 reported AEFIs (76,01%) resolved within the third day after vaccination. Only 41 out of 596 completed follow-ups with at least one referred AEFI (6.88%) highlighted unresolved adverse events by the seventh day after vaccination. However, all of them had undergone complete resolution by the time of the subsequent

follow-up, i.e. at least 3 months after completing the vaccination series. The distribution of reported AEFIs by time of onset and resolution is depicted in Supplementary Graph S2 and S3, respectively, while Graph 1 shows the evolution in time of reported adverse events categories.

Local events (injection site pain/itching, redness, swelling and/or induration) were the most frequently reported AEFIs category (RR 39.04%; 527/1,350), followed by systemic symptoms (RR 15.11%; 204/1,350) and fever (RR 10.30%; 139/1,350). No anaphylaxis events were observed. General practitioner's attention was required after 1.33% of immunizations (18/1,350). Table 1 provides information about AEFIs distribution, both as single events and by belonging category.

Four serious adverse events (SAEs) were reported (RR 0.30/100 completed follow-ups), but only three were deemed to have a consistent causal association with RZV administration (RR: 0.22/100 completed follow-ups) upon causality assessment [29]. These included two cases of hyperpyrexia (highest temperature 40°C/104°F) resolved within 72 hours after onset and one case of a self-described severe local reaction, for which the patient accessed the emergency room (ER), resolved in 4 weeks with anti-histaminic therapy. A table providing details about all reported SAEs, as well as causality assessment evaluation, is available in Supplementary Table S5.

Multivariable logistic regression models fitted to investigate the risk of AEFIs showed a significant protective effect of male



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

Table 1. Distribution of signs and symptoms, as single events and by belonging category. *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.

AEFIs by belonging category and single events	Number of reports	Reporting rate/1,350 administered doses (per 100 completed follow-ups) *
Local reactions	527	39.04
· Injection site pain/itching	502	37.19
· Injection site redness	95	7.04
· Injection site swelling	92	6.81
· Injection site induration	23	1.70
Systemic reactions	204	15.11
· Asthenia/malaise	172	12.74
· Arthromyalgia	74	5.48
· Lymphadenopathy	8	0.59
· Skin rash	12	0.89
Fever	139	10.30
Neurological symptoms	54	4.00
· Headache	48	3.56
· Drowsiness/insomnia	8	0.59
· Irritability/nervousness	5	0.37
Gastrointestinal symptoms	10	0.74
· Nausea/vomit	7	0.52
· Diarrhoea/abdominal pain	5	0.37
Allergic reactions	6	0.44
· Urticaria-like reaction	6	0.44
· Anaphylaxis	0	0
Others	16	1.19

sex (OR: 0.78; 95%CI: 0.63–0.98; p-value < 0.05), older age (OR: 0.97; 95%CI: 0.96–0.97; p-value < 0.001) and a history of cardiovascular disease (OR: 0.64; 95%CI: 0.49–0.86; p-value < 0.05). Endocrine-metabolic diseases, instead, determined a higher risk of AEFIs (OR: 1.41; 95%CI: 1.05–1.09; p-value < 0.05), as well as a history of splenectomy (OR: 2.28; 95%CI: 1.11–4.68; p-value < 0.05).

3.3. Baseline disease flares (outcome 2)

At the follow-up performed at least 3 months after completing RZV vaccination series, 16/1,350 doses (1.19%), administered to 16 different patients, resulted in a flare-up/worsening of the vaccinees baseline chronic condition within 3 months (mean interval 33.88 ± 24.88 days, range 0–68 days). Table 2 shows the distribution of flare-ups based on defining criteria.

In detail, 11 patients experienced a worsening of their rheumatological baseline condition, 2 of their preexisting hematological disease, 2 of their baseline gastroenterological illness, and 1 of the underlying neurological condition. Overall, disease flares did not result in long-term sequelae; all cases either resolved without intervention or responded to therapeutic management by branch physicians, with clinical improvement or sustained stabilization without disease progression.

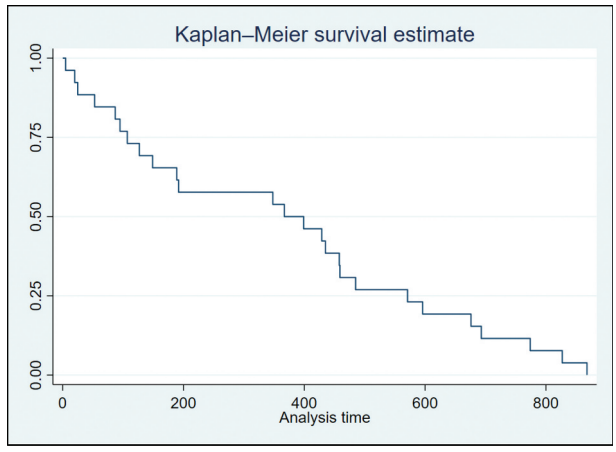
The multivariable logistic regression models investigating the risk of baseline illness flare showed a protective role of male sex (OR: 0.13; 95%CI: 0.03–0.59; p-value < 0.01). A significantly higher risk of disease reactivation was observed in vaccinees with multiple baseline disorders (OR: 1.97; 95%CI: 1.37–2.83; p-value < 0.001) and in patients with rheumatological conditions (OR: 11.67; 95%CI: 2.00–68.27; p-value < 0.01).

