

Varicella zoster virus and the central nervous system

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Abstract

Varicella zoster virus (VZV) causes varicella, also known as chickenpox, after which VZV remains latent in neural ganglia. VZV reactivation can result in herpes zoster, also known as shingles. In addition to its well-known effects on the peripheral nervous system, reports increasingly suggest that VZV can have potentially devastating effects on the central nervous system (CNS). Several epidemiological studies indicate that VZV reactivation is associated with stroke and interest is growing in potential associations of VZV with dementia. In the past 5–6 years, vaccination against herpes zoster has been reported to reduce the risk of developing cardiovascular events (including stroke) and dementia in observational studies, although interpretation of their findings is hindered by complex methodological challenges. This Review considers the relationship between VZV and the CNS from a multidisciplinary perspective that focuses on VZV physiology and immunity. The strengths and weaknesses of published studies are discussed, and areas for future investigation that remain to be addressed before the links between VZV and CNS conditions can be considered definitive and medically actionable are highlighted. Finally, these insights are integrated into an overarching conclusion that addresses potential consequences of the connection between VZV and the CNS for both public health and healthy ageing.

Sections

Introduction

VZV biology and pathogenesis

VZV manifestations in the CNS

An epidemiological perspective

Anti-VZV immune responses

VZV-specific adaptive immunity

Preventive vaccine efficacy

Conclusions and future perspectives

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Introduction

Varicella zoster virus (VZV; also known as human herpesvirus 3) is an ubiquitous herpesvirus that causes varicella (also known as chickenpox) mainly during childhood and subsequently causes herpes zoster (also known as shingles or zona) mainly in individuals older than 60 years. Varicella typically presents as a fairly mild febrile illness characterized by sequential skin rashes (initially papules, then vesicles and finally crusts), although some individuals can develop severe complications, such as bacterial superinfection or pneumonia^{1–3}. After varicella resolves, VZV remains latent in sensory ganglia of the peripheral nervous system (PNS). Herpes zoster occurs when latent VZV successfully reactivates and spreads to the skin via anterograde axonal transport, where it causes a painful local varicella-like rash with a dermatomal distribution. Live attenuated vaccines have been developed against varicella (very effective)⁴ and herpes zoster (less effective)⁵. Recombinant zoster vaccine (RZV), which consists of VZV envelope glycoprotein E (gE) and an adjuvant system, is highly effective against herpes zoster^{6,7}.

VZV has long been known to cause acute encephalitis⁸, acute cerebellitis⁹ and even stroke¹⁰ up to 6 months after a primary varicella infection. However, in the past decade, several papers have reported an association between herpes zoster and subsequent stroke¹¹. Moreover, some researchers have speculated that herpesviruses (including VZV) could be involved in the development of dementia¹². Interestingly, reduced risks of both stroke and dementia have been reported in adults who received either live attenuated VZV vaccine¹³ or RZV^{14,15}, which implies the potential existence of a widespread benefit of adult vaccination against herpes zoster. However, it is important to consider this evidence carefully in light of the methodological challenges inherent in observational vaccine studies (such as the healthy vaccinee bias, discussed later in this article).

This Review focuses on the CNS effects of VZV infection in adults aged over 50 years. We describe VZV biology and disease from a CNS perspective, including how VZV enters and causes damage to the CNS. We critically evaluate epidemiological evidence of the relationships between VZV and CNS conditions, particularly stroke and dementia. Finally, we summarize the roles of innate and adaptive immune responses in VZV-associated CNS disease, describe known human inborn errors of immunity that predispose to VZV infection in the CNS, and consider how herpes zoster vaccination might reshape VZV-specific immunity.

VZV biology and pathogenesis

VZV is an alphaherpesvirus of the *Varicellovirus* genus. Its virion comprises an icosahedral capsid enclosing a linear double-stranded DNA (dsDNA) genome, which is surrounded by a protein-rich tegument and enveloped within a host-derived lipid bilayer that incorporates viral glycoproteins (Fig. 1a). The VZV genome (~125 kb) encodes at least 71 unique open reading frames (ORFs) as well as various non-coding and circular RNAs, but no known microRNAs^{16–19} (Fig. 1b,c). Like all herpesviruses, VZV alternates between productive (lytic) infection and a non-productive (latent) phase (Fig. 1d). During a lytic infection of epithelial cells, coordinated viral gene expression leads to the production of new VZV particles^{20,21}. By contrast, the latent viral state is defined by the presence of the VZV genome in host cells without de novo virion production while maintaining the capacity to reinstate lytic VZV infection (reactivation)²².

VZV is an obligate human pathogen²³. Although some aspects of its biology can be modelled in humanized severe combined

immunodeficient (SCID) mice²⁴, the virus does not cause disease or establish a persistent latent state that is capable of reactivation in small animal models²⁵. Consequently, current understanding of VZV pathogenesis and the mechanisms underlying VZV-associated neurological disorders remains incomplete and is largely based on clinical observations, studies inpatient-derived samples and emerging data from in vitro neuron models.

Primary VZV infection

VZV infection can be transmitted via aerosols or direct contact^{26,27}. Viral replication in the respiratory tract and pharyngeal lymphoid tissue results in VZV infection of lymphocytes^{28,29}. VZV-infected T cells then transfer virus to the skin, which results in a generalized skin rash^{30,31}. During a primary infection, VZV is also seeded into nerve ganglia, where a lifelong latent infection is established by around 13 days after infection³². Although viraemia might also facilitate ganglionic seeding of VZV^{33,34}, the main route through which VZV reaches sensory neurons is thought to be direct infection of nerve endings in affected skin or mucosa followed by retrograde axonal transport to the ganglia^{35,36} (Fig. 2a). Support for this idea is provided by the recurrence of herpes zoster at previous varicella or vaccination sites and studies in stem cell-derived neuron models^{37,38}.

VZV latency and reactivation

Latent VZV persists primarily in sensory neurons of the dorsal root ganglia (DRG) and trigeminal ganglia^{10,39–46}. These neurons are technically categorized as part of the PNS because their cell bodies lie outside the spinal cord, but functionally they lie at the interface between the central nervous system (CNS) and PNS. Trigeminal ganglia and DRG sensory neurons are pseudounipolar and have a single axon that splits to project both peripherally and centrally (that is, towards the spinal cord and brain)⁴⁷. About 2–5% of trigeminal ganglia neurons harbour latent VZV, which occurs as 5–7 VZV genome copies per neuron nucleus, arranged as circular episomes^{48–50}. These episomes are bound to host chromatin and are probably repressed by histone modifications^{16,41–43}. Latency is marked by the selective expression of VZV latency-associated transcript gene (*VLT*) and, to a lesser extent, the expression of two splice variants spanning *VLT* and *ORF63* loci (*VLT63-1* and *VLT63-2*)^{16,44} (Fig. 2c,d). In situ hybridization studies show that fewer neurons contain *VLT* (0.49%) and *VLT63* (0.36%) RNA than contain VZV DNA, which suggests that not all latent VZV genomes are transcriptionally active^{16,48–50}.

Apart from DRG and trigeminal ganglia, the only other clinically confirmed sites of VZV latency and reactivation are the geniculate ganglia (linked to Ramsay Hunt syndrome) and sensory ganglia of the glossopharyngeal and vagal nerves (linked to pharyngolaryngeal herpes zoster)^{45,46,51,52}. VZV DNA has additionally been detected in other cranial sensory ganglia (notably those of the spiral and vestibular nerves) as well as in cranial, thoracic and enteric autonomic ganglia^{45,52–57}, but true latency and reactivation from these sites remain to be demonstrated. Moreover, no evidence indicates that VZV can establish latency in the CNS. Although one study detected VZV DNA in more than 26% of brain samples⁵⁸, other studies did not detect any VZV DNA by polymerase chain reaction, RNA sequencing^{59–61} or metagenomics analyses of over 100 individuals with encephalitis⁶².

