

Varicella zoster virus infection

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Abstract

Varicella zoster virus (VZV) is an exclusively human alphaherpesvirus that infects >90% of the global population. Primary infection typically causes varicella (chickenpox), after which VZV establishes lifelong latency in ganglionic neurons along the entire neuroaxis. Virus reactivation, typically triggered by age-associated immune dysfunction or immune suppressive conditions, produces herpes zoster (shingles) that can be complicated by post-herpetic neuralgia. In limited instances, VZV reactivation (and rarely primary infection) also produces multisystem disease including vasculopathy, cranial neuropathies, myelopathy and cardiovascular or gastrointestinal complications; these complications can occur without, or temporally dissociated from, rash. Diagnosis of varicella or herpes zoster relies on clinical presentation of a disseminated or dermatomal-distribution rash, respectively; diagnosis of VZV infection (owing to replicating virus) is more challenging when cases are atypical and/or occur without rash. Prevention strategies include administration of live attenuated varicella vaccine and recombinant zoster vaccine. VZV infection is treated with antiviral drugs including oral valacyclovir (drug of choice), famciclovir, acyclovir or amenamevir; for severe or disseminated disease, intravenous acyclovir or foscarnet (when other drugs fail) are used. Critical challenges remain in recognizing and diagnosing atypical presentations, developing novel therapeutics, establishing the causal role of VZV in vascular and neurodegenerative disease, and achieving broader vaccine implementation worldwide.

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Introduction

Varicella zoster virus (VZV; human herpesvirus 3) is one of nine double-stranded DNA human herpesviruses characterized by their ability to infect humans, establish latency and then reactivate throughout the host's lifetime. VZV is genomically classified as an alphaherpesvirus, along with herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), which share their ability to establish latency in ganglionic neurons.

Primary infection with VZV typically causes varicella (chickenpox), followed by establishment of lifelong latency within cranial, enteric, dorsal root and autonomic ganglionic neurons^{1–7}. Patients with age-associated immune dysfunction or immune suppressive conditions (for example, inborn errors of immunity, HIV, cancer, pathogen-associated immune dysfunction, and immune suppressive medications or therapies) are at the highest risk of virus reactivation, which produces a painful, unilateral, dermatomal-distribution, vesicular rash (herpes zoster (HZ), also known as shingles) that can be complicated by post-herpetic neuralgia (PHN). VZV can also manifest as unilateral, dermatomal-distribution pain without rash (*zoster sine herpette*). In addition, VZV reactivation can present as a spectrum of diseases involving multiple organs with or without associated rash, which complicates clinical recognition and delays antiviral therapy. These clinical manifestations include VZV vasculopathy^{8–11}, cranial neuropathies^{12,13}, ophthalmological complications^{14–17}, myelopathy¹⁸, cardiovascular disease¹⁹ and gastrointestinal disease^{20,21}. These manifestations can also be seen during primary infection, albeit rarely. Furthermore, epidemiological studies have reported associations of HZ with increased risk of stroke, transient ischaemic attacks, cardiovascular events, and cognitive decline or dementia, with varying degrees of hazard ratios depending on age and site of VZV reactivation^{19,22–25}.

The burden of VZV disease (varicella, HZ and all related viral complications) is substantial, given that >90% of the population harbour latent VZV that will reactivate in more than one-third of individuals in their lifetime. Furthermore, the number of HZ cases is rising, in part owing to the increased risk associated with COVID-19 (ref. 26). Thus, it is essential to understand the scope of VZV disease, the diagnostic tests and their limitations, and treatment options.

In this Primer, we summarize the epidemiology of varicella and HZ, including known risk factors for VZV reactivation. We summarize disease pathophysiology, highlighting mechanisms of viral spread to skin and other organs during varicella and VZV reactivation. We also summarize the broad spectrum of disease produced by VZV reactivation and discuss diagnostic methods, particularly for challenging cases without rash, prevention of varicella and HZ by currently available vaccines, and antiviral treatments. We provide an overview of patient quality of life (QoL) and have identified areas of future research, including improvements in recognizing and diagnosing atypical presentations of VZV disease, development of novel therapeutics, investigation of the mechanistic underpinnings by which VZV contributes to stroke, cardiovascular disease and dementia, and implementation of broader vaccine coverage worldwide.

Epidemiology

Varicella incidence and prevalence

Varicella, owing to primary VZV infection, is endemic worldwide. It is typically acquired in early childhood in temperate zones; in some tropical countries²⁷, varicella occurs later in adolescence and adulthood, although geographic comparisons are hampered by a lack of global data. The age-standardized incidence rate of VZV infection has increased slightly worldwide from 1990 to 2019 (estimated annual

percentage changes (EAPC) of 0.03, 95% CI 0.02 to 0.04), while the age-standardized death rate (EAPC of –2.31, 95% CI –2.37 to –2.24) and disability-adjusted life years (EAPC of –1.61, 95% CI –1.65 to –1.56) have fallen²⁸. Specifically, in Europe, varicella incidence is highest in children aged <5 years with 7,052–16,122 cases reported per 100,000 (ref. 29). By 15 years of age, >90% of individuals have been infected⁹. North America saw a similar pattern of high incidence in early childhood before the introduction of varicella vaccine, which was initially implemented as a single dose in 1995, then as a two-dose schedule in 2006 owing to breakthrough cases observed during the one-dose programme. Declines of 90–95% in varicella incidence in children aged 5–19 years in the USA occurred between 1995 and 2009 (ref. 30). In Latin America and the Caribbean³¹, the Middle East³² and temperate zones of the Asia Pacific region³³, the most commonly affected age group is children aged <10 years. Later infections and lower seroprevalence in late adolescence or early adulthood are seen in countries such as Sri Lanka (37% seropositive in 15–19-year-olds³⁴) and Singapore (71% seropositive at 13–17 years³⁵). Limited data available from Africa suggest that, although VZV seroprevalence is typically high in adults, it is lower in children compared with temperate zones³⁶. By 2023, 45 countries had introduced universal varicella vaccination, which led to rapid declines in infection incidence and burden in those settings. Nevertheless, ~84 million incident cases of VZV were recorded globally in 2019, with 949,523 disability-adjusted life years and 14,553 deaths²⁸.

There are striking patterns of seasonality that differ by latitude: seasonal outbreaks occur in temperate zones, typically peaking in March–May in the Northern Hemisphere and October–December in the Southern Hemisphere³⁷. Climatic factors, including temperature and humidity, may influence varicella transmission through altering human activity, weakening immune responses or other factors that are not well characterized³⁸. Increased urbanization, levels of overcrowding and school-age mixing are also suggested as contributing to an increase in varicella incidence over time in some settings such as Latin America and the Caribbean³¹.

Varicella risk factors

Risk factors for varicella infection include lack of immunity in an individual because they have had no prior exposure through infection or vaccine, close contact with an infected individual, or having spent a substantial amount of time in environments with high transmission rates (for example, daycares and schools). Varicella complications include pneumonia, sepsis, haemorrhage and severe skin infections^{39,40}. Although rare, these complications occur more frequently among immunocompromised individuals (with primary or secondary immune deficiencies, or on immunosuppressive therapies such as corticosteroids), infants and pregnant women⁴⁰. Severe neurological and central nervous system (CNS) complications can also occur including acute cerebellar ataxia, encephalitis, stroke and meningitis⁴¹. In a prospective cohort study, approximately one-third of arterial ischaemic strokes in children were attributed to preceding varicella⁴². Neonates whose mothers develop varicella from 5 days before to 2 days after delivery are at particularly high risk for severe disease.

HZ incidence and prevalence

VZV can reactivate to cause HZ. In immunocompetent populations, the incidence rate of HZ ranges from 5.23 to 10.9 cases per 1,000 person-years worldwide⁴³. Despite the availability of a zoster vaccine, HZ incidence has increased over time, with striking increases over a 60-year period in the USA⁴⁴. Increases in HZ incidence have been

shown across countries in North America, Europe, Asia Pacific and Oceania⁴³. HZ incidence increases sharply with age and can affect up to 50% of people aged more than 85 years⁴⁵. HZ is more common in females than males (cumulative incidence of 3.22–11.2 cases in females versus 2.44–8.0 in males per 1,000 person-years)⁴³. Among immunocompromised populations, incidence estimates are markedly higher, ranging from 9 to 92 HZ cases per 1,000 patient-years in the USA⁴⁶; similar elevated incidences have been observed in multiple European countries⁴⁷. The highest rates are seen among individuals who have received stem cell transplants or solid organ transplants and those with haematological malignancies^{46,47}. Of note, rates of HZ are lower in paediatric populations that are vaccinated against varicella compared with unvaccinated cohorts^{48,49}.

HZ risk factors

A meta-regression of worldwide HZ incidence rates confirms associations with older age and female sex noted above, as well as income level and geographic region; HZ incidence tends to be highest in high-income Asia Pacific region (EAPC of 0.21, 95% CI 0.14 to 0.28) compared with smaller, yet still increasing, rates in Western Europe (EAPC of 0.03, 95% CI –0.01 to 0.07) and high-income North America (EAPC of 0.08, 95% CI –0.02 to 0.17)²⁸. Variation by race and ethnicity is well recognized, with HZ rates markedly lower among individuals not of white ethnicity (white ethnic background odds ratio: 2.00; 95% CI 1.40 to 2.88)⁵⁰. Other risk factors for HZ include immunosuppression owing to medications used to treat autoimmune diseases, cancer and transplant rejection; recent physical trauma (particularly cranial trauma); systemic physiological stress associated with acute illness or tissue injury; and a wide range of autoimmune, immunocompromising and chronic inflammatory conditions including rheumatic disorders, systemic lupus erythematosus, HIV, inherited immune deficiencies and diabetes mellitus^{47,51,52}. Acute systemic illness owing to COVID-19 has also been linked to increased HZ risk (2.16-fold; 95% CI 1.24 to 3.76)⁵³. Subclinical VZV reactivation without rash may occur with physiological stress, such as among critically ill patients in intensive care units⁵⁴ and astronauts during spaceflight⁵⁵.

