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Varicella-Zoster Virus: Advances in Vaccination Strategies and Emerging Immunological Implications

Marco Vinícios de Oliveira Santana[1], Carlos Henrique Marchiori[1*], Klebert de Paula Malheiros[1]
[1]Institute Marco Santana, Goiânia, Goiás, Brazil

Abstract: Varicella-zoster virus (VZV) is a ubiquitous human herpesvirus responsible for varicella during primary infection and herpes zoster following viral reactivation. Despite the widespread nature of primary infection, herpes zoster remains a significant public health concern, particularly in aging populations, largely due to immunosenescence and the progressive decline of VZV-specific cellular immunity. Advances in basic and clinical research over the past decade have improved understanding of viral latency, immune surveillance, and the mechanisms underlying reactivation, highlighting the central role of cell-mediated immunity in maintaining viral quiescence throughout life. The objective of this review is to synthesize current scientific evidence on VZV biology, epidemiology, vaccination strategies, and emerging immunological implications. Particular emphasis is placed on mechanisms of viral latency, the impact of immunosenescence on reactivation risk, and immune responses induced by recombinant herpes zoster vaccines. These vaccines demonstrate high and sustained efficacy across age groups, including older adults and immunocompromised individuals, by inducing robust cell-mediated immune responses that counteract age-related immune deficits and reduce the incidence and severity of herpes zoster and its complications. Emerging evidence suggests that herpes zoster and its prevention may be associated with broader systemic outcomes, including neurovascular and cognitive effects. Ongoing challenges related to vaccine implementation, durability of protection, and global access remain relevant for optimizing prevention strategies and supporting healthy aging in older populations.

Keywords: Cellular Immunity, Herpes Zoster, Immunosenescence, Vaccination, Varicella-Zoster Virus.

Research Paper

***Corresponding Author:**
Carlos Henrique Marchiori
Institute Marco Santana, Goiânia, Goiás, Brazil

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1.0. INTRODUCTION

Varicella-Zoster Virus (VZV) is a strictly human, neurotropic alpha herpesvirus responsible for two distinct clinical conditions: varicella, typically acquired in childhood, and herpes zoster, which results from viral reactivation later in life. Following primary infection, VZV establishes lifelong latency in sensory dorsal root and cranial nerve ganglia, where it persists within neurons in a transcriptionally restricted state. This biological capacity for long-term neuronal persistence reflects highly adapted viral survival strategies that enable silent host colonization for decades. The combination of durable latency and age-associated immune decline has made VZV a paradigmatic model for investigating host–virus interactions in aging populations (Heininger and Seward, 2006; Gershon *et al.,* 2018).

During latency, VZV exhibits extremely limited viral gene expression in the absence of productive replication, reflecting a tightly regulated equilibrium between viral persistence mechanisms and host immune control. Maintenance of this dormant state depends largely on cell-mediated immunity, particularly VZV-specific $CD4^+$ and $CD8^+$ T lymphocytes, which continuously survey latently infected ganglionic neurons and constrain viral transcriptional activity. This immunological containment is essential for preventing transition from quiescence to replicative reactivation. Disruption of this regulatory balance may permit renewed viral activity and ultimately lead to the clinical manifestation of herpes zoster (Gershon *et al.,* 2019; Arvin *et al.,* 2024).

Immunosenescence constitutes a central pathogenic determinant of herpes zoster by progressively impairing antiviral cellular responses over time. Age-

related immune remodeling includes reduced thymic output, functional decline of memory T-cell populations, and the development of chronic low-grade inflammation. Collectively, these alterations diminish VZV-specific immune competence and compromise the effectiveness of neuronal immune surveillance. The resulting immunological permissiveness facilitates the reactivation of viruses in previously controlled latent reservoirs. Consistently, large population-based studies demonstrate a marked increase in herpes zoster incidence after the age of 50, underscoring aging as the principal risk factor for reactivation (Schmader, 2018; Levin *et al.,* 2019).

At the same time, the expansion of vaccine coverage has drawn attention to transient immune responses observed following immunization, particularly after the first dose of recombinant vaccines. Local and systemic reactogenicity reflects early innate immune activation induced by the adjuvant system. Such responses are typically mild to moderate in intensity and self-limited in duration. Understanding the immunological mechanisms underlying these transient effects is important for patient counseling and expectation management. In addition, effective communication regarding vaccine safety supports adherence to complete vaccination schedules. These aspects are essential for reinforcing the favorable benefit–risk profile of herpes zoster immunization programs (Anderson *et al.,* 2022).

The global epidemiology of herpes zoster reflects profound demographic and immunological transitions occurring worldwide. Rising life expectancy and population aging have expanded the proportion of individuals at risk for VZV reactivation. Concurrently, improved survival among immunocompromised patients has increased susceptibility at the population level. Recent surveillance studies indicate a steady rise in herpes zoster incidence across multiple geographic regions, including countries with established varicella vaccination programs. Taken together, these observations emphasize the need for continuous reassessment of prevention strategies adapted to evolving population structures and risk profiles (Kawai *et al.,* 2018; Marra *et al.,* 2020; Harpaz *et al.,* 2022).

Beyond advancing age, several host-related factors modulate susceptibility to herpes zoster, including chronic diseases, immunosuppressive therapies, and psychological stress. Metabolic and systemic conditions such as diabetes mellitus, chronic kidney disease, and autoimmune disorders have been consistently associated with impaired VZV-specific immune responses. Prolonged use of immunosuppressive medications further compromises cellular immunity. Together, these determinants not only increase the likelihood of viral reactivation but also contribute to more severe disease courses and higher complication rates. Psychological stress has likewise been implicated as a modulator of immune function. Recognition of these multifactorial interactions is essential for identifying high-risk groups who may benefit most from targeted vaccination and prevention strategies (Yawn *et al.,* 2017; Forbes *et al.,* 2019; Zhang *et al.,* 2021).

From a public health perspective, herpes zoster represents a substantial economic and societal burden worldwide. Direct medical expenditures related to antiviral therapy, pain management, outpatient visits, and hospitalization place significant pressure on healthcare systems. This burden is compounded by indirect costs associated with work absenteeism, reduced productivity, and long-term disability, particularly among older adults. The chronic nature of postherpetic neuralgia further amplifies long-term healthcare utilization. Cost-effectiveness analyses conducted across diverse healthcare systems consistently support herpes zoster vaccination as a valuable and economically sound intervention. Such findings reinforce immunization as a cornerstone of healthy aging policies and preventive public health strategies (Le *et al.,* 2018; Curran *et al.,* 2020; Drolet *et al.,* 2023).

The objective of this review is to critically examine recent advances in the basic and clinical understanding of varicella-zoster virus biology. In addition, the article evaluates current developments in herpes zoster vaccination strategies and their immunological foundations. Emerging evidence regarding broader immunological and systemic effects beyond viral prevention is also considered. Particular attention is given to recent findings related to transient post-vaccination immune responses and their clinical relevance. By integrating insights from basic science, clinical data, and public health research, this review aims to provide a comprehensive overview of current knowledge. Ultimately, it seeks to highlight future research directions and implications for prevention in aging and high-risk populations.

2. METHODS

This study was designed as a narrative review aimed at synthesizing current scientific evidence related to varicella-zoster virus, herpes zoster vaccination, and emerging immunological implications. The review addressed advances in basic and clinical research, vaccination strategies, systemic immunological effects, and transient post-vaccination immune responses. A narrative framework was selected to enable comprehensive integration of diverse lines of evidence and to support contextual interpretation of mechanistic, clinical, and epidemiological findings. Unlike systematic

reviews, this format permits conceptual synthesis across disciplines. Such an approach was considered appropriate given the complexity and heterogeneity of the available literature.

Scientific literature was identified through structured searches of major biomedical databases, including PubMed, Scopus, and Web of Science. Combinations of controlled vocabulary and free-text terms related to varicella-zoster virus, herpes zoster, vaccination, immunosenescence, immune responses, and neurological outcomes were applied. Boolean operators were used to refine search results and maximize coverage. The intentionally broad strategy allowed inclusion of multidisciplinary evidence derived from virology, immunology, clinical medicine, and public health research. Searches were updated to incorporate the most recent publications available at the time of analysis.

Eligible publications included original research articles, systematic reviews, meta-analyses, clinical trials, and authoritative reports published in English. Priority was assigned to studies addressing adult and elderly populations, vaccine-induced immune responses, and clinically relevant outcomes. Investigations involving immunocompromised populations were also considered when relevant to herpes zoster prevention. Articles exclusively focused on pediatric varicella without implications for adult immunity or viral reactivation were excluded. These criteria ensured alignment with the objectives of the review, with emphasis placed on studies demonstrating methodological rigor and relevance to aging populations.

Data extraction was conducted qualitatively, with emphasis on study design, population characteristics, immunological mechanisms, and reported outcomes. Key findings were organized according to predefined thematic domains, including virological mechanisms, vaccination efficacy, systemic immunological effects, and post-vaccination immune dynamics. Owing to heterogeneity across study designs, results were synthesized thematically rather than quantitatively. Comparative analysis was applied to identify converging and diverging evidence. The Results and Discussion sections were structured according to these thematic axes to support a coherent analytical narrative.

3. RESULTS

The literature search initially identified a total of 642 scientific records across the selected databases. Following removal of duplicate entries and preliminary screening based on titles and abstracts, 214 articles remained eligible for full-text evaluation. After a detailed assessment using predefined eligibility criteria aligned with the objectives of this review, 59 publications were ultimately included in the qualitative synthesis. These studies constituted the evidentiary basis for subsequent analysis, supporting evaluation of virological mechanisms, vaccination strategies, systemic immunological effects, and post-vaccination immune responses. Implementation of this structured selection process enhanced consistency and thematic relevance across the analyzed literature.

