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Cost-effectiveness of the recombinant zoster vaccine (RZV) against herpes zoster: An updated critical review

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ABSTRACT

The objective of this study was to critically review the cost-effectiveness (CE) of the recombinant zoster vaccine (RZV) against herpes zoster (HZ). A literature review was conducted in PubMed, Embase, and Cochrane between January 1, 2017, and February 28, 2022, and on select public healthcare agency websites to identify and collect data from CE studies comparing RZV to zoster vaccine live (ZVL) or to no vaccination. Study characteristics, inputs, and outputs were collected. The overall CE of RZV was assessed. RZV vaccination against HZ is cost-effective in 15 out of 18 studies included in the present review. Varying incremental cost-effectiveness ratios (ICERs) observed may be associated with different assumptions on the duration of protection of RZV, as well as different combinations of structural and disease-related study (model) inputs driving the estimation of ICERs.

PLAIN LANGUAGE SUMMARY

What is the context?

- Herpes zoster, also known as shingles, may cause painful rashes and skin alterations.
- Chronic pain, also referred to as post-herpetic neuralgia, may persist for months or even years after the initial rash.
- The disease is caused by reactivation of the varicella zoster virus.
- The recombinant zoster vaccine (RZV) and the zoster vaccine live (ZVL) are approved for the prevention of herpes zoster and post-herpetic neuralgia.
- We reviewed published evidence from the past 5 years on RZV.

What is new?

- Out of 18 selected studies, RZV vaccination against herpes zoster and post-herpetic neuralgia is cost-effective in 15.
- In the 15 studies establishing RZV cost-effectiveness, RZV is always cost-effective or frequently cost-saving in direct comparisons to ZVL, when applicable.
- RZV was found cost-saving in several immune-compromised populations.

What is the impact?

- The overview of the currently available body of evidence related to cost-effectiveness of RZV may help informing decision makers about the value of vaccination against herpes zoster.

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Introduction

Herpes zoster (HZ), commonly referred to as shingles, is caused by the reactivation of latent varicella-zoster virus (which causes both varicella and herpes zoster). HZ frequently presents as a painful debilitating rash, including skin inflammation and blisters, and sometimes causes scarring and permanent pigment changes. Anyone with a previous record of varicella (chickenpox) is at risk of developing herpes zoster. The frequency of HZ increases with age due to age-related decline in immunity.[1] The cumulative incidence of HZ was recently estimated between 2.9 and 19.5 cases per 1000 population worldwide, and the HZ incidence rate was estimated between 5.23 and 10.9 cases per 1000 person-years.[2]

Chronic pain persisting 3 months after initial rash detection or HZ diagnosis with an average pain score above 3 on the Likert scale[3] is commonly defined as post-herpetic neuralgia (PHN) and may continue for months or even years.[4] HZ and PHN have been shown to adversely affect healthy aging and quality of life (QoL).[5]

The recombinant zoster vaccine (RZV, *Shingrix*, GSK, Belgium) was approved by the Food and Drug Administration (FDA) in 2017[6] and was preferentially recommended by the Advisory Committee on Immunization Practices (ACIP)[7] shortly thereafter for the prevention of HZ in immunocompetent adults aged 50 years and above and in immunocompetent adults who were previously vaccinated with zoster vaccine live (ZVL, *Zostavax*, Merck Sharp & Dohme Co, United States). It is currently also recommended by ACIP for immunocompromised adults aged 19 years and above.[8] RZV was approved by the European Medicines Agency (EMA) in 2018[9] for the prevention of HZ and PHN in older adults aged 50 years and above and in younger adults aged 18 years and above who are at increased risk of HZ. The vaccine is recommended and reimbursed in a number of countries

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worldwide.[10] ZVL was approved by the FDA in 2006[11] and by the EMA[12] the same year. ZVL is no longer available for use in the United States (US) as of November 2020.[13]

Many health technology assessment (HTA) bodies and national immunization technical advisory groups are currently evaluating RZV worldwide. As such, it is relevant to provide an overview of the inputs, assumptions, and results presented in cost-effectiveness (CE) of RZV publications to date.

Methods

Study selection

The main literature search was performed on PubMed, Embase, and Cochrane reviews with additional queries on select governmental public health online repositories. Publication dates of interest were between January 1, 2017, and February 28, 2022. The exact search queries are shown in Appendix A. Results were analyzed individually to determine inclusion eligibility into the present study. Only CE or equivalent types of studies (i.e., cost-utility analyses) involving RZV were considered. Cost-of-illness and budget impact studies were excluded by default. Conference abstracts (indexed in Embase) were also excluded by default. Studies deemed eligible for inclusion into the present critical review were further searched manually (references) for potential identification of additional sources.

A summary of the search and screening strategy and its outcomes is depicted graphically in an adapted PRISMA-2020[14] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart suitable for reviews including records from databases, registries, and other sources (Figure 1).

Known governmental public health online repositories searched manually for additional sources included the Centers for Disease Control and Prevention (CDC)/ACIP (US), the National Advisory Committee on Immunization (Canada), the Institut National de Santé Publique du Québec (Canada), and the Standing Committee on Vaccination (STIKO, Germany).

Data extraction

For each study included in the review, the extracted information was study characteristics, model attributes, and CE parameters. Detailed input data were collected by type (epidemiological, vaccine profiles, costs, QoL and utilities, adverse events). Top-level and detailed CE results were also extracted.

Quality assessment

The latest version of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[15] was used to objectify and formally assess the quality of each study,