Mechanisms/pathophysiology

Primary varicella infection

Primary VZV infection occurs after exposure to individuals with varicella or HZ and is transmitted via aerosolization or direct contact with skin lesions (Fig. 1a). VZV infection begins in the mucosal epithelial cells of the upper respiratory tract and culminates in the skin, whereby the virus actively replicates (Fig. 1b) and ultimately causes the formation of skin blisters containing the infectious virions that can infect new susceptible hosts^{56,57}.

Specifically, from the upper respiratory tract, VZV accesses tonsils and other lymphoid tissues, where it infects T lymphocytes, causing viraemia. The events leading to infection of T cells are unclear but could involve in-between infection of dendritic cells, which probably transport the virus to other lymphoid tissues, further expanding T cell infection, or through direct contact with mucosal epithelial cells^{58,59}. Although these events are not yet fully elucidated, the importance of infected T cells in delivering the virus to other organs, particularly the skin, is well established. VZV remodels T cells to express skin-homing proteins^{60–62}. Natural killer cells are also remodelled by VZV; however, whether they contribute to VZV transport to the skin has not been formally demonstrated⁶³. Although infected T cells travel to the skin within days post-infection, the interval between infection and blister

formation is between 10 and 21 days. In this time, the virus, through evasion of immune and apoptotic responses, replicated undetected⁶⁴.

VZV and the skin. Histological analyses of varicella and HZ biopsy samples identified the hair follicles as the first site of VZV infection in the skin^{65,66}. This observation has been documented in SCID-hu mice with VZV-infected skin grafts; initial accumulation of VZV-infected T cells in hair follicles before transmission to basal progenitor keratinocytes of the interfollicular epidermis was documented^{65–67}. Within the epidermis, VZV is highly cell-associated, and it can fully replicate and mature into infectious cell-free virions only once the infected keratinocytes commit to terminal differentiation, probably requiring several epidermal differentiation markers to be expressed to complete its life cycle⁶⁸. The end point of VZV replication is the formation of blisters, which are laden with the infectious virions, necessary not only to infect new hosts, but also for latency, as the blisters are probably where the cell-free virus encounters and infects nerve endings, although this has not been fully elucidated⁶⁹. In varicella, the blisters appear as discrete lesions throughout the epidermis owing, in part, to the production of interferon- α (IFN α), pSTAT1 and promyelocytic leukaemia nuclear bodies (PML-NBs) in adjacent uninfected keratinocytes, which prevents more extensive spread^{64,67}. In addition, VZV appears to preferentially infect progenitor keratinocytes, which may limit cell-to-cell spread in more differentiated keratinocytes, thereby contributing to the discrete nature of the lesions^{68,70}.

The interplay between VZV and epidermal differentiation is intertwined, with VZV also directly altering the expression of several differentiation markers for its replication. One such marker is keratin 10 (K10), which is an essential protein for keratinocyte differentiation and epidermal barrier formation. K10 expression is reduced by VZV^{68,71}, both at the transcription and the proteasome level (the latter is mediated by the activation of the KLK6–MDM2 axis⁷¹), and is probably involved in VZV pathogenesis. K10 depletion is thought to be involved in blister formation, as reduction in K10 expression is a common feature in several skin blistering diseases, as is the downregulation of desmosomal proteins, such as desmocollin-1 (DSC1) and desmoglein-1 (DSG1), which are also downregulated by VZV. Moreover, VZV-mediated K10 depletion appears to have a signalling effect, by inducing autophagy pathways⁷¹. Another epidermal protein, the keratin K15, which is normally mainly expressed in the stem cells of the hair follicles and in the progenitor keratinocytes of the interfollicular epidermis, is upregulated in keratinocytes infected with VZV, and this facilitates VZV replication⁷².

Aside from innate immune responses during varicella, including type I IFN and PML-NB responses, T cell-mediated immunity is required to resolve primary infection^{73,74}. In rhesus macaques infected with simian varicella virus (SVV; the non-human primate (NHP) homologue of VZV that recapitulates VZV disease), SVV-specific IgM antibodies emerge, followed by SVV-specific IgG antibodies that are detected 7 days post-inoculation and peak 18–20 days post-inoculation, consistent with what has been observed in humans infected with VZV^{73,75}. Despite contributing to the control of SVV or VZV infection, antibody immune responses are less crucial than T cell-mediated immunity because B cell immunodeficiencies are not associated with more severe varicella disease^{74,76}.

Latency

After primary infection, VZV establishes latency in cranial nerve, dorsal root, autonomic and enteric ganglionic neurons from where they can

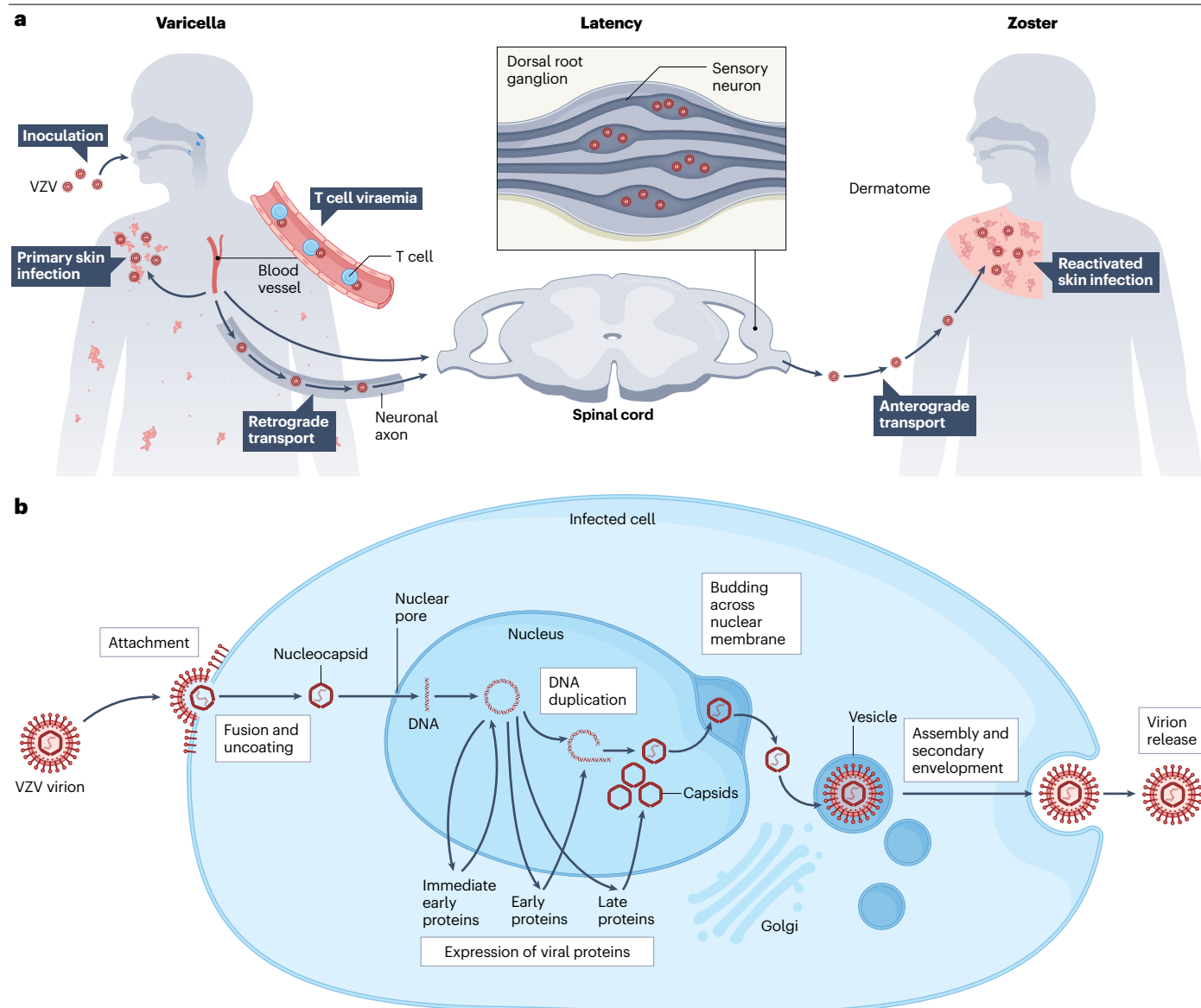


Fig. 1 | Varicella zoster virus life cycle. a, Primary varicella zoster virus (VZV) infection begins when virions reach mucosal epithelial sites of entry. Local replication is followed by spread to tonsils and other regional lymphoid tissues, where VZV gains access to T cells. Infected T cells then deliver the virus to cutaneous sites of replication. VZV establishes latency in sensory ganglia after transport to neuronal nuclei along neuronal axons or by viraemia. Reactivation from latency enables a second phase of replication to occur in skin, which typically causes lesions in the dermatome that is innervated by the affected sensory ganglion. **b**, VZV virions attach to cell membranes, fuse and release tegument proteins (proteins lining space between viral envelope

and nucleocapsid). Nucleocapsids move along microtubules to nuclear pores, where uncoating occurs and genomic DNA is injected into the nucleus. The linear genome circularizes and is chromatinized. Immediate early genes are expressed, followed by early and late genes. Nucleocapsids are assembled and package newly synthesized genomic DNA, move to the inner nuclear membrane and bud across the nuclear membrane. Capsids enter the cytoplasm, and virion glycoproteins mature in the *trans*-Golgi region and tegument proteins assemble in vesicles; capsids undergo secondary envelopment and are transported to cell surfaces, where newly assembled virions are released by exocytosis. Figure adapted with permission from ref. 64, Springer Nature Limited.

later reactivate, producing HZ and other neurological and systemic disease. VZV DNA has also been found, albeit at a low frequency (6%), in normal adrenal glands; adrenal medullary cells are likely to harbour latent virus because they are derived from the neural crest, similar to neural crest-derived cells in the cranial nerve, dorsal root, autonomic and enteric ganglia. However, a demonstration of specific cells

containing virus in its latent concatemeric form in adrenal glands has yet to be completed^{2-6,77}. Proposed mechanisms for virus entry to ganglia include (1) retrograde axonal transport from infected skin⁷⁸⁻⁸⁰ and/or (2) haematogenous dissemination through infected T cells^{1,79}. In latently infected human ganglia obtained at autopsy, the VZV genome has been shown to be in a circular–concatemeric configuration within

the nucleus⁸¹, and there are five to seven genome copies in ~2–5% of sensory neurons^{78,80}. Virus transcription in human ganglia obtained <6 h after death is restricted to the VZV latency-associated transcript (VLT) and the VLT–open reading frame 63 fusion transcript^{1,82}. CD4⁺ T cell responses are involved, in part, in the establishment of latency as shown by depletion of CD4⁺ T cells (but not CD8⁺ T cells or B cells) leading to impairment of latency in NHPs infected with SVV⁸³; given that CD4⁺ T cells are important for the dissemination of virus to skin and ganglia⁶⁷, this impairment may therefore be facilitating reduced latency establishment.

