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Systematic review of incidence and complications of herpes zoster: towards a global perspective

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ABSTRACT

Objective: The objective of this study was to characterise the incidence rates of herpes zoster (HZ), also known as shingles, and risk of complications across the world.

Design: We systematically reviewed studies examining the incidence rates of HZ, temporal trends of HZ, the risk of complications including postherpetic neuralgia (PHN) and HZ-associated hospitalisation and mortality rates in the general population. The literature search was conducted using PubMed, EMBASE and the WHO library up to December 2013.

Results: We included 130 studies conducted in 26 countries. The incidence rate of HZ ranged between 3 and 5/1000 person-years in North America, Europe and Asia-Pacific, based on studies using prospective surveillance, electronic medical record data or administrative data with medical record review. A temporal increase in the incidence of HZ was reported in the past several decades across seven countries, often occurring before the introduction of varicella vaccination programmes. The risk of developing PHN varied from 5% to more than 30%, depending on the type of study design, age distribution of study populations and definition. More than 30% of patients with PHN experienced persistent pain for more than 1 year. The risk of recurrence of HZ ranged from 1% to 6%, with long-term follow-up studies showing higher risk (5–6%). Hospitalisation rates ranged from 2 to 25/100 000 person-years, with higher rates among elderly populations.

Conclusions: HZ is a significant global health burden that is expected to increase as the population ages. Future research with rigorous methods is important.

Strengths and limitations of this study

- We comprehensively reviewed the global burden of herpes zoster.
- We found a similar age-specific incidence of herpes zoster in North America, Europe and Asia-Pacific; however, there is a scarcity of research from other regions.
- Because the quality of the study, study design and study population varied widely across studies, we could not synthesise the data quantitatively.

INTRODUCTION

Herpes zoster (HZ), also known as shingles, is typically characterised by painful, blistering dermatomal rash.[1 2] The estimated lifetime risk of HZ in the general population is approximately 30%, with the risk increasing sharply after 50 years of age.[3] After conducting a careful long-term observational study in the 1960s, Hope-Simpson[4] showed that HZ results from reactivation of the varicella-zoster virus (VZV) in sensory ganglia after a long latency period following primary infection from varicella (chickenpox). In some patients particularly in the elderly, the pain continues to persist after the rash heals and develops into postherpetic neuralgia (PHN), which is the most common complication. PHN causes physical disability, emotional distress and interference with daily activities and sleep.[5] HZ also causes neurological sequelae, HZ ophthalmicus (HZO) with eye involvement or disseminated disease. Severe cases of these complications often require hospitalisation.

A live-attenuated VZV vaccine (ZOSTAVAX by Merck) has been demonstrated to significantly reduce the incidences of HZ and PHN in addition to the severity and duration of pain associated with HZ.[6] Public health interventions that promote healthy ageing are increasingly becoming more important, as the elderly population is growing rapidly worldwide. Over the next half century, the proportion of people ≥60 years of age is projected to double, reaching more than 20% of the total population in all regions of the world.[7] Moreover, the prevalence of disability in the elderly populations is increasing across the world.[8]

It is essential for healthcare practitioners and health policymakers to be informed by the best available and up-to-date evidence on the HZ burden of disease. In a previous

review by Thomas and Hall[9], there were limited population-based studies on HZ incidence. Since then, many studies have been conducted across countries to examine the incidence rates and temporal trends of HZ. Other reviews have been restricted to specific geographic regions.[10 11] Moreover, to the best of our knowledge, there has been no systematic review of studies examining the risk of complications and hospitalisation. The objective of this study is to characterise the incidence rates of HZ and risk of complications across the world. We systematically reviewed studies examining the incidence rates of HZ, temporal trends of HZ, risk of HZ complications including PHN and HZ-associated hospitalisation and mortality rates in the general population.

METHODS

Literature search

We performed a literature search in PubMed, EMBASE, and the WHO's Global Health Library Regional Index up to December 2013. For PubMed, we used Medical Subject Headings (MeSH) and the title terms 'herpes zoster', 'zoster' or 'shingles' in combination with the term 'incidence'. We also searched eligible articles using MeSH and the title terms 'postherpetic neuralgia' or 'post-herpetic neuralgia'. We used the same search strategy with text terms in EMBASE and the WHO library. We manually searched the references cited by the retrieved articles and review articles for additional references. Two investigators (KK and BG) independently conducted a systematic review of the literature, assessed study eligibility and extracted data. Discrepancies were settled through discussion with a third investigator (CJA).

Inclusion and exclusion criteria

We included studies examining the incidence of HZ, risk of PHN, risk of a recurrent episode of HZ, risk of HZO, HZ-associated hospitalisation or HZ-associated mortality. For studies examining the efficacy or effectiveness of vaccination against HZ, we included estimates of incidence rates among unvaccinated individuals. We did not apply language restrictions. We did not include studies limited to children, immunocompromised populations (eg, HIV, cancer and chronic kidney disease) or patients on immunosuppressive therapy (eg, corticosteroids). We also excluded review articles and case reports.

Data extraction

We developed a standard abstraction form for data extraction. We extracted information regarding authors, publication year, journal, country, study design, study year(s), population, number of cases, number at risk, case definition, case ascertainment, incidence rates of HZ (per 1000 person-years), risk of PHN and other complications, HZ-associated hospitalisation rates and HZ-associated mortality rates. For studies on incidence that did not report 95% CI, we computed exact 95% CI.

RESULTS

After conducting a literature search, we included 130 studies conducted in 26 countries in this review (figure 1). There were 63 studies on the incidence of HZ from 22 countries[3 4 6 12–71]; 25 studies on trends of HZ from 7 countries[3 12 15–19 23–25 27 28 49 53 65 68 72–80]; 60 studies on PHN from 19 countries[3 4 6 12 18 33–36 38 40 42 43 46 54 56 60–63 69 81–118]; 9 studies on HZ recurrence from 5 countries[4 12 13 57 60 119–122]; 12 studies on HZO from 5 countries[12 35 43 61 123–130]; 28 studies on hospitalisation rates from 14 countries[24 26 27 30 37 41 44 46 48 52 55 56 58 62–64 72 73 76 77 131–137] and 10 studies on mortality rates from 10 countries.[26 30 37 41 44 48 58 62 134 138]

Incidence rates of HZ

Studies examining the incidence rates of HZ were conducted in countries from North America (N=18), Europe (N=33), Asia (N=7), South America (N=3) and the Middle East (N=2; table 1). The incidence rate of HZ ranged between 3 and 5/1000 person-years in North America, Europe and Asia-Pacific, based on studies using prospective surveillance, electronic medical record data or administrative data with medical record review. The age-specific incidence rates of HZ were similar across countries, with a steep rise after 50 years of age (figure 2). The incidence rate was about 6–8/1000 person-years at 60 years of age and 8–12/1000 person-years at 80 years of age. We observed an increase in the reported incidence rate over time within a country. For example, studies conducted more than 20 years ago in the USA by Ragozzino *et al*[12] and Donahue *et al*[13] showed lower rates compared with studies conducted in recent years. It is noteworthy that prospective population-based studies that identified relatively small numbers of patients with HZ (eg, by Scott *et al*,[33] Paul and Thiel,[39] Di Legami *et al*[55] and Lionis *et al*[59]) estimated lower incidence compared with other studies.

