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Can the herpes zoster vaccination be a strategy against dementia?

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SUMMARY: Herpes Zoster (HZ), caused by the reactivation of the varicella-zoster virus (VZV), is a common infectious disease. Recent studies suggest a potential association between HZ and the development of dementia, particularly Alzheimer's disease and other neurodegenerative disorders. Epidemiological evidence indicates that HZ infection, especially in individuals with central nervous system involvement, may increase the risk of dementia. Pathologically, VZV may contribute to neuronal dysfunction and degeneration by inducing chronic neuroinflammation, infection-related cerebrovascular lesions, and direct central nervous system toxicity. HZ vaccines, particularly novel recombinant subunit vaccines (*e.g.*, Shingrix), not only effectively prevent HZ but may also confer cognitive protection through mechanisms such as "trained immunity" activation and anti-inflammatory response modulation. Multiple natural experiments and retrospective cohort studies have found that HZ vaccination is significantly associated with a reduced risk of dementia, with particularly pronounced protective effects in women and older adults. Although most evidence currently stems from observational studies and is subject to potential confounding factors, the biological plausibility and consistent findings support the potential of HZ vaccination as an adjunctive strategy for dementia prevention. Future prospective randomized controlled trials are needed to further clarify the causal relationship and underlying neuroimmune mechanisms, providing a stronger evidence base for establishing scientific vaccination strategies for older adults and dementia prevention systems.

Keywords: Alzheimer's disease, vaccine, neuroinflammation, recombinant vaccine, immunosenescence, neurodegenerative diseases

1. Vaccines and dementia

As the aging population grows, dementia, particularly Alzheimer's disease (AD), has become one of the most pressing global public health challenges (*1*). With no curative treatments available, identifying modifiable risk factors and preventive strategies has become a research priority. In recent years, clinical studies have revealed a potential link between varicella-zoster virus (VZV) and dementia onset (Table 1) (*2-8*). This raises the question: could vaccines that prevent herpes zoster (HZ) also inadvertently protect the brain?

A nationwide cohort study in South Korea found that individuals with HZ had a significantly higher risk of dementia (adjusted hazard ratio, HR = 1.12), while antiviral treatment reduced this risk (adjusted HR = 0.76) (*9*). However, a UK CPRD database study found no significant association between HZ and dementia (*10*). A Danish national cohort study indicated that HZ involving the central nervous system (CNS) nearly doubled the risk of dementia (HR = 1.94). This suggests that direct viral invasion of the brain may be a key risk factor (*11*).

2. Vaccination: More than just preventing HZ?

The most exciting findings come from vaccine research. In a "natural experiment" conducted in Wales, UK, Eyting *et al.* used birth date cutoffs to determine vaccine eligibility and found a 20% reduction in dementia incidence among those vaccinated with the live vaccine (*11*). A U.S. natural experiment based on electronic medical records revealed that Shingrix, a recombinant vaccine, delayed dementia diagnosis by an average of 164 days compared to unvaccinated individuals, demonstrating a significant neuroprotective effect (*4*). Retrospective cohort studies and systematic reviews further support this view (*6,12*). HZ vaccines not only prevent disease but may also "prevent dementia".

Table 1. Characteristics and key findings of studies investigating HZ vaccination as a protective factor against dementia

Author (Ref)	Study design	Age (years)	Female : male	Vaccine(s) employed	Vaccinated (n)	Unvaccinated (n)	Dementia definition	Results
Eyting *et al.* (*2*)	A natural experiment	80 (Mean)	55:45	Zostavax	84,071	198,470	Read/ICD-9/ICD-10 codes	HZ vaccination was associated with a 20.0% relative reduction in the incidence of newly diagnosed dementia over a 7-year follow-up period, with a stronger protective effect observed in females than in males.
Harris *et al.* (*3*)	Retrospective cohort study	72 (Mean)	59:41	Zostavax/Shingrix	16,106	21,417	ICD-9/ICD-10 codes	During follow-up, 8.1% of vaccinated individuals and 10.7% of unvaccinated individuals developed AD, corresponding to a relative risk of 0.75 and an absolute risk reduction of 2%.
Taquet *et al.* (*4*)	A natural experiment	71 (Mean)	53:42	recombinant vaccine/ live vaccine	200,405	7269	ICD-10 codes	Recombinant zoster vaccine was associated with a significantly reduced risk of dementia within six years post-vaccination and a 164-day delay in dementia diagnosis.
Tang *et al.* (*5*)	Retrospective cohort study	62 (Mean)	49:51	RZV/Shingrix	666,710	3,835,968	ICD-10 codes	Adjusted analyses showed that both two-dose (HR 0.68) and single-dose (HR 0.89) vaccination were associated with reduced dementia risk, while prior HZ diagnosis increased the risk (HR 1.47). Antiviral treatment was linked to lower dementia incidence.
Lophatananon *et al.* (*6*)	Retrospective cohort study	≥70	52:48	Varicella/Shingles/ Zostavax	854,745	8,490,813	ICD-10 codes	Zoster vaccination was associated with reduced risk of all-cause dementia (HR 0.78), AD (HR 0.91), and other dementias (HR 0.71).
Lophatananon *et al.* (*7*)	Case-control study	≥70	55:45	Zostavax	35,116	193,020	ICD-9/ICD-10 codes	Shingles history ≥3 years prior showed no significant association with dementia risk (OR 1.09), while Zostavax vaccination was linked to a significantly reduced risk (OR 0.81).
Lehrer *et al.* (*8*)	Cross-sectional, interviewed	70 (Mean)	37:33	Zostavax/Shingrix	99	176	Social activities hampered by disorientation or memory loss	In BRFSS 2017 data, HZ vaccination was associated with a lower prevalence of social impairment due to disorientation or memory loss (61.6% *vs.* 46.6%). Multivariate analysis confirmed a significant protective effect of vaccination.

