7 Herpes Zoster and the Zoster Eye Disease Study (ZEDS)

Elisabeth J. Cohen and Bennie H. Jeng

Herpes zoster (HZ)/shingles is caused by the reactivation of latent varicella zoster virus (VZV) in persons who have had varicella/chicken pox, the primary infection caused by VZV. After primary VZV infection, latent VZV is present diffusely in sensory ganglia. The cause of localized reactivation is incompletely understood, although it is known that decline in VZV-specific cellular immunity due to age, immunosuppression, or other reasons are important factors. HZ is usually associated with a typical unilateral, painful, often vesicular rash in a dermatomal/radicular distribution. Unilateral pain precedes the rash in a majority of cases, and the pain is unlike any pain the person has experienced before [1]. The diagnosis is usually not made until the typical rash develops. However, Herpes Zoster Sine Herpete, the term used to describe radicular pain due to VZV in the absence of a rash can occur, and without a rash the diagnosis is often not considered and missed [2]. Herpes zoster ophthalmicus (HZO) refers to HZ when the fifth cranial/trigeminal nerve is affected and accompanied by ocular involvement.

E. J. Cohen (✉)
NYU School of Medicine, NYU Langone Health, Department of Ophthalmology, New York, NY, USA
e-mail: Elisabeth.Cohen@nyumc.org

B. H. Jeng
University of Maryland School of Medicine, Baltimore, MD, USA

Relatively new information regarding the epidemiology of HZ, vaccines to prevent HZ and its complications, and treatment of HZ, including current and possible new treatment under investigation, will be reviewed. Evidence regarding the increasing incidence and decreasing age at the onset of disease, as well as the possibility that VZV is the trigger for temporal/giant cell arteritis will be presented. Current information on the efficacy, safety, Food and Drug Administration (FDA) approvals [3, 4], and Centers for Disease Control and Prevention (CDC) [5] recommendations for two vaccines against HZ, the Zoster Vaccine Live (ZVL), and the Recombinant Zoster Vaccine (RZV) will be discussed. Current recommended treatment for HZ and HZO will be reviewed, and possible new treatment for HZO using prolonged suppressive antiviral medication currently under investigation in the Zoster Eye Disease Study (ZEDS), a multicenter randomized controlled clinical trial (RCT) funded by the National Eye Institute (NEI) of the National Institutes of Health (NIH), will also be discussed. Participation in this clinical trial is a unique opportunity to determine whether or not suppressive antiviral treatment of HZO will reduce complications and improve outcomes in eye disease caused by VZV, as it has been proven to do for herpes simplex virus eye disease.

K. Colby, R. Dana (eds.), *Foundations of Corneal Disease*,
https://doi.org/10.1007/978-3-030-25335-6_7

Epidemiology

HZ is a common disease with over 1,000,000 new cases per year in the USA [6] and with up to 20% involving the trigeminal nerve, resulting in possible HZO [7]. According to the CDC, over 99% of people aged 40 years and older born in the USA have had varicella/chicken pox, whether they know it or not, and they are at risk for HZ [5]. Approximately 30% of people will have HZ during their lifetime. Although HZ is more common and severe in immunocompromised persons, over 90% of people with zoster are not immunocompromised [8]. It is a common misconception that healthy people are not at risk for HZ and its potentially disabling sequelae, when in fact they are. Although the incidence of HZ increases with age, the greatest number of cases of HZ, including HZO, occur in people in their fifties [9–11]. The incidence of HZ rises significantly in people in their forties, and sharply in people in their fifties [12]. A common misconception is that HZ is a disease of the elderly, when in fact it affects a large number of people under the age of 60 years. In fact, the mean age of the onset of HZO has decreased from the sixties to the fifties [13, 14].

The incidence of HZ has increased over fourfold during the past 60 years across all age groups for unknown reasons [15] (Fig.7.1). Although many people think that the vaccination of children against varicella contributes to the increase in HZ incidence by limiting boosting of immunity to VZV by exposure to chicken pox according to the Hope Simpson hypothesis, the evidence does not support this [8, 16]: the increase began before the introduction of childhood varicella vaccination in the USA in 1995 and has continued afterward. In addition, routine vaccination against varicella is not widespread in Europe, and the incidence of HZ is similar there to that in the USA [10, 16]. The increase in HZ cases also cannot be accounted for by an aging population or by the rate of immunocompromise, and thus the reasons for it remain unknown.

