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Cost-effectiveness of vaccination against herpes zoster

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Abbreviations: DES, Discrete event simulation; EMA, European Medicines Agency; FDA, Food and Drugs administration; HZ, Herpes zoster; PHN, Postherpetic neuralgia; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life year; SPS, Shingles prevention study; STPS, Short-term persistence substudy; TPP, Third-party-payer; VZV, Varicella zoster virus; ZBPI, Zoster brief pain inventory;

Herpes zoster (HZ) is a common disease among elderly, which may develop into a severe pain syndrome labeled postherpetic neuralgia (PHN). A live-attenuated varicella zoster virus vaccine has been shown to be effective in reducing the incidence and burden of illness of HZ and PHN, providing the opportunity to prevent significant health-related and financial consequences of HZ. In this review, we summarize the available literature on cost-effectiveness of HZ vaccination and discuss critical parameters for cost-effectiveness results. A search in PubMed and EMBASE was performed to identify full cost-effectiveness studies published before April 2013. Fourteen cost-effectiveness studies were included, all performed in western countries. All studies evaluated cost-effectiveness among elderly above 50 years and used costs per quality-adjusted life year (QALY) gained as primary outcome. The vast majority of studies showed vaccination of 60- to 75-year-old individuals to be cost-effective, when duration of vaccine efficacy was longer than 10 years. Duration of vaccine efficacy, vaccine price, HZ incidence, HZ incidence and discount rates were influential to the incremental cost-effectiveness ratio (ICER). HZ vaccination may be a worthwhile intervention from a cost-effectiveness point of view. More extensive reporting on methodology and more detailed results of sensitivity analyses would be desirable to address uncertainty and to guarantee optimal comparability between studies, for example regarding model structure, discounting, vaccine characteristics and loss of quality of life due to HZ and PHN.

Introduction

Varicella zoster virus (VZV) causes chickenpox (varicella) and shingles (herpes zoster [HZ]). Varicella commonly occurs during childhood and is regarded as a mild self-limiting disease.[1] After remission, however, the virus remains latent, residing in the sensory nerve ganglia of the dorsal root, and can be reactivated decades later in life.[2] This reactivation episode is labeled HZ and is characterized by a painful dermatomal skin rash.[1] The lifetime risk to encounter HZ has been estimated at 20–30%[3] and the probability to develop HZ as well as the severity of pain increase with age.[4,5] Besides age, other risk-factors to HZ are a compromised or suppressed immune system and the female gender.[6,7] Although the rash heals within a month,[8] complications might occur. The most serious complication is postherpetic neuralgia (PHN), defined as a neuropathic pain persisting longer than three months.[9] It has been estimated that approximately 8–33% of HZ patients develop PHN, and the risk increases with age.[4,10-12] Pain due to PHN may remain for months or even years[13,14] and available therapeutic options are only partially effective.[15] PHN has been shown to have a substantial impact on the patient's quality of life and functional status. Often reported sequelae of PHN comprise sleeping problems, chronic fatigue, anorexia, weight loss and depression, resulting in substantial interference with social life and self-care.[4,14,16,17]

In 2006, a VZV vaccine with the tradename Zostavax® (Sanofi-Pasteur/MSD) was approved by the US Food and Drug Administration (FDA) as well as by the European Medicines Agency (EMA).[18,19] Zostavax® contains a live attenuated strain of VZV and is thought to induce primarily T-cell-mediated immunity against VZV. A large double-blind placebo-controlled clinical trial including 38,546 immunocompetent adults > 60 y of age (Shingles Prevention Study [SPS]) has demonstrated that the vaccine reduces the incidence of HZ by 51%, the pain burden by 61%, and the incidence of PHN by 67%.[20,21] However, the vaccine-induced protection seems to decline with age, with an efficacy against HZ of 64% among individuals of 60 to 69 y of age and 38% in individuals aged 70 y or older.[20,21] A more recent trial additionally showed that efficacy against HZ was 70% among of 50 to 59 y of age.[22] Regarding safety of the vaccine, multiple studies have shown that Zostavax® is well-tolerated and that side reactions are generally mild.[20,20,23-26] However, as the mean follow-up time of the SPS was limited to 3.1 y,[20,21] the duration of the vaccine protection is still unknown. A short-term persistence substudy (STPS) of the SPS recently showed that vaccine efficacy persists for at least 7 y, but also

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demonstrated that protection is waning in time.[27] Notably, the vaccine is contraindicated for immunocompromised patients, as it comprises a live attenuated virus.[19]

Given all this evidence, vaccination against HZ might be an interesting option for introduction into national immunization programs. Besides reducing the disease burden itself, prevention of HZ and PHN may yield a significant benefit in limiting the economic burden to the healthcare. For instance, in the US, healthcare costs per acute episode of HZ were estimated at $431 and in the UK, healthcare costs of HZ and PHN were ≤103 and ≤397 per episode, respectively.[28,29]

After the results of the SPS were published, multiple cost-effectiveness analyses for different countries have been performed. The aim of this review is to summarize and synthesize the literature on cost-effectiveness of routine vaccination against HZ and to identify those input parameters that are crucial in determining cost-effectiveness outcomes.

Methods

Search strategy

A bibliographic search was performed in MEDLINE and EMBASE for relevant papers assessing the cost-effectiveness of HZ vaccination (April 10, 2013). The search was restricted to the English language and the search algorithm was as follows: ('herpes zoster' OR 'shingles' OR 'postherpetic neuralgia') AND ('vaccination' OR 'vaccine' OR 'Zostavax' OR 'immunization') AND ('cost-effectiveness' OR 'cost-utility' OR 'cost-benefit' OR 'economic evaluation' OR 'pharmacoeconomics'). The search was limited to articles with an abstract. Only cost-effectiveness studies of HZ vaccination were assessed and original full papers were considered; reviews, editorials and letters were excluded. We screened titles, abstracts and finally the full content of the articles identified and selected. Studies on varicella vaccination only were excluded. Studies combining varicella and HZ vaccination were excluded in the main analysis, but briefly discussed in a separated section. A manual examination of reference sections of included papers was performed in order to identify further material of interest (snowballing).

Synthesis of results

We focused in particular on those variables exhibiting a large impact on the cost-effectiveness and we assessed these parameters critically. Obviously, our analysis plan comprised a review of the main characteristics of the studies, including type of analysis, perspective, targeted population, time horizon, discount rates and a short description of main results. Furthermore, results were stratified by vaccination age, as incidence of HZ, risk to PHN and vaccine efficacies are highly dependent on age. Finally, we analyzed per study which parameters influenced cost-effectiveness results significantly. To improve the comparability of the selected studies, costs were standardized to 2006 euros according to country-specific harmonized consumer price indices. If the costing year was not provided in the study, we assumed a costing year of 'publication year – 3 y'. Studies were evaluated with regards to various aspects, including model type, perspective taken and quality according to previously defined criteria.