The included publications encompassed a broad range of methodological designs, including observational cohort studies, randomized clinical trials, experimental immunological investigations, and population-based surveillance reports. Most focused on adult and elderly populations, reflecting the epidemiological relevance of herpes zoster in these age groups. Several investigations also incorporated immunocompromised individuals when relevant to disease severity or vaccine response. Studies originated from diverse geographic regions, with substantial representation from North America, Europe, Asia, and Latin America, thereby supporting the international applicability of the synthesized evidence. Overall, methodological variability permitted a comprehensive evaluation of both clinical and immunological outcomes.

Epidemiological data analysis demonstrated that herpes zoster remains highly prevalent worldwide, with estimates indicating that approximately one in three individuals will develop the disease during their lifetime. Globally, several million new cases are reported annually, contributing to a considerable public health burden. Incidence rates increase markedly after 50 years of age and continue to rise with advancing age, a pattern consistently observed across regions and healthcare systems. Aging was therefore identified as the principal determinant of herpes zoster risk and disease burden.

In Brazil, available epidemiological data indicate an increasing burden of herpes zoster, particularly among older adults. Although the disease is not classified as a condition of compulsory notification, regional studies and healthcare utilization databases provide indirect estimates of its frequency. These sources suggest that hundreds of thousands of cases occur annually nationwide. Hospital admissions related to herpes zoster and associated complications have also increased over time. Neurological involvement and prolonged pain syndromes represent important contributors to hospitalization. Together, these trends highlight the importance of preventive strategies within the national healthcare context.

Recent regional healthcare utilization data and outpatient clinical observations in Brazil have indicated a sustained increase in herpes zoster diagnoses across different age groups in the post-pandemic period. In addition to classical dermatomal manifestations,

involvement of autonomic sensory pathways has been reported in a subset of patients, including presentations associated with urinary dysfunction and prolonged neuropathic pain syndromes. Clinical reports have also described herpes zoster reactivation following acute physiological stressors such as intoxication, infection, trauma, or inflammatory conditions in individuals without prior immunocompromising disease. These findings suggest that transient alterations in host immune surveillance may contribute to viral reactivation patterns in contemporary populations, potentially influencing the clinical spectrum of varicella-zoster virus–associated disease.

Clinical manifestations reported across the analyzed literature ranged from uncomplicated dermatomal herpes zoster to severe and prolonged disease courses. Acute presentations typically included a localized vesicular rash accompanied by intense neuropathic pain. Postherpetic neuralgia emerged as the most frequently reported chronic outcome and was consistently associated with substantial impairment in quality of life. Neurological complications, including encephalitis, vasculopathy, and stroke, were reported less frequently; however, when present, they were linked to significant morbidity and increased healthcare utilization. Collectively, these observations underscore the systemic impact of varicella-zoster virus reactivation beyond cutaneous disease (Table 1).

Table 1: Clinical manifestations and complications associated with varicella-zoster virus. This table summarizes the main clinical manifestations and complications associated with varicella-zoster virus reactivation in adult and elderly populations

Clinical manifestation	Affected system	Typical age group	Frequency	Clinical impact
Acute neuritic pain	Nervous	≥50 years	Very common	Functional limitation
Dermatomal rash	Integumentary	≥50 years	Very common	Acute discomfort
Disseminated zoster	Systemic	Immunocompromised	Rare	High severity
Encephalitis	Central nervous system	Older adults	Rare	Severe morbidity
Myelitis	Central nervous system	Adults	Rare	Motor dysfunction
Ophthalmic zoster	Ocular	Older adults	Uncommon	Visual impairment
Otic zoster	Auditory	Adults	Rare	Hearing loss
Postherpetic neuralgia	Nervous	Older adults	Common	Chronic pain
Vasculopathy	Vascular	Older adults	Rare	Stroke risk

Comparative analysis of vaccination strategies revealed marked differences in efficacy and population suitability. Live-attenuated vaccines provided moderate protection, with effectiveness declining progressively in older age groups. These constraints were especially pronounced among individuals over 60 years of age and within immunocompromised populations. In contrast, recombinant subunit vaccines exhibited high efficacy across all age strata, including individuals over 70 years of age, independent of baseline immune status. Variations in duration of protection, magnitude of immune response, and safety profiles were systematically documented between platforms. These comparative outcomes were synthesized to highlight vaccine-specific performance characteristics (Table 2).

Table 2: Comparison of herpes zoster vaccines. This table compares the main characteristics of available vaccine platforms used for the prevention of herpes zoster in adults

Vaccine type	Platform	Target population	Efficacy	Main limitations
Live-attenuated	Replicating virus	Adults ≥50 years	Moderate	Lower efficacy in the elderly
Live-attenuated	Replicating virus	Immunocompetent	Moderate	Contraindicated if immunosuppressed
Live-attenuated	Replicating virus	Adults ≥60 years	Moderate	Shorter protection
Recombinant	Subunit (gE)	Adults ≥50 years	High	Higher reactogenicity
Recombinant	Subunit (gE)	Adults ≥70 years	High	Cost
Recombinant	Subunit (gE)	Immunocompromised	High	Limited access
Recombinant	Subunit (gE)	Adults ≥60 years	High	Two-dose schedule
Recombinant	Subunit (gE)	Chronic disease	High	Availability
Recombinant	Subunit (gE)	Older adults	High	Program inclusion

Immunological outcomes reported in the studies analyzed highlighted the central role of cellular immunity in protection against herpes zoster. Across multiple investigations, preservation and enhancement of T-cell–mediated responses were consistently associated with reduced risk of viral reactivation. Recombinant vaccination was strongly linked to $CD4^+$ T-cell activation and the development of sustained

immune memory, including in populations traditionally characterized by age-related immune decline. Notably, these responses were maintained across different age groups and clinical settings. The capacity of recombinant vaccines to induce durable cell-mediated immunity supports their effectiveness in overcoming immunosenescence-related dysfunction. These immunological outcomes were systematically summarized (Table 3).

Table 3: Immunological responses induced by herpes zoster vaccination. This table summarizes the main immunological mechanisms activated following herpes zoster vaccination

Immune component	Immune response	Vaccine platform	Duration	Functional relevance
Antigen presentation	Enhanced	Recombinant	Short-term	T-cell priming
Antibody response	Moderate	Recombinant	Long-term	Supportive role
$CD4^+$ T cells	Moderate activation	Live-attenuated	Shorter	Partial control
$CD4^+$ T cells	Strong activation	Recombinant	Long-term	Viral control
$CD8^+$ T cells	Moderate activation	Recombinant	Long-term	Cytotoxicity
Cytokine production	Increased	Recombinant	Long-term	Immune coordination
Immune exhaustion	Reduced	Recombinant	Long-term	Functional preservation
Innate immunity	Rapid activation	Recombinant	Short-term	Adjuvant effect
Immune memory	Robust	Recombinant	>10 years	Sustained protection

Several studies examined relationships between herpes zoster or vaccination status and broader systemic outcomes. Observational data indicated that viral reactivation was linked to increased risks of cardiovascular events and neurological complications. Such relationships were identified across different study designs and populations. In contrast, vaccinated individuals consistently demonstrated lower rates of selected systemic outcomes compared with unvaccinated cohorts, particularly in relation to neurovascular and inflammatory conditions. Although these findings do not establish causality, similar patterns were reported across independent cohorts. These systemic outcomes were organized and summarized thematically to facilitate comparison across studies (Table 4).

Table 4: Systemic outcomes associated with herpes zoster and vaccination. This table outlines systemic outcomes linked to herpes zoster infection and vaccination status

Outcome	Associated condition	Population	Direction of association	Clinical relevance
Cardiovascular events	Herpes zoster	Adults	Increased	Systemic impact
Dementia	Unvaccinated status	Older adults	Increased	Cognitive decline
Dementia	Vaccinated status	Older adults	Reduced	Neuroprotection
Hospitalization	Herpes zoster	Older adults	Increased	Health burden
Neuroinflammation	Herpes zoster	Older adults	Increased	Cognitive impact
Stroke	Herpes zoster	Older adults	Increased risk	High morbidity
Vasculopathy	Herpes zoster	Adults ≥50 years	Increased risk	Vascular damage
Chronic pain	Herpes zoster	Older adults	Increased	Quality of life
Systemic inflammation	Vaccination	Adults	Transient	Immune activation

Transient immune and clinical responses following vaccination were frequently documented across clinical trials and post-marketing surveillance studies. Local injection-site reactions, including pain, erythema, and swelling, were commonly reported. Short-term systemic symptoms such as fatigue, myalgia, headache, and low-grade fever occurred particularly after the first vaccine dose. These responses reflected early innate immune activation induced by vaccination. Reported events were generally mild to moderate in intensity and resolved spontaneously within a few days without requiring medical intervention. No evidence of persistent or long-term adverse outcomes was identified across the studies analyzed.

Synthesis of the results indicated a consistent pattern across the analyzed literature. Varicella-zoster virus reactivation was strongly associated with aging-related decline in cellular immune function, whereas vaccination functioned as an effective preventive intervention capable of restoring protective immune responses. The compiled evidence demonstrated reductions in herpes zoster incidence, disease severity, and complication rates among vaccinated populations. These benefits were documented across diverse age

groups and clinical settings. Additionally, emerging data suggested potential effects extending beyond classical disease prevention. Methodological heterogeneity across studies reinforces the importance of integrative interpretation rather than isolated analysis of individual findings (Table 5).

Table 5: Post-vaccination immune and clinical responses. This table summarizes common immune and clinical responses observed following herpes zoster vaccination

Response type	Clinical manifestation	Frequency	Duration	Severity
Immune response	Cytokine release	Common	Short-term	Mild
Local reaction	Injection-site pain	Very common	1–3 days	Mild
Local reaction	Erythema	Common	1–3 days	Mild
Reactogenicity	After the first dose	Common	Short-term	Moderate
Reactogenicity	After the second dose	Less common	Short-term	Mild
Serious adverse events	Severe reactions	Rare	—	Severe
Systemic symptom	Fatigue	Common	1–3 days	Mild
Systemic symptom	Myalgia	Common	1–3 days	Mild
Systemic symptom	Fever	Uncommon	<48 hours	Mild

Differences in reactogenicity profiles between vaccine platforms were consistently observed across the analyzed studies. Recombinant vaccines were associated with higher short-term reactions compared with live-attenuated formulations, primarily reflecting enhanced innate immune activation induced by the adjuvanted platform. Despite this increased response, reported symptoms were predominantly mild to moderate in intensity. Rates of vaccine discontinuation remained low across all age groups, and high completion rates of the vaccination schedule indicated good acceptability among vaccinated individuals. Collectively, these findings support a favorable tolerability profile for recombinant herpes zoster vaccines.