There is an ever-growing list of risk factors for the development of HZ in addition to the well-known ones, including increasing age, immunocompromise, and female sex [17]. This list includes family history, depression, stress, past history of zoster, heart failure, traumatic brain injury, diabetes, asthma, acute kidney disease, and autoimmune disease. An interesting recent addition to the list is the use of statins, which in a large population-based study was associated with a modest 13% increased risk that was dose dependent and doubled with use of high dose statins, and it decreased with duration of time since statin use, consistent with a causal effect [18]. Rather than considering the implications regarding the importance of vaccination against zoster in patients with a wide variety of medical conditions, it is more efficient to recommend vaccination for all people aged 50 years and older, as discussed in the next section.

There is also an expanding list of complications after HZ, including neurologic conditions, cardiac issues, and possibly giant cell arteritis/temporal arteritis, in addition to the most common ones of postherpetic neuralgia (PHN), eye disease after HZO, and hearing loss when the eighth cranial nerve is affected (Ramsey Hunt). PHN, defined as pain beyond 3 months after the onset of zoster, is the most common complica-

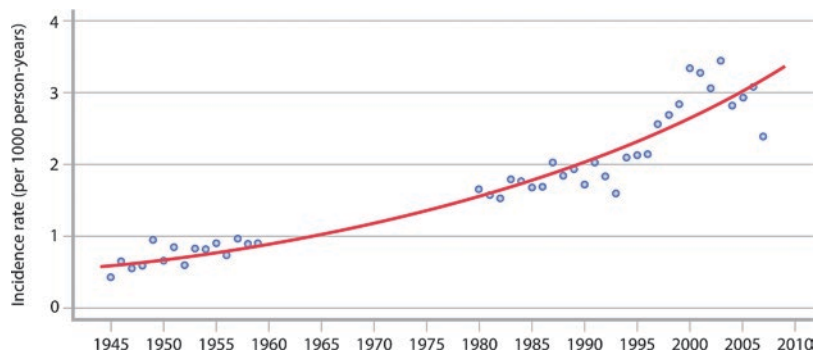

Fig. 7.1 Incidence of herpes zoster in Olmsted County, Minnesota, 1945–2007, showing the temporal trend beginning prior to the introduction of antiviral medications (mid-1980s) and extending beyond the introduction of childhood varicella vaccinations (1996)

tion, and it occurs in approximately 30% of HZO patients, primarily with the onset of HZO at age 65 years or more [19]. Risk factors for PHN, in addition to increasing age, include HZO, amount of acute pain, and severity of the rash [20]. HZ has been found to be a risk factor for the development of major depression and reported to be the most common cause of suicide due to pain in people age 70 years and older [21, 22]. Postherpetic neuralgia often has a devastating effect on the quality of life in older patients with zoster, that frequently lasts for the rest of their lives. It is not prevented by recommended acute antiviral treatment of HZ. As of right now, the only way to prevent PHN is to prevent HZ through vaccination.

HZO is frequently associated with dendriform keratitis, stromal keratitis, and iritis/uveitis, often accompanied by elevation intraocular pressure, and neurotrophic keratopathy, but it can involve all parts of the eye, orbit, and optic nerve and result in permanent loss of vision [23]. Acute antiviral treatment within 72 hours of the onset of the rash is recommended with high dose oral valacyclovir (1000 mg 3 times daily), famciclovir (500 mg 3 times daily), or acyclovir (800 mg 5 times daily) for 7 days, and this has been shown to reduce eye disease at 6 months after onset from 50% to 30% [24]. It is very important to begin treatment as soon as possible, as complications occur after 72 hours, and one cannot predict who will have complications. Non-PHN complications, including eye disease, are as common in younger as older HZ patients [8]. HZO can be complicated by chronic and/or recurrent eye disease, with the latter increasing over time to 25% by 5 years [25]. Many HZO patients require chronic topical steroids, with their potential complications, to control anterior segment inflammation. Cataract surgery in well-controlled HZO can result in initial improvement in visual acuity (VA), followed by decreased VA due to retinal problems, which may be underdiagnosed in HZO [26].

HZ has long been known to be a risk factor for potentially fatal strokes, and in recent years in population-based studies, it has been reported to be a risk factor for heart disease [27]. These vascular complications occur in relatively young patients. The risk of stroke is greater after HZO than after HZ in other locations, most likely because the virus spreads directly from the nerves to arteries, causing inflammation [28, 29].