The development of stem cell-derived neuron models provided insights into the host cell pathways and viral genes (especially *VLT63*) that are involved in VZV reactivation from latency^{44,63–66}. At the ganglion level, whether VZV reactivates in one or multiple neurons

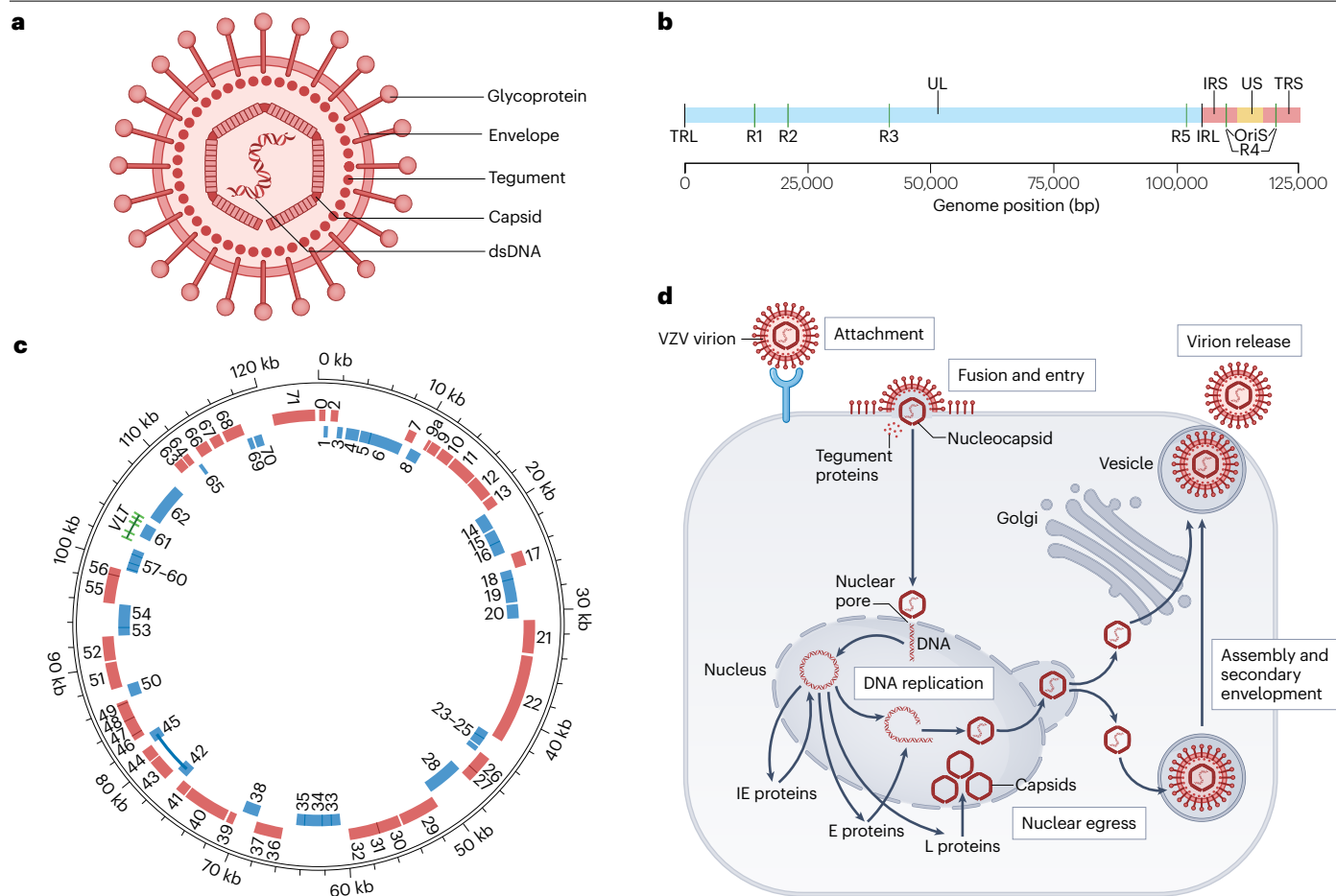


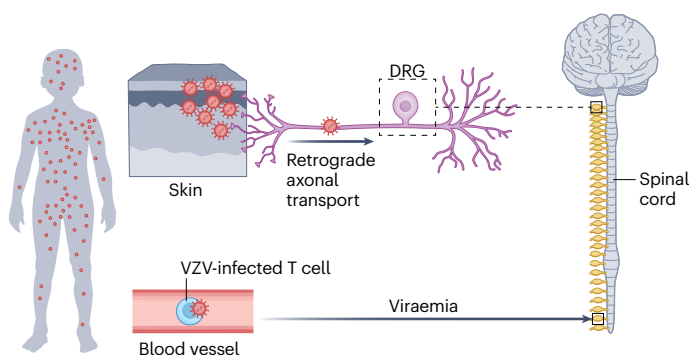
Fig. 1 | Structure and lytic replication cycle of varicella zoster virus. **a**, Varicella zoster virus (VZV) virions consist of linear double-stranded DNA (dsDNA) VZV genomes packaged within an icosahedral capsid core, which is surrounded by a protein tegument layer and a host cell-derived envelope that carries viral glycoproteins. The VZV genome encodes 11 glycoproteins that are involved in viral attachment and entry into the host cell, envelopment of the virus, viral egress and cell-to-cell spread²⁴⁶. Tegument proteins delivered into newly infected cells rapidly modulate host pathways to suppress antiviral defences and promote viral gene replication²⁴⁷. **b**, The ~125,000 bp VZV genome is organized in unique long (UL) and unique short (US) segments flanked by several repeat regions: terminal repeat long (TRL), terminal repeat short (TRS), internal repeat long (IRL) and internal repeat short (IRS). The VZV genome also contains five tandem repeat regions (numbered R1–R5) and two origins of replication (OriS)^{201,248}. **c**, The VZV genome contains at least 71 protein-coding genes that are expressed from both strands of the viral genome (red, sense strand; blue, reverse strand). Note that ORF42–ORF45 encode a single gene product and the genes

that encode ORF62–ORF71, ORF63–ORF70 and ORF64–ORF69 are duplicated. The VZV latency-associated transcript (*VLT*) gene is indicated in green. **d**, VZV initiates a lytic infection by tethering to heparan sulphates on the cell surface, after which the virus engages with its entry receptors (including mannose-6-phosphate receptors, myelin-associated glycoprotein and nectin-1) to mediate membrane fusion^{249–251}. Upon cell entry, tegument proteins are released and capsids traffic to nuclear pores, where viral DNA is injected into the nucleus and circularizes. Transcription is thought to proceed in a temporally regulated cascade of immediate early (IE), early (E) and late (L) genes^{20,21}. Newly replicated viral genomes are packaged into nucleocapsids, which bud through the nuclear membrane (primary envelopment), enter the cytoplasm and acquire their tegument proteins and glycoproteins by fusion with Golgi-derived vesicles or via trafficking through the trans-Golgi network (secondary envelopment)^{252–254}. Virus particles are released at the cell surface, where (in vitro at least) they remain highly cell associated.

simultaneously remains unclear. Although individual herpes zoster vesicles are typically founded by a single virion, the existence of distinct VZV genotypes in separate vesicles from a single patient with herpes zoster rash and in the cerebrospinal fluid (CSF) of patients with VZV encephalitis indicate that reactivation originates in multiple neurons^{32,67,68}. Histopathological analyses of DRG and trigeminal ganglia during active herpes zoster indicate that local VZV replication and spread occur before anterograde VZV transport to the innervated dermatome manifests clinically as herpes zoster^{69,70} (Fig. 2b).