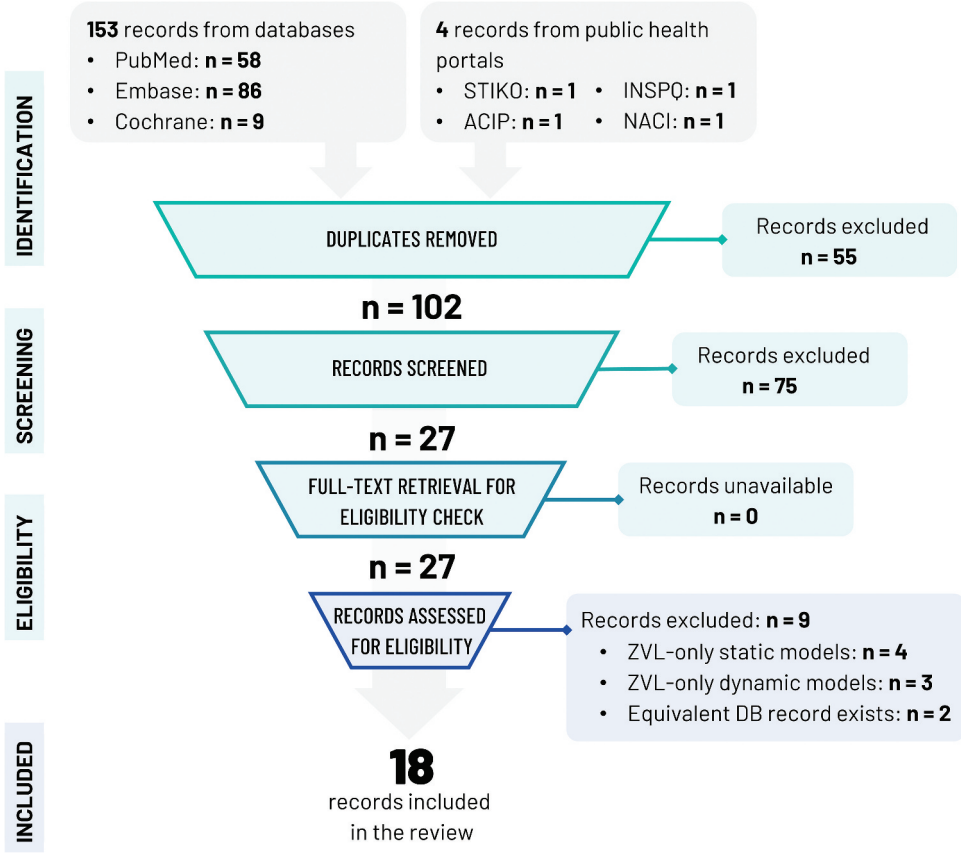

Figure 1. PRISMA flowchart.
Note: ACIP: Advisory Committee on Immunization Practices, DB: database, INSPQ: Institut National de Santé Publique du Québec, NACI: National Advisory Committee on Immunization, STIKO: Standing Committee on Vaccination, ZVL: zoster vaccine live.

incorporating a total of 28 items recommended for best reporting of health economic evaluations.

Further elaboration on the quality of selected studies forms part of the Discussion of the present review.

Aggregated and detailed CE results were compiled under separate tables. Detailed public health impact outcomes were not in scope of the review.

Results

The literature search on PubMed, Embase, and Cochrane reviews yielded 153 records; 16 studies were admitted to review.

Manual search of the public health online repositories mentioned in the Study Selection revealed four additional studies.[16–19] Two[16,17] were deemed equivalent to Drolet et al.[20] and were excluded from further review.

The PRISMA flowchart of identification and screening is shown in Figure 1. In total, 18 studies were subjected to detailed review.

All studies explicitly stated the study objective, target population, setting, comparators, study perspective, time horizon, discount rates, and choice of health outcomes. All but one[18] study explicitly described analytic methods, reported input parameters in detail, and characterized uncertainty via sensitivity analyses. In view of its outline nature, the report of Ortega-Sanchez et al.[18] recapping two original CEAs on immunocompromised populations did not follow CHEERS closely; this observation does in no way speak to the quality of the original research summarized therein.

Study Characteristics

The study characteristics are summarized in Table 1. Of the 18 studies included, nine studies were performed in North America,[18,20–27] five in Europe,[19,28–31] and four in Asia.[32–35]

All but one[18] study examined the CE of RZV and/or ZVL on populations of older adults 50 years and above.

All studies compared RZV to no vaccination; four studies[21,22,26,32] additionally directly compared RZV to ZVL and two[29,30] compared a boosting strategy for ZVL to no vaccination. Three studies[21,23,24] examined the CE of RZV on cohorts previously vaccinated with ZVL. Many studies[20,24,25,29,30,32] additionally performed CE analyses of ZVL vaccination vs no vaccination[13].

Most studies examined cohorts aged 50 years and above; four[19,26,27,31] focused on 60 years and above, and two[32,33] on 65 years and above. The immunocompromised cost-effectiveness analysis (CEA)[18] was performed on immunocompromised adults older than 18 years of age (YOA).

Eleven studies[19–21,24,25,27,29,30,32,34,35] were funded independently; six studies[22,23,26,28,31,33] were funded by the vaccine manufacturer. One study[18] compared the results of two separate CEA analyses on immunocompromised populations <50 YOA (one conducted by the CDC, the other by the vaccine manufacturer).

All studies used the quality-adjusted life year (QALY) to measure health benefits and a monetary value (MV) to express costs in a currency appropriate to the study locale, and all studies reported incremental cost-effectiveness ratios (ICERs) defined as the ratio of incremental costs over incremental benefits between two interventions. One study[32] additionally applied the net monetary benefit (NMB) metric. NMB is calculated as NMB = [Incremental Benefits] × WTP – [Incremental Costs], with WTP representing a known willingness-to-pay threshold[36] for one unit of incremental benefit.

Model design

The studied model design parameters are shown in Table 2.

All studies utilized a combination of decision tree (for the different vaccination strategies under consideration) and Markov state-transition models deployed within each branch of the decision tree representing a distinct vaccination strategy or no vaccination.

Most models[22,23,25,26,28,29,33] were implemented in *Excel* but a few[24,32,35] relied on various versions of *TreeAge Pro*.[37] Two models[19,30] were implemented in *R*.[38]

All but one study utilized a lifetime horizon; de Boer et al.[29] utilized a time horizon of 15 years. A few studies limited the time horizon to 100[25,32,35] or 103[30] years, and one[34] imposed an upper limit on the follow-up period equal to 50 years.

Only a few studies[19,21,34,35] incorporated state-transition diagrams distinguishing between health states for male and female (M/F) subjects. The study of Hoshi et al.[32] reported core model input data differentiated between M/F subjects but no M/F health state differentiation was evident from the state transition diagram.

Model cycle time was generally 1 year; You et al.[34,35] utilized a cycle time of 1 month, and Ultsch et al.[19] a cycle time of 3 months.

An examination of the state transition diagrams for each study under consideration, cross-checked against model and methods description, revealed that all but one study[29] associated PHN with a distinct health state. Complications were generally also taken into account with the exception of Hoshi et al.,[32] Pieters et al.[30] and Ultsch et al.[19]

The modeling of recurrent HZ varied between studies. Many analyses[21–23,25,26,28,33] assumed a recurrent HZ incidence rate equal to that of first time HZ incidence. Recurrence was not implemented in the studies of de Boer et al.[29] and You et al.[34] or was restricted to a one-time event in the studies of You et al.[35] and Hoshi et al.[32] In one study,[24] a cumulative recurrence rate was applied. The implementation of recurrence in the studies of Drolet et al.[20] and Pieters et al.[30] is unclear; the state transition diagram of Drolet et al.[20] implies inclusion of recurrent HZ.

Most studies kept track of healthcare resources such as hospitalizations and general practitioner (GP) visits; in two studies[34,35] a more general classification under inpatient/outpatient was preferred.

