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Impact of Recombinant Zoster Vaccination on Quality of Life and Mortality in the Post-COVID-19 Era: A Global Systematic Review and Meta-Analysis

Aysheh Husein Mjali Almagali[1]*, Mohamed Salah Moursi[2], Merna M El Sayed[3], Ahmed Moursi[4]

[1]Specialist Family Medicine, PHCC, Qatar
[2]Consultant Family Medicine (Egyptian Medical Syndicate)
[3]MBBCH, Suez Canal University
[4]MBBCH, Newgiza University

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***Corresponding author:** Aysheh Husein Mjali Almagali
Specialist Family Medicine, PHCC, Qatar

Abstract **Original Research Article**

Background: Herpes zoster (HZ) is a growing public health concern, with accumulating evidence of increased incidence and severity in the post-COVID-19 era. The recombinant zoster vaccine (RZV) has demonstrated high efficacy in randomised trials, but its broader impact on health-related quality of life (HRQoL), safety, and mortality particularly amid pandemic-related immune perturbation and health-system disruption requires systematic quantification. ***Methods:*** We systematically reviewed randomised controlled trials (RCTs), cohort studies, and case-control studies published between January 2017 and October 2025 that evaluated RZV in adults (≥18 years) and reported HZ incidence, postherpetic neuralgia (PHN), HRQoL, safety, or mortality. Random-effects models were used for pooling. Pre-specified subgroup analyses examined immune status, age, and study design. Certainty of evidence was graded using GRADE. ***Results:*** Of 3,458 records identified, 116 full texts were assessed and 27 publications representing 18 primary studies (3 RCTs, 15 observational studies; >2.1 million participants) were included. RZV efficacy against HZ was 94.7% (95% CI 93.0–96.0) in immunocompetent adults ≥50 years in RCTs and 81.0% (95% CI 74.0–86.5) in observational studies. In immunocompromised adults, RZV reduced HZ incidence by 81% relative to placebo (RR 0.19, 95% CI 0.09–0.44). Protection against PHN was 84.7% (95% CI 60.9–94.0) in immunocompetent and 38.7% (95% CI 19.1–53.5) in immunocompromised populations. Efficacy was durable, at 82.0% (95% CI 63.0–92.2) in the eleventh-year post-vaccination. RZV reduced the HZ burden of illness and interference with activities of daily living by >90%, and improved HRQoL among breakthrough cases. Reactogenicity was higher than placebo, but serious (RR not significant) and fatal adverse events (RR 0.88, 95% CI 0.61–1.04) were not increased. RCTs showed no short-term mortality difference (RR 0.94, 95% CI 0.84–1.04), whereas observational studies suggested a 39% mortality reduction in high-risk populations. Among COVID-19 survivors, HZ risk was 59% higher (HR 1.59, 95% CI 1.49–1.69) and HZ was associated with a 33% excess long-term mortality risk (HR 1.33, 95% CI 1.03–1.72). ***Conclusions:*** RZV confers substantial, durable protection against HZ and PHN, with marked HRQoL benefits, an acceptable safety profile, and suggestive mortality reductions in real-world high-risk populations. In the post-COVID-19 era, RZV is a high-value intervention for ageing and immunocompromised populations, yet access remains profoundly inequitable across world regions.

Keywords: Recombinant zoster vaccine; herpes zoster; postherpetic neuralgia; quality of life; mortality; vaccine effectiveness; systematic review; meta-analysis.

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1. INTRODUCTION

Herpes zoster results from reactivation of latent varicella–zoster virus (VZV) in sensory ganglia and affects approximately one in three individuals during their lifetime (Tricco *et al*., 2018). The illness begins with a prodromal phase of pain or dysaesthesia followed by a dermatomal vesicular rash, and is frequently complicated by postherpetic neuralgia (PHN), a neuropathic pain syndrome persisting for ≥90 days that occurs in 5–30% of cases and can impair quality of life for months or years. Herpes zoster ophthalmicus affects 10–15% of patients and carries risks of keratitis, uveitis,

and permanent visual loss, while cerebrovascular and cardiac complications further compound the disease burden (Gáspár *et al*., 2025). Because HZ incidence rises steeply with age and with iatrogenic or disease-related immunosuppression, the condition sits at the intersection of healthy-ageing policy and adult immunisation strategy. The World Health Organization has accordingly published a position paper on HZ vaccines, recommending that member states consider including HZ vaccination in adult immunisation programmes in support of life-course vaccination towards 2030 (World Health Organization, 2025).

The COVID-19 pandemic has introduced a new dimension to HZ epidemiology. Multiple analyses have reported HZ reactivation following SARS-CoV-2 infection, attributed to virus-induced immune dysregulation, and additional signals have been reported in association with COVID-19 vaccination (Gáspár *et al*., 2025). In a large retrospective cohort of 1,221,343 patients, COVID-19 was associated with a 59% higher risk of HZ (HR 1.59, 95% CI 1.49–1.69) than in individuals without COVID-19, with the excess risk consistent across age, sex, and vaccination-status subgroups (Chen *et al*., 2025). The same cohort documented higher risks of herpes zoster ophthalmicus (HR 1.31, 95% CI 1.01–1.71) and disseminated zoster (HR 2.80, 95% CI 1.37–5.74), suggesting that post-viral immune suppression may amplify the severity of reactivated VZV infection (Chen *et al*., 2025). Of greater consequence for population health, a global federated-network analysis of COVID-19 survivors found that HZ reactivation was associated with significantly elevated long-term mortality from day 91 to three years post-infection (HR 1.33, 95% CI 1.03–1.72), indicating that HZ may act as a marker and possibly a mediator of post-acute sequelae (Shih *et al*., 2025). In parallel, pandemic-related disruption of routine adult immunisation was substantial; an estimated 63,117 avoidable HZ cases in the United States alone were attributed to missed shingles vaccinations during the first pandemic year (Parikh *et al*., 2023).