Globally, herpes zoster affects approximately one-third of the population over the course of a lifetime, resulting in tens of millions of new cases annually. Epidemiological analyses consistently demonstrate that incidence increases sharply after 50 years of age, with the highest rates observed among individuals aged 70 years and older, reflecting cumulative immune decline. In Brazil, available epidemiological estimates suggest that several hundred thousand new cases occur each year, predominantly among older adults. Although mortality directly attributable to herpes zoster is low, fatal outcomes occur mainly in elderly and immunocompromised individuals. Long-term sequelae, particularly postherpetic neuralgia, represent the major contributor to disease burden, with prevalence increasing markedly with advancing age (Table 6).

Table 6: Estimated global and Brazilian burden of herpes zoster by age group. This table summarizes approximate epidemiological estimates of herpes zoster worldwide and in Brazil, stratified by age group, including incidence patterns, mortality, and long-term sequelae

Region / Population	Age group	Estimated annual cases	Mortality (approx.)	Sequelae prevalence
Brazil	50–59 years	High	Very rare	10–15%
Brazil	60–69 years	Very high	Low	15–25%
Brazil	≥70 years	Highest	Moderate	25–30%
Brazil	All ages	Several hundred thousand	Rare overall	—
Global	<40 years	Low (<3 per 1,000)	Rare	<5%
Global	40–49 years	Moderate	Very rare	5–10%
Global	50–59 years	High	Low	10–15%
Global	60–69 years	Very high	Low–moderate	15–25%
Global	≥70 years	Highest	Moderate	25–30%

Health economic outcomes reported in the analyzed studies consistently indicated that herpes zoster vaccination is associated with reductions in long-term healthcare costs. Fewer hospital admissions related to

acute disease and complications contributed substantially to these savings, alongside decreased demand for chronic pain management, particularly for postherpetic neuralgia. Vaccination was also associated with fewer outpatient visits and a reduced need for prolonged pharmacological therapy. Indirect economic benefits were observed through reductions in productivity losses and caregiver burden. These favorable economic profiles were most pronounced in older age groups, reflecting the higher baseline disease burden and complication rates in aging populations.

Across the analyzed studies, postherpetic neuralgia emerged as the most frequently reported complication of herpes zoster, particularly among older adults. This chronic pain condition is consistently associated with significant impairment in daily functioning and quality of life. Additional complications included secondary bacterial skin infections, scarring, and ophthalmic involvement with potential visual impairment. Severe systemic outcomes such as pneumonia, encephalitis, and cerebrovascular events occurred less frequently and were observed predominantly in immunocompromised individuals. Early initiation of antiviral therapy, particularly within the first 72 hours of rash onset, was consistently associated with reduced disease severity. Supportive treatments were commonly employed to control pain, prevent secondary infections, and improve symptom resolution (Table 7).

Table 7: Post-exposure prophylaxis strategies for varicella in high-risk populations. This table summarizes post-exposure prophylaxis strategies for varicella in immunosuppressed individuals, pregnant women, and neonates, based on current public health recommendations

Risk group	Exposure context	Preferred PEP strategy	Alternative option	Clinical considerations
Healthcare workers	Occupational exposure	Antivirals if susceptible	Vaccination	Prevent nosocomial transmission
Immunosuppressed adults	Household or close contact	Oral antivirals	VZIG (if available)	Early treatment reduces severity
Immunosuppressed children	Healthcare or household exposure	Oral antivirals	VZIG if antivirals contraindicated	Monitor for breakthrough infection
Neonates (peripartum exposure)	Maternal infection near delivery	Antivirals + IVIG	—	Highest risk of severe disease
Neonates (postnatal exposure)	Household or hospital contact	Oral antivirals	IVIG if high risk	Assess maternal immunity
Other high-risk contacts	Household exposure	Antivirals	—	Risk stratification required
Pregnant women (>20 weeks)	Confirmed exposure	Oral antivirals	VZIG (limited supply)	Avoid hospital attendance
Pregnant women (<20 weeks)	Confirmed exposure	Specialist assessment	Individualized decision	Fetal monitoring recommended
Preterm infants	Hospital exposure	Antivirals	IVIG	Immature immune system

Health economic outcomes reported in the analyzed studies consistently indicated that herpes zoster vaccination reduces long-term healthcare costs. Fewer hospital admissions related to acute disease and severe complications represented a major source of economic savings, alongside decreased demand for chronic pain management, particularly for postherpetic neuralgia. In addition to direct medical costs, vaccination was associated with reduced indirect costs related to work absenteeism and productivity losses. Together, these effects contributed to favorable economic profiles across different healthcare settings. The economic benefits of vaccination were particularly pronounced in older age groups, reflecting the higher baseline disease burden and complication rates observed in aging populations.

4. DISCUSSION

This review highlights that varicella-zoster virus remains a major public health concern despite decades of scientific investigation. The persistence of lifelong viral latency, combined with progressive age-related immune decline, creates a distinctive epidemiological and clinical profile in aging societies. Classical studies established the central role of cellular immunity in controlling viral reactivation and limiting disease expression. More recent investigations have refined this understanding by identifying specific immune pathways selectively affected by immunosenescence. In particular, age-related alterations in T-cell–mediated immune surveillance have been consistently linked to increased susceptibility to herpes zoster. These immunological mechanisms help explain the sharp rise in disease incidence observed in older populations and reinforce the importance of cellular immunity as a key determinant of VZV reactivation risk

(Figure 1) (Schmader, 2018; Levin *et al.*, 2019; Arvin *et al.*, 2024).

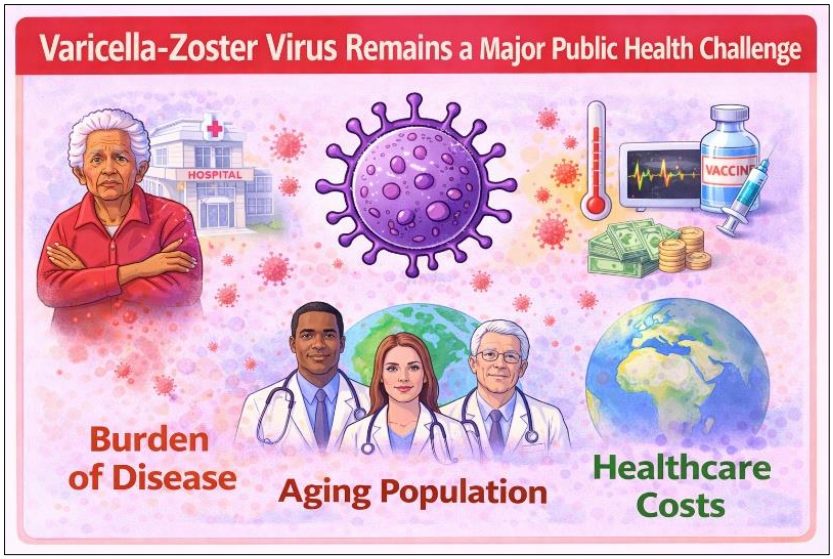

Figure 1: Varicella-zoster virus as a major public health concern. VZV infection contributes to a substantial burden of disease, particularly in aging populations. Its impact extends to increased healthcare costs and highlights the importance of preventive strategies such as vaccination

Epidemiological data from Brazil have suggested a potential increase in herpes zoster incidence during the COVID-19 pandemic period. Analyses based on national health system records indicated a rise in reported diagnoses between March and August 2020 compared with previous years, which may reflect the impact of pandemic-related immunological stressors on viral reactivation. Although a direct causal relationship has not been established, these findings support the hypothesis that transient alterations in immune function at the population level may influence herpes zoster epidemiology (Maia *et al.*, 2021).

Experimental models have provided important insights into the biological mechanisms underlying varicella-zoster virus latency and reactivation. Advances in in vitro human neuronal culture systems capable of supporting latent infection and subsequent experimental reactivation have improved the study of viral persistence and host–virus interactions. Experimental evidence suggests that cellular signaling pathways, including c-Jun N-terminal kinase (JNK), phosphoinositide 3-kinase (PI3K), and nerve growth factor (NGF), may influence the balance between viral quiescence and reactivation. These systems contribute to understanding the restrictive nature of viral gene expression during latency and the immunological factors involved in maintaining viral quiescence, while also supporting the development of future prophylactic and therapeutic strategies targeting VZV-associated complications (Figure 2) (Baird *et al.*, 2019; Laemmle *et al.*, 2019; Goldstein and Kensington, 2023).