Finally, all model implementations enabled the conduct of deterministic and probabilistic sensitivity analyses (DSA/PSA). The CEA of Drolet et al.[20] was probabilistic by design; all outcomes were presented as median values and percentiles from an extensive Monte-Carlo simulation encompassing 30,000 runs. A few studies[24,25,29] performed 1- and 2-way DSAs; one study[21] presented 1-, 2-, and 3-way DSAs.

Table 1. Studies included in the review and main study characteristics.

PMID	Author/year	Funding	Locale	Comparisons	Population	Cohorts	CE metric	PHI/NNV
29297049	Le and Rothberg (2018)[21]	Independent	US	RZV vs no vaccination RZV vs ZVL	ARDI-60+	60, 70, 80	ICER	Not reported
29958739	You et al (2018)[34]	Independent	CN (HK)	RZV vs no vaccination	ARDI-50+	50, 60, 70	ICER	Not reported
30017145	Curran et al (2018)[22]	Industry	US	RZV vs no vaccination RZV vs ZVL	ARDI-50+	50, 60, 65, 70, 80	ICER	Reported
29987323	Le and Rothberg (2018b)[27]	Independent	US	RZV vs no vaccination RZV vs prior vaccination with ZVL	ARDI-50+	50–59; 60/70/80 (ZVL vaccination)	ICER	Not reported
30518427	de Boer et al (2018)[29]	Independent	NL	RZV vs no vaccination ZVL vs no vaccination ZVL+boost vs no vaccination	ARDI-50+	50, 60, 70, 80	ICER	Reported
30130448	Van Oorschot et al (2019)[26]	Industry	GE	RZV vs no vaccination	ARDI-60+	60+, 70+, 60, 65, 70	ICER	Reported
30625011	Curran et al (2019)[23]	Industry	US	RZV vs prior vaccination with ZVL	ARDI-60+	60+	ICER	Not reported
30608953	You et al (2019)[35]	Independent	CN (HK)	RZV vs no vaccination	ARDI-50+	50–80 (31 total)	ICER	Reported
30776797	Prosser et al (2019)[24]	Independent	US	RZV vs no vaccination RZV vs ZVL RZV vs prior vaccination with ZVL ZVL vs no vaccination	ARDI-50+	50–59, 60–69, 70–79, 80–89, 90–99, 60+	ICER	Not reported
30929219	Shiragami et al (2019)[33]	Industry	JP	RZV vs no vaccination	ARDI-65+	65+, 50+, 60+, 70+	ICER	Not reported
31153691	Hoshi et al (2019)[32]	Independent	JP	RZV vs no vaccination ZVL vs no vaccination	ARDI-65+	65–84, 70–84, 75–84, 80-84	ICER, NMB	Not reported
31289726	Carpenter et al (2019)[25]	Independent	US	RZV vs no vaccination ZVL vs no vaccination	ARDI-50+	50, 60, 70	ICER	Not reported
31451524	Drolet et al (2019)[20]	Independent	CA	RZV vs no vaccination ZVL vs no vaccination	ARDI-50+	50, 60, 65, 70, 75, 80, 85	ICER	Reported
31250218	McGirr et al (2019)[26]	Industry	CA	RZV vs no vaccination RZV vs ZVL	ARDI-60+	60+	ICER	Reported
34905463	Curran et al (2021)[28]	Industry	GE	RZV vs no vaccination	ARDI-50+	50, 60, 65, 70, 50+, 60+, 70+	ICER	Reported
35094374	Pieters et al (2022)[30]	Independent	BE	RZV vs no vaccination ZVL vs no vaccination ZVL+boost vs no vaccination	ARDI-50+	50, 60, 70, 80, 85	ICER	Reported
NA	Ortega-Sanchez (2021)[18]	Independent	US	RZV vs no vaccination	IC-18+	CDC: 19–29, 30–39, 40-49 GSK: 18-49	ICER	Reported
NA	Ultsch et al (2017)[19]	Independent	GE	RZV vs no vaccination ZVL vs no vaccination	ARDI-50+	60, 50, 55, 65, 70, 75, 80	ICER	Reported

Note: For each study, costs were represented in MV and benefits in QALY.

ARDI: age-related decline in immunity; CDC: Centers for Disease Control and Prevention; CE: cost-effectiveness; IC: immunocompromised; ICER: incremental cost-effectiveness ratio; MV: monetary value; NA: not applicable; NMB: net monetary benefit; NNV: number needed to vaccinate; PHI: public health impact; PMID: PubMed identifier; QALY: quality-adjusted life year; ZVL: zoster vaccine live.

Locale abbreviations: BE: Belgium; CA: Canada; CN: China; GE: Germany; HK: Hong-Kong; JP: Japan; NL: The Netherlands; US: United States.

CE parameters

CE parameters are summarized in Table 3.

Most studies were conducted from the societal costing perspective; four studies[20,26,30,32] were performed under the healthcare payer perspective, and four[19,22,24,33] investigated both. The RZV manufacturer CEA on immunocompromised populations[18] was also conducted from both perspectives.

ICERs were generally measured against known or assumed WTP thresholds. In one case,[29] the WTP threshold was defined unambiguously in national health technology assessment (HTA) recommendations.[39] WTPs were otherwise chosen empirically relying on either World Health Organization (WHO) guidelines[40] or unofficial precedent.

Cost and benefits were generally discounted in agreement with prior health economic practice for the locale of interest. Notably, two CEAs conducted in Japan[32,33] employed different discounting factors (2% vs 3% for both costs and benefits, respectively). Discounting rates of 2% have been recommended by the Japanese Ministry of Health, Labor and Welfare.[41]

In a similar fashion for two Canadian CEAs, Drolet et al.[20] employed 3% for costs and benefits while McGirr et al.[26] applied a rate of 1.5% for costs and benefits. Discounting factors of 1.5% in the base-case are recommended by the Canadian Agency for Drugs and Technologies in Health.[42]

Model inputs

Detailed model inputs are organized under Tables B1 to B7 of Appendix B.

Epidemiology

Epidemiological model inputs are compiled under Table B1.

All but two[34,35] analyses relied on one or more local epidemiological sources for the incidence rate of HZ. The CEAs of You et al.[34,35] reused international data sources excluding case reports. The study of Pieters et al.[30] used local HZ incidence rates derived from medically attended HZ rates (ambulatory and hospitalized) but relative PHN incidence from

Table 2. Core model characteristics.

