

Global herpes zoster incidence, burden of disease, and vaccine availability: a narrative review

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Abstract: Herpes zoster (HZ) is a neurocutaneous disease that causes significant morbidity worldwide. The disease is caused by the reactivation of the varicella-zoster virus (VZV), which leads to the development of a painful, vesicular rash and can cause complications such as post-herpetic neuralgia and vision loss. Globally, the incidence of HZ is increasing, and it incurs billions in cost annually to the healthcare system and to society through loss of productivity. With the advent of effective vaccines such as the live attenuated vaccine, Zostavax®, in 2006, and more recently the adjuvant recombinant subunit vaccine, Shingrix®, in 2017, HZ has become a preventable disease. However, access to the vaccines remains mostly limited to countries with developed economies, such as the United States and Canada. Even among countries with developed economies that license the vaccine, few have implemented HZ vaccination into their national immunization schedules due to cost-effectiveness considerations. In this review, we discuss the currently available HZ vaccines, landscape of HZ vaccine guidelines, and economic burden of disease in countries with developed and developing economies, as well as barriers and considerations in HZ vaccine access on a global scale.

Keywords: access, developed countries, developing countries, herpes zoster, shingles, vaccine

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Introduction

The varicella-zoster virus (VZV) is a highly infectious member of the alpha Herpesviridae family. Humans are the only reservoir for the virus, which causes both varicella (chickenpox) as well as herpes zoster (HZ), colloquially known as shingles.^{1,2} The virus is transmitted *via* direct contact with primary skin lesions or *via* inhalation of aerosolized droplets from acute vesicles. As primary varicella infection resolves, the virus remains dormant in the dorsal root ganglia and/or cranial nerves and can reactivate later in life, causing HZ. Reactivation from latency occurs sporadically with age-related decrease in cellular immunity but can also occur with immunosuppression due to medication or concomitant disease such as HIV.

HZ is a painful, infectious, neurocutaneous disease. In its early stages, HZ is typically foreshadowed by prodromal symptoms such as pruritus, numbness, and tingling, and/or pain in a unilateral dermatomal pattern, which evolves into a painful vesicular rash that lasts a variable amount of time.³ While rarely lethal with a mortality rate of 0.28–0.69 cases per 1 million, HZ causes significant morbidity and societal costs.¹ Complications of HZ include secondary infections, neurological adverse events such as post-herpetic neuralgia (PHN), facial paralysis, stroke, and ophthalmological adverse events such as keratitis and loss of vision.^{1,4} Annually in the United States alone, it is estimated that HZ results in \$2.6 billion in direct medical costs.⁵

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With the advent of universal childhood varicella vaccinations in the United States, the incidence of primary varicella has decreased by 97%.¹ However, the incidence of HZ has continued to increase. In a large study of 27 million persons over the ages of 35 in the U.S from 1993 to 2006, the estimated incidence of HZ was 2.5 per 1000 persons in 1993, 6.1 per 1000 persons in 2006, and up to 7.2 per 1000 persons in 2016.⁶ The incidence of HZ further varied when stratified by age. In older adults, the incidence of HZ is estimated to be between 8.45 for those aged 50–59, and 10.46 for those greater than 60 years of age.⁷ Several hypotheses exist to explain the increased HZ incidence over time: first is that of exogenous boosting, which argues that the rise in HZ incidence is related to the implementation of childhood varicella vaccination programs, which reduces exposure to wild-type VZV.⁶ Other countering perspectives argue that the incidence of HZ was increasing even before universal varicella vaccination implementation and that other independent variables, such as demographic changes, increased use of immunosuppressants, and increased health literacy and awareness around HZ, may be contributing to increased rates of diagnosis and treatment.^{6,8–10} Nevertheless, given that over 95% of individuals older than 50 years of age have prior exposure to VZV globally, most individuals worldwide are at risk of developing HZ.⁴ Without vaccination, individuals who live to 85 years old have an approximately 50% lifetime risk of developing HZ.¹¹ Hence, HZ prevention is an important global health priority.

The objectives of this global scale narrative review are to (1) synthesize available information on HZ epidemiology and economic burden of disease in developed and developing countries that license HZ vaccines; (2) summarize data on existing HZ vaccines and timeline of vaccine introduction into the countries' national vaccine schedules (if at all); and (3) assess current global challenges in HZ vaccine introduction and considerations in expanding access and vaccine uptake.

Current landscape of HZ vaccines

Mechanisms of action

After varicella exposure and/or vaccination, individuals mount an immune response to VZV. With gradual decline in immunity due to aging or immunosuppression, the population of T-cells

available to inhibit VZV replication decreases over time, leading to manifestation of HZ. The role of HZ vaccines is to re-sensitize the immune system to VZV and inhibit the virus from reactivation. Currently, two main vaccine formulations are available for use – the live attenuated zoster vaccine, also known as zoster vaccine live (ZVL, or Zostavax, developed by Merck & Co., Inc), and the adjuvant recombinant subunit zoster vaccine (RZV, or Shingrix, developed by GlaxoSmithKline, Inc).^{3,12} ZVL contains live attenuated VZV similar to the varicella vaccine. However, it has greater potency, given the higher number of viral plaque-forming units contained^{3,12} (Table 1).

In contrast, RZV is composed of a highly immunogenic antigen glycoprotein E – a main target of human CD4+ T-cell response to VZV. It also contains liposomal adjuvants comprised of 3-O-desacyl-4'-monophosphoryl lipid A, an immunomodulator that targets toll-like receptor 4, and saponin QS-21³ (Table 1).

