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EFFECTIVENESS AND SAFETY OF THE RECOMBINANT HERPES ZOSTER VACCINE IN DIFFERENT POPULATION GROUPS: A SYSTEMATIC REVIEW AND META-ANALYSIS

AGUSTÍN BENGOLEA[1,4], FLORENCIA CHAMORRO[1], JOSE T. RAMOS[2,3], GABRIEL RADA[2], HUGO N. CATALANO[1,4], ARIEL IZCOVICH[1,4]

[1]Servicio de Clínica Médica, Hospital Alemán, Buenos Aires, [2]Fundación Epistemonikos, Chile, [3]Escuela de Odontología, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile, [4]Escuela de Medicina, Facultad de Medicina Universidad del Salvador, Buenos Aires, Argentina

Postal address: Agustín Bengolea, Hospital Alemán, Av. Pueyrredón 1640, 1118 Buenos Aires, Argentina
E-mail: agustinmbengolea@gmail.com
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Abstract

Varicella-zoster virus infections have increased globally, with complications such as postherpetic neuralgia and neurological sequelae. The recombinant vaccine against herpes zoster is proposed as a preventive strategy. This systematic review evaluates its effectiveness and safety in healthy and high-risk populations. A systematic review of randomized controlled trials comparing the effectiveness and safety of the vaccine was conducted. The search was carried out in Epistemonikos. Two researchers independently assessed the eligibility of the studies and the risk of bias was evaluated using the Cochrane Risk of Bias 2 tool. A meta-analysis of homogeneous results was conducted, and the certainty of the evidence was evaluated using GRADE. A minimally contextualized approach was adopted using predetermined thresholds. Nine randomized controlled trials were selected. The vaccine demonstrated a significant reduction in the incidence of herpes zoster in high-risk populations (risk difference of 140 fewer per 1000) with high certainty. However, in healthy populations, the effect was trivial (28 fewer per 1000). No significant differences were observed in postherpetic neuralgia in any of the populations analyzed. Adverse events increased in both populations, though no discrepancies in serious adverse events were noted. In high-risk populations, where the incidence of herpes zoster and its complications is higher, the vaccine demonstrated effectiveness in lowering the incidence of the disease, though not in that of postherpetic neuralgia. Conversely, in healthy populations, the impact of the vaccine was trivial. Individualized and informed recommendations are crucial when considering this vaccine.

Key words: zoster, vaccine, Argentina, systematic review

Resumen

Efectividad y seguridad de la vacuna recombinante para herpes zóster en diferentes poblaciones: revisión sistemática y metaanálisis

Las infecciones por el virus de la varicela-zóster han aumentado globalmente, con complicaciones como neuralgia postherpética y secuelas neurológicas. La vacuna recombinante contra el herpes zóster se propone como estrategia preventiva. Esta revisión sistemática evalúa su efectividad y seguridad en poblaciones sanas y de alto riesgo. Se realizó una revisión sistemática de ensayos controlados aleatorios que comparaban la efectividad y seguridad de la vacuna. La búsqueda se efectuó en Epistemonikos. Dos investigadores evaluaron independientemente la elegibilidad de los estudios y se evaluó el riesgo de sesgo con la herramienta Cochrane Risk of Bias 2. Se realizó un metanálisis de resultados homogéneos y se evaluó la certeza de la evidencia mediante GRADE. Se adoptó un enfoque mínimamente contextualizado

utilizando umbrales predeterminados. Se seleccionaron 9 ensayos controlados aleatorios. La vacuna demostró una reducción significativa en la incidencia de herpes zóster en poblaciones de alto riesgo (diferencia de riesgo de 140 menos por 1000) con alta certeza. Sin embargo, en poblaciones sanas, el efecto fue trivial (28 menos por 1000). No se observaron diferencias significativas en la incidencia de neuralgia postherpética en ninguna de las poblaciones. En cuanto a la seguridad, se registró un aumento de eventos adversos en ambas poblaciones, aunque no se presentaron diferencias en los eventos adversos graves.

