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Review article

Postherpetic neuralgia in Europe: The scale of the problem and outlook for the future

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ABSTRACT

Herpes zoster (HZ; shingles) is a viral disease characterized by a painful unilateral rash involving one or two adjacent dermatomes. HZ results from reactivation of the varicella zoster virus (VZV) acquired during chickenpox. Following this primary VZV infection, the virus establishes latency in sensory nerve ganglia, until it reactivates decades later. The rash usually heals within 2–4 weeks, but some individuals experience residual neuropathic pain, known as postherpetic neuralgia (PHN), for months or even years, which can seriously impact their quality of life. We reviewed the epidemiological data for PHN in Europe since 2000 after the introduction of antiviral drugs. The overall lifetime risk for HZ was 23–30% and increased to 50% in those >80 years old. Defining PHN as pain persisting 3 months after rash onset, between 10% and 30% of patients with HZ developed PHN; this increased to 60–70% in those age ≥60 years. Some trials have reported that antiviral agents given soon after rash onset may prevent PHN. Vaccination programs with a zoster vaccine have been shown to prevent PHN, particularly in older patients. The various definitions used for PHN in different studies make it difficult to acquire a meaningful measurement of the true burden of PHN. In addition, comparisons between various studies and the prevalence and incidence data from different countries are difficult, because of this heterogeneity. This article provides a balanced overview of the important clinical and epidemiological studies carried out with respect to the definition, prevention, and treatment of this debilitating condition.

1. Introduction

Herpes zoster (HZ), or shingles, is the clinical manifestation of the reactivation of latent varicella zoster virus (VZV) in the dorsal root ganglia, which can occur up to several decades after the initial infection with varicella virus (chickenpox; Fig. 1).[1] A decline in VZV-specific immunity, either due to natural immunosenescence with aging or immunosuppression secondary to certain diseases (malignancies, HIV/AIDS) or immunosuppressant therapy, is known to favor symptomatic reactivation of VZV. Stress can also induce this reactivation process.

HZ is characterized by a vesicular skin rash that usually heals within 2–4 weeks and which is often preceded or accompanied by acute pain or itching. In some individuals, pain may persist for months or years after the rash has resolved, a chronic pain situation known as postherpetic neuralgia (PHN). Other complications of HZ include secondary bacterial infection, ophthalmic complications, motor paresis, cerebral angiitis, Guillain-Barré syndrome, and visceral dissemination of the virus.[2] However, PHN is the most common and debilitating complication of HZ. It can have a devastating impact on patients' quality of life and, in very severe cases, can lead to drug dependency, depression, or even suicide.[3]

In temperate regions without a varicella vaccination program, >95% of the population will have had varicella before they are 30 years of age[4]; consequently, most of the population is at risk of developing HZ and thus PHN. The potential burden of illness from HZ and PHN is high and thus a major public health problem. HZ and PHN result in significant costs for patients, healthcare providers, and society as a whole.[5,6]

Reports in the literature on the proportion of patients who present with HZ and consequently develop PHN vary considerably, depending on the definition of PHN and the study design. Historically, PHN has been reported to occur in 9–34% of patients who have HZ.[7] It is likely that the incidence of PHN is similar across temperate regions, but there are few published studies from

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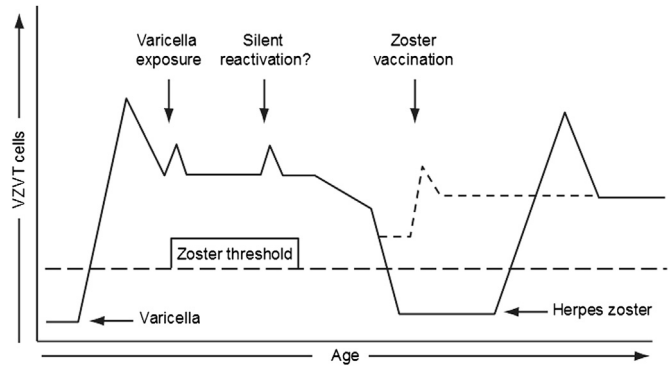