Vaccine administration and special considerations

The ZVL vaccine is recommended for use in adults over 50 years of age. It can be administered subcutaneously or intramuscularly and requires only a single dose.²² Contraindications to vaccination include hypersensitivity to active ingredients, excipients, and neomycin (possible trace amounts present), immunodeficiency states, active tuberculosis, and pregnancy (Table 1). It can be however co-administered with other vaccines such as inactivated influenza vaccines and 23-valent pneumococcal polysaccharide vaccine (PPSV23).²² Furthermore, ZVL's safety profile has been evaluated in several special populations: adults with history of prior HZ, adults on chronic corticosteroids, adults with human immunodeficiency virus (HIV) infection without severe immunosuppression, and adults that are VZV seronegative; in all of these populations, no significantly different rates of adverse events were observed compared to controls in the Adverse Event Monitoring Substudy of the Shingles Prevention Study.^{22,23} No data are currently available on ZVL usage in pediatric populations.

Currently, the RZV vaccine is recommended to be administered in adults over 50 years of age and in adults over 18 years of age who are at greater risk

Table 1. Comparison of live attenuated and recombinant subunit herpes zoster vaccines.

	Live attenuated VZV zoster vaccine (ZVL, or Zostavax)	Adjuvant recombinant subunit zoster vaccine (RZV, or Shingrix)
Mechanism	Contains a minimum of 19,400 plaque forming units (PFUs) of the Oka/Merck strain of live attenuated VZV ¹	Contains antigen gE (glycoprotein E), the main target of CD4+ T-cell response and liposome-based AS01 _B adjuvant ³
Formulation	Lyophilized ¹²	Lyophilized (reconstituted with AS01 _B adjuvant) ¹³
Approval date by FDA	5/2006 (for >60 years old), 3/2011 (for 50–59 years old) ¹³	10/2017 (for >50 years old) ¹³
Vaccine schedule (U.S.)	Previously in >60 years old <i>via</i> a single dose. No longer used in the United States as of 11/2020 ¹⁴	Adults >50 years old in two-dose series (2–6 months apart); immediate use as booster in patients previously vaccinated with ZVL ¹⁵
Duration of protection	8 years (for reducing HZ incidence); 10 years (for reducing HZ burden of disease, e.g., pain and discomfort) ¹⁶	7 years (for reducing HZ incidence); ¹⁴ 10 years (for immunogenicity)
Vaccine efficacy	Reduces incidence of HZ by 51.3%. Reduces incidence of PNH by 66.5% ¹⁷	Reduces incidence of HZ by 96.6%. Reduces incidence of PNH by 88.8% ¹⁸
Vaccine adverse effects	Local, systemic, and serious adverse effects: ¹⁷ Local reaction: Vaccinated: 48.3%. Placebo: 16.6%. AR: 31.7% [95% CI, 28.3–32.6] Systemic reaction: Vaccinated: 6.3%. Placebo: 4.9%. AR: 1.4% [95% CI, 0.3–2.5] Serious AEs: Vaccinated: 1.9%. Placebo: 1.3%. AR: 0.1% [95% CI, –8.8 to 9.0]	Local, systemic, and serious adverse effects: ^{19,18} Local reaction: Vaccinated: 81.5% [80.3–82.6]. Placebo: 11.9% [11.0–12.9]. AR: 69.6% Systemic reaction: Vaccinated: 66.1% [64.7–67.6]. Placebo: 29.5% [28.2–30.9]. AR: 36.6%. Serious AEs: Vaccinated: 9.0% [8.3–9.6]. Placebo: 8.9% [8.3–9.6]. AR: 0.1%.
Contra-indication	Immunosuppression, prior history of anaphylactic reaction to vaccine or vaccine component, active untreated tuberculosis, and pregnancy	Prior history of anaphylactic reaction to vaccine or vaccine component
Vaccine cost-effectiveness	Cost-effective	Highly cost-effective
Global availability	>60 countries, 34 million doses distributed ^{12,20}	>30 countries, including but not limited to the United States, European Union, Canada, Japan, Australia, and China ²¹
AE, adverse events; AR, attributable risk; CD4, cluster of differentiation 4; CI, confidence interval;; FDA, United States Food and Drug Administration; HZ, herpes zoster; PHN, post-herpetic neuralgia; PFU, plaque-forming unit; RZV, recombinant zoster vaccine, or Shingrix; VZV, varicella-zoster virus; ZVL, zoster vaccine live, or Zostavax.		

for HZ, such as individuals who are immunocompromised due to disease or therapy.²⁴ The vaccine is administered intramuscularly, and the schedule is comprised of two doses with the second administered 6 months after the first. In immunocompromised individuals or individuals anticipating becoming immunodeficient, however, the second

dose can be administered as early as 1 to 2 months after the initial dose.²⁴

Regarding RZV administration in patients previously vaccinated for HZ, a phase-III, multi-center trial on RZV vaccine immunogenicity in previous ZVL vaccines compared to non-ZVL vaccinated

patients demonstrated sustained humoral and cell-mediated immune responses regardless of prior vaccination status;²⁵ moreover, no difference in adverse events was observed, suggesting that RZV can be safely used in patients previously vaccinated with ZVL.²⁵ The recommended interval between vaccination with the two HZ vaccines varies from country to country, with some without recommended minimum interval (e.g. Italy), while others recommend at least 5-year interval in between the two vaccines (e.g. Germany and Spain).²⁰

Furthermore, the RZV vaccine can be administered with other non-HZ vaccines such as the inactivated influenza vaccine, PPSV23, and reduced antigen diphtheria-tetanus-acellular pertussis vaccine without affecting the immunogenicity of the other vaccines.²⁴ Contraindications to the RZV vaccine include hypersensitivity to active and excipient ingredients. No data are currently available on RZV usage in pediatric populations and pregnant patients.