En poblaciones de alto riesgo, donde la incidencia de herpes zóster y sus complicaciones es más alta, la vacuna demostró eficacia en la reducción de la incidencia de la enfermedad, aunque no en la de la neuralgia postherpética. Por otro lado, en población sana, el impacto de la vacuna fue trivial. Es crucial adoptar un enfoque individualizado e informado al recomendar esta vacuna.

Palabras clave: zóster, vacuna, Argentina, revisión sistemática

KEY POINTS:

Current knowledge

- Herpes zoster, characterized by a painful rash, has witnessed a substantial rise in global incidence, particularly impacting immunosuppressed individuals and the elderly. The associated complications, including postherpetic neuralgia, underscore the urgency for effective preventive measures to address this public health concern.

Article's contribution to current knowledge

- This systematic review evaluates the effectiveness and safety of the recombinant herpes zoster vaccine in both healthy and high-risk populations. It highlights disparities between these populations, showing clear benefits for high-risk groups. However, the limited benefits and uncertainty regarding safety in healthy populations, including older adults, underscore the need for informed decision-making in healthcare.
- Notably, this systematic review was utilized by the internal medicine service of the Hospital Aleman in Argentina to formulate recommendations concerning the herpes zoster vaccination in healthy and high risk populations. The insights from this review contribute to shaping future research and public health strategies related to zoster vaccination at the local level.

The varicella-zoster virus (VZV) presents itself in two distinct clinical forms: primary infection, known as varicella, predominantly observed in children and characterized by lesions with erythematous bases at various stages of evolution; and the reactivation of latent infection, termed herpes zoster (HZ), which manifests through a highly painful vesicular rash, usually occurring in one or more dermatomes.

The incidence of HZ exhibits worldwide similarities and increases with age. In the United States, a significant increase in cases has been observed, rising from 2.5 per 1000 person-years in 1993 to 7.2 per 1000 person-years in 2016[1]. The magnitude of the impact is considerable, with over 1.2 million cases annually. According to the Centers for Disease Control and Prevention (CDC), it is estimated that 30% of people will experience herpes zoster at some point in their lives[2]. In Argentina, the incidence between 2000 and 2005 was 3.5 per 1000 person-years[3].

Among the risk factors associated with HZ, age stands out as a frequently mentioned element. Other risk factors such as immunosuppression, autoimmune diseases, immunosuppressive treatment, chemotherapy, and HIV increase susceptibility to this condition[4].

Complications stemming from HZ constitute a critical aspect to consider. These include postherpetic neuralgia, characterized by persistent pain lasting over 90 days, presenting a significant concern. Other severe presentations or complications of the disease encompass HZ ophthalmicus, Ramsay Hunt syndrome (otic HZ), and neurological complications such as encephalitis, aseptic meningitis, and myelitis. The risk of neurological complications or disseminated zoster is higher in immunosuppressed patients[5].

The HZ vaccine emerges as a preventive measure to reduce the risk of developing the disease. Since 2023, the recombinant HZ vaccine has been available in Argentina[6]. This recombinant vaccine contains the E glycoprotein of

the varicella-zoster virus in combination with an adjuvant (AS01B). Although no immunological correlate for protection against HZ has been identified, current knowledge suggests that cell-mediated immunity specific to VZV is of paramount importance in preventing HZ[7].

This systematic review aims to assess the effectiveness and safety of the recombinant HZ vaccine in both healthy and high-risk populations. Special attention will be devoted to older adults, who are considered more vulnerable, as well as individuals facing various health conditions including immunosuppression, transplant recipients, those diagnosed with HIV/AIDS, and patients undergoing cancer treatment. A meticulous subgroup analysis will be conducted to explore potential effect modifiers within these diverse populations.

Methods

This manuscript was developed following the guidelines of the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRISMA) for reporting systematic reviews and meta-analyses[8].