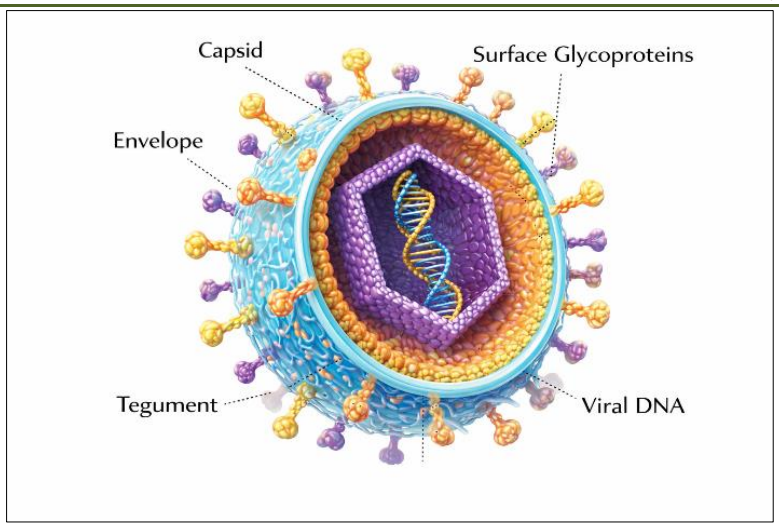

Figure 2: Structural organization of the varicella-zoster virus (VZV). This figure illustrates the structural components of the varicella-zoster virus, including the lipid envelope with surface glycoproteins, the tegument layer, the icosahedral capsid, and the double-stranded viral DNA genome

These elements contribute to viral attachment, entry, replication, and immune evasion. The findings of this review reinforce immunosenescence as the primary biological driver underlying the increased risk of herpes zoster. Progressive deterioration of T–cell–mediated immunity compromises immune surveillance of latent varicella-zoster virus, facilitating viral reactivation. Contemporary studies indicate that this process involves not only a quantitative reduction in immune cells but also functional impairments, including disrupted cytokine signaling, reduced proliferative capacity, and features of immune exhaustion. Such qualitative alterations further weaken antiviral defenses in older individuals. Together, these mechanisms provide a coherent biological framework linking aging to the rising burden of herpes zoster observed in older populations (Figure 3) (Crooke *et al.*, 2019; Gershon *et al.*, 2019; Weinberger *et al.*, 2022).

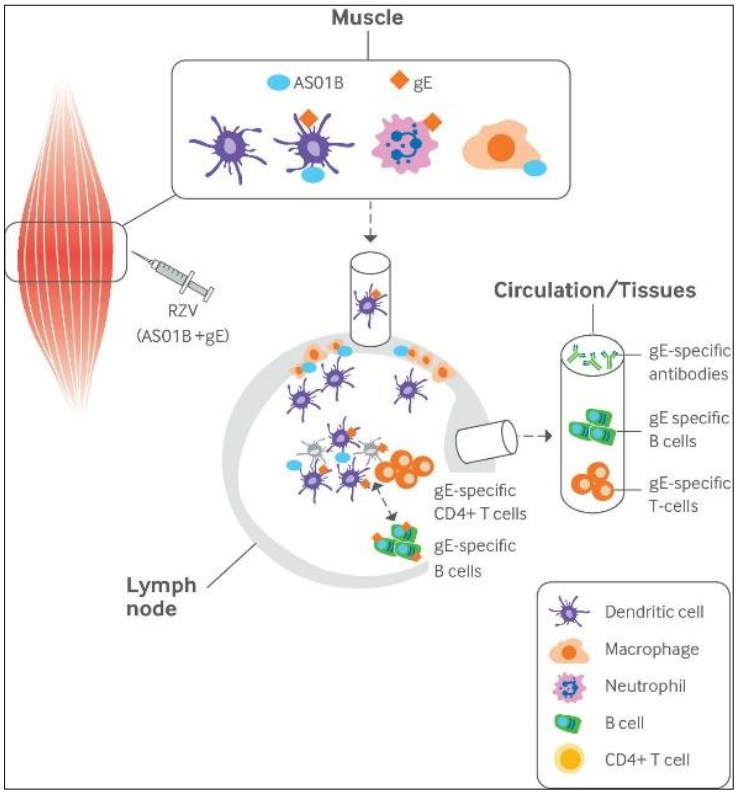

Figure 3: Structure of the varicella-zoster virus (VZV). The virus consists of a lipid envelope with surface glycoproteins, a tegument layer, and an icosahedral capsid containing double-stranded DNA. These structural components are essential for viral entry, replication, and interaction with host cells

Clinical outcomes associated with herpes zoster extend beyond acute cutaneous manifestations. Postherpetic neuralgia remains the most prevalent chronic complication and disproportionately affects older adults, contributing substantially to long-term morbidity. In addition to chronic pain, accumulating evidence supports an association between varicella-zoster virus reactivation and serious neurological outcomes, including encephalitis, myelitis, and virus-associated vasculopathy with cerebrovascular involvement. These complications reflect the neurotropic nature of the virus and its capacity to induce systemic pathology. Observations reported across clinical and pathological studies support a broader disease concept. Collectively, these findings reinforce the need to conceptualize varicella-zoster virus as a systemic pathogen with multisystem implications rather than a purely dermatological condition (Nagel *et al.*, 2017; Breuer *et al.*, 2018; Gershon *et al.*, 2020; Breuer *et al.*, 2021; Marra *et al.*, 2022).

Herpes zoster is clinically characterized by a unilateral dermatomal vesicular rash frequently accompanied by severe neuropathic pain. In a substantial proportion of patients, pain may persist beyond lesion resolution, resulting in postherpetic neuralgia, the most common long-term complication. This condition affects up to 20% of affected adults, with increasing incidence and severity observed in older populations. Additional complications, including ophthalmic involvement, meningoencephalitis, Ramsay Hunt syndrome, and disseminated disease, may occur, particularly in immunocompromised individuals, further contributing to functional impairment and reduced quality of life (Bardach *et al.*, 2021; Marra *et al.*, 2022).

Vaccination has fundamentally altered the prevention landscape of herpes zoster and its associated complications. While live-attenuated vaccines provided initial proof of concept, their reduced efficacy in older adults and contraindications in immunocompromised populations limited their overall public health impact. The advent of recombinant subunit vaccines represents a paradigm shift in prevention strategies, demonstrating consistently high efficacy across age groups, including individuals of advanced age. This technological advance directly addresses the biological challenges imposed by immunosenescence by inducing robust and sustained cell-mediated immune responses that restore effective immune surveillance. This mechanistic advantage underpins the superior clinical performance of recombinant vaccines in aging populations (Figure 4) (Lal *et al.*, 2015; Cunningham *et al.*, 2018; Lal *et al.*, 2019; Dagnew *et al.*, 2021).

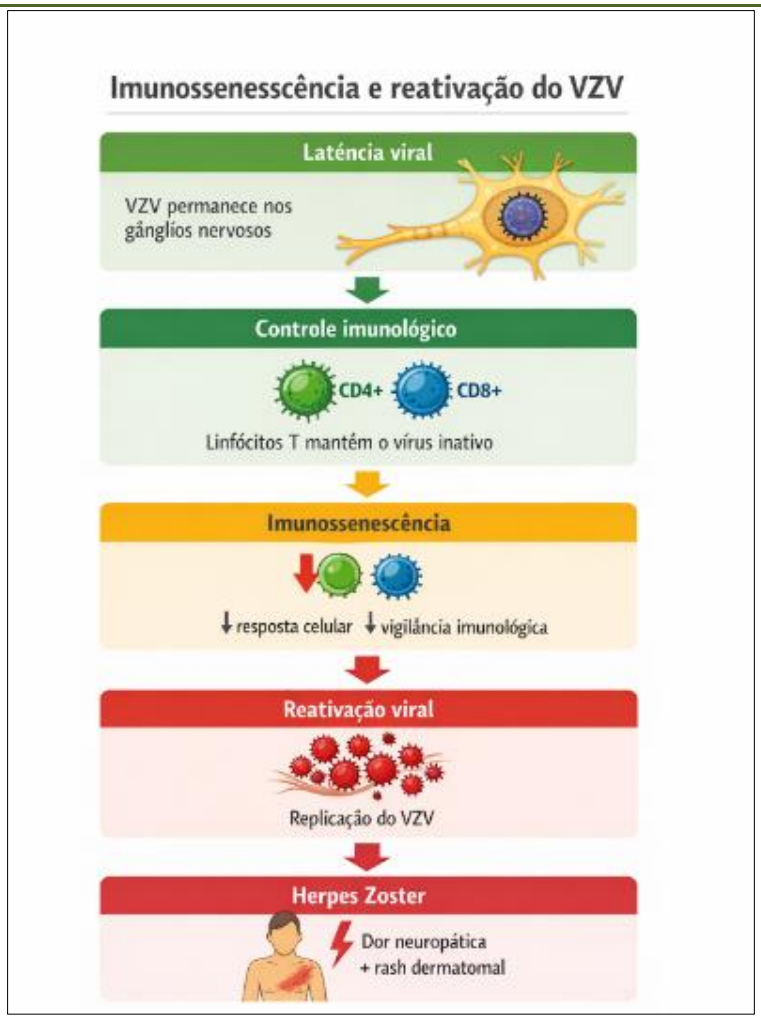

Figure 4: Immunosenescence and reactivation of varicella-zoster virus (VZV). Immunosenescence leads to a progressive decline in VZV-specific T lymphocytes, resulting in impaired cellular immune surveillance. This reduction in immune control facilitates the reactivation of latent varicella-zoster virus in sensory ganglia, increasing the risk of herpes zoster in older adults

Mechanistically, recombinant vaccines achieve superior performance through targeted induction of cellular immune responses. The combination of varicella-zoster virus glycoprotein E with a potent adjuvant system enhances antigen uptake and presentation by antigen-presenting cells, resulting in activation and expansion of $CD4^+$ T lymphocytes essential for long-term viral control. Long-term follow-up studies demonstrate durable immune memory extending beyond a decade after vaccination. These responses are particularly relevant in older adults, whose baseline immunity is compromised by immunosenescence. By restoring effective cell-mediated immunity, recombinant vaccines compensate for age-related immune decline. Collectively, these findings underscore the importance of vaccine design specifically tailored to aging immune systems (Levin *et al.*, 2019; Boutry *et al.*, 2020; Anderson *et al.*, 2022).

Population-level modeling studies have suggested that herpes zoster reactivation may be influenced not only by age-related immune decline but also by epidemiological and environmental factors. Mathematical analyses examining seasonal patterns of varicella transmission and zoster incidence have indicated that reexposure to circulating virus may transiently enhance VZV-specific immunity. At the same time, ambient factors such as ultraviolet radiation have been associated with an increased risk of reactivation. These findings highlight the potential contribution of ecological dynamics to latency maintenance and reactivation patterns across populations (Bakker *et al.*, 2021).