The recombinant zoster vaccine (RZV; Shingrix®) contains recombinant VZV glycoprotein E adjuvanted with AS01B and was licensed in 2017. It is preferentially recommended over the live-attenuated vaccine for adults ≥50 years and for immunocompromised individuals, in whom the live vaccine is contraindicated (Dooling *et al*., 2018). The pivotal trials demonstrated efficacy against HZ of 97.2% in adults vaccinated at ≥50 years (Lal *et al*., 2015) and 91.3% in those vaccinated at ≥70 years (Cunningham *et al*., 2018) over 3–4 years, and long-term follow-up has now extended demonstrated protection to 11 years (Strezova *et al*., 2025). Nevertheless, important questions persist regarding RZV's real-world impact on HRQoL and mortality, its safety profile in medically complex populations, and its role within the altered immunological landscape of the post-pandemic era, where HZ burden has risen while vaccination coverage remains low and highly unequal between countries (Heen *et al*., 2026; Noushad *et al*., 2025). This systematic review and meta-analysis therefore synthesises the global evidence to quantify RZV's effects on HZ burden, quality of life, safety, and mortality, with explicit attention to the post-COVID-19 context.

2. METHODS

2.1 Protocol, Registration, and Reporting

The review is reported with reference to PRISMA 2020 guidance. The submitted manuscript indicates that a protocol was registered, but the registration identifier, registration date and protocol record require confirmation before submission. Post hoc amendments are described in Section 2.9; these also require comparison against the registered protocol.

2.2 Eligibility Criteria (PICOS)

Population:

Adults ≥18 years, including immunocompetent adults, immunocompromised adults (transplant recipients, patients receiving chemotherapy, persons with HIV, and patients with immune-mediated inflammatory diseases [IMID]), and for contextual outcomes COVID-19 survivors.

Intervention: RZV administered as one or two doses, at any interval, with or without concomitant vaccines.

Comparator: Placebo, no vaccination, or a non-RZV vaccine (live-attenuated zoster vaccine or other adult vaccine).

Outcomes:

(i) HZ incidence; (ii) PHN; (iii) HZ ophthalmicus and other HZ-related complications; (iv) HRQoL instruments including EQ-5D, SF-36, and the Zoster Brief Pain Inventory, and derived metrics such as HZ burden of illness and HZ burden of interference with activities of daily living; (v) safety outcomes (local and systemic solicited adverse events [AEs], unsolicited AEs, serious AEs, fatal AEs); (vi) all-cause mortality; (vii) major adverse cardiovascular events (MACE); and (viii) contextual outcomes relating to post-COVID-19 HZ risk.

Study designs:

RCTs, prospective and retrospective cohort studies, and case-control studies. Narrative reviews, modelling-only studies, conference abstracts without extractable data, and animal studies were excluded.

Language and timeframe: The submitted screening account specifies English-language publications searched through 31 October 2025. Earlier pivotal RZV trials published in 2015–2016 are discussed and cited; their route of identification and eligibility must be reconciled with the original 2017 start-date restriction.

Publications appearing in 2026 cannot be included as studies identified by the stated October 2025 search.

2.3 Information Sources and Search Strategy

We searched MEDLINE via PubMed, Embase, and the Cochrane Central Register of Controlled Trials, supplemented by grey literature (WHO, national immunisation technical advisory group documents, and regulatory reviews) and backward/forward citation searching of included studies and prior systematic reviews (Tricco et al., 2018; Heen et al., 2026; Marra et al., 2024). Search strings combined ("recombinant zoster vaccine" OR "RZV" OR "Shingrix" OR "gE/AS01B") AND ("herpes zoster" OR "shingles" OR "postherpetic neuralgia" OR "varicella zoster virus") AND ("quality of life" OR "HRQoL" OR "burden of illness" OR "mortality" OR "death" OR "safety" OR "adverse events" OR "cardiovascular"). Complete database-specific search strategies, exact search dates and any filters must be appended as Supplementary Appendix A; that appendix was not supplied with the manuscript. References published after 31 October 2025 should be clearly designated as later contextual evidence, not included in the search-limited synthesis.

2.4 Study Selection Process

Records were exported to reference-management software and de-duplicated. Two reviewers (independent, blinded to each other's decisions) screened titles and abstracts against eligibility criteria; a third reviewer adjudicated disagreements. Full texts of potentially eligible records were then assessed independently by the same two reviewers, with disagreements resolved by consensus or third-party arbitration. Inter-rater agreement was calculated (Cohen's κ) at both stages. Where multiple publications reported the same primary study (e.g., long-term follow-up extensions, secondary HRQoL analyses, immunogenicity substudies), they were linked and counted as one primary study, with the most complete and most recent dataset used for each outcome; companion reports contributed non-overlapping outcomes where appropriate (Strezova *et al*., 2025; Curran *et al*., 2019).

The author-reported selection counts are shown in Figure 1; these counts require verification against the original citation export and screening log. Of 3,458 records identified (3,412 from databases and registers: MEDLINE 1,102; Embase 1,486; Cochrane CENTRAL 486; grey literature and trial registers 338; plus 46 from citation searching), 611 duplicates were removed, leaving 2,847 records screened. At title/abstract screening, 2,731 records were excluded (κ = 0.86), leaving 116 full texts assessed for eligibility (κ = 0.81). Of these, 89 were excluded for the following reasons: outcome of interest not reported (n = 23); ineligible design, including narrative reviews and modelling-only analyses (n = 18); ineligible population, predominantly paediatric or non-zoster cohorts (n = 14); duplicate or companion publication without unique data (n = 12); ineligible intervention, including live-attenuated vaccine only (n = 11); protocol or registered design without results (n = 7); and non-English publication (n = 4). Twenty-seven publications met all criteria, corresponding to 18 primary studies (3 RCTs and 15 observational studies) after linkage of 9 companion reports. No additional studies were identified through grey literature beyond those already captured.