Results

Study selection

A total of 369 studies were found in MEDLINE and EMBASE. After evaluation of titles, abstracts or full contents, 18 studies were identified that assessed the cost-effectiveness of HZ vaccination. Two studies were excluded, because full texts were not available.[30,31] However, their main results will be briefly mentioned when cost-effectiveness results are discussed. Two studies were excluded from the main analysis, but described in a separated section, because they assessed the cost-effectiveness of HZ vaccination combined with varicella vaccination.[32,33] Finally 14 cost-effectiveness studies of HZ vaccination remained and were systematically reviewed.[34-47]

Main study characteristics

Table 1 summarizes the main characteristics of the included studies ordered by publication date. Several studies did not mention all the main features reported in **Table 1**, such as time horizon, costing year, sensitivity analysis and funding. In these cases, we estimated most plausible values and options and explicitly marked this in the table.

Country and funding

Of the 14 studies included, 9 were conducted in European countries (UK, Belgium, The Netherlands, Switzerland and France)[34-47] and 5 in non-European countries (US and Canada).[35-39] Six studies were funded by the pharmaceutical industry,[36,38,41,42,44,46] five studies by public resources[34,37,39,40,43,45] and two studies were performed without external funding.[35,47]

Type of analysis

All 14 studies used the incremental cost-effectiveness ratio (ICER) as primary outcome, in which costs are expressed as monetary units and effects as quality-adjusted life years (QALY) gained. Several studies also performed a cost-effectiveness analysis, presenting results as costs per averted HZ case,[36,41,42,44,46] per averted PHN case,[36,41,42,44,46] or per life year gained.[34]

Model design and alternatives

A total of 13 studies used a "traditional" decision analytic model to calculate the cost-effectiveness of vaccination against HZ.[34-47] Decision models which were predominantly used concern Cohort models and Markov models. One study used discrete event simulation (DES) modeling.[39] DES models are able to track the process of individual patients through particular states instead of cohorts. This provides the model with a 'memory function' because specific attributes can be assigned to individuals and might in specific situations provide a superior alternative over adding "tunnel states" into the Markov model to artificially create memory. Within the context of the 14 studies analyzed, a total of 9 different models were used[34,35,37-40,42,45,47] as some authors adapted already available models.[36,41,43,44,46] As no country already implemented HZ vaccination in its national immunization program when the analysis was performed, all

studies compared routine vaccination against HZ with no such vaccination.

Perspective

The perspective that was most often used is that of the healthcare payer, which only includes medical costs.[34,36,38,40-43,45-47] A total of 8 studies used the societal perspective, taking into account medical costs as well as costs due to productivity losses.[35-37,41-44,47] The third-party payer's (TPP) perspective, only including reimbursed medical costs, was used by four studies.[39,41,44,46] Notably, one study can provide results from multiple perspectives.

Target group and time horizon

All studies targeted on population groups of 60 y of age or higher, however, some studies also assessed vaccination ages below this age.[34,38,41,42] Vaccination age was explicitly varied in sensitivity analyses by all studies. Most studies indicated that VZV vaccination was restricted to the immunocompetent population,[35-37,39-44,46,47] as the manufacturer of the VZV vaccine states that immunocompromised patients are contraindicated for the vaccine.[19] Only one study considered a scenario in which also immunocompromised patients would be vaccinated.[45] All studies used the life-time horizon,[34-47] which can be regarded as optimal.[48]

Discounting

Discounting adjusts benefits and costs for the so-called 'time preference', since it is generally advantageous to receive a benefit earlier or to pay costs later (see **Appendix A in Supplemental material**). The discount rates applied are highly dependent on national guidelines of the country for which the analysis is performed. A total of 9 studies applied an equal discount rate for costs and health effects[34-40,42,46] and 5 studies discounted costs at an higher rate than QALYs (differential discounting).[41,43-45,47]

Sensitivity analysis

To deal with uncertainty, studies generally perform sensitivity analyses investigating the impact of varying parameters on the study results (see **Appendix A in Supplemental material** for detailed information on different types of sensitivity analyses). All reviewed studies performed a one-way sensitivity analysis.[34-47] In addition, two studies performed a multiway sensitivity analysis[37,45] and nine studies a probabilistic sensitivity analysis (PSA).[35,37-43,46]

Quality assessment

A review of Szucs et al.[49] evaluated the quality of 11 of the included studies using the *British Medical Journal* (BMJ)'s checklist by Drummond and Jefferson[50] and the "Quality of Health Economic Studies" evaluation tool by Ofman et al.[51] Szucs et al.[49] concluded that the quality of these studies varied from 'Moderate' [37, 38, 4337, 38, 43] to 'Moderate-Good'[35,36,39-42,44]. We assessed the three other included studies using the same criteria as Szucs et al.[49] used. The study of Bilcke et al.[45] was judged as 'Good' and the study of Bresse et al.[46] and de Boer et al.[47] were evaluated as 'Moderate-Good'.

Main input parameters

An overview of input parameters used for the four important domains, i.e., epidemiological, QALY losses, vaccine characteristics and costs are shown in **Table 2**.

Epidemiological input

HZ incidence is obviously an important parameter in economic evaluations of HZ vaccination given the direct relation with HZ and PHN cases potentially to be prevented. **Table 2** shows that the ranges of HZ incidence used in the various studies varied little between different countries. Studies performed in the US seem to use on average somewhat higher incidence rates as compared with the rates used in European studies, especially in the age range of 60–70 y.[35-37,39] Logically, the HZ incidence increases with age in all studies. Multiple studies used HZ incidence rates adjusted to a immunocompetent population to be in line with the included population of the vaccine efficacy data.[35,36,39,40,42,43,45]Concerning PHN incidence, most studies quantified the number of PHN cases directly from the number of HZ cases by using proportions.[34-47] One study used a different method by quantifying HZ on the basis of a severity of illness score, in which the burdens of HZ and PHN are combined.[45] The proportion of HZ cases developing PHN varied extensively between the studies. For example, in a Dutch study the proportion PHN cases out of HZ ranged between 4.7–11.7% among the different age groups,[47] whereas a British study used a range of 9–52%.[40] A compromising factor in comparing the studies was the way PHN was defined in the models. In most studies, PHN was defined as pain persisting longer than 3 mo,[36-40,43,46,47] but other studies used PHN proportions after 1 mo[34,41,42,44] or after 6 mo.[35] Consequently, also the duration of PHN differed among the various studies - 8.3 mo to 4.2 - years, as this is directly related to the definition of PHN used.

QALY losses

The calculation of the QALYs gained depends on two parameters, i.e., the weight of the health-related quality of life attributed to a health state of disease (utility) and the time spent in this health state (general information on utilities can be found in **Appendix A in Supplemental material**). For a detailed look into the health effects of HZ and PHN, we refer to a recently published paper of Drolet et al.[15] **Table 2** shows that most studies split up HZ and PHN in mild, moderate and severe pain states, according to the validated pain inventory measurement Zoster Brief Pain Inventory (ZBPI),[52] which was also used in the SPS. The assignment of HZ and PHN cases between the different pain states differs among the selected studies. Some studies assigned around 20% of HZ/PHN cases as moderate/severe,[34,40] while in other studies this proportion varied between 58–83% of PHN, depending on the age of diagnosis.[41,42,44,46,47] Consequently, also the PHN duration varied between these studies, with studies reporting lower proportions of moderate/severe cases applying longer PHN durations (**Table 2**). Pain severity and pain duration were influential for the cost-effectiveness results. For example, the study of Moore et al.[42] showed that using data on pain severity/pain duration from a general practitioner's database instead of the SPS study increased the ICER from €19,003 per QALY gained to €36,908 per QALY gained.