Abbreviations: AD, Alzheimer's disease; ARR, Absolute risk reduction; BRFSS, Behavioral Risk Factor Surveillance System; CI, Confidence interval; HR, Hazard ratio; HZ, Herpes zoster; ICD-9/10, International Classification of Diseases, 9th/10th Revision; OR, Odds ratio; RZV, Recombinant zoster vaccine; VHA, Veterans Health Administration.

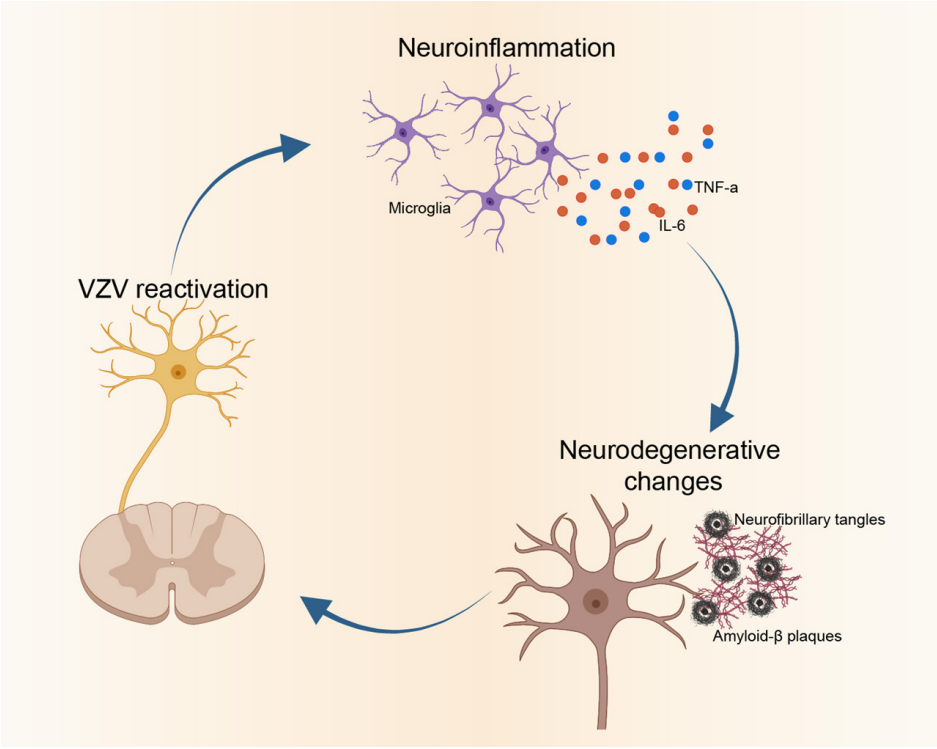

Figure 1. Proposed mechanism linking VZV reactivation to neurodegenerative processes. Abbreviations: VZV, varicella-zoster virus.

3. Pathogenic mechanisms

Current research suggests that VZV may contribute to or accelerate neurodegenerative processes through multiple pathways, including neural invasion, amplified inflammatory responses, and vascular damage (*13-16*). Additionally, the "off-target" immunomodulatory effects of vaccines may underlie their ability to reduce dementia risk (*17*). (Figure 1)

3.1. VZV latent infection and neural reactivation

Following primary infection, VZV establishes latency in the dorsal root ganglia (DRG) or cranial nerve ganglia, where it can persist for decades (*18,19*). Under conditions such as immunosenescence, immunosuppression, or acute stress, the virus can reactivate, spreading *via* anterograde transport to infect the peripheral or CNS (*18*). Studies have detected VZV DNA and proteins in the cerebrospinal fluid and serum of some patients without skin symptoms, indicating its ability to breach the blood-brain barrier (BBB) (*20*). Such subclinical or focal reactivation may not present as typical rashes but can induce localized inflammation or vascular lesions in the brain, leading to long-term neurological damage (*11*).

