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REVIEW

Herpes Zoster Recurrence: A Narrative Review of the Literature

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ABSTRACT

Introduction: Herpes zoster (HZ; shingles) is a painful, cutaneous disease caused by reactivation of the varicella zoster virus, which causes varicella (chickenpox) typically during childhood. The considerable healthcare burden of HZ is relatively well documented, with approximately one in three individuals experiencing at least one episode during their lifetime, debilitating symptoms including neuropathic pain, and complications such as post-herpetic neuralgia, vision loss, and rarely, stroke, and increased severity in immunocompromised individuals. However, we are not aware of a comprehensive review of literature specifically examining the burden of HZ recurrence.

Methods: We conducted a PubMed search (1 January 2003–2 February 2023) to assess available literature on the incidence, risk factors, and clinical features of HZ recurrence.

Results: The incidence of HZ recurrence reported by the studies identified was wide ranging. Studies in general populations of immunocompetent or immunocompetent/immunosuppressed (mixed) populations with an initial HZ episode estimate that approximately 1.2–9.6% of individuals may experience HZ recurrence, with an incidence rate of 1.7–16.6 cases per 1000 person-years. HZ recurrence was reported in 0.0–18.2% of immunocompromised individuals with HZ, with an incidence rate of 17.0–55 cases per 1000 person-years. Incidence rates varied according to study design, follow-up, and study populations. Recognized risk factors for HZ recurrence include immunocompromised status, female sex, family history, and comorbidities such as diabetes. Other factors that may predispose individuals to recurrence include long-lasting pain after the initial HZ episode and the presence of herpes zoster ophthalmicus.

Discussion: Our review underlines that following an initial HZ episode, individuals remain at risk of HZ recurrence, adding to the disease burden in a population. As HZ is preventable by vaccination, national HZ vaccination recommendations should include the need for and

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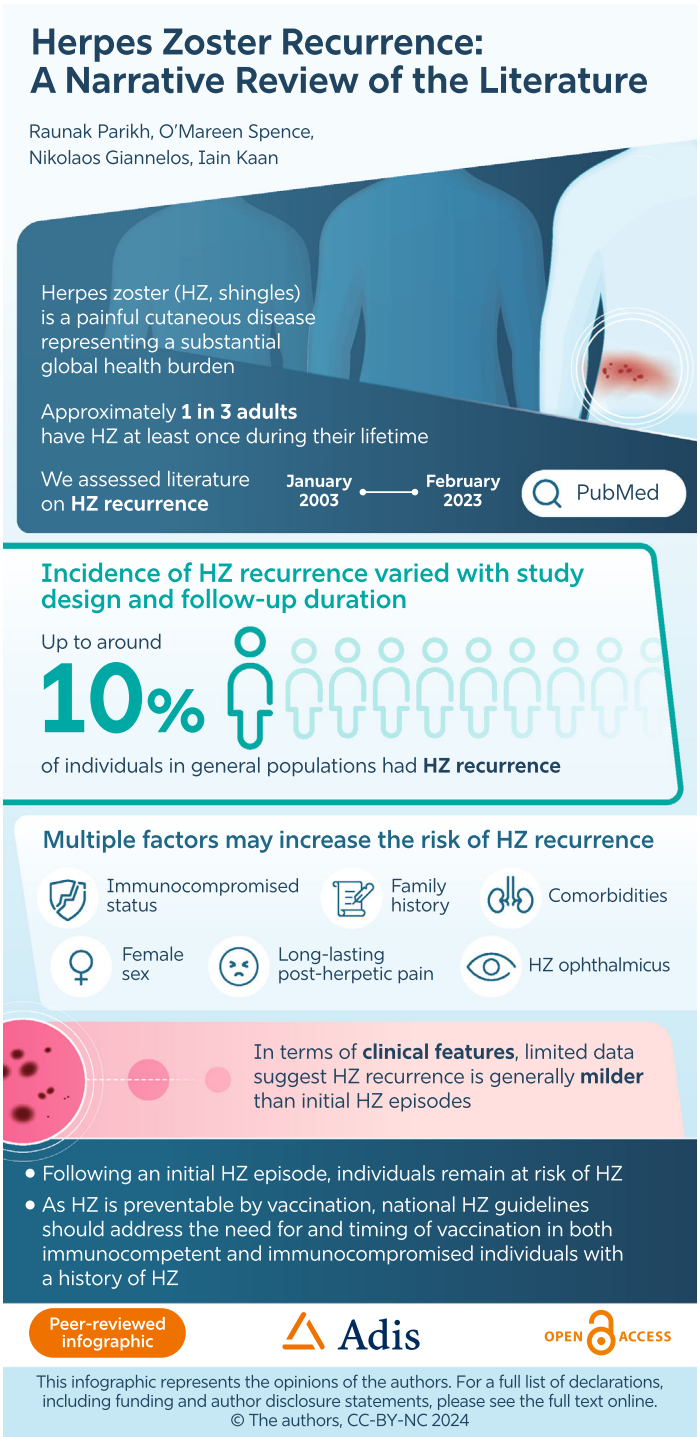
timing of vaccination in both immunocompetent and immunocompromised individuals who have a history of HZ.

PLAIN LANGUAGE SUMMARY

Herpes zoster (HZ), also known as shingles, results from the same virus that causes chickenpox in childhood. In shingles, the chickenpox virus is reactivated, most commonly causing a painful skin rash. About one in three people have shingles at least once in their lifetime. Neuralgia (a burning, stabbing, and sometimes severe pain along a nerve pathway) may continue for months after the initial rash. Shingles may lead to loss of vision and rarely stroke. Shingles is more severe in people with weakened immunity. We reviewed published information on shingles recurrence (i.e., a second, third, or later episode of shingles), as we were not aware of a broad review of information specifically on recurrence. We focused on the rate of recurrence and factors that increase the risk of recurrence. Overall, in around one-tenth of individuals who experience shingles, the disease may reoccur after complete resolution. The rate of recurrence varied on the basis of how the studies were carried out and the type of patients included in the studies. Well-known factors that increase the risk of shingles recurrence are reduced immunity, female sex, family history, and other conditions (e.g., diabetes). Other factors that may increase the risk of shingles recurrence include pain that lasts for a long time after the first episode of shingles and having herpes zoster ophthalmicus, which leads to eye complications. Our review summarizes available data. As shingles is preventable by vaccination, strategies to prevent this disease should include those who have a history of shingles.