1. Formulation of PICO question

PICO Question:

- Patients (P): Healthy population (adults) and high-risk individuals (immunosuppressed individuals, transplant recipients, diagnosed with HIV/AIDS, cancer patients, and those under chronic treatment with corticosteroids, immunosuppressants, or chemotherapy)
- Intervention (I): Recombinant vaccine for HZ Shingrix[9]
- Comparator (C): Placebo
- Outcomes(O):
  - Incidence of HZ: diagnosed through Polymerase chain reaction (PCR) in patients with clinically compatible symptoms
  - Incidence of postherpetic neuralgia: diagnosed through clinically compatible symptoms
  - Pain assessed with the Zoster Brief Pain Inventory[10] (ZBPI) score >3
  - Adverse events of any type: definition according to primary studies
  - Serious adverse events: definition according to primary studies

2. Literature search

2.1. Electronic search

A search was conducted in the Epistemonikos Database. This database is regularly updated through searches in multiple sources and has been validated as a comprehensive source of systematic reviews and randomized controlled trials (RCTs). These sources include the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effectiveness (DARE), PubMed, LILACS, CINAHL, PsycINFO, EMBASE, EPPI-Centre Evidence Library, Systematic Reviews and Policy Briefs Campbell Library, and The JBI Database of Systematic Reviews and Implementation Reports[11,12]. The identification of primary studies was complemented with a specific search in the PubMed database. All searches covered the period from the database inception dates until 01/04/2024, with no restrictions on publication date, status, or language. The search strategy is available in Appendix 1 – Supplementary material.

2.2. Other search sources

To ensure the identification of articles that may not have been detected by the search strategy or are not available in the included databases, the following sources of information were included:

- RCTs included in other relevant systematic reviews, identified through a search in the Epistemonikos Database.
- Manual review of references from included studies.

3. Study selection

The study selection process was conducted using the *Collaboratron software*, a screening tool developed within the *Sustainable Knowledge* (SK) platform by the Epistemonikos Foundation[13]. Two independent researchers (AB, FC) evaluated the title and abstract of all articles according to eligibility criteria for population, intervention, comparison, and study design. The full text of all potentially eligible studies was obtained, and two researchers (AB, FC) assessed their eligibility. Any disagreements were resolved through discussion, and if necessary, an additional reviewer (AI) was involved. Exclusion reasons for

clinical trials and the selection process were recorded in the PRISMA flow diagram.

This systematic review included RCTs that assessed efficacy, defined as the ability of an intervention to produce the desired effect under ideal or controlled conditions, and the safety of using recombinant vaccine against HZ compared to placebo in the general population and high-risk population. The aim was to draw conclusions on effectiveness, understood as outcomes in real clinical practice.

4. Data extraction

Data extraction was performed by two researchers (AB, FC) using standardized forms. Detailed information on demographic characteristics, study methodology, included population, interventions performed, comparison used, and reported outcomes was collected.

5. Risk of bias assessment

We assessed the risk of bias in each randomized trial using the *Risk of Bias 2* (Rob 2) tool developed by the Cochrane Collaboration[14]. The five domains of bias considered in this tool were: bias due to the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in selection of the reported result.

6. Effect measures

In the analysis of dichotomous outcomes, we expressed the estimation of the therapeutic impact of the intervention using risk measures along with the 95% confidence interval (CI). For continuous outcomes, we used the mean difference and standard deviation along with the 95% CI.

7. Heterogeneity assessment

Variations in the treatment effect among the different included clinical trials were assessed using the X^2 test (Q statistic) and the I^2 statistic. Statistically significant heterogeneity was considered when the p-value was <0.1.

8. Data synthesis

We conducted a meta-analysis through the SK platform, integrating multiple statistical approaches, including those recommended by the Cochrane Collaboration[15]. This involved selecting studies with significant homogeneity in design, population, interventions, comparators, and reported outcome measures. Using the inverse variance method and a random-effects model, we examined the results of clinically homogeneous studies.