Fig. 1. Lifetime changes in cell-mediated immunity to varicella zoster virus. Varicella is the primary infection caused by the varicella zoster virus (VZV) and results in the induction of VZV-specific memory T-cells after initial exposure (solid line on graph). This immunity to VZV may be boosted periodically by subsequent exposure to varicella or subclinical reactivation of the latent virus (see initial peaks on graph). The number of VZV-specific memory T cells decline with age. The risk of herpes zoster (HZ) increases if the decline falls below a threshold (dashed line on graph). HZ is associated with an increase in the number of VZV-specific T-cells. Administration of zoster vaccine to the elderly may prevent the number of VZV-specific T cells from declining below the threshold for HZ occurrence (dotted line on graph). *Note*. From "Aging, immunity, and the varicella-zoster virus," by A. Arvin, 2005, *N Engl J Med, 352,* p. 2267. Copyright 2005, Massachusetts Medical Society. Reproduced with permission.

European countries. The objective of the present article is to describe the epidemiology of PHN in Europe after the introduction of antiviral drugs, based on a literature review of epidemiological studies, clinical trials, and reviews published since 2000, and to briefly review the opportunities for prevention and treatment.

2. Definition of PHN

Although PHN may persist for many years in some individuals, the occurrence of PHN naturally decreases in the months after resolution of the rash.[5,8,9] A 12-month, community-based study conducted in the United Kingdom showed that, among patients with HZ, 95.8% of patients experienced pain at presentation, 38.2% at 6 weeks, 27.4% at 3 months, 15.9% at 6 months, and 9.0% at 12 months.[9] In another 12-month study of 1358 patients consulting general practitioners for HZ, despite receiving antiviral drugs (94% overall; 77% within 3 days after HZ rash onset) the prevalence of pain was 43.2% at day 15, 11.6% at 3 months, 7.4% at 9 months, and 6% at 12 months.[10] For patients aged >70 years, the pain was higher at each time point: 48.1%, 14.3%, 9.3%, and 7.7%, respectively.[10]

PHN is indeed a well-known neuropathic pain syndrome, but its definition remains controversial. There is no universal agreement as to when HZ-associated pain becomes PHN or if pain intensity or typology should be included in the definition. A single, internationally recognized definition of PHN would allow meaningful measurement of the burden of illness, as well as comparison across studies and countries. Some studies have identified three distinct phases of zoster-associated pain (acute herpetic neuralgia, subacute herpetic neuralgia, and PHN), and suggest that PHN should be defined as neuropathic pain persisting beyond 3 months after the onset of the herpetic rash.[11–13] This definition is consistent with the distinction between acute and chronic pain proposed in the classification of chronic pain syndromes by the International Association for the Study of Pain (IASP).[14] By contrast, the International Herpes Management Forum (IHMF) defines PHN as pain persisting beyond 4 months from onset of the prodrome of HZ, without reference to the type of pain (neuropathic or not).[15]

Definitions of PHN used in some clinical trials have included the usual requirement for chronic pain after healing to be significant, i.e., rated as ≥3 on a scale ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine").[16,17] It has been suggested that the definition of PHN should be revised to include only cases of clinically meaningful PHN, in which pain is sufficiently severe to produce disability or require medical treatment [i.e., average daily pain ratings over the previous 48 hours ≥30 on a 0–100 visual analog scale (VAS) at 6 months after rash onset].[18] This suggestion has been countered on the basis that this stringent definition of PHN would limit research on the prevention of PHN, because of difficulties in recruiting enough patients into clinical trials.[19] Furthermore, this definition may be regarded as dismissive of the importance of pain rated >0 and <30 on the VAS to patients.