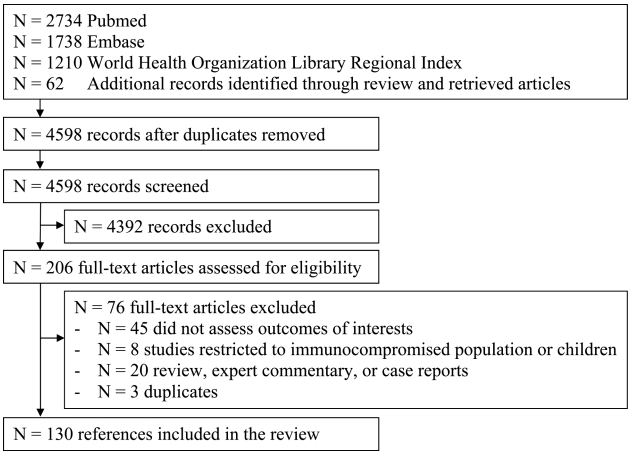

Figure 1 Study selection.

Table 1 Incidence of HZ

Country	Author	Study design and population	Case ascertainment	Year	HZ cases	Age	Incidence 1000 person-years	95% CI
USA	Ragozzino	Medical records database in Minnesota	ICD-9 confirmed by medical records	1945–1959	590	All ages	1.31	1.15 to 1.35*
USA	Donahue	Health maintenance organisation claims database in Massachusetts	ICD-9 confirmed by medical records	1990–1992	1075	All ages	2.15	2.02 to 2.28*
USA	Insinga	MarketScan claims database in the USA	ICD-9	2000–2001	9152	All ages	3.20	3.10 to 3.20
USA	Mullooly	Kaiser Northwest health maintenance organisation claims database	ICD-9 multiplied by positive predictive value	1997–2002	9895	All ages	3.69	3.58 to 3.82
USA	Yih	Annual random-digit telephone survey in Massachusetts	Survey from patients	1999–2003	194	All ages	4.33	3.72 to 4.93*
USA	Jumaan	Health maintenance organisation claims database in Washington	ICD-9	1992–2002	357	All ages	3.71	
USA	Oxman	Zostavax trial in the control group	Notified by physicians and PCR/culture confirmation	1998–2001	642	≥60 years	11.12	
USA	Yawn	Retrospective population-based study confirmed by medical records in Minnesota	ICD-9 confirmed by medical records	1996–2001	1669	≥22 years	3.60	3.40 to 3.70
USA	Rimland	National Veterans Affairs claims database	ICD-9	2000–2007†	28 710	All ages	5.22	
USA	Leung	MarketScan claims database	ICD-9	1993–2006†	48 000	All ages	4.40	4.30 to 4.40
USA	Tseng	Kaiser Southern California health maintenance organisation claims database in the unvaccinated group	ICD-9	2007–2009	4606	≥60 years	13.0	12.6 to 13.3
USA	Langan	Medicare claims database in the unvaccinated group	ICD-9	2007–2009	19 385	≥65 years	15.1	14.9 to 15.3
USA	Chen	Commercial, Medicare and Medicaid MarketScan claims database	ICD-9	2005–2009	435 378	≥18 years	4.82	4.81 to 4.84
USA	Hales	Medicare claims database	ICD-9	1992–2010†	281 317	≥65 years	14.2	14.0 to 14.5
Canada	Brisson	Administrative claims database in Manitoba	ICD-9	1979–1997†	NA	All ages	3.48	
Canada	Russell	Health insurance claims database in Alberta	ICD-9/ICD-10	1986–2002†	NA	All ages	4.30	
Canada	Edgar	Administrative claims database in British Columbia	ICD-9	1994–2003	114 596	All ages	2.89	
Canada	Tanuseputro	Administrative claims database in Ontario	ICD-9	1992–2010	686 763	All ages	3.23	
Canada	Russell	Health insurance claims database in Alberta	ICD-9/ICD-10	1994–2010†	213 265	All ages	4.50	
UK	Hope-Simpson	Prospective population-based study in Cirencester	Medical records by GP	1947–1962	192	All ages	3.39	
UK	Ross	Prospective population-based study in Glasgow	Notified by 10 GPs	1972–1973	87	All ages	2.40	
UK	Brisson	RCGP database in England and Wales	ICD-9 medical records by GPs	1979–1997†	NA	All ages	3.82	
UK	Brisson	RCGP database in England and Wales	ICD-9 medical records by 69 GPs	1991–2000	NA	All ages	3.73	
UK	Fleming	RCGP database in England and Wales	ICD-9 medical records by GPs	1994–2001†	14 532	All ages	3.90	
UK	Chapman	RCGP database in England and Wales	ICD-9 medical records by GPs	1994–2001	NA	≥15 years	3.95	