Clinical trials

For ZVL, the initial large-scale randomized, double-blind, placebo-controlled trial of 38,546 adults over the ages of 60 found that the incidence of HZ was reduced by 51.3% and that the incidence of PHN was reduced by 66.5%, with overall burden of disease reduced by 61.1% following vaccination.¹⁷ Vaccine efficacy varied by age, with reduction in incidence of HZ by 37.6% in subjects greater than 70 years of age and 63.9% among individuals 60–69 years of age¹⁷ (Table 1). In a separate randomized, double-blind, placebo-controlled trial of 22,439 individuals between the ages of 50–59, the efficacy of the vaccine in reducing incidence of HZ was 69.8% [CI 54.1–80.6].²⁶ In terms of duration of vaccine efficacy, a long-term persistence sub-study (LTPS) of ZVL showed that while vaccination continued to reduce HZ incidence, HZ burden of disease, and PHN incidence 7–11 years after vaccination; its efficacy waned to 21.1%, 37.3%, and 35.4% for these three measures, respectively.¹⁶ Consistent with the LTPS, a separate cohort study of 1.4 million patients found that ZVL vaccine efficacy diminished over time from 67.5% during the first year of vaccination to 47.2% in the second year and to 31.8% by year 8 across all ages of vaccinees.²⁷ Similar results were found in a 2017

Australian cohort after introduction of ZVL into the National Immunization Program (NIP), with vaccine efficacy diminishing from 63.5% to 48.2% in first and second year after vaccination, respectively.²⁸

For the RZV vaccine, in a large-scale randomized, placebo-controlled phase-3 trial in 18 countries with 15,411 participants over the ages of 50, RZV vaccine reduced the incidence of HZ by 97.2%¹⁹ (Table 1). There was mild variation in efficacy by age: the vaccine was 96.6% effective in reducing the incidence of HZ in adults 50–59 years old, 97.4% in adults 60–69 years old, and 91.3% in adults 70 years and older.^{19,18} The RZV vaccine was also 88.8% effective in reducing the incidence of PHN.¹⁸ Among immunocompromised individuals over 18 years of age, two phase-III trials have demonstrated efficacy of the vaccine as well, with a range of 68.2%–87.2% reduction in incidence of HZ.^{29,30} Although these two trials only included patients who received autologous hematopoietic stem cell transplantation and hematological malignancies, other studies in patients with malignancies receiving immunosuppressive medications and in patients with HIV infections have demonstrated immunogenicity to RZV vaccine as well.^{31–33}

In terms of duration of vaccine efficacy, while a decrease in efficacy is observed over time with 87.9% reduction in HZ incidence at year 4, the vaccine is still significantly protective¹⁸ (Table 1). Interim results from long-term follow-up study of RZV vaccine are consistent with this finding, with overall vaccine efficacy between year 5–7 of follow-up at 84% and high immunogenicity at 8 years of follow-up.³⁴ Moreover, a recent phase-III trial by Bastidas *et al.*²⁹ found persistence of humoral and cell-mediated immune responses up to 10 years after initial RZV vaccination; using mathematical modeling, the authors predicted persistent immune response up to 15 years.²⁹ These findings demonstrate the superiority of RZV to ZVL in terms of both short- and long-term efficacy against HZ.

Adverse events

Compared to placebo, both ZVL and RZV vaccines were more reactogenic. Subjects vaccinated with ZVL had 23.7-fold [21.3–26.0] higher rate of AEs compared to placebo. The majority of AEs

were localized to the injection site with erythema (35.8% of vaccinated group), tenderness (34.5%), swelling (26.2%), and pruritus (7.1%).¹⁷ There was a slight increase in vaccine-related systemic AEs with a non-significant risk difference of 1.4 [0.3–2.5] and serious AEs with a non-significant risk difference of 0.7 [0.1–1.3].¹⁷ Overall, ZVL was well tolerated with 10-year post-market surveillance reports demonstrating that vast majority of vaccine recipients (93.0%) experienced only minor AEs such as injection site reactions.¹²

For patients vaccinated with RZV, vaccinated individuals (84.4%) had higher rates of AEs compared to placebo (37.8%).¹⁹ The majority of AEs were localized injection-site reactions, including pain (79.1%), redness (38%), and swelling (26.3%) at local injection sites. A greater number of vaccine recipients (66.1%) reported systemic symptoms such as myalgias, fever, fatigue, headache, shivering, and gastrointestinal symptoms compared to placebos (29.5%).¹⁹ However, there were no significant differences in rates of serious AEs, immune-mediated disease, or deaths.¹⁹ Recent trials in immunocompromised individuals (e.g. due to history of transplant or HIV infection) have demonstrated accepted safety profiles with comparable rates of serious, fatal, and immune-mediated diseases in those vaccinated with RZV compared to placebo.³⁵

Cost-effectiveness

Multiple studies in different national contexts have examined the cost-effectiveness of ZVL and RZV vaccines. In 2007, Pellissier *et al.*³⁶ examined the cost-effectiveness of ZVL vaccines among a representative cohort of 1 million individuals older than 60 years in the United States, using quality-adjusted life-year (QALY) gained as the primary outcome. It was determined that vaccination would prevent 75,548–88,928 HZ cases and 20,000 PHN cases, enabling savings of \$285 million in direct costs (healthcare payer perspective) related to diagnosis and treatment of HZ and its associated complications. Depending on the input parameters (including but not limited to presumed vaccine efficacy, vaccine costs, incidence of included age groups, and duration of vaccine effect), the incremental cost-effectiveness ratio (ICER) ranged between \$26,048 and \$44,312.³⁶ In an updated systematic review of cost-effective analyses on ZVL in 2019, it was

found that 60% of studies concluded ZVL was generally cost-effective, with variance due to aforementioned factors as well as individual country thresholds for cost-efficacy.¹³ Of note, the majority of studies on cost-effectiveness are limited to countries with developed economies in Europe and North America.