9. Subgroup analysis

We explored the following potential effect modifiers: 1) Risk of bias, we anticipated bigger beneficial effects in high risk of bias studies. 2) Age, we anticipated bigger beneficial effects in older populations. 3) Risk of zoster, we anticipated bigger beneficial effects in high risk individuals.

To assess the possibility of a subgroup effect, we employed the Instrument for *Credibility Assessment of Effect Modification* (ICEMAN)[16,17] designed to evaluate the credibility of a claim of effect modification, also known as a subgroup effect, statistical interaction, moderation, or heterogeneity of treatment effects.

10. Certainty of evidence assesment

The certainty of evidence for all selected outcomes was assessed using the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) methodology, through the domains of risk of bias, consistency, indirect evidence, imprecision, and publication bias. Certainty was classified as high, moderate, low, or very low. For the main comparisons and outcomes, *Summary of Findings* (SoF) tables were prepared[18,19].

We defined the goal of certainty of evidence following a minimally contextualized approach[20]. No specific publications reporting clinically relevant thresholds for this condition were detected; therefore, we reached a consensus on the following thresholds for the clinically minimally important difference in each outcome assessment.

- Incidence of HZ: 50 less per 1000
- Incidence of postherpetic neuralgia: 25 less per 1000
- Pain assessed with the Zoster Brief Pain Inventory[10] (ZBPI) score greater than 3: 25 less per 1000
- Adverse events of any type: 100 less per 1000
- Serious adverse events: 25 less per 1000

Results

1. Search results

Through the search strategy, 282 references were identified for screening by title and abstract. Of these, 79 references were included for full-text evaluation. Finally, 9 RCTs reported in 12 references[21-32] that met the selection criteria were included. Exclusion reasons for clinical trials and the selection process were recorded in the PRISMA flow diagram (Fig. 1 and Appendix 2 and 3 – Supplementary material).

2. Description of included studies

The included studies addressed diverse populations, ranging from healthy adults over 50 years to patients with HIV, undergoing chemotherapy, with post-immunosuppression hematologic neoplasms, renal transplant recipients, and autologous hematopoietic cell transplant recipients. Follow-up varied between 12 months and 10 years. The characteristics of the included studies for analysis are shown in Table 1.

3. Risk of bias assessment

Although certain considerations were identified in some domains of Cochrane's Rob 2, the overall interpretation of the risk of bias in the primary studies was low for all outcomes except for adverse events in the high-risk population. Detailed risk of bias assessment is shown in Figure 2 and Appendix 3 – Supplementary material.

4. Efficacy and safety of recombinant HZ vaccine

Table 2 presents a summary of the interventions effects on all the assessed outcomes. An interactive version of table 2 is available at: https://isof.epistemonikos.org/#/finding/65fdb04de3089d04ceba0ec8

4.1. Incidence of HZ *(Fig. 3 – Supplementary material)*

Three clinical trials[23,24,27] with a total of 31 032 participants reported this outcome with a relative risk (RR) of 0.12 (95% CI: 0.04 - 0.38; I2=95.3%). The follow up ranged from 1.8 to 3.7 years. Considering the predetermined threshold (50 less per 1000), the use of the recombinant HZ vaccine results in a trivial reduction in the incidence of HZ in the healthy population (risk difference of 28 fewer per 1000, from 31 fewer to 20 fewer, high certainty of evidence). However, in the high-risk population the vaccine led to an important reduction in the incidence of HZ (risk difference of 140 fewer per 1000, from 153 less to 99 less, high certainty of evidence). The different interpretations of the results stem from variations in the baseline.

4.2. Incidence of postherpetic neuralgia *(Fig. 4 – Supplementary material)*

Two clinical trials[24,27] with a total of 19 252 participants reported this outcome with a RR of 0.16, (95% CI: 0.07 - 0.37; I2=0%). The follow up ranged from 1.8 to 3.7 years. Considering the predetermined threshold (25 less per 1000), the use of the recombinant HZ vaccine results in a trivial reduction in the incidence of postherpetic neuralgia in both the healthy (risk difference of 3 fewer per 1000, from 4 fewer to 3 fewer, high certainty of evidence) and the high risk population (risk difference of 9 fewer per 1000, from 10 fewer to 7 fewer, high certainty of evidence).