In the selected studies, some differences were present in assigning utilities to HZ and PHN. Most studies assigned equal utilities to pain caused by HZ or PHN, while two studies distinguished

Table 1. Main characteristics and results of the included studies

Reference; country	Type of analysis	Model design; Alternatives	Perspective	Targeted population: Vaccination age in years (range)	Time Horizon	Currency year; Discount rate	Sensitivity analysis	Cost-effectiveness results, ICER (cost per QALY gained) (Short description of the studies in Appendix B)	Funding
Edmunds et al. (2000);[34] England and Wales	CUA, CEA	DA model; HZ vaccination vs. no vaccination	Health Care provider	65 (45–80)	Lifetime[a]	£ (1998); C: 3% E: 3%	One-way, multi-way	£8684 for a 65 y old assuming 10 y protection and £3560 assuming lifelong protection (≤80 per vaccine course).	Public
Hornberger et al. (2006)[35]; USA	CUA	DA model; HZ vaccination vs. no vaccination	Society	≥ 60, median age 69 (60–85)	Lifetime	US$ (1995); C: 3% E: 3%	One-way, multi-way, PSA	Cost-effective ($50,000 threshold) if vaccine price is $100 and duration of vaccine protection is at least 20 y.	No funding
Pellissier et al. (2007)[36]; USA	CUA, CEA	DA model; HZ vaccination vs. no vaccination	Health Care payer and Society	≥ 60 (60–85)	Lifetime	US$ (2006); C: 3% E: 3%	One-way, PSA	$18,439–27,609 from payer's perspective and $16,229–25,379 from societal perspective depending on input data source and assuming lifelong vaccine efficacy (vaccine price: $168). Cost-effective below threshold of $50,000 when vaccine duration of efficacy is at least 12 y.	Industry
Rothberg et al. (2007)[37]; USA	CUA	DA model; HZ vaccination vs. no vaccination	Society	≥ 60 (60–69, ≥ 70)	Lifetime[a]	US$ (2005); C: 3% E: 3%	One-way, multi-way	$44,000 for a 70-y-old woman to $191,000 for a 80-y-old man (10 y duration of vaccine efficacy and vaccine price of $149). Cost-effective below threshold of $50,000 for all adults ≥ 60 if vaccine cost of $46.	Public
Brisson et al. (2008);[38] Canada	CUA	DA model; HZ vaccination vs. no vaccination	Health Care provider	65 (50- 80)	Lifetime	Can$ (2005); C: 5% E: 5%	One-way, PSA	Can$1277 to Can$73,609, depending on age and vaccine cost, assuming lifelong vaccine efficacy. Vaccinating between 60–75 y is likely cost-effective below Can$40,000 threshold if duration of vaccine efficacy is at least 22 y (vaccine cost Can$150)	Industry
Najafzadeh et al. (2009);[39] Canada	CUA	DES model; HZ vaccination vs. no vaccination	TPP	> 60 (60–74; > 75)	Lifetime	Can$ (2008); C: 5% E: 5%	One-way, PSA	Can$41,709 for vaccinating age-group > 60 y, assuming vaccine cost of Can$150 and a vaccine efficacy half-life of 15 y. When vaccine cost is higher than Can$150, the ICER increases above threshold of Can$50,000.	Public
Van Hoek et al. (2009);[40] England and Wales	CUA	DA model; HZ vaccination vs. no vaccination	Health Care provider	60, 65, 70, 75	Lifetime[a]	£ (2006); C: 3.5% E: 3.5%	One-way, PSA	Between £15,146 and £26,705 depending on age if duration of protection is 7.5 y and vaccination costs are ≤65. Vaccine cost allowed to increase to £90-£100 to hold cost-effectiveness below £30,000 threshold.	Public
Annemans et al. (2010);[41] Belgium	CUA, CEA	DA model; HZ vaccination vs. no vaccination	TPP, Health Care payer and Society	≥ 60 (≥ 50, ≥ 65, 60–64, 65–69, 60–69)	Lifetime	€ (2007); C: 3% E: 1.5%	One-way, PSA	€6799 (TPP), €7168 (health care) and €7137 (societal) for elderly aged ≥ 60 y, assuming lifelong vaccine efficacy and vaccine cost of €141. One-way sensitivity analyses showed ICERs of €4,959–19,052, all below unofficial cost-effectiveness threshold of €30,000.	Industry
Moore et al. (2010)[42]; UK	CUA, CEA	DA model; HZ vaccination vs. no vaccination	NHS and Society	> 50 (50- ≥ 100 in 5-y age-groups)	Lifetime	£ (2006); C: 3.5% E: 3.5%	One-way, PSA	£13,077 (NHS) and £ 11,417 (societal) for vaccinating elderly aged ≥ 50 y, assuming lifelong vaccine efficacy and vaccine cost of £ 105. Duration of vaccine efficacy has to exceed 10 y to remain cost-effective (£ 30,000 threshold).	Industry

C, costs; Can$, Canadian dollar; CEA, Cost-effectiveness analysis; CHF, Swiss franc; CUA, Cost-utility analysis; DA, Decision analytic; DES, Discrete event simulation; E, effects; HZ, Herpes Zoster; NA, Not available; NHS, National Health Service; TPP, Third-party payer; [a]: Not clearly stated, assumed by the authors, [b]: 2% after 30 y

Table 1. Main characteristics and results of the included studies (continued)

Van Lier et al. (2010)[43]; The Netherlands	CUA	DA model; HZ vaccination vs. no vaccination	Society and Health Care payer	60, 65, 70, 75, 80	Lifetime[a]	€ (2008); C: 4% E: 1.5%	One-way, PSA	Societal: €21,716–38,519 depending on age, assuming duration of vaccine efficacy of 7.5 y and vaccine cost of €83. Healthcare: €40,503 (age 60 y). Cost-effective for all vaccination ages except 80 y, if duration of vaccine efficacy was 16.1 y (€20,000 threshold).	Public[a]
Szucs et al. (2011);[44] Switzerland	CUA, CEA	DA model; HZ vaccination vs. no vaccination	TPP and Society	70–79 (60–69, ≥ 65, ≥ 75)	Lifetime	CHF (NA); C: 3.5% E: 1.5%	One way	CHF25,538 (€16,390) from TPP and CHF28,544 (€18,320) from societal perspective for 70–79 y olds, assuming lifelong vaccine efficacy and vaccine cost of CHF266 (€171). A 12 y duration of vaccine efficacy resulted in an ICER of CHF31,553 (€20,251), below unofficial threshold of €30,000.	Industry
Bilcke et al. (2012);[45] Belgium	CUA, CEA	DA model; HZ vaccination vs. no vaccination	Health Care payer	60, 70, 80, 85	Lifetime	€ (NA); C: 3% E: 1.5%	One-way, Multi-way	€1251–5498 most in favor and €45,160–297,141 least in favor of vaccination depending on age and assuming vaccine cost of €112. Vaccination cost needs to decrease below €67 to be cost-effective among all scenarios (unofficial threshold of €30,000)	Public
Bresse et al. (2013);[46] France	CUA, CEA	DA model; HZ vaccination vs. no vaccination	TPP and Health Care payer	70–79, ≥ 65	Lifetime	€ (1998); C: 4%[b] E: 4%[b]	One-way, PSA	€9513 from TPP and €14,198 from societal perspective (70–79 y olds), assuming 10 y duration of vaccine protection and vaccine cost of €125.	Industry
De Boer et al. (2013)[47]; The Netherlands	CUA	DA model; HZ vaccination vs. no vaccination	Society and Health Care payer	60, 65, 70, 75	Lifetime	€ (2010); C: 4% E: 1.5%	One-way	€29,664–35,555 from societal and €29,881–42,004 from health care payer's perspective, depending on age and assuming 12 y protection and vaccine cost of €93. Vaccination was cost-effective for 60 to 75 y-olds, using €50,000 threshold. When €20,000 threshold was applied, vaccination was only cost-effective assuming lifelong duration of vaccine protection	No funding