A neuropathic pain expert group in France proposed a definition describing PHN as persistent pain at the involved site after the rash has healed, displaying features of neuropathic pain.[20] This definition is based on the identification of one or more clinical features of neuropathic pain, i.e., the presence of spontaneous permanent (burning, pressure) and/or paroxysmal pain (electric shocks), and/or evoked pain (mechanical or thermal hyperalgesia and/or allodynia).[21] Moreover, painful symptoms occur in circumscribed neurological areas in which a sensory deficit can be demonstrated, and may be associated with dysesthesia and/or paresthesia. In light of the controversy surrounding the timing of PHN and the recent definition of neuropathic pain,[20] the absence of a latency period or a specified duration of pain makes this definition a putative starting point for expert discussion on a universally accepted definition.

3. Incidence of HZ and proportion of patients developing PHN

3.1. Incidence of HZ

The current estimated lifetime risk of developing HZ in Europe is 23–30%, with a reported lifetime risk of recurrence of <5%.[4,6,22,23] The risk increases considerably with age, reaching 50% in individuals aged >80 years (Fig. 2).[6,24–26] Immunocompromized individuals are at higher risk of developing HZ, even at a younger age. In the general population of Europe, the overall annual incidence of HZ is reported to be around 3 per 1000 population.[27] However, patient awareness of HZ is low in many countries in Europe, and many cases of HZ are probably unreported.[28] Recent estimates of the annual incidence of HZ from several European countries range from 1.6 per 1000 population to 5.2 per 1000 population.[3,6,29–33] The annual incidence in France increased from 2.2 per 1000 in individuals <20 years of age to 2.4 per 1000 in 20–39-year-olds, 5.4 per 1000 in 40–59-year-olds, 9.9 per 1000 in 60–74-year-olds, and 12.8 per 1000 in individuals >74 years of age.[3] Based on the estimates of incidence rates, it is estimated that about 1.7 million cases

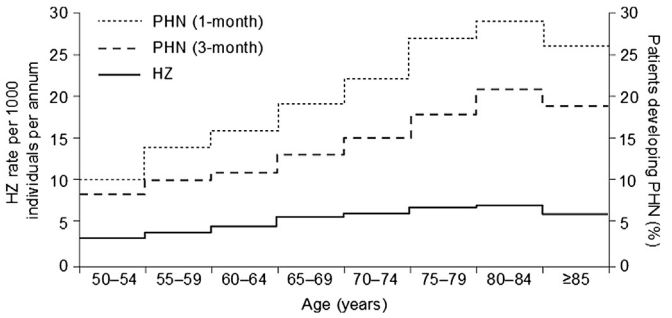

Fig. 2. Epidemiology of herpes zoster (HZ) and post-herpetic neuralgia (PHN) (based on data published in 2008). *Note*. From "Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom," by A. Gauthier, J. Breuer, D. Carrington, M. Martin, and V. Remy, 2009, *Epidemiol Infect, 137,* p. 41–42. Copyright 2009, Cambridge Journals. Adapted with permission.

of HZ occur annually in the European Union (population, 460 million).[4]

3.2. Proportion of HZ patients who develop PHN

Estimates of the prevalence of PHN vary widely depending upon the definition of PHN used, the study methodology, and the age distribution of the study population.[2] The prevalence of PHN among patients aged >50 years with HZ reported in the literature varies by more than 25%, primarily as the result of differences in the definition of PHN.[4] In addition, the absence of International Statistical Classification of Diseases and Related Health Problems (10th revision: ICD-10) code for PHN makes it difficult to extract information from healthcare databases.