4.3. Pain evaluated with ZBPI >3 *(Fig. 5 – Supplementary material)*

A combined analysis of three clinical trials[30] with a total of 29 643 healthy participants reported this outcome with a RR 0.12 (95% CI: 0.09 - 0.15; I2=0%). The follow up ranged from 1.8 to 3.7 years. Considering the predetermined threshold (25 less per 1000), the use of the vaccine probably results in a reduction in pain events (risk difference of 32 fewer per 1000, from 33 fewer to 31 fewer, moderate certainty of evidence). However, the threshold used is that set by the authors of the primary studies and not a threshold of clinical relevance[20]. The certainty of evidence was classified as moderate due to serious considerations of indirect evidence due to the absence of a clinically important or significant difference to contextualize the vaccine's effect in terms of symptomatic improvement.

4.4. Serious adverse events *(Fig. 6 – Supplementary material)*

Six clinical trials[21,23,24,26,29] with a total of 30 779 participants reported this outcome with a RR of 0.96, 95% (CI: 0.91 - 1.02; I2=0%). The follow up ranged from 1.8 to 3.7 years. Considering

Table 1 | General characteristics of included clinical trials

Study and year	Country	Participants	Intervention	Comparison	Outcomes	Follow up
ZOSTER-010 (2013)[21]	USA, Czech Republic, and Spain	Healthy immunocompetent adults over 50 years	2 doses of herpes zoster vaccine, separated by 2 months	Placebo	Local and systemic adverse effects	12 months
ZOSTER-015 (2014)[22]	Germany, USA, and United Kingdom	Adults over 18 years diagnosed with HIV	3 doses of recombinant vaccine (0, 2, and 6 months)	3 doses of placebo	Local and systemic adverse effects	1.5 years
ZOSTER-028 (2019)[26]	Canada, Czech Republic, France, South Korea, Spain, and United Kingdom	Adults over 18 years diagnosed with solid tumors undergoing chemotherapy (Cytotoxic or immunosuppressive)	2 doses of recombinant vaccine separated by 2 months	Placebo	Local and systemic adverse effects	12 meses
ZOSTER-039 (2019)[28]	Australia, Belgium, Canada, Czech Republic, Finland, France, Hong Kong, Italy, South Korea, New Zealand, Pakistan, Panama, Poland, Russia, Singapore, Spain, Sweden, Taiwan, Turkey, United Kingdom, and USA	Adults over 18 years with hematologic neoplasms during or after immunosuppressive treatment	2 doses of recombinant vaccine separated by 1 or 2 months	Placebo	Local and systemic adverse effects	13 months
ZOSTER-041 (2020)[29]	Belgium, Canada, Czech Republic, Finland, Italy, Panama, South Korea, Spain, and Taiwan	Adults over 18 years with kidney transplant between 4 and 18 months prior receiving daily immunesuppressants	2 doses of recombinant vaccine separated by 1-2 months	Placebo	Local and systemic adverse effects	12 months
ZOSTER-50 (2023)[23,32,30]	18 Countries (Europe, North America, Latin America, Asia, and Australia)	Healthy immunocompetent adults over 50 years	2 doses of recombinant vaccine separated by 2 months	Placebo	Pain (ZBPI) and use/duration of pain medication (classified as opioids and non-opioids)	3.2 years
ZOSTER-70 (2016)[24,30]	18 Countries (Europe, North America, Latin America, Asia, and Australia)	Healthy immunocompetent adults over 70 years	2 doses of recombinant vaccine separated by 2 months	Placebo	Occurrence of confirmed herpes zoster (PCR) and postherpetic neuralgia (Zoster Brief Pain Inventory questionnaire), adverse effects	3.7 years