C, costs; Can$, Canadian dollar; CEA, Cost-effectiveness analysis; CHF, Swiss franc; CUA, Cost-utility analysis; DA, Decision analytic; DES, Discrete event simulation; E, effects; HZ, Herpes Zoster; NA, Not available; NHS, National Health Service; TPP, Third-party payer; [a]: Not clearly stated, assumed by the authors, [b]: 2% after 30 y

between these two diseases.[35,37] One study combined QALY loss of HZ and PHN in a severity of illness measurement.[45] In the study of Van Hoek et al.,[40] a model was used to determine weights of health related quality of life from several pain severity states of HZ in time, using 6 studies of EQ-5D. EQ-5D is an generic instrument quantifying quality of life taking into account five dimensions of health status.[53] Regarding utilities, the weight of mild pain ranged between 0.69–0.77 and of severe pain between 0.25–0.55. Because the vaccine was regarded as safe and side effects were generally mild and restricted to local reactions at the vaccination side, only two studies included a QALY penalty for side effects.[35,37]

Vaccine characteristics

Concerning vaccine efficacy, 13 studies used data from the SPS,[20,21] the only clinical trial supplying data on this aspect. One study was forced to assume a vaccine efficacy rate, because it was performed before the SPS was conducted.[34] Yet, when vaccine efficacy against HZ incidence between selected studies was compared, differences were observed (**Table 2**). These differences can be assigned to two main causes. First, the SPS has shown that HZ vaccine efficacy depends on the age of vaccination, being lower in the higher age groups. This trend was applied or modeled differently among the analyzed studies, resulting in differences in vaccine efficacy. Second, the duration of vaccine-induced protection is still unknown. Several studies have imposed a waning function in their base-case analysis and among them two studies have combined this parameter within the vaccine efficacy function itself.[40,43] These different approaches hampers the comparability of the studies. The used duration of protection in the base-case analysis ranged from 7.5 y[40,43] to a lifetime protection.[36,38,41,42,44] All industry-funded studies except one assumed lifelong vaccine-induced protection in their base-case analyses, while publicly funded studies were more conservative by assuming limited durations of protection. Notably, all studies explicitly varied the duration of vaccine-induced protection in the sensitivity analyses. The study of Bilcke et al.[45] also assessed the influence of the type of function used to model vaccine efficacy on cost-effectiveness results. This was based on previous work of the same authors,[54] in which was evaluated what function of time since vaccination and age at vaccination fitted the data of the SPS and STPS best. Although the results showed that models with different functions (e.g., linear, logarithmic, exponential etc.) fitted the data comparably, they differ substantially in how they estimate vaccine efficacy as a function of time and age of vaccination. Notably, the study of Bilcke et al.[45] demonstrated

Table 2. Input data of main parameters of the included studies (continued)

Reference; country	HZ incidence per 10,000 person years (range)[a]	Proportion of PHN cases (range)[a]	Average PHN duration	Proportion of cases in each pain state	Utilities	Vaccine efficacy [base or (range)[a]]	Duration of protection (years) [base (range)]	Vaccination costs in €2006 [original base case value (range)]
Edmunds et al. (2000);[34] England and Wales	(39.5–115.8)	(3.3–34.4%)[b]	1.4 y	Mild: 77% Severe: 23%	Mild: 0.73 Severe: 0.47 (HZ and PHN)	70% (10–90%)	(2.5-lifetime)	€131(€65-131)
Hornberger et al. (2006)[35]; USA	(99.5–142.9)	5.1%[c]	8 mo	NA	HZ: 0.811 PHN: 0.594	HZ: (13.2–65.4%)[d] PHN: 43.1%[d] BOI: 1.4%[d] (HZ utilities)	(3–30)	€223 (€56-559)
Pellissier et al. (2007)[36]; USA	(69.4–109.4)	(12.0–32.2%)[e]	NA	NA	Mild: 0.77 Moderate: 0.68 Severe: 0.55	HZ: (27.1–69.8%) PHN: 66.5%	Lifetime (12-lifetime)	€142 (€84-211)
Rothberg et al. (2007)[37]; USA	(49–117)	(6.9–18.5%)[e]	4.2y[f]	NA	HZ: 0.0129 (age: 60–69y) or 0.0216 (age: ≥ 70y)[g] PHN: 0.67	HZ:10.3–72.1% BOI: 4–29%	10 (4–18)	€130 (€26-131)
Brisson et al. (2008);[38] Canada	(38.3–95.9)	(11.9–32.2%)[e]	0.31–1.50 y	Mild/moderate: 77%	Mild/moderate: 87% Severe: 51%	HZ: (26–75%) PHN: 67%	Lifetime (12-lifetime)	€111 (€37-148)
Najafzadeh et al. (2009);[39] Canada	(99.5–115.7)	(6.9–18.5%)[e]	1.8 y	NA	Mild: 0.69 Moderate: 0.58 Severe: 0.30	HZ: (13.2–65.4%)[d] PHN: (4.3–47%)[d]	Half-life: 15 (5–30)	€104 (€35-104)
Van Hoek et al. (2009);[40] England and Wales	(70.6–121.6)	(9–52%)[e]	1013 d (Long-term CRP)	Moderate/severe: 21%	Mild: 91% Moderate: 71% Severe: 32%	HZ: 37–78% BOI: incorporated in QALY weights PHN: 0% (0–44%)	7.5 (3.6–100)	€94 (€15-160)
Annemans et al. (2010);[41] Belgium	(40–182)	(10.3–28.9%)[b]	(8.3–10.9 mo)	HZ: 32–41 (mild), 18–23 (moderate), 14–19 (severe) PHN: 17–42 mild, 9–16 (moderate), 49–67 (severe)	Mild: 0.69 Moderate: 0.58 Severe: 0.25	HZ: 37.6–63.9% PHN: 65.7–66.8% BOI: 2.2–3.3 mo reduction of PHN length	Lifetime (12-lifetime)	€139 (€98-157)
Moore et al. (2010)[42]; UK	(33.4–72.9)	(10.3–28.9%)[b]	(10.3–12.9 mo)	HZ: 32–41 (mild), 18–23 (moderate), 14–19 (severe) PHN: 17–42 mild, 9–16 (moderate), 49–67 (severe)	Mild: 0.69 Moderate: 0.58 Severe: 0.25	HZ: 37.6–63.9% PHN: 66.7–66.8% BOI: 2.2–3.3 mo reduction of PHN length	Lifetime (12-lifetime)	€153 (€94-182)
Van Lier et al. (2010)[43]; The Netherlands	(50.9–116.9)	As Van Hoek et al.[40]	As Van Hoek et al.[40]	As Van Hoek et al.[40]	As Van Hoek et al.[40]	As Van Hoek et al.[40]	7.5 (3.6–100)	€80 (€53-85)