3.4. Post-vaccination HZ episodes (outcome 3)

Considering all the enrolled patients who completed at least one of the medium- to long-term follow-ups, 787 contributed 525,295 fully vaccinated person-days. Considering as follow-up time only the days up to the first HZ episode, if any, our patient population contributed 514,799 fully vaccinated person-days.

Out of 787 followed-up subjects, 26 experienced at least one Herpes Zoster episode after completing the vaccination cycle (3.30%). On average, HZ occurred about one year after the second RZV dose (362,85 ± 269,71 days). The cumulative incidence rate of post-vaccination HZ episodes was 5.05 per 100,000 person-days.

Graph 2 shows the Kaplan-Meier survival curve for subjects who experienced a post-vaccination HZ episode ($n = 26$), considering as endpoint the first HZ episode occurred after completing the vaccination cycle.



Graph 2. Kaplan-meier survival curve for subjects who experienced at least a HZ episode after completing the vaccination cycle ($n = 26$).

Considering the subpopulation of individuals who were followed-up for more than 2 years ($n = 445$, accounting for 367,281 person-days), 19 post-vaccination HZ episodes occurred, with a cumulative incidence rate of 5.17 per 100,000 person-days.

Calculating the cumulative incidence rate ratios (IRR), the incidence of HZ episodes after completing the vaccination cycle was found to be significantly lower in males (IRR: 0.28; 95%CI: 0.09–0.73; p-value < 0.05) and in patients under immunosuppressive treatment (IRR: 0.38; 95%CI: 0.14–0.92; p-value < 0.05); this finding was confirmed when considering the whole population of subjects suffering from conditions associated with an immunocompromised state, as well (IRR: 0.12; 95%CI: 0.05–0.30; p-value < 0.001). On the other hand, belonging to the patient's group enrolled due to history of recurrent/severe HZ resulted in a significantly higher incidence of manifesting at least one HZ episode after receiving the vaccination cycle (IRR: 14.35; 95%CI: 5.64–34.04; p-value < 0.001). A similar result emerged for patients who reported a HZ episode before completing RZV prophylaxis, regardless of the reason of RZV eligibility and referred comorbidities (IRR: 8.71; 95%CI: 3.51–24.51; p-value < 0.001).

4. Discussion

The present investigation addressed the limited availability of comprehensive real-world evidence regarding the safety and effectiveness of RZV in vulnerable populations by examining a substantial cohort of patients with diverse underlying pathologies and clinical conditions ($n = 787$).

In terms of safety, the occurrence of AEFIs and baseline disease flares were investigated. The adverse reaction

Table 2. Flare-up and worsening of baseline disease, by classification criteria.

Flare-up definition criteria	Number of flare-ups < 3 months postvaccination
Need for therapy changes.	4
Need for increased dosage of previous therapy.	3
Need to add new drugs to existing therapy.	2
Worsening of the disease certified by imaging diagnostics and/or biochemical tests.	2
Worsening of signs and symptoms certified by a branch physician	5

reporting rate during the seven days post-vaccination period was 44.15%. Despite heterogeneity among vulnerable cohorts [38,39], our findings are consistent with those provided by a recent Italian observational study examining a medically diverse patient population [40], likely due to comparable underlying comorbidity profiles. In contrast, the diminished AEFIs incidence reported in passive surveillance investigations is coherent with the phenomenon of underreporting in passive monitoring systems [41,42]. Reporting rates are even lower when derived from administrative databases, relying on hospital admissions and drug prescriptions [43]. Both AEFIs distribution and rate of serious adverse events (SAEs) with consistent causal association with vaccination (0.22%) align with previous real-life active surveillance studies in vulnerable populations [23,38,40,44–46].

Regarding demographic data, the analysis demonstrated that male sex and older age were associated with a decreased risk of AEFIs. Both findings are consistent with previously literature about RZV and other vaccines as well [47–49].

Among RZV eligibility criteria, only splenectomy history was significantly associated with increased AEFIs risk. However, in this subgroup (22/675 patients), most AEFIs were local reactions with few cases of mild asthenia/malaise and fever (< 38.5°C) lasting ≤2 days. None required medical consultation or hospitalization. Therefore, this isolated finding does not compromise vaccine safety in this population. Further comparison with safety data in RZV recipients with asplenia would be valuable when available.