An emerging area of research focuses on the potential systemic effects of herpes zoster vaccination beyond its prevention of cutaneous disease. Observational studies have reported associations between vaccination and reduced risks of cardiovascular

events and adverse neurological outcomes, suggesting that suppression of viral reactivation may mitigate chronic inflammatory and vascular processes. Additional evidence from large population-based cohorts, including studies involving more than 280,000 adults, has also indicated a lower frequency of incident dementia diagnoses among vaccinated individuals during long-term follow-up (Wouters *et al.,* 2023). Furthermore, a recent international meta-analysis reported a reduced incidence of major cardiovascular events, such as myocardial infarction and stroke, among vaccinated populations compared with unvaccinated groups. Although these findings do not establish causality, they support the hypothesis that prevention of viral reactivation may influence systemic inflammatory and neurovascular pathways and highlight the need for further mechanistic and longitudinal investigation (Figure 5) (Langan *et al.,* 2014; Tseng *et al.,* 2020; Wouters *et al.,* 2023).

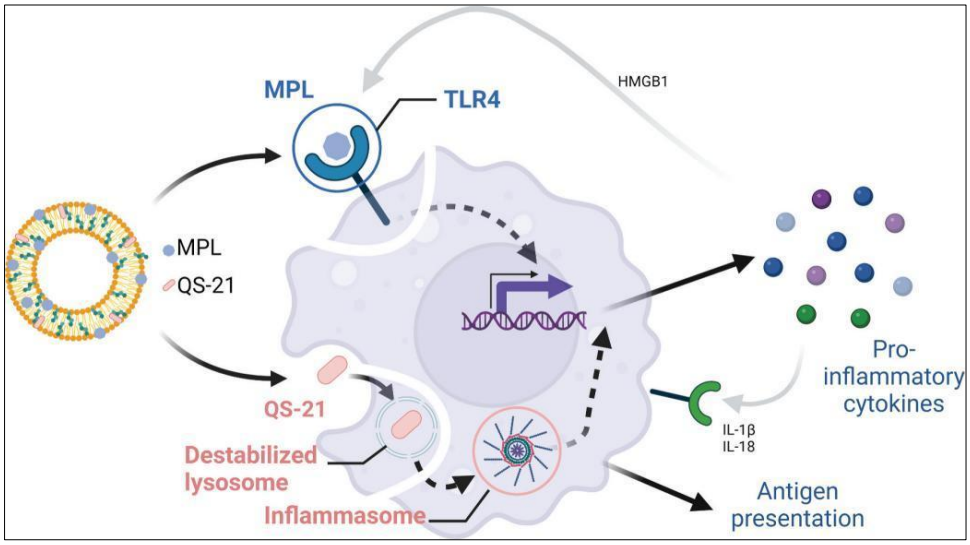

Figure 5: Mechanism of action of the recombinant herpes zoster vaccine. The gE antigen combined with the AS01B adjuvant is taken up by antigen-presenting cells and presented via MHC II, leading to $CD4^+$ T-cell activation. This induces a strong cell-mediated immune response and long-lasting immunological memory, reducing the risk of VZV reactivation

Genetic epidemiological evidence further supports a potential link between VZV-specific immune responses and systemic health outcomes. A phenome-wide Mendelian randomization analysis has identified causal associations between anti-VZV immunoglobulin G levels and multiple clinical traits, including autoimmune and neurological conditions. These findings suggest that host immune responses to latent or reactivated infection may contribute to disease susceptibility beyond classical cutaneous manifestations and highlight the importance of genetic determinants in modulating immune-mediated outcomes (Yu *et al.*, 2023).

The potential link between varicella-zoster virus infection, vaccination, and cognitive decline has attracted increasing scientific attention in recent years. Several large population-based studies have reported a lower incidence of dementia among individuals who received herpes zoster vaccination. Proposed mechanisms include reduced neuroinflammatory burden, preservation of cerebral vascular integrity, and decreased cumulative viral reactivation over time. These pathways are biologically plausible given the neurotropic nature of VZV and the potential for recurrent viral activity to contribute to chronic inflammatory processes in the central nervous system. Although these hypotheses remain under investigation, consistent epidemiological observations support further exploration. Collectively, these findings position herpes zoster vaccination as a potential modifier of brain aging trajectories (Figure 6) (Chen *et al.*, 2022; Arvin *et al.*, 2024; Taquet *et al.*, 2024).

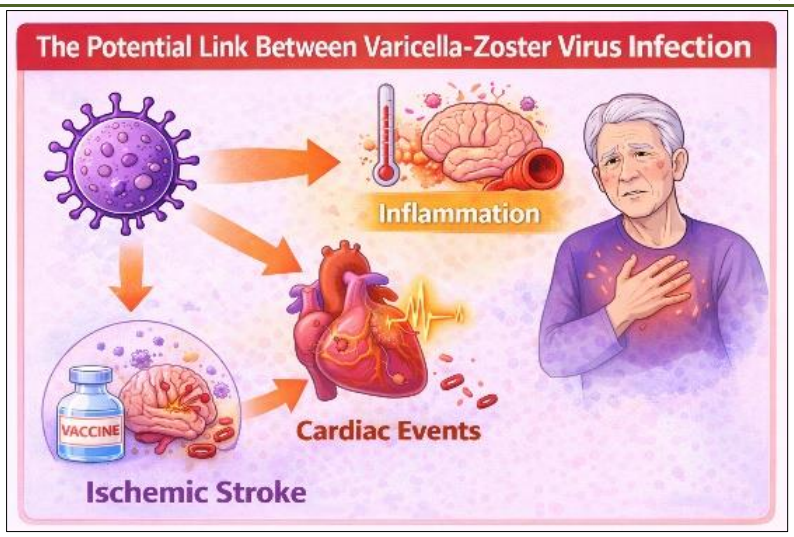

Figure 6: Potential link between varicella-zoster virus infection and cardiovascular and neurological outcomes. VZV infection and reactivation may trigger systemic inflammation, contributing to vascular injury and organ dysfunction. These mechanisms are associated with increased risk of cardiac events, ischemic stroke, and neurological complications

Despite these promising associations, several important limitations must be considered. Most studies evaluating systemic and neurological outcomes related to herpes zoster vaccination are observational in nature and therefore subject to residual confounding and potential selection bias. Differences in healthcare access, health-seeking behavior, socioeconomic status, and baseline comorbidities may influence observed associations. In addition, vaccinated individuals may differ systematically from unvaccinated populations in ways that are difficult to fully adjust for statistically. These methodological challenges underscore the need for cautious interpretation of current findings and highlight the importance of prospective studies and mechanistic investigations to clarify causality (Nagel and Gilden, 2014; Freer *et al.,* 2018; Forbes *et al.,* 2019; Jiang *et al.,* 2022; Zhu *et al.,* 2025).

Transient immune responses following herpes zoster vaccination also represent an important consideration. Increased reactogenicity observed with recombinant vaccines reflects strong innate immune activation induced by the adjuvant system. These responses manifest primarily as local and short-term systemic symptoms. While generally mild to moderate and self-limited, such effects may influence vaccine acceptance and completion rates in some populations. Understanding the immunological basis of these reactions is therefore important, and clear communication regarding their transient nature can improve patient confidence and adherence. Optimizing educational strategies is essential for maximizing the public health impact of vaccination programs (Figure 7) (Harbecke *et al.*, 2018; Marra *et al.*, 2020; Anderson *et al.*, 2022; Drolet *et al.*, 2023).

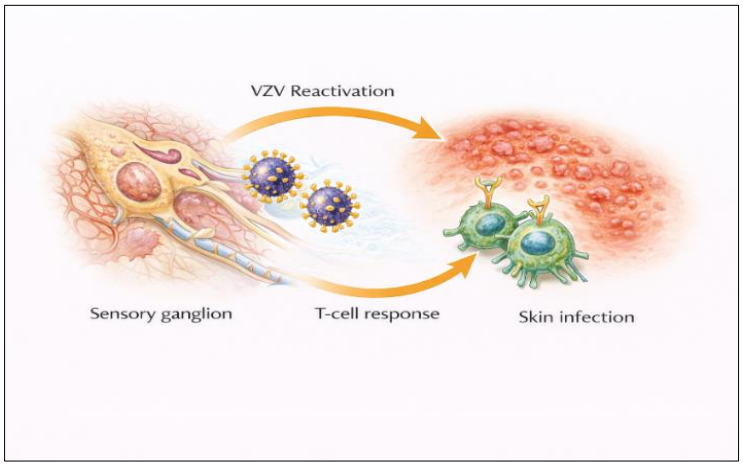

Figure 7: Potential pathways linking varicella-zoster virus, inflammation, and the brain. This figure presents a hypothetical model showing how varicella-zoster virus reactivation may promote neuroinflammation and cerebral

vasculopathy. These processes can contribute to vascular dysfunction and chronic inflammation in the central nervous system, potentially increasing the risk of cognitive impairment and dementia in susceptible individuals

From a health systems perspective, herpes zoster vaccination demonstrates consistently favorable cost-effectiveness profiles across different healthcare settings. Economic evaluations indicate reductions in long-term healthcare utilization following vaccination, driven primarily by fewer hospitalizations related to acute disease and severe complications. Decreased need for chronic pain management, particularly for postherpetic neuralgia, contributes to these savings. Indirect economic benefits, including reductions in productivity losses and caregiver burden, have also been documented. The magnitude of these effects is greatest in older populations. These findings support prioritization of herpes zoster vaccination within aging-focused public health policies (Figure 8) (Kawai *et al.*, 2018; Le *et al.*, 2018; Curran *et al.*, 2020; Kawai *et al.*, 2021).