Mechanisms of reactivation and HZ

Immune suppression owing to genetic mutations, host-neutralizing autoantibodies to type I IFNs and deficits in cell-mediated immunity predispose individuals to VZV reactivation with severe complications (recurrent zoster and CNS disease), as well as to severe varicella^{84,85}. Specifically, a *DOCK8* mutation was found in a 6-year-old boy with VZV vasculopathy owing to virus reactivation without rash⁸⁶; *DOCK8* is involved with normal immune cell function. Other genetic mutations related to immunity that predispose to severe VZV infection include RNA polymerase III, *TLR3*, *GATA2*, *DOCK2*, *CORO1A*, *WAS*, *MAGT1*, *IFNGR1*, *STAT5B* and *GINS1* (refs. 84,85). The list of inborn errors of immunity continues to grow as cases are reported and risk genes identified. Multiple reports of complicated VZV infection have also been attributed to host-neutralizing autoantibodies to type I IFNs⁸⁴. Deficits in cell-mediated immunity also predispose to severe infectious complications and reactivation. For instance, low CD4⁺ T cell count (as documented in some people with HIV) has been associated with severe VZV disease^{87–89}. Furthermore, in the SVV model of infection, depletion of CD4⁺ or CD8⁺ T cells resulted in virus reactivation^{90,91}. Natural killer cell deficiencies or dysfunction also lead to severe VZV infections^{92,93}. B cell depletion (for example, rituximab therapy) can also increase HZ risk⁹⁴.

Additional triggers for VZV reactivation include stress, physical trauma⁵² and immunosuppressive or autoimmune conditions. VZV reactivates from one or more ganglia with new infectious virions produced. These virions can travel along neurites peripherally to the skin to produce HZ or centrally to other organs to produce corresponding disease with or without rash. VZV has multiple strategies to evade the host antiviral response and establish productive infection. Viral proteins interfere with type I IFN signalling^{95–97}, block IRF3 phosphorylation^{98,99}, lead to impairment of TLR9 signalling in VZV-infected dendritic cells¹⁰⁰, disrupt antiviral PML-NBs¹⁰¹ and disrupt the NF-κB pathway^{102–104}. A new mechanism of innate immunity evasion has been described: non-infectious, pathogenic exosomes released from VZV-infected human sensory neurons have been shown to suppress the type I IFN response, thereby promoting neuroinvasion of a secondary pathogen in a mouse model of HSV-1 infection¹⁰⁵.

Aside from innate antiviral responses suppressed by specific viral proteins, VZV downregulates major histocompatibility complex class I in infected cells contributing to viral immune evasion of the CD8⁺ T cell response^{59,106,107}. In vitro experiments of VZV-infected peripheral blood mononuclear cells have demonstrated that VZV inhibits CD8⁺ T cell effector function through induction of PDL1 expression¹⁰⁸. Inhibition of the JAK–STAT pathway by VZV contributes to the evasion of the cell-mediated immune response^{109–111}. VZV was also documented to interfere with the function of natural killer cells through the modulation of the cell surface expression of NKG2D ligand^{63,112}. Finally, experimental immunosuppression of SVV-infected rhesus

macaques resulted in reactivation of latent virus and HZ, confirming the importance of a robust immune system in humans to maintain latency. The finding of viral antigen in multiple tissues months after HZ in NHPs confirms the finding of persistent or recurrent VZV reactivation in humans post-HZ, as demonstrated by the presence of VZV DNA in saliva of two-thirds of individuals after HZ resolution, even 12 years after rash¹¹³.

Spectrum of disease owing to VZV reactivation

The widespread latency of VZV within neurons spanning the entire neuroaxis enables reactivation to organs and arteries directly innervated by these neurons, giving rise to a broad spectrum of diseases that may occur with or without a skin rash (Fig. 2). While the spectrum of neurological and systemic disease caused by VZV reactivation continues to grow, we highlight below the more prominent clinical manifestations of VZV reactivation.

Herpes zoster. During virus reactivation from sensory neurons, VZV travels peripherally towards the skin to produce a unilateral, fluid-filled vesicular rash in the corresponding sensory dermatome that is associated with severe neuropathic pain. Of note, VZV reactivation from the trigeminal ganglia can produce a rash in the ophthalmic distribution (V1; HZ ophthalmicus), which can be complicated by VZV keratitis (particularly if Hutchinson's sign is present; that is, the presence of a rash on the tip, side or root of the nose) that is frequently recurrent and difficult to treat (Fig. 3). In addition, VZV reactivation in the facial nerve can produce one-sided facial paralysis or weakness, accompanied by a painful rash with fluid-filled blisters on, in or around the ipsilateral ear (Ramsay Hunt syndrome; HZ oticus); early disease, presenting as unilateral ear pain, redness, and swelling prior to blister formation, can be misdiagnosed as a bacterial infection. HZ typically resolves within 2 weeks; associated pain and sensory abnormalities resolve within 6–8 weeks. Recurrent zoster is rare and warrants an evaluation of contributing immunosuppressive conditions, therapies and other exposures.

PHN and zoster sine herpete. PHN is defined as pain persisting for >3 months post-HZ. Proposed mechanisms of PHN include virus-mediated and inflammatory-mediated damage to nociceptive (pain) neurons and/or persistent VZV replication and inflammation in sensory ganglia (VZV ganglionitis)^{114,115}; however, the molecular mechanisms ultimately leading to neuronal dysfunction are largely unknown. In post-mortem studies, dorsal horn atrophy and cell, axon and myelin loss with fibrosis in the sensory ganglion were found only in individuals with PHN and were absent in sensory ganglia from individuals without pain¹¹⁶. Additional studies of PHN sensory ganglia reveal diffuse and focal infiltration by chronic inflammatory cells, raising the possibility of prolonged viral infection^{116,117}. Within sensory ganglia, reactivated VZV may spread from infected neurons to adjacent neurons and satellite glial cells, a process that can amplify local viral replication and promote inflammation and injury¹¹⁸. Such involvement of the neuron–satellite cell microenvironment is thought to contribute to the neuropathic pain that characterizes PHN. Detection of VZV DNA and proteins in peripheral blood mononuclear cells of patients with PHN^{119,120}, studies of patients with *zoster sine herpete* (radicular pain without rash)^{121,122} and improvement of PHN with intravenous (IV) acyclovir¹²³ further support the notion that low-grade viral ganglionitis contributes to PHN. However, other studies have found limited protection of antivirals during acute HZ to reduce PHN onset¹²⁴, but antiviral

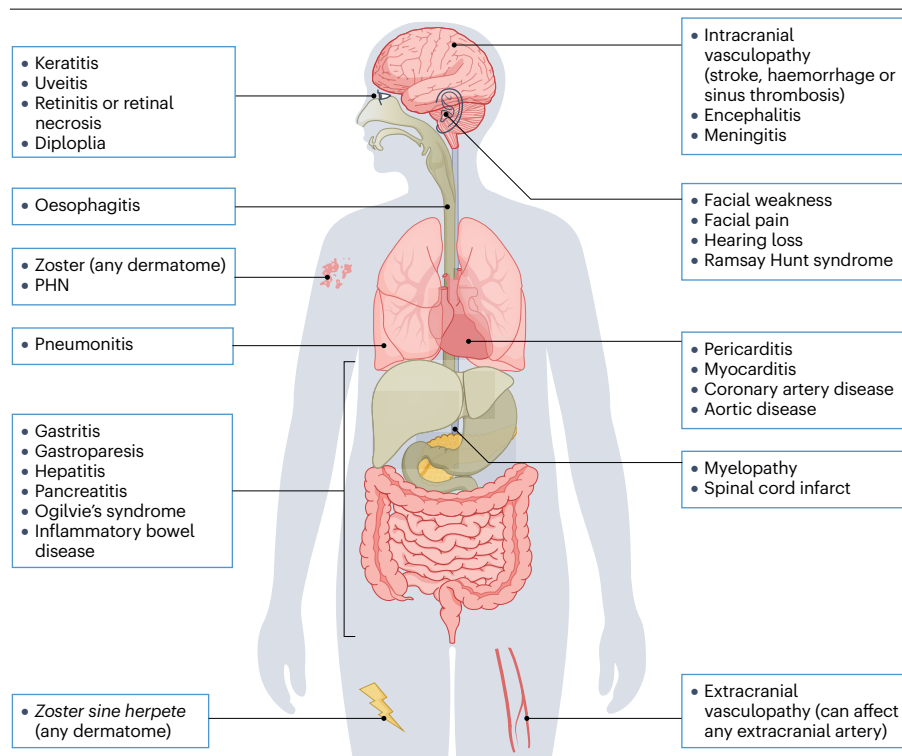


Fig. 2 | Spectrum of disease owing to varicella zoster virus reactivation. The distribution of latent varicella zoster virus within neurons spanning the entire neuraxis enables reactivation to organs and arteries that are directly innervated by these neurons, giving rise to a broad spectrum of diseases that may occur with or without a skin rash. PHN, post-herpetic neuralgia.

treatment during PHN does appear to modestly lower overall pain and pain medication usage, although not reduce the prevalence¹²⁵, suggesting that additional mechanisms aside from chronic VZV ganglionitis are involved in PHN pathogenesis.

Persistent peripheral nerve damage is observed in PHN but not understood. A consistent finding in skin biopsy samples from patients with PHN is a substantial reduction in cutaneous nerve fibre density within the involved dermatome, suggestive of peripheral denervation^{126–128}. Counterintuitively, this structural loss of sensory fibres is often accompanied by heightened pain perception, a phenomenon observed in other clinical neuropathic pain conditions^{129–131}. PHN can, in some patients, involve reduced pain and temperature sensitivity coupled with severe mechanically evoked pain (allodynia), which may arise, in part, through ectopic circuit formation linking large-diameter low-threshold mechanoreceptors to central nociceptive neurons¹³². In addition, degeneration of peripheral nerve fibres may reduce inhibitory modulation of remaining nociceptors, contributing to amplified pain despite sensory loss^{133,134}.