3.2. Neuroinflammation

VZV infection can activate resident immune cells in the brain, particularly microglia and astrocytes, leading to upregulated expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α) (*21,22*). These inflammatory signals not only directly induce neuronal apoptosis but also contribute to AD pathology by promoting β-amyloid (Aβ) deposition and Tau protein hyperphosphorylation (*23*). Animal studies and autopsies have shown that viral infections significantly enhance the cleavage of amyloid precursor protein (APP) and the accumulation of phosphorylated Tau, triggering synaptic dysfunction and neuronal loss (*24*). In addition, VZV can amplify central immune responses by activating the NLRP3 inflammasome pathway, creating a "low-grade, chronic" neuroinflammatory environment (*25*).

3.3. Vascular damage

VZV can directly infect endothelial cells of cerebral small vessels, inducing vasculitis, smooth muscle cell damage, and thrombosis, leading to perfusion deficits and white matter degeneration, thereby increasing the risk of vascular cognitive impairment (*10,11*). This mechanism is particularly pronounced in HZ ophthalmicus (*11*). This "HZ-associated vasculopathy" may present with subacute or chronic progression and can manifest on imaging as features similar to small vessel dementia, such as periventricular white matter hyperintensities (*16*).

3.4. Direct CNS infection

Compared to individuals with normal immune function, those with compromised immunity face a 51% higher

risk of developing HZ, a 25% higher recurrence rate, and a 2.37-fold increased likelihood of HZ complications(*16*). This may explain the elevated HZ risk in older adults, particularly in those with immunocompromised (IC) conditions due to diseases or treatments that alter immune responses (*e.g.*, immunodeficiency disorders, autoimmune diseases, HIV, cancer, organ transplantation) (*26*). In immunocompromised individuals, VZV can breach the BBB and invade the brain parenchyma, causing meningitis, encephalitis, or even myelitis (*27*). Although such CNS infections are rare, they can result in long-term neurocognitive sequelae even after recovery. Long-term follow-up data indicate a significantly increased dementia risk in patients with central nervous system HZ, supporting the direct neurotoxic effects of the virus (*11*).

3.5. Vaccine-induced "trained immunity" and systemic immune reprogramming

HZ vaccines, particularly the recombinant subunit vaccine Shingrix, not only induce specific $CD4^+$ T-cell responses and neutralizing antibodies but also promote a "trained immunity" state by activating innate immune components such as monocytes and natural killer cells (*28,29*). This epigenetic reprogramming-driven, non-specific immune enhancement has been shown to improve the body's ability to regulate responses to various pathogens and chronic inflammatory conditions (*30*). In older adults, this vaccine effect may facilitate "anti-inflammatory reprogramming," mitigating systemic low-grade inflammation associated with immunosenescence (inflammaging), thereby indirectly slowing the progression of neurodegenerative diseases (*2,4*).

4. From "viral risk" to "vaccine opportunity"

Although most current studies are observational and have not fully ruled out confounding factors, their findings are biologically plausible and have been consistently validated across diverse populations. Given the global accessibility, safety, and established benefits of HZ vaccines, their "additional neuroprotective effects" hold significant public health implications.

However, confirming their true efficacy in dementia prevention requires further evidence from long-term, prospective, randomized controlled trials. In the context of persistent vaccine hesitancy and suboptimal vaccination rates among older adults, clearly communicating the potential of HZ vaccines to "reduce dementia risk" to the public, clinicians, and policymakers could be a critical step in challenging entrenched perceptions and improving vaccine uptake.

The link between vaccines and neurodegenerative diseases was once considered an "unexpected discovery," but with accumulating evidence, we may be on the cusp of a new preventive pathway. It is time to reconsider the role of infectious factors in dementia and the strategic value of vaccines in an aging society.

5. Conclusion

In summary, VZV reactivation may contribute to dementia pathogenesis through chronic neuroinflammation, vascular damage, and direct neurotoxicity. Concurrently, HZ vaccination demonstrates neuroprotective potential beyond its role in preventing HZ. Although current studies are primarily observational, their biological plausibility and consistency across populations underscore the need for further research. As dementia prevalence rises and therapeutic options remain limited, incorporating HZ vaccination into broader preventive strategies may offer a feasible and cost-effective approach to supporting cognitive health in aging populations.

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