Of great importance to ophthalmologists is evidence that VZV may be the trigger for giant cell/temporal arteritis (GCA/TA) [30]. In studies with 50 sections per temporal artery biopsy, VZV antigen was found in three quarters (61/82, 74%) of the biopsies that were positive for giant cells, and in sections adjacent to VZV antigen, giant cells were located in almost 90%. This led to the conclusions that GCA may be VZV vasculopathy of the temporal artery, and antiviral treatment of steroid-treated GCA may be beneficial, and it merits further study. These findings have been questioned in another study in which a minority (3/25) of giant cell positive TA biopsies were positive for VZV, including one case where TA developed soon after HZO [31]. The discrepancy in the results was attributed to false positives for VZV antigen in calcifications and muscle in the biopsies. The answer is not yet known on this subject, but it merits further study as it has important implications regarding the optimal treatment of GCA.

Vaccination Against Herpes Zoster

There are currently two vaccines against HZ: the Zoster Vaccine Live (ZVL. Zostavaz, Merck) and the Recombinant Zoster Vaccine (RZV, Shingrix, GlaxoSmithKline). ZVL has been CDC recommended since 2008 for immunocompetent adults aged 60 years and older, and FDA approved since 2011 for immunocompetent adults aged 50 years and older [3]. RZV was FDA approved for all adults aged 50 years and older in October 2017 [4], and CDC recommended for immunocompetent adults aged 50 years and older in January 2018. CDC recommends RZV for people who have been previously vaccinated with ZVL, and as preferred over the ZV [32].

ZVL was approved after it was shown to decrease the burden of disease by 61%, PHN by 66%, and the incidence of HZ by 51% [33]. However, it was more effective in reducing the

incidence of HZ in persons aged 60–69 years (64%) than 70 years and older (38%). FDA approval of ZVL for immunocompetent adults aged 50 years and older followed evidence that it decreased the incidence of HZ by 70% in people aged 50–59 years, but the CDC recommendation remains unchanged [34]. Contraindications for ZVL include diseases and treatments impairing cell-mediated immunity, because the vaccine contains a live attenuated virus that is a real safety risk for these populations. In addition, anaphylactic reaction to neomycin or gelatin as well as pregnancy are contraindications. Since the live attenuated virus is sensitive to antivirals, vaccine recipients must be off of valacyclovir, famciclovir, and acyclovir 1 day before and 2 weeks after vaccination. The most common side effects to ZVL are local injection site reactions, which are more common in vaccine recipients in their fifties than in older vaccine recipients [33, 35]. In addition to reduced efficacy against zoster in older persons, another limitation of ZVL is that its efficacy in persons aged 60 years and above wanes after 3–10 years [36–38].

RZV, also referred to as the herpes zoster subunit (HZ/su) vaccine, contains a recombinant VZV protein in a novel immunogenic adjuvant. It is a two-injection series given intramuscularly 2–6 months apart, and it is refrigerated, in contrast to the ZVL, which is a single injection given subcutaneously and requires frozen storage. In an RCT conducted in 2010–2011 of immunocompetent adults aged 50 years and older, it was 97% effective in preventing HZ compared to placebo [39]. When results were pooled with a concomitant RCT of immunocompetent adults aged 70 years and older, it was approximately 90% effective in reducing the incidence of HZ in adults aged 70 years and older, which is much more effective than ZVL [40]. In addition, efficacy against HZ remained at 85% after 4 years, also superior to ZVL. However, grade 3 acute local and systemic reactions interfering with normal activities were reported in up to 17% of vaccine recipients, and this raised concern about adherence to the 2-dose schedule required for efficacy outside of a clinical trial in a real-world setting.

The FDA approved RZV for all adults aged 50 years and older, and the CDC recommended it for immunocompetent adults aged 50 years and older [32]. The FDA label notes that immunosuppressive treatment may reduce the effectiveness. The CDC limited its recommendation to immunocompetent adults, because immunocompromised adults were excluded from the RCTs. The FDA label allows for the administration of the two injections 2–6 months apart, which facilitates giving them at the time of routine office visits, based on evidence that the humoral antibody response was not inferior when given 6 months compared to 2 months apart [41]. In addition, according to the label, there is no evidence of interference with the immune response when given at the same time of a quadrivalent influenza vaccine. This is supported again by evidence of lack of interference with the humoral antibody response, but it is unclear if even this can be extrapolated to influenza vaccines in general [42, 43]. According to the FDA label, the only contraindications to the vaccine are a history of anaphylaxis to a vaccine component or to the first dose. Information about relatively common acute local and systemic reactions to the RZV are provided in the label, including that they are more common in persons aged 50–69 years than people aged 70 years and older. In addition, local reactions occur at a similar frequency after the first and second injection, whereas grade 3 systemic reactions are more common after the second injection. The label emphasizes the importance of completing the two injections on schedule, and informing people in advance about the possibility of adverse reactions. The vaccine requires two shots to stimulate cell-mediated immunity against VZV in order to be effective in preventing zoster. Of note, gout occurred in 0.18% of vaccine recipients, compared to 0.05% of placebo within 30 days, but a causal relationship was not determined.