PHN defined classically as pain persisting at 3 months after rash onset has been reported to occur in 10–20% of patients with HZ.[4–6] However, the prevalence and severity of PHN increase markedly with increasing age (Fig. 2).[7,24,34] The risk of developing PHN after HZ infection may be as high as 60–70% among those ≥60 years of age.[26,35]

Epidemiological data published since the year 2000 from seven European countries (France, Germany, Iceland, Italy, The Netherlands, Spain, and the United Kingdom) showing the percentage of patients with HZ developing PHN is summarized in Table 1.[5,6,9,29,30,36–40] Across countries in Europe, PHN defined as pain at 1 month after HZ rash onset has been reported to occur in 6.5–44.6% of patients, whereas, with a definition of pain at 3 months after rash onset, PHN occurred in 2.6–32.9% of patients (Table 1). Few European studies published since 2000 have reported PHN beyond 3 months after rash onset, but long-term studies of patients with HZ in Iceland and the United Kingdom have shown a consistent reduction in the proportion of patients of all ages experiencing PHN at 6 months and 12 months.[5,9,37,39] Recent studies in Iceland and The Netherlands have, however, shown a consistent age-related increase in the percentage of patients with HZ who develop PHN.[30,37]

4. Risk factors for developing PHN

Several risk factors for the development of PHN have been identified. These include older age, presence of a prodrome prior to rash, greater severity of rash, greater severity of acute pain, ophthalmic involvement, and possibly female sex, psychological stress, and concomitant disease such as diabetes mellitus.[13,41,42] The age at which HZ appears is the principal risk factor for the development of PHN. The risk of PHN increases dramatically with age, as does the severity and duration of related pain.[6,37,39,43,44] This has been demonstrated in several European studies.[6,9,10,29,30,45,47,49] In one study in Canada, functional status (i.e., limitation in performing usual activities) prior to HZ was found to be an independent predictor of PHN, in addition to age and severity of pain at recruitment into the study.[46] Female sex has also been reported to be an independent risk factor for the development of HZ.[47] However, whereas some studies have indicated a greater risk for women

Table 1
Percentage of patients with herpes zoster (HZ) developing postherpetic neuralgia (PHN) in Europe.

Country/reference or study/database	Definition of PHN (time of pain persistence from onset of zoster rash)							
	1 mo		3 mo		6 mo		12 mo	
	% of patients with HZ developing PHN							
	Overall	By age (y)	Overall	By age (y)	Overall	By age (y)	Overall	By age (y)
France								
Czernichow et al 2001[29]	18.4	<50: 2.5 ≥50: 25.0						
Mick et al 2010[36]	44		32.1		17.6			
Germany								
AOK	10.1		6.9					
IMS	12.5		2.8–3.6					
Iceland								
Helgason et al 2000[37]		<50: 5.6 50–59: 22.7 60–69: 39.2 ≥70: 50.0		<50: 1.3 50–59: 3.8 60–69: 12.1 ≥70: 28.1				<50: 0 50–59: 3.7 60–69: 4.5 ≥70: 15.0
Italy								
Di Legami et al 2007[33]			17.4[a]					
SIMG	9.4		7.2					
The Netherlands								
Opstelten et al 2002[30]	6.5	≤44: 0.9 45–54: 3.9 55–64: 6.5 65–74: 10.7 ≥75: 18.0	2.6	≤44: 0.3 45–54: 0.8 55–64: 2.9 65–74: 3.3 ≥75: 9.0				
Spain								
Cebrian et al 2008[38]	32							
Cebrian-Cuenca et al 2011[40]	47.6	<50: 21 50–59: 40 60–69: 69 >70: 59	14.5	<50: 0 50–59: 14 60–69: 26 >70: 19	9.0		5.9	
United Kingdom								
Scott et al 2003[9]	38.2[b]		27.4		15.9		9.0	
Coen et al 2006[39]	20.1[b]		9.6		6.9		4.6	
Scott et al 2006[5]			13.4		5.4			
Gauthier et al 2009[6]	19.5		13.7					

AOK = Allgemeine Ortskrankenkasse; IMS = Intercontinental Marketing Services; SIMG = Società Italiana di Medicina Generale.
[a] Pain occurring within 2 months of the diagnosis of HZ.
[b] Pain at 6 weeks after rash onset.

to develop PHN after HZ, other studies have failed to show this.[6,13,30,37,39,43,48,49]