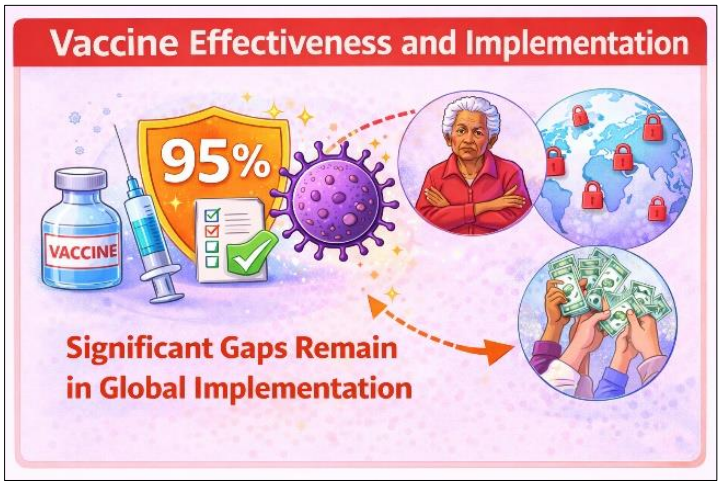

Figure 8: Vaccine effectiveness and challenges in global implementation. Vaccination provides high protection against the varicella-zoster virus and reduces disease burden. However, disparities in access, cost, and healthcare infrastructure contribute to gaps in global vaccine coverage

Despite strong evidence supporting vaccine effectiveness, significant gaps remain in global implementation. In many middle- and low-income countries, limited access, high costs, and lack of inclusion in national immunization programs restrict uptake. Structural barriers such as insufficient cold-chain infrastructure and limited healthcare coverage further contribute to these challenges, resulting in persistent disparities in herpes zoster burden across regions. These inequities disproportionately affect older and vulnerable populations. Addressing these gaps requires coordinated policy-level interventions and international cooperation. Expanding equitable access to vaccination remains a critical public health priority (Harpaz *et al.,* 2022; World Health Organization, 2023; World Health Organization, 2025a; World Health Organization, 2025b).

Another unresolved challenge involves optimizing vaccination strategies for immunocompromised populations. Although recombinant vaccines offer improved safety compared with live-attenuated formulations, uncertainties remain regarding optimal timing and dosing schedules, as well as the durability of vaccine-induced protection in individuals receiving immunosuppressive therapies. Variability in immune reconstitution across clinical conditions further complicates standardized recommendations. As the population of immunocompromised adults continues to grow, these questions gain increasing relevance. Tailored vaccination strategies may be necessary to maximize protection in these groups. Addressing these uncertainties is essential for inclusive and effective prevention strategies (Dagnew *et al.*, 2021; Boutry *et al.*, 2022; Anderson *et al.*, 2024).

Recent changes in post-exposure prophylaxis strategies for varicella reflect broader challenges in managing varicella-zoster virus–related disease in vulnerable populations. The progressive replacement of varicella zoster immunoglobulin with antiviral agents highlights both supply constraints and evolving evidence supporting antiviral efficacy. These strategies have been adopted particularly for immunosuppressed individuals, pregnant women, and neonates. Observational data indicate that antiviral prophylaxis is comparable to immunoglobulin in preventing or attenuating severe disease. Such policy shifts emphasize the importance of

adaptable prevention approaches and reinforce the need for comprehensive VZV control across the lifespan, particularly among populations at increased risk of complications (Figure 9) (Heininger and Seward, 2006; Gershon *et al.*, 2015; Nagel *et al.*, 2017; UK Health Security Agency, 2025).

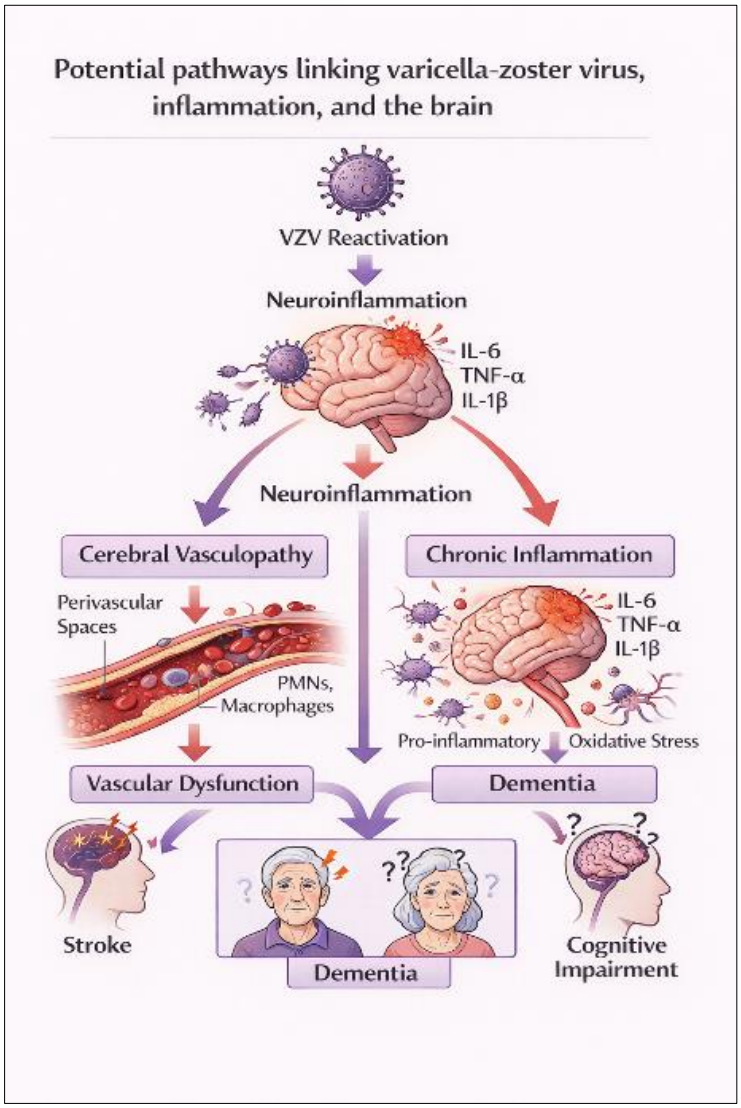

Figure 9: Potential pathways linking varicella-zoster virus, inflammation, and the brain. VZV reactivation may induce neuroinflammation and cerebral vasculopathy, leading to vascular dysfunction in the central nervous system. These processes are associated with increased risk of stroke, chronic inflammation, cognitive impairment, and dementia

Emerging vaccine platforms have introduced novel approaches for the prevention of varicella-zoster virus reactivation. Messenger RNA (mRNA-based) vaccines are currently being investigated as potential alternatives to existing live-attenuated and recombinant subunit formulations. Although currently licensed vaccines have substantially reduced disease burden, limitations related to safety in immunocompromised populations and reactogenicity remain. Emerging technologies, including mRNA, viral vector, and Virus-Like Particle (VLP) platforms, may improve immunogenicity while maintaining favorable safety profiles. Continued research will be required to determine their long-term effectiveness and potential role in future herpes zoster prevention strategies (Casabona *et al.*, 2025; Liu *et al.*, 2025).

Future research should prioritize mechanistic investigations exploring how varicella-zoster virus reactivation and its suppression may influence systemic inflammatory responses associated with aging. Integrative approaches combining immunology, neurology, and vascular biology may provide deeper insight into the multisystem consequences of viral

latency and reactivation. Advances in immune profiling have the potential to improve individual risk stratification and support the development of more personalized vaccination strategies. In particular, understanding interindividual variability in vaccine-induced immune responses may help optimize preventive interventions in aging populations. Such efforts may ultimately expand the clinical impact of herpes zoster prevention strategies beyond conventional infectious disease outcomes (Figure 10) (Weinberger *et al.*, 2022; Taquet *et al.*, 2024).

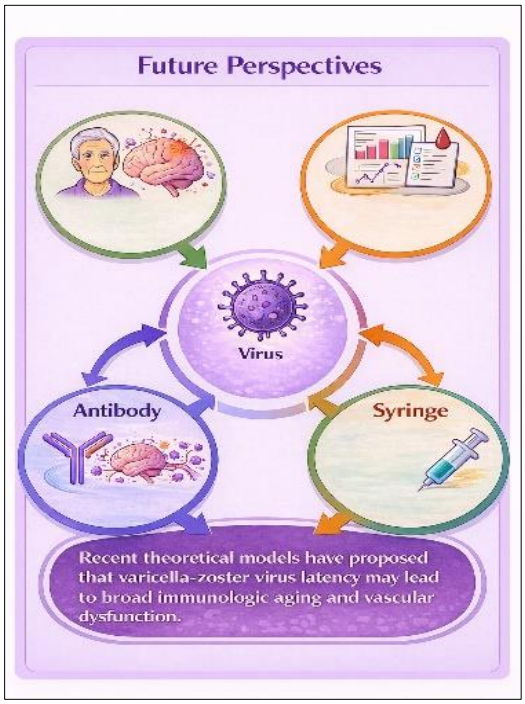

Figure 10: Future perspectives in varicella-zoster virus research and prevention. Integrative approaches combining immunology, neurology, and vascular biology may clarify the systemic effects of VZV reactivation and aging-related inflammation. Advances in immune profiling may enable personalized vaccination strategies and improved risk stratification in aging populations

Recent multi-proteomic analyses of the varicella-zoster virus–host interface have identified host cellular factors that may influence viral replication and susceptibility to severe infection, including in neurological contexts. These findings provide further insight into molecular pathways associated with viral persistence and may support the future development of targeted antiviral strategies aimed at limiting infection and related complications (Girault *et al.*, 2025).

Recent theoretical models have proposed that varicella-zoster virus latency may represent an adaptive host–virus interaction rather than a purely dormant state. The so-called immunosensor hypothesis suggests that latent infection within sensory ganglia may contribute to immune surveillance while facilitating long-term viral persistence. Within this framework, viral behavior across the host lifespan has been conceptualized as a temporally partitioned strategy involving primary infection, latency during immune competence, and reactivation associated with immune decline. Although primarily conceptual, this model provides a potential explanation for age-dependent patterns of herpes zoster and highlights the importance of host–virus coadaptation in shaping disease risk (Figure 11) (Han, 2025).