The CDC recommends RZV for immunocompetent adults aged 50 years and older, including persons who received ZVL at least 2 months ago. There is evidence of a strong immune response and comparable adverse reactions to RZV in people aged 65 years and older who received ZVL at least 5 years previously [44]. The CDC does not specify when to give RZV after ZVL, but given the limited efficacy of ZVL against HZ in persons aged 70 and older, it is reasonable to have

then get the RZV as soon as possible. Vaccination against zoster is recommended for persons with a past history of zoster, as second episodes of disease can occur in 6% within 8 years [45]. Local and general reactions to RZV are more common in persons with a past history of zoster within 4 years compared to 5 or more years prior to vaccination [46]. The CDC recommends RZV as preferred over ZVL due to its greater and more long-lasting efficacy. The CDC recognizes that continued monitoring for adverse events using the Vaccine Adverse Events Reporting System (VAERS) is particularly important for RZV due to its novel adjuvant with high reactogenicity and immunogenicity.

Under usage of ZVL for a variety of reasons has been a problem, limiting its impact on HZ, and hopefully vaccination against zoster will increase with the current approval and recommendations for RZV. According to CDC, as of 2015, the most recent year with available data, 31% of immunocompetent persons aged 60 years and older have received ZVL, while only 6% of those aged 50–59 years received it, probably due to the lack of CDC recommendation for this age group [47, 48]. In the USA, emergency room visits for HZ between 2006 and 2013 increased overall due to an increase among people aged 50–59 years, but decreased among age groups where the CDC recommended vaccination [49].

There are a number of barriers to vaccination against HZ, including high cost, complex and partial insurance coverage, and lack of strong recommendation by physicians [50, 51]. Despite interventions targeted to increase vaccination against zoster including education, increased availability, and electronic medical record reminders and alerts, primary care doctors do not consider vaccination against zoster as important as vaccination against influenza and pneumonia [52, 53]. The American Academy of Ophthalmology (AAO) issued a clinical statement in 2016 (cosponsored by the American Dermatological Association in 2017), updated in 2018, and accepted for publication as a policy statement in *Ophthalmology*), recommending vaccination against zoster for adults aged 50 years and older without contraindications [54].

A number of factors influence attitudes of physicians regarding vaccines, including evidence on the benefits of the vaccine, insurance coverage, cost to supply in the office, and whether or not it is tracked as a performance measure [51]. Hopefully, the increased efficacy of RZV will result in stronger recommendations for vaccination against HZ. Although RZV is more cost-effective than ZVL [55], cost remains high, and insurance coverage is complex with coverage under medical insurance for non-Medicare patients versus Medicare Part D, making it difficult to administer in office for the Medicare patients. Tracking vaccination according to current CDC recommendations as a performance measure is a relatively easy change to implement to try to improve attitudes and practices. Vaccination rates against HZ go up when family members are affected in proportion to the severity of their disease, but physicians should not need to experience this to improve [56]. Increasing vaccination among doctors and other health-care workers is a strong evidence of the importance of vaccination and is a good preventive medicine [57]. The bioethicist Arthur Caplan teaches that "A moral obligation to do the right thing is necessary to improve vaccination rates".

The Zoster Eye Disease Study (ZEDS)

ZEDS is a very important study to determine whether or not prolonged suppressive antiviral treatment with valacyclovir reduces complications of HZO, including eye disease and/or postherpetic neuralgia. It is a multicentered randomized controlled clinical trial funded by the National Eye Institute that has over 200 study investigators and will enroll 1050 study participants at 60 participating clinical centers across the USA. Successful completion of this study is necessary to determine if suppressive antiviral treatment is effective and should become the standard of care for HZO. While acute high-dose oral antiviral treatment is approved and recommended for HZO, there is no standard approach to the antiviral treatment of the complications of HZO.