Recently, several studies have also examined the cost-effectiveness of the RZV vaccine. In 2018, Curran *et al.*³⁷ used a multi-cohort Markov model of 1 million individuals and estimated that RZV vaccination would prevent 103,603 cases of HZ, 11,197 cases of PHN, and 14,455 cases of other complications (e.g. ocular, neurologic and cutaneous disease). Compared to ZVL, the RZV vaccine is significantly more effective at all age groups, thus preventing an additional 71,638 cases of HZ, 6403 cases of PHN, and over 10,582 cases of other complications in the model.³⁷ RZV would enable approximate savings of \$218 million in direct costs and \$71 million in indirect costs for the cohort of 1 million individuals studied. With an estimated cost of vaccination efforts of \$319 million, the ICER would be \$12,444 per QALY gained.³⁷ In another modeling study, the authors reached similar conclusions of RZV's high cost-effectiveness and efficacy compared to both ZVL and no vaccination, with the ICER estimated to be between \$21,541 and \$32,340 per QALY gained.³⁸

Methods

Search criteria

Our search was conducted in PubMed, EMBASE, and Google Scholar databases to identify English-language articles on HZ vaccination in countries with developed and developing economies. The literature search was conducted with the key words: ((shingles) OR (herpes zoster) OR (varicella-zoster)) AND ((immunization) OR (vaccination)) AND ((developing country) OR (developed country)). National immunization policies were queried using relevant articles yielded from search terms in databases as described above, as well Google searches for government and health society recommendations. Countries were included if they were licensed for the ZVL and/or RZV vaccines AND if either country-specific HZ epidemiology data OR economic burden of disease data were available based

on the search strategy described above.³⁹ Given limited data available from countries with developing economies, the latter were included if they were licensed for the ZVL and/or RZV vaccines AND either recommend HZ in their national immunization guidelines OR if country-level HZ epidemiology data OR economic burden of disease data were available based on the search strategy described above. Exclusion criteria included articles exclusively written in a non-English language, case reports, and case series.

Country classification

Countries were classified into those with either developing economies or developed economies according to the International Monetary Fund (IMF) classification of countries in 2019.⁴⁰

Outcome conversion to standard metric

All numerical costs reported are in 2020 U.S. Dollars (USD). The costs were adjusted for inflation using the 2020 Consumer Price Index of the relevant country, with all non-U.S. currencies converted to U.S. dollars according to average country to country exchange rates in 2020.

Results

HZ vaccines in countries with developed economies

After the first HZ vaccine ZVL was developed by Merck and Co., Inc in 2006, it became licensed for use in over 60 countries, including the United States, United Kingdom, Canada, the European Union, South Korea, and Australia.¹ Notably, despite being licensed in the European Union, only seven of the 27 EU countries currently have national guidelines recommending HZ vaccination.⁴¹

RZV was approved by the United States Food and Drug Administration (FDA) in 2017 for use in individuals 50 years and older.¹⁵ Since then, RZV has been approved for use in 35 countries, including but not limited to the E.U., Canada, Japan, Australia, and China.³⁹ In practice, it is only available for use in eight countries including but not limited to the United States, Canada, Germany, China, and so on.^{39,21} This section will provide an overview of the current landscape of

HZ vaccination in countries with developed economies.

In Table 2, countries with developed economies with HZ vaccination as part of their national recommended schedule are compared in further detail. Due to the lack of sufficient epidemiological data and/or literature available for review in English, a select number of countries with HZ vaccination are not discussed here. Notably, while a number of countries are licensed to use the ZVL vaccines, the vast majority do not have HZ vaccination recommended in their national vaccination schedules.

North America

Canada. In 2008, ZVL was approved for use in Canada as part of a universal immunization program for individuals over the age of 50.⁷² With the authorization of the RZV vaccine in October 2017, the Canadian government commissioned the National Advisory Committee on Immunization (NACI) to conduct a head-to-head comparison of ZVL to RZV.^{42,73} The 2018 report found that overall, both vaccines were more cost-effective than no vaccination, but RZV was the preferred vaccine given greater cost-effectiveness and efficacy at all age groups. Therefore, in 2018, NACI recommended adoption of RZV as the primary modality of HZ vaccination for individuals over 50 years of age.⁷³ The cost of the vaccine for eligible individuals varies between provinces with some provinces providing it for free while others require payment out of pocket or through supplemental insurance coverage.⁷⁴

United States. In 2006, the first shingles vaccine ZVL was developed by Merck & Co., Inc. and approved by the FDA for use for individuals over the ages of 60.⁷⁵ In 2011, the eligibility criteria for HZ vaccine expanded to include individuals 50–59 years of age.⁷⁶ With the development of the highly effective RZV vaccine in 2017 by GlaxoSmithKline, Inc., the Centers for Disease Control (CDC) updated its vaccination recommendation guidelines with preference for RZV in January of 2018.¹⁵ As of November 2020, the ZVL vaccine is no longer offered as a vaccination option; all individuals over the age of 50 are eligible for the RZV vaccine only. The vaccine is typically covered by private insurance, but those without insurance coverage are required to pay out of pocket.