Continued

Table 1 Continued

Country	Author	Study design and population	Case ascertainment	Year	HZ cases	Age	Incidence 1000 person-years	95% CI
UK	Scott	Prospective population-based study in East London	Notified by 18 GPs and PCR confirmation	NA	186	All ages	1.85	
UK	Gauthier	GPRD in UK	Medical records by 603 GPs	2000–2006	27 225	≥50 years	5.23	5.17 to 5.29
France	Chidiac	Prospective sentinel surveillance	Notified by 4635 GPs and 513 dermatologists	1997–1998	8103	All ages	4.80	
France	Czernichow	Retrospective population-based study	Survey from 744 GPs	1998	605	All ages	3.20	3.00 to 3.40
France	Gonzalez-Chiappe	Prospective sentinel surveillance	Notified by 1200 GPs	2005–2008	2375	All ages	3.82	3.64 to 4.05
France	Mick	Retrospective population-based study	Survey from 231 GPs, 41 dermatologists and 15 neurologists	2005	777	≥50 years	8.99	8.34 to 9.64
Germany	Paul	Prospective population-based study in Ansbach	Notified by GPs, dermatologists and others	1992–1993	152	All ages	2.26	
Germany	Schiffner-Rohe	National Statutory Health Insurance claims database	ICD-10	2004	1170	≥50 years	9.80	9.20 to 10.40
Germany	Ultsch	National Statutory Health Insurance claims database	ICD-10	2007–2008	374 645	≥50 years	9.60	9.56 to 9.63
Germany	Ultsch	National Statutory Health Insurance claims database	ICD-10	2004–2009	5384	All ages	5.79	5.64 to 5.93
The Netherlands	Opstelten	Huisartsen Netwerk Utrecht database in six locations	Medical records from 22 GPs	1994–1999	837	All ages	3.40	2.90 to 3.90
The Netherlands	de Melker	Prospective sentinel surveillance	Notified by 43 GPs	1998–2001	NA	All ages	3.25	
The Netherlands	Opstelten	National survey of physicians	Medical records from 104 GPs	2001	1080	All ages	3.22	3.00 to 3.40
The Netherlands	Pierik	Retrospective population-based study in Almere	Medical records from 22 GPs	2004–2008	3371	All ages	4.75	4.06 to 5.44
Switzerland	Richard	Prospective sentinel surveillance	Notified by 250 physicians	1998–2001	2236	All ages	2.36	
Belgium	Bilcke	Retrospective population-based study	Notified by 150 GPs	2000–2007	NA	All ages	3.78	
Spain	Pérez-Farinós	Prospective sentinel surveillance in Madrid	Notified by GPs	1997–2004†	1798	All ages	3.59	3.22 to 3.97
Spain	García Cenoz	Primary care database in Navarre	Medical records from GPs	2005–2006	4959	All ages	4.15	
Spain	Cebrián-Cuenca	Prospective population-based study in Valencia	Notified by 25 GPs	2006–2007	146	≥14 years	4.10	3.40 to 4.70
Spain	Morant-Talamante	Electronic medical record database in Valencia	ICD-9	2007–2010	85 586	All ages	4.60	4.57 to 4.63
Spain	Esteban-Vasallo	Electronic medical record in the Madrid regional public health system	ICPC	2005–2012†	211 650	All ages	4.82	
Italy	di Luzio Paparatti	Retrospective population-based study	Survey from 71 GPs	1995	408	≥15 years	4.14	3.75 to 4.56
Italy	Di Legami	Prospective population-based study in Piedmont	Notified by 24 GPs	2004	46	≥14 years	1.74	1.28 to 2.32

Continued

Table 1 Continued

Country	Author	Study design and population	Case ascertainment	Year	HZ cases	Age	Incidence 1000 person-years	95% CI
Italy	Gialloreti	National primary-care database (Societa Italiana Medici Generici)	Medical records from 342 GPs	2003–2005	5675	All ages	4.31	4.11 to 4.52
Iceland	Helgason	Prospective population-based study	Notified by 62 GPs	1990–1995	462	All ages	2.00	1.80 to 2.20
Sweden	Studahl	Swedish National Pharmacy register	Prescriptions for antiviral medications	2006–2010	127 832	All ages	2.70	
Greece	Lionis	Prospective population-based study in rural Crete	Notified by 19 GPs	2007–2009	58	All ages	1.60	
Israel	Weitzman	Maccabi Healthcare Services claims database	ICD-9	2006–2010	28 977	All ages	3.46	
Saudi Arabia	Alakloby	Medical records from the dermatology clinic	Medical charts from the dermatologist	1988–2006	141	All ages	6.20	5.18 to 7.22*
Australia	Stein	National GP database (Bettering the Evaluation of Care and Health)	Medical records of GPs	2000–2006	379	≥50 years	9.67	8.66 to 10.68
Taiwan	Jih	Taiwan National Health Insurance claims database	ICD-9	2000–2006	34 280	All ages	4.89	4.76 to 5.04*
Taiwan	Lin	Taiwan National Health Insurance claims database	ICD-9	2000–2005	672 782	All ages	4.97	4.96 to 4.98
Taiwan	Chao	Taiwan National Health Insurance claims database	ICD-9	2000–2008	11 908	All ages	5.67	
South Korea	Park	NA	NA	1999–2003	1089	All ages	2.98	
South Korea	Choi	Health Insurance claims database (estimated prevalence)	ICD-10	2003–2007	2 431 744	All ages	9.97	
Japan	Toyama	Prospective population-based study in Miyazaki	Notified by 46 dermatology clinics	1997–2006	48 388	All ages	4.15	4.12 to 4.19*
Argentina	Vujacich	Medical records from the ID reference centre	Medical charts from IDs	2000–2005	302	All ages	3.57	3.17 to 3.97*
Brazil	Castro	Medical records from the dermatology clinic	Medical charts from the dermatologist	1987–1989	469	All ages	5.62*	
Colombia	Gaitan	Medical records from the oncology, radiology and nuclear medicine centre	Medical charts from patients without cancer	NA	75	NA	6.50*	

*We computed the overall estimate or 95% CI based on the study results.
†The estimate from the latest study year.
GP, general practitioner; GPRD, general practice research database; HZ, herpes zoster; ICD, International Classification of Diseases; ICPC, International Classification For Primary Care; RCGP, Royal College of GPs.