Graphical Abstract:



Keywords: Complications; Epidemiology; Herpes zoster; Incidence; Older adults; Recurrence; Risk factors; Shingles

Key Summary Points

Approximately one third of adults experience herpes zoster (HZ) during their lifetime, representing a substantial global health burden.

HZ recurrence is not limited to immunocompromised individuals; studies in the general population estimate that approximately 10% of individuals may experience an HZ recurrence in the first decade after an initial HZ episode.

Estimates for the incidence of HZ recurrence varied according to study follow-up duration and study population, with an incidence rate of up to 55 per 1000 person-years in certain immunocompromised individuals, and HZ can reoccur multiple times.

Factors that may predispose individuals to HZ recurrence include immunocompromised status, female sex, long-lasting post-herpetic pain, chronic conditions (e.g., diabetes, kidney disease, chronic obstructive pulmonary disease), and herpes zoster ophthalmicus.

As HZ is preventable by vaccination, national guidelines should address the need for and timing of vaccination in both immunocompetent and immunocompromised individuals who have a history of HZ.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24998819.

INTRODUCTION

Varicella zoster virus (VZV) is a double-stranded DNA alphaherpesvirus that causes both varicella (chickenpox) and herpes zoster (HZ; shingles) [1, 2]. Varicella is the clinical presentation of primary infection [1]. Most individuals are affected by VZV during childhood [1]. VZV remains latent in ganglionic neurons, primarily in the trigeminal nerve and dorsal roots of spinal nerves [3], and can become reactivated, sometimes more than once, to cause episodes of HZ.

The considerable healthcare burden of HZ is relatively well documented. HZ is characterized by a painful, erythematous, maculopapular, vesicular rash [1, 2, 4], typically on one or two adjacent facial or thoracic dermatomes [5], and can lead to a range of complications. Up to 30% of individuals with HZ experience post-herpetic neuralgia (PHN); other potential complications include scarring, secondary bacterial infections, myelitis, meningitis, and stroke [1, 6–8]. In addition, involvement of the ophthalmic branch of the trigeminal nerve, known as herpes zoster ophthalmicus (HZO), affects 10–20% of patients, causing ocular symptoms and risk of vision loss [2, 9].

Approximately one in three individuals experience HZ at least once during their lifetime, representing a substantial global health burden [1, 6]. VZV reactivation is a consequence of declining cell-mediated immunity, and HZ is therefore a particular concern in older individuals, people with immunocompromising disease, or people receiving immunocompromising treatments, which can result in more severe, complicated disease manifestations [1, 6]. Other established risk factors for HZ include family history and female sex [1, 2, 4].

Following an initial episode, HZ can reoccur. Although discussed in general reviews of HZ, to the best of our knowledge, there has been no comprehensive review of available literature specifically examining the burden and characteristics of HZ recurrence. Recurrence is not limited to immunocompromised individuals, and can occur more than once in the same

individual [10, 11]. Recommendations on the use of HZ vaccines from the Advisory Committee on Immunization Practices (ACIP), which is composed of medical and public health experts who develop recommendations on the use of vaccines in the civilian population of the USA, include that adults with a history of HZ should receive recombinant zoster vaccine [12, 13]. To consolidate the literature on the burden of recurrent HZ, we conducted a non-systematic literature review, and discuss what is known about the incidence of, risk factors for, and clinical features of recurrent HZ.

METHODS

We searched the National Library of Medicine PubMed database on 2 February 2023, using the search string "(zoster[title/abstract]) AND (recurren*)," between 1 January 2003 and 2 February 2023. Editorials, case reports, narrative reviews, and non-English articles were excluded. Included studies were categorized according to data collection (retrospective or prospective); data source (medical records, insurance claims, or physician survey); case definition (based on clinical presentation, antiviral prescription, or confirmed laboratory test); country; inclusion criteria (general population or limitations by specific medical conditions or immune status); duration of follow-up; and statistical/analytical approaches used. This article is based on previously conducted studies and does not contain any new studies (with human participants or animals) performed by any of the authors. Here, we provide a narrative review of the study findings, organized around the following questions: (1) How common is HZ recurrence? (2) What factors increase the risk of HZ recurrence? (3) What are the clinical features of recurrent HZ? and (4) How does the incidence and course of recurrent HZ change in patients with HZO?

RESULTS AND DISCUSSION

A total of 617 records were identified and manually reviewed (titles/abstracts) by the authors for relevance; 44 records were selected for full-text review, after which 28 studies reporting on HZ recurrence in adults, and one systematic literature review of HZ incidence and recurrence rates, were included in this review. Overall, HZ identification was based largely on diagnostic codes (with or without data on antiviral prescriptions). Other studies identified HZ on the basis of review of medical records or clinical history, with polymerase chain reaction (PCR) testing in some cases. A prospective Japanese study [14] and a South Korean study [15] used telephone calls and follow-up clinical assessments, with PCR testing and serology. Overall, PCR testing was involved to some extent in only six studies [10, 14–18]. Where reported, duration of follow-up was shortest at approximately 2 years (median) and longest at up to 27 years.

Table 1 summarizes the results of 12 studies reporting HZ recurrence rates in immunocompetent or immunocompetent/immunosuppressed (mixed) patient populations. Table 2 summarizes the results of 14 studies reporting recurrence rates in immunocompromised populations. Table 3 summarizes the results of eight studies reporting recurrence rates in individuals with HZO.

How Common Is HZ Recurrence?

Proportion of Subjects with HZ Recurrence

In total, 11 of the studies in populations of immunocompetent or immunocompetent/immunosuppressed (mixed) individuals with an initial HZ episode reported on the percentage of individuals who experienced HZ recurrence, with estimates ranging from 1.2% to 9.6% (Table 1, Fig. 1) [10, 11, 14–16, 19–24]. Of these 11 studies, one provided only the percentage of study participants developing recurrent HZ, with no data on incidence rates per 1000 person-years (PY) and no time-to-event analyses [15]. The study was relatively large and long-term, surveying 14,343 inpatients and outpatients diagnosed with HZ between January 2005 and December 2015 at six hospitals in South Korea. The study reported that 169 patients experienced recurrence (a recurrence frequency

Table 1 Rates of HZ recurrence in population-based studies in immunocompetent or immunocompetent/immunosuppressed (mixed) patient populations