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Study and year	Country	Participants	Intervention	Comparison	Outcomes	Follow up
ZOSTER-HSCT (2019)[25,27]	28 Countries	Adults over 18 years with autologous hematopoietic cell transplant	2 doses of recombinant vaccine separated by 1 or 2 months	Placebo	Occurrence of confirmed herpes zoster (PCR) and adverse effects	1.8 years
ZOSTER-LTFU (2022)[31]	Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan, South Korea, Mexico, Spain, Sweden, Taiwan, United Kingdom, and USA	Healthy immunocompetent adults over 50 years	2 doses of vaccine separated by 2 months	Placebo	Local and systemic adverse effects	10 years

Table 2 | Summary of findings table
Interactive version: https://isof.epistemonikos.org/#/finding/65fdb04de3089d04ceba0ec8

Outcomes	Absolute effect Placebo or no vaccination	Absolute effect Recombinant HZ vaccine	Relative effect (95% CI) Number of participants and studies	Certainty of the evidence (GRADE)	Key messages
Incidence of herpes zoster Follow-up: Range from 1.8 to 3.7 years					
High risk population	159 per 1000	19 per 1000	RR 0.12 (0.04 a 0.38)		The recombinant HZ vaccine reduces the incidence of herpes zoster in the high risk population
	Difference: 140 patients less per 1000 (95% IC: 153 to 99 less patients		Based on data from 31 032 individuals in 3 RCTs,[24,27]	⊕⊕⊕⊕ High	
Healthy population	32 per 1000	4 per 1000			The recombinant HZ vaccine does not reduce the incidence of herpes zoster in healthy population
	Difference: 28 patients less per 1000 (95% IC: 31 to 20 less patients)				
IIncidence of Postherpetic neuralgia Follow-up: Range from 1.8 to 3.7 years					
High risk population	11 per 1000	2 per 1000	RR 0.16 (0.07 a 0.37)		The recombinant HZ vaccine does not reduce the incidence of postherpetic neuralgia in the high risk population
	Difference: 9 patients less per 1000 (95% IC: 10 to 7 less patients)		Based on data from 19 252 individuals in 2 RCTs24,27	⊕⊕⊕⊕ High	

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Outcomes	Absolute effect Placebo or no vaccination	 Recombinant HZ vaccine	Relative effect (95% CI) Number of participants and studies	Certainty of the evidence (GRADE)	Key messages
	Healthy population				
	4 per 1000	1 per 1000			The recombinant HZ vaccine does not reduce the incidence of postherpetic neuralgia in healthy population
	Difference: 3 patients less per 1000 (95% IC: 4 to 3 less patients)				
Pain evaluated by ZBPI Follow-up: Range from 1.8 to 3.7 years					
	36 per 1000	4 per 1000	RR 0.12 (0.09 a 0.15)		The recombinant HZ vaccine probably reduces the pain of herpes zoster
	Difference: 32 patients less per 1000 (95% IC: 33 a 31 less patients		Based on data from 29 643 individuals in 3 RCTs30	⊕⊕⊕◯ Moderate[a]	
Serious adverse events Follow-up: Range from 1.8 to 3.7 years					
	High risk population				
	217 per 1000	206 per 1000	RR 0.96 (0.91 a 1.02)		The recombinant HZ vaccine does not increase the risk of serious adverse events
	Difference: 11 patients less per 1000 (95% IC: 20 less to 4 more patients)		Based on data from 30 779 individuals in 6 RCTs[21,23,24,26,29]	⊕⊕⊕⊕ High	
	Healthy population				
	129 per 1000	124 per 1000			
	Difference: 5 patients less per 1000 (95% IC: 12 less to 3 more patients)				
Any type of adverse events Follow-up: Range from 1.8 to 3.7 years					
	High risk population				
	434 per 1000	981 per 1000	RR 2.26 (1.53 a 3.34)		The recombinant HZ vaccine may increase the risk of adverse events
	Difference: 547 patients more per 1000 (95% IC: 230 to 1016 more patients)		Based on data from 11 525 individuals in 7 RCTs[21-24,26,28,29]	⊕⊕◯◯ Low[b]	
	Healthy population				
	276 per 1000	624 per 1000			
	Difference: 348 patients less per 1000 (95% IC: 146 to 646 more patients)				