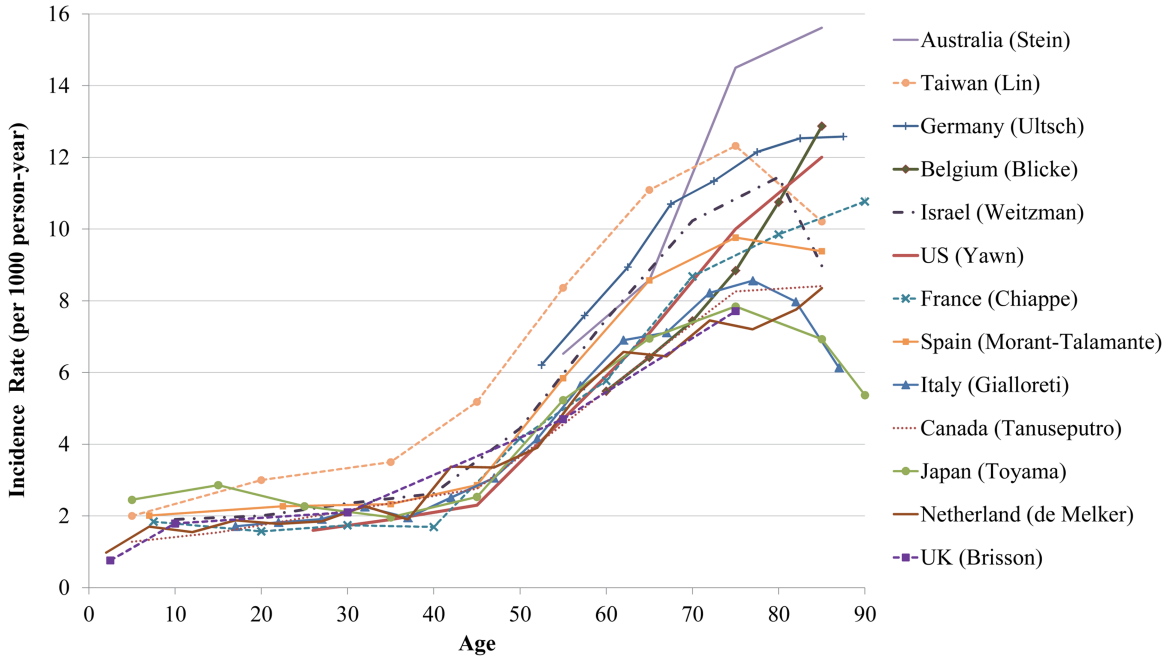

Figure 2 Age-specific incidence rate of herpes zoster in North America, Europe and Asia-Pacific.

Trends of HZ incidence

In the USA, studies conducted during the postvaricella vaccination era showed inconsistent results, with some showing no change in incidence but others reporting an increase in HZ incidence, suggesting a potential impact of varicella vaccination (table 2). However, Leung *et al*,[19] Hales *et al*[23] and Yawn *et al*[75] examined trends over a longer period and found that incidence rates increased continuously across all age groups before the introduction of the varicella vaccination programme and continued to increase throughout the postvaccination era. These studies concluded that the increase was not due to the varicella vaccination programme. Most studies conducted in Canada, the UK, Spain, Taiwan and Japan reported an increase in the incidence of HZ over the past decade often occurring in the absence of the national varicella vaccination programmes.[24 25 49 65 68] Several studies in Australia suggested increasing trends in HZ outpatient visits or hospitalisation during prevaricella and postvaricella vaccination eras.[76 77 79]

Risk of PHN

The risk of developing PHN varied from 5% to more than 30% (table 3; 49 studies). The estimated risk of PHN varied by study design, age distribution of study populations and definitions used for PHN. For studies that used multiple definitions of PHN, we present results based on the definition of at least 90 days of persistent pain. Studies that reported risk of PHN by age groups consistently found that older patients have a greater risk of developing PHN (see online supplementary table S1). In this review, we found that researchers have used a different duration of persistent pain (persisting for 30, 90 or 180 days) and severity of pain (clinically meaningful pain or any pain) to define PHN. For example, 18% of patients had pain for at least 30 days and 10% for at least 90 days in a population-based study using medical records by Yawn *et al*[3] in the USA. Similarly, 20% of patients had pain for at least 30 days and 14% for at least 90 days in a study by Gauthier *et al*[34] in the UK. Administrative database studies (eg, Ultsch *et al*[42] (4.5%), Opstelten *et al*[43] (2.6%) and Gialloreti *et al*[56] (6.2%)) were more likely to report a lower estimated risk of PHN compared with other studies. Researchers have used diagnosis and medication data in various algorithms, many of which are not validated. It is noteworthy that retrospective studies involving specialists (eg, Mick *et al*[38] (32.5%), Kanbayashi *et al*[102] (52%) and Ro *et al*[103] (39.4%)) may have included existing severe cases of patients with PHN and possibly overestimated the overall risk of PHN.

We identified six prospective cohort and three cross-sectional studies examining the duration of PHN in North America and Europe (table 4). Several studies reported that PHN may last up to 10 years. Prospective cohort studies demonstrated that approximately 30–50% of patients with PHN experienced pain lasting for more than 1 year. Cross-sectional studies also reported a similar high proportion of patients with PHN; however, these studies are most likely an overestimate because they are more likely to include patients experiencing a longer duration of pain.

Risk of recurrence

A limited number (N=9) of studies examined recurrence of HZ. Four studies reported a risk of <1.5%, with three of these studies conducted over 1–2 years of follow-up.[13 57 119 122] About 2.9% of patients had

Table 2 Temporal trends of herpes zoster

Country	Author	Study periods	Varicella vaccination era	Trends
USA	Ragozzino	1945–1959	Pre	Incidence increased from 1.1 to 1.5/1000 person-years between 1945–1949 and 1955–1959
USA	Jumaan	1992–2002	Pre and post (1996–)	Incidence did not change between 1992 and 2002
USA	Yih	1998–2003	Post	Incidence increased from 2.8 to 5.3/1000 person-years between 1999 and 2003
USA	Mullooly	1997–2002	Post	Incidence did not change between 1997 and 2002
USA	Yawn	1996–2005	Post	Incidence increased from 3.2 to 4.1/1000 person-years between 1996–1997 and 2000–2001
USA	Patel	1993–2004	Pre and post	Hospitalisation rate did not change during 1993–2000 but increased between 2001 and 2004
USA	Jackson	1992–2004	Pre and post	Hospitalisation rate did not change during 1992–2004
USA	Civen	2000–2006	Post	Incidence increased between 2000 and 2006 among unvaccinated adolescents 10–19 years
USA	Rimland	2000–2007	Post	Incidence increased from 3.1 to 5.2/1000 person-years between 2000 and 2007
USA	Yawn	1945–2008	Pre and post	Incidence increased from 0.8/1000 person-years in 1945–1947, to 1.6/1000 person-years in 1980–1982, to 3.0/1000 person-years in 2005–2007
USA	Leung	1993–2006	Pre and post	Incidence increased from 1.7 to 4.4/1000 person-years between 1993 and 2006
USA	Hales	1992–2010	Pre and post	Incidence increased from 10.0 to 13.9/1000 person-years between 1992 and 2010 in adults ≥65 years
Canada	Brisson	1979–1997	Pre	Incidence increased from 2.6 to 3.5/1000 person-years between 1979 and 1997
Canada	Russell	1986–2002	Pre and post (2001–)	Incidence increased from 2.8 to 4.2/1000 person-years between 1986 and 2002
Canada	Tanuseputro	1992–2010	Pre and post	Incidence did not change during 1992–2009
Canada	Russell	1994–2010	Pre and post	Incidence increased from 3.5 to 4.5/1000 person-years between 1994 and 2010
UK	Brisson	1979–1997	Pre	Incidence increased from 3.2 to 3.9/1000 person-years between 1979 and 1997
Spain	Perez-Farinos	1997–2004	Pre	Incidence increased from 2.5 to 3.6/1000 person-years between 1997 and 2004
Spain	Esteban-Vasallo	2005–2012	Pre and post (2006–)	Incidence increased from 3.6 to 4.8/1000 person-years between 2005 and 2012
Australia	Macintyre	1993–1999	Pre	Hospitalisation rate increased between 1993 and 1999
Australia	Carville	1995–2007	Pre and post (2005–)	Hospitalisation rate increased from 6.3 to 9.1/100 000 person-years between 1995 and 2007
Australia	Nelson	1998–2009	Pre and post	Incidence increased from 1.7 to 2.4/1000 person-years between 1998 and 2008
Australia	Jardine	1998–2007	Pre and post	Hospitalisation rate did not change during 1992–2009
Taiwan	Chao	2000–2008	Pre and post	Incidence increased from 4.5 to 6.9/1000 person-years between 2000 and 2008
Taiwan	Wu	2000–2009	Pre and post	Incidence increased from 4.0 to 6.2/1000 person-years between 2000 and 2009
Japan	Toyama	1997–2006	Low coverage (20–30%)	Incidence increased from 3.8 to 4.5/1000 person-years between 1997 and 2006