Some evidence from small studies indicates that subclinical VZV reactivation can occur⁷¹, but the frequency and correlates of this phenomenon remain unknown. Detection of elevated serum levels of VZV-specific IgM and IgG antibodies, fluctuations in serum levels of VZV-specific IgG over time⁷² and detection of viral DNA in saliva or blood from individuals without a clinical diagnosis of herpes zoster are often used as a proxy for subclinical VZV reactivation (which occurs with increased frequency in elderly and immunocompromised individuals and has also been reported in people undergoing stressful situations or

a Primary infection (varicella)



b Reactivation (herpes zoster)

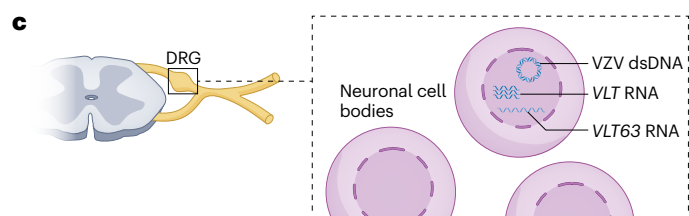
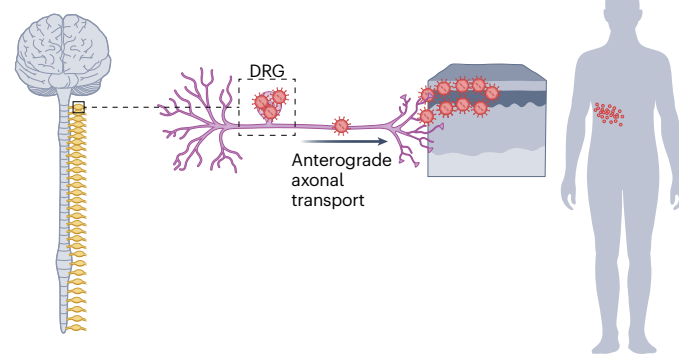


Fig. 2 | Establishment, maintenance and reactivation from latency of varicella zoster virus infection. **a**, During primary varicella zoster virus (VZV) infection, the virus gains access to sensory neurons in dorsal root ganglia (DRG) and trigeminal ganglia via infection of free nerve endings in varicella skin lesions. In addition, VZV-infected T cells can seed virus to these ganglia. **b**, VZV reactivation

results in local VZV amplification, followed by anterograde axonal transport to the innervated dermatome, which causes herpes zoster. **c**, The latent VZV genome persists in the nuclei of DRG and trigeminal ganglia neurons, where viral gene expression is limited to *VLT* and *VLT63*. **d**, The transcript structure and genomic positions of latent *VLT*, *VLT63-1* and *VLT63-2* isoforms. ORF, open reading frame.

during pregnancy)^{73–79}. Whether these antibody changes are because of endogenous or exogenous VZV exposure remains unclear. Moreover, rashes and pain are common medical complaints, and some mild episodes of symptomatic herpes zoster might escape diagnosis or be misdiagnosed on the basis of clinical symptoms alone. Hence, the contribution of subclinical VZV reactivation to VZV-associated CNS disease remains to be determined⁷⁹.

VZV manifestations in the CNS

Clinically significant CNS infection can occur during either primary VZV infection or VZV reactivation.

VZV reactivation most often causes PNS complications (Box 1), although reactivated virus can also spread along the central branches of DRG axons to the spinal cord, CSF and CNS⁴⁷, a process that is associated with CNS disease in some individuals.

Acute CNS complications

Acute CNS complications of VZV infection include encephalitis, meningitis, cerebellitis and myelitis. These inflammatory conditions can be related to either primary varicella or herpes zoster, with onset typically within a few weeks of skin manifestations⁸⁰. The virological factors underlying these acute CNS complications are poorly understood; however, VZV infection and centripetal axonal spread from the DRG and trigeminal ganglia could deliver virus to the spinal cord and brainstem, where VZV replication might induce direct cytopathology or indirect immune-mediated neuropathology. VZV DNA and intrathecally produced anti-VZV antibodies are both frequently detected in CSF, which is consistent with the presence of viral antigen in the CNS^{81–87}. However, no differentially neurotropic VZV strains have been identified, and only limited direct histopathological evidence suggests that viral replication

occurs in the CNS tissue of patients with myelitis, acute vasculopathy or (rarely) encephalitis^{88–91}. The lack of direct evidence is partly because of the rarity of biopsy sampling and post-mortem studies and partly because of the timing of tissue collection; vasculopathy often occurs weeks to months after herpes zoster, whereas brain tissue from deceased patients with VZV encephalitis is typically obtained only after long hospitalization and high-dose antiviral treatment. Inflammation is prominent in VZV-affected CNS tissues and is postulated (along with the potential presence of VZV-induced autoantibodies) to be a relevant driver of many VZV CNS complications^{92–96}.

VZV-associated CNS vasculopathy, including transient ischaemic attacks and strokes, can present either as acute complications or manifest up to months or years after an acute varicella or herpes zoster episode^{97,98}. Foci of VZV that persist in cerebral arteries are hypothesized to drive local inflammation^{99–101}, although this notion lacks conclusive evidence^{102–104}. Possible routes by which VZV could infect cerebral arteries include direct viremic spread and (more likely) indirect axonal spread from trigeminal ganglia neurons that innervate the arterial adventitia¹⁰⁰. In addition to neurons that innervate cutaneous, ocular and oronasal surfaces, trigeminal ganglia also contain neurons that receive sensory information from the dura mater and large cerebral arteries^{105,106}. Moreover, the cell bodies of cerebral artery-innervating and skin-innervating neurons co-localize within the ophthalmic division of trigeminal ganglia^{107,108}. Therefore, VZV reactivation could facilitate the intraganglionic spread of VZV to these vasculature-innervating neurons and enable viral entry into the cerebral arteries. Alternative hypotheses include herpes zoster-induced inflammatory changes in the systemic circulation that could cause widespread endothelial dysfunction and hypercoagulability^{109–111} or the release of extracellular vesicles from VZV-infected cells into the CNS circulation¹¹².

Chronic CNS complications

Interest is growing in whether VZV infection is associated with chronic CNS conditions such as dementia. Gaps in our understanding of dementia risk factors (dementia can be attributed to known modifiable risk factors in only 45% of individuals¹¹³) combined with the growing burden of dementia associated with population ageing make the identification of new and potentially preventable risk factors a research priority. However, convincing data that link VZV with chronic brain diseases are scarce. Detection of VZV DNA or RNA is inconsistent in the brains of individuals with dementia and CSF biomarkers for dementia are similarly inconsistent in patients with VZV CNS disease^{58,59,114–117}. VZV proteins might promote amyloid- β (A β) aggregation, which is linked to several forms of dementia¹¹⁸, but VZV infection does not increase tau phosphorylation or A β accumulation in cultured stem cell-derived neurons and glia or in brain tissue from individuals with VZV encephalitis^{119,120}. However, the association of VZV infection with vascular pathology might provide a rationale for a role of VZV in vascular dementia^{121,122}. The high human specificity of VZV prevents the use of small animals, such as transgenic mouse models of Alzheimer disease, to investigate the role of VZV in dementia^{123,124}.

In summary, whereas VZV latency and reactivation in DRG and trigeminal ganglia are well documented, the evidence for true latency in other (cranial) ganglia and subclinical VZV reactivation remains equivocal. Both primary and reactivated VZV infection can cause acute, chronic and delayed CNS disease. However, the precise mechanisms by which VZV gains access to the CNS are poorly defined. Further research is needed to identify the virological and host-related factors that contribute to VZV-associated neurological complications, vasculopathies and potentially dementia.

An epidemiological perspective

Data from population-level studies show how primary VZV infections and VZV reactivation could influence CNS health parameters.