Table 2. Herpes zoster incidence, burden of disease, and vaccine availability in countries with developed economies.

Country	ZVL license year	RZV license year	Year HZ vaccine in schedule	Eligible age	Vaccine(s) currently in use	Estimated annual incidence per 1000 person years (age range)	Estimated annual cost of HZ ^a (Direct ^b /Indirect ^c), in millions
North America							
Canada	2011	2017	2011	50+	RZV	2011: 9.7 [60–64], 12.7 [65–69], 14.6 [70–74], 15.2 [75–79] ⁴²	\$65.43 ⁴³ /–
United States	2006	2017	2006	50+	RZV	2011: 8.46 [50–59], 10.46 [60+] [2011] ⁴⁴	\$2645.11 ⁵ /–
Europe							
Austria	2006	2018	2019	50+, 18+ (ICs)	RZV		
Czech Republic	2006	2018	2019	50+, 18+ (ICs)	ZVL/RZV	2008: 1.55 [70+] ⁴⁵	–
France	2006	2018	2015	65–74	ZVL	2005–8: 4.16 [45–54], 5.77 [55–64], 8.68 [65–74], 9.85 [75–84] ⁴⁶	\$237.03 ⁴⁷
Germany	2006	2018	2018	60+, 50+ (MCs)	RZV	2007–8: 6.21 [50–54], 7.59 [55–59], 8.94 [60–64], 10.70 [65–69], 11.34 [70–74], 12.15 [75–79] ⁴⁸	\$135.46/234.33 ⁴⁹
Greece	2006	2018	2011	60+	ZVL	2007–9: 1.6 [all ages] ⁵⁰	
Ireland	2006	2018	–	50+ (MCs)	ZVL/RZV		\$2.65 ⁵¹ /–
Italy	2006	2018	2017	65+, 50+ (MCs)	ZVL/RZV	2013–15: 3.95 [50–54], 5.55 [55–59], 6.45 [60–64], 6.07 [65–69], 9.06 [70–74], 8.19 [75–79] ⁵²	\$39.73/18.31 ⁵³
Spain	2006	2018	2021	50+, 18+ (ICs)	ZVL/RZV	2006–7: 6.7 [50–59], 5.2 [60–69], 11.1 [70+] ⁵⁴	\$4.48/4.97 ⁵⁵
The Netherlands	2006	2018	2019 (Conditional)	60+	ZVL/RZV	2011: 3.6 [all age groups] ⁵⁶	\$3.08/\$1.72 ⁵⁷
Norway	2006	2018		50+	ZVL	2008–14: 2.77 [50–59], 4.38 [60–69], 6.63 [70–79], 7.59 [80+] ⁵⁸	9.65 ⁹ /–
Sweden	2006	2018		50+	ZVL/RZV	2011: 3.15 [all ages], 5.77 [50+] ⁶⁰	–/(\$28.0 ⁶⁰)

(Continued)

Table 2. (Continued)

Country	ZVL license year	RZV license year	Year HZ vaccine in schedule	Eligible age	Vaccine(s) currently in use	Estimated annual incidence per 1000 person years (age range)	Estimated annual cost of HZ ^a (Direct ^b /Indirect ^c), in millions
Switzerland	2007	-	2017	65-79, 50+ if anticipate immunosuppression	ZVL	2010: 3.06 [50-54], 3.06 [55-59], 4.14 [60-64], 4.14 [65-69], 5.99 [70-74], 5.99 [75-79] ⁶¹	\$4.63/15.71 ^{61,62}
United Kingdom	2006	-	2013	70-79	ZVL	2000-6: 4.90 [60-69], 5.96 [65-69], 6.34 [70-74], 7.09 [75-79] ⁶³	\$29.25 ⁶³ /-
Oceania							
Australia	2006	2018	2015	60+, 50-59 (IC)	ZVL/RZV	2007-12: 6.3 [50-59], 13.66 [60-69], 15.31 [70-79] ⁶⁴	\$31.75 ⁶⁵
New Zealand	2012	2020	2018	65. 50-64 (MCs)	ZVL	2005-15: 4.86 (all ages) ⁶⁶	
Asia							
Japan	2016 (VLL)	2018	2016	50+	WVL/RZV	1997-2006: 5.23 [50-59], 6.95 [60-69], 7.84 [70-79] ⁶⁷	\$185.33/241.52 ⁶⁸
Singapore	2008	2021	2016	60+	ZVL/RZV		-\$40.9 ⁶⁹
South Korea	2009	2017 (Sky-Zoster)	2012	60+, 50+ (MCs)	ZVL/Sky-Zoster	2011: 17.4 [50-59], 22.4 [60-69], 21.8 [70-79] ⁷⁰	\$189.67/30.84 ⁷¹

COPD, chronic obstructive pulmonary disease; HZ, herpes zoster; IC, with immunocompromised state; MCs, with medical comorbidities; RZV, recombinant zoster vaccine, or Shingrix; ZVL, varicella-zoster virus; WVL, varicella vaccine live; ZVL, zoster vaccine live, or Zostavax.

^aCost of HZ and its complications (e.g. PHN).

^bDirect costs include cost to healthcare system and/or direct medical costs.

^cIndirect costs include societal costs incurred due to loss of productivity (e.g. time away from work).