PMID	Author/year	Model type	Subtype	Implementation	Follow-up	Cycle time	M/F States	PHN	Other complications	HZ recurrence
29297049	Le and Rothberg (2018)[21]	Static	Markov	TreeAge Pro 2017	Lifetime (120 YOA)	1 yr	Yes	Yes	Monocular blindness, monaural deafness	Equal to first-time incidence
29958739	You et al. (2018)[34]	Static	Markov	TreeAge Pro 2009	50 years	1 mo	Yes	Yes	Central nervous system infection, Ramsay Hunt syndrome, secondary SSTI, HZ ophthalmicus, disseminated HZ	No recurrence
30017145	Curran et al. (2018)[22]	Static	Markov	Excel/VBA	Lifetime	1 yr	No	Yes	Ocular, neurological, cutaneous, other non-pain	Equal to first-time incidence
29987323	Le and Rothberg (2018b)[27]	Static	Markov	Excel/VBA	Lifetime	1 yr	Yes	Yes	Monocular blindness, monaural deafness	Equal to first-time incidence
30518427	de Boer et al. (2018)[29]	Static	Markov	Excel	15 years	1 yr	No	No	No	No recurrence
30130448	Van Oorschot et al. (2019)[26]	Static	Markov	Excel/VBA	Lifetime	1 yr	No	Yes	Ocular, neurological, cutaneous, other non-pain	Equal to first-time incidence
30625011	Curran et al. (2019)[23]	Static	Markov	Excel/VBA	Lifetime	1 yr	No	Yes	Ocular, neurological, cutaneous, other non-pain	Equal to first-time incidence
30608953	You et al. (2019)[35]	Static	Markov	TreeAge Pro 2009	Lifetime (100 YOA)	1 mo	Yes	Yes	Central nervous system infection, Ramsay Hunt syndrome, secondary SSTI, HZ ophthalmicus, disseminated HZ	One-time only
30776797	Prosser et al. (2019)[24]	Static	Markov	TreeAgo Pro 2017	Lifetime	1 yr	No	Yes	Ocular, neurological, cosmetic	Yes, cumulative rate applied
30929219	Shiragami et al. (2019)[33]	Static	Markov	Excel/VBA	Lifetime	1 yr	No	Yes	Misc non-PHN	Equal to first-time incidence
31153691	Hoshi et al. (2019)[32]	Static	Markov	TreeAge Pro 2018	Lifetime (100 YOA)	1 yr	No* (Yes in the input data)	Yes	No	One-time only
31289726	Carpenter et al. (2019)[25]	Static	Markov	Excel	Lifetime (100 YOA)	1 yr	No	Yes	Acute ocular	Yes, unlimited
31451524	Drolet et al. (2019)[20]	Static	Markov	Not specified	Lifetime	1 yr	No	Yes	Ocular	Unclear
31250218	McGirr et al. (2019)[26]	Static	Markov	Excel/VBA	Lifetime	1 yr	No	Yes	No (not reported)	Equal to first-time incidence
34905463	Curran et al. (2021)[28]	Static	Markov	Excel/VBA	Lifetime	1 yr	No	Yes	Ocular, neurological, cutaneous, other non-pain	Equal to first-time incidence
35094374	Pieters et al. (2022)[30]	Static	Markov	R	Lifetime (103 YOA)	1 yr	No	Yes	No	Unclear
NA	Ortega-Sanchez (2021)[18]			GSK: Excel/VBA CDC: not reported	Lifetime or 30 years	1 yr	No	Yes		CDC: unclear
NA	Ultsch et al. (2017)[19]	Static	Markov	R	Lifetime	3 mo	Yes	Yes	No	Yes

CDC: Centers for Disease Control and Prevention; HZ: herpes zoster; M/F: male/female; Misc: miscellaneous; mo: month(s); NA: not applicable; PHN: post-herpetic neuralgia; PMID: PubMed identifier; SSTI: skin and soft tissue infection; VBA: Visual basic for applications; YOA: years of age; yr: year.

a retrospective database analysis performed in the UK.[43] The Canadian CEA by McGirr et al.[26] utilized data from the province of British Columbia.[44]

Vaccine efficacy – RZV

Vaccine efficacy (VE) and waning model inputs are summarized in Table B2 for RZV and Table B3 for ZVL.

All studies relied on ZOE50 and ZOE70 clinical trial data[45,46] to model RZV initial efficacy and waning over time. One recent analysis[28] used updated efficacy data from the long-term follow-up (LTFU) study investigating the efficacy of RZV up to 8 years post-vaccination.[47]

One CEA[34] reused the RZV efficacy model presented to ACIP in 2017.[48]

Most studies implemented simple linear modeling of RZV efficacy over time, with the exception of Drolet et al.[20] and Pieters et al.,[30] who investigated multiple non-linear efficacy models in addition to the linear one. In Pieters et al.,[30] base-case results were reported for two distinct models: (a) an optimistic logarithmic model potentially underestimating waning effects and, (b) a pessimistic 1-minus exponential model resulting in rapid waning of efficacy over time. The CEA of Drolet et al.[20] is unique in that it reports median (and percentile) ICERs from a total of 30,000 simulations, during which the VE model is sampled stochastically amongst a family of six frequently used VE model types. Model parameter values are not stated explicitly in Drolet et al.[20]

Vaccine efficacy – ZVL

All but one[32] study modeled ZVL VE based on the Shingles Prevention Study (SPS)[49] and its follow-ups.[50,51] Some studies[21–23] explicitly took Zoster Efficacy, Safety, and

Table 3. Cost-effectiveness model parameters.

PMID	Author/year	Perspective	WTP	WTP maximum	WTP reference	Fiscal basis	Currency	Costs discounting	Benefits discounting
29297049	Le and Rothberg (2018)[21]	Societal	50 K	100 K		2016	USD	3.0%	3.0%
29958739	You et al. (2018)[34]	Societal	44 K	131 K	WHO	2016	USD	3.0%	3.0%
30017145	Curran et al. (2018)[22]	Healthcare/ Societal	100 K			Not reported (2017 implied)	USD	3.0%	3.0%
29987323	Le and Rothberg (2018b)[27]	Societal	50 K	100 K		2017	USD	3.0%	3.0%
30518427	de Boer et al. (2018)[29]	Societal	20 K		NHCI NL	2016	EUR	4.0%	1.5%
30130448	Van Oorschot et al. (2019)[26]	Societal	50 K			2017	EUR	3.0%	3.0%
30625011	Curran et al. (2019)[23]	Societal	100 K			2016	USD	3.0%	3.0%
30608953	You et al. (2019)[35]	Societal	46.153 K	100 K	WHO	2017	USD	3.0%	3.0%
30776797	Prosser et al. (2019)[24]	Healthcare/ Societal	100 K			2016	USD	3.0%	3.0%
30929219	Shiragami et al. (2019)[33]	Healthcare/ Societal	5 M		Local	2017	Yen	2.0%	2.0%
31153691	Hoshi et al. (2019)[32]	Healthcare	5 M		Local	2016	Yen	3.0%	3.0%
31289726	Carpenter et al. (2019)[25]	Societal	50 K	100 K		2018	USD	3.0%	3.0%
31451524	Drolet et al. (2019)[20]	Healthcare	45 K			2018	CAD	3.0%	3.0%
31250218	McGirr et al. (2019)[26]	Healthcare	50 K	100 K		2016	CAD	1.5%	1.5%
34905463	Curran et al. (2021)[28]	Societal	50 K			2020	EUR	3.0%	3.0%
35094374	Pieters et al. (2022)[30]	Healthcare	40 K			2018	EUR	3.0%	1.5%
NA	Ortega-Sanchez (2021)[18]	Healthcare/ Societal	Not reported (100 K assumed)			2020	USD	3.0%	3.0%
NA	Ultsch et al. (2017)[19]	Healthcare/ Societal	20 K, 30 K	110 K		2017	EUR	3.0%	3.0%