Acute CNS complications

A review of studies of VZV encephalitis found that it has a global geographic distribution and an annual incidence of around 0.2–0.4 per 100,000, which was typically because of reactivation of latent virus rather than primary infection¹²⁵. For VZV meningitis, a cohort study from Denmark estimated the annual incidence at 0.7 per 100,000¹²⁶. In a UK-based matched cohort study that included 178,964 immunocompetent adults with herpes zoster, 0.48% experienced a neurological complication other than post-herpetic neuralgia (PHN) in the 3 months following herpes zoster¹²⁷. In the USA, a slightly higher risk of any non-PHN neurological complication (0.77%) after VZV infection was found in a chart review of 600 randomly sampled immunocompetent, non-vaccinated adults aged ≥ 50 years who had herpes zoster¹²⁸. In an electronic health record-based cohort of 442,979 individuals aged ≥ 18 years with herpes zoster from Germany, 0.3% experienced encephalitis, myelitis or encephalomyelitis, 0.7% had VZV vasculopathy and 1.2% lateral hemiparesis (presumably caused by stroke), in contrast to the 27.0% who experienced PHN, the most common herpes zoster complication¹²⁹. In summary, acute CNS complications are relatively rare compared to PHN, although the incidence of all neurological complications of VZV infection tends to be higher among immunocompromised individuals¹³⁰.

Despite its infrequent occurrence, stroke is an extensively investigated complication of VZV reactivation. The most recent systematic review of 18 cohort studies and self-controlled case series (in which

data were obtained during different time periods, which enabled individuals to act as their own controls) found a pooled relative risk (RR) of 1.22 (95% CI 1.12–1.34) for any stroke after herpes zoster¹³¹. Another systematic review, which included 17 mostly overlapping studies of 1,124,778 patients with herpes zoster, presented pooled estimates of stroke risk by time elapsed after herpes zoster. The results showed a marked temporal gradient, in which the risk of stroke reduced over time from RR 1.80 (95% CI 1.42–2.29) in the 14 days after herpes zoster diagnosis to 1.45 (95% CI 1.33–1.58) at 90 days and 1.27 (95% CI 1.15–1.40) at 1 year after herpes zoster diagnosis¹³² (Fig. 3). Despite many case reports and case series of post-varicella strokes, few population-based incidence estimates are available. Evidence from one high-quality self-controlled case series of 560 individuals (including 60 children) from four UK databases who experienced both varicella and stroke at any time point showed a fourfold increased risk of stroke in the 6 months following varicella for children (summary incidence rate (IR) 4.07, 95% CI 1.96–8.45) and a less marked increase in the risk of stroke among adults over the same time period (random-effects summary IR 2.13, 95% CI 1.05–4.36)¹⁰.

Box 1 | Varicella zoster virus in the peripheral nervous system

After primary varicella infection, varicella zoster virus (VZV) remains latent in neural ganglia until it undergoes reactivation. Symptomatic VZV reactivation, termed herpes zoster or shingles, occurs in approximately one-third of individuals. Known risk factors for herpes zoster include ageing (immunosenescence), female sex, depression and immunocompromised states arising from disease or immunosuppressive treatment^{255–257}.

Although herpes zoster is typically self-limiting without treatment or resolves within a few weeks following brief treatment with antiviral agents, post-herpetic neuralgia (PHN) is characterized by the persistence of herpes zoster-evoked pain for months to years, which is highly detrimental. PHN was initially proposed to result from ongoing ganglionic VZV reactivation²⁵⁸. However, controlled trials did not show any clinical benefit of antiviral therapy in individuals with PHN²⁵⁹, and immunohistological studies of dorsal root ganglia from patients with PHN did not detect VZV antigens⁷⁰. VZV DNA can persist in saliva after resolution of herpes zoster, but levels are similar in those with or without PHN⁷⁵. Pathological and MRI findings suggest that spinal cord inflammation and nerve damage, rather than ongoing VZV replication, might play a role in PHN development²⁶⁰.

Cranial nerve X (the vagus nerve) controls muscles of the larynx and voice function through the recurrent and superior laryngeal nerves. The neuron cell bodies of vagus nerve fibres reside both in the central nervous system for motor control and in the jugular and nodose ganglia in the peripheral nervous system for sensation. Laryngeal involvement in herpes zoster is well described, although the neural pathways involved are not precisely known²⁶¹. Adverse effects of recurrent VZV on the facial musculature (Bell palsy), and on hearing and balance (Ramsay Hunt syndrome), are well known to clinicians as manifestations of damage to cranial nerves VII and VIII, respectively. The most distal neuronal cell bodies that supply these cranial nerves lie either within the brain or in ganglia located deep within cranial structures.

Chronic CNS complications

Epidemiological evidence on the relationship between VZV and dementia is mixed (Table 1). Several large, population-based matched cohort studies from the UK, Denmark and USA found no association between herpes zoster and dementia risk^{133–136}, and their null findings are supported by the results of case-control studies from the UK and Korea^{137,138}. One Mendelian randomization study suggests a protective effect of genetic variants associated with herpes zoster on Alzheimer disease¹³⁹. By contrast, cohort studies from Korea, Taiwan, Germany, Denmark, Italy and the USA suggest an association between herpes zoster and raised dementia risk, with effect sizes ranging from 1.08 to 2.97^{12,134,140–146}. These conflicting results could be partly explained by differences in herpes zoster definitions: the studies of severe or complicated herpes zoster are those most likely to find an association with increased dementia risk (Table 1). For example, one study that used the presence of VZV DNA in the CSF on lumbar puncture to define individuals as having an acute severe CNS complication of VZV infection (44% of whom had VZV encephalitis and 21% had VZV meningitis) did show an association between these CNS complications and increased dementia risk¹⁴⁴. Other cohorts that consisted solely of hospitalized (that is, severely affected) patients with herpes zoster or individuals with herpes zoster ophthalmicus (HZO), which is strongly associated with ocular complications, also showed associations with increased dementia risk^{143,145}. In a USA propensity score-matched cohort, herpes zoster recurrence, which might reflect an increased severity of the initial herpes zoster episode¹⁴⁷, was associated with a small but nonsignificant increase in dementia risk at 3 years compared to a single herpes zoster episode (RR 1.07, 95% CI 0.98–1.16)¹². This increase in risk became marginally significant by 6 years of follow-up (RR 1.09, 95% CI 1.02–1.17)¹². Importantly, some studies with positive findings were affected by methodological challenges, including the use of future information to define covariates and/or ‘healthy vaccinee bias’ – the selection of comparator patients from among those who did not experience herpes zoster at any point during the study period (which would tend to select healthier individuals with a lower risk of dementia as controls), rather than by the date of herpes zoster diagnosis of their matched comparator^{141,143,146}.

Several systematic reviews of dementia risk in people with herpes zoster also have methodological limitations, including inappropriate pooling of estimates derived from both studies of patients with herpes zoster who experienced acute CNS complications and studies of those

with uncomplicated herpes zoster^{148,149}. Individuals who experience encephalitis of any cause, including VZV, are well known to have an increased risk of developing chronic neurological sequelae¹⁵⁰. A large UK electronic health record study of 2,460 patients with all-cause encephalitis matched to 47,914 individuals without encephalitis identified substantial increases in the risk of epilepsy (adjusted RR 31.90, 95% CI 25.38–40.08), cognitive impairment (adjusted RR 3.07, 95% CI 2.54–3.71) and dementia (RR 2.66, 95% CI 1.94–3.65)¹⁵⁰. Moreover, VZV-induced stroke, similar to strokes of other causes, can lead to post-stroke disability and dementia. At 1 year after a severe stroke, the risk of dementia is estimated to be 34%, compared to 8% among those 1 year after a minor stroke¹⁵¹. Other studies have shown that hospitalization for a severe infection of any cause (including VZV) might result in an increased long-term risk of dementia^{152,153}. A more relevant question is whether the occurrence of non-severe herpes zoster without acute CNS complications (the most common phenotype of VZV infection in immunocompetent adults) affects their future dementia risk. Future studies that present their findings stratified by herpes zoster severity are needed to avoid inflated estimates of dementia risk derived from comparing patients with herpes zoster and acute CNS or other complications with those who have uncomplicated herpes zoster. Such studies will need to carefully consider the timing of VZV exposure, outcome measurements and covariate measurements to avoid the introduction of time-related biases.