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Crude rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Batram 2021 [19]	Germany	Retrospective matched cohort based on claims data	Patients with incident HZ diagnosis in 2008 (N = 43,003)	HZ diagnostic codes and corresponding antiviral prescription	NR	4141/43,003 (9.6%)	NR	Aged < 50 years, 10-year follow-up: > 15% aged ≥ 60 years, 10-year follow-up: 5–10%
Qian 2021 [20]	Australia	Prospective cohort	Patients with an initial HZ episode, 2006–2009 (N = 17,413)	HZ diagnostic codes or antiviral prescription	Up to 8 years	675/17,413 (3.9%)	11.1	NR
Sun 2021 [21]	China	Retrospective review of electronic health records	Patients aged ≥ 50 years with an initial HZ episode, 2015–2017 (N = 4314; 16.0% IC)	HZ diagnostic codes	Up to 3 years	99/4313 (2.3%)	16.6	NR
Muñoz-Quiles 2020 [25]	Spain	Retrospective review of electronic health records	Immunocompetent adults aged ≥ 18 years, 2009–2014 (N = 4,382,590; number with an initial HZ episode NR)	HZ diagnostic codes	Up to 6 years	NR	15.6	NR
Tseng 2020 [22]	USA	Retrospective review of electronic health records	Immunocompetent, unvaccinated patients aged ≥ 50 years, with an initial episode, 2007–2008 (N = 11,716)	HZ diagnostic codes and antiviral prescription	Mean 5.6 years	713/11,716 (6.1%)	11.0	10 years: 10.3%

Table 1 continued

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Crude rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Kim 2018 [11]	South Korea	Retrospective review of health insurance database	Patients aged ≥ 20 years with an initial HZ episode, 2002–2013 (*N* = 39,441; 13.7% IC)	HZ diagnostic codes and antiviral dispensation	Mean 4.4 years	2100/39,441 (5.3%)	12.0	10 years: > 10%
Ha 2017 [15]	South Korea	Retrospective review of medical records and telephone survey	Patients with an HZ episode, 2005–2015 (*N* = 14,343; 11.6% IC)	Clinical history, dermatologist review and, if needed, laboratory testing	NR	169/14,343 (1.2%)	NR	NR
Shiraki 2017 [16]	Japan	Physician survey	Patients with an HZ episode, 2009–2015 (*N* = 16,784)	Clinical with laboratory testing	NR	1076/16,784 (6.4%)	1.7	NR
Nakamura 2016 [14]	Japan	Prospective cohort	Patients aged ≥ 50 years with an initial HZ episode, 2008–2011 (*N* = 1992)	Telephone call, followed-up with clinical assessment plus PCR testing and serology	Up to 3 years	60/1992 (3.0%)	10.1	NR
Russell 2014 [23]	Canada	Retrospective review of administrative health databases	Patients with a medically attended HZ episode, 1994–2010 (*N* = 194,584) 57.4% of patients aged ≥ 45 years	HZ diagnostic codes[a]	Up to 16 years	194,584/3,109,255 (6.3%)	4.5	NR

Table 1 continued

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Crude rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Tseng 2012 [24]	USA	Retrospective review of electronic health records	Immunocompetent, VZV-unvaccinated patients aged ≥ 60 years with a first episode of HZ, 2007–2010 (*N* = 5180)	HZ diagnostic codes	Up to 4.3 years	77/5180 (1.5%)	7.5	NR
Yawn 2011 [10]	USA	Retrospective review of medical records	Patients with an initial episode of HZ, 1996–2001 (*N* = 1669; 8.3% IC)	Detailed medical record review, with laboratory confirmation in 24.8% of cases	Mean 7.3 years	95/1669 (5.7%)	NR	8 years: 6.2%

HZ herpes zoster, *IC* immunocompromised, *NR* not reported, *PCR* polymerase chain reaction, *PY* person-years, *VZV* varicella zoster virus

[a]Recurrent HZ is HZ diagnostic code ≥ 180 days after the first

Table 2 Rates of HZ recurrence in immunocompromised patient populations

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Jeong 2022 [26]	South Korea	Retrospective review of health insurance database	Patients with RA prescribed bDMARDs or tofacitinib between 2010 and 2019 with a history of HZ (*N* = 1722)	HZ diagnostic codes and antiviral prescription	Median 2.7 years	314/1722 (18.2%)	NR	NR
Winthrop 2022 [27]	International	Post hoc analysis of pooled data from 21 RA and 3 PsA clinical studies	Patients aged ≥ 18 years clinically determined to have HZ during the studies (*N* = 783)	Clinically determined	Median 3.2 years	RA: 63/783 (8.0%) PsA: 1/783 (2.8%)	NR	NR
Qian 2021 [20]	Australia	Prospective cohort	Patients with an initial HZ episode, 2006–2009 (*N* = 17,413)	HZ diagnostic codes or antiviral prescription	Up to 8 years	NR	17.0	NR
Sun 2021 [21]	China	Retrospective review of electronic health records	Patients aged ≥ 50 years with an initial HZ episode, 2015–2017 [*N* = 4314; *n* = 692 (16.0%) IC]	HZ diagnostic codes	Up to 3 years	0/692 (0%)	NR	NR

Table 2 continued

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Muñoz-Quiles 2020 [25]	Spain	Retrospective review of electronic health records	Adults aged ≥ 18 years, 2009–2014 [*N* = 4,382,590; number with an initial HZ episode NR; *n* = 584,873 (15.2%) IC]	HZ diagnostic codes	Up to 6 years	NR	22.8 overall HSCT: 55 HN: 34 HIV+ : 32 SOT: 30 SLE: 28 Neoplasias: 25 IBD: 25 RA: 24 SON: 24 Autoimmune: 21 MS: 19 AT: 18 PsO: 18	NR

Table 2 continued

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Kim 2018 [11]	South Korea	Retrospective review of health insurance database	Patients aged ≥ 20 years with an initial HZ episode, 2002–2013 [*N* = 39,441; *n* = 5408 (13.7%) IC]	HZ diagnostic codes and antiviral prescription	Mean 4.4 years	373/2100 (17.8%) Autoimmune disease: 172/2100 (8.2%) Solid cancer: 150/2100 (7.1%) Chronic renal disease: 75/2100 (3.6%) Hematologic malignancy: 25/2100 (1.2%) Chronic hepatic disease: 21/2100 (1.0%) HIV/AIDS: 3/2100 (0.1%)	NR	NR
Ha 2017 [15]	South Korea	Retrospective review of medical records and telephone survey	Patients with an HZ episode, 2005–2015 [*N* = 14,343; *n* = 1663 (11.6%) IC]	Clinical history, dermatologist review, and if needed, lab testing	NR	40/1663 (2.4%)	NR	NR