5. Effect of HZ and PHN on quality of life

It has been reported in a literature review that acute HZ pain and PHN can significantly impair quality of life in the general population. The quality of life in older persons, who are particularly concerned by these pathologies, is more impaired, compared with younger persons.[50] In one patient-reported outcomes survey involving over 11,000 participants, it was found that pain (both acute HZ pain and PHN) disrupted many aspects of daily living, including sleep, normal work, and mood.[51] Some non-pain complications, such as HZ ophthalmicus, can increase the risk of permanent physical deterioration. An acute episode of HZ in elderly individuals may lead to permanent loss of independence.[52] In a French study, two-thirds of the patients reported that HZ had a moderate to very serious impact on their daily lives.[10] PHN also had a negative impact on their psychological states and quality of life.[10]

6. Treatment of established PHN

Irrespective of the definition of PHN used, the proportion of patients with HZ developing PHN remains high, despite therapeutic advances in the treatment of HZ.[6] The main therapeutic agents for treating PHN are systemic drugs such as tricyclic antidepressants, α2δ-ligands (gabapentin and pregabalin), and opioids, or topical agents such as lidocaine and capsaicin (Table 2).[4,53–55] These drugs can be used alone or in combination.[56] Nevertheless, established PHN is difficult to manage and is frequently refractory to treatment. Treatment of PHN is difficult because no single therapy is completely effective for numerous patients.[56–58] Current therapies often fail to provide significant benefit for about 50% of patients with PHN.[2,53] This may be because multiple pain mechanisms are involved.[15,44,59] Moreover, side effects and drug interactions are particularly common in older patients receiving multiple medications, and may lead to discontinuation of therapy (Table 2).[60,61]

Recent European guidelines on the treatment of PHN published by the European Federation of Neurological Societies (EFNS) recommend that tricyclic antidepressants or α2δ-ligands should be used as first-line treatment in patients with PHN.[56] They also recommend that lidocaine should be used as first-line treatment in the elderly, because of its excellent tolerability, despite its less consistent results. As second choice treatments, the guidelines recommend strong opioids or capsaicin; the long-term effects of repeated application of the latter are unknown.[56]

7. Prevention of PHN

7.1. Antiviral agents

Antiviral agents are widely used in the treatment of HZ if patients present early in the course of the disease (Table 2). European treatment guidelines recommend the use of antiviral drugs in patients >50 years of age with acute HZ presenting within 72 hours of rash onset, or in patients who are in severe pain at any age.[35,62–64] Treatment with antiviral drugs within 72 hours of HZ rash onset aims to reduce viral shedding and formation of new lesions, accelerate rash healing, and reduce acute pain. Antiviral therapy also helps to minimize long-lasting damage to nerves by inhibiting viral replication.

Lack of symptom awareness among patients and general practitioners, as well as atypical presentation of HZ, often prevent timely antiviral treatment, and some studies suggest that only 25–50% of patients with HZ receive antiviral agents at an early stage.[6,9,65] However, in a recent study in France involving 1358 patients who consulted their physician for HZ, 94% received antiviral therapy, with 77% receiving treatment within 3 days of HZ rash onset.[10] Awareness programs have attempted to increase understanding of the symptoms of HZ and the importance of the 72-hour "window of opportunity" for antiviral therapy.[28] However, these efforts have had little impact on the proportion of cases of HZ treated with antiviral drugs, and delayed presentation is still reported to be a significant problem. Nevertheless, early administration of antiviral drugs (acyclovir, valacyclovir, famciclovir, and brivudin) to patients most at risk of developing PHN, has been shown to reduce the duration and severity of PHN.[6,66] A recent Cochrane review analyzed results from six randomized controlled trials, with a total of 1211 participants; five trials evaluated oral acyclovir, and one trial with 419 participants evaluated oral famciclovir.[66] They reported no significant difference between the oral acyclovir and control groups for the incidence of PHN 4 months [risk ratio (RR) = 0.75; 95% confidence interval (CI) = 0.51–1.11; $p = 0.15$] or 6 months (RR = 1.05; 95% CI = 0.87–1.27; $p = 0.62$) after the onset of the acute herpetic rash. Although there was some evidence for a reduction in the incidence of pain 4 weeks after the onset of rash, authors concluded that oral acyclovir was ineffective in reducing the incidence of PHN defined as pain lasting ≥4 months after rash onset, and that there is insufficient evidence to support the use of other antiviral drugs, such as oral famciclovir, for preventing PHN.[67]