Role of vaccines in preventing CNS complications

Strong evidence from randomized controlled trials supports the good efficacy of live attenuated vaccines and even better efficacy of RZV for reducing the incidence of both herpes zoster and PHN^{7,154}. Herpes zoster vaccination programmes have been widely rolled out to individuals aged over 50 years. However, the original trials were not designed to assess rare and nonspecific complications (such as stroke) nor to include long-term follow-up for dementia. Real-world evidence has, therefore, increasingly been used to investigate associations between herpes zoster vaccination and the risks of stroke and dementia. The potential for vaccination against herpes zoster to directly protect individuals against stroke by reducing herpes zoster risk and severity is fairly plausible, given that stroke is a recognized complication of herpes zoster. Indeed, cohort studies conducted in administrative and electronic health record datasets typically show marked reductions in the risks of stroke (hazard ratios (HRs) ranging from 0.58 to 0.76)^{14,155,156} and dementia (HRs ranging from 0.65 to 0.90)^{156–162} among individuals aged >50 years who were vaccinated against herpes zoster compared with those risks in non-vaccinated individuals. Of note, however, studies of vaccination against other infections (including influenza, hepatitis A, typhoid, diphtheria, tetanus, pertussis and *Streptococcus pneumoniae*) also show protective associations against dementia, with mostly similar effect sizes^{157,158,162,163}. Despite approaches such as propensity score matching, inverse probability of treatment weighting and multivariable adjustment, concerns remain about healthy vaccinee and frailty selection biases in these studies¹⁶⁴. If health-conscious individuals are more likely to be vaccinated and less likely to experience poor outcomes than the general population, whereas vaccination is underused in a subset of very frail individuals, this situation would tend to overestimate vaccine effectiveness, especially for off-target outcomes such as dementia. One hypothesis-generating study noted that several vaccines that appeared to protect recipients against dementia were travel vaccines, which suggests that this association potentially represents reverse causation (meaning that people with incipient dementia are less

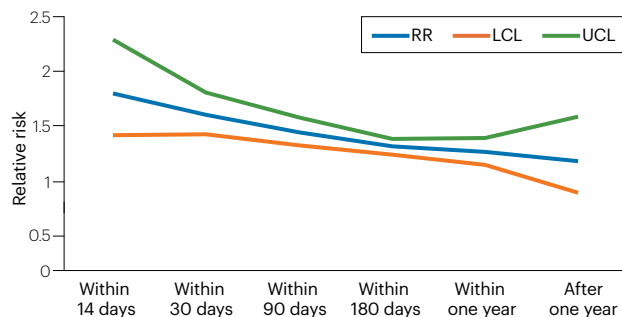


Fig. 3 | Relative risk of stroke by time elapsed since the onset of herpes zoster. Stroke risk is highest in the 14 days after herpes zoster and tapers over time until this risk is no longer elevated 1 year after herpes zoster. LCL, lower confidence limit; RR, relative risk; UCL, upper confidence limit. Adapted from ref. 132, Springer Nature Limited.

Table 1 | Characteristics of epidemiological studies of varicella zoster infection and dementia risk

Study population	Case ascertainment	Effect size (95% CI)	Ref.
Severe exposure			
USA: 97,432 people with multiple HZ episodes versus a historical cohort of 97,342 people with one HZ episode matched on propensity scores	Diagnosis of HZ and all-cause dementia based on ICD-9 or ICD-10 codes in the Optum EHR database	3 years: RR 1.07 (0.98–1.16) 9 years: RR 1.09 (1.01–1.19)	12
Taiwan: 846 people with HZO versus a historical cohort of 2,538 people without HZO matched on propensity score	Diagnosis of HZO using ICD-9 codes in National Health Insurance data; two or more all-cause dementia diagnoses by a certified neurologist	HR 2.97 (1.90–4.67)	143
Denmark: 517 people with VZV; historical cohort of 9,823 without VZV matched on age and sex	CSF VZV DNA detected on lumbar puncture; all-cause dementia based on ICD-10 codes in national registries	RR 2.4 (1.4–4.1)	144
Italy: 12,088 patients with HZ versus two historical cohorts — 60,440 people from the general population without HZ (group 1) and 60,440 hospitalized people without HZ (group 2)	Hospitalization with HZ based on ICD-9-CM codes in regional registry; all-cause dementia based on hospital diagnoses, prescriptions, administrative certificates and long-term care facility admissions	sdHR 1.13 (1.07–1.19) sdHR 1.08 (1.03–1.14)	145
Unclear or mixed exposure			
UK: 177,144 people with HZ versus a historical cohort of 706,901 people without HZ matched on age, sex, GP and calendar time	Diagnosis of all-cause dementia, HZ or referral records for HZ or all-cause dementia in CPRD primary care records	HR 0.92 (0.89–0.95)	133
Wales: 37,439 people with HZ versus a historical cohort of 389,906 people without HZ or HSV; Germany: 13,643 people with HZ versus a historical cohort of 32,249 people without HZ or HSV ^a	Diagnosis of HZ in primary or secondary care records in SAIL databank (Wales) or IMS Disease Analyser (Germany); all-cause dementia diagnostic codes from hospital (Wales), primary care (Wales, Germany) or death record (Wales)	Wales: HR 0.90 (0.83–0.99) Germany: HR 1.20 (1.06–1.35)	134
Denmark: 247,305 people with HZ versus a historical cohort of 1,235,890 people without HZ matched on birth year and sex	Diagnosis of HZ and all-cause dementia based on ICD-10 codes in inpatient, outpatient or emergency department settings or prescription of relevant antiviral and antidementia drugs in national registries	HR 0.93 (0.90–0.95)	135
USA: 25,332 people with HZ versus a historical cohort of 75,996 people without HZ matched on age, sex and membership duration	Diagnosis of HZ and all-cause dementia using ICD-9-CM or ICD-10-CM codes in Kaiser Permanente data	HR 0.99 (0.93–1.05)	136
South Korea: 11,445 people with dementia versus 45,780 controls matched on age, sex, income, region and medical history	Diagnosis of dementia and HZ based on ICD-10 codes and antiviral treatment in National Health Insurance data	OR 0.90 (0.84–0.97)	137
UK: 2,348 people with dementia versus 225,845 non-matched controls included in the UK Biobank	Diagnosis of HZ and all-cause dementia using ICD-9 and ICD-10 codes, primary care records and self-report	OR 1.09 (0.98–1.21)	138
Multinational Mendelian randomization study. HZ: GWAS summary statistics from 23andMe cohort. Dementia: summary statistics from International Genomics of AD Project	HZ measured by self-report in questionnaires. All-cause dementia diagnosed at autopsy or clinically confirmed from healthcare records	OR 0.87 (0.78–0.96)	139
South Korea: 34,505 patients with HZ versus a historical cohort of 195,089 people without HZ ^b	Diagnosis of HZ and all-cause dementia based on ICD-10 codes and antidementia drug prescriptions in National Health Insurance data	HR 1.12 (1.05–1.19)	140
South Korea: 97,323 people with HZ versus a historical cohort of 183,779 people without HZ or HSV matched on age and sex	Diagnosis of HZ and all-cause dementia based on ICD-10 codes and antidementia drug treatment in National Health Insurance data	HR 1.09 (1.07–1.11)	141
South Korea: 184,331 people with HZ versus a non-matched historical cohort of 567,874 people without HZ	Diagnosis of HZ or all-cause dementia using ICD-10 codes and antiviral or antidementia drug treatment in National Health insurance data	HR 1.41 (1.37–1.46)	142
Taiwan: 39,205 people with HZ versus a historical cohort of 39,205 people without HZ matched on age, sex and residence	Diagnosis of HZ and all-cause dementia based on ICD-9-CM codes in National Health Insurance data	HR 1.11 (1.04–1.17)	146

^aThis study analysed antiviral medication given for herpes simplex virus or HZ in data from four countries, but only Wales and Germany included diagnostic information on herpes subtype.