Table 2 continued

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Barton 2012 [33]	USA	Retrospective review of medical records	Adults (aged ≥ 18 years) with CVID/IgGSD attending outpatient departments, 1998–2008 (*N* = 212; *n* = 31 with HZ recurrence)	HZ diagnostic codes	Mean 7.6 years	5/31 (16.1%)	NR	NR
Yawn 2011 [10]	USA	Retrospective review of medical records	Patients with an initial episode of HZ, 1996–2001 [*N* = 1669; *n* = 139 (8.3%) IC]	Detailed medical record review, with laboratory confirmation in 24.8% of cases	Mean 7.3 years	15/139 (10.8%)	NR	8 years: 12.0%
Borba 2010 [30]	Brazil	Retrospective review of database records	Patients with SLE and definitive HZ infection (*N* = 51)	Clinical history	NR	4/51 (7.8%)	NR	NR
Charlier 2009 [29]	France	Retrospective review of medical charts	Patients aged ≥ 12 years with WG, 1984–2006 (*N* = 113)	HZ diagnostic codes	Median 6 years	9/113 (8.0%)	NR	NR

Table 2 continued

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Fuks 2009 [32]	Israel	Retrospective review of medical records	Adults (aged ≥ 18 years) who received lung transplantation between 2001 and 2007, with post-transplant episode of HZ (*N* = 198; *n* = 23 with first HZ episode)	HZ diagnostic codes and antiviral prescription	Median 34 months	0/23 (0%)	NR	NR
Manuel 2008 [31]	Canada	Retrospective review of medical records	Adults (aged ≥ 18 years) who received lung transplantation, 2001–2005 (*N* = 239; *n* = 29 with first HZ episode)	Clinically determined	Median 23.7 months	4/29 (13.8%)	NR	NR
Gebo 2005 [28]	USA	Retrospective review of medical records	HIV+ patients with an HZ episode, 1997–2001 (*N* = 239; *n* = 158 incident cases)	HZ diagnostic codes	Up to 4 years	HIV+ : 8/158 (5.1%) within 6 months of initial event; 7/158 (4.4%) between 60 and 180 days of initial event; 10% by 1 year	NR	NR

AIDS acquired immunodeficiency syndrome, *AT* autoimmune thyroiditis, *bDMARD* biologic disease-modifying anti-rheumatic drug, *CVID* common variable immunodeficiency, *HIV* human immunodeficiency virus, *HN* hematologic neoplasia, *HSCT* hematopoietic stem cell transplant, *HZ* herpes zoster, *IBD* inflammatory bowel disease, *IC* immunocompromised, *IgGSD* immunoglobulin G subclass deficiency, *MS* multiple sclerosis, *NR* not reported, *PsA* psoriatic arthritis, *PsO* psoriasis, *PY* person-years, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *SON* solid organ neoplasia, *SOT* solid organ transplant, *WG* Wegener granulomatosis

Table 3 Rates of HZ recurrence in individuals with HZO

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Crude rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Lee 2021 [37]	South Korea	Retrospective review of medical records	Patients diagnosed with HZO, 2009–2016 ($N = 130$)	HZ diagnostic codes and antiviral prescription	Up to 7 years	19/130 (14.6%)	NR	NR
Lu 2019 [39]	New Zealand	Retrospective review of medical records	Patients with HZ-related keratitis and/or uveitis who had cataract surgery ($N = 57$)	HZ diagnostic codes	NR	23/57 (40.4%) after surgery	NR	NR
Tran 2016 [35]	USA	Retrospective review of medical records	Patients with HZO clinical diagnosis (with or without eye involvement), 2010–2014 ($N = 90$; $n = 83$ with recurrent HZ)	HZ diagnostic codes	Mean 3.9 years	16/83 (19.3%)	NR	1 year: 8% 3 years: 17% 5 years: 25% 6 years: 31%
He 2015 [40]	USA	Retrospective review of medical records	Patients with history of HZO who had cataract surgery ($N = 24$ eyes)	Clinical history	NR	Recurrent keratouveitis: 5/24 (20.8%) before surgery; 6/24 (25.0%) after surgery	NR	NR

Table 3 continued

Study	Country	Design	Population (*N*)	HZ diagnosis	Follow-up duration	Recurrence		
						Crude rate, *n/N* (%)	Incidence, cases per 1000 PY	Cumulative risk, %
Miserocchi 2014 [17]	Italy	Retrospective review of medical records	Patients with herpetic ocular infection, 2006–2013 (*N* = 241; *n* = 189 with HSV, *n* = 45 with VZV, and *n* = 7 with CMV)	Clinical and laboratory history	Mean 24.9 months	Recurrent eye disease: 148/241 (61.4%) overall, 123/189 (65.1%) for HSV, 23/45 (51.1%) for VZV, and 2/7 (28.6%) for CMV	NR	NR
Yawn 2013 [36]	USA	Retrospective review of medical records	Patients with confirmed HZ and eye involvement, 1980–2007 (*N* = 184)	HZ diagnostic codes	Up to 27 years	Recurrent uveitis: 14/184 (7.6%) Recurrent keratitis: 13/184 (7.1%)	NR	NR
Hu 2010 [18]	USA	Retrospective review of medical records	Patients with history of HZO and late VZV dendriform keratitis (*N* = 20)	HZ diagnostic codes and PCR of VZV DNA	Mean 2.7 years	10/19 (52.6%)	NR	NR
Tugal-Tutkun 2010 [38]	Turkey	Retrospective review of medical records	Patients diagnosed with herpetic anterior uveitis, 1996–2006 (*N* = 111)	HZ diagnostic codes and antiviral prescription	Median 22.4 months	43/111 (38.7%)	NR	NR

CMV cytomegalovirus, *HSV* herpes simplex virus, *HZ* herpes zoster, *HZO* herpes zoster ophthalmicus, *NR* not reported, *PCR* polymerase chain reaction, *PY* person-years, *VZV* varicella zoster virus