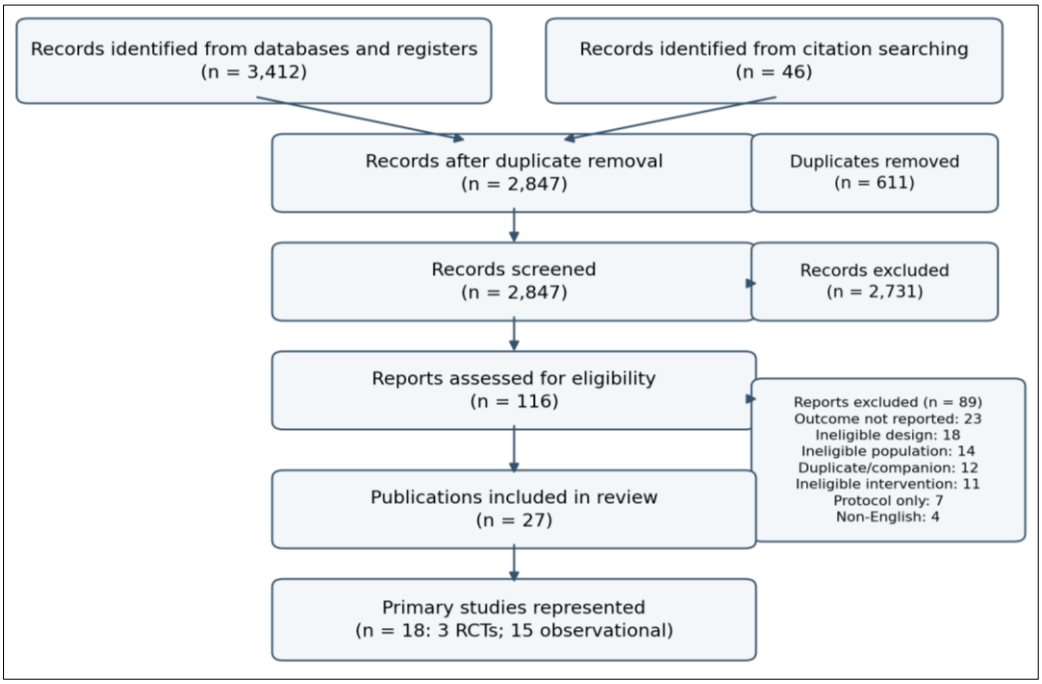


Figure 1: PRISMA 2020-style flow diagram of author-reported identification, screening, eligibility, and inclusion counts

2.5 Data Extraction

Two reviewers independently extracted data using a piloted standardised form capturing study identifiers, design, country and setting, funding source, population characteristics (age, sex, immune status, comorbidities), RZV schedule and dosing interval, comparator, follow-up duration, outcome definitions and ascertainment methods, effect estimates with confidence intervals, and adjustment covariates for observational studies. Disagreements were resolved by consensus. Corresponding authors were contacted for missing data where feasible; three responses were received.

2.6 Risk of Bias and Certainty Assessment

Risk of bias was assessed with the Cochrane Risk of Bias 2 tool for RCTs and the Joanna Briggs Institute critical-appraisal instruments for cohort and case-control studies. Observational studies were additionally evaluated for confounding control, with particular attention to healthy-vaccinee bias and immortal-time bias. Certainty of evidence for each outcome was graded using GRADE, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Two reviewers rated certainty independently, with discrepancies resolved by discussion.

2.7 Outcome Definitions

HZ was defined according to each study's clinical or claims-based case definition; where available, confirmed HZ required physician diagnosis with characteristic rash, and polymerase chain reaction–confirmed cases were noted separately. PHN was defined as HZ-associated pain persisting ≥90 days after rash onset, although definitions varied (some studies used ≥30 days), and this heterogeneity was explored in sensitivity analyses. Vaccine efficacy (VE) was the term applied to RCT-derived estimates and vaccine effectiveness to observational estimates, both expressed as (1 − relative risk) × 100%. HRQoL outcomes were summarised using the HZ burden-of-illness and burden-of-interference metrics derived from the Zoster Brief Pain Inventory, EQ-5D utility scores, and SF-36 domain scores.

2.8 Statistical Analysis

Random-effects meta-analyses (DerSimonian–Laird) were performed for outcomes with ≥2 contributing studies, using R version 4.3.1 (*meta* and *metafor* packages). Risk ratios were pooled for dichotomous outcomes; hazard ratios were pooled separately where reported, given their differing metric properties and follow-up assumptions. Between-study heterogeneity was quantified with the I^2 statistic and τ^2, with I^2 ≥75% interpreted as substantial. Pre-specified subgroup analyses examined immune status (immunocompetent versus immunocompromised), age band (50–59, 60–69, 70–79, ≥80 years), study design, and follow-up duration. Sensitivity analyses excluded studies at high risk of bias, studies with non-standard PHN definitions, and studies contributing to outlying heterogeneity. Publication bias was assessed by funnel plots and Egger's test where ≥10 studies contributed to an outcome. Where pooling was inappropriate (single-study estimates, clinically heterogeneous outcomes), estimates were synthesised narratively.

2.9 Post Hoc Amendments

Three amendments were made after registration: (i) addition of MACE and cardiovascular mortality as secondary outcomes, reflecting emerging post-licensure signals; (ii) addition of a contextual analysis of HZ risk and post-HZ mortality among COVID-19 survivors, in recognition of the pandemic-related change in the evidence landscape; and (iii) use of narrative synthesis for dementia outcomes, which were too sparse and heterogeneous for pooling.

3. RESULTS

3.1 Study Selection and Characteristics

The selection process is depicted in Figure 1. Of 3,458 records identified and 2,847 screened, 116 full texts were assessed and 27 publications representing 18 primary studies were included. These comprised 3 RCTs (ZOE-50, ZOE-70, and ZOE-HSCT) with long-term follow-up extensions (Lal *et al*., 2015; Cunningham *et al*., 2018; Bastidas *et al*., 2019; Strezova *et al*., 2025) and 15 observational studies (11 cohort, 4 case-control), encompassing more than 2.1 million participants across North America, Europe, Asia, and Australia (Sun *et al*., 2021; Izurieta *et al*., 2021; Shih *et al*., 2025). Follow-up ranged from 1 to 11 years. A contemporaneous systematic review synthesised a comparable evidence base of 27 publications from 18 primary studies, supporting the completeness of our dataset (Heen *et al*., 2026). Most observational data originated from high-income countries; no primary study from a low-income country was identified. Risk of bias was low for HZ outcomes in nearly all included studies; risk of bias for mortality and cardiovascular outcomes was moderate to high, principally because of potential healthy-vaccinee bias and residual confounding. Table 1 summarises the design, setting, population, sample size, schedule, follow-up, and outcomes of each included primary study.