^bPropensity score matching was done within the HZ group to match the characteristics of patients with and without antiviral prescriptions. AD, Alzheimer disease; CPRD, Clinical Practice Research Datalink; CSF, cerebrospinal fluid; EHR, electronic health record; GP, general practitioner (primary care provider); GWAS, genome-wide association study; HR, hazard ratio; HZ, herpes zoster; HZO, herpes zoster ophthalmicus; HSV, herpes simplex virus; ICD, International Classification of Diseases; OR, odds ratio; RR, risk ratio; SAIL, secure anonymised information linkage; sdHR, sub-distribution hazard ratio; VZV, varicella zoster virus.

likely than cognitively healthy people to travel) rather than the vaccines themselves offering true protection against dementia¹⁶³.

Other studies have used different methods to avoid comparing vaccinated with nonvaccinated populations. One propensity score-matched cohort that compared individuals who received a specific live attenuated zoster vaccine (ZVL) with those who received RZV found a reduction in dementia risk associated with RZV vaccination (HR 0.83, 95% CI 0.79–0.87)¹⁵, although the extension of follow-up into the COVID-19 pandemic in this study made it difficult to account

fully for time-related changes in diagnostic patterns. Another study of dementia risk in individuals receiving various vaccines showed that vaccination with either RZV or ZVL was associated with reduced HRs for dementia compared to vaccination with Pneumovax 23 (which protects against 23 types of pneumococcal bacteria). Surprisingly, another comparison of RZV and ZVL reported greater protection against dementia for vaccination with ZVL, which is a less effective vaccine than RZV in terms of herpes zoster prevention¹². Two studies that used regression discontinuity designs to analyse routinely collected electronic health

record data from Wales¹³ and Australia¹⁶⁵ both showed reductions in dementia diagnoses associated with eligibility for zoster vaccination, which in the Welsh cohort was evident only in women^{13,165}. The notion that vaccination of individuals at 79–80 years of age (the most over-represented population in these studies) has a major protective effect against dementia is of uncertain plausibility, given the long trajectory of dementia development and the difficulty of finding risk factors that reliably predict dementia in this age group¹⁶⁶.

The mechanism of any protective association between herpes zoster vaccine and dementia is challenging to explain, given the considerable number of studies that show no specific association between herpes zoster and dementia risk. However, some researchers have hypothesized that vaccines might decrease dementia risk via mechanisms unrelated to the prevention of infection. Immune response modulation by adjuvants, the vaccine microbial component or factors secondary to the *in vivo* acquired immune response might alter the pathogenesis of dementia. For example, intravesicular treatment of bladder cancer with live bacillus Calmette–Guérin (BCG) bacteria, which has a wide spectrum of immunomodulatory effects, was associated with decreased progression to dementia in a single-centre study¹⁶⁷. Vaccination against respiratory syncytial virus (RSV), which is likely to stimulate a recall T cell and B cell response given the ubiquity and frequency of RSV infections, has been reported to be associated with decreased dementia risk¹⁶⁸. RZV shares two adjuvant ingredients with the specific RSV vaccine shown to be associated with decreased dementia risk, namely monophosphoryl lipid A (MPL) and QS21 (derived from *Quillaja saponaria*). MPL is a Toll-like receptor 4 (TLR4) agonist that strongly potentiates antibody and CD4⁺ T cell immune responses via effects on antigen-presenting cells and the entrainment of innate cytokine responses¹⁶⁹. The mechanisms underlying the adjuvant activity of saponins, such as QS21, are less well delineated than those of MPL but are likely to involve inflammasome activation¹⁷⁰. These adjuvant compounds are also used in various doses and combinations in licensed vaccines for malaria, hepatitis B and human papillomavirus¹⁷¹. Studies of a viral hepatitis vaccine that included these adjuvants have shown effects of the vaccine on monocyte-trained immunity¹⁷². Of note, RZV vaccination has been associated with epigenetic changes in monocytes¹⁷³. Consistent with this theme, BCG vaccination for tuberculosis prevention also causes epigenetic trained immunity in monocytes¹⁷⁴. Microglia are monocyte-like brain-resident cells that display an activated phenotype in Alzheimer disease¹⁷⁵. Early *in vivo* and *in vitro* studies show effects of licensed adjuvants and vaccine delivery formats (such as RNA-containing lipid nanoparticles) on cells and pathways implicated in dementia^{171,176}. Further investigation is required to create testable hypotheses that relate to possible non-specific influences of vaccination on the progression of neurodegenerative disorders.

Perhaps related to pathogen-independent protective mechanisms of vaccination, sex differences in the results of some studies might reflect differences between men and women in either the pathogenetic mechanisms of dementia or in the innate immune effects of vaccines. Both post-mortem and *in-life* CSF and PET scan studies consistently show higher levels of tauopathy in women than in men among individuals with an increased risk of Alzheimer disease, such as apolipoprotein E (APOE) $\epsilon 4$ carriers. Microglial activation might have an increased contribution to Alzheimer disease in women versus men¹⁷⁷. Sex differences in responses to both infections and vaccines are anchored by substantial clinical evidence for the increased susceptibility of male individuals to some pathogens, the increased incidence and severity

of autoimmunity in women, and the necessity of allograft tolerance during pregnancy. Imperfect X chromosome inactivation and dosage effects for some X-linked genes such as *TLR7* have been postulated as mechanisms that might account for the observed sex differences. Empirical data suggest that desirable specific immune responses are frequently stronger in women than in men (reviewed elsewhere)¹⁷⁸. However, a meta-analysis of RZV studies did not show differences in antigen-specific response rates between men and women¹⁷⁹ in agreement with the findings of two small studies that included both ZVL and RZV^{180,181}.

In summary, good evidence indicates that both varicella and herpes zoster can lead to acute inflammatory and vascular CNS complications, including stroke. The evidence for long-term CNS effects of varicella and herpes zoster is less clear. Although individuals with herpes zoster who experience acute CNS complications or severe systemic illness do have an increased risk of dementia, this effect might be pathogen agnostic rather than specific to VZV. Further research is needed on the potential benefits of herpes zoster vaccination for long-term brain health, ideally in studies with randomized designs that address known sources of confounding and bias. Further mechanistic research is also needed on possible nonspecific effects of vaccines on the progression of neurodegenerative disorders.

Anti-VZV immune responses

Both innate immunity to VZV and inborn errors of immunity can predispose individuals to severe CNS infection with VZV.

Inborn errors of immunity

The detection of VZV dsDNA genomes or replication intermediates in the form of single-stranded or double-stranded RNA triggers both innate immune responses and the maturation of adaptive immunity through the production of type I and type III interferons (IFNs)^{182,183}. A prime illustration of the key antiviral role of type I and type III IFNs against VZV comes from reports of severe disseminated VZV infection occurring in Inuit people who have homozygous deficiency of type I IFN receptor subunit 2 (IFNAR2) after receiving live attenuated VZV vaccines, as well as similar phenotypes of indigenous people from Polynesia who have defects in type I IFN receptor subunit 1 (IFNAR1) after they received live attenuated vaccines^{184–186}. Of note, Inuit people with homozygous IFNAR2 deficiency can also experience severe or fatal outcomes after the administration of live attenuated measles mumps and rubella (MMR) vaccines and natural infections with influenza virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and herpes simplex virus (HSV) types 1 or 2.