BOI, Burden-of-illness; Can$, Canadian dollar; CHF, Swiss franc; HZ, Herpes zoster; NA, Not available; PHN, Postherpetic neuralgia; QALY, Quality-adjusted life year; SOI, Severity of illness; [a] Depending on age and sex(minimum and maximum values are given); [b] PHN proportions after 1 mo; [c] PHN proportion after 6 mo; [d] Calculated by the authors; [e] PHN proportions after 3 mo; [f] If duration PHN longer than 12 mo; [g] Total QALY loss per HZ episode

Table 2. Input data of main parameters of the included studies (continued)

Szucs et al. (2011);[44] Switzerland	(30.6–81.7)	(10.3–28.9%)[b]	(8.3–10.9 mo)	HZ: 32–41 (mild), 18–23 (moderate), 14–19 (severe) PHN: 17–42 mild, 9–16 (moderate), 49–67 (severe)	Mild: 0.69 Moderate: 0.58 Severe: 0.25	HZ: 37.6–63.9% PHN: 65.7–66.9% BOI: 2.2–3.3 mo reduction of PHN length	Lifetime (12-lifetime)	€171 (€137-186)
Bilcke et al. (2012);[45] Belgium	(54.8–128.7)	NA	Combined with HZ into SOI episode	NA	QALY loss per HZ case: (0.12–0.52)[a]	HZ: 35–78% Age/model/time-dependent efficacy	Most favor.: 7; Least favor.: lifetime	€110 (€23-110)
Bresse et al. (2013);[46] France	(81.4–112.0)	(11.4–14.3%)[e]	(8.3–10.9 mo)	HZ: 32–41 (mild), 18–23 (moderate), 14–19 (severe) PHN: 17–42 mild, 9–16 (moderate), 49–67 (severe)	Mild: 0.69 Moderate: 0.58 Severe: 0.25	HZ: (18–64%) PHN: (5–55%) BOI: 2.2–3.3 mo reduction of PHN length	10 (7.5–20)	€143 (€114-171)
De Boer et al. (2013)[47]; The Netherlands	(65.8–83.5)	(4.7–11.1%)[e]	(8.3–10.9 mo)	HZ: 32–41 (mild), 18–23 (moderate), 14–19 (severe) PHN: 17–42 mild, 9–16 (moderate), 49–67 (severe)	Mild: 0.69 Moderate: 0.58 Severe: 0.25	HZ: 41.2–69.4% PHN: 0–44.0% BOI: 0–28.9%	12 (3.1-lifetime)	€88 (€78-135)

BOI, Burden-of-illness; Can$, Canadian dollar; CHF, Swiss franc; HZ, Herpes zoster; NA, Not available; PHN, Postherpetic neuralgia; QALY, Quality-adjusted life year; SOI, Severity of illness; [a] Depending on age and sex(minimum and maximum values are given); [b] PHN proportions after 1 mo; [c] PHN proportion after 6 mo; [d] Calculated by the authors; [e] PHN proportions after 3 mo; [f] If duration PHN longer than 12 mo; [g] Total QALY loss per HZ episode

that function type influences cost-effectiveness substantially in age-cohorts > 75 y in the scenario most in favor of vaccination (includes waning of vaccine efficacy in time).

Besides efficacy against HZ incidence, most studies included additional efficacy of vaccination toward PHN[35,36,38,39,41,42,46,47,49] or toward the burden of disease (BOI)[35,37,40-46] in the base-case scenario. Two studies imposed additional efficacy against PHN in a scenario analysis.[40,43] A general note regarding this additional efficacy is that the SPS publications reported efficacy against BOI and incidence of PHN for the entire population, and not just for those who developed HZ.[20,21] Thus, these measures incorporated the decreasing HZ incidence, which implies that vaccine efficacy rates against PHN and BOI should be corrected before it can be directly applied on the BOI or the risk on PHN per HZ case itself. Papers demonstrated that after this correction, additional vaccine efficacy against PHN or BOI might only be present above the age of 70.[37,55]

Costs

In general, a distinction can be made between medical costs and societal costs. All studies included the three major direct cost burdens, i.e., GP costs, hospitalization costs and drug costs. Four studies used cost data specified for the immunocompetent population, as this is the targeted population.[36,40,42,47] Societal costs due to productivity losses were included in 8 of the 14 studies.[35-37,41-44,47] Cost parameters were not regarded as influential parameters in many studies. Just one study reported that PHN costs had a large impact on the ICER.[36] Since the targeted population consisted of the elderly in all studies, indirect costs did not influence the ICER to a considerable extent, as the labor participation among the vaccinated population is generally low. However, since the age of retirement will probably rise in most countries due to healthy aging, this might change in the future.

As the vaccine price was still unknown at the moment of analysis of the studies, authors had to assume the vaccine price. Although the vaccine price for the private sector is nowadays known in some countries, it is not clear which reduction can be expected when the vaccine is bought in bulk quantities. **Figure 1** shows the vaccination costs used among the selected studies (expressed in 2006 euros). These vaccination costs include the vaccine price as well as the costs of vaccine administration. When only a range of vaccine prices was presented, vaccination costs as used in the sensitivity analysis were taken. Not all studies differentiated vaccination costs between vaccine price and administration costs. Among studies stating the separated vaccine price, the price varied between €65 and €154. The total vaccination costs ranged from €83 to €223. Highest vaccination costs were used by Hornberger et al.,[35] ranging from $50 to $500 and using a value of $200 in the one-way sensitivity analysis. Notably, industry-funded studies used on average higher vaccine prices in the base-case as compared with studies funded from other sources. Among the six studies with the highest vaccine price, five studies were funded by industry.[35,36,41,42,44,46] The vaccine pricelist of the US Centers for Disease Control and prevention (CDC) of 2013 presents a price per dose of $166 and $114 for the private sector and CDC itself, respectively.[56] This would imply a 30% reduction for buying the vaccine in bulk quantities. As authors were forced to

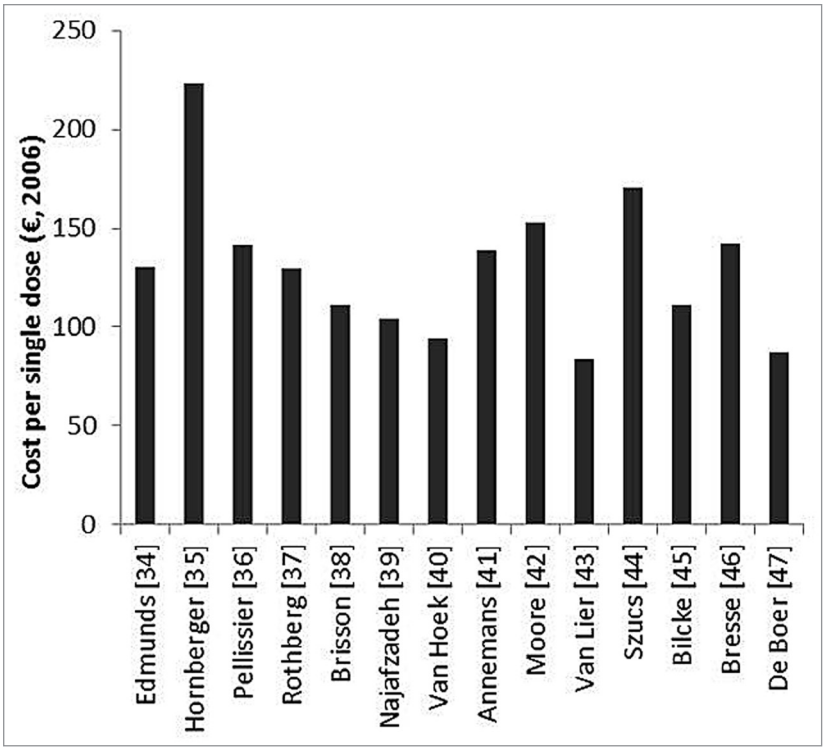

Figure 1. Cost of vaccination per single dose as used in base-case scenario.

assume the vaccine price, this parameter was explicitly altered in the sensitivity analysis by all studies.