RZV pre-marketing evaluations showed that neither type nor count of preexisting medical conditions did affect RZV safety profile [50]. Our real-world data confirmed that comorbidity count did not influence AEFIs risk, while specific conditions showed associations: cardiovascular disease history conferred protection against AEFIs, while endocrine-metabolic disorders increased the risk. Both findings align with previous research about SARS-CoV2 vaccine, indicating safety in patients with cardiovascular disorders [51] and higher AEFIs reporting rates among diabetic recipients compared to non-diabetic vaccinees [52].

Most of the available real-life data about post-RZV relapses of baseline disease focus on patients with rheumatological conditions [23,38,44–46,53,54]. In our study population, 2.37% of patients (16/675) reported a flare-up/worsening of their baseline chronic condition within three months after completing the vaccination course (mean interval 33.88 ± 24.88 days). Most of these (11/16) experienced a flare of symptoms related to rheumatoid and/or psoriatic arthritis. Considering rheumatologic patients only, the rate of disease flare-up (11/174, 6.32%) is consistent with previous findings, despite great heterogeneity between studies (ranging from no exacerbations [44] to flares recorded in 16% of patients in the post-vaccination risk period) [38,45,46,53,54]. Inferential statistical analysis confirmed that patients with rheumatological conditions exhibited a significantly higher risk of disease reactivation following RZV (OR: 11.67; 95%CI: 2.00–68.27; p-value < 0.01). Notably, in our patients, clinical improvement occurred either spontaneously or through therapeutic intervention, with none resulting in permanent disease progression. Thus, although our model indicated an increased risk of post-RZV flare-ups in rheumatology patients, such finding – alongside the characteristics of the observed flares – suggest that these exacerbations may be of limited clinical concern. Supporting the overall safety profile of RZV in this population, a recent study found no higher relative risk of disease relapse in rheumatoid arthritis patients when post-vaccination flare rates were compared to self-controlled comparison periods [55]. Moreover, further investigation about these patients is warranted, given preliminary data suggesting that RZV may not only be safe, but also potentially confer additional benefits, including reduced disease activity and mortality [56].

Multivariate regression analyses also showed that a greater number of comorbidities was associated with a higher risk of disease flare-up, consistent with previous evidence regarding the association between multiple comorbid conditions and patient-reported flares following SARS-CoV-2 vaccination [57].

The remaining baseline disease worsening cases included: transient paresthesia in a patient with multiple sclerosis (MS), who had experienced similar symptoms following other vaccinations; a neurological complication in a patient with leukemia; deteriorating laboratory parameters in an onco-hematological patient; intestinal symptoms flares in two patients with inflammatory bowel disease (IBD). As these represent isolated events in our cohort, such findings would need to be compared with larger real-life studies to better understand their significance. Available evidence indicates that patients with IBD who receive RZV do not demonstrate an increased risk of disease flare compared to unvaccinated IBD patients [58]. As regards patients with MS, vaccination did not lead to a change in the annualized relapse rate and the risk of hospitalization due to MS flare compared to a pre-vaccination period [59,60].

Within our cohort, male sex demonstrated a protective effect against the risk of baseline disease exacerbation. Although this finding may be influenced by sex distribution of patients with rheumatologic conditions (73.56% females), it aligns with previous evidence indicating female sex as a risk factor for post-vaccination disease flares [61,62].

Despite not employing a gold standard methodology for vaccine effectiveness assessment, this study captured data on reported HZ episodes over a medium to long-term follow-up period, ranging from 3 to 38 months following completion of the 2-dose RZV series. Incident HZ occurred in 26/787 patients who completed the vaccination cycle (3.30%, cumulative incidence rate 5,05 per 100,000 person-days), approximately one year after the second RZV dose (range 5 - 868 days). Several post-marketing studies evaluating the real-world effectiveness of RZV vaccination have recently been published [16,17,22–24,63–65]. However, these studies used different criteria for identifying post-vaccination HZ cases and various methodologies for estimating vaccine protection. As a result, data are highly heterogeneous and difficult to compare with our findings. Among these works, a retrospective cohort study of 132,672 patients with iatrogenic immunosuppression due to inflammatory arthritis found that only 256 patients (0.19%) experienced a HZ episode after completing the 2-dose RZV regimen [63]. A single-center, prospective, cohort study in allogeneic hematopoietic stem cell transplant recipients aged ≥18 years, who received complete RZV prophylaxis, reported

an HZ incidence of 7.75/100,000 person-days [64]. In contrast, another investigation detected a much lower HZ incidence rate (0.49/100,000 person-days) in vaccinated IBD patients over 60 years of age [65].