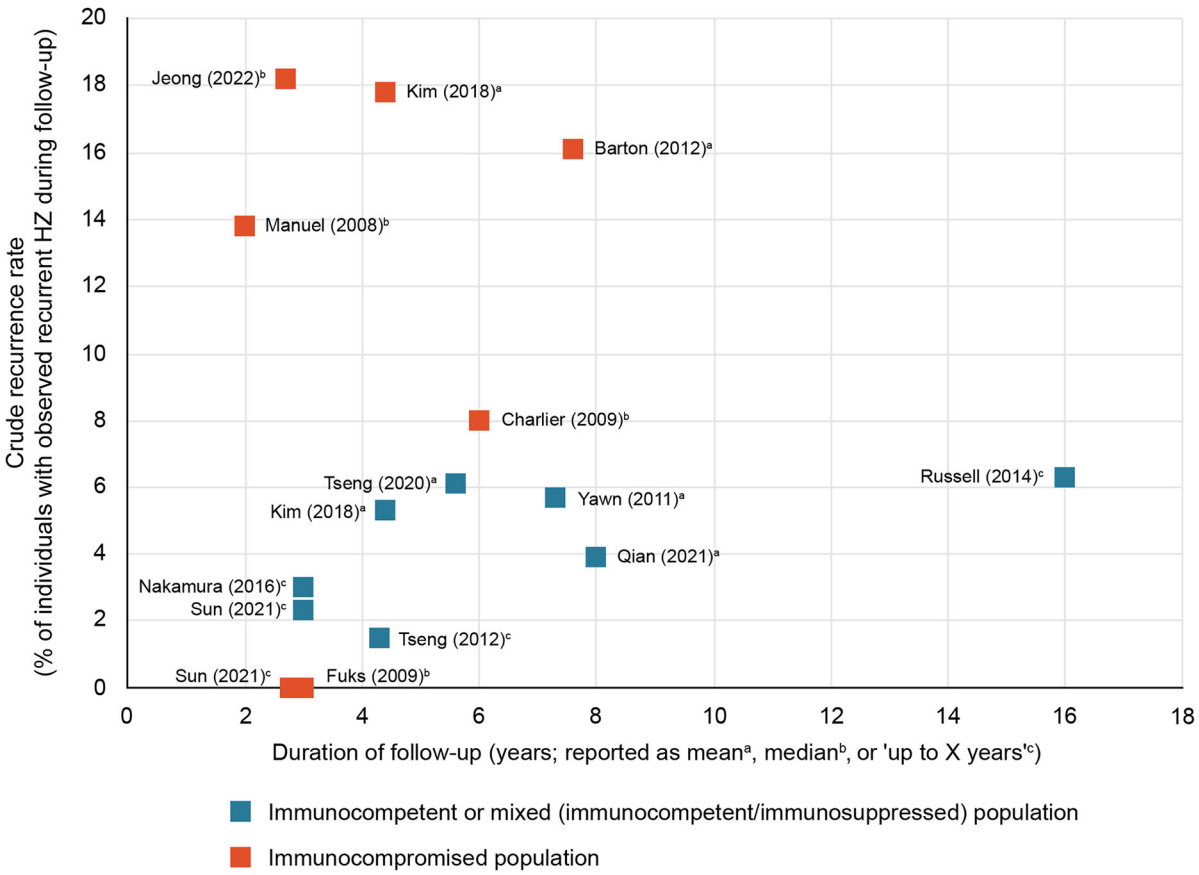


Fig. 1 Recurrence of HZ reported in studies identified in the literature search. [a]Mean duration of follow-up; [b]median duration of follow-up; [c]duration of follow-up up to the number of years shown on the *x*-axis. *HZ* herpes zoster

of 1.2%); however, the number of recurrences per patient was not reported [15].

Incidence Rates for HZ Recurrence

A total of eight of the studies (two each in Japan and the USA, and one each in Australia, China, South Korea, and Spain) in immunocompetent only or immunocompetent/immunosuppressed (mixed) populations with an initial HZ episode reported incidence rates per 1000 PY, with estimates ranging from 1.7 to 16.6 [11, 14, 16, 20–22, 24, 25]. Most of these studies were retrospective reviews of electronic health records. The lowest recurrent incidence rate (1.7 per 1000 PY) was reported in one of the Japanese studies (a physician survey) [16]; the next lowest recurrent incidence rate (7.5 per 1000 PY) was reported in a US retrospective study with up to 4.3 years of follow-up [24]. The other Japanese study, a prospective cohort study of individuals aged ≥ 50 years with up to 3 years of follow-up, reported a recurrent incidence rate of 10.1 per 1000 PY [14]. A similar recurrent incidence rate of 11.1 per 1000 PY was reported in the only other prospective cohort study, an Australian study including all individuals with an initial HZ episode between 2006 and 2009, and with up to 8 years of follow-up [20].

Time-to-Event Analyses

A total of three studies (two of which are discussed above) in immunocompetent or mixed populations with an initial HZ episode included a time-to-event analysis in the overall population. All three were retrospective studies; one from South Korea [11] and two from the USA [10, 22]. A fourth study, from Germany, included a time-to-event analysis stratified by age,