Table 3 Risk of PHN in patients with herpes zoster

Country	Author	Study design	Definition of PHN*	Year	PHN cases	Age	Risk of PHN (%)
USA	Ragozzino	Medical records database in Minnesota	Physician diagnosis	1945–1959	55	All ages	9.3
USA	Galil	Administrative claims database confirmed by medical records in Massachusetts	Pain persisted for ≥60 days from medical records	1990–1992	68	All ages	7.9
USA	Oxman	Zostavax trial in the control	Pain ≥3 score for ≥90 days	1998–2001	80	≥60 years	14.0
USA	Yawn	Retrospective population-based study confirmed by medical records in Minnesota	Pain persisted for ≥90 days from medical records	1996–2001	171	≥22 years	10.0
USA	Thyregod	Prospective cohort study in California	Pain persisted for ≥180 days	1999–2003	30	≥50 years	31.9
USA	Klompas	Administrative claims database confirmed by medical records in Massachusetts	Pain persisted for ≥30 days and required pain medication from medical records	2008	237	≥20 years	12.2
USA	Rimland	Atlanta Veterans Affairs claims database confirmed by medical records	Physician diagnosis from medical charts	2000–2007	205	All ages	19.6
USA	Katz	Prospective cohort study in New York	Pain persisted for ≥120 days	NA	20	≥18 years	19.6
Canada	Drolet	Prospective cohort study, recruited by 83 physicians throughout country	Pain ≥3 score for ≥90 days	2005–2006	56	≥50 years	22.5
UK	Hope-Simpson	Prospective population-based study in Cirencester	Physician diagnosis	1947–1962	46	All ages	14.3
UK	Scott	Prospective cohort study	Pain persisted for ≥90 days	NA	45	All ages	27.4
UK	Jung	Prospective cohort study (combined two trials)	Pain persisted for ≥120 days	NA	114	≥15 years	12.8
UK	Scott	Prospective cohort study in East London	Pain persisted for ≥90 days	NA	9	All ages	13.4
UK	Coen	Prospective cohort study, recruited by GPs	Pain ≥3 score for ≥90 days	1998–2001	24	All ages	9.0
UK	Gauthier	GPRD in the UK	Physician diagnosis or pain medication at 90 days from medical records	2000–2006	415	≥50 years	13.7
France	Chidiac	Prospective sentinel surveillance	Physician diagnosis	1997–1998	935	All ages	10.3
France	Czernichow	Retrospective population-based survey from GPs	Pain persisted for ≥30 days and required treatment from medical records	1998	111	All ages	18.4
France	Mick	Retrospective population-based survey from GPs, dermatologists and neurologists	Pain persisted for ≥90 days from medical records	2005	227	≥50 years	32.5
France	Bouhassira	Prospective cohort study, recruited by GPs	Pain persisted for ≥90 days	2007–2008	127	≥50 years	11.6
Germany	Meister	Retrospective population-based survey from GPs, dermatologists and specialists	Pain persisted for ≥30 days and physician diagnosis	NA	131	≥50 years	20.6
Germany	Schiffner-Rohe	National Statutory Health Insurance claims database	Pain persisted for ≥90 days and diagnosis or pain medication from ICD-10	2004	NA	≥50 years	6.9
Germany	Weinke	Telephone survey of patients, previous HZ diagnosis in 5 years	Pain persisted for ≥90 days	2008	32	≥50 years	11.4

Continued

Table 3 Continued

Country	Author	Study design	Definition of PHN*	Year	PHN cases	Age	Risk of PHN (%)
Germany	Ultsch	National Statutory Health Insurance claims database	Pain persisted for ≥90 days and diagnosis or pain medication from ICD-10	2004–2009	18 160	All ages	4.5
The Netherlands	Opstelten	Huisartsen Netwerk Utrecht database in six locations	Pain persisted for ≥90 days and required treatment from medical records	1994–1999	22	All ages	2.6
The Netherlands	Opstelten	Prospective cohort study, recruited by GPs (PINE trial)	Pain ≥3 score for ≥90 days	2001–2004	46	≥50 years	7.1
The Netherlands	Pierik	Population-based GPs database in Almere	Physician diagnosis from medical codes	2004–2008	195	All ages	5.8
Spain	Cebrian-Cuenca	Prospective cohort study, recruited by 25 GPs in Valencia	Pain persisted for ≥90 days	2006–2007	19	≥14 years	14.5
Spain	Sicras Mainar	Medical records from six primary care and one hospital	Physician diagnosis from medical records	2007–2010	228	≥30 years	15.1
Italy	di Luzio Paparatti	Retrospective population-based survey from GPs	Pain persisted for ≥30 days from medical records	1995	275	≥15 years	19.6
Italy	Volpi	Prospective cohort study, recruited by dermatologists	Pain ≥3 score for ≥180 days	2001	70	NA	32.0
Italy	Parruti	Prospective cohort study, recruited from GPs and hospitals in Pescara	Pain persisted for ≥90 days	2006–2008	130	NA	30.0
Italy	Gialloreti	National primary care database (Societa Italiana Medici Generici)	Pain persisted for ≥90 days and diagnosis or pain medication from ICD-9	2003–2005	350	≥50 years	6.2
Italy	Bricout	Prospective cohort study, recruited from GPs	Pain persisted for ≥90 days	2009–2010	85	≥50 years	20.6
Iceland	Helgason	Prospective population-based study	Physician diagnosis at 90 days	1990–1995	28	All ages	7.2
6 European countries	Lukas	Telephone survey, previous 5 years	Pain persisted for ≥90 days	2008—2009	131	≥50 years	13.0
Israel	Weitzman	Maccabi Healthcare Services claims database	ICD-9 code and healthcare service code	2006–2010	1508	All ages	5.2
Saudi Arabia	Alakloby	Medical record database from the dermatology clinic	Physician diagnosis	1988–2006	21	≥18 years	14.9
Australia	Stein	National GP database (Bettering the Evaluation of Care and Health)	Physician diagnosis from medical codes	2000–2006	57	≥50 years	15.0
Taiwan	Jih	Taiwan National Health Insurance claims database	Pain persisted for ≥90 days and diagnosis or pain medication from ICD-9	2000–2006	2944	All ages	8.6
Taiwan	Tsai	Prospective cohort study in five centres	Pain ≥3 score for ≥90 days	2008–2009	31	≥50 years	20.7
Japan	Kurokawa	Prospective cohort study in hospitals and clinics in Hyogo	Pain persisted for ≥90 days	NA	37	≥20 years	26.2