The cumulative incidence rate of post-vaccination HZ episodes was comparable in the subgroup of individuals ($n = 445$) who were followed up for > 24 months (5.17 per 100,000 person-days), in line with previous evidence showing minimal waning of vaccine effectiveness 4 years after vaccination [22]. This result may suggest that vaccine-induced immune protection could be more strongly influenced by the individual patient's characteristics than by the time elapsed since the completion of the vaccination regimen.

Among the 26 post-vaccination HZ cases in our cohort, only one developed post-herpetic neuralgia, with no hospitalizations required. With 19 of 26 cases occurring in patients with previous HZ, prior HZ history was demonstrated to be associated with significantly increased incidence of post-vaccination HZ episodes (IRR: 8.71; 95%CI: 3.51–24.51; $p < 0.001$), in line with available evidence [66]. The risk was particularly pronounced in those vaccinated due to recurrent/severe HZ history (IRR: 14.35; 95%CI: 5.64–34.04; $p < 0.001$). However, 12/26 patients reported milder symptoms compared to pre-vaccination episodes. Males demonstrated significantly lower post-vaccination HZ incidence compared to females (IRR: 0.28; 95%CI: 0.09–0.73; $p < 0.05$), consistent with previous epidemiological data [67,68]. Interestingly, patients suffering from conditions associated with an immunocompromised state (91.11% of the sample) were shown to have a significantly lower incidence of post-vaccination HZ episodes (IRR: 0.12; 95%CI: 0.05–0.30; p-value < 0.001). These findings suggest that timely vaccine administration may be protective even in individuals with compromised immune function, further supporting current recommendations to vaccinate patients with primary or secondary immune deficiency (including those with scheduled immunosuppressive therapy), prior to possible onset of HZ manifestations.

One of the strengths of this study lies in the implementation of a prospective active safety surveillance program, along with additional medium- to long-term investigations about RZV-related HZ protection, in a relevant number of frail patients with heterogeneous medical conditions. This is particularly important as post-vaccination real-life data in vulnerable populations are still sparse, especially those that consider RZV impact on chronic baseline conditions and evaluate long-term protection. Moreover, we investigated the role of a significant number of demographic and clinical variables on the outcomes of interest.

However, our sample size might be insufficient to detect rare AEFIs, assess long-term protective effect induced by RZV, or draw statistically significant conclusions about specific patient subgroups. In addition, data collection relied primarily on patient self-reporting during scheduled phone contacts and patient-provided medical documentation, without direct medical assessment or linkage to administrative data/information systems (e.g. hospital discharge summaries, prescription records). Furthermore, given the relapsing-remitting nature of many underlying pathologies, the lack of review of pre-vaccination medical records prevented comparison of baseline disease exacerbation rates before and after RZV administration. Moreover, the lack of a control group did not allow vaccine effectiveness assessment. Additionally, our analysis did not evaluate how ongoing pharmacological interventions might have influenced the outcomes of interest.

Therefore, further investigation of these findings is warranted. Expanding the sample size would be beneficial to examine rare AEFIs and enhance the statistical power of the observed associations between variables and outcomes. Incorporating retrospective medical record review or comparison with a matched historical control cohort would enable more robust assessment of post-vaccination disease exacerbation risk. Furthermore, implementing a control group would allow evaluation of RZV effectiveness in immunocompromised patients, addressing a critical knowledge gap regarding vaccine effectiveness and duration of protection in vulnerable populations. In future articles, it would also be interesting to evaluate the role of incident infections requiring immunosuppressive therapy (e.g. corticosteroids), such as SARS-CoV-2. This would allow to identify possible interference by further sources of immune suppression on RZV effectiveness.

In conclusion, our findings support the active promotion and implementation of RZV vaccination within tailored and timely immunization programs for vulnerable patients. This target requires a multifactorial approach, including collaboration between medical specialists and healthcare authorities, to achieve substantial HZ protection in high-risk populations.

Author contributions

CRediT: **Pasquale Stefanizzi:** Conceptualization, Writing – original draft, Writing – review & editing; **Lorenza Moscara:** Conceptualization, Writing – original draft; **Claudia Palmieri:** Writing – original draft; **Andrea Martinelli:** Formal analysis; **Antonio Di Lorenzo:** Formal analysis; **Chiara Scaltrito:** Data curation; **Petra Buonvino:** Data curation; **Francesca Oliveto:** Data curation; **Giovanna Pice:** Data curation; **Laura Marchisella:** Formal analysis; **Giuseppe Spinelli:** Data curation; **Silvio Tafuri:** Supervision, Writing – review & editing.

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Declaration of interest

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Ethical statement

This study was performed in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Bari Policlinico General Hospital.

AI-based tools and technologies

This paper did not include use of any AI-based tools and technologies in its development.

ORCID

Pasquale Stefanizzi http://orcid.org/0000-0002-3279-0196
Silvio Tafuri http://orcid.org/0000-0003-4194-0210

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