CAD: Canadian dollars; EUR: euro; K: thousand(s); M: million(s); NA: not applicable; NHCI NL: National Health Care Institute (The Netherlands); PMID: PubMed identifier; US: United States; USD: US dollars; WHO: World Health Organization; WTP: willingness to pay.

Tolerability (ZEST)[52] into account. The study of Hoshi et al.[32] relied on real-world evidence data from Baxter et al.[53] The study of Carpenter et al.[25] reused the ZVL VE modeling of a previous CEA.[54]

Top-up efficacy (ZVL) was implemented for the burden of illness (BOI) in the study of Le and Rothberg.[27] Top-up efficacies for PHN were implemented in the studies of Le and Rothberg,[21] McGirr et al,[26] Ultsch et al.[19] and Curran et al.[22,23]

Most studies resorted to linear modeling of ZVL efficacy, with the exception of the studies of de Boer et al.,[29] Drolet et al.,[20] Pieters et al.,[30] and Hoshi et al.[32] The 1-minus exponential VE model was reported to be the best fit in the studies of de Boer et al.[29] and Pieters et al.[30] The CEA of Drolet et al.[20] reported median outcomes from a large number of stochastic simulations (30,000), during which the ZVL VE model type was sampled uniformly from a superset of six different non-linear models. Model parameter values were not reported explicitly in Drolet et al.,[20] but may be inferred from earlier work.[55,56]

Direct costs

Direct HZ treatment costs are reported in Table B4.

All studies incorporated local sources for estimating the direct costs of treating a case of HZ and PHN. With the exception of Le and Rothberg.,[21] You et al.,[34,35] Shiragami et al.,[33] Carpenter et al.,[25] and Drolet et al.,[20] direct costs were stratified by age or age group.

For the Dutch CEA,[29] hospitalization rates, one-day hospitalization rates, GP visit rates, and over-the-counter medication costs per HZ case were combined to derive our own estimates of the aggregate HZ treatment costs.

In the Belgian CEA,[30] costs were reported for hospitalized and ambulatory cases of HZ and PHN based on (pain) severity; an estimation of the aggregate costs of treating HZ and/or PHN is included in Table B4. Similarly in You et al.,[34,35] direct costs per PHN case were estimated from a reported flat cost per month and a PHN persistence (duration) model detailed in the original reports.

Several studies[21–24,34,35] reported costs for complications explicitly, and a few[22,23,26,28,33] took into account the costs of treating adverse events due to vaccination.

None of the studies included other costs such as training, communication about the vaccine or logistic costs.

Indirect costs

Indirect costs are shown in Table B5.

All but four studies[20,26,30,32] reported indirect costs in line with the costing perspective chosen for the analysis (see also Table 3). Three studies[29,34,35] added lifetime earning losses (attributable to HZ death) to productivity losses due to HZ illness; one study[29] relied on the friction approach[57] for estimating productivity losses due to HZ death specifying a friction period of 84 days.

In two studies,[34,35] indirect costs were not reported explicitly but background data relating to labor force participation by gender, unemployment rates, median monthly income, and length of hospitalization by complication type were reported; the estimates shown in Table B5 are based on the same data.

Similarly for one USA CEA,[25] indirect cost data per HZ and PHN case were deduced by lost time reported in hours by severity of pain and a flat average hourly wage.

QoL and utilities

QoL and utility inputs are reported in Table B6.

Several studies[20–26,28,29,32,33] reported QALY losses per case of HZ directly.

In most cases QALY losses were age-specific, but two studies[25,26] reported aggregate losses averaged across all age groups. Only two studies[22,23] reported different QALY losses for vaccinated and unvaccinated subjects in line with the observations of the SPS[49] and following the QALY loss implementation in a previous CEA for ZVL.[58]

The Dutch CEA[29] did not distinguish between a case of HZ with or without PHN; average values were employed and reported.

In the Hong Kong CEAs,[34,35] disutility values were reported for outpatient & inpatient cases of HZ with or without complications, along with a complex non-linear model for estimating the persistence of PHN beyond 12 months. These data formed the basis of HZ and PHN QALY loss estimation by case shown in Table B6.

The CEAs by Le and Rothberg[21] reported QALY losses for HZ explicitly but refrained from providing concrete values for PHN. Additional pain data from a previous epidemiological study performed in the UK[59] were reported by the authors for PHN, and those formed the basis of our own estimates of age-specific QALY losses for PHN included in Table B6.

HZ and PHN QALY losses in Pieters et al.[30] relied on previous work[60] demonstrating QALY/utility loss factors by severity of pain as well as data on the proportion of subjects in each pain state from an older epidemiological study conducted in the UK.[43] These were combined to complete the estimates under Table B6.

Finally, QALY losses per HZ and PHN case were not stated explicitly in Ultsch et al.[19] despite explicit reference to a previous prospective QoL study in Canada;[61] the estimations shown in Table B6 were based on the same source.

Adverse events (AEs)

Model input parameters related to AEs post-vaccination are compiled in Table B7, including information on frequency by AE type, treatment costs by type, as well as utility/QALY losses by type when available. The aggregated treatment costs of AEs per inoculation are shown in Table B4 (direct costs).

Model outputs

Top-level CE results are summarized in Table 4. A more detailed list of ICERs is compiled under Table B8.

Top-level CE results

All but three studies[29,30,32] demonstrated the cost-effectiveness of RZV vaccination vs no vaccination or vaccination with ZVL.

Three studies established the cost-effectiveness of RZV revaccination for subjects previously vaccinated with ZVL.[21,23,24]

Many studies[19–22,24–26,28,33] demonstrated the CE of RZV across all age groups investigated.