Continued

Table 3 Continued

Country	Author	Study design	Definition of PHN*	Year	PHN cases	Age	Risk of PHN (%)
Japan	Kurokawa	Prospective cohort study in hospitals and clinics in Hyogo	Pain persisted for ≥90 days	2001–2003	78	All ages	24.7
Japan	Kanbayashi	Retrospective cohort study in pain treatment hospital	Pain persisted for ≥90 days	2008–2010	38	NA	52.0
South Korea	Ro	Retrospective, dermatology department hospital	NA	2007–2011	826	NA	39.4
South Korea	Song	Prospective cohort study in clinics	Pain ≥3 score for ≥90 days	2009–2010	58	≥50 years	38.4
South Korea	Cho	Prospective cohort study in clinics	Pain ≥3 score for ≥90 days	2010–2012	19	≥18 years	6.2
Thailand	Tunsuriyawong	Retrospective study of medical records at hospital	Physician diagnosis from medical record	1995–2000	67	All ages	16.8
Thailand	Aunhachoke	Prospective cohort study, recruited by GPs	Pain persisted for ≥90 days	2007–2008	35	≥50 years	19.4
Singapore	Goh	Prospective cohort study in dermatology clinic	Pain persisted for ≥90 days	1994–1995	46	All ages	28.0
India	Chaudhary	NA	NA	NA	33	NA	14.3
India	Abdul Latheef	NA	NA	NA	21	All ages	10.2
Argentina	Vujacich	Medical record database from ID reference centre	Pain persisted for ≥60 days and diagnosis from medical records	2000–2005	39	All ages	12.9
Argentina	Vujacich	Prospective cohort study, recruited by GPs	Pain ≥3 score for ≥90 days	NA	11	≥50 years	11.5

*For studies that used multiple definitions of PHN, we present results based on the definition that used at least 90 days of persistent pain.
GP, general practitioner; GPRD, general practice research database; HZ, herpes zoster; ICD, International Classification of Diseases; PHN, postherpetic neuralgia.

Table 4 Duration of postherpetic neuralgia (sorted by study design)

Country	Author	Method	Population	Duration of PHN
USA	Reda	A prospective cohort study of 8-year follow-up	14 patients with PHN with a median age of 65 years	Up to 4 years: 14%
Canada	Watson	A prospective cohort study of 11-year follow-up	156 patients with PHN with a median age of 71 years	1–11 years: 56%
UK	Hope-Simpson	A prospective cohort study of 26-year follow-up	46 patients with PHN ≥60 years of age	1–2 years: 7% 2–10 years: 22%
UK	McKendrick	A prospective cohort study of 9-year follow-up	158 patients with HZ ≥60 years of age	21% of patients with HZ had pain for >8 years
Iceland	Helgason	A prospective cohort study of 7-year follow-up	23 patients with PHN ≥60 years of age	1–7 years: 35% >7 years: 17%
France	Bouhassira	A prospective cohort study of 1-year follow-up	127 patients with PHN ≥50 years of age	>1 year: 50%
USA	Oster	A cross-sectional study	385 patients with PHN with a mean age of 77 years	1–2 years: 21% 2 to >10 years: 46%
UK	Bowsher	A cross-sectional study	39 patients with PHN with a mean age of 66 years	1–2 years: 21% 2 to >10 years: 33%
6 European countries	van Seventer	A cross-sectional study	84 patients with PHN with a mean age of 71 years	>1 years: 45%

HZ, herpes zoster; PHN, postherpetic neuralgia.

recurrence of HZ in Israel during 2 years of follow-up, while 2.3% of patients had recurrence in South Korea up to 10 years of obervation.[60 121] However, studies with a long-term follow-up period tended to report a higher risk of recurrence. Hope-Simpson *et al*[115] reported that 4.7% had recurrence of HZ during 16 years of follow-up in the UK. Similarly, Ragozzino *et al*[12] reported that 5.3% of patients had episodes of recurrence during more than 20 years of follow-up. A recent study by Yawn *et al*[120] also demonstrated that a recurrence of HZ occurred with a rate of 6.2% after 8 years of follow-up. The risk of recurrence may also depend on immune status.[120] Thus, overall risk of recurrence may vary by inclusion of those immunocompromised individuals.

Risk of HZO

HZO occurs when VZV reactivation affects the distribution of the ophthalmic division of the trigeminal nerve and can occur with or without eye involvement. Although the number of population-based studies is limited, similar risks of HZO were reported across studies. The reported risks of HZO among patients with HZ were 10.1% (Ragozzino *et al*,[12] USA), 12.3% (Chidiac *et al*,[35] France), 14.4% (Opstelten *et al*,[43] the Netherlands) and 14.9% (Alakloby *et al*,[61] Saudi Arabia). Borkar *et al*[124] reported an overall incidence of 30.9/100 000 person-years, which corresponds to an approximately 10% risk among patients with HZ in the USA. As has been previously recognised, the risk of HZO is similar across age groups.[123 124]

A wide range of eye complications, such as keratitis, uveitis and conjunctivitis, could result from HZO. The reported risk of these eye complications in patients with HZO ranged widely from approximately 30% to 78%.[125–129] In a population-based study in the USA, the risk of HZO with eye involvement among patients with HZ was 2.5%.[130] The HZ-associated eye complications required an average of 10 months of medical care with 6% of cases resulting in vision loss.[130]