Europe

European Union (E U.). Although the ZVL vaccine had been licensed by the European Medicines Agency (EMA) for use since 2006, only a few European countries have recommended it as part of the routine vaccination schedule.⁷⁷ This list includes Austria, Czech Republic, France, Greece, and Italy, with funding at the national level in France, Greece, and Italy.⁷⁸ The list has changed partly with the development of the more effective RZV vaccine, which was licensed for use in 2018 by the European Commission.⁷⁹ In addition to the list above, Estonia, Spain, and Germany now also have HZ vaccination as part of their vaccination schedules. The eligible age of vaccination varies from country to country, with some recommending initiation at age 50 (Czech Republic, Austria) while others recommending eligibility at age 65 (Estonia, France, and Italy).⁴¹

Austria. In 2007, Austria became the first European country to recommend HZ vaccination in individuals older than 60 years of age.⁸⁰ Since 2019, the RZV vaccine has replaced ZVL as the vaccine of choice for individuals older than 50 years of age.⁷⁸ Given limited efficacy as well as contraindication among immunocompromised individuals, ZVL is no longer recommended for use.²⁰ The national health system does not cover the cost of vaccination.⁴¹

Czech Republic. In 2019, HZ vaccination with RZV was introduced for the first time into the country's national vaccine schedule.^{41,81} However, the national health system does not cover the cost of vaccination.⁴¹

France. Since June 2015, HZ vaccination with ZVL has been recommended nation-wide for individuals between the ages of 65 and 74 with the cost of vaccination covered by the governmental health system.⁸²

Germany. In Germany, the ZVL vaccine became available for public use as of September 2013. However, it was not recommended as part of the standard vaccine schedule by the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute.⁸³ This decision was reached given the limited duration of vaccine protection in older individuals as well as its contraindication in immunocompromised individuals who are most at risk of HZ and HZ-related complications.^{83,84}

With development of the RZV vaccine, which has shown greater efficacy and duration of protection, the STIKO updated its decision in December 2018 and now recommends RZV vaccine for all individuals over the age of 65.^{83,84} The cost of the vaccine is covered by the public health insurance.

Greece. Since 2011, HZ vaccination has been recommended by the National Vaccination Program for individuals over the age of 60. However, the percentage of vaccinated elderly individuals remains low at 20% in a cross-sectional study reported in 2020 despite the cost of vaccination being covered through the National Insurance System.⁸⁵ Given lack of routine collection of morbidity data, little epidemiological and cost-effectiveness studies are available.⁵⁰

Ireland. Since 2018, RZV has been licensed and recommended for use, but the vaccine was not yet available in the country as of 2020.⁸⁶ While HZ vaccination is recommended for individuals greater than 50 years of age with medical co-morbidities, neither ZVL nor RZV are part of the NIP.⁴¹ For this reason, the national health system does not cover the cost of vaccination.

Italy. In Italy, the ZVL vaccine was implemented into the NIP between 2017 and 2019, and it is universally covered for individuals over the age of 65 and for those over 50 years of age with co-morbidities such as diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease, or anticipation of immunosuppressive therapy.⁸⁷ While the RZV vaccine was licensed as of 2018, it did not become available for use until 2021.⁸⁷

Spain. In 2015, pilot programs of ZVL vaccination were established in the Castilla–Leon region for individuals 60–64 years of age with chronic obstructive pulmonary disease.⁸⁸ The RZV vaccine was licensed as of 2018, and in 2021, it was recommended for use in the national vaccine schedule.²⁰

The Netherlands. Although the ZVL vaccine was licensed for use since 2006, the Health Council of the Netherlands advised against inclusion of ZVL in the NIP in 2016, given its limited efficacy and inability to be used in immunocompromised patients.⁵⁶ The ICER per QALY gained per ZVL vaccine was estimated to be \$27,383 to \$37,405 (depending on age of vaccination).⁸⁹ With the current RZV pricing,

the ICER per QALY gained for RZV is currently estimated to be \$52,960, exceeding the \$25,219 threshold typically applied for preventive vaccinations.⁵⁶ Therefore, the council conditionally recommended the RZV vaccine for HZ prevention with reservations about the program's cost-effectiveness;⁵⁶ for this reason, the national health system does not cover the cost of vaccination.

Norway. In Norway, neither the ZVL nor RZV vaccine is a part of the national immunization recommendations. The ZVL vaccine is available for use but requires payment out of pocket.⁹⁰ The RZV vaccine is not available for use as of 2019.⁹¹

Sweden. In Sweden, neither the ZVL nor RZV vaccine is a part of the national immunization recommendations.⁹² Furthermore, while the ZVL vaccine was temporarily covered by the national pharmaceutical benefit plan in 2013–2014, it was removed from the plan in 2014, and patients are now required to pay out of pocket for the vaccine.⁹³

Switzerland. In Switzerland, the cost of the ZVL vaccine is not reimbursed through the country's basic health insurance.⁹⁴ The RZV vaccine is not approved for use as of 2019.⁹⁵

United Kingdom. In 2013–2014, the United Kingdom became the first European country to implement a universal immunization program for HZ with the ZVL vaccine provided free of charge for all eligible individuals.^{96,97} Studies have compared the cost-effectiveness of RZV to ZVL; in a UK-based vaccination cohort, a study estimated that compared to no vaccination, RZV led to a reduction of 30,262 HZ cases compared to 7909 HZ cases among the ZVL group;⁹⁸ it further recommended expanding the age range of vaccine eligibility to 60–65 years of age, but this has not been implemented in practice.⁹⁸ In 2018, the Joint Committee on Vaccination and Immunization recommended use of RZV in immunocompromised individuals 70–79 years old; however, RZV did not become available in the country until September 2021.⁹⁹

Oceania

Australia. In Australia, the ZVL vaccine is provided free of charge through the NIP for individuals between the ages of 70 and 79.¹⁰⁰ The RZV vaccine was licensed for use in 2018 and became available for use in 2021; however, it is not funded by the NIP.^{100–102}