In immunocompromised populations,[18] RZV was found cost-saving in hematopoietic stem cell transplantation (HSCT) patients by two models (industry/CDC). RZV was also found cost-saving in renal transplant (industry model) and multiple myeloma (CDC model); RZV was cost-effective in hematologic malignancy and human immunodeficiency virus (HIV) patients (CDC model), and HIV, breast cancer, Hogkin lymphoma patients (industry model).

Sensitivity analyses

All studies provided a number of model input parameters with the greatest effect on CE. Those included structural model inputs such as discount rates, but also vaccination costs (i.e., vaccine prices per dose), vaccine efficacy and waning parameters, HZ and PHN incidence, QALY losses, and direct treatment costs. A non-exhaustive list by study is shown in Table 4.

Detailed CE results

A non-exhaustive list of ICERs reported by each study by age group, costing perspective, com-parison type (i.e., RZV vs no vaccination or RZV vs ZVL, etc.), and corresponding vaccine price per dose is compiled under Table B8.

Discussion

The CE of HZ vaccination in older adults has been reviewed in the past.[62–64] The present study focuses on the CE of HZ vaccination with RZV. While one and nine manuscripts on the CE of RZV vaccination were identified in the systematic reviews of Chiyaka et al.[62] and Udayachalerm et al.,[64] respectively, our search has in the meantime identified an additional nine records, for a total of 18 studies included in the present review. All studies were performed in high-income countries, consistent with the observation of Chiyaka et al.[62] The CHEERS checklist indicates studies of high quality, with the exception of the presentation to the CDC,[18] which does not reflect on the quality of the original research contained within (two unrelated CE models on select immunocompromised cohorts, one by the CDC, the other by the vaccine manufacturer). Our CE findings are generally in good agreement with previous reports.[62,64] Overall, RZV was found cost-effective in 15 out of 18 studies, cost-effective or cost-saving in the subset of the aforementioned 15 studies where a direct comparison to ZVL was applicable, and cost-effective in revaccinating cohorts previously vaccinated with ZVL. RZV was additionally found cost-effective or cost-saving in a variety of immunocompromising conditions.

A quantitative exploration of CE outcomes such as the meta-analysis of net monetary benefits in Udayachalerm et al.[64] was not attempted. Instead, a critical review of variations in CE levels based on an in-depth look into modeling structure and model input data was undertaken, and main findings are discussed below.

All 18 models in this review were static models, i.e., no dynamic models evaluating RZV were identified. The comparison of CE analyses performed under varying assumptions is difficult in view of variation in methodological approaches. While a typical static multi-cohort health economic model using state transition probabilities (Markov model) is

Table 4. Cost-effectiveness results.

Author/year	CE outcome	Parameters affecting DSA	PSA runs	PSA results
Le and Rothberg (2018)[21]	RZV was cost-effective vs no vaccination at all ages; RZV was cost-saving vs ZVL at all ages; RZV was most cost-effective at 70 YOA with an ICER of $20K (USD)	RZV price per dose; RZV efficacy & waning; PHN incidence (duration over 12 mo); RZV 2nd dose compliance	10,000	RZV had between 73% and 91% probability of being cost-effective at a WTP threshold of $50K (USD), and between 78% and 93% probability of being cost-effective at WTP of $100K (USD), depending on vaccination age
You et al. (2018)[34]	RZV was cost-effective vs no vaccination; RZV was most cost-effective at 70/60 YOA with ICERs of $46.3K/$47.4K (USD)	RZV price per dose; 2-dose RZV efficacy waning; HZ outpatient treatment cost; QALY losses outpatient HZ	10,000	RZV had 100% probability of being cost-effective at all ages with a WTP threshold equal to 3 times the GDP per capita; RZV had 60.1%/53.1%/23.9% probability of being cost-effective at 70/60/50 YOA with a WTP threshold equal to the GDP per capita; RZV had 90% probability of being cost-effective at 70/60/50 YOA with WTP thresholds equal to $53.76K/$57.68K/$78.4K (USD)
Curran et al. (2018)[22]	RZV was cost-effective at all ages vs no vaccination; RZV was cost-saving vs ZVL at 60+ YOA	RZV efficacy waning (all ages); HZ incidence; Discount rates; 2-dose RZV efficacy waning (≥70 YOA)	5000	RZV vaccination at 60+ YOA vs no vaccination had 98%/99.5% probability of being cost-effective below WTP thresholds of $80K/$100K (USD); RZV vaccination at 60+ YOA vs ZVL vaccination at 60+ YOA had a 99% probability of being cost-saving
Le and Rothberg (2018b)[27]	RZV vaccination with 56.2% second dose compliance was cost-effective vs no vaccination with ICERs below $100K (USD) at 53.2+ YOA and below $50K (USD) at 57.1+ YOA; RZV vaccination with 100% second dose compliance was cost-effective vs no vaccination with ICER below $100K (USD) at approx. 52+ YOA; Revaccination with RZV at 100% series compliance would be cost-effective at 61+ or 71+ YOA given prior ZVL vaccination at 60 or 70 YOA; Revaccination with RZV at 56% series compliance would be cost-effective at 64+ or 74+ YOA given prior ZVL vaccination at 60 or 70 YOA	PHN incidence; QALY losses; RZV efficacy & waning; RZV price per dose	10,000	RZV had 23% probability of being cost-effective at 50 YOA (results for other ages not reported)
de Boer et al. (2018)[29]	RZV was most cost-effective at 70 YOA with maximum prices at threshold estimated at €54.5/€137.45 at WTP thresholds of €20K/€50K; ZVL was most cost-effective at 60 YOA at a price of €51.37 at the WTP threshold of €20K	QALY loss HZ; RZV efficacy waning after 4 years; HZ incidence (immunocompetent population)	10,000	RZV had over 90% probability of being the most cost-effective option vs no vaccination when vaccine costs per dose were kept below €49.74, €85.8, and €83.64 for 50, 60, and 70 YOA respectively; at 60 YOA, pricing scenarios dictated which vaccine is most cost-effective
Van Oorschot et al. (2019)[26]	RZV was cost-effective vs no vaccination at 60+ and 70+ YOA; RZV was most cost-effective at 60 and 65 YOA with an ICER of approx. €29.5K	HZ incidence; PHN incidence (initial); RZV efficacy waning (≥70 YOA); QALY loss unvaccinated case with PHN	5000	RZV had 84%/67% probability of being cost-effective at 60+/70+ YOA
Curran et al. (2019)[23]	RZV revaccination at 60+ YOA was cost-effective vs control previously vaccinated with ZVL (5 years earlier) with an ICER of approx. $59K (USD); RZV revaccination was cost-saving vs ZVL revaccination at 60+ YOA	RZV efficacy waning; RZV efficacy waning (≥70 YOA); HZ incidence; Discount rates (costs and benefits); Time elapsed between original vaccination and revaccination	5000	RZV vaccination vs no revaccination had 75% probability of being cost-effective
You et al. (2019)[35]	RZV was cost-effective for M and F 50–80 YOA at a price per dose of $80 (USD); RZV was cost-effective for M 54–74 YOA and F 50–79 YOA at a price per dose of $100 (USD); RZV was cost-effective for F 58–72 YOA at a price per dose of $120 (USD)	Age (M and F); Vaccine cost (M)	10,000	RZV had 85.5%/99.7%/99.7%/77% probability of being cost-effective (WTP = 1×GDP per capita) in females 50/60/70/80 YOA; RZV had 57.9%/98.6%/95.6%/26.5% probability of being cost-effective (WTP = 1×GDP per capita) in males 50/60/70/80 YOA
Prosser et al. (2019)[24]	RZV vaccination vs no vaccination was cost-effective at all ages under the societal perspective with ICERs ranging from $10K to $47K (USD); RZV was most cost-effective at 60+ YOA with an ICER of approx. $19K (USD) under the societal perspective; under the healthcare payer perspective, RZV was most cost-effective at 60+ YOA with an ICER of approx. $29K (USD); RZV revaccination vs control previously vaccinated with ZVL was cost-effective at all age groups under the societal perspective, except for immediate revaccination at 50–59 YOA. ICERs were lower at 80–89 and 70–79 YOA	Initial RZV efficacy; HZ incidence; PHN incidence; RZV cost per dose; PHN cost;	10,000	RZV had 84%/95%/99% probability of being cost-effective at 50-79/60-69/70–99 YOA