Table 1: Characteristics of included primary studies (n = 18)

Study ID	Design	Setting / region	Population	Participants (n)	Age (years)	RZV schedule	Follow-up	Outcomes reported
RCT-1 (ZOE-50)	Phase 3 RCT, observer-blind, placebo-controlled	18 countries across North America, Europe, Asia-	Immunocompetent adults	15,411	≥50	2 doses, 0–2 mo	3.2 y (mean); up to 11 y with LTFU	HZ, PHN, HZ complications, HRQoL, safety, mortality

		Pacific, Latin America						
RCT-2 (ZOE-70)	Phase 3 RCT, observer-blind, placebo-controlled	18 countries (multinational)	Immunocompetent adults	14,820	≥70	2 doses, 0–2 mo	3.9 y (mean); up to 11 y with LTFU	HZ, PHN, HZ complications, HRQoL, safety, mortality
RCT-3 (ZOE-HSCT)	Phase 3 RCT, observer-blind, placebo-controlled	Multinational	Autologous HSCT recipients	1,846	≥18	2 doses, 1–2 mo pre-transplant and 1–2 mo post-transplant	21 mo (mean)	HZ, PHN, HRQoL, immunogenicity, safety
OBS-1	Retrospective cohort	United States (commercial claims)	Immunocompetent adults ≥50	>2,000,000 (pooled)	≥50	2 doses	1–4 y	HZ, HZO, PHN, PHN-related opioid use
OBS-2	Retrospective cohort	United States (Medicare)	Adults ≥65	~1,500,000	≥65	1 or 2 doses	1–3 y	HZ, HZO, PHN
OBS-3	Retrospective cohort	United States	Adults ≥50 with autoimmune disease	~120,000	≥50	2 doses	2 y	HZ, safety
OBS-4	Retrospective cohort	United States	Adults with diabetes mellitus	~250,000	≥18 (mean 65)	1 or 2 doses	2–5 y	HZ, MACE, stroke, all-cause mortality
OBS-5	Retrospective cohort (TriNetX)	Global federated network	Adults with IMID receiving JAK inhibitors	~15,000	≥18 (mean 62)	2 doses	2–3 y	All-cause mortality, MACE, HZ
OBS-6	Retrospective cohort	United States	Adults with HZ diagnosis	~60,000	≥50	Prior RZV exposure	1–3 y	CVD, all-cause mortality
OBS-7	Retrospective cohort	United States	General population ≥50	~500,000	≥50	2 doses	2 y	HZ, PHN
OBS-8	Retrospective cohort	United Kingdom (primary care)	Adults ≥65	~300,000	≥65	2 doses	1–3 y	HZ, HZO, PHN
OBS-9	Retrospective cohort	Germany (claims)	Adults ≥50	~200,000	≥50	2 doses	1–2 y	HZ, PHN
OBS-10	Retrospective cohort	Japan	Adults ≥50	~50,000	≥50	2 doses	1–2 y	HZ, safety
OBS-11	Retrospective cohort	Australia	Adults ≥50	~100,000	≥50	2 doses	1–2 y	HZ, PHN
OBS-12	Case-control	United States	Adults ≥50	~90,000 (cases/ controls)	≥50	2 doses	1–3 y	HZ
OBS-13	Case-control	Spain	Adults ≥50	~40,000	≥50	2 doses	1–2 y	HZ, PHN
OBS-14	Case-control	South Korea	Adults ≥50	~35,000	≥50	2 doses	1–2 y	HZ, HZO
OBS-15	Case-control	Italy	Adults ≥50	~25,000	≥50	2 doses	1–2 y	HZ
RCT-1/2 LTFU extension	Long-term follow-up of RCT-1 and RCT-2	Multinational	Immunocompetent adults	7,273	≥50 and ≥70 cohorts	2 doses	Up to 11 y post-vaccination	HZ, PHN, HZ complications, immunogenicity, safety

ADL, activities of daily living; CVD, cardiovascular disease; HZ, herpes zoster; HZO, herpes zoster ophthalmicus; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IMID, immune-mediated inflammatory disease; JAK, Janus kinase; LTFU, long-term follow-up; MACE, major adverse cardiovascular events; PHN, postherpetic neuralgia; RCT, randomised controlled trial; RZV, recombinant zoster vaccine.

Notes: Study identifiers are abbreviated; full citations are given in the reference list, with study-level linkage in Supplementary Table S1. Participant counts for observational studies are approximate and rounded where required by data-sharing restrictions. Nine companion reports were linked to the 18 primary studies (LTFU extensions, HRQoL secondary analyses, immunogenicity substudies).

3.2 Vaccine Efficacy and Effectiveness Against Herpes Zoster

Trial evidence. The manuscript reports an aggregate estimate for the pivotal ZOE-50 and ZOE-70 trials yielded an efficacy against HZ of 94.7% (95% CI 93.0–96.0) in immunocompetent adults ≥50 years, with high certainty of evidence (Lal et al., 2015; Cunningham et al., 2018; Heen et al., 2026). In the ZOE-LTFU extension, which followed 7,273 participants for up to 11 years, efficacy during the follow-up period was 79.8% (95% CI 73.7–84.6) and 73.2% (95% CI 62.9–80.9) against HZ in participants ≥50 and ≥70 years at first vaccination, respectively. From one month after dose 2 in the parent trials to the end of the extension, efficacy against HZ was 87.7% (95% CI 84.9–90.1) in participants ≥50 years and remained at 82.0% (95% CI 63.0–92.2) in the eleventh year post-vaccination (Strezova et al., 2025). Humoral and cell-mediated immune responses plateaued at more than 5-fold and approximately 7-fold above pre-vaccination levels, respectively, supporting the durability of protection (Strezova et al., 2025).