A major advance in the understanding of innate immunity to VZV was the identification and characterization of an autosomal dominant defect in RNA polymerase III (Pol III) in four otherwise healthy children with severe CNS or pulmonary VZV infection^{187,188}. This multisubunit protein complex has essential housekeeping functions in the transcription of transfer RNAs (tRNAs) and small RNAs in the nucleus. In addition, Pol III serves as a cytosolic sensor that recognizes AT-rich DNA and converts it into 5'-triphosphorylated RNAs, which trigger the production of type I IFNs by inducing the production of the dsRNA sensor retinoic acid-inducible gene 1 protein (RIG-I, also known as ATP-dependent RNA helicase DDX58)¹⁸⁹. The four affected children were found to have rare heterozygous missense mutations in *POLR3A* or *POLR3C*, which encode different components of the Pol III complex. Leukocytes from all four children had impaired induction of IFN α /IFN β and IFN γ in response to either (synthetic) AT-rich DNA or VZV infection,

which together impair the control of VZV replication¹⁸⁷. *POLR3F* mutations were subsequently reported in monozygotic adult twins who experienced repeated episodes of CNS vasculitis that resembled stroke (with hemiparesis, sensory deficits and headache) and were clinically diagnosed as recurrent VZV reactivation¹⁹⁰. Likewise, *POLR3A* and *POLR3C* mutations have been identified in adults with VZV encephalitis or acute retinal necrosis caused by reactivation of alphaherpesviruses (specifically VZV and HSV1)^{190–192}. Collectively, these data suggest an important contribution of innate immunity to antiviral defences against VZV mediated by recognition of the AT-rich VZV genome and demonstrate an important role of type I and III IFNs in anti-VZV immunity. Moreover, these observations raise the possibility that Pol III and type I or type III IFNs could be important not only in protection against primary VZV infections of the CNS but also in prevention of VZV reactivation mediated by the maintenance of VZV latency in sensory ganglia in the PNS. The description of recurrent HZO in a patient with autosomal dominant TLR3-dependent type I IFN deficiency provides additional support for a role of innate immunity in protection against VZV reactivation¹⁹³. However, further investigations of the underlying molecular and cellular mechanisms are required to clarify the role of IFN-mediated immunity in VZV infection and not least its precise roles in protection against VZV reactivation and the maintenance of VZV latency suggested by these clinical disease presentations.

The development of human induced pluripotent cells (iPSCs) that can be differentiated into neurons and immune cells, including macrophage-like cells and astrocytes, has greatly facilitated the study of VZV pathobiology. Co-cultures of iPSC-derived neurons and autologous immune cells have enabled the detailed quantification and investigation of VZV infection. These models showed that IFN responses are not mounted in VZV-infected monocultures of iPSC-derived neurons, co-cultures of iPSC-derived neurons and iPSC-derived macrophages, or iPSC-derived neurospheroids that contain both neurons and astrocytes. The absence of an IFN response in these VZV infection models is probably because of immune evasion and suggests that additional immune cells are needed to generate type I and type III IFNs in response to VZV exposure^{194–196}.

Beyond interferon-mediated immunity

Whole exome sequencing of large cohorts of patients with various CNS VZV infections, including encephalitis, meningoencephalitis, stroke and acute retinal necrosis, suggests that pathways other than those involving classical adaptive and innate IFNs are operative in immune responses to VZV^{8,190–192}. The resulting datasets have revealed potentially disease-causing (pathogenic) gene variants in multiple pathways related to cell death, ubiquitination, nuclear factor (NF)- κ B pathway activation, inflammation and autophagy. In particular, reduced autophagy and enhanced VZV replication in vitro are evident in neuronal cell lines that harbour autophagy-related gene variants derived from patients with severe ocular and brain VZV infections¹⁹². These observations suggest an early (neuro)protective antiviral effect of autophagy that might limit excessive inflammation and immunopathology and thereby maintain both neuronal and CNS homeostasis^{8,192,197,198}. The findings of these unbiased whole exome sequencing studies provide a knowledge base for the validation of causality as well as for further mechanistic or functional studies to explore the molecular and immunological mechanisms underlying the full spectrum of protective immune and cellular pathways that are operative against VZV and capable of protecting humans from severe VZV CNS infection (among other circumstances).

VZV-specific adaptive immunity

Several observations suggest that VZV-specific adaptive immunity could be instrumental in preventing the CNS complications of VZV infection. For example, the increased incidence of VZV encephalitis in persons with CD4⁺ T cell lymphopenia due to HIV infection and in those with other forms of immunosuppression suggests that acquired immunity might have a protective role¹⁹⁹. Additionally, a patient with VZV-related CNS vasculitis showed marked infiltration of CD8⁺ and CD4⁺ T cells, B cells and innate immune cells in various layers of their large arteries at autopsy²⁰⁰.

Antibody specificity and function

VZV encodes about 70 proteins; accordingly, the antigen specificities of antibodies and T cells that target VZV are just coming into view²⁰¹. Most VZV proteins stimulate immunoglobulin production after hyperimmunization²⁰². Analyses of polyclonal human sera reveal strong responses to VZV envelope glycoproteins as well as to capsid and other cell-associated proteins²⁰³. As yet, proteome-covering arrays to disclose the overall breadth of antigenicity (as reported for HSV²⁰⁴) have not been published. However, convalescent serum IgG from individuals after VZV encephalitis that was used to probe phage display libraries revealed binding to myriad as-yet-unidentified, short linear VZV protein fragments²⁰⁵.

Blood samples from patients recovering from VZV infection or individuals after live attenuated VZV vaccination for herpes zoster, as well as in vitro immunization methods, have been used to produce VZV-specific human monoclonal antibodies^{206–212}, most of which recognize VZV envelope glycoproteins. Anti-gE monoclonal antibodies often have potent complement-dependent neutralizing activity against cell-free virus. Monoclonal antibodies that recognize epitopes of the gH–gL heterodimer can have potent neutralizing activity even without complement, whereas those that target the major VZV fusion protein (gB) as well as the gH–gL heterodimer inhibit VZV-mediated cell-to-cell fusion – an important route of VZV spread in vivo.

Although B cells infiltrate the ganglia where latent herpes zoster can persist, as well as arteries affected by VZV-related CNS vasculitis and skin in individuals with herpes zoster or model antigen challenges, whether these B cells are VZV specific is unclear^{101,200,213–215}. Whether the antibody specificities relevant to CNS VZV infections differ meaningfully from those occurring in other VZV infections also remains unknown. CSF enrichment of VZV-reactive immunoglobulins in individuals with VZV encephalitis or meningitis has historically been measured using undisclosed, crude or cell-associated VZV antigens. The current trend towards using purified VZV gE in commercial clinical serological assays could have as-yet-undetermined effects on the accuracy of CSF and serum immunoglobulin-based indices for diagnosis of VZV CNS infections²¹⁶.