7.2. Vaccination

A high-potency VZV vaccine (Zostavax) has been developed to boost VZV-specific immunity and protect against HZ and PHN. The

Table 2
Summary of interventions for the prevention and treatment of postherpetic neuralgia (PHN).

Intervention	Effectiveness	Adverse effects
Prevention		
Vaccination[68]	66.5% reduction of PHN incidence	Vaccine is well tolerated and injection site reactions are generally mild
Antiviral agents[67]	Reduction of PHN pain intensity and duration, but 20–30% of treated patients in clinical trials still develop PHN	Few adverse events
Corticosteroids[55]	Ineffective in preventing PHN	No serious adverse events
Treatment of established PHN		
Antiviral agents[67]	Weak evidence to suggest reduced intensity and duration of PHN	Significant adverse events in older patients
Anticonvulsants[15]	Reduction in pain associated with PHN	Drowsiness, dizziness, ataxia, cognitive impairment (especially in elderly patients)
Tricyclic antidepressants[4,53]	Reduction in pain associated with PHN, plus sedative action, may improve sleep disturbances and anxiety	Dizziness, sedation, dry mouth, constipation
Topical agents[52]	Lidocaine and capsaicin patches have been shown to provide some pain relief	Some discomfort reported with capsaicin patches
Epidural therapies and nerve blocks	Prolonged, but not single dose, epidural local anesthetic has been shown to reduce pain	Not practical for widespread use and associated with risk of adverse effects

Table 3
Summary of results from the Singles Prevention Study (SPS) and the Short-term Persistence Substudy (STPS).[17,69]

	Incidence in zoster vaccine group per 1000 participants/y		Incidence in placebo group per 1000 participants/y		Vaccine efficacy	
	Herpes zoster	PHN	Herpes zoster	PHN	Herpes zoster point estimate (95% CI)	PHN point estimate (95% CI)
SPS (0 – 4.9 y)[17]	5.4	0.46	11.1	1.39	51.3 (44.2; 57.6)	66.5 (47.5; 79.2)
STPS (3.3 – 7.8 y)[69]	8.4	0.70	14.0	1.78	39.6 (18.2; 55.5)	60.1 (−9.8; 86.7)
SPS and STPS (0 – 7.8 y)[69]	5.9	0.50	11.4	1.43	48.7 (42.0; 54.7)	64.9 (47.4; 77.0)