Hospitalisation rates associated with HZ

We identified 28 studies that reported HZ-associated hospitalisation (table 5). All studies used hospital discharge or claims data. Rates of HZ-related hospitalisation ranged widely from 2 to 25/100 000 person-years in studies examining all ages. The variation in the estimates may reflect the differing admission criteria in the different settings. Hospitalisations with a primary diagnosis of HZ accounted for about 29–42% of HZ-related hospitalisations.[37 62 73] Studies that included hospitalisations with non-primary diagnosis codes (eg, secondary) may have overestimated the hospitalisation rate because they may represent prior or incidental HZ. Hospitalisation rates increased steeply with age, with the majority of the cases occurring in adults ≥50 years of age. For example, Jackson *et al*[73] reported HZ-associated hospitalisation rates (confirmed with medical records) ranging from 10/100 000 in adults 60–69 years of age to 65/100 000 in

Table 5 Hospitalisation rates associated with herpes zoster

Country	Author	Study design/database	Case ascertainment	Years	Age	Hospitalisation, 100 000 person-years	Older age group
USA	Lin	Hospital discharge data in Connecticut	ICD-9 primary or secondary	1986–1995	All ages	16.1	144.2 in ≥80 years
USA	Coplan	Kaiser Northern California	ICD-9 primary confirmed by medical charts	1994	All ages	2.1	9.3 in ≥60 years
USA	Patel	National inpatient sample data	ICD-9 any diagnostic position	1993–2004	All ages	25.0	112.3 in ≥60 years
USA	Jackson	Group Health in Washington medical records	ICD-9 primary confirmed by medical charts	1992–2004	≥50 years	14.0	65.1 in ≥80 years
Canada	Brisson	Hospital claims in Manitoba	ICD-9 any diagnostic position	1979–1997	All ages	NA	86.0 in ≥65 years
Canada	Edgar	Ministry of health service data in British Columbia	ICD-9/ICD-10 any diagnostic position	1994–2003	All ages	10.0	99.0 in ≥80 years
Canada	Tanuseputro	Hospital discharge data in Ontario	ICD-9/ICD-10 any diagnostic position	1992–2010	All ages	6.7	75.0 in ≥80 years
UK	Brisson	Hospitalisation episode statistics in England	ICD-9/ICD-10 any diagnostic position	1995–1996	All ages	NA	148.0 in ≥65 years
UK	Brisson	Hospitalisation episode statistics in England	ICD-10 primary diagnosis	1991–2000	All ages	4.4	19.1 in ≥60 years
France	Gonzalez-Chiappe	National hospital data	ICD-10 primary diagnosis	2005–2008	All ages	4.1	–
Germany	Ultsch	Federal health monitoring system	ICD-10 primary diagnosis	2007–2008	≥50 years	44.6	102.5 in ≥80 years
The Netherlands	de Melker	National healthcare registry	ICD-9/ICD-10 primary or secondary	1998–2001	All ages	2.7	19.0 in ≥80 years
The Netherlands	Pierik	Retrospective population-based study, GPs in Almere	Hospital referrals by GPs	2004–2008	All ages	15.5	–
Belgium	Bilcke	National Christian Sickness Fund	ICD-9 primary or secondary	2000–2007	All ages	14.2	85.0 in ≥80 years
Spain	Gil	National hospital data	ICD-9 any diagnostic position	1999–2000	All ages	8.4	–
Spain	Gil	National hospital data	ICD-9 primary or secondary	1998–2004	≥30 years	13.4	54.3 in ≥80 years
Spain	Bayas	National hospital data in Catalonia	ICD-9 any diagnostic position	1993–2003	All ages	9.7	–
Spain	Morant-Talamante	Electronic medical record database in Valencia	ICD-9 any diagnostic position	2007–2010	All ages	3.0	15.7 in ≥80 years
Spain	Gil-Prieto	National hospital data	ICD-9 any diagnostic position	2005–2010	All ages	10.3	–
Italy	Di Legami	Hospital discharge records in Piemonte	ICD-9 primary or secondary	2004	≥14 years	12.0	46.0 in ≥80 years
Italy	Gialloreti	National hospital discharge records	ICD-9 primary diagnosis	2003–2005	All ages	5.6	26.0 in ≥80 years
Portugal	Mesquita	National public hospital data	ICD-9 primary diagnosis	2000–2010	All ages	1.9	–
Sweden	Studahl	National patient register	ICD-10 primary diagnosis	2006–2010	All ages	6.9	–

Continued

Table 5 Continued

Country	Author	Study design/database	Case ascertainment	Years	Age	Hospitalisation, 100 000 person-years	Older age group
Australia	MacIntyre	National hospital morbidity data	ICD-9/ICD-10 any diagnostic position	1998–1999	All ages	25.0	300.0 in ≥80 years
Australia	Stein	National hospital morbidity data	ICD-10 primary diagnosis	1998–2005	≥50 years	28.0	95.8 in ≥80 years
Australia	Carville	Victoria admitted episode data	ICD-10 primary diagnosis	2006–2007	All ages	9.1	89.4 in ≥80 years
Taiwan	Jih	National health insurance registry	ICD-9	2000–2006	All ages	16.1	100.0 in ≥80 years
Taiwan	Lin	National health insurance registry	ICD-9	2000–2005	All ages	14.6	–

GP, general practitioner; ICD, International Classification of Diseases.

adults ≥80 years of age in the USA. Similarly, the rate of hospitalisation with primary diagnosis of HZ ranged from 13/100 000 in adults 60–64 years of age to 96/100 000 in adults ≥80 years of age in Australia.[62] The rates ranged from 31/100 000 in adults 60–64 years of age to 100/100 000 in adults ≥80 years of age in Germany.[41]

Mortality rates associated with HZ

Mortality rates associated with HZ ranged from 0.017 to 0.465/100 000 person-years in studies (see online supplementary table S2). Most studies reported that the majority of deaths occurred in adults ≥60 years of age.

DISCUSSION

HZ is a significant global health burden that is expected to increase as the population ages. The incidence rises steeply after 50 years of age and many working-age adults and elderly individuals are at increased risk. Risk of complications, particularly debilitating and long-lasting PHN, and hospitalisation is common in the elderly population. The major strength of our study is that we assessed the HZ burden across the globe and comprehensively reviewed incidence, risk of complications, hospitalisation and mortality. Our review included 63 studies on incidence, substantially more than the prior review by Thomas and Hall,[9] which included 17 studies with overall incidence ranging from 1.2 to 4.8/1000 person-years. Other reviews were restricted to specific geographic regions and/or assessed only incidence.[10 11]

Relatively similar estimates of the HZ incidence rate (between 3 and 5/1000 person-years) were reported in North America, Europe and Asia-Pacific. However, we observed some variations in estimates most likely due to the various study designs, case ascertainments, age distributions of the population and year of the study. It is difficult to accurately estimate the incidence rates because it is not a commonly reportable disease and surveillance systems are not usually in place. Most studies had limitations in their study methodology. Almost all studies may be susceptible to under-reporting due to patients who did not seek medical care. However, administrative database studies using diagnostic and billing codes may have overestimated the incidence due to misclassification. Several validation studies reported a relatively high sensitivity for the International Classification of Diseases (ICD)-9 code (98%) and positive predictive value (PPV; 84–94%).[15 83 139] Furthermore, studies using administrative insurance data may lack generalisability because they may not be representative of the general population. Population-based surveillance studies face difficulty in estimating the numbers of the population at risk in the study catchment area. Several prospective cohort studies that identified relatively small numbers of patients with HZ (eg, by Scott *et al*, Paul and Thiel, Di Legami *et al* and Lionis *et al*) may have

underestimated the rate of HZ due to under-reporting of cases or inaccuracy in estimating the numbers of the population at risk. In spite of these limitations, it is reassuring to find similar incidences across countries in well-conducted studies.