Cost-effectiveness results

Effects of HZ vaccination on health outcomes and related QALY gains, incremental costs and cost-effectiveness results are shown in **Table 3** and **Figure 2**. Generally, cost-effectiveness studies assuming a life-long duration of vaccine-induced protection showed the lowest cost-effectiveness results, in the range of €5000 – €25,000 per QALY gained.[36,38,41,42,44] Studies assuming a shorter duration of protection (range 7.5 and 15 y) in their base-case analysis, found higher cost-effectiveness results varying between €25,000 – €40,000 per QALY gained.[39,40,43,47] Two studies reported ICERs in the range of €10,000–15,000, despite a duration of protection that was limited to 10 y.[34,46] For Edmunds et al.[34] this could be explained by the fact this study was performed before the SPS results came out and therefore assuming a relatively high vaccine efficacy of 70% for all age groups. In the study of Bresse et al.[46] a relatively high amount of medical costs were prevented as compared with other studies. Two studies for the US showed cost-effectiveness results exceeding €50,000 per QALY gained.[35,37] This might be explained by that both studies assigned lower QALY losses to HZ and PHN cases as compared with other studies. Moreover, the study of Hornberger et al.[35] assumed a relatively high vaccine price and a low risk to develop PHN. One study was difficult to compare with other studies, because only best-case and worst-case scenarios were presented in the results, representing an extremely broad range of for instance €2294 to €73,513 per QALY gained for vaccinating a cohort of 70 y olds.[33]

All studies, except one, stated in their conclusion that HZ vaccination may be cost-effective referring to the results of their base-case analysis. Only the Dutch study of Van Lier et al.[43] concluded that vaccination was marginally cost-effective from the societal perspective as well as from the health care payer's perspective.[43] However, in this study a cost-effectiveness threshold of €20,000 per QALY gained was applied, which is low compared with that of other countries or compared with the GDP per capita of the Netherlands. When a threshold of €50,000 per QALY gained would be used, a value which also has been suggested for the Netherlands, the results of Van Lier et al.[43] would be regarded as cost-effective. This higher threshold was also used in the other Dutch study included in our analyses by de Boer et al.[47] Two German studies on cost-effectiveness of HZ vaccination were identified, but not included because full content was not available for evaluation.[30,31] The study of Wasem et al.[30] found that vaccination of people above 60 y of age was cost-effective with an ICER of €20,139 per QALY gained from the TPP's perspective. The study of Ultsch et al.[31] presented no cost-utility results, but found that vaccination of a cohort aged 50–54 y would cost €280 per HZ case prevented from the societal perspective.

Optimal vaccination age

Table 3 shows that cost-effectiveness of HZ vaccination varies significantly over a range of vaccination ages. Different optimal vaccination ages were found and this was also dependent on the duration of vaccine efficacy which was assumed. Studies with limited durations of vaccine protection found an optimum vaccination age in the range of 70 to 75 y,[37,39,43,46,47] while studies assuming life-long protection reported ages between 60 and 69

Table 3. Modeled health and economic impact of vaccinating 1 million elderly against HZ (continued)

Reference; country	Age cohort and perspective	Avoided HZ cases	Avoided PHN cases	Incremental QALYs gained	Incremental health care costs (millions)	ICER (costs per QALY gained)	Most and least favorable vaccination age (ICER [costs per QALY gained])	Influential parameters toward ICER
Edmunds et al. (2000);[34] England and Wales	65y, Health care provider	NA	NA	7600[a]	€108[a]	€14,171[a]	Most: > 70y (€12,000)[a] Least: 45y (€23,000)[a]	Vaccination costs, vaccine efficacy, duration of protection, PHN length
Hornberger et al. (2006)[35]; USA	> 60y, Societal	60,000[b]	NA	1600[b]	€159.8[b]	€104,033[b]	Most: 60–64y (€40,000)[b] Least: > 80y (€390,000)[b]	Vaccination costs, duration of vaccine efficacy, quality-of-life adjustment, risk for HZ
Pellissier et al. (2007)[36]; USA	> 60y, Societal	75,548	20,901	3478	€72.0	€21,433	Most: 60–70y (NA) Least: 85y (NA)	Vaccination costs, PHN costs, waning rate, baseline QALY weight, vaccine efficacy PHN
Rothberg et al. (2007)[37]; USA	> 60y, Societal	16,983	2753	1163	€114.0	€97,962	Most: 70y women (€38,052) Least: 80y men (€166,820)	Vaccine variables (duration, cost, efficacy, and side effects), PHN variables (incidence, duration, and utility, HZ variables (incidence and severity), discount rate
Brisson et al. (2008);[38] Canada	65y, Health care provider	57,570	13,370	3140	€77.1	€24,584	Most: 70y (€23,479) Least: 50y (€37,555)	Waning of vaccine protection, PHN vaccine efficacy, QALYs-lost to PHN, vaccination costs
Najafzadeh et al. (2009);[39] Canada	> 60y, Third-party payer	24,000	NA	2800	€80.0	€29,000	Most: 70–74y (€22,000) Least: 85–89y (€90,000)	Duration of vaccine protection, vaccination costs, QALY weights for HZ and PHN, average PHN length
Van Hoek et al. (2009);[40] England and Wales	65y, Health care provider	30,635	4141	3006	€89.2	€29,663	Most: 70y (€22,010) Least: 60y (€38,808)	Vaccine efficacy/duration of vaccine protection, HZ incidence, duration of long-term CRP, quality of life weight of moderate pain
Annemans et al. (2010);[41] Belgium	> 60y, Health care payer	85,183	29,002	16,387	€115.4	€7040	Most: 65–69 (€5546) Least: > 65y (€7439)	Duration of vaccine efficacy, PHN duration/pain split, HZ incidence/PHN rates, discount rates
Moore et al. (2010)[42]; UK	> 50y, Third party payer	64,914	17,101	7136	€135.6	€19,003	Most: 65–69y (€14,932) Least: > 100y (€98,984)	Duration of vaccine protection, discount rate, utility decrements, pain severity split
Van Lier et al. (2010)[43]; The Netherlands	65y, Societal	26,021	3062	2587	€77.6	€29,987	Most: 70y (€20,853) Least: 60y (€36,988)	Vaccine price, duration of protection, discount rate