New Zealand. In New Zealand, the ZVL vaccine became a part of the national immunization schedule in April 2018 and is provided free of charge for individuals older than 65 years of age through the governmental health program.^{103,104}

Asia

Japan. In Japan, the ZVL vaccine is not available for prevention of HZ. Instead, since March 2016, the Oka varicella vaccine – varicella vaccine live (VVL) – was approved for extended use to prevent HZ in individuals older than 50 years of age.¹⁰⁵ In 2018, the RZV vaccine was also approved for use in adults over 50 years of age by the Japanese Ministry of Health, Labor, and Welfare.¹⁰⁶

Singapore. In Singapore, the ZVL vaccine was recommended for use in individuals greater than 60 years of age as of 2016 by the Society of Infectious Disease's Clinical Practice Guidelines on Adult Vaccination.¹⁰⁷ As of 2021, RZV was also approved for use.

South Korea. In South Korea, the Korean Society of Infectious Diseases initially recommended HZ vaccination with ZVL only in individuals over 60 years of age. In 2015, eligibility was expanded to include individuals of ages 50–59 with medical co-morbidities.¹⁰⁸ In 2017, the Korean Ministry of Food and Drug Safety approved of an inactivated HZ vaccine developed by Korean company SK Biochemical – Sky Zoster – for use in individuals over the age of 50. The RZV vaccine is not available in South Korea.¹⁰⁹

HZ vaccines in countries with emerging markets and developing economies

A number of countries with developing economies are licensed to distribute HZ vaccines, including Mexico, Argentina, Brazil, China, Thailand, Malaysia, and others (Table 3). However, limited information is available on the accessibility and implementation of HZ vaccination into national vaccine schedules.

Asia

China. In China, the ZVL vaccine was not licensed for use and no HZ vaccination program was available prior to 2019. In 2019, RZV vaccine was approved by the National Medical Products Administration for use in adults 50 years of age and older. The vaccine became available for use in

Table 3. Herpes zoster incidence, burden of disease, and vaccine availability in countries with developing economies.

Country	ZVL license year	RZV license year	Year HZ vaccine in schedule	Eligible age	Vaccine(s) currently in use	Estimated annual incidence per 1000 person years (age range)	Estimated annual cost of HZ ^a (Direct ^b /Indirect ^c), in millions
Asia							
China	–	2019	–	50+ ¹¹⁰	RZV	2015–17: 6.64 [50+, Mainland China] 2000–08: 2.9–5.8 [50+, Taiwan] 5.7–6.2 [all ages, Taiwan] ¹¹⁰	–/ \$219.16 (mainland China) ¹¹¹
Malaysia	2012	–	2014	60–79, 50–59 optional ¹¹²	ZVL	–	–
Philippines	2012	–	2012	60+ ¹¹³	ZVL	–	–
Thailand	2012	–	2014	60+	ZVL	2007–8: 0.3 [All ages] ¹¹⁴	Per case: \$120.21 ¹¹⁴ /–
Europe							
Poland	2006	2018			ZVL	3.39 [all ages], 6.14 [50+] ¹¹⁵	
Latin America and The Caribbean							
Argentina	2012	–	?	50+ ¹¹⁶	ZVL	2000–5: 3.57 (all ages) ^{117,118}	Per case: \$856.34/\$1011.14 ¹¹⁹
Brazil	2012	–	–	?	ZVL	2000–5: 5.62 (all ages) ¹¹⁸	Per case: \$1264.03/\$575.90 ¹¹⁹
Mexico	2012	–	–	?	ZVL		Per case: \$788.36/\$437.83 ¹¹⁹
Middle East and Central Asia							
Qatar	?	–			ZVL	2012–17: 0.362 (all ages) ¹²⁰	
<p>HZ, herpes zoster; RZV, recombinant zoster vaccine, or Shingrix; VZV, varicella-zoster virus; ZVL, zoster vaccine live, or Zostavax.</p> <p>^aCost of HZ and its complications (e.g. PHN).</p> <p>^bDirect costs include cost to healthcare system and/or direct medical costs.</p> <p>^cIndirect costs include societal costs incurred due to loss of productivity (e.g. time away from work).</p>							

2020, is not state funded, and requires payment out of pocket.¹²¹

Malaysia. In Malaysia, the ZVL vaccine was recommended for use in individuals 60 years and older in 2014, but the vaccine is not state funded and requires payment out of pocket.^{80,113}

Philippines. In the Philippines, the ZVL vaccine was recommended for use in individuals over 60 years of age in 2012.^{39,113}

Thailand. In Thailand, the ZVL vaccine was recommended for use in individuals 60 years and older in 2014.³⁹

Europe

Poland. In Poland, the ZVL and RZV vaccines were licensed in 2006 and 2018 respectively, but limited information is otherwise available.

Latin America and the Caribbean. The incidence of HZ among the general population in Latin America and the Caribbean is unknown, but the incidence of HZ among high-risk individuals is estimated to range between 6.4 and 36.5 cases per 1000 person years.¹¹⁶ High risk is defined as those who are immunosuppressed through disease or medication (e.g. systemic corticosteroids). The overall direct cost per case was estimated to be \$851.72, and the indirect cost was estimated to be \$782.76 per HZ episode in Latin America.¹¹⁹ Limited information is available on individual countries.⁸⁰ While HZ vaccination with the ZVL vaccine is available, the RZV vaccine is not licensed for use in Argentina, Brazil, and Mexico.³⁹

Middle East & Central Asia. One epidemiology study on the incidence of HZ in Qatar is available, but otherwise, there is limited information on HZ vaccines in this geographical region (Table 3).