The rationale for ZEDS is twofold: firstly, the relatively recent evidence of the infectious pathogenesis of complications of HZ, including HZO; and secondly, the significant benefit of suppressive antiviral treatment for herpes simplex virus (HSV) keratitis, which has become the standard of care and has reduced recurrences. Evidence of recurrent varicella zoster virus (VZV) infection has been found by polymerase chain reaction (PCR) to cause dendriform epithelial keratitis (DEK) and iritis due to HZO [58–60]. The Herpetic Eye Disease Study (HEDS) Acyclovir Prevention Trial (APT) showed that suppressive antiviral treatment reduced recurrent HSV by 45% after 1 year of treatment [61]. ZEDS is analogous to HEDS APT for ocular disease caused by VZV, a different herpes virus, in that immunocompetent study participants aged 18 years and older will be randomized to suppressive antiviral treatment versus placebo for 1 year and followed every 3 months for 18 months.

To be eligible for ZEDS, one must have a history of a typical unilateral rash and a documented episode of dendriform epithelial keratitis, stromal keratitis, endothelial/disciform keratitis, or iritis within 1 year prior to enrollment. Study participants will be randomized 1:1 to double-masked valacyclovir 1000 mg daily versus placebo in four strata based on age at the onset of HZO and disease duration at the time of enrollment. Exclusion criteria, in addition to immunocompromise, are primarily the contraindications to valacyclovir, including renal insufficiency and pregnancy, or need for antiviral treatment of HSV disease.

The primary objective of ZEDS is to determine whether or not suppressive valacyclovir compared to placebo delays the time to occurrence of dendriform epithelial keraititis (DEK), stromal keratitis without ulceration (SK), endothelial keratitis (EK), iritis (IR) or stromal keratitis with ulceration (SKU) (Fig.7.2). The

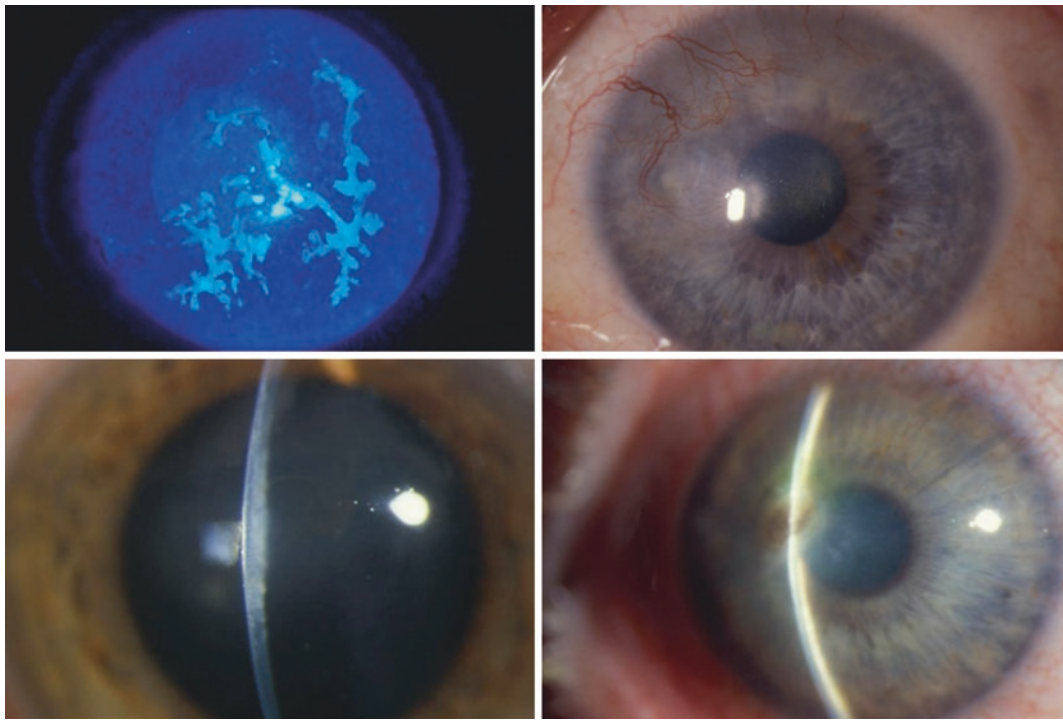

Fig. 7.2 Top left: Dendriform epithelial keratitis. Top right: Stromal keratitis without ulceration. Bottom left: Endothelial keratitis. Bottom right: Stromal keratitis with ulceration

second aim of the study is to determine whether or not suppressive valacyclovir treatment compared to placebo reduces the incidence, severity, and duration of postherpetic neuralgia after 12 months of treatment, and if it persists for 6 months afterward.