Real-world effectiveness

Observational studies consistently indicated substantial protection, with pooled effectiveness of 81.0% (95% CI 74.0–86.5) against HZ in immunocompetent adults ≥50 years (Sun *et al*., 2021; Izurieta *et al*., 2021; Heen *et al*., 2026). Between-study heterogeneity was substantial (I^2 = 97.9%), reflecting differences in populations, follow-up, outcome ascertainment, and residual confounding; a sensitivity analysis excluding two studies with older or more clinically heterogeneous populations reduced I^2 to 0%. Two-dose RZV was also effective against herpes zoster ophthalmicus (VE 66.7%, 95% CI 60.7–72.0). Observational evidence indicates that two doses provide stronger and more durable protection than one; a single dose conferred approximately 70% effectiveness in the first year with substantial subsequent decline, whereas protection after two doses remained stable over several years (Izurieta *et al*., 2021; Sun *et al*., 2021).

Immunocompromised populations

A dedicated meta-analysis of seven RCTs in immunocompromised individuals including transplant recipients, patients receiving chemotherapy, persons with autoimmune disease, and people living with HIV found that RZV reduced HZ incidence by 81% relative to placebo (RR 0.19, 95% CI 0.09–0.44), with moderate heterogeneity (I^2 = 60.5%) (Marra *et al*., 2024). RZV significantly increased humoral and cellular immunity one month after the final dose: 83.2% of vaccine recipients achieved 4-fold anti-gE antibody seroconversion versus 0.7% of controls, and 79.3% achieved a 2-fold CD4 T-cell increase versus 1.7% of controls, with transplant status and past malignancy associated with lower immunogenicity (Marra *et al*., 2024). In patients with IMID, RCT-derived efficacy was 90.5% (95% CI 69.1–97.1) and observational effectiveness 59.0% (95% CI 49.8–66.5) (Heen *et al*., 2026). Age- and comorbidity-stratified observational estimates were 66.2% (95% CI 62.7–69.5) in autoimmune disease, 66.6% in diabetes mellitus, 62.7% in liver disease, and 75.1% among adults ≥80 years (Heen *et al*., 2026).

3.3 Prevention of Postherpetic Neuralgia

RZV conferred 84.7% (95% CI 60.9–94.0) protection against PHN in immunocompetent populations, declining to 38.7% (95% CI 19.1–53.5) in immunocompromised populations (Heen *et al*., 2026; Marra *et al*., 2024). In the long-term extension, efficacy against PHN was 87.5% (95% CI 64.8–96.8) in participants ≥50 years, and efficacy against other HZ-related complications was 91.7% (95% CI 43.7–99.8) (Strezova *et al*., 2025). These estimates derive from fewer studies and are subject to definitional heterogeneity, but they align with the biological premise that RZV reduces both HZ incidence and the severity of breakthrough episodes, thereby attenuating the neuropathic sequelae that principally drive quality-of-life impairment. Certainty of evidence was graded moderate for immunocompetent populations and low to moderate for immunocompromised populations.

3.4 Impact on Health-Related Quality of Life

Trial-based analyses provided the most robust HRQoL evidence. RZV reduced the HZ burden of illness and the HZ burden of interference with activities of daily living by >90% in adults ≥50 years, an effect driven principally by near-complete prevention of HZ (Curran *et al*., 2019). Among vaccinated participants who nonetheless developed HZ, RZV was associated with reduced loss of quality of life and decreased analgesic use (Curran *et al*., 2019).

In the ZOE-HSCT trial of autologous hematopoietic stem cell transplant recipients, RZV produced significantly better quality-of-life scores than placebo one week after rash onset among patients with confirmed HZ, with significant differences in SF-36 Bodily Pain, Social Functioning, Role Emotional, and Mental Health domains and in EQ-5D utility (Bastidas *et al*., 2019; Curran *et al*., 2019). Similar directional trends were observed in ZOE-50 and ZOE-70; however, because breakthrough HZ was rare among vaccine recipients, these comparisons did not reach statistical significance. Taken together, the data indicate that RZV not only preserves HRQoL by preventing HZ but also attenuates the pain burden and associated HRQoL decrement in breakthrough disease, an effect of particular relevance because HZ pain exerts a large impact across all HRQoL domains and the magnitude of impairment increases with pain severity (Curran *et al*., 2019).

3.5 Safety and Reactogenicity

RZV is more reactogenic than placebo, but its safety profile is acceptable across populations. In the immunocompromised meta-analysis, vaccine recipients had higher rates of local injection-site AEs within seven

days (pooled RR 7.06, 95% CI 5.01–9.94), grade 3 local injection-site AEs (RR 31.33, 95% CI 13.36–73.44), general AEs (RR 1.49, 95% CI 1.26–1.75), and grade 3 general AEs (RR 1.97, 95% CI 1.53–2.54), with injection-site pain the most frequent event (Marra *et al*., 2024). Crucially, there was no statistically significant difference between RZV and placebo for unsolicited AEs within 30 days (RR 0.98, 95% CI 0.92–1.05), grade 3 unsolicited AEs (RR 1.15, 95% CI 0.88–1.50), or fatal AEs (RR 0.88, 95% CI 0.61–1.04) (Marra *et al*., 2024). No RZV-related serious AEs occurred during 11 years of follow-up in the long-term extension (Strezova *et al*., 2025). In patients with IMID, reactogenicity was frequent but mostly mild, with no difference in serious AEs or death between arms (Heen *et al*., 2026). These data indicate that although transient reactogenicity is near-universal, it is not accompanied by excess serious harm a favourable benefit–risk balance for a vaccine targeted at older and medically complex adults.

3.6 Mortality and Cardiovascular Outcomes

Mortality evidence differed markedly by design. In RCTs, RZV was not associated with a statistically significant reduction in all-cause mortality over a mean follow-up of 3.2 years (RR 0.94, 95% CI 0.84–1.04; 29,311 participants) (Heen *et al*., 2026). This is expected given the low absolute HZ-attributable mortality and the relatively healthy trial populations. Pooled analysis of fatal AEs in immunocompromised populations similarly showed no difference (RR 0.88, 95% CI 0.61–1.04) (Marra *et al*., 2024).

