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Advances in the understanding of the pathogenesis and epidemiology of herpes zoster

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SUMMARY

The primary varicella zoster virus (VZV) infection results in chickenpox (varicella), which is transmitted via the airborne route. VZV is highly infectious, but in the USA the incidence of varicella has been reduced by 76–87% as a result of the varicella vaccine.

The virus establishes latency in the dorsal root ganglia during varicella and, when reactivated, travels along the sensory nerve axons to cause shingles (herpes zoster [HZ]). There are over 1 million cases of HZ in the USA each year, with an estimated lifetime attack rate of 30%. The incidence of HZ, which causes significant morbidity, increases with age and reaches approximately 10 cases per 1,000 patient-years by age 80. Cell-mediated immunity (CMI) is known to decline with age as part of immunosenescence, and decreased CMI is associated with reactivation of VZV.

This article provides an overview of our emerging understanding of the epidemiology and pathogenesis of varicella and HZ, in addition to exploring the current theories on latency and reactivation. Understanding the risk factors for developing HZ and the complications associated with infection, particularly in older people, is important for prompt diagnosis and management of HZ in primary care, and they are therefore also reviewed.

Abbreviations

VZV:	varicella zoster virus
HZ:	herpes zoster
CMI:	cell-mediated immunity
PCR:	polymerase chain reaction
MHC:	major histocompatibility class
IFN:	interferon
MSGP4:	Fourth Morbidity Survey in General Practice
RCGP:	Royal College of General Practitioners
DRG:	dorsal root ganglia
CRG:	cranial root ganglia
OR:	odds ratio
HLA:	human leukocyte antigen
PHN:	post-herpetic neuralgia

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1. Introduction

Varicella zoster virus (VZV) causes two distinct diseases, chickenpox (varicella) and shingles (herpes zoster [HZ]). The link between these two diseases has been understood for over 100 years and is based on two observations: (a) VZV remains latent in human neurons for decades after varicella infection and (b) sufficient VZV-specific cell-mediated immunity (CMI) is necessary to maintain latency.

The segmental nature of HZ and its origin in individual sensory ganglia were appreciated when ganglionitis was observed during autopsies performed on patients with HZ in the early 20th century. In 1892, von Bokay[1,2] recorded cases of varicella in children exposed to adults with HZ, and the link between varicella and HZ was later proven by an analysis of isolates from a patient who had had varicella followed by HZ some years later. These isolates had identical molecular profiles.[3,4]

Before the introduction of varicella vaccination, there were 4 million cases of varicella per year in the USA, with an incidence of 15–16 cases per 1,000 population.[5] The varicella vaccine was licensed in the USA in 1995, and consequently the incidence of varicella has been reduced by 76–87% in the period 1995–2000.[6]

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There are over 1 million cases of HZ in the USA each year, with an estimated lifetime attack rate of 30%.[7]

This article reviews the epidemiology of varicella in temperate and tropical climates, and the ability of current diagnostic techniques to provide information about its molecular epidemiology. Our contemporary understanding of viral pathogenesis and the major theories explaining latency and reactivation will also be examined. An understanding of the risk factors and complications associated with HZ, particularly in older people, will be discussed in relation to primary healthcare management.

2. Epidemiology

VZV is unique among the human alphaherpes viruses in that it is transmitted via the airborne route, leading to a typical winter-spring seasonality pattern of primary infection for varicella.[8] VZV can also be transmitted by fomites from skin lesions of varicella and HZ. HZ does not follow a seasonal pattern and does not occur in epidemics because it results from the reactivation of each patient's latent endogenous virus; therefore, the incidence rate of HZ is generally more stable than that of varicella (Figure 1).[8]

The incidence of HZ increases with age, with an inflection point at around age 50 and an incidence of approximately three cases per 1,000 patient-years. By age 80, the incidence reaches about 10 cases per 1,000 patient-years (Figure 2).[9,10]

In many temperate countries, varicella predominantly affects children under 10 years of age, and the incidence of HZ across these countries is very similar. In contrast, in many tropical countries, the incidence of varicella in children is low and the virus frequently occurs in late adolescence or early adulthood. Hence, the cumulative proportion of people who develop varicella approaches that of temperate climates by 30 years of age. There are no data available for the incidence of HZ in tropical countries.

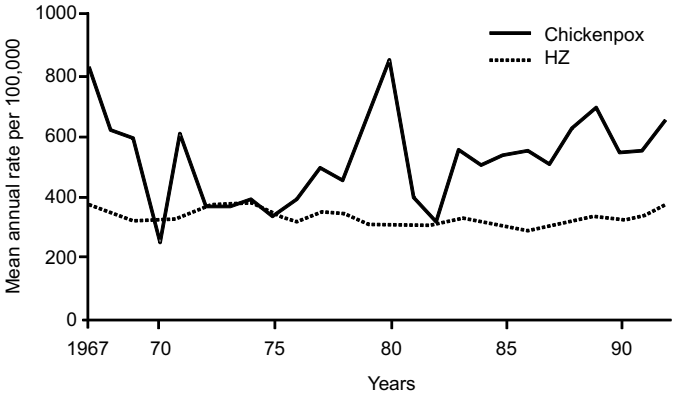

Fig. 1. Varicella and HZ cases reported to the Royal College of General Practitioners, England and Wales, 1967–92.[8] Reproduced with permission from Miller E, Marshall R, and Vurdien J. Epidemiology, outcome and control of varicella-zoster infection. *Rev Med Microbiol* 1993;4:222–230.