HZ: herpes zoster; RR: relative risk; CI: confidence interval; RCTs: randomized controlled trials; ZBPI: Zoster Brief Pain Inventory Explanations

[a] The certainty of the evidence was classified as moderate due to serious indirectness: threshold used is that set by the authors of the primary studies and not a threshold of clinical relevance.

[b] The certainty of the evidence was classified as low due inconsistency and indirectness

the predetermined threshold (25 less per 1000), the use of the recombinant subunit HZ vaccine results in a trivial reduction in serious adverse events in both the healthy (risk difference of 5 fewer per 1000, from 12 fewer to 3 more, high certainty of evidence) and in the high risk population (risk difference of 9 fewer per 1000, from 20 fewer to 4 more, high certainty of evidence).

4.5. Any type of adverse events *(Fig. 7 – Supplementary material)*

Seven clinical trials[21-24,26,28,29] with a total of 11 525 participants reported this outcome with a RR of 2.26 (95% CI: 1.53 - 3.34; I2=97.6%). The follow up ranged from 1.8 to 3.7 years. Considering the predetermined threshold (100 less per 1000), the use of the recombinant adjuvanted subunit vaccine may increase in adverse events of any type in both the healthy (risk difference of 348 more per 1000, from 146 to 646 more, low certainty of evidence) and in the high risk population (risk difference of 547 more per 1000, from 230 more to 1016 more, low certainty of evidence). The certainty of evidence was classified as low due to inconsistency and indirect evidence, primarily stemming from limitations in the detection of rare or unexpected adverse events in the primary studies. Despite the considerable observation time in the primary studies, there still exists the possibility of infrequent or unexpected adverse events that may not have been adequately captured[33].

5. Subgroup analysis

We did not find credible subgroup effects for any of the explored potential effect modifiers in any of the assessed outcomes. A detailed description of the assessment is subgroup analysis credibility assessments is available in Appendix 4 – Supplementary material. This finding remains consistent when analyzing different baseline risks, including those for populations older than 60 and 70 (Appendix 5 – Supplementary material).

Methodologically, limitations arose in our attempts to conduct a subgroup analysis. We were unable to perform a within-study analysis of age as an effect modifier; however, in the between-study analysis, no effect modifier was identified.

5.1. Results of the subgroup analysis

Although we did not find credible effect modification according to the risk of developing VZV, we provide the results of our analysis separately for both healthy and high-risk individuals below.

Healthy population interactive version: https://isof.epistemonikos.org/#/finding/65dd5402e3089d04ceba0ec4

High-risk population interactive version: https://isof.epistemonikos.org/#/finding/65dd5e9ae3089d04ceba0ec5

5.1.1. Incidence of HZ in healthy population (*Fig. 8 – Supplementary material*)

Two clinical trials[23,24] with a total of 29 311 participants reported this outcome. The follow up ranged from 3.2 to 3.7 years. The use of the recombinant HZ vaccine results in a trivial incidence of HZ in the healthy population (RR 0.07, 95% CI: 0.02 - 0.23; I2=89.0%). The certainty of evidence was classified as high.

5.1.2 Incidence of HZ in high-risk population (*Fig. 9 – Supplementary material*)

One clinical trial[27], with a total of 1 721 autologous marrow transplant patients, reported this outcome. The use of the recombinant HZ vaccine probably reduces the incidence of HZ in the high-risk population (RR 0.36, 95% CI: 0.26 - 0.49; I2=0%). The certainty of evidence was classified as moderate due to serious considerations in the imprecision domain.