Finally, it is important to recognize the entity of dermatomal-distribution pain without preceding HZ, known as *zoster sine herpette*¹²¹. This is probably owing to VZV reactivation causing a chronic ganglionitis^{114,122} and pain without peripheral spread of virus to skin.

VZV vasculopathy. VZV reactivation can also produce cerebrovascular disease (intracranial VZV vasculopathy) with or without associated rash, including ischaemic or haemorrhagic stroke, aneurysm, aortic dissection and dolichoectasia (abnormal arterial dilation and elongation)^{8,9}. VZV reactivation, manifesting as HZ, is reported to increase the risk of transient ischaemic attacks and stroke (VZV vasculopathy); HZ in the ophthalmic distribution and age <40 years confers a higher

risk, and HZ vaccination reduces risk^{22–24}. In a study of 30 individuals with virologically confirmed VZV vasculopathy, one-third did not have an associated zoster rash or cerebrospinal fluid (CSF) pleocytosis; small, medium and large vessels were involved; and detection of intrathecal anti-VZV antibody synthesis was a better test for diagnosis than detection of VZV DNA in CSF^{10,135}. In the VIPS II study (Vascular Effects of Infection in Paediatric Stroke), evidence of recent, clinically silent VZV reactivation (elevated VZV IgM antibodies at stroke baseline) was detected in a subset of children with arterial ischaemic stroke, despite being in an era of widespread varicella vaccination, supporting the view that VZV remains a relevant but under-recognized paediatric stroke trigger, particularly in cases of focal cerebral arteriopathy¹³⁶.

The spectrum of VZV vasculopathy has expanded to include the extracranial circulation. Temporal arteries from patients with giant cell arteritis (GCA; the most common systemic vasculitis in older people) contain VZV antigen (74%) or both VZV antigen and DNA (40%)¹³⁷. Furthermore, the role of VZV in GCA pathogenesis was supported by host transcriptional profiling of GCA temporal artery biopsy samples, which demonstrated robust antiviral responses and inflammation compared with non-GCA temporal artery samples¹³⁸. VZV antigen has also been found in multiple systemic arteries including aorta, coronary arteries, pulmonary arteries and renal arteries, supporting a role for VZV vasculopathy extracranially¹³⁹. Of note, some studies using differing methodology have failed to detect VZV in temporal arteries at the same frequency; thus, further investigations are warranted^{140,141}.

Mechanisms of intracranial VZV vasculopathy include direct infection of the arterial wall and/or vasculitis and thrombosis, mediated, in part, by pathogenic, circulating exosomes produced during VZV reactivation¹⁴². Post-mortem studies of VZV-infected cerebral arteries

from individuals with VZV vasculopathy report virus antigen in adventitia early in infection and in the media and intima layer, supporting the notion that after reactivation from trigeminal and/or head or neck autonomic ganglia, VZV spreads transaxonally to the arterial adventitia followed by transmural spread of virus¹¹. Increased pro-inflammatory cytokines (IL-6 and IL-8) are produced by VZV-infected cerebrovascular cells¹⁴³ and also found in VZV vasculopathy CSF¹⁴⁴, contributing to a robust inflammatory infiltrate comprised of neutrophils, macrophages and T cells consistent with a vasculitis¹¹. Inflammation-associated disruption of the internal elastic lamina, progressive accumulation of myofibroblasts in the intima and decreased smooth muscle cells in the media seen in VZV vasculopathy arteries may alter arterial calibre and contractility, as well as disruption of arterial wall integrity, leading to ischaemic or haemorrhagic stroke, aneurysm formation and other vascular abnormalities. These same mechanisms probably apply when VZV is deposited in extracranial arteries. Aside from direct infection of cerebral arteries, emerging preliminary evidence indicates that non-infectious, pathogenic exosomes from individuals with HZ can induce inflammation, potentially worsening the vasculitis, and facilitate a hypercoagulable state leading to clot formation¹⁴². Finally, analyses of VZV vasculopathy CSF and virus-infected brain vascular adventitial fibroblasts indicate that VZV vasculopathy results in amyloid deposition, which can perpetuate inflammation and cytotoxicity even after virus is cleared^{145,146}.

Other complications. VZV can reactivate from one or more cranial nerves and cause corresponding unilateral disease such as facial paralysis, facial pain, hearing loss, tinnitus, vertigo, burning mouth syndrome, spontaneous tooth exfoliation (tooth loss), double vision and other vision problems (diplopia, keratitis, uveitis and retinal necrosis) with or without associated zoster rash^{147–150}. VZV can produce unilateral diaphragmatic paralysis owing to phrenic nerve injury^{151,152}. VZV reactivation can produce myelopathy characterized by an enhancing serpiginous lesion (extending in a curved pattern, snake-like) in the cord on imaging. In addition, it can produce a spinal cord infarction^{18,153}. VZV can reactivate from enteric neurons and cause gastrointestinal disease (enteric zoster) including oesophagitis, severe abdominal pain, ulcers, gastroparesis, Ogilvie's syndrome

(acute colonic pseudo-obstruction), inflammatory bowel disease and bleeding²¹. VZV can also produce myocarditis, pericarditis, hepatitis, pancreatitis, pneumonia and other organ diseases. It is important to note that all these clinical manifestations of VZV reactivation can occur without rash or be temporally separated by months after HZ, making diagnosis challenging.

Association with dementia. Interest is growing in the association between VZV reactivation, manifesting as HZ, and dementia risk, because VZV reactivation may be a potential modifiable risk factor for dementia. Although evidence is mixed, some epidemiological studies show an increased risk of dementia diagnoses following HZ, particularly when HZ is severe or associated with CNS or ophthalmic complications²⁵. HZ vaccination is also associated with dementia protection in some studies, although it remains unclear whether associations are causal^{154–162}. Nevertheless, among all dementia risk factors, VZV has arguably the strongest mechanistic evidence of contributing to established pathologies of dementia (neuroinflammation, amyloid deposition and vascular disease), thereby accelerating disease progression.

Similar to dementia, VZV reactivation causes neuroinflammation. Although HZ is considered a 'peripheral' disease with skin rash, HZ in the SVV model in NHPs demonstrate that multiple pro-inflammatory cytokines are also transiently elevated in CSF¹⁶³. Furthermore, although VZV reactivation can manifest as HZ in a specific dermatome, the virus can also reactivate in other ganglia, such as trigeminal ganglia and autonomic ganglia of the head and neck, and cause CNS disease with or without a rash (namely VZV vasculopathy), with associated neuroinflammation (elevated CSF IL-6 and IL-8 compared with controls)^{143,144}. Studies on circulating HZ-associated exosomes from patients have reported that these exosomes also promote a persistent pro-inflammatory state¹⁴².

Multiple in vitro and in vivo studies show that VZV promotes an amyloidogenic state that can further accelerate dementia. Compared with controls, HZ plasma had significantly ($P < 0.05$) elevated amyloid that correlated with A β 42 and amylin levels; and increased amyloid aggregation with addition of exogenous A β 42 or amylin¹⁶⁴. Compared with controls, VZV vasculopathy CSF had increased total

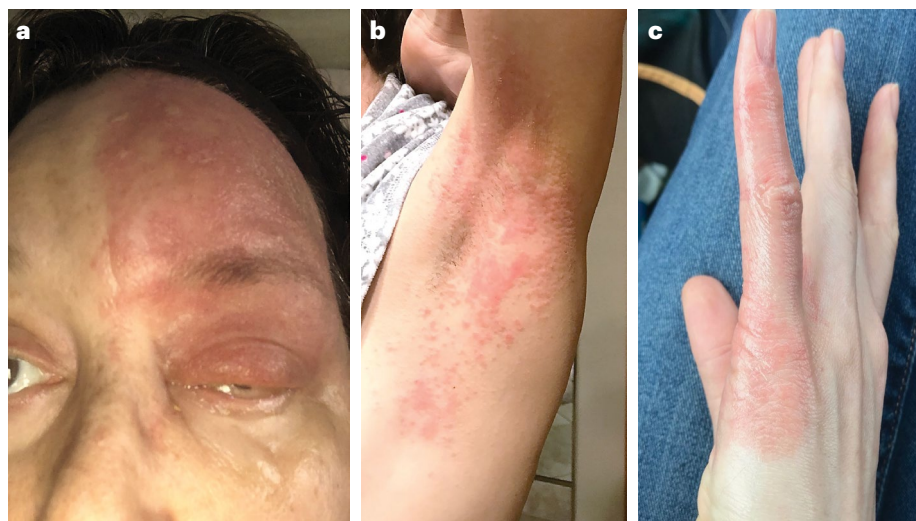


Fig. 3 | Representative images of varicella zoster virus reactivation. **a**, Herpes zoster ophthalmicus owing to varicella zoster virus reactivation from the left trigeminal ganglia (cranial nerve V1, ophthalmic branch). **b,c**, Herpes zoster owing to varicella zoster virus reactivation from left C8 sensory ganglia resulting in dermatomal distribution of the rash under the arm with various stages of blister formation (**b**), and on the medial left hand with an atypical, non-vesicular rash with erythema (**c**).

amyloid that positively correlated with amylin and anti-VZV antibody levels; A β 40 was reduced and A β 42 unchanged¹⁴⁵. The direct role of VZV infection in amyloid formation was demonstrated in VZV-infected primary human astrocytes, primary human brain vascular adventitial fibroblasts and primary human perineurial cells; intracellular VZV antigen co-localized with amylin, A β peptides and amyloid; uninfected bystander cells did not contain these proteins or peptides^{145,146,165}. Compared with controls, conditioned supernatant from VZV-infected cells promoted aggregation of amyloidogenic peptides, in part through VZV gB peptides that self-aggregate to form amyloid fibrils seen on transmission electron microscopy and that serve as a nidus for amyloid propagation¹⁶⁵. Importantly, VZV gB peptides are also catalytic and can induce misfolding of amylin and A β 42 into amyloid fibrils¹⁶⁵. The formation of amyloid fibrils by viral peptides is not unique to VZV and has been shown in HIV and HSV-1, as well as other pathogens^{166,167}.