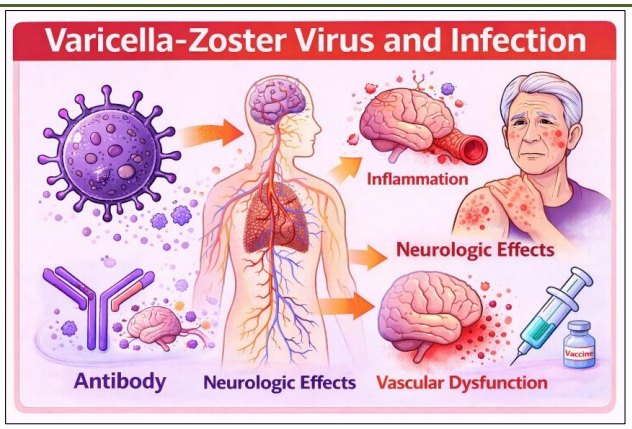

Figure 11: Graphical Abstract. Overview of varicella-zoster virus infection and its systemic consequences. ZV infection and reactivation are associated with neuroinflammation, vascular dysfunction, and neurological complications. Immune responses and vaccination strategies play a key role in modulating disease outcomes and preventing herpes zoster

Current antiviral therapies remain an essential component of clinical management for varicella-zoster virus–associated disease, particularly in individuals who are not immunized or are immunocompromised. However, limitations of currently approved agents, including modest effectiveness in preventing postherpetic neuralgia and the need for complex dosing regimens in patients with renal impairment, highlight the need for novel therapeutic options. The development of emerging antiviral compounds and helicase–primase inhibitors may represent a promising avenue for improving treatment outcomes in high-risk populations (Andrei and Snoeck, 2021).

Prospective clinical trials will also be necessary to clarify causal relationships between herpes zoster vaccination and non-classical outcomes, including cognitive decline. Randomized study designs with long-term follow-up will be essential to disentangle vaccine-specific effects from residual confounding. Incorporation of neurocognitive endpoints and imaging biomarkers may strengthen causal inference. Such evidence could expand the perceived value of vaccination beyond infectious disease prevention. Ultimately, these data may redefine the role of herpes zoster vaccination within broader strategies for healthy aging and disease prevention (Figure 12) (Chen *et al.*, 2022; Wouters *et al.*, 2023; Taquet *et al.*, 2024; Zhu *et al.*, 2025).

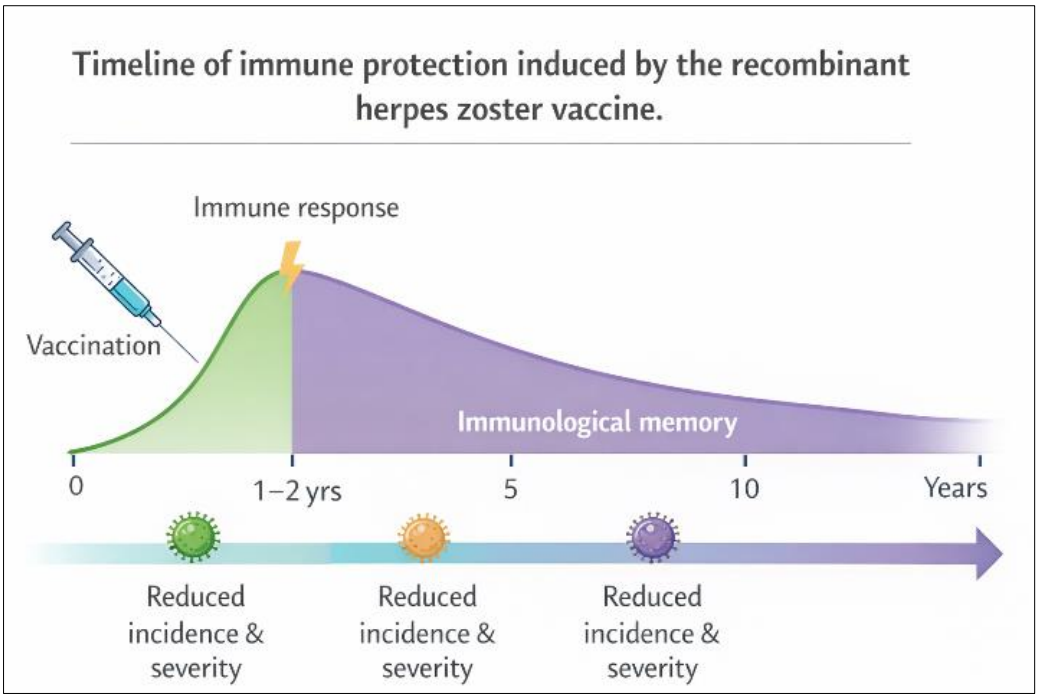

Figure 12: Timeline of immune protection induced by the recombinant herpes zoster vaccine. This figure illustrates the temporal dynamics of vaccine-induced immunity, including the initial immune response following vaccination, the establishment of long-term immunological memory, and the sustained duration of protection. The timeline highlights immune persistence extending beyond ten years, supporting long-term protection against herpes zoster

In summary, the accumulated evidence positions herpes zoster vaccination as a critical intervention not only for preventing viral reactivation but also for potentially modulating broader health outcomes associated with aging. By restoring effective cell-mediated immunity, vaccination addresses the biological mechanisms underlying increased susceptibility in older adults. Beyond classical disease prevention, emerging data suggest influences on systemic inflammatory processes and age-related comorbidities. These findings broaden the relevance of herpes zoster vaccination within strategies for healthy aging. Continued scientific innovation will be necessary to refine vaccine design and optimize long-term protection, together with equitable implementation of vaccination programs across diverse healthcare settings. Interdisciplinary research integrating immunology, neurology, and public health will support the full realization of the population-level impact of varicella-zoster virus control (Figure 13) ((Chen *et al.*, 2022; Wouters *et al.*, 2023; Taquet *et al.*, 2024; Zhu *et al.*, 2025) ault *et al*., 2025).

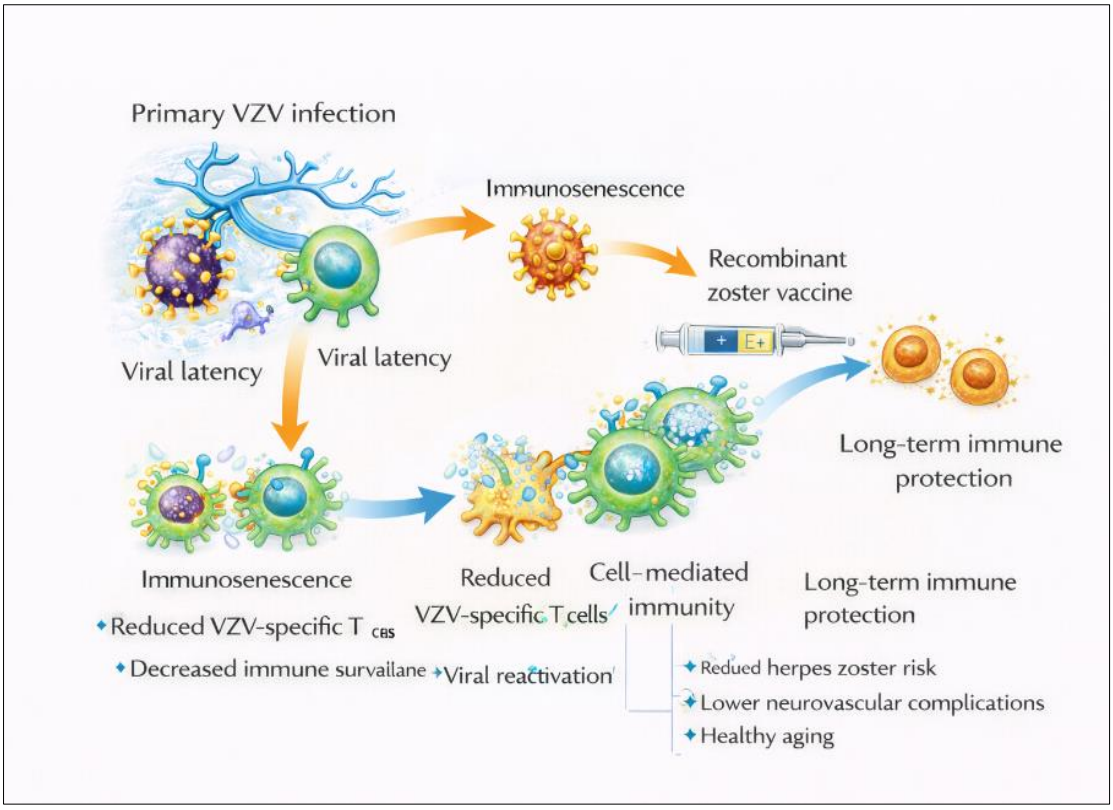

Figure 13: Graphical abstract summarizing varicella-zoster virus infection, immunosenescence, and vaccine-induced protection. This graphical abstract integrates varicella-zoster virus latency and reactivation, the impact of immunosenescence on cellular immune control, and the protective role of recombinant herpes zoster vaccination through enhanced cell-mediated immunity and long-term protection

5.0. CONCLUSION

This review demonstrates that varicella-zoster virus remains a significant clinical and public health challenge, particularly in aging populations. The lifelong establishment of viral latency combined with progressive immune decline creates a biological environment that favors viral reactivation and disease manifestation. These mechanisms explain the strong age dependence of herpes zoster incidence and complications. Understanding the complex interactions between viral persistence, host immunity, and aging is essential for guiding prevention strategies and improving clinical outcomes. Addressing these interactions remains a priority in the context of global population aging.

Advances in herpes zoster vaccination, particularly with the introduction of recombinant subunit vaccines, have substantially improved disease prevention. These vaccines provide robust and durable protection across age groups, including older adults and individuals with compromised immune function, by inducing strong cell-mediated immune responses that counteract the effects of immunosenescence. Beyond reducing herpes zoster incidence and classical complications, vaccination may also influence broader systemic outcomes. These observations reinforce the relevance of vaccination within comprehensive approaches to healthy aging and extend its value beyond infectious disease control.