Support of ZEDS by the adequate enrollment of study participants is critical to achieve our purpose of determining optimal treatment for HZO and improving outcomes. Approximately half of our study investigators currently use suppressive antiviral treatment for HZO, and even more think it is effective [62]. However, rather than starting this treatment, which is currently not evidence based, we urge ophthalmologists to refer their HZO patients for possible enrollment into ZEDS so that it can be determined if this treatment is effective, and if so, it will become the standard of care and improve outcomes in HZO. For further information regarding ZEDS, please refer to our website at https://med.nyu.edu/research/zoster-eye-disease-study/zoster-eye-disease-study.

Conclusion

Herpes zoster is a common preventable disease with serious life-threatening and altering complications, including eye disease, chronic pain, and neurologic diseases. It is very important for health-care professionals, including ophthalmologists, to strongly recommend vaccination against zoster for adults aged 50 years and older. Participation in the Zoster Eye Disease Study is necessary in order to determine the efficacy of suppressive antiviral treatment in reducing chronic and/or recurrent eye disease due to HZO, as well as postherpetic neuralgia, and to determine optimal evidence-based standard of care to improve outcomes.

References

1. Lee HL, Yeo M, Choi GH, Lee JY, Kim JS, Shin DI, et al. Clinical characteristics of headache or facial pain prior to the development of acute herpes zoster of the head. ClinNeurolNeurosurg. 2017;152:90–4.
2. Lewis GW. Zoster sine herpete. Br Med J. 1958;2(5093):418–21.
3. Food and Drug Administration. Zoster Vaccine Live. 2006. Available from: https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm136941.htm.
4. Food and Drug Administration. Zoster Vaccine Recombinant, Adjuvanted. 2017. Available from: https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm581491.htm.
5. Centers for the Disease Control and Prevention. Shingles (Herpes Zoster). Available from: https://www.cdc.gov/shingles.
6. Suaya JA, Chen SY, Li Q, Burstin SJ, Levin MJ. Incidence of herpes zoster and persistent post-zoster pain in adults with or without diabetes in the United States. Open Forum Infect Dis. 2014;1(2):ofu049.
7. Liesegang TJ. Herpes zoster ophthalmicus natural history, risk factors, clinical presentation, and morbidity. Ophthalmology. 2008;115(2Suppl):S3–12.
8. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007;82(11):1341–9.
9. Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. The incidence of herpes zoster in a United States administrative database. J Gen Intern Med. 2005;20(8):748–53.
10. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology. 2013;81(10):928–30.
11. Ghaznawi N, Virdi A, Dayan A, Hammersmith KM, Rapuano CJ, Laibson PR, et al. Herpes zoster ophthalmicus: comparison of disease in patients 60 years and older versus younger than 60 years. Ophthalmology. 2011;118(11):2242–50.
12. Rimland D, Moanna A. Increasing incidence of herpes zoster among veterans. Clin Infect Dis. 2010;50(7):1000–5.
13. Chan AY, Conrady CD, Ding K, Dvorak JD, Stone DU. Factors associated with age of onset of herpes zoster ophthalmicus. Cornea. 2015;34(5):535–40.
14. Davies EC, Pavan-Langston D, Chodosh J. Herpes zoster ophthalmicus: declining age at presentation. Br J Ophthalmol. 2016;100(3):312–4.
15. Kawai K, Yawn BP, Wollan P, Harpaz R. Increasing incidence of herpes zoster over a 60-year period from a population-based study. Clin Infect Dis. 2016;63(2):221–6.
16. Gershon AA. Is chickenpox so bad, what do we know about immunity to varicella zoster virus, and what does it tell us about the future? J Infect. 2017;74(Suppl 1):S27–s33.
17. Kawai K, Yawn BP. Risk factors for herpes zoster: asystematic review and meta-analysis. Mayo Clin Proc. 2017;92(12):1806–21.
18. Matthews A, Turkson M, Forbes H, Langan SM, Smeeth L, Bhaskaran K. Statin use and the risk of herpes zoster: a nested case-control study using primary care data from the U.K. Clinical Research Practice Datalink. Br J Dermatol. 2016;175(6):1183–94.