T cell specificity and function

In adults, trigeminal ganglia inevitably harbour VZV DNA and a subset of trigeminal ganglia will have HSV-1 co-infection. A comparison of immunohistology and gene expression in VZV⁺HSV-1[–] and VZV⁺HSV-1⁺ trigeminal ganglia showed that inflamed neurons in dual-infected trigeminal ganglia were surrounded by rosettes of leukocytes (including CD4⁺ and CD8⁺ T cells) that express cytotoxicity markers. By contrast, neurons in VZV mono-infected trigeminal ganglia were not inflamed and their resident T cells lacked these markers²¹⁷. Proteomic studies of CD8⁺ and CD4⁺ T cell reactivity in dual-infected trigeminal ganglia identified

that many of these T cells respond to HLA-restricted HSV-1 peptides²¹⁸. A subset of HSV-1-reactive T cells also responded to identical or slightly sequence-divergent VZV peptides. This cross-reactivity, which occurs at both the clonal and population levels, reflects a general property of CD4⁺ and CD8⁺ T cells that target the alphaherpesviruses that infect humans (namely VZV, HSV-1 and HSV-2)^{219–221}. Similar studies of T cells from VZV mono-infected trigeminal ganglia show low (but not zero) levels of reactivity to VZV epitopes²²². The blood of a patient with VZV encephalitis showed prominent expansion of highly activated cytotoxic CD8⁺ T cells, which targeted a VZV epitope with cross-reactivity for HSV and Epstein–Barr virus (EBV) antigens²²¹, along with a small CD4⁺ T cell response²²³. Proteomic screening of T cells in post-herpes zoster skin samples disclosed prevalent CD4⁺ and CD8⁺ T cell responses to RZV antigens gE and VZV ORF9, respectively. Tissue-resident memory T (T_{RM}) cells persisted in skin for up to 1 year after recovery from herpes zoster, and T cell receptor (TCR) sequencing confirmed the high abundance and persistence of VZV-specific CD8⁺ T_{RM} cells²²⁴. Interestingly, gaps in the VZV-specific TCR repertoire have been suggested to have an important role in herpes zoster susceptibility²²⁵. Prospective studies of the natural history of VZV infection indicate that low T cell responses to VZV are a better predictor of herpes zoster than low anti-VZV antibody titres^{225,226}.

Preventive vaccine efficacy

Live attenuated vaccines are effective against both varicella and herpes zoster, whereas RZV is currently licensed only for the prevention of herpes zoster. Varicella-associated VZV encephalitis is rare, but observational studies suggest that its incidence is reduced by paediatric vaccination^{24,227}. Herpes zoster-associated VZV encephalitis and meningitis are also uncommon, but existing studies of herpes zoster vaccination have not been sufficiently statistically powered to identify a protective effect of vaccination^{6,154}. In recipients of live attenuated varicella vaccine, the fold rise in serum antibody levels (rather than the antibody titre itself) was associated with protection from herpes zoster. Specifically, the subgroup with highest vaccine efficacy (90%) had the highest (5.26-fold) increase in serum antibody titre²²⁸. Among RZV recipients, VZV antibody and CD4⁺ T cell levels decline gradually over time, concurrently with a modest rise in the risk of herpes zoster that is most notable 10 years after vaccination^{226,229,230}. However, whether a causal relationship exists between these temporal changes remains unclear^{226,229,230}. RZV strongly and durably boosts the levels of both CD4⁺ T helper type 1 (T_H1) cells and VZV-specific immunoglobulins, which makes it challenging to parse the mechanisms underpinning the protective effect of this vaccine²³⁰. Epitope-specific and TCR-informed studies of RZV that focused on vaccine-elicited CD4⁺ T cell responses to gE suggest that VZV-specific T_H1-biased CD4⁺ memory cells are recruited from both naive and pre-vaccine memory compartments, that programmed phenotypic changes in vaccine-boosted T cells outlast acute activation-associated perturbations, and that VZV-specific TCRs show convergence between HLA-sharing individuals^{224,231}. As yet, the exact anatomical loci (in ganglia, the PNS and perhaps the CNS) that are involved in vaccine-elicited T cell or antibody-mediated immune responses and anti-herpes zoster effects (and could potentially also reduce VZV CNS disease) are unclear.

The potential connection between VZV and CNS disease goes beyond concerns related to adults aged >50 years, although this link pushes us to better understand healthy ageing. Indeed, preventive strategies against VZV could start during childhood, when children are vaccinated using a live attenuated VZV vaccine. Global epidemiological

studies of VZV vaccination have consistently illustrated that two doses of varicella vaccine achieve a high level of protection from varicella and substantially reduce the circulation of this disease in the population²³². Although it is tempting to speculate that universal varicella vaccination could reduce the long-term population risk and consequences of VZV CNS complications, the reader should note that the VZV-specific adaptive immunity elicited by varicella vaccination wanes over time, that wild type VZV infection can occur in previously vaccinated children (in whom it is termed breakthrough varicella), and that breakthrough varicella can still establish latency of circulating wild type VZV strains²³³. Indeed, breakthrough varicella occurs in up to 10% of children after a single dose of live attenuated VZV vaccine²³⁴.

Moreover, the live attenuated VZV virus used in vaccines can itself (albeit extremely rarely) cause severe acute VZV complications, including encephalitis^{89,235,236}. Attenuated VZV strains used in varicella vaccines can also infect sensory ganglia in vivo and establish a lifelong latent infection^{32,237,238} that occasionally results in herpes zoster²³⁹ in vaccinated individuals. Nonetheless, clinical VZV reactivation in vaccine recipients most often results from reactivation of wild type VZV rather than vaccine strains of VZV²³⁹. Although vaccine-associated herpes zoster is clinically similar to that caused by wild type VZV²⁴⁰, its incidence is considerably lower: VZV-vaccinated children have a 78% lower probability of developing herpes zoster²⁴¹. Among VZV-vaccinated children, rates of herpes zoster caused by vaccine strains and wild type VZV were approximately equal^{242,243}, which probably reflects the reduced capacity of VZV vaccine strains for reactivation (but not latency) that has been shown in stem cell-derived neurons⁶⁵. Meningitis can, albeit rarely, be caused by reactivation of varicella vaccine virus^{91,241,242}. However, the potential effects of varicella vaccine virus reactivation on chronic CNS complications associated with VZV infection remain unclear. Further studies are needed to determine whether vaccination of children with live attenuated VZV could lead to subsequent VZV-related CNS disease.

Finally, the reduction in rates of primary infection with wild type varicella resulting from universal varicella vaccination has been hypothesized to lead to a temporary increase in herpes zoster incidence because of reduced natural boosting of immunity associated with early exposure to wild type VZV strains³⁷. However, the validity of this hypothesis remains heavily challenged by epidemiological and immunological research^{244,245}.

Conclusions and future perspectives

This Review presents a critical analysis of epidemiological studies that investigated whether CNS conditions (particularly stroke and dementia) are linked to symptomatic VZV infections (both varicella and herpes zoster) and asymptomatic VZV reactivation. Strong evidence, triangulated across epidemiological studies with different designs, data sources and settings, indicates that herpes zoster can lead to stroke. However, the evidence for an association between herpes zoster and dementia risk is conflicting. In general, studies of severe acute CNS complications of herpes zoster (such as encephalitis) or severe systemic herpes zoster-related illnesses are most likely to show an association with dementia risk, but these effects might not be specific to VZV. Although some observational studies report large protective effects of herpes zoster vaccination against dementia, it is unclear whether the researchers have adequately addressed potential sources of bias. The mechanisms of protection also remain unclear. These uncertainties highlight the need for further robust research into the effects of herpes zoster vaccination on future brain health. Although the results

of several studies support the premise that VZV can both reach the CNS and cause pathology there, the exact route of transport of VZV to the CNS remains debated. Future research could benefit from the development of iPSC-derived organoids that enable in-depth investigations into how VZV might cause CNS pathology.

Studies of the associations between defects in innate and adaptive immunity and VZV CNS disease have convincingly shown that VZV can reach the CNS and cause inflammation within the CNS when defence mechanisms are hampered. However, how herpes zoster vaccination might prevent both stroke and dementia remains to be properly understood. This benefit could be derived from either a direct protective effect of the increase in VZV-specific T cells, cross-reactivity between VZV-specific T cells and HSV-specific T cells, or trained immunity effects²¹⁹. We conclude that although VZV is likely to be involved in CNS disease in the acute setting, further research is needed on the role of VZV in chronic CNS disease. Given the dire consequences of dementia in an ageing population, we believe that randomized controlled trials designed to evaluate the potential mitigating effect of RZV on dementia are urgently needed.

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