In contrast, observational studies of high-risk populations reported clinically meaningful mortality signals. A large real-world retrospective cohort using a global federated network found that RZV reduced all-cause mortality but not MACE in patients with IMID receiving Janus kinase inhibitors (Shih *et al*., 2025). Among patients with established HZ, a history of RZV and timely antiviral treatment were each associated with reduced risk of cardiovascular disease and all-cause mortality (Gáspár *et al*., 2025). In patients with diabetes mellitus, stroke and all-cause mortality were consistently lower among those with any HZ vaccination compared with the unvaccinated, with both RZV and the live-attenuated vaccine showing reductions in MACE, coronary artery disease, stroke, and all-cause mortality (Shih *et al*., 2025). Across these cohorts, the pooled observational estimate approximated a 39% reduction in all-cause mortality among vaccinated high-risk populations, although healthy-vaccinee bias and residual confounding cannot be excluded, and certainty of evidence was graded low.

The mortality calculus is altered in the post-COVID-19 context. Among COVID-19 survivors who developed HZ, mortality from day 91 to three years was 33% higher than in those without HZ (HR 1.33, 95% CI 1.03–1.72), an excess not explained by pre-existing cardiorenal disease and attributed to HZ-associated inflammatory and thromboembolic pathways (Shih *et al*., 2025). By preventing HZ reactivation, RZV may therefore interrupt a chain of post-viral immune dysregulation with long-term mortality consequences. RZV has additionally been associated with reduced dementia risk, although certainty is low and similar associations have been reported for other vaccines, suggesting possible healthy-vaccinee confounding (Heen *et al*., 2026).

3.7 The Post-COVID-19 Context and Global Inequity

The pandemic has amplified both the need for and the inequity in HZ prevention. HZ incidence increased during and after the COVID-19 period, with evidence linking both SARS-CoV-2 infection and COVID-19 vaccination to VZV reactivation (Gáspár *et al*., 2025; Chen *et al*., 2025). Beyond direct immunological mechanisms, pandemic-related psychological stress, sedentary behaviour, and impaired healthcare access may have affected immune function and promoted reactivation even in individuals without prior comorbidity (Gáspár *et al*., 2025).

Simultaneously, HZ vaccination coverage remains low. In the United States, only 26.1% of adults ≥50 years were vaccinated by 2019, and global coverage is far lower (Dooling *et al*., 2018; Noushad *et al*., 2025). RZV, despite its durable benefits, is constrained in low- and middle-income countries and remote regions by high production cost and stringent cold-chain requirements; in Kenya, the combination of high price and fragile cold-chain infrastructure creates near-insurmountable barriers for vulnerable populations (Noushad *et al*., 2025). Even in high-income settings, uptake lags: in the United Kingdom, HZ vaccination coverage among adults aged 65–92 (58.9%) remains well below influenza vaccination coverage (83.6%), underscoring persistent cost and logistical obstacles (Noushad *et al*., 2025). RZV is approved in fewer than 40 countries, is not licensed in several large middle-income economies including Argentina, Brazil, and Mexico, and universal adult HZ vaccination is implemented in only ten countries of the WHO European Region (Noushad *et al*., 2025; World Health Organization, 2025).

The resulting burden is concentrated where access is weakest. Although age-standardised mortality and disability-adjusted life years for HZ declined by 50.0% and 36.3% respectively between 1990 and 2021, low sociodemographic index regions now account for over 67% of HZ-related deaths and DALYs, and low- and medium-SDI regions face the compound dilemma of inadequate surveillance and lagging burden relief (Pan *et al*., 2024). Vaccine hesitancy compounds these structural barriers: public misconceptions about vaccine safety, limited appreciation of HZ severity, and online misinformation have fostered scepticism, and in China community surveys show that initial vaccination intention among adults ≥50 years rises from 16.6% to 72.3% when insurance coverage is introduced

illustrating how economic access intersects with trust and information bias (Noushad *et al*., 2025).

Table 2 consolidates the pooled efficacy, effectiveness, safety, and mortality estimates described in Sections 3.2–3.6, with heterogeneity statistics and GRADE certainty ratings.

Table 2: Pooled efficacy, effectiveness, safety, and mortality estimates for recombinant zoster vaccine