Aside from VZV reactivation contributing to neuroinflammation and amyloid deposition seen in Alzheimer's disease and related dementias, HZ is also associated with an increased risk of cerebrovascular disease mediated by direct virus infection of cerebral arteries with pathological vascular remodelling and pro-inflammatory, prothrombotic exosomes (described in the 'VZV vasculopathy' section)^{8,10,11,168,169}. As cerebrovascular disease is a key feature of vascular dementia (the second most common form of dementia) and seen concurrently in other dementia subtypes, this raises the possibility that a subset of vascular disease in dementia represents a VZV vasculopathy. Indeed, targeted RNA sequencing of human brain vascular adventitial fibroblasts show that compared with uninfected fibroblasts, VZV-infected cells were enriched for pathways associated with Alzheimer's disease, amyloidosis and tauopathy, with upstream regulators similar to that seen in dementia (for example, amyloid precursor protein, apolipoprotein E, microtubule-associated protein tau, presenilin-1 and islet amyloid polypeptide)¹⁴⁶.

Finally, two cases of cerebral amyloid angiopathy showed VZV antigen and DNA co-localizing with amyloid in affected arteries¹⁷⁰. Taken together, the predominant mechanism by which VZV contributes to dementia progression is probably through its ability to produce cerebrovascular disease with associated neuroinflammation and amyloid deposition.

Diagnosis, screening and prevention

Diagnosis

Varicella, HZ and PHN. Diagnosis of varicella is based on clinical presentation with itchy, painful, fluid-filled blisters on the face, torso and limbs; diagnostic laboratory testing is not necessary in these cases. Despite receiving the varicella vaccine, an individual may later develop an atypical rash that is (1) not vesicular or widespread, representing primary infection with wild-type VZV and incomplete protection with the varicella vaccine; or (2) dermatomal in distribution, representing reactivation of the vaccine or wild-type strain. Thus, in cases of atypical rash, laboratory confirmation is needed to diagnose VZV infection (Table 1); sequencing to distinguish vaccine versus wild-type strain can also be done but would not change management¹⁷¹. Similarly, diagnosis of HZ is based on clinical presentation with itchy, painful vesicles in a unilateral, dermatomal distribution. HZ rash may be atypical, appearing as petechiae or raised, erythematous, non-fluid-filled lesions; therefore, laboratory confirmation is also needed in these cases (Table 1). However, it is important to note that for any unilateral, dermatomal-distribution rash that does not cross midline and persists >24 h, the diagnosis of HZ should be high on the differential diagnosis, and if confirmatory

testing is difficult to obtain or delayed, a trial of antivirals should be considered, with rapid resolution of rash if owing to VZV. Although the closely related alphaherpesviruses (HSV-1 and HSV-2) also reactivate in a dermatomal distribution, they typically present as a cluster of vesicles on a circular, erythematous base. Diagnostic testing for viral DNA and antigen can distinguish these alphaherpesviruses but treatment is with the same class of antiviral drugs, although at differing doses.

To confirm diagnosis of an atypical varicella or HZ rash (Table 1), the most straightforward diagnostic test is detection of VZV DNA by PCR from scabs, vesicular fluid or cells at the base of the lesion. Less sensitive and specific tests include detection of VZV antigen by immunohistochemistry and viral cultures. However, VZV is notoriously difficult to culture from skin scrapings; cultures are most successful from fluid within vesicles. Detection of VZV DNA in blood would be supportive of a VZV infection. Less specific tests are a Tzanck smear, wherein a positive test supports VZV or HSV infection.

Positive serum VZV IgM is supportive of a recent reactivation event (within a 6–8-week time period). A fourfold or greater rise in serum VZV IgG titre is diagnostic of VZV reactivation, yet it is infrequent that titres are measured before illness. It is important to note that a single positive VZV IgG only indicates prior exposure to VZV; it is not helpful in diagnosing active VZV disease because >90% of the global population have been exposed to VZV, harbour the latent virus and are serum VZV IgG-positive. Negative results for some individual tests do not exclude VZV disease because VZV DNA extraction from dried skin lesions may be challenging. Serum VZV IgM is only transiently positive during acute reactivation but can be negative during persistent disease. If both VZV DNA and antigen are absent in the rash, then the rash is unlikely to be owing to VZV. If tests are inconclusive but an atypical rash follows a classic dermatomal-distribution pattern, not crossing midline, a trial of antivirals can be considered for atypical HZ.

Neuropathic pain at the site of HZ can persist for weeks, even after rash has fully resolved. However, if pain persists for >3 months, individuals are diagnosed with PHN, which is notoriously difficult to manage and is among the most common causes of suicide in older adults with chronic pain¹⁷². No additional laboratory testing is needed beyond the clinical history of HZ, neuropathic pain occurring concurrently in the same dermatome and pain persisting for >3 months after HZ onset. Physical examination demonstrates unilateral dermatomal-distribution disease, cutaneous scarring from HZ, sensory alterations such as pain from light touch (allodynia) or increased pain sensitivity (hyperalgesia) and autonomic dysfunction (that is, excessive or decreased sweating in the same dermatome(s))¹⁷³. Prospective cohort studies show a 20–30% risk of PHN in older patients with HZ, with age being the most important independent risk factor for PHN, possibly owing to decreased cellular immune function^{174,175}.

VZV disease beyond skin rash. Diagnosis of VZV disease without rash or temporally remote from rash is more challenging. VZV disease encompasses a wide spectrum of neurological disorders including *zoster sine herpette*, VZV vasculopathy (transient ischaemic attacks, stroke and aneurysm), encephalitis, meningitis, myelopathy and wide a spectrum of systemic disease affecting multiple organs, including the eye (keratitis and retinitis), gastrointestinal tract (gastritis and gastroparesis) and, rarely, the cardiovascular system (myocarditis, pericarditis and myocardial infarction).

A diagnosis of *zoster sine herpette* should be suspected if pain presents in a unilateral dermatomal distribution and examination findings are consistent with PHN without a prior history of HZ and with exclusion

Table 1 | Disease management for varicella zoster virus infection

Condition	Clinical presentation	Diagnosis	Treatment
Varicella	Disseminated vesicular rash	No additional diagnostic testing required For atypical rashes: VZV DNA PCR of scabs, vesicular fluid or cells at the base of the lesion + VZV antigen by immunohistochemistry + viral cultures of rash/fluid + VZV DNA PCR blood + serum VZV IgM + fourfold increase in VZV IgG titre over baseline + Tzanck smear (nonspecific for VZV or HSV)	For healthy children, no antivirals required. Symptomatic treatment of itching (for example, calamine lotion) and pain (NSAIDs, excluding aspirin and ibuprofen) For individuals who are >12 years of age, have chronic skin or lung disease, receive long-term salicylate or steroid therapy, are pregnant or have weakened immune systems, oral antivirals (valacyclovir, famciclovir) should be started within the first 24 h of rash onset IV antiviral therapy ± corticosteroids for severe disease (acyclovir first line; foscarnet if acyclovir fails)
Herpes zoster	Unilateral dermatomal-distribution vesicular rash	No additional diagnostic testing required For atypical rashes, diagnostic tests similar to varicella	Oral antivirals ± corticosteroids and symptomatic pain management; antimicrobials if secondary infection develops (for example, <i>Staphylococcus aureus</i>) IV antivirals ± corticosteroids for complicated cases and immunocompromised patients
<i>Zoster sine herpete</i>	Unilateral dermatomal pain without rash	Exclude other aetiologies including compressive/structural lesion by MRI + intrathecal synthesis of anti-VZV antibodies + VZV DNA PCR, CSF or blood + serum VZV IgM + fourfold increase in VZV IgG titre over baseline	Oral antivirals ± corticosteroids and symptomatic pain relief IV antivirals ± corticosteroids for severe, intractable pain where oral antivirals failed
VZV keratitis	Recent history of herpes zoster ophthalmicus on the affected side, often with Hutchinson's sign (rash on tip, side or root of nose)	Ophthalmology examination required with various findings such as pseudodendrites, stromal keratitis, endothelitis, uveitis, decreased corneal sensation + VZV DNA by PCR on corneal scraping or tear fluid, blood + serum VZV IgM + fourfold increase in VZV IgG titre over baseline	Oral antivirals, corticosteroids and symptomatic pain relief Interventions to prevent further corneal damage (for example, lubricating eye drops) Antiviral prophylaxis owing to recurrence
VZV CNS disease	Stroke or TIA, focal neurological deficits (cranial nerve deficits, motor and/or sensory abnormalities); cognitive changes; new headache; word-finding difficulties	Brain imaging confirms stroke (for example, MRI, CTA), cranial nerve enhancement, or spinal cord lesions + intrathecal synthesis of anti-VZV antibodies + VZV DNA PCR, CSF or blood + serum VZV IgM + fourfold increase in VZV IgG titre over baseline	IV antivirals ± corticosteroids
VZV systemic disease	Systemic or vascular disease of unclear aetiology	May be a current or remote history of HZ + VZV DNA PCR blood, affected tissue if possible + serum VZV IgM + fourfold increase in VZV IgG titre over baseline For VZV GI disease, can do VZV DNA PCR on saliva but not an established test	Oral antivirals ± corticosteroids and symptomatic pain relief as required IV antivirals ± corticosteroids for severe, intractable pain where oral antivirals failed

The diagnostic approach and treatment strategy vary according to the clinical presentation. Diagnosis relies on a combination of clinical features and laboratory confirmation, including serology (VZV IgM/IgG), molecular testing (VZV DNA by PCR, VZV antigen by immunohistochemistry) and, where indicated, CSF analysis. Treatment is guided by disease severity, host immune status, and risk for nephrotoxicity. CNS, central nervous system; CSF, cerebrospinal fluid; CTA, computed tomography angiography; GI, gastrointestinal; HSV, herpes simplex virus; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; TIA, transient ischaemic attack; VZV, varicella zoster virus.

of compressive or structural spinal cord or nerve lesions by imaging (Table 1). For *zoster sine herpete*, as well as neurological manifestations of VZV disease, the best test for diagnosis is detection of intrathecal anti-VZV IgG or IgM synthesis followed by detection of VZV DNA in CSF by PCR, which is only 30% sensitive in cases of VZV vasculopathy^{10,135}. Detection of VZV DNA in blood by PCR, serum VZV IgM positivity and a fourfold increase in VZV IgG titre would also be supportive of the diagnosis. Quantitative VZV IgG titre can potentially be used to follow course of disease – with a decline seen after antiviral therapy and an increase seen during another reactivation event; however, no studies using this technique in a case series or prospective study have been published. For VZV systemic disease, the presence of varicella or HZ during acute presentation or months prior would be supportive of diagnosis; there are no clear studies on how remote the rash can be before systemic manifestations of VZV disease. However, epidemiological studies show that stroke risk is elevated up to 1 year after rash^{22–24}. Overall, diagnosis of VZV systemic disease is similar to that of atypical rash, except that

rash-based assays are excluded when a rash is not present at the time of examination. Finally, detection of VZV DNA in saliva is indicative of reactivation but there are no standardized diagnostic procedures¹⁷⁶ and yields are often too low for VZV DNA detection.