5.1.3. Any type of adverse events in healthy population (*Fig. 10 – Supplementary material*)

Three clinical trials[21,23,24] with a total of 10 346 participants reported this outcome. The use of the recombinant vaccine could increase the risk of any type of adverse events in the healthy population (RR 2.09, 95% CI: 0.97 - 4.5; I2=98.6%). The certainty of evidence was classified as low due to serious considerations of inconsistency and indirect evidence.

5.1.4. Any type of adverse events in high-risk population (*Fig. 11 – Supplementary material*)

Four clinical trials[22,26,28,29] with a total of 1 179 immunosuppressed or oncology-treated participants reported this outcome. The use of the recombinant vaccine could increase the risk of

any type of adverse events in the high-risk population (RR 2.62, 95% CI: 1.34-5.13; I2=97%). The certainty of evidence was classified as low due to risk of bias and indirect evidence.

Discussion

This systematic review provides evidence regarding the efficacy of the recombinant HZ vaccine in reducing the incidence of both HZ and postherpetic neuralgia. However, the magnitude of these benefits varies across different populations, including both healthy individuals and those at high risk.

In individuals at high risk of developing VZV (e.g., immunocompromised), the estimated effects were significant. This is particularly noteworthy given the heightened susceptibility to complications associated with HZ infection in these individuals. However, in individuals with average VZV risk, including older adults, the effects were very small or even trivial. Conversely, in high-risk populations, the vaccine demonstrated a substantial reduction in the incidence of HZ, thus providing robust support for vaccination within these cohorts.

Although we did not find an increase in severe adverse events, it is essential to acknowledge the limitations of the included studies when addressing vaccine safety considerations. Given that randomized controlled trials often struggle to effectively monitor unforeseen adverse events and lack the necessary power to detect very rare adverse events[33], it is relevant to consider including emerging observational studies, such as large-scale cohort studies, in future research. This introduces uncertainty regarding potential long-term effects or rare adverse events not adequately captured.

It is important to recognize that there is variability in the interpretation of benefits and harms, and therefore, in the thresholds to define a significant effect. Hence, tailored discussions with patients are essential to align vaccination decisions with their individual values and preferences. This underscores the importance of shared decision-making processes between healthcare providers and patients, especially within the healthy population, to effectively communicate these findings and establish appropriate expectations.

Our findings are similar to the conclusions of the systematic review published by Xia (2022)[34], which evaluated the efficacy, effectiveness, and safety of the recombinant herpes zoster vaccine (RZV) and the zoster vaccine live (ZVL) in immunocompetent and immunocompromised subjects. This publication concluded that both in immunocompetent and immunocompromised subjects, RZV was superior to placebo. On the other hand, it is important to highlight that a systematic review of observational studies conducted by Mbinta (2022)[35] showed that the effectiveness of both vaccines (RZV and ZVL) against herpes zoster was lower than that reported in meta-analyses of randomized controlled trials.

As a methodological strength of this review, we employed the GRADE methodology and a minimally contextualized approach to evaluate the magnitude of benefits, thus contributing to the robustness of our findings.

Nevertheless, this review has limitations, including the absence of pharmacovigilance studies, which could offer valuable insights into vaccine safety.

In summary, our findings support the efficacy of the recombinant HZ vaccine in reducing the incidence of both HZ and postherpetic neuralgia. However, the magnitude of this benefit varies across different population groups. While the vaccine may offer marginal benefits in healthy individuals, its impact is more pronounced among high-risk populations (immunosuppressed individuals, transplant recipients, those diagnosed with HIV/AIDS, cancer, and those undergoing chronic treatment with corticosteroids, immunosuppressants, or chemotherapy). These findings underscore the importance of individualized risk-benefit assessment when considering HZ vaccination, emphasizing the need for informed healthcare decision-making tailored to the specific characteristics of each population group. Thus, an individualized and evidence-based approach is crucial when recommending this vaccine.

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Conflict of Interests: None to declare

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