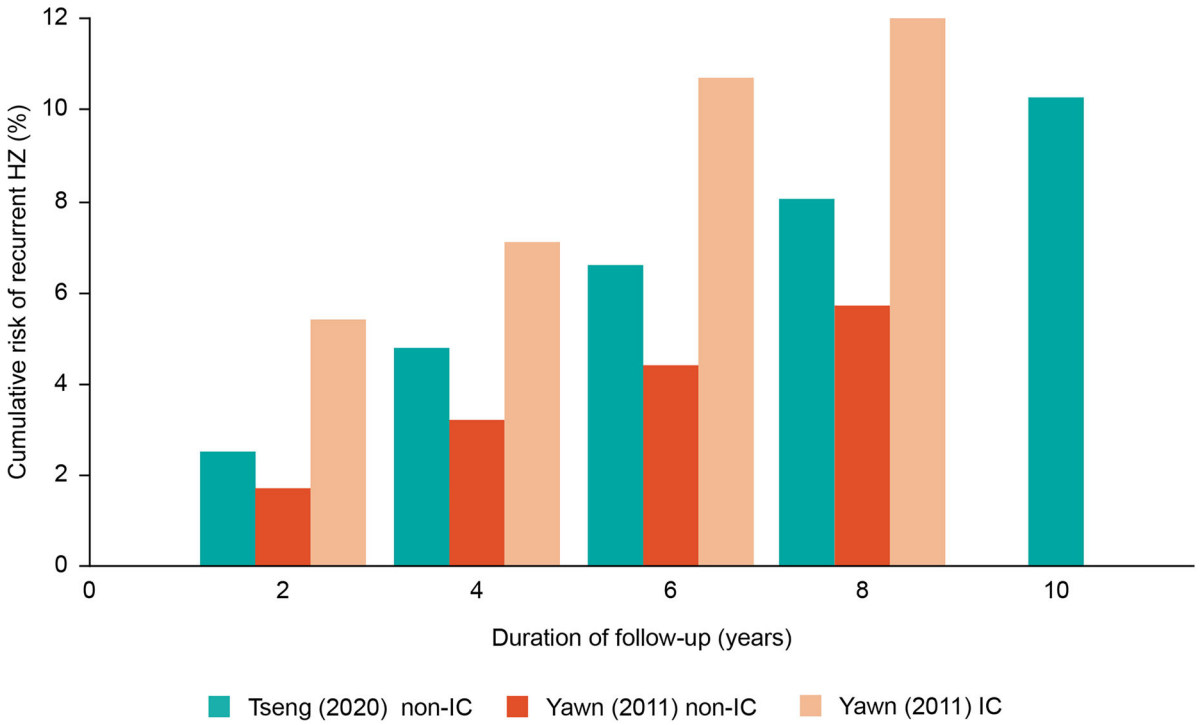


Fig. 2 Time-to-event analysis of the cumulative risk of HZ reported in studies identified in the literature search[a]. [a]After 10 years' follow-up in other studies, the cumulative risk of HZ was reported as < 15% (Batram 2021; patients aged > 50 years), ≥ 10% (Kim 2018), or 5–10% (Batram 2021; patients aged ≥ 60 years). *HZ* herpes zoster, *IC* immunocompromised, *non-IC* non-immunocompromised

without reporting overall population results [19]; this study is listed in Table 1 but is discussed separately in a subsequent section on older age. The most recent of the three time-to-event studies was a US study that used state (California) electronic health records to analyze the first recurrence of HZ in immunocompetent, unvaccinated individuals aged ≥ 50 years who experienced an initial HZ episode between 2007 and 2008 [22]. Individuals were followed up until 2016, and recurrence was based on HZ International Classification of Diseases (ICD)-9 codes 053.xx (or ICD-10 codes B02.xx beginning from October 2015) and antiviral prescription (aciclovir, famciclovir, or valaciclovir). The cumulative risk of HZ recurrence was estimated as 2.5% at 2 years, 4.8% at 4 years, 6.6% at 6 years, 8.0% at 8 years, and 10.3% at 10 years (Fig. 2). These findings were consistent with an earlier US study that analyzed HZ recurrence among 1669 residents of Olmsted County, Minnesota, USA, of whom most (91.7%) were immunocompetent [10]. Following an initial HZ episode between 1996 and 2001, 95/1669 individuals (5.7%) had subsequent HZ episodes over a mean follow-up period of 7.3 years. Recurrence was based on detailed medical record review and was supported by laboratory testing in 24.8% of cases. Time-to-event analyses estimated the cumulative recurrence risk as 2.0% at 2 years, 3.6% at 4 years, 4.9% at 6 years, and 6.2% at 8 years (Fig. 2). Among immunocompetent individuals only, 80/1530 individuals (5.2%) had recurrence, with the 8-year cumulative recurrence risk estimated as 5.7% [10].

The third study using time-to-event analyses was conducted in South Korea and based on a national health insurance records database [11]. The study population was made up of 39,441 individuals with an initial HZ episode between 2002 and 2013 who were followed-up for recurrence, defined by diagnostic coding and antiviral prescription. Time-to-event curves indicated a linear increase in the cumulative

rate of HZ recurrence in the decade following the initial episode, with an estimated cumulative rate exceeding 10% at 10 years [11]. Overall, the three time-to-event studies yielded broadly consistent findings, with no evidence of plateauing of HZ recurrence in the time periods covered (up to 10 years after the initial HZ episode). These studies suggest that individuals may be exposed to a uniformly increasing cumulative risk of HZ recurrence after the first episode. More studies of this type are required to confirm this hypothesis, both in more varied populations and over longer time periods, given that, when reported, mean time between the first HZ episode and first recurrent HZ episode ranged between 2.0 and 13.7 years [11, 15, 16, 20].

Number of Recurrent Episodes

Another measure of the burden of HZ recurrence is the number of individuals who experience multiple recurrences; however, few studies provided this information. In the US study from Olmsted County, 6.3% of individuals had two recurrences, and 2.1% had three recurrences during follow-up [10]. In the South Korean study, 11.0% of individuals with recurrences had two recurrences and 1.2% had three recurrences [11]. Our review also identified a Canadian retrospective analysis of data for 194,584 individuals with HZ between 1994 and 2010, in which 15,909 individuals (8.2%) had one recurrence and 3964 (2.0%) had multiple recurrences [23]. A German analysis of health insurance records reported that 25% of patients (1030/4141) who experienced a first recurrence also experienced at least one further recurrence during the 10-year analysis; the authors also noted that the risk of a second recurrence was higher than the risk of a first recurrence [19].

What Factors Increase the Risk of HZ Recurrence?

Immunocompromised Status

Immunocompromised status is an important risk factor for HZ recurrence, with most [10, 11, 15, 20, 25], although not all [14, 21], studies that directly compare immunocompetent and immunocompromised individuals describing significantly higher recurrence rates in the latter subgroup. Two of the time-to-event studies compared HZ recurrence rates between immunocompetent and immunocompromised individuals. The South Korean study [11] and the US study from Olmsted County [10] reported significantly higher recurrence rates in immunocompromised individuals ($p < 0.0001$ and $p = 0.006$, respectively). However, only the US study from Olmsted County reported the specific recurrence rate, estimating an 8-year cumulative risk of HZ recurrence for immunocompromised individuals of 12.0%, which was more than twice that for immunocompetent individuals (5.7%) [10]. Moreover, only two studies reported incidence rates. A prospective Australian cohort study reported a recurrence rate of 17.0 per 1000 PY compared with 10.5 per 1000 PY in individuals without recent immunosuppression [20]. A Spanish retrospective study that included the electronic health records of 4.4 million individuals reported a recurrent HZ incidence rate of 22.8 per 1000 PY in immunocompromised individuals versus 15.6 per 1000 PY in immunocompetent individuals, which corresponds to a 25% increase in risk after adjustment for age, sex, comorbidities, reporting health department, and reporting year [25]. This study also provided rates for specific immunocompromising conditions, as summarized in Table 2. The highest rate reported was in hematopoietic stem cell transplant recipients (55 per 1000 PY), whereas the lowest rate was in patients with autoimmune thyroiditis or psoriasis (18 per 1000 PY) [25].