It is important to note that HSV-1 and HSV-2 rashes can appear similar to VZV rashes but tend to be recurrent in the same dermatome and are typically clustered in a patch. Thus, HSV should also be considered with HSV DNA PCR of the lesions and immunostaining for HSV antigens on biopsy samples. Unfortunately, there are no commercially available HSV IgM tests because they were deemed nonspecific. If VZV testing is negative, resolution of the single or clustered rash with antivirals would be supportive of HSV reactivation.

Screening

Serum VZV IgG positivity in non-immunocompromised patients indicates past infection and the level of immunity to VZV, with >90% of the world population harbouring the latent virus and expected to test

positive for VZV IgG. Thus, VZV IgG screening would only be used to test whether individuals have been exposed to VZV (and thus have latent virus and immune protection), including women planning a pregnancy, because developing varicella during pregnancy can be harmful to the fetus⁴⁰; individuals who have been vaccinated (two doses), if there is concern about whether they can mount an antibody response (although VZV IgG titres are typically lower with vaccine immunity); individuals working with live virus in laboratory settings, although theoretical because no reports of laboratory infection have been documented; individuals in settings with high risk of transmission (for example, daycares, schools and nursing homes); and individuals who will be receiving immunosuppressive therapy that may increase the risk of severe varicella if VZV IgG-negative.

Prevention

Varicella vaccination. For prevention of primary varicella infection, live attenuated vaccines based on the Oka strain of VZV (Varivax from Merck, Varilrix from GlaxoSmithKline (GSK), OkaVax from Biken and Baiké from Chanchung Biotechnology) or on other VZV-attenuated strains (Barycela from GC Biopharma and SKY Varicella from SK Bioscience) are recommended¹⁷⁷. Varicella vaccines were first administered in healthy children in Japan and South Korea in 1989 (ref. 178) and were subsequently introduced as part of the Universal Immunization Program (UIP) in the USA in 1995 (refs. 179,180). Varicella vaccination is included in the UIPs of 44 countries and 29 countries have adopted the complete vaccine schedule with two doses¹⁸¹. In India, it is available only in the private sector¹⁸². The cost–benefit analysis of the varicella vaccine in the USA showed that the benefits of administering the vaccine outweighed the cost owing to the number of school days missed by children and work absence for their caretakers¹⁸³. In addition, complications of varicella were also reduced following varicella vaccination, including severe CNS complications¹⁸⁴ and secondary bacterial infections¹⁸⁵. Despite strong evidence regarding the immunogenicity and efficacy of the varicella vaccine in several countries, some questions about the introduction of the varicella vaccine in the UIP still exist¹⁸⁶. The belief in lifelong immunity to VZV disease after primary infection and the high cost of the varicella vaccine (US\$23.76) are major obstacles in introducing varicella vaccination in the UIP in India^{180,187}.

In Europe, the first two countries to adopt universal vaccination against varicella were Italy in 2003 (but initially only in some pilot regions) and Germany in 2004 (ref. 188). By 2018, ten additional European countries had followed (Andorra, Cyprus, Austria, the Czech Republic, Spain, Latvia, Finland, Greece, Hungary and Luxembourg). In other European countries, such as France, the vaccination is currently recommended only in certain risk groups¹⁸⁹.

Varicella vaccination became part of the routine childhood vaccination programme offered within the National Health Service in the UK in January 2026. The vaccine is administered in two doses (at 12 and 18 months of age) and is included in the combined MMRV vaccine (measles, mumps, rubella and varicella). The initial recommendation not to provide routine vaccination was based on modelling that predicted that the decline in circulating varicella caused by the vaccine would decrease exogenous boosting of immunity to VZV and, consequently, increase in VZV reactivation (HZ) cases. In 2023, this modelling was revisited to incorporate the real-world data from the vaccination programme implemented in the USA since 1995 (ref. 190). This showed that the duration of protection of circulating varicella for prevention of HZ was much shorter than initially predicted and

that implementation of a childhood varicella vaccination programme would be cost-effective¹⁹¹.

In the Asia Pacific region, only a few countries have introduced varicella vaccination in the UIP. In Japan, two doses of varicella vaccine were rolled out in 2014; one dose of the varicella vaccine provided 76% efficacy while two doses gave protection up to 94%^{181,192}. In Taiwan, after the introduction of the varicella vaccine there was an 82% reduction in the incidence of varicella and an 85% reduction in hospitalizations¹⁹³. Publicly funded varicella vaccination programmes (with two doses) have been implemented for children in Hong Kong in 2004. However, there is a one-dose schedule in Taiwan (2004), South Korea (2005) and New Zealand (2017)³³. Among the southeast Asian countries, only a few countries, including China, India, Indonesia, Malaysia, Singapore, the Philippines and Thailand, recommend varicella vaccination, but it is not part of the UIP in these countries³³. In 2004 in Sri Lanka, it was introduced in the private sector, but is not part of the UIP³⁴.

In the USA, varicella vaccination is administered as a routine two-dose series. The first dose is recommended at 12–15 months of age, with the second dose administered at 4–6 years of age^{194,195}. For adolescents and adults aged 13 years and older without evidence of immunity, two doses should be administered 4–8 weeks apart. Two doses of varicella are ~90% effective at preventing varicella, with vaccine effectiveness against severe varicella approaching 100%^{194,195}. A combination of measles, mumps, rubella, and varicella (the MMRV vaccine; Proquad from Merck and Priorix Tetra from GSK) is also available for children aged 12 months to 12 years. Varicella vaccination with the live attenuated vaccine is not indicated for immunosuppressed individuals.

HZ vaccination. A recombinant zoster vaccine (RZV; Shingrix from GSK) is the current standard for preventing both HZ and PHN in the USA. Shingrix, a two-dose subunit vaccine composed of recombinant VZV glycoprotein E formulated with the AS01B adjuvant system, received FDA approval in 2017 for adults aged 50 years and older and is now recommended as the preferred vaccine over the earlier live attenuated formulation (Zostavax)¹⁹⁶. Clinical trials demonstrated high efficacy: two doses prevented 97% of HZ cases in adults aged 50–69 years and 91% in adults aged 70 years and older, with similarly strong protection against PHN – 91% and 89% in these respective age groups. These results far exceed those of the formerly available live attenuated vaccine (Zostavax), which provided ~51% overall protection and exhibited substantial decline with advancing age^{196,197}.

The RZV series consists of two intramuscular doses administered 2–6 months apart. Vaccination is recommended regardless of prior HZ history or prior receipt of Zostavax but should not be given during active VZV infection¹⁹⁶. The Advisory Committee on Immunization Practices has also expanded RZV recommendations to include immunocompromised adults aged 19 years and older who are, or will become, at increased risk for HZ because of underlying disease or therapy. For individuals who require faster protection, the second dose may be administered 1–2 months after the first¹⁹⁶.

In the UK, the Shingrix vaccine is currently offered as a two-dose regimen by the National Health Service to all adults turning 65 years old, adults aged 70–79 years, and to individuals more than 18 years old who are severely immunocompromised. Until 2019, the Zostavax (live-attenuated vOka) vaccine was offered as one dose regimen to 70–79-year-old adults in the UK. In the rest of Europe, there is heterogeneity in the adoption of the HZ vaccine, as in the case of the varicella vaccine. The HZ vaccine is recommended in 17 of the 27 European Union member states and there is also heterogeneity in the age recommendation, with some countries

recommending the vaccination of adults more than 50 years old and others more than 60 or 65 years old¹⁹⁸. Currently, both Zostavax and Shingrix are available in India. Shingrix was recently rolled out by GSK in April 2023 in India; however, the cost is high (US\$118.80)¹⁸².

Management

Antiviral therapy

Currently, only one class of antiviral drugs is available for VZV infection globally: nucleoside–nucleotide analogues, which inhibit viral DNA synthesis and are active only in cells with replicating virus. These agents do not eradicate latent infection. Acyclovir is selectively monophosphorylated by VZV thymidine kinase and subsequently converted by host cellular kinases to acyclovir triphosphate, which competitively inhibits viral DNA polymerase and acts as a DNA chain terminator¹⁹⁹. Valacyclovir is the L-valyl ester prodrug of acyclovir with superior oral bioavailability (fraction of oral dose that reaches systemic circulation, ~55% versus 15–20%), enabling less frequent dosing^{200,201}. Famciclovir is the prodrug of penciclovir, which undergoes similar thymidine kinase-dependent activation and inhibits viral DNA polymerase through an analogous mechanism²⁰². Acyclovir is the only drug in this class with an IV formulation. Brivudine is also a nucleoside analogue with potent antiviral activity against VZV that is used in several European countries (except the UK) and China⁴⁰. It is not approved in the USA or Canada.

The three widely used oral antivirals (valacyclovir, famciclovir and acyclovir) demonstrate comparable efficacy for uncomplicated HZ, with the choice often driven by dosing convenience, cost and availability. Valacyclovir and famciclovir offer the advantage of less frequent dosing compared with acyclovir, potentially improving adherence. All agents require dose adjustment in patients with reduced renal function to prevent drug accumulation and toxicity²⁰³. Topical acyclovir-containing creams are used for herpes simplex lesions but are not standard treatment for VZV infections. VZV is less sensitive to acyclovir than HSV, in part because of differences in viral thymidine kinase, and effective treatment of VZV may require systemic therapy if oral antivirals are ineffective^{204–206}. In Japan, a new class of an oral antiviral drug (amenamevir; sold under the brand name Amenalief) is available for the treatment of HZ as well as recurrent herpes simplex. Unlike the nucleoside analogues above, amenamevir inhibits the viral helicase–primase enzyme complex, preventing viral DNA replication. It is highly effective against acyclovir-resistant VZV and HSV isolates²⁰⁷. For varicella, antiviral medication is FDA-approved in the USA and is recommended for individuals at risk for complications (see the ‘Disease-specific management’ section).