19. Borkar DS, Tham VM, Esterberg E, Ray KJ, Vinoya AC, Parker JV, et al. Incidence of herpes zoster ophthalmicus: results from the Pacific Ocular Inflammation Study. Ophthalmology. 2013;120(3):451–6.
20. Forbes HJ, Thomas SL, Smeeth L, Clayton T, Farmer R, Bhaskaran K, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. Pain. 2016;157(1):30–54.
21. Chen MH, Wei HT, Su TP, Li CT, Lin WC, Chang WH, et al. Risk of depressive disorder among patients with herpes zoster: a nationwide population-based prospective study. Psychosom Med. 2014;76(4):285–91.
22. Hess TM, Lutz LJ, Nauss LA, Lamer TJ. Treatment of acute herpetic neuralgia. A case report and review of the literature. Minn Med. 1990;73(4):37–40.
23. Yawn BP, Wollan PC, St Sauver JL, Butterfield LC. Herpes zoster eye complications: rates and trends. Mayo Clin Proc. 2013;88(6):562–70.
24. Hoang-Xuan T, Buchi ER, Herbort CP, Denis J, Frot P, Thenault S, et al. Oral acyclovir for herpes zoster ophthalmicus. Ophthalmology. 1992;99(7):1062–70; discussion 70–1.
25. Tran KD, Falcone MM, Choi DS, Goldhardt R, Karp CL, Davis JL, et al. Epidemiology of herpes zoster ophthalmicus: recurrence and chronicity. Ophthalmology. 2016;123(7):1469–75.
26. He Y, de Melo Franco R, Kron-Gray MM, Musch DC, Soong HK. Outcomes of cataract surgery in eyes with previous herpes zoster ophthalmicus. J Cataract Refract Surg. 2015;41(4):771–7.
27. Breuer J, Pacou M, Gautier A, Brown MM. Herpes zoster as a risk factor for stroke and TIA: a retrospective cohort study in the UK. Neurology. 2014;83(2):e27–33.
28. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. Clin Infect Dis. 2014;58(11):1497–503.
29. Nagel MA, Gilden D. The relationship between herpes zoster and stroke. CurrNeurolNeurosci Rep. 2015;15(4):16.
30. Gilden D, White T, Khmeleva N, Heintzman A, Choe A, Boyer PJ, et al. Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis. Neurology. 2015;84(19):1948–55.
31. Buckingham EM, Foley MA, Grose C, Syed NA, Smith ME, Margolis TP, et al. Identification of herpes zoster-associated temporal arteritis among cases of giant cell arteritis. Am J Ophthalmol. 2018;187:51–60.
32. Dooling KL, Guo A, Patel M, Lee GM, Moore K, Belongia EA, et al. Recommendations of the advisory committee on immunization practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep. 2018;67(3):103–8.
33. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352(22):2271–84.
34. Schmader KE, Levin MJ, Gnann JW Jr, McNeil SA, Vesikari T, Betts RF, et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clin Infect Dis. 2012;54(7):922–8.
35. Tseng HF, Liu A, Sy L, Marcy SM, Fireman B, Weintraub E, et al. Safety of zoster vaccine in adults from a large managed-care cohort: a vaccine safety Datalink study. J Intern Med. 2012;271(5):510–20.
36. Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clin Infect Dis. 2012;55(10):1320–8.
37. Morrison VA, Johnson GR, Schmader KE, Levin MJ, Zhang JH, Looney DJ, et al. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis. 2015;60(6):900–9.
38. Tseng HF, Harpaz R, Luo Y, Hales CM, Sy LS, Tartof SY, et al. Declining effectiveness of herpes zoster vaccine in adults aged ≥60 years. J Infect Dis. 2016;213(12):1872–5.
39. Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang SJ, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med. 2015;372(22):2087–96.
40. Cunningham AL, Lal H, Kovac M, Chlibek R, Hwang SJ, Diez-Domingo J, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. N Engl J Med. 2016;375(11):1019–32.
41. Lal H, Poder A, Campora L, Geeraerts B, Oostvogels L, Vanden Abeele C, et al. Immunogenicity, reactogenicity and safety of 2 doses of an adjuvanted herpes zoster subunit vaccine administered 2, 6 or 12 months apart in older adults: results of a phase III, randomized, open-label, multicenter study. Vaccine. 2018;36(1):148–54.
42. Schwarz TF, Aggarwal N, Moeckesch B, Schenkenberger I, Claeys C, Douha M, et al. Immunogenicity and safety of an Adjuvantedherpes zoster subunit vaccine coadministeredwith seasonal influenza vaccine in adults aged 50 years or older. J Infect Dis. 2017;216(11):1352–61.
43. Oxman MN, Harbecke R, Koelle DM. Clinical usage of the adjuvantedherpes zoster subunit vaccine (HZ/su): revaccination of recipients of live attenuated zoster vaccine and coadministrationwith a seasonal influenza vaccine. J Infect Dis. 2017;216(11):1329–33.
44. Grupping K, Campora L, Douha M, Heineman TC, Klein NP, Lal H, et al. Immunogenicity and safety of the HZ/suadjuvantedherpes zoster subunit vaccine in adults previously vaccinated with a live attenuated herpes zoster vaccine. J Infect Dis. 2017;216(11):1343–51.
45. Yawn BP, Wollan PC, Kurland MJ, St Sauver JL, Saddier P. Herpes zoster recurrences more frequent than previously reported. Mayo Clin Proc. 2011;86(2):88–93.
46. Godeaux O, Kovac M, Shu D, Grupping K, Campora L, Douha M, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit candidate vaccine in adults ≥50 years of age with a prior history of herpes zoster: a phase III, non-randomized,