vaccine has been approved for use by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in all individuals ≥50 years of age. The efficacy of the vaccine in reducing the incidence of HZ and PHN and attenuating the severity of PHN in cases of HZ was investigated in 38,546 individuals age ≥60 years.[17,68] Over a mean follow-up period of 3.13 years, the burden of illness due to HZ (a composite measure of incidence, severity, and duration of pain and discomfort) was significantly reduced by 61.1%, the prevalence of PHN reduced by 66.5% (95% CI = 47.5–79.2), and the prevalence of HZ reduced by 51.3% (Table 3). In addition, in a subanalysis on individuals ≥70 years of age, it was demonstrated that the efficacy of prevention of PHN was higher [66.8% (95% CI = 43.3–81.3)]. A subsequent study monitoring 7320 vaccine recipients from the previous trial showed that vaccine efficacy (burden of illness due to HZ and incidence of HZ) persists for up to 7 years postvaccination.[69] The efficacy, safety, and immunogenicity of the vaccine were also assessed in 22,439 individuals aged 50–59 years old (Table 3).[70] In this population, the vaccine displayed a statistically significant reduction in the incidence of HZ by 69.8% (95% CI = 54.1–80.6%) for up to 2 years. The number of patients reporting one or more serious adverse event was low and similar between the vaccine and placebo groups. A recent systematic review from the Cochrane Collaboration (based on the only published randomized controlled trials to date) concluded that the vaccine did not show any efficacy for prevention of PHN over and above that for prevention of HZ.[71] However, these authors used the definition of PHN of 4 months of persistent neuropathic pain after HZ rash onset, instead of 3 months. In the original trial, the definition used was 3 months persistent neuropathic pain after HZ rash onset; this definition has been accepted by licensing agencies, e.g., the FDA in the United States and the EMA in Europe. In addition, this Cochrane review did not perform an age-stratified analysis. However, in the analyzed trial, vaccine efficacy against HZ decreased with age, but efficacy for PHN remained constant with age, thus additional vaccine efficacy against PHN would be expected to be age-dependent. This means that an age-stratified analysis is needed to assess whether the vaccine reduced the incidence of PHN beyond the reduction in PHN resulting from the prevention of HZ.[72] Finally, results from recent modeling studies estimate that vaccination programs for prevention of HZ and PHN in the UK, Belgium, and The Netherlands may be considered cost-effective, especially within the 60–69-year-old age group.[73–78]

7.3. *Impact of childhood varicella vaccination on the incidence of HZ*

Varicella vaccination has decreased the incidence of varicella and varicella-related outcomes in children.[79] Because shingles is caused by reactivation of the varicella virus that remains dormant after the primo-infection, and exposure to varicella is thought to boost immunity against this reactivation, questions about the impact of childhood varicella vaccination on the incidence of shingles arise.[80] Results from a more recent modeling study in the UK suggest that if childhood vaccination coverage is high (i.e., 90% for the first dose and 80% for the second), it is unlikely that there will be an increase in the incidence of adult varicella.[81] In addition, analyses of data from an American healthcare database (MarketScan) show that although there has been an increase in the incidence of HZ from 1993 to 2006, there is no evidence that this is due to the childhood varicella vaccination program.[78] To summarize, there is no conclusive evidence that universal childhood varicella vaccination has had an impact on the epidemiology of HZ. Long-term surveillance studies are needed to improve our understanding of the potential impact.

8. Outlook for the future

In the absence of an internationally accepted definition for PHN (particularly duration and severity of HZ-associated pain required to qualify for PHN), it remains difficult to assess the true prevalence of PHN in Europe. Defining PHN as neuropathic pain at the affected site, after the rash has healed, may be a good starting point for a discussion on a consensus definition. Recent studies in Europe used various designs and different definitions of PHN, and hence, reported proportions of patients with HZ developing PHN vary considerably and comparisons across studies are difficult (Table 1). It is, however, currently estimated that >20% of patients >50 years old with HZ will develop PHN.

Currently available medications do not prevent PHN, or sufficiently control pain in a large proportion of patients. Antiviral therapy may improve HZ symptoms if administered within 72 hours of rash onset, but antiviral drugs are often not prescribed, because patients do not present sufficiently early after disease onset. The incidence of HZ (and therefore of PHN) can be expected to increase as the: (1) mean age of the population continues to rise; (2) prevalence of malignancies and autoimmune diseases increases; and (2) use of immunosuppressant therapies increases. Furthermore, the widespread introduction of varicella immunization programs among children may result in fewer opportunities for boosting immunity through exogenous exposure to wild-type virus. This may lead to an increased incidence of HZ and PHN in adults, until the pool of individuals infected by wild-type VZV is reduced. However, no increase in HZ incidence that can be attributed to routine varicella vaccination, which has been in place since 1996, has been observed in the US.[77] Prevention of PHN through vaccination would seem to be a cost-effective alternative, because there is insufficient evidence that antiviral therapy can prevent the development of PHN.

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