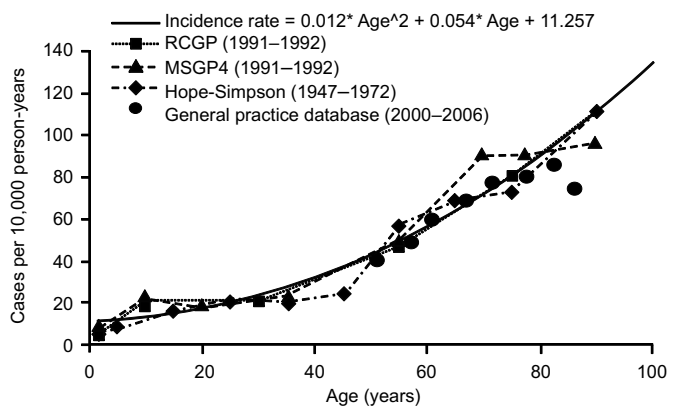

Fig. 2. The incidence of HZ increases with age. Figure adapted from Edmunds et al, 2001 and Gauthier et al, 2009.[9,10] Abbreviations: MSGP4, Fourth Morbidity Survey in General Practice; RCGP, Royal College of General Practitioners.

2.1. Molecular epidemiology of VZV

Many laboratories have developed polymerase chain reaction (PCR) methodologies for the diagnosis of HZ and to better understand the pathogenesis of VZV. In one study, VZV was detected by PCR in the saliva of patients with HZ, which persists in the host after the HZ rash disappears; 20% of saliva specimens were positive for VZV at 15 days after rash onset.[11] There are significant correlations between the presence and amount of virus in saliva and high pain score ($p < 0.005$).[11] Similarly, recent research has shown that VZV DNA remains detectable in the blood by PCR for up to 6 months in 80% of patients with HZ, and the viral load shows a trend towards higher levels in people with pain (Breuer J, personal communication, 2009).

Isolates from varicella (acquired as an exogenous infection) and HZ (resulting from endogenous reactivation) can be studied as five distinct genotypes of VZV from specific geographical areas: Clade 1, genotype C (E1/A); Clade 2, genotype J (C); Clade 3, genotype B (E2/D); Clade 4, genotype J2 (M2/B); Clade 5, genotype A1 (M1). These five genotypes differ in their global distribution: genotypes B and C are found mainly in Europe and North America, genotypes J2 and A1 are found mainly in Africa and Asia, and viruses of genotype J are mostly found in Japan. This distribution has remained stable; for example, VZV genotyping from Caucasians with HZ who have lived in the UK all their lives revealed a prevalence of 85–90% of the European genotypes.[12]

The five distinct genotypes of VZV can be separated into two groups by a single restriction-site difference (Figure 3).[13–17] Advanced genotyping techniques have demonstrated that co-infection with more than one genotype can occur in a child,[18] which provides an opportunity for virus recombination.[16] It is also possible that both co-infecting genotypes can establish latency within the host, and both have the potential for

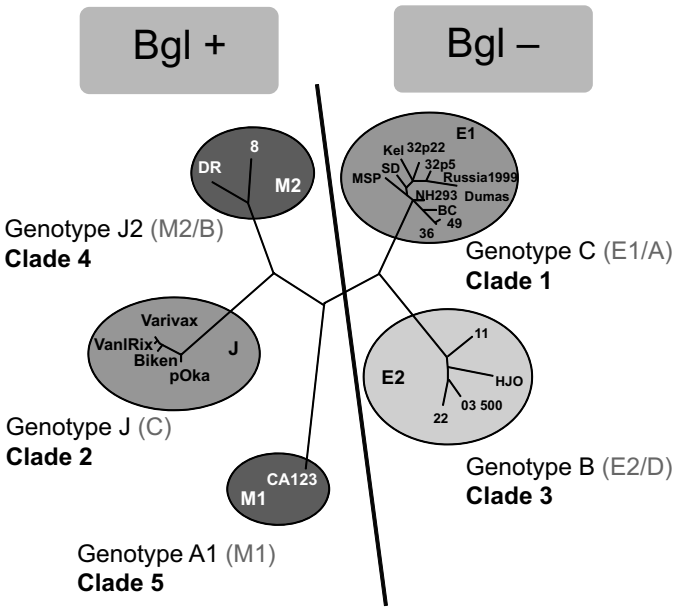

Fig. 3. Phylogeny of VZV.[13–17] Figure adapted from Loparev et al, 2007.[13]