HZ, Herpes zoster; ICER, Incremental cost-effectiveness ratio; PHN, Postherpetic neuralgia; QALY, Quality-adjusted life years ; [a] assuming duration of vaccine protection of 10 y; [b] assuming 30 y vaccine efficacy

Table 3. Modeled health and economic impact of vaccinating 1 million elderly against HZ (continued)

Szucs et al. (2011);[44] Switzerland	70–79y, Societal	31191	13347	8090	€148.4	€18,326	Most: 60–69y (€12,835) Least: > 70y (€22,170)	Discount rates, HZ incidence, vaccine price, duration of vaccine efficacy, utilities
Bilcke et al. (2012);[45] Belgium	70y, Most in favor, Health care payer	59,056	14,904	29089	€65.5	€2253	Most: 60y (€1229) Least: 85y (€5400)	Duration of vaccine protection, vaccine cost, duration and severity of pain and QALYs lost due to HZ
	70y, Least in favor, Health care payer	12,586	2038	1478	€105.8	€72,197	Most: 60y (€84,101) Least: 85y (€298,267)	
Bresse et al. (2013);[46] France	> 65y, Health care payer	23,467	14,152	5055	€106.0	€20,959	Most: 70–79y (€16,186) Least: > 65y (€20,959)	Pain severity classification, vaccination costs, utilities, discount rates
De Boer et al. (2013)[47]; The Netherlands	65y, societal	36,310	3470	2420	€79.7	€32,933	Most: 70y (€27,796) Least: 60y (€33,316)	Vaccination costs, HZ incidence, vaccine efficacy, duration of vaccine efficacy, QALY weight of mild pain

HZ, Herpes zoster; ICER, Incremental cost-effectiveness ratio; PHN, Postherpetic neuralgia; QALY, Quality-adjusted life years ;[a] assuming duration of vaccine protection of 10 y;[b] assuming 30 y vaccine efficacy

as most beneficial.[35,36,41,42,44] Also inclusion of additional efficacy against PHN and BOI or not was an important factor to determine the optimal vaccination age. For instance, the study of Van Hoek et al.,[40] considering no additional efficacy against PHN in the base-case scenario, found an optimum age of 65 y. However, when additional protection against PHN was taken into account, the optimum vaccination age increased to 75 y.

Gender

Two studies also stratified results by gender.[37,47] Both studies concluded that vaccination of women is more cost-effective than vaccination of men, because HZ incidence is higher among women (**Table 3**).

Influential parameters for cost-effectiveness

Sensitivity analyses provide information on which parameters can be regarded as most influential to the cost-effectiveness ratio. Parameters most often considered as influential are the duration of vaccine efficacy and the vaccine price (**Table 3**). All studies except one,[46] showed that duration of vaccine-induced protection or waning rate affected the ICER considerably. Only two studies came to the conclusion that vaccine price does not have a high impact on cost-effectiveness.[41,42] Other often mentioned parameters influencing the ICER largely were vaccine efficacy,[34,37,40,47] HZ incidence[40,44,47] and discount rates.[37,39,41-44,46] Also utilities, pain severity split and duration of HZ and especially PHN, all involved in the calculation of the QALY losses, was reported to influence cost-effectiveness outcomes largely.[34,35,39,42,44,46,47]

Combined varicella and zoster vaccination strategies

An interesting target of HZ vaccination might be the use in combination with varicella vaccination. As mentioned in the introduction, VZV is responsible for varicella as well as HZ. However, it has been hypothesized decades ago that re-exposure to circulating VZV could inhibit the reactivation of VZV.[2] This theory is also known as the 'exogenous boosting' theory and would imply that if adults come into contact with varicella infected children, their immunity against VZV is boosted and consequently the risk of developing HZ reduces. Consequently, in case universal varicella vaccination among children is implemented, a temporary increase of HZ incidence might arise due to an absence of exogenous boosting. Although the exact consequences of this theory are still under debate,[57-63] a recently published systematic review concluded that exogenous boosting exists, however it seems not to account for all populations and all situations.[64]

As mentioned above, two studies were found analyzing the cost-effectiveness of a combined varicella and HZ vaccination program.[32,33] Both studies used an dynamic transmission model which accounted for passive immunity (herd immunity), age structures, gradual loss of vaccine or disease-acquired immunity and social contact mixing patterns.[65] The two studies also included the effect of exogenous boosting in their base-case analysis. The results showed that both models predicted an increase of HZ incidence in at least the first five decades following varicella vaccination, depending on the duration of protection of natural boosting. As HZ has a much higher disease burden than varicella, varicella vaccination was not deemed to be cost-effective within a time frame of 50 y, but might be cost-effective when an

infinite time-horizon is used. Both studies demonstrated that combining varicella vaccination with HZ vaccination of the elderly is more cost-effective than varicella vaccination alone. In the study of Van Hoek et al.,[32] the probabilistic sensitivity analysis demonstrated that 70% of the simulations were cost-effective for the combined vaccination strategy and 50% of the simulations for varicella vaccination alone (willingness-to-pay threshold of ≤30,000 per QALY gained, infinite time horizon). In the study of Bilcke et al.,[33] the time horizon in which more than 50% of the simulations was cost-effective (threshold €35,000 per QALY gained) decreased from 99 y to 90 y, when HZ vaccination was added to varicella vaccination. The time horizon could decline further to 56 y, when the duration of protection of the HZ vaccine is extended to lifelong.

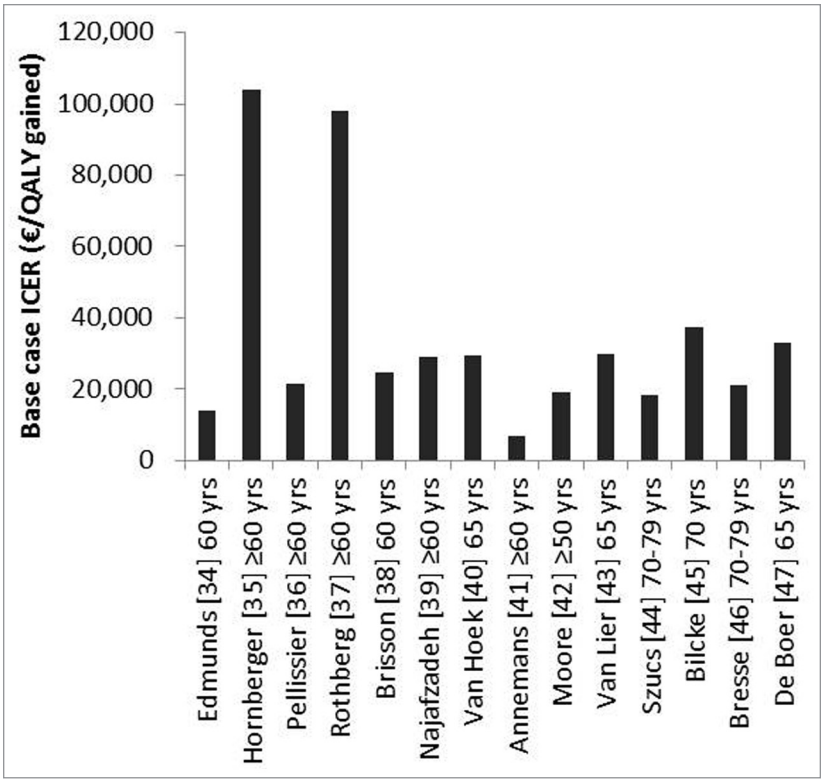

Figure 2. The incremental cost-effectiveness ratios (ICERs) of the included studies. For the study of Bilcke et al.[45] the median between the best case and worst case scenario was taken.