(*Continued*)

Table 4. (Continued).

Author/year	CE outcome	Parameters affecting DSA	PSA runs	PSA results
Shiragami et al. (2019)[33]	RZV was cost-effective at 65+ YOA with ICERs of ¥4316K/¥4036K under the payer/societal perspective	RZV efficacy waning (≥70 YOA); PHN incidence; HZ incidence; Vaccine price per dose	5000	RZV had 72.2%/79.7% probability of being cost-effective under the payer/societal perspective at a WTP threshold of ¥5 M
Hoshi et al. (2019)[32]	RZV was marginally cost-effective at 80–84 YOA with an ICER of approx. ¥5.26 M per QALY gained; ZVL was more cost-effective than RZV at all age groups and most cost-effective at 80–84 YOA with an ICER of approx. ¥2.6 M	RZV price per dose; RZV waning duration (2-dose); QALY losses HZ (with or without PHN)	1000	RZV had 43.8% probability of being cost-effective at 65–84 YOA at the WTP threshold of ¥5 M; ZVL had 56.2% probability of being cost-effective at 65–84 YOA at the WTP threshold of ¥5 M
Carpenter et al. (2019)[25]	RZV was more cost-effective than ZVL at all age groups; RZV was most cost-effective at 70/60 YOA with ICERs of $1.4K/$19.3K (USD)	1-way: efficacy waning; 2-way: efficacy waning and age of vax		RZV had 82%/69% probability of being cost-effective at WTP thresholds of $100K/$50K (USD) for all ages (weighed average)
Drolet et al. (2019)[20]	RZV was cost-saving or cost-effective at all ages; RZV was more cost-effective than ZVL at all ages; RZV was most cost-effective at 75/70/65 YOA with approx. ICERs of $0.8K/$4.2K/$5.3K (CAD)	NA	30,000	RZV had 75% probability of being cost-effective at all ages ≥60 with a vaccine price per dose of $100 (CAD)
McGirr et al. (2019)[26]	RZV was cost-effective vs no vaccination at 60+ YOA with an ICER of $28.36K (CAD); RZV was cost-effective vs ZVL with an ICER of $2.4K (CAD)	RZV vs control: 2-dose RZV efficacy waning (≥70 YOA); HZ incidence; PHN incidence (first time) RZV vs ZVL: RZV second dose compliance; 2-dose RZV efficacy waning (≥70 YOA); RZV price per dose	5000	RZV had 63.5%/99.2%/100% probability of being cost-effective vs no vaccination at WTP thresholds of $30K/$50K/$100K (CAD); RZV had 100% probability of being cost-effective vs ZVL at the WTP threshold of $50K (CAD), and 48.2% probability of being cost-neutral or cost-saving
Curran et al. (2021)[28]	RZV was cost-effective at all ages investigated at the revised price of €133.62 per dose and most cost-effective at 50+ YOA with an ICER of €31.7K	HZ incidence; PHN incidence; Annual waning of RZV; QALY loss of unvaccinated HZ case with PHN	5000	RZV had a 94%/92.9% probability of being cost-effective at 50+/60+ YOA; at 60+ YOA the maximum RZV price per dose retaining cost-effectiveness below the WTP threshold of €50K was estimated at €163
Pieters et al. (2022)[30]	RZV was generally not cost-effective; Under the logarithmic VE model for RZV at a price per dose of €140.26 and at 50 YOA, RZV would only be cost-effective at a WTP threshold of €90K or higher; At 50 YOA the maximum cost-effective price per dose with a WTP threshold of €40K was €55.4	RZV price per dose Duration of protection (VE model)		No explicit ICER acceptability results were discussed
Ortega-Sanchez (2021)[18]	RZV was cost-saving in HSCT patients by both models (industry/CDC); RZV was cost-saving in renal transplant patients (industry model) and multiple myeloma (CDC model); RZV was cost-effective in hematologic malignancy and HIV (CDC model) with ICERs of $10K and $79K (USD) respectively; RZV was cost-effective in HIV, breast cancer, and Hodgkin's lymphoma (industry model) with ICERs of $33K, $68K, and $96K (USD) respectively	Not elaborated		RZV had a 72% probability of being cost-effective (CDC model); RZV had a 90% probability of being cost-effective and a 50% probability of being cost-saving (industry model)
Ultsch et al. (2017)[19]	RZV was most cost-effective at 60 and 65 YOA with an ICER of approx. €24K; ZVL at 60 YOA was not cost-effective with an ICER exceeding €88K.	Vaccination age; Max duration of protection 5 years, Vaccination costs; PHN incidence; Discounting factors; Recurrent HZ; Baseline utilities	10,000	RZV had a 90%/50% probability of being cost-effective at WTP thresholds of €30K/€20K; ZVL had a 90%/50% probability of being cost-effective only at substantially higher WTP thresholds (€110K/€90K)

CAD: Canadian dollars; CDC: Centers for Disease Control and Prevention; CE: cost-effectiveness; DSA: deterministic sensitivity analysis; GDP: gross domestic product; HIV: human immunodeficiency virus; HSCT: hematopoietic stem cell transplantation; HZ: herpes zoster; ICER: incremental cost effectiveness ratio; K: thousand(s); M/F: male/female; M: million(s); PHN: post-herpetic neuralgia; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; RZV: recombinant zoster vaccine; US: United States; USD: US dollars; VE: vaccine efficacy; WTP: willingness to pay; YOA: years of age; ZVL: zoster vaccine live.

straightforward to construct for HZ and PHN, ICER estimation is invariably non-linear in nature and remains sensitive to the range of inputs. Structural parameters such as discounting rates and model time horizon (follow-up period) are known to have a pronounced effect on ICERs, rendering the direct comparison of models developed for different locales under different prevailing HTA guidelines challenging. In addition, ICERs are not directly comparable when key inputs vary between models, including RZV price per dose and 2nd dose RZV series compliance.