open-label clinical trial. Hum VaccinImmunother. 2017;13(5):1051–8.
47. Williams WW, Lu PJ, O'Halloran A, Kim DK, Grohskopf LA, Pilishvili T, et al. Surveillance of vaccination coverage among adult populations –United States, 2015. MMWRSurveillSumm(Washington, DC: 2002). 2017;66(11):1–28.
48. Lu PJ, O'Halloran A, Williams WW, Harpaz R. National and state-specific shingles vaccination among adults aged ≥60 years. Am J Prev Med. 2017;52(3):362–72.
49. Dommasch ED, Joyce CJ, Mostaghimi A. Trends in Nationwide herpes zoster emergency department utilization from 2006 to 2013. JAMA Dermatol. 2017;153(9):874–81.
50. Hurley LP, Lindley MC, Harpaz R, Stokley S, Daley MF, Crane LA, et al. Barriers to the use of herpes zoster vaccine. Ann Intern Med. 2010;152(9):555–60.
51. Hurley LP, Bridges CB, Harpaz R, Allison MA, ST OL, Crane LA, et al. Physician attitudes toward adult vaccines and other preventive practices, United States, 2012. Public Health Rep (Washington, DC: 1974). 2016;131(2):320–30.
52. Elkin ZP, Cohen EJ, Goldberg JD, Li X, Castano E, Gillespie C, et al. Improving adherence to national recommendations for zoster vaccination through simple interventions. Eye Contact Lens. 2014;40(4):225–31.
53. Tsui E, Gillespie C, Perskin M, Zabar S, Wu M, Cohen EJ. Evaluating physician attitudes and practices regarding herpes zoster vaccination. Cornea. 2018;37(8):947–51.
54. Ophthalmology AAo. Recommendations for herpes zoster vaccine for patients 50 years and older – 2016. Available from: https://www.aao.org/clinical-statement/recommendations-herpes-zoster-vaccine-patients-50.
55. Le P, Rothberg MB. Cost-effectiveness of the recommendations of the advisory committee on immunization practices for the recombinant adjuvantedzoster subunit vaccine. JAMA Intern Med. 2018;178(9):1277–8.
56. Harpaz R, Leung J. When zoster hits close to home: impact of personal zoster awareness on zoster vaccine uptake in the U.S. Vaccine. 2017;35(27):3457–60.
57. Bonanni P, Bonaccorsi G, Lorini C, Santomauro F, Tiscione E, Boccalini S, et al. Focusing on the implementation of 21st century vaccines for adults. Vaccine. 2018;36(36):5358–65.
58. Pavan-Langston D, Yamamoto S, Dunkel EC. Delayed herpes zoster pseudodendrites. Polymerase chain reaction detection of viral DNA and a role for antiviral therapy. ArchOphthalmol (Chicago, Ill: 1960). 1995;113(11):1381–5.
59. Hu AY, Strauss EC, Holland GN, Chan MF, Yu F, Margolis TP. Late varicella-zoster virus dendriform keratitis in patients with histories of herpes zoster ophthalmicus. Am J Ophthalmol. 2010;149(2):214–20.e3.
60. Takase H, Kubono R, Terada Y, Imai A, Fukuda S, Tomita M, et al. Comparison of the ocular characteristics of anterior uveitis caused by herpes simplex virus, varicella-zoster virus, and cytomegalovirus. Jpn J Ophthalmol. 2014;58(6):473–82.
61. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Herpetic Eye Disease Study Group. N Engl J Med. 1998;339(5):300–6.
62. Lo D, Jeng B, Gilliespie C, Wu M, Cohen E. Current practice patterns and opinions in the management of recent onset or chronic Herpes Zoster Ophthalmicus of Zoster Eye Disease Study investigators. Cornea. 2019;38(1):13–7.