Discussion

While HZ is a disease with significant morbidity that affects populations on a global scale, HZ vaccines are limited in availability, access, and uptake. Despite being licensed in 2006, ZVL has only been approved in fewer than 70 countries as of 2020.²⁰ It is only a part of the national vaccination schedule in handful of countries (Table 1 and Table 2) and is reimbursed or funded by national health systems in only 8 countries. The adjuvanted recombinant vaccine RZV was licensed in 2017 and is approved in fewer than 40 countries.²⁰ There is a disproportionately lower number of countries that have HZ vaccination programs among developing nations, and research on epidemiology and cost-effectiveness of HZ vaccination is very limited in these regions (Table 2). Considerations for implementation of HZ vaccination include cost-effectiveness of vaccination and other public health concerns such as exogenous boosting as well as public perception, education, and awareness.

Overall, there are a limited number of cost-effectiveness studies on HZ vaccination specific to

national contexts, especially in developing countries.^{43,62,122,123} A systematic review of studies on cost-effectiveness of HZ vaccinations in countries with developed economies found that all studies except one concluded that HZ vaccination was cost-effective. Although there was significant heterogeneity between studies due to variability in input data such as cost of vaccination, age of vaccination eligibility, and thresholds considered by each nation as cost-effective, most studies determined that HZ vaccination was cost-effective when given at age 65 or 70.^{4,62} Nevertheless, individual countries, such as the Netherlands and Germany, determined that HZ vaccination with ZVL was not cost-effective, given contraindication of ZVL in immunocompromised individuals (who are most risk from HZ complications).^{57,84} With the advent of the new RZV vaccine, several studies have determined it to be relatively more cost-effective than the ZVL vaccine, leading to implementation of HZ vaccination in countries where it was previously not recommended (e.g. China and Germany).^{37,124,125}

An argument against the necessity of HZ vaccination that has arisen is the concept of exogenous boosting, which postulates that natural exposure to varicella increases cell-mediated immunity and is thus protective against HZ.¹²⁶ This hypothesis has led to concerns that introduction of mass varicella vaccination may lead to increased burden of reactivated HZ. Although to date, there is no unequivocal evidence proving or disapproving of the hypothesis, most literature demonstrates that the incidence of HZ had begun rising prior to varicella vaccination.^{6,39,113,127,128} It is nevertheless challenging to untangle the effects of changing epidemiology, public awareness, and varicella vaccination; therefore, such perceptions and concerns may affect the public acceptability of varicella and zoster vaccines.

In countries with HZ vaccination programs, maintaining high rates of vaccine uptake is essential for successful public health intervention. A survey study of the general public in Spain found that only 10% of participants were aware that a vaccine for shingles exists, highlighting the importance of increased education and awareness.¹²⁹ Several studies have found that patients are more likely to accept the HZ vaccine if they have been advised by a general practitioner or other health-care provider to receive the vaccine.¹³⁰⁻¹³² For

example, one survey of individuals in the United Kingdom found that those who were vaccinated were more likely to have been offered the vaccine by their general practitioner (GP) or nurse, have been told about shingles by their GP or nurse, advised to receive the vaccine by vaccinated relatives or friends, or know someone who had shingles vaccination.¹³³

Moreover, lack of information and education around the vaccine is a barrier that disproportionately affects certain patient populations; one cross-sectional survey in the United States found that the HZ vaccination rates were 2% for African Americans and 14% for Whites, with only 13.7% reporting having communicated with their provider about the vaccine.¹³⁴ 70% of unvaccinated participants had never heard of the vaccine, and 59% demonstrated interest in vaccination after participating in the survey study.¹³⁴ Other studies have found that older patients and those with higher levels of education were more likely to have heard of and have received the vaccine.¹³⁵ These findings suggest that minority patient groups and those with lower levels of education and healthcare access may be less likely to be vaccinated.

Conclusion

HZ is an infectious disease that causes significant morbidity. It is painful, and it disproportionately affects the elderly and immunocompromised, leading to complications such as prolonged neuropathic pain. The disease incurs significant costs worldwide both directly to medical systems and indirectly in the form of lost productivity and decreased quality of life. Overall, vaccines against HZ have shown cost-effectiveness in multiple populations *via* prevention of acute and chronic disease burden. Licensed in 2006, the live attenuated zoster vaccine Zostavax® is currently employed in the majority of countries with HZ vaccination recommendations. Licensed in 2017, the newer adjuvanted recombinant zoster vaccine Shingrix® has proven to be more effective and safer in immunocompromised patients but requires two shots. Nevertheless, it has become the vaccine of choice in multiple countries including but not limited to the United States, Canada, China, and Germany.

The vast majority of vaccine distribution occurs in countries with developed economies. In

countries with developing economies, there is very limited data available about HZ disease burden and few formal recommendations regarding the vaccine. Given the significant morbidity and cost to healthcare and society worldwide, HZ vaccination is an effective approach to preventing disease. Multiple barriers to widespread vaccine implementation on a global scale need to be addressed, including public education and awareness, effective vaccine delivery, and country-specific studies on cost-effectiveness to inform HZ vaccination recommendations. Our review highlights the need for expanded access to HZ vaccination, especially in countries with developing economies, as a means of expanding health equity and reducing overall global disease burden.

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Catherina X. Pan: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Validation; Writing – original draft; Writing – review & editing.

Michelle S. Lee: Data curation; Investigation; Validation; Writing – original draft.

Vinod E. Nambudiri: Conceptualization; Funding acquisition; Project administration; Writing – review & editing.

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