In total, 11 studies reported the percentage of immunocompromised individuals with observed HZ recurrence during follow-up, with estimates of 0–18.2%; the wide range is in part attributable to the fact that some studies focused on specific immunocompromising conditions, such as rheumatoid arthritis [26, 27], human immunodeficiency virus (HIV) infection [28], Wegener granulomatosis [29], systemic lupus erythematosus [30], or lung transplant [31, 32], while other studies included multiple conditions [11, 15, 21, 33]. The wide

range is also likely a consequence of small population sizes in some studies.

The South Korean time-to-event study reported that 17.8% of individuals with HZ recurrence were immunocompromised, compared with 13.5% of individuals without HZ recurrence ($p < 0.001$). Notably, individuals with HZ recurrence had an increased prevalence of solid cancers, hematologic malignancies, autoimmune diseases, and chronic renal disease (all $p < 0.05$ versus individuals without HZ recurrence; see Table 2 for percentages) [11]. No differences were observed between individuals with HIV infection or chronic hepatic disease, although these subgroups were small [11]. For individuals with HIV infection, this may be an encouraging reflection of the efficacy of current antiretroviral therapies. For patients with autoimmune diseases receiving immunosuppressive therapy, it can be difficult to separate the effects of disease and treatment, but a retrospective South Korean study of individuals receiving biologic disease-modifying drugs found that tofacitinib increased the risk of recurrence compared with abatacept [adjusted hazard ratio 2.46; 95% confidence interval (CI) 1.61–3.76; $p < 0.001$], indicating that the risk may be differentially modulated by specific immunosuppressive medications [26].

Sex

HZ recurrence is more frequently reported in women than men. One of the time-to-event studies assessed cumulative risk of HZ recurrence by sex. The US study from Olmsted County reported a significantly ($p = 0.04$) higher cumulative risk of recurrence in women than men, with 8-year recurrence rates estimated as 7.2% and 4.5%, respectively [10]. Two studies reported the relative risk of HZ recurrence by sex, with both studies finding a significantly greater risk for women than men. In a Spanish study, women had a 19% greater risk of HZ recurrence (95% CI 1.14–1.24) [25], while in a South Korean study, women had a 48% greater risk (95% CI 1.35–1.62) [11].

Most studies reporting the incidence rate of HZ recurrence by sex show higher rates in women. In a prospective Australian study, the incidence rate was 12.8 recurrences per 1000 PY for women versus 8.3 recurrences per 1000 PY for men [20]. Similarly, a Japanese prospective study reported an incidence per year for recurrent HZ of 1.07% for women versus 0.91% for men [14]. A US retrospective study in individuals aged ≥ 60 years reported incidence rates for recurrent HZ of 9.5 cases per 1000 PY for women versus 4.5 cases per 1000 PY for men [24]. However, a retrospective Chinese study in individuals aged ≥ 50 years reported incidence rates of 14.3 recurrences per 1000 PY for women versus 19.5 recurrences per 1000 PY for men [21]. Such variation could be explained by different approaches to surveillance for HZ in different countries; differences in healthcare-seeking behavior between women and men; and cultural factors, such as the use of traditional Chinese medicine or patient stoicism, leading to underreporting of symptoms and underuse of antivirals.

Older Age

Older age might be expected to increase the risk of HZ recurrence, given that it is an established risk factor for the first episode of HZ, but this was not seen consistently across the studies identified in our review. The Korean national health-insurance-based study reported that the risk of HZ recurrence was 45% higher for individuals aged 51–70 years versus 21–50 years (95% CI 1.31–1.60) [11]. A large Spanish cohort study found that, relative to individuals aged 18–29 years, the risk of HZ recurrence increased for individuals aged 40–49 years (relative risk 1.14; 95% CI 1.01–1.28), and then increased further in each decade of life up to ≥ 80 years of age (relative risk 2.14; 95% CI 1.91–2.40) [25]. Conversely, in the California time-to-event study, the 10-year cumulative risk of recurrence was 11.1% for individuals aged 50–59 years, decreasing consistently in older cohorts to 9.0% for individuals aged ≥ 80 years [22]. The US study from Olmsted County did not find a significant increase with age ($p = 0.65$), although there was an increase in the estimated cumulative 6-year (the longest timepoint for the analysis) recurrence risk for men only (3.3% versus 5.5% in those aged < 50 years versus ≥ 70 years) [10]. The German health insurance study noted above, which used a matched-

cohort design, conducted a time-to-event analysis stratified by age, and reported that the highest risk, of > 15% at 10 years, was observed in individuals aged < 50 years and with ≥ 1 underlying condition, whereas the lowest risk was observed in individuals aged ≥ 60 years, who had a cumulative 10-year risk of recurrence of between 5 and 10% [19]. People who are older at the time of an initial HZ diagnosis may be more likely to die before experiencing a recurrence than those who are younger on initial HZ diagnosis, which may influence recorded data on risk of HZ recurrence by age.

Long-Lasting Post-herpetic Pain

Long-lasting pain following an initial HZ episode was only assessed in a few studies in our review, but was consistently identified as a significant predictor of subsequent recurrence. The US study from Olmsted County study reported that pain lasting ≥ 30 days was a significant ($p < 0.001$) predictor of recurrence compared with pain lasting < 30 days, and the effect was stronger in younger individuals (aged ≤ 50 years) and during the first 3–4 years after the initial episode [10]. In the South Korean national health insurance study, cumulative recurrence rates were 4.9%, 5.7%, and 10.2% in individuals with durations of HZ-related pain of < 31, 31–90, and > 90 days, respectively ($p < 0.001$) [11]. In another South Korean study, the reported cumulative risk of recurrence was significantly different between individuals with pain lasting < 30 days (0.9%), 30–90 days (2.2%), or ≥ 90 days (1.8%) ($p < 0.001$) [15].

Non-immunocompromising Medical Conditions

In addition to immunocompromising medical conditions, other comorbidities were associated with an increased risk of recurrent HZ in the studies we reviewed. The list of comorbidities reported, and their effect sizes, varied between studies. A large German analysis of health insurance data that included patients with asthma, coronary heart disease, chronic heart failure, chronic obstructive pulmonary disease (COPD), depression, diabetes, and rheumatoid arthritis reported that the presence of any of these comorbidities increased the cumulative risk of recurrent HZ in all age groups by approximately 10–17% over 10 years. Overall, 9.6% of the study population had at least one HZ recurrence, and 25% of these patients had at least two HZ recurrences [19]. However, the authors did not report recurrence risks associated with the individual comorbidities [19]. A large Spanish epidemiologic study reported increases in recurrent HZ risk of 63% for heart failure, 26% for COPD, 20% for chronic kidney disease, and 5% for diabetes [25]. South Korean and Chinese analyses also described associations with dyslipidemia, hypertension, and/or diabetes [11, 21]. Further studies are required to understand the impact of specific non-immunocompromising medical conditions on HZ recurrence.