IV antiviral therapy. IV acyclovir is indicated for severe or complicated VZV disease, including disseminated HZ, HZ ophthalmicus with ocular involvement, VZV vasculopathy, meningoencephalitis, myelitis or other CNS manifestations. IV therapy is also recommended for immunocompromised patients with complicated VZV infection and for patients unable to tolerate or absorb oral medications. Treatment duration is typically 10–14 days, depending on disease severity and clinical response. Close monitoring of renal function and adequate hydration are essential during IV acyclovir therapy.

Antiviral resistance. In some cases, IV acyclovir may be ineffective. This can occur, in part, if an acyclovir-resistant VZV strain is present (uncommon; however, can occur in severely immunocompromised patients through mutations in the viral thymidine kinase or DNA

polymerase genes)²⁰³. In these cases, IV foscarnet can be used. Foscarnet is a pyrophosphate analogue that directly inhibits viral DNA polymerase without requiring thymidine kinase activation and is the treatment of choice for resistant infections. For acyclovir-resistant VZV, cidofovir (IV) can also be considered for off-label use, although it has only been FDA-approved for cytomegalovirus infections and has substantial nephrotoxicity²⁰³.

Safety and adverse effects. Oral acyclovir, valacyclovir and famciclovir are generally well tolerated. Adverse effects include nausea, headache, abdominal discomfort or pain, and diarrhoea. The most substantial safety concern is nephrotoxicity, particularly with IV acyclovir, which can cause crystalline nephropathy through precipitation in renal tubules²⁰⁸. Risk factors include dehydration, rapid infusion, high doses and pre-existing renal insufficiency²⁰⁸. Adequate hydration and dose adjustment for renal function are essential preventive measures. Similarly, amenamevir is well tolerated, with reported adverse effects of mild abdominal discomfort or pain, headache, or temporary elevations in liver or renal enzymes. Brivudine is contraindicated with fluoropyrimidines (used for certain cancer treatments) such as 5-fluorouracil, which can be fatal²⁰⁹.

Neurotoxicity is a less common but serious complication, manifesting as confusion, hallucinations, tremors, myoclonus or seizures²¹⁰. Neurotoxic effects are more likely with high-dose valacyclovir or IV acyclovir, or in patients with renal impairment leading to drug accumulation²¹⁰. Symptoms typically resolve upon discontinuation or dose reduction²¹⁰.

Foscarnet, used for acyclovir-resistant VZV, carries substantial toxicity, including nephrotoxicity, electrolyte disturbances (hypocalcaemia, hypomagnesaemia, hypophosphataemia and hyperphosphataemia) and genital ulcerations²¹¹. Close monitoring of renal function and electrolytes is mandatory during foscarnet therapy, with aggressive hydration and electrolyte replacement as needed. Cidofovir also has a substantial nephrotoxicity risk.

Drug shortages, particularly of IV acyclovir, represent an important practical challenge in VZV management. These shortages are not restricted to low-resource settings but rather occur when there are manufacturing delays, raw material shortages and increased demand. As an example, the American Society of Health-System Pharmacists noted IV acyclovir shortages in 2021, 2022, 2024 and, most recently, in 2026. Healthcare systems should establish protocols for prioritizing IV antiviral use in the most critically ill patients and consider alternative formulations or agents when shortages occur.

Disease-specific management

Varicella. Varicella is typically a self-limiting disease. For healthy individuals with uncomplicated varicella, the Centers for Disease Control and Prevention and the American Academy of Paediatrics do not routinely recommend antiviral medications²¹². For individuals at risk for severe varicella complications, such as all individuals who are >12 years of age, have chronic skin or lung disease, receive long-term salicylate or steroid therapy, are pregnant or have weakened immune systems, oral antivirals should be started within the first 24 h of rash onset. Oral valacyclovir and famciclovir are preferred over acyclovir because of less frequent dosing. IV antiviral therapy is reserved for severe disease (for example, pneumonia and encephalitis) and immunocompromised patients, with IV acyclovir being the preferred therapy and foscarnet used only in cases in which varicella complications progress despite IV acyclovir. Supportive care is the mainstay of

treatment for varicella. Itching can be relieved with calamine lotion, oatmeal baths (or colloidal baths) and cool compresses. Fever and pain can be relieved with non-aspirin medications, such as acetaminophen. Ibuprofen should be avoided if possible because ibuprofen has been associated with life-threatening bacterial skin infections. Aspirin should also not be used in children with varicella because it is associated with Reye's syndrome that affects the liver and brain and is potentially fatal.

Herpes zoster. For acute HZ, antiviral treatment should ideally be initiated within 72 h of rash onset and should not be delayed for laboratory confirmation²¹³. Early treatment reduces viral replication, accelerates rash healing, and decreases the severity and duration of acute pain. Although the benefit of antivirals is greatest when started early, many experts also start treatment beyond 72 h of onset if new lesions are still forming, if patients are immunocompromised, or if there is concerning involvement such as ophthalmic, neurological or extensive cutaneous disease^{213,214}. Similar to management of individuals with varicella complications, oral antivirals (valacyclovir and famciclovir) are prescribed²⁰³; for complicated HZ, IV antivirals are prescribed²⁰³. Symptomatic treatment of neuropathic pain is described below.

HZ ophthalmicus. Patients with HZ affecting the ophthalmic division of the trigeminal nerve (V1 distribution; the forehead and around the eye) require urgent ophthalmologic evaluation, particularly if the nasociliary branch is involved (Hutchinson's sign)²¹⁵. Oral or IV antiviral therapy should be initiated promptly, along with topical corticosteroids under ophthalmologic guidance to reduce intraocular inflammation²¹⁵. Early intervention reduces the risk of vision-threatening complications.

CNS complications. VZV vasculopathy, meningoencephalitis and myelitis require IV acyclovir. CSF analysis can support the diagnosis with intrathecal synthesis of VZV antibodies more sensitive than detection of VZV DNA. Adjunctive corticosteroids are sometimes used for vasculopathy, although evidence is limited. Long-term suppressive antiviral therapy may be considered in patients who are immunocompromised and at risk of recurrent reactivations following CNS VZV disease.

Management of patients who are immunocompromised. Individuals with impaired cell-mediated immunity, including those with HIV or AIDS, those with haematological malignancies, solid organ or haematopoietic stem cell transplant recipients, and patients on immunosuppressive therapy, are at increased risk for severe, disseminated or prolonged VZV disease. These patients typically require IV acyclovir initially, with transition to oral therapy once clinical improvement is evident²⁰³. Extended treatment courses and suppressive antiviral therapy may be necessary to prevent recurrence.

Symptomatic and adjunctive management

Acute pain management. Adequate analgesia during the acute phase of HZ is important for patient comfort. Options include acetaminophen and other non-steroidal anti-inflammatory drugs (excluding ibuprofen, which is associated with life-threatening bacterial skin infections), opioids for moderate-to-severe acute pain and adjunctive agents such as gabapentin or pregabalin, which can be initiated early for neuropathic pain control²⁰³.

Corticosteroids. Oral corticosteroids may be considered as adjunctive therapy to the antiviral treatment in patients more than 50 years

of age who are immunocompetent with moderate-to-severe acute pain. Corticosteroids can reduce acute pain severity and improve QoL during the acute phase but do not prevent PHN^{203,216}. Corticosteroids should be avoided in patients who are immunocompromised, owing to the risk of disseminated VZV disease. Corticosteroids should only be administered concurrently with antivirals to avoid immunosuppression and increased VZV reactivation if used alone.

PHN. Management of established PHN requires a multimodal approach and remains challenging. First-line pharmacological options include gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants (amitriptyline and nortriptyline) and topical lidocaine patches or capsaicin cream. Opioids may be necessary for refractory cases. Non-pharmacological interventions, including physical therapy, cognitive behavioural therapy, nerve blocks and nerve stimulators, may provide additional benefit for selected patients²⁰³.

Quality of life

Varicella

Each episode of varicella leads to one primary healthcare visit on average²¹⁷, with most indirect costs resulting from workdays lost by caregivers of infected pre-school children²¹⁸. As varicella is self-limited, QoL is only affected during the few weeks of acute disease when the individual may have a fever and be home-bound because of virus-associated fatigue and pain.

HZ, PHN and other VZV diseases

HZ is associated with a substantial disease burden, which is expected to increase worldwide with population growth and ageing⁴³. The most common post-HZ complication is PHN, followed by ocular and cutaneous complications²¹⁹. Projected annual outcomes for an unvaccinated population in the USA include 1.1 million HZ cases, 114,000 PHN cases and 43,000 ocular complications, resulting in approximately 67,000 quality-adjusted life years lost. This equates to annual costs of US\$2.4 billion in direct medical costs and productivity losses²²⁰.

During the acute stage of HZ, intense neuropathic pain and the appearance of vesicular lesions markedly reduce individuals' QoL. Although most individuals experience symptom resolution within a few weeks and recover without persistent deficits, a considerable proportion will develop PHN. Specifically, there is a 20–30% risk of PHN in older patients with HZ^{174,175}. For these patients, the long-term impact on QoL can mirror the burden associated with severe medical or major psychiatric illnesses.

PHN affects multiple domains of well-being, extending beyond pain to influence physical functioning, emotional health and social engagement. Patients frequently report chronic fatigue, disrupted sleep, difficulty concentrating, depressed mood, anxiety, diminished appetite, unintentional weight loss and withdrawal from social interactions^{221,222} (Box 1). These symptoms commonly interfere with routine activities of daily living, including personal care, mobility, shopping, cooking and housekeeping, often leading to reduced independence and prolonged periods at home^{222,223}. Pain intensity is a major determinant of the extent of QoL disruption. In a cohort of 50 patients with HZ with pain scores ≥ 4 on a 10-point scale, participants identified substantial limitations in daily functioning, particularly in their ability to work, sleep and derive enjoyment from day-to-day activities²²⁴.