There is a scarcity of research examining the incidence of HZ in Asia, Latin America and Africa. HZ may be regarded as a low health priority in many of these countries; however, the proportion of people ≥60 years of age is projected to double in the next several decades, and the numbers of HZ cases are expected to increase substantially. Further research is needed because it is unclear whether the incidence would be similar in these regions. Age-specific incidence rates may vary because of the regional differences in epidemiology of varicella infection and VZV genotype distribution. Varicella primarily affects young children in temperate countries, whereas varicella tends to occur at a later age during adolescence and adulthood, presenting in severe form with frequent risks of complication and mortality in tropical countries.[140 141] Severe varicella infections during adolescence may result in greater numbers of VZVs remaining latent and possibly resulting in earlier reactivation of VZV.[142] The distribution of VZV clades varies globally.[143 144] VZV can be classified into at least five major clades. VZV clades 1 and 3 are dominant strains in Europe and the Americas, whereas clade 2 is a dominant strain in Asia and clade 5 in Africa.[143] Molecular epidemiology of VZV is still an active area of investigation and requires more research. Furthermore, the incidence of HZ may be higher in the countries heavily affected by HIV/AIDS or other immunocompromising conditions.

Hope-Simpson[4] hypothesised that exogenous exposure to VZV from individuals with varicella or HZ may boost VZV-specific cell-mediated immunity and thereby decrease the risk of HZ. Because varicella vaccination programmes reduce VZV circulating in the community, thus potentially leading to a decrease in the opportunity for boosting immunity against VZV, it has been hypothesised that the introduction of varicella vaccination might increase the incidence of HZ in the population. However, based on the current literature, there is no conclusive evidence as to whether varicella vaccination programmes have been associated with an increase in the incidence of HZ. In fact, a number of studies across countries have found an increase in the incidence of HZ before introduction of the varicella vaccination programme. It is unclear why the incidence of HZ is increasing. The temporal change or emergence of infectious disease is usually due to changes in the society, technology, virus itself or environment, such as climate change.[145] The temporal increase was independent of age. It may partly be explained by an increase in the prevalence of risk factors, an increase in the use of immunosuppressive agents (eg, chemotherapy) or an increase in diagnosis through improved access to healthcare and public awareness. Because HZ is usually clinically diagnosed, diagnostic modalities are unlikely to have affected the reported incidences. Given the steady continuous increase in the incidence of HZ across age groups, it is plausible that a genetic change in the VZV may be playing a role. For example, a study in the UK suggested that changes in genotype distribution have occurred through importation of different strains.[146] Although VZV is considered a genetically stable virus, a recombination between different VZV strains could possibly occur.[143 147]

We reviewed the risk of PHN in patients with HZ. Several long-term prospective cohort studies demonstrated that more than 30% of patients with PHN could experience pain lasting for more than 1 year. The reported risk of developing PHN in patients with HZ varied widely from 5% to more than 30%. The risk of PHN may have differed across countries due to the varying prevalence of disability and other underlying comorbidities in the elderly population.[8 148] However, we could not conclude whether the risk of PHN differed by country because of wide variation. The wide variation in the estimates could be partly due to the different study designs used in prior studies. Prospective cohort studies of patients with HZ tend to report greater risk of PHN than studies utilising electronic medical records or administrative databases. We found that administrative database studies often face a numbers of challenges in identifying patients with PHN and they are likely to underestimate the risk of PHN. Currently, there is only one study, by Klompas *et al*,[83] that developed and validated an algorithm for PHN using ICD-9 codes and claims for a filled prescription. The algorithm detected PHN with a sensitivity of 86% and PPV of 78%; however, they defined PHN as a persistent pain for 30 days or more after zoster onset rather than 90 days or more. More validation studies are needed.

Researchers used different definitions of PHN. A difficulty in reaching consensus on a definition for PHN is probably due to a multifactorial pathophysiological nature of the condition and difficulty in objectively assessing the pain.[149] Patients with PHN also experience different types of pain including a steady burning pain, a sudden stabbing pain or stimulus-evoked pain (allodynia). The best option for defining PHN would be clinically meaningful pain lasting for more than 90 days after rash onset, considering the pathophysiology and definitions suggested from prior trials on antiviral treatment and zoster vaccination.[6 150 151] We also believe that healthcare utilisation patterns and prescribed treatment for PHN vary across countries and that characterising the treatment patterns would be important for future research.

Several prior studies with a long-term follow-up found that recurrence of HZ is frequent, with a rate of 5–6%, which is comparable to rates of first occurrence of HZ. However, a limited number of studies examined the risk of recurrence and more studies are needed to confirm these findings. There were a limited number of population-based studies examining HZO, a severe condition that may lead to significant visual impairment.

Several limitations of this review are worth noting. Because the quality of the study, study design and age distribution of population varied widely across studies, we could not synthesise the data quantitatively to estimate the pooled incidence rates. We did not conduct a formal study quality assessment. However, we described the study design and outcome ascertainment of each study and discussed limitations of studies. Our review focused on general populations, primarily immunocompetent populations, and we did not include studies restricted to immunocompromised populations (such as HIV/AIDS, malignancy or autoimmune disease). Our review also did not include uncommon complications of HZ, such as Ramsay Hunt syndrome, Bell's palsy and transverse myelitis.

In conclusion, similar age-specific incidence of HZ was reported in North America, Europe and Asia-Pacific; however, there is a scarcity of research from other regions. Risk of complications, particularly PHN, and hospitalisation is common in the elderly population. HZ is a global health burden that is expected to increase as the population ages across the world in the near future. The prevalence of disability in the elderly populations is also increasing. It is important for healthcare practitioners and health policymakers to consider implementing effective preventive measures such as vaccination against HZ across the globe.

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