Future efforts should focus on expanding equitable access to herpes zoster vaccination worldwide and optimizing immunization strategies for vulnerable populations. Addressing remaining knowledge gaps regarding long-term systemic and neurological effects will be important. Continued interdisciplinary research integrating virology, immunology, neurology, and public health may deepen mechanistic understanding and support evidence-based refinement of vaccination policies. Ultimately, these efforts may help maximize the population-level benefits of varicella-zoster virus control.

REFERENCES

- Anderson, T. C. *et al.* (2022). Use of recombinant zoster vaccine in immunocompromised adults aged 19 years. *Morbidity and Mortality Weekly Report, 71*(3), 85–90.
- Andrei, G., & Snoeck, R. (2021). Advances and perspectives in the management of varicella-zoster virus infections. *Molecules, 26*(4), 1132.
- Arvin, A. M., Abendroth, A., Moffat, J. F., & Oliver, S. L. (2024). Varicella-zoster virus: Genetics, pathogenesis, and immunity. London: Springer Nature.
- Baird, N. L., Zhu, S., Pearce, C. M., & Viejo-Borbolla, A. (2019). Current in vitro models to study varicella zoster virus latency and reactivation. *Viruses, 11*(2), 103.
- Bakker, K. M., Eisenberg, M. C., Woods, R., & Martinez, M. E. (2021). Exploring the seasonal drivers of varicella zoster virus transmission and reactivation. *American Journal of Epidemiology, 190*(9), 1814–1820.
- Bardach, A. E. *et al.* (2021). Herpes zoster epidemiology in Latin America: A systematic review and meta-analysis. *PLoS ONE, 16*(8), e0255877.
- Boutry, C. *et al.* (2020). Long-term persistence of immune responses to recombinant zoster vaccine. *Journal of Infectious Diseases, 221*(11), 1830–1839.
- Boutry, C. *et al.* (2022). Safety and immunogenicity of recombinant zoster vaccine in immunocompromised populations. *Clinical Infectious Diseases, 74*(8), 1365–1373.
- Breuer, J., Schmid, D. S., & Gershon, A. A. (2021). Varicella zoster virus infections of the nervous system. *Lancet Neurology, 20*(9), 770–781.
- Casabona, G. *et al.* (2025). Breaking the cycle: considerations for a life-course vaccination strategy against varicella-zoster virus. *Expert Review of Vaccine, 24*(1), 556-569.
- Chen, L. K. *et al.* (2022). Looking back and moving forward: A review of herpes zoster and vaccination in older adults. *Aging Clinical and Experimental Research, 34*(6), 1213–1225.
- Crooke, S. N. *et al.* (2019). Immunosenescence and human vaccine immune responses. *Immunology, 158*(3), 167–179.
- Cunningham, A. L. *et al.* (2018). Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *New England Journal of Medicine, 375*(11), 1019–1032.
- Curran, D. *et al.* (2020). Cost-effectiveness of herpes zoster vaccination in older adults. *Vaccine, 38*(38), 5857–5867.
- Dagnew, A. F. *et al.* (2021). Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in adults with hematologic malignancies. *Clinical Infectious Diseases, 73*(9), e2630–e2638.
- Drolet, M. *et al.* (2023). The impact of herpes zoster and postherpetic neuralgia on health-related quality of life. *Vaccine, 41*(3), 547–556.
- Forbes, H. J. *et al.* (2019). Quantification of risk factors for herpes zoster. *BMJ, 365*, l227.
- Freer, G., & Pistello, M. (2018). Varicella-zoster virus infection: natural history, clinical manifestations, immunity and current and future vaccination strategies. *New Microbiologica, 41*(2), 95-105.
- Gershon, A. A. (2015). Varicella zoster virus infection. *Nature Reviews Disease Primers, 1*, 15016.
- Gershon, A. A. *et al.* (2018). Latency of varicella zoster virus in dorsal root, cranial, and enteric ganglia. *Journal of Virology, 92*(3), e01508–17.
- Gershon, A. A., Gershon, M. D., & Breuer, J. (2019). Advances in varicella-zoster virus research. *Current Opinion in Virology, 37*, 1–7.
- Gershon, A. A., Nagel, M. A., & Gilden, D. (2020). Varicella-zoster virus in the nervous system. *Lancet Neurology, 19*(11), 997–1007.
- Girault, V. *et al.* (2025). Multi-proteomic profiling of the varicella-zoster virus–host interface reveals host susceptibilities to severe infection. *Nature Microbiology, 10*, 2048–2072.

- Goldstein, R. S., & Kinchington, P. R. (2023). Varicella zoster virus neuronal latency and reactivation modeled in vitro. *Current Topics in Microbiology and Immunology, 438*, 103–134.
- Han, D.-G. (2025). Strategic latency with temporal mutualism: A coevolutionary model of the host–varicella-zoster virus relationship. *Frontiers in Immunology, 16*, 1682707.
- Harbecke, R., Cohen, J. I., & Oxman, M. N. (2018). Herpes zoster vaccines. *Journal of Infectious Diseases, 218*, S96–S103.
- Harpaz, R., Leung, J. W., & Brown, C. J. (2022). Global burden of herpes zoster. *Vaccine, 40*(6), 873–879.
- Heininger, U., & Seward, J. F. (2006). Varicella. *Lancet, 368*(9544), 1365–1376.
- Jiang, B. *et al.* (2022). Willingness to accept herpes zoster vaccines and the influencing factors in China. *BMC Infectious Diseases, 22,* 888.
- Kawai, K., Gebremeskel, B. G., & Acosta, C. J. (2018). Systematic review of incidence and complications of herpes zoster. *BMC Infectious Diseases, 18*, 66.
- Kawai, K., Yawn, B. P., Wollan, P., & Harpaz, R. (2021). Increasing incidence of herpes zoster over time. *Mayo Clinic Proceedings, 96*(8), 2034–2043.
- Laemmle, L., Goldstein, R. S., & Kinchington, P. R. (2019). Modeling varicella zoster virus persistence and reactivation—Closer to resolving a perplexing persistent state. *Frontiers in Microbiology, 10*, 1634.
- Lal, H. *et al.* (2015). Efficacy of an adjuvanted herpes zoster subunit vaccine. *New England Journal of Medicine, 372*(22), 2087–2096.
- Lal, H., Poder, A., & Heineman, T. C. (2019). Recombinant zoster vaccine efficacy and safety. *Human Vaccines & Immunotherapeutics, 15*(7–8), 1687–1696.
- Le, P., Rothberg, M. B., & Nguyen, A. T. (2018). Cost-effectiveness of herpes zoster vaccination strategies. *Annals of Internal Medicine, 168*(6), 432–443.
- Levin, M. J. *et al. (*2019). Persistence of immunity to the recombinant zoster vaccine. *Journal of Infectious Diseases, 220*(6), 939–948.
- Maia, C. M. F. *et al.* (2021). Increased number of Herpes Zoster cases in Brazil related to the COVID-19 pandemic. *International Journal of Infectious Disease, 104*, 732–733.
- Marra, F., & Lalji, F. (2022). Prevention of herpes zoster: A focus on the effectiveness and safety of herpes zoster vaccines. *Viruses, 14*, 2667.
- Marra, F., Parhar, K., Huang, B., & Vadlamudi, N. (2020). Risk factors for herpes zoster infection. *Open Forum Infectious Diseases, 7*(1), ofaa005.
- Nagel, M. A. *et al.* (2017). Varicella zoster virus vasculopathy. *Neurology, 88*(7), 676–682.
- Nagel, M. A., & Gilden, D. (2014). Neurological complications of varicella zoster virus reactivation. *Current Opinion in Neurology, 27*(3), 356–360.
- Schmader, K. E. (2018). Herpes zoster in older adults. *Clinical Infectious Diseases, 66*(2), 185–190.
- Taquet, M. *et al.* (2024). Incidence of neurological outcomes following herpes zoster. *Nature Medicine, 30*(2), 315–322.
- Tseng, H. F. *et al.* (2020). Effectiveness of herpes zoster vaccine in preventing dementia. *Journal of Infectious Diseases, 222*(8), 1305–1314.
- UK Health Security Agency. (2025). Guidelines on post-exposure prophylaxis for varicella or shingles. Retrieved Abr, 15, 2026, fromhttps://www.gov.uk/government/publications/post-exposure-prophylaxis-for-chickenpox-and-shingles/guidelines-on-post-exposure-prophylaxis-pep-for-varicella-or-shingles-january-2023
- Weinberger, B., Grubeck-Loebenstein, B., & Vaccari, M. (2022). Immunosenescence and vaccination in the elderly. *Frontiers in Immunology, 13*, 846102.
- World Health Organization (2025a). Varicella (Chickenpox) and Herpes Zoster (Shingles). Retrieved Feb, 15, 2026, from https://www.immunize.org/official-guidance/who/
- World Health Organization (2025b): Weekly epidemiological record. *Position Papers, Resources and Publications 47*(100), 567–590.
- World Health Organization. (2023). Herpes zoster vaccines*:* Position paper. Retrieved Feb, 15, 2026, from https://www.immunize.org/official-guidance/who/.
- Wouters, O. J., McKee, M., & Luyten, J. (2023). Estimated impact of herpes zoster vaccination on dementia risk. *The Lancet Healthy Longevity, 4*(5), e221–e229.
- Yawn, B. P., Wollan, P. C., St Sauver, J. L., & Butterfield, L. C. (2017). Herpes zoster recurrence and risk factors. *Mayo Clinic Proceedings, 92*(7), 1053–1064.
- Yu, X., Lophatananon, A., Mekli, K., Muir, K. R., & Guo, H. (2023). Exploring the causal role of the immune response to varicella-zoster virus on multiple traits: A phenome-wide Mendelian randomization study. *BMC Medicine, 21*(1), 143.
- Zhang, J. X. *et al.* (2021). Association of chronic disease with herpes zoster risk. *Clinical Infectious Diseases, 73*(9), e2763–e2770.
- Zhu, Y. *et al.* (2025). Vaccination coverage, willingness, and determinants of herpes zoster vaccine among individuals aged 50 and above in Ningbo, China: A population-based cross-sectional

study. *Human Vaccines & Immunotherapeutics, 21*(1), 2524247.