For VZV disease manifestations beyond HZ, systematically collected QoL data are scarce, and patient outcomes vary considerably

Box 1 | Living with post-herpetic neuralgia (patient testimony)

I developed a painful rash along my left torso when I was 62 years old. I was diagnosed with shingles and treated with antivirals and pain medication. After the rash cleared, the pain stayed and I have suffered from severe post-herpetic neuralgia for the past 15 years.

The pain feels as if someone is pulling my nerves with a pair of pliers. It starts out aching and progresses to sharp pains moving around my left torso above the belt line. The pain is a 10/10 without medication. As the medication wears off, I get an oncoming, gradual, somewhat anticipated aching feeling progressing to a sharp bolt that makes me flinch with a pressing need to lie down.

My doctors have tried many treatments: over-the-counter anti-inflammatories, gabapentin, pregabalin, tricyclic antidepressants, benzodiazepines, lidocaine patches, three nerve blocks, chemical nerve ablation, ketamine infusions and even an implanted spinal cord stimulator, but none provided substantial relief. I also tried more than a dozen alternative treatments, including acupuncture, cold laser therapy, transcutaneous electrical nerve stimulation, physiotherapy, a gluten-free diet for 4 years, nutritional supplements (e.g., vitamin B12, C), topical anti-inflammatory creams and compounds created specifically for me, medicinal marijuana, and so on. Now, I am on

fentanyl patches and oxycodone for the breakthrough pain; these at least allow me to get out of bed.

I currently structure my day around the pain. Mornings are the hardest. I read and often lay down with fatigue and/or pain as early as 1–2 h after my first oxycodone in the morning. The medication tires me out, as does the pain, so I try not to schedule anything until around noon. Pain comes periodically during the day; in the afternoon I can generally space out the pain meds and evenings are usually better. I rest two to three times a day for 30–60 min.

Post-herpetic neuralgia affects my relationship with my wife and our social plans. I may need to alter plans or ‘double up on oxy’ to get through an event, which creates more fatigue and anxiety. I use Effexor and Mind Body Medicine Therapy affirmations like ‘I am safe, these are only neurons firing’ with only little success.

At this point, I have not lost all hope, but it can be very depressing. My hope now is more for controlling the virus. It controls me, but I am still walking and have been able to fly and visit family when I feel I can. More funded research is the key. I am hopeful I can at least control the pain better.

depending on clinical severity and the degree of functional recovery. In paediatric cases, intracranial VZV vasculopathy is frequently monophasic, with 80–90% of children achieving good neurological outcomes over the long term²²⁵. By contrast, ocular complications, most notably VZV keratitis, can lead to irreversible visual impairment, which can markedly disrupt activities of daily living and diminish overall QoL. The lack of comprehensive QoL evaluations across the diverse range of VZV-associated disorders highlights a critical gap and an opportunity for future investigation.

Outlook

As the global population ages and the prevalence of immunocompromising conditions increases, VZV reactivation will become an increasingly important clinical challenge. Patients with VZV-related disease will continue to present across primary care and specialty settings, necessitating enhanced clinical vigilance and diagnostic capabilities.

Current challenges

Several critical barriers impede optimal VZV prevention, diagnosis and treatment. A fundamental challenge is the difficulty in recognizing and diagnosing VZV disease, particularly in atypical presentations or in cases without the characteristic rash. Comprehensive education of healthcare providers regarding the full spectrum of VZV disease manifestations is essential, alongside public health initiatives to raise awareness among patients and the general population.

Therapeutic limitations present additional obstacles. The current antiviral options are limited, with nucleoside analogues carrying risks of nephrotoxicity and supply chain vulnerabilities. Furthermore, critical knowledge gaps remain regarding zoster vaccine efficacy beyond preventing HZ and PHN, particularly for preventing VZV vasculopathy and other neurological complications.

Progress in basic and translational VZV research is substantially hampered by the absence of a tractable small animal model. As an exclusively human pathogen, VZV cannot productively infect rodents

then reactivate to produce disease resembling that seen in humans. Notwithstanding, *in vitro* culture of human skin cells and skin tissues, as well as skin, T cell and sensory ganglion tissue xenografts in SCID mice, have provided valuable information on VZV pathogenesis. Human primary keratinocytes models recapitulating individual stages of epidermal differentiation have provided critical insights on how VZV interacts with epidermal differentiation for replication^{68,70,71}. Skin, T cell and sensory ganglion xenografts have each been instrumental in defining the cellular tropism of VZV and, when infected with recombinant viruses, in assigning *in vivo* functions to individual viral genes that cannot be resolved in cultured cells^{61,64,226–228}. These models remain underexploited and could be applied more broadly to dissect the underlying mechanisms driving VZV latency, evaluate candidate antivirals and vaccines, and, when combined with reconstitution of a human immune system, to interrogate virus–host immune interactions in a setting that more closely mirrors human infection. Furthermore, although SVV in NHPs recapitulates the full spectrum of VZV disease, financial and ethical constraints limit widespread NHP research. Overall, these limitations create a disproportionate gap in fundamental knowledge about a virus that infects more than 90% of the world’s population.

Establishing definitive causality between VZV and neurological sequelae, including stroke, cardiovascular disease and dementia, remains challenging despite robust epidemiological associations. The primary obstacle is the paucity of detectable VZV nucleic acids or antigens in affected tissues at the time of analysis or autopsy. However, recent breakthroughs demonstrating the pathogenic role of non-infectious VZV-induced extracellular vesicles offer promising mechanistic insights, in addition to direct virus infection, that may help resolve this paradox¹⁴².

Priorities for the next decade

Addressing these challenges will require coordinated efforts across prevention, therapeutics, research and implementation.

Expanding vaccination and prevention. Universal implementation of HZ vaccination programmes remains a global health priority, particularly in low-income and middle-income countries. Longitudinal studies must clarify vaccine efficacy against the full spectrum of VZV complications beyond HZ and PHN, including VZV vasculopathy and neurological sequelae. Research into optimal vaccination strategies for immunocompromised populations and potential booster dose requirements will be essential for comprehensive prevention.

Developing novel therapeutics. The antiviral pipeline requires urgent expansion beyond nucleoside analogues. Priorities include developing agents with alternative mechanisms of action, improved oral bioavailability and reduced nephrotoxicity. Specifically, the development of drugs that synergize with the mechanisms of action of nucleoside analogues, such as alternate viral and cellular targets, as well as topicals, is likely to provide considerable benefit to patients. Ensuring stable drug supply chains and stockpiling strategies will mitigate shortages during critical situations.

Advancing diagnostics and establishing causality. Rapid, point-of-care diagnostic tests, particularly for atypical presentations without rash, would improve clinical management. Biomarkers predictive of disease severity and complications are needed for personalized treatment approaches. Large-scale prospective cohort studies with standardized methodologies are essential to definitively establish the role of VZV in stroke, dementia and other chronic neurological conditions. Mechanistic investigations exploring extracellular vesicles, persistent viral proteins and immune dysregulation should be prioritized.

Overcoming research infrastructure barriers. The development of improved model systems, such as human organoids, induced pluripotent stem cell-derived neurons and engineered rodent models, would accelerate fundamental VZV research. Alternatively, international consortia for coordinated NHP studies could maximize scientific value while addressing ethical and financial constraints. Increased research funding commensurate with VZV's global disease burden is critical.

Implementation and education. Comprehensive educational initiatives should target healthcare providers across specialties, emphasizing recognition of atypical presentations and evidence-based management. Public awareness campaigns highlighting vaccination importance and early symptom recognition would improve health-seeking behaviours. These efforts should align with WHO frameworks for vaccine-preventable diseases, including strengthening surveillance systems, ensuring equitable vaccine access and establishing global registries for VZV complications to inform evidence-based policy development.

Harnessing artificial intelligence and computational approaches. Artificial intelligence and advanced computational tools represent a transformative opportunity for both VZV clinical management and fundamental research. On the clinical side, machine learning applied to large-scale electronic health records holds considerable promise for identifying individual risk factors for severe varicella, HZ and its complications, refining treatment algorithms and quantifying the real-world durability of vaccine-induced protection across diverse populations. In the laboratory, these same tools are positioned to accelerate breakthroughs that have been constrained by the complexity of VZV biology. For example, artificial intelligence-assisted structural biology and protein interaction mapping can illuminate how VZV

proteins exploit human cellular machinery; computational genomics can expose vulnerabilities in the viral life cycle; and integrating artificial intelligence-driven transcriptomic and proteomic analyses of human tissue bank samples of ganglia harbouring latent VZV can help resolve the molecular events governing the establishment of latency and reactivation, one of the most intractable problems in VZV biology. Together, these tools have the potential to accelerate the timelines for antiviral drug discovery, potentially delivering new therapeutic options for individuals who bear the greatest burden of VZV disease.

Published online: 03 September 2026

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Acknowledgements

Publication of this work was made possible by NIH grants 1R01AG079193 (to M.A.N.), 1R01AG085406 (to A.N.B.), 1R21AI176110 (to A.N.B.) and generous gifts from J. and W. Stapleton, J. and T. Bechtolsheimer and the Kallman Foundation (to M.A.N.). C.W.-G. is supported by a Wellcome Career Development Award (no. 225868/Z/22/Z).

Author contributions

Introduction (M.A.N. and A.N.B.); Epidemiology (M.A.N., A.N.B. and C.W.-G.); Mechanisms/pathophysiology (M.A.N., R.M., J.B., A.N.B., C.T. and P.S.); Diagnosis, screening and prevention (M.A.N., A.N.B. and C.T.); Management (M.A.N. and A.N.B.); Quality of life (M.A.N. and A.N.B.); Outlook (M.A.N. and A.N.B.).

Competing interests

M.A.N. has an advisory role and participates in studies supported by GSK (makers of Shingrix). R.M. participates in studies supported by GSK. C.W.-G. declares consulting fees from GSK, received by the London School of Hygiene and Tropical Medicine. The other authors declare no competing interests.

Informed consent

The authors affirm that patient participants provided informed consent for publication of their experiences in Box 1 and for publication of the images in Fig. 3.

Additional information

Peer review information *Nature Reviews Disease Primers* thanks T. Mogensen, T. Yoshikawa and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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