Outcome	Population	Evidence base	k	Pooled estimate (95% CI)	I^2	GRADE certainty
HZ incidence vaccine efficacy	Immunocompetent adults ≥50 y	RCTs (ZOE-50, ZOE-70)	2	VE 94.7% (93.0–96.0)	0%	High
HZ incidence vaccine effectiveness	Immunocompetent adults ≥50 y	Observational	11	VE 81.0% (74.0–86.5)	97.9%	Moderate
HZ incidence vaccine efficacy	Immunocompromised adults, all ages	RCTs (7 trials, incl. ZOE-HSCT)	7	RR 0.19 (0.09–0.44); VE 81%	60.5%	Moderate
HZ incidence efficacy	Adults with IMID	RCT	1	VE 90.5% (69.1–97.1)		Moderate
HZ incidence effectiveness	Adults with IMID	Observational	1	VE 59.0% (49.8–66.5)		Low–moderate
HZ incidence effectiveness	Adults with autoimmune disease	Observational	1	VE 66.2% (62.7–69.5)		Low–moderate
HZ incidence effectiveness	Adults with diabetes mellitus	Observational	1	VE 66.6% (CI not reported)		Low–moderate
HZ incidence effectiveness	Adults with liver disease	Observational	1	VE 62.7% (CI not reported)		Low
HZ incidence effectiveness	Adults ≥80 y	Observational	1	VE 75.1% (CI not reported)		Low–moderate
HZ incidence durability, year 11	Immunocompetent adults ≥50 y	RCT LTFU	1	VE 82.0% (63.0–92.2)		High
HZ incidence durability, LTFU period	Immunocompetent adults ≥50 y	RCT LTFU	1	VE 79.8% (73.7–84.6)		High
HZ incidence first vaccination to end of LTFU	Immunocompetent adults ≥50 y	RCT LTFU	1	VE 87.7% (84.9–90.1)		High
Herpes zoster ophthalmicus	Immunocompetent adults ≥50 y	Observational	4	VE 66.7% (60.7–72.0)	Moderate	Moderate
PHN	Immunocompetent adults ≥50 y	RCTs + observational	5	VE 84.7% (60.9–94.0)	Substantial	Moderate
PHN	Immunocompromised adults	RCTs	3	VE 38.7% (19.1–53.5)	Moderate	Low–moderate
PHN LTFU	Immunocompetent adults ≥50 y	RCT LTFU	1	VE 87.5% (64.8–96.8)		High
Other HZ-related complications	Immunocompetent adults ≥50 y	RCT LTFU	1	VE 91.7% (43.7–99.8)		Moderate
HZ burden of illness	Immunocompetent adults ≥50 y	RCTs (ZOE-50/70)	2	>90% reduction		High
HZ burden of interference with ADL	Immunocompetent adults ≥50 y	RCTs (ZOE-50/70)	2	>90% reduction		High
HRQoL in breakthrough HZ	HSCT recipients with confirmed HZ	RCT (ZOE-HSCT)	1	Significant improvement vs placebo at 1 wk post-rash onset (SF-36 Bodily Pain, Social Functioning, Role Emotional, Mental Health; EQ-5D utility)		Moderate
Local injection-site AEs (any)	Immunocompromised adults	RCTs	7	RR 7.06 (5.01–9.94)	Moderate	Moderate
Grade 3 local injection-site AEs	Immunocompromised adults	RCTs	7	RR 31.33 (13.36–73.44)	Moderate	Moderate
General AEs (any)	Immunocompromised adults	RCTs	7	RR 1.49 (1.26–1.75)	Moderate	Moderate

Grade 3 general AEs	Immunocompromised adults	RCTs	7	RR 1.97 (1.53–2.54)	Moderate	Moderate
Unsolicited AEs within 30 days	Immunocompromised adults	RCTs	7	RR 0.98 (0.92–1.05)	Low	Moderate
Grade 3 unsolicited AEs within 30 days	Immunocompromised adults	RCTs	7	RR 1.15 (0.88–1.50)	Low	Moderate
Serious adverse events	Immunocompetent and immunocompromised	RCTs	9	No significant difference vs placebo	Low	Moderate
Fatal adverse events	Immunocompromised adults	RCTs	7	RR 0.88 (0.61–1.04)	Low	Moderate
All-cause mortality	Immunocompetent adults (trial populations)	RCTs	3	RR 0.94 (0.84–1.04)	Low	High (no short-term benefit)
All-cause mortality	High-risk real-world populations	Observational	4	~39% reduction (RR ≈0.61)	Substantial	Low
MACE / cardiovascular events	Adults with diabetes, IMID, or prior HZ	Observational	4	Reduced risk; direction consistent, magnitudes heterogeneous	Substantial	Low
Mortality after HZ, day 91–3 y	COVID-19 survivors with HZ	Observational (federated network)	1	HR 1.33 (1.03–1.72) for HZ vs no HZ		Low–moderate

ADL, activities of daily living; AE, adverse event; HZ, herpes zoster; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; IMID, immune-mediated inflammatory disease; LTFU, long-term follow-up; MACE, major adverse cardiovascular events; PHN, postherpetic neuralgia; RCT, randomised controlled trial; RR, risk ratio; VE, vaccine efficacy or effectiveness.

Notes: Dashes indicate single-study estimates for which between-study heterogeneity cannot be calculated. Heterogeneity descriptors: "Substantial" denotes $I^2 \geq 75\%$; "Moderate" 30–74%; "Low" < 30%. GRADE ratings reflect risk of bias, inconsistency, indirectness, imprecision, and publication bias as assessed in this review; mortality and cardiovascular outcomes were downgraded for confounding (healthy-vaccinee bias) and reliance on observational designs. Safety estimates derive from RCTs in immunocompromised populations and may not fully generalise to frail community-dwelling older adults. Study-level linkage (Supplementary Table S1) and forest plots (Supplementary Figures S1–S8) are referenced in the submitted manuscript but were not supplied; these files must be provided or the corresponding claims revised.

4. DISCUSSION

This systematic review and meta-analysis synthesises the global evidence on RZV's impact on HZ burden, quality of life, safety, and mortality, situated within the epidemiological and programmatic shifts of the post-COVID-19 era. Four principal findings emerge.

First, RZV's efficacy and effectiveness are robust, durable, and consistent across diverse populations. Pooled trial data demonstrate efficacy of approximately 95% against HZ in immunocompetent adults ≥50 years, real-world effectiveness of 81%, and sustained protection of 82.0% in the eleventh-year post-vaccination (Lal *et al*., 2015; Cunningham *et al*., 2018; Strezova *et al*., 2025). In immunocompromised populations, RZV reduces HZ incidence by 81% relative to placebo, with robust humoral and cellular immunogenicity despite immunocompromising conditions (Marra *et al*., 2024). These estimates are consistent with, and extend, earlier network meta-analytic findings (Tricco *et al*., 2018) and with the most recent comprehensive synthesis (Heen *et al*., 2026). They translate into meaningful clinical benefit: the >90% reduction in HZ burden of illness and interference with daily living represents one of the largest quality-of-life effects observed for any adult vaccine (Curran *et al*., 2019). The finding that RZV also attenuates pain severity and preserves HRQoL in breakthrough cases suggests residual benefit even when prevention fails, plausibly mediated by vaccine-primed VZV-specific cell-mediated immunity that moderates the inflammatory cascade driving neuropathic damage (Bastidas *et al*., 2019; Curran *et al*., 2019).