Discussion

This review assesses the available literature on health-economic evaluations of HZ vaccination. To assure that no studies examining the cost-effectiveness of HZ vaccination were missed, the search was performed within two distinct databases using an extensive range of related search-terms. Moreover, reference lists of potential articles were additionally screened. A total of 14 studies were included for extensive review. All studies concluded that HZ zoster might be cost-effective; however, this was not the case in all scenarios and at all vaccination ages. Generally, all studies showed that vaccination against HZ is cost-effective when vaccination is administered between the age of 60 and 75 y and the duration of vaccine-induced protection is longer than 10 y. These findings are consistent with other reviews summarizing evidence on the cost-effectiveness of HZ vaccination.[15,49] However, compared with the review of Szucz et al.,[49] three more studies were included. Moreover, this review contains more specific data on the clinical results found in the studies, the influence of the modeling of vaccine efficacy on cost-effectiveness results and the optimum age of vaccination. Finally, results from studies combining HZ vaccination with varicella vaccination were also summarized. Differences in modeling approaches and input parameters hampered a straightforward comparison of the cost-effectiveness studies. It should however be noted that the heterogeneity between studies supports the credibility and robustness of HZ vaccination as a cost-effective intervention. The major key drivers for cost-effectiveness turn out to be duration of vaccine-induced protection, vaccine price and vaccination age.

Most studies targeted elderly above the age of 60 y, because this age-group was included in the SPS study providing evidence on vaccine efficacy.[20,21] Later studies also included vaccination ages between 50 and 60 y, when efficacy data specifically for this age-group came available.[22] The optimal vaccination age from cost-effectiveness point of view ranges between 60 and 75, depending on duration of vaccine-induced protection and additional efficacy against BOI and PHN above the age of 70. To provide insight in the optimal vaccination age, modeling is needed, as several input parameters have been shown to vary during aging. On one hand, the SPS has shown that vaccine efficacy decreases during aging, which would imply that vaccinating at younger age would be more cost-effective. On the other hand the incidence of HZ and the risk to develop PHN after HZ reactivation increases with age. A crucial role in this specific research question is reserved for the duration of vaccine protection. As mentioned, some studies assumed that the duration of vaccine-induced protection is lifelong, while others assumed durations varying from 7.5 to 15 y. It seems plausible that, assuming lifelong protection, the scenario with the youngest vaccination age would be most cost-effective, because in that case the vaccinees are protected earlier. However, this is not necessarily the case. Among the six studies using lifelong protection in the base-case analysis[36,38,41,42,44] or almost lifelong (30 y),[35] five studies indeed showed that the optimum vaccination age was in the younger age groups (range 60–69 y). However, among three of these five studies also a scenario of vaccination between 50–59 y was applied, which means that the youngest vaccination age was not necessarily the most cost-effective vaccination age. The study of Brisson et al.[38] even found an optimum vaccination age of 70 y, unless a lifelong protection was assumed. Responsible for this potentially counterintuitive phenomenon is the discounting factor. HZ and

PHN incidence is highest beyond the age of 70. Assuming lifelong protection, these cases are prevented independent of vaccination age. However, the counting of discountable years starts at the time-point of vaccination and as costs and QALYs are generally saved beyond the age of 70, outcomes are much more affected by discounting if the vaccination age is 50 y than if the age of 70 y. This explains why the youngest age is not necessarily the most optimal vaccination age even if a lifelong protection is assumed, but ages in the range of 60 to 70 y.

The major limitation within assessing the cost-effectiveness of HZ vaccination is the unknown duration of vaccine-induced protection. Up to now, protection has been shown to persist for at least 7 y.[27] Assumptions concerning duration of vaccine-induced protection vary from 7.5 y to lifelong. Follow-up of vaccine efficacy has to be maintained to provide more certainty about the duration of protection. To address uncertainty of duration of vaccine protection toward cost-effectiveness results, studies should vary this duration for specific age-groups as this duration might be age-dependent.[54] Another limitation is the unknown vaccine price when the vaccine is bought in bulk quantities. As this is generally kept confidential by pharmaceutical companies, such information unfortunately will not be available for cost-effectiveness analyses. Studies funded by pharmaceutical companies assumed in general a lifelong vaccine induced protection, which provides the opportunity to generate cost-effective results in the base-case analysis while using significant higher vaccine prices. Concerning HZ incidence, data was mainly obtained from general practitioners (GP) databases. Using such a source implies a risk for underestimation if not all HZ patients visit a GP. Incidence rates were similar between different studies, although in the United States it seemed somewhat higher. However, this might also be caused by differences in the surveillance systems. A recently published study showed that HZ incidences were similar between European countries.[66] Studies performed in countries which include varicella vaccination in their immunization programs should use updated data on HZ incidence, because circulation of varicella might have an impact on the occurrence of HZ in elderly. With our analysis applied to the Netherlands without a universal varicella vaccination,[47] one should be aware that for countries with a universal varicella vaccination, this policy might influence the cost-effectiveness of HZ vaccination. Parameters as severity of pain and duration of pain due to HZ/PHN are influential for the amount of QALYs gained and different sources estimating utilities should be used to address uncertainty into QALY losses. Moreover, studies using validated instruments to estimate quality of life should be preferred. Factors which were ignored in most studies but should be incorporated to achieve a complete view of the consequences of HZ vaccination are complications from ophthalmic manifestations of HZ and vaccine adverse events vaccination. Also productivity losses might become more important as a consequence of healthy aging and the evidence of vaccine efficacy in the younger age group between 50–59 y.

Further research will better inform on the duration of protection of the vaccine and reduce uncertainty in this area. With various initiatives to synthesize health-economic methods between countries, it might be expected that future cost-effectiveness analyses in the area will be even better comparable, enhancing this type of evidence synthesis as done here and allowing even conclusions to be drawn. With price being an important determinant of cost-effectiveness of HZ-vaccination, outcomes of price negotiations, potential tendering and price-volume deals might crucially influence the outcomes of future cost-effectiveness analyses being embarked upon.

Conclusion

In the light of current published studies, HZ vaccination of the elderly seems to be cost-effective, with the exact cost-effectiveness profile being dependent on the vaccination age, duration of vaccine efficacy and vaccine price. In general HZ vaccination was cost-effective in all studies, when vaccine protection was at least 10 y. Because of aging of the population, the burden of HZ and PHN might have a growing impact on the health-care budget and the population's health-related quality of life. Therefore, universal HZ vaccination might present an interesting opportunity to reduce this burden. When updated information on the duration of vaccine-induced protection, HZ incidence or vaccine price becomes available, cost-effectiveness results should be updated in order to reassess vaccination recommendations and optimum vaccination age. To improve possibilities for a direct comparison of different cost-effectiveness studies, more extensive reporting on methodology and more detailed results of sensitivity analyses would be desirable.

Disclosure of Potential Conflicts of Interest

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Supplemental Materials

Supplemental materials may be found here:
www.landesbioscience.com/journals/vaccines/article/28670

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