What are the Clinical Features of Recurrent HZ?

Severity

The severity of HZ recurrences may be inferred from factors such as the proportion of study participants with complications (e.g., PHN) or who require hospitalization, and by patient-reported outcome measures (PROMs; e.g., pain severity). Evidence regarding the severity of recurrence versus initial HZ episodes is limited and mixed. In a prospective Japanese study, HZ recurrence was characterized by a significantly lower severity of skin lesions and pain ($p < 0.001$) and a reduced incidence of PHN ($p = 0.03$) in individuals aged 50–79 years when compared with an initial HZ episode [14]. In an Australian study, although the hospitalization rate was similar between initial HZ episodes and recurrence (2.5% versus 2.7%; $p = 0.8$), fewer individuals with a recurrent HZ episode received pain medication (9.3% versus 14.8%; $p < 0.001$) [20]. Further, in a pooled analysis of tofacitinib trials in rheumatoid arthritis, second versus first HZ episodes were less likely to be classified as severe (1.6% versus 4.3%) or serious (4.8% versus > 7.0%), or lead to PHN (3.2% versus 6.9%) [27]. Taken together, these data suggest generally milder events at the time of

clinical presentation with recurrence. A Chinese study reported a longer duration of hospitalization for recurrent than initial HZ episodes (mean 24.0 versus 21.6 days; $p = 0.573$), but this finding was not statistically significant [21].

Distribution

HZ typically erupts in one or, less frequently, two contiguous dermatomes, commonly affecting the thoracic, cervical, and trigeminal dermatomes [34]. Evidence indicates that the dermatome(s) affected, and the anatomic distribution of recurrent HZ episodes, frequently differ from those of the initial HZ episode. In the US study from Olmsted County, 44.2% of individuals had a recurrence contralateral to the first episode [10]. Notably, ipsilateral recurrence was observed in all ten individuals with multiple recurrences ($p = 0.008$) [10]. In two studies recording dermatomal distribution, dermatomes supplied by the thoracic, trigeminal, and/or cervical nerves were frequently involved in recurrent HZ episodes [15, 16]. Recurrence usually involved a single dermatome (76.3% of individuals) [16], and more commonly affected different dermatome(s) compared with the initial HZ episode [15, 16].

How Does the Incidence and Course of HZ Recurrence Change in Patients with HZO?

Studies reporting HZ recurrence in individuals with HZO are summarized in Table 3. Only one study, a US medical chart review of 83 individuals with a resolved episode of HZO, provided an estimate of cumulative recurrence risk, rising from 8% after 1 year to 31% after 6 years [35]. Although this study was noncomparative, it appears to describe a notable increase in recurrence risk for individuals with HZO. However, as seen in earlier discussions, cumulative recurrence risk varies widely between studies. Seven other studies (three in the USA, and one each in Italy, New Zealand, South Korea, and Turkey) reported the percentage of individuals with observed HZ recurrence during follow-up, ranging between 7.1% and 52.6% [17, 18, 36–40].

Risk factors for HZO recurrence included epithelial or stromal keratitis, uveitis, ocular hypertension, and prior chronic HZO [35, 37]. Notably, late VZV dendriform keratitis had a crude recurrence rate of 52.6% ($n = 19$), with individuals often having multiple recurrences [18]. In patients with ocular HZ undergoing surgical procedures, recurrence following cataract surgery was observed in 23/57 individuals (40.4%) and 6/24 individuals (25.0%) in studies in New Zealand [39] and the USA [40], respectively, and after laser in situ keratomileusis in 0/4 individuals in Spain [41].

LIMITATIONS

This non-systematic review was based on qualitative assessment of studies in heterogeneous populations and using different methodologies, which limits study comparability. In addition, only English language articles were included in the review. Several of the studies are from real-world settings, such that results are shaped by numerous population and healthcare system factors. For example, in many studies, suspected HZ infection was identified from ICD diagnostic codes, rather than confirmed by PCR test, which may have resulted in overreporting of true HZ incidence rates. In addition, several studies did not report on antiviral prescription to validate the ICD diagnostic codes in the claims data analyzed. The studies also lacked data on PROMs and on patient-reported experience measures, and indeed, a need exists for further qualitative research and analyses of patients' perspectives on HZ recurrences and burden of disease. There may also be systemic challenges in the assessment of recurrent HZ. For example, a survey of 14,654 US individuals aged $\geq$ 55 years found that individuals with recurrent HZ were less likely to seek healthcare than those with an initial episode [42], suggesting that at least some of the studies in our review may underestimate the true risk of recurrent HZ, and that recurrent episodes of HZ may be milder than initial episodes. In addition, HZ episode definition varied across studies, which would have affected the number of HZ episodes included in the analyses. Another

limitation is that some of the studies are old, including data going back, for example, to 1984, and HZ disease awareness may have improved, including since the introduction of vaccines [43].

CONCLUSIONS

Our review of recent literature underlines that following an initial HZ episode, individuals remain at risk of HZ recurrence. General population studies estimate that approximately 10% of individuals may experience an HZ recurrence in the first decade after an initial HZ episode [11, 22]; multiple recurrences are observed in up to 25% of this group [10, 11, 19, 23]. The risk of recurrence increases in women, immunocompromised populations, and populations with comorbidities. Other factors that may predispose individuals to recurrence include long-lasting pain after the initial HZ episode and the presence of HZO [10, 11, 35]. Further studies are required to understand the impact of age on recurrence risk. Some large studies reported that younger individuals were at greater risk of recurrence, in contrast to the general finding that older individuals are at increased risk of a first HZ episode [19, 22]. Overall, recurrent HZ adds to the burden of HZ in a population. As HZ is preventable by vaccination, national HZ vaccination recommendations should include the need for and timing of vaccination in both immunocompetent and immunocompromised individuals who have a history of HZ.

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Declarations

Conflict of Interest. Raunak Parikh, O'Mareen Spence, and Nikolaos Giannelos are employees of GSK and may hold stock or stock options. Iain Kaan was an employee of GSK while working on this manuscript and may hold stock or stock options. Iain Kann is now an employee of Aeolian Logic Pte Ltd, Singapore and may hold stock or stock options.

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