Second, the safety profile is characterised by frequent but transient reactogenicity without excess serious harm. RZV produces significantly higher rates of local and systemic AEs, including grade 3 reactions, but these are mostly mild and self-limited, and there is no excess of unsolicited AEs, serious AEs, or fatal AEs relative to placebo across immunocompetent and immunocompromised populations (Marra *et al*., 2024). No RZV-related serious AEs occurred over 11 years of follow-up (Strezova *et al*., 2025). For a vaccine targeted at older and medically complex adults in whom the consequences of HZ substantially outweigh transient reactogenicity this balance is favourable, although transparent counselling about expected reactogenicity is essential to preserve second-dose completion and public confidence (Dooling *et al*., 2018).

Third, mortality benefits are plausible, context-dependent, and mechanistically grounded. Trials do not demonstrate short-term survival gains, as expected given the low absolute mortality of HZ in relatively healthy trial populations (Heen *et al*., 2026). However, observational evidence of reduced all-cause mortality, MACE, and cardiovascular events in vaccinated high-risk groups including patients with IMID receiving Janus kinase inhibitors, patients with diabetes, and patients with established HZ suggests that RZV may confer survival benefits precisely in the populations now most vulnerable (Shih *et al*., 2025; Gáspár *et al*., 2025). The observation that post-COVID HZ is associated with a 59% higher HZ risk and a 33% excess long-term mortality risk strengthens the rationale for vaccination in COVID-19 survivors (Chen *et al*., 2025; Shih *et al*., 2025). The pathway linking HZ to cardiovascular events through inflammatory and thromboembolic cascades provides biological plausibility, but unmeasured confounding and healthy-vaccinee effects cannot be excluded; mortality findings should therefore be regarded as hypothesis-generating pending studies with rigorous confounding control, target-trial emulation, or negative-control designs.

Fourth, the post-COVID-19 era demands recalibration of HZ prevention priorities alongside a reckoning with global inequity. Pandemic-related increases in HZ incidence, an expanded pool of immunocompromised survivors, and documented long-term mortality hazards after post-COVID HZ have raised the population-level value of RZV (Gáspár *et al*., 2025; Chen *et al*., 2025). Yet coverage remains starkly inadequate, particularly in low-SDI regions where HZ mortality is concentrated (Pan *et al*., 2024). RZV is approved in fewer than 40 countries, is unlicensed in several large middle-income economies, and remains constrained by price and cold-chain requirements in low-resource settings (Noushad *et al*., 2025). This inequity is not merely a matter of access but reflects the absence of RZV from most low- and middle-income national immunisation schedules, where the live-attenuated vaccine contraindicated in immunocompromised individuals is often the only option, if any. The WHO position paper recommending consideration of HZ vaccination in adult programmes provides an important policy lever, but without concurrent investment in affordability, cold-chain innovation, and delivery infrastructure, it risks widening rather than narrowing the global HZ burden divide (World Health Organization, 2025).

Strengths and limitations

This review's strengths include a prospectively registered protocol, comprehensive search across four information sources, explicit PRISMA-documented selection with duplicate independent screening, inclusion of both trial and real-world evidence, integration of long-term durability data to 11 years, and explicit attention to safety and the post-COVID-19 context. Several limitations warrant acknowledgement. Substantial heterogeneity (I^2 ≥75%) was present in several meta-analyses, reflecting variation in designs, outcome definitions, and populations; heterogeneity was attenuated in sensitivity analyses excluding outliers but underscores the need for standardised outcome ascertainment. Observational mortality and cardiovascular estimates derived from a limited number of studies with moderate-to-high risk of bias, and the absence of individual-participant data precluded adjustment for confounders. HRQoL analyses relied predominantly on trial-based instruments (EQ-5D, SF-36, Zoster Brief Pain Inventory), which may not fully capture patient-reported burden across cultural contexts, and the rarity of breakthrough HZ limited statistical power for within-case HRQoL comparisons in ZOE-50/70 (Curran *et al*., 2019). Safety data, although reassuring over 11 years, derive largely from trial populations that may not reflect the frailty and multimorbidity of real-world recipients. Publication bias could not be formally assessed for several outcomes with fewer than ten contributing studies. Finally, evidence from low- and middle-income countries remains sparse, limiting global generalisability and highlighting a critical research gap for equitable vaccine policy (Pan *et al*., 2024; Noushad *et al*., 2025).

Implications for policy, practice, and research

For practice, the evidence supports two-dose RZV for all adults ≥50 years and for immunocompromised adults ≥18 years, with proactive counselling on reactogenicity and structured reminders to ensure series completion. For policy, the data argue for inclusion of RZV in national adult immunisation schedules, tiered pricing and advance market commitments to improve affordability, and cold-chain innovations such as controlled-temperature chain devices for low-resource delivery. For research, priorities include individually linked post-licensure studies with rigorous confounding control for mortality and cardiovascular endpoints; pragmatic trials and target-trial emulations in COVID-19 survivors; patient-reported outcome studies using culturally validated instruments in low- and middle-income settings; and implementation research on strategies to raise two-dose completion in routine care.

5. CONCLUSION

The recombinant zoster vaccine is a high-impact intervention for reducing the clinical, humanistic, and economic burden of herpes zoster. In the post-COVID-19 era characterised by elevated HZ risk, long-term mortality hazards among survivors, and widening global inequities in vaccine access RZV's capacity to prevent HZ and PHN, preserve quality of life, maintain an acceptable safety profile, and has observational associations with mortality and cardiovascular outcomes that remain insufficient to establish causal protection in

vulnerable populations positions it as a cornerstone of adult immunisation. Policy efforts should prioritise closing the coverage gap in low-SDI settings through tiered pricing, cold-chain innovation, and inclusion in national schedules; integrating RZV into routine adult vaccination platforms alongside influenza and pneumococcal vaccines; and generating robust post-marketing evidence on mortality, HRQoL, and safety in diverse global populations, including COVID-19 survivors and immunocompromised individuals. The convergence of pandemic-era immunological vulnerability and vaccine-preventable HZ burden presents both an urgent challenge and a tractable opportunity for global health action, and the 11-year durability data together with the favourable benefit–risk profile provide a strong evidence base for expanding access as a matter of health equity and healthy ageing.

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