Because vaccine efficacy and waning over time coupled with HZ incidence rates determine the number of incident HZ cases as a function of time, the RZV vaccine efficacy model chosen by each study (and the corresponding ZVL vaccine efficacy model for direct comparisons) was an important input in the reviewed CE analyses. As an example, three CEAs conducted in the US[22,24,25] predicted widely varying ICERs at 50 (or 50–59) YOA: $14.9K, $46.8K, and $91.2K, respectively. A simple estimation of the RZV duration of protection (from initial efficacy to zero) in the three studies from the VE data of Table B2 suggests 35, 19.4, and 17.8 years respectively. However, updated clinical trial data[28,47] estimate a vaccine efficacy of 84.1% eight-year post-vaccination with 2-doses of RZV, indicating that waning of efficacy to zero after 17.8 or even 19.4 years is unlikely.

A quick comparison of other inputs between Curran et al.[22] and Prosser et al.[24] reveals slightly lower HZ incidence rates in Prosser et al.,[24] lower QALY losses per HZ case in Curran et al.,[22] and higher costs per HZ case in Prosser et al.[24] (but lower for PHN). Similarly, the estimated QALY losses per HZ and PHN case are higher in Carpenter et al.[25] than in Curran et al.,[22] and HZ incidence is identical. Yet ICER in Carpenter et al.[25] is several times higher than in Curran et al.,[22] specifically for the 50–59-year-old age group, due to the differences in the duration of protection as outlined above.

The optimal age of vaccination with RZV varied between studies. In the German CEA of Curran et al.,[28] which made use of 8-year long VE data for RZV, the cohort of 50+ YOA was established as the most cost-effective under the societal perspective, while the independent investigation of Prosser et al.[48] estimated the CE-optimal vaccination cohort at 60+ YOA.

Two alternative CEAs conducted in the setting of Japan[32,33] also deserve a more detailed comparative analysis and interpretation. The study of Shiragami et al.[33] supports RZV CE, while Hoshi et al.[32] indicates marginal CE for RZV at 80+ YOA only (see Table B8 for the details). A careful investigation of structural model parameters reveals that Hoshi et al.[32] utilized discounting rates of 3% vs 2% in Shiragami et al.[33] The RZV price per dose in Hoshi et al.[32] was approximately 16% higher than the one quoted in Shiragami et al.[33] Costs were comparable across the two studies but QALY losses for HZ and PHN were slightly lower in Hoshi et al.[32] Most importantly, RZV efficacy modeling in Hoshi et al.[32] assumed faster waning over time resulting in diminished (zero) protection after 19.4 years, which is not supported by the latest RZV vaccine efficacy data.[28,47] At the same time, efficacy and waning of ZVL in Hoshi et al.[32] followed Baxter et al.,[53] which estimates VE at 31.8% (95% confidence interval [CI] 15.1% to 45.2%) after 8 years, while a similar RWE study[65] indicates only 4.2% (95% CI 24.0% to 25.9%) at year 8, and the long-term persistence substudy[51] reports a vaccine efficacy for incidence of HZ of 31.1% (22.4% to 36.2%) at year 8, but only 6.8% (−4.9% to 13.4%) at year 9, and already negative at −1.7% (−14.2% to 4.8%) 11 years post-vaccination.

In the case of one CEA conducted in the Netherlands,[29] low RZV CE levels may similarly follow as the synergistic effect of the following factors: (a) a modeled time-horizon restricted to 15 years, (b) assumed RZV vaccine efficacy waning of 4.1% annually for 50–69 YOA after 4 years post-vaccination and for 70+ YOA, (c) recurrent HZ incidence not included in the model, (d) adjustment (lowering) of the nationally reported HZ incidence by 10% for possible false-positive diagnoses, and, (e) low relative PHN incidence, which implicitly affects the estimation of QALY losses.[66]

In the Belgian CEA,[30] the atypically low RZV CE outcomes may be traced to adjustments performed on the overall HZ incidence rates to immunocompetent specific incidence rates, using a simplistic calculation (the overall HZ incidence rates are presented in Bilcke et al.[67]) Appropriate adjustments would rely on knowledge of the true proportion of immunocompetent individuals in the population, as well as on appropriate risk ratios, i.e., the risk of HZ in the immunocompromised population *versus* the risk of HZ in the immunocompetent population. Consequently, the adjustments performed resulted in artificially low HZ incidence rates leading to low RZV CE outcomes. Moreover, RZV is indicated in individuals who are immunocompromised. As such, an analysis of the cost-effectiveness of RZV could be done on all patients applying overall HZ incidence rates, making the need to perform adjustments on the overall incident rates redundant.

In a previous review of HZ vaccine cost-effectiveness manuscripts, Szucks et al noted that a limitation of most modeling studies was that outdated input data were used.[68] The authors further noted that cost-effectiveness models should be updated when new evidence becomes available to support the effect on a potential vaccination recommendation. In the case of RZV, because longer-term follow-up study results on the efficacy of the vaccine become continuously available,[69] future studies examining the CE of RZV in different settings should be expected, potentially exhibiting less variability in outcomes as a consequence of reduced uncertainty in vaccine efficacy estimates over time.

Most cost-effectiveness models focused on costs of administering a vaccine (e.g. vaccine and administration costs, costs of treating adverse events) and did not include other costs such as training, communication about the vaccine, and logistics.

As a final point, most analyses did not include differential utility losses for vaccinated and unvaccinated cases. Similar to other vaccine preventable diseases, it has been demonstrated that in breakthrough cases of HZ following vaccination there is an attenuation in the severity of the disease,[70] and future studies would be expected to implement utility loss values differentiating between vaccinated and unvaccinated subjects accordingly.

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Contributorship

All authors were involved in the design of the study, collected or generated the data, analyzed and/or interpreted the data and participated to the development of this manuscript and in its critical review with important intellectual contributions. All authors had full access to the data and gave approval of the final manuscript before submission. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The work described was carried out in accordance with ICMJE recommendations for conduct, reporting, editing and publications publishing of scholarly work in medical journals. The corresponding author had the final responsibility to submit for publication.

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