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Systematic review of health economic evaluation studies on new herpes zoster vaccine among elderly

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Abstract

A newer vaccine is generally more expensive than its previous version. Therefore, cost-effectiveness evidence is necessary for considering the implementation of such vaccines into a national health system. This research aimed to collect and analyze economic evaluations of the new herpes zoster vaccine for the elderly published worldwide, regarding the economic value of this vaccine and its context, as supporting evidence for healthcare stakeholders. The authors systematically searched 4 electronic databases, namely Medline, Scopus, Google Scholar, and Google search engine from inception until August 2020. The inclusion criteria is a full economic evaluation, assessing the efficiency of the new herpes zoster vaccine. A standardized form was designed to extract relevant information from all included studies. The authors screened 771 records obtained from the search, and 620 records have been excluded by their titles and abstracts indicating they were not a full economic evaluation study. Then, 151 records were recruited for second-round screening, and 9 full-text studies were finally included. All were conducted in developed countries and used a cost-utility analysis approach. Six studies had shown that the new vaccine against shingles was cost-effective, but 3 studies from the United States, Hong Kong, and Japan indicated cost-ineffective. Under the context of developed countries, the new herpes zoster vaccine offers a good value for money. However, developing countries such as Thailand and Vietnam may need to lower their vaccine prices to be a cost-effective intervention. Health professionals can use these findings for supporting their decision on this vaccine implementation.

Keywords*: *cost-effectiveness*; economic evaluation; *herpes zoster vaccine; herpes zoster; systematic review

1. Introduction

Herpes zoster or shingles is a neurocutaneous disease, which occurs from the reactivation of the latent varicella-zoster virus that causes chickenpox (Schmader, 2018). Varicella zoster virus can spread through the air through the contaminated aerosols from the infected patient by inhalation among the susceptible population. Direct touching the rash skin of chickenpox patients or their belongings can also be infected since childhood. The common symptoms begin with a low fever in combination with fatigue, muscle aches, and rash, where the rash starts from the body and face and spreads to the limbs. After that, the rash will become an itching bulge with clear water inside that will then be dried and scaled scars. After the affected patients recovered from chickenpox, this virus is still hiding in their neural ganglia. When these patients' immune system is weak, the virus increases substantially and causes nerve

inflammation, resulting in neuralgia or pain along the nerve branches. In general, 80% of all patients under 15 years of age were already exposed and infected with this virus (Arlant et al., 2019). The morbidity of herpes zoster increases with age; two-thirds of the exposed population is at risk of developing herpes zoster after their 50 years old (Kawai, Yawn, Wollan, & Harpaz, 2016). Symptoms of shingles start with burning pain in the skin and, after a few days, the affected patients will have a red rash on the painful area. The red rash will turn into a clear bulge, and some patients may also have a fever. The rash appears as a cluster or a line along the nerve branches. When the bulge burst, it will form a wound and scar. Generally, these symptoms heal by themselves within 2 weeks; however, some patients still have a pain left called post-herpetic neuralgia. Other complications found include prolong pain for years, bacterial infection, eye inflammation, corneal ulcer, and ear symptoms. Shingles can be more severe among immunocompromised people such as HIV or cancer patients on chemotherapy.

Globally, the incidence of herpes zoster in the Americas, Europe, and Asia-Pacific, is about 3005-00 cases per 100,000 person-year. In people aged 60 years, the incidence is about 600-800 cases per 100,000 person-year and 800-1,200 cases per 100,000 person-year in people aged 80 years old (Kawai, Gebremeskel, & Acosta, 2014). In Southeast Asia, the incidence seems to be lower a report from Thailand showed that shingle incidence is about 26 per 100,000 person-year among patients aged 45 and over (Aunhachoke et al., 2011). Standard treatment of shingles is a symptomatic-based treatment using corticosteroids or analgesics with antiretroviral therapy such as acyclovir 800 mg given 5 times a day for 7 days, famcyclovir 500 mg given 3 times a day for 7 days, or valacyclovir 500 mg given twice a day for 7 days (Grahn et al., 2011). Today, there is an alternative for herpes zoster prevention through vaccination using a live-attenuated zoster vaccine or recombinant zoster vaccine.

A preventive vaccine has 2 different versions. The old one is the live-attenuated Oka strain developed in Japan during the 1970s as a vaccine for the prevention of varicella. It was derived from the varicella virus isolated from a boy with varicella and passaged in human embryonic fibroblasts, guinea pig fibroblasts, and then human diploid fibroblasts. The new vaccine is a subunit vaccine containing recombinant varicella glycoprotein E formulated with an adjuvant (Bharucha, Houlihan, & Breuer, 2019). A systematic review of the literature and meta-analysis study showed that a new recombinant zoster vaccine in older adults reduced the incidence of laboratory-confirmed herpes zoster by 94% (95% CI: 79% to 98% (compared to placebo, but the old live-attenuated zoster vaccine can reduce only 57% (95% CI: 61% to 84%(with no statistical significance compared to placebo (Tricco et al., 2018). Another study comparing the new zoster subunit vaccine compared to a placebo found that the effectiveness of all vaccinated subjects was 90% (95% CI: 84% to 94%) for elderly aged 70 - 79 years old, and 89% (95% CI: 75% to 96%) for elderly aged over 79 years old (Cunningham et al., 2016). A subsequent study showed that people who received the new recombinant varicella zoster vaccine (Shingrix®; GSK) had a 96 %reduction in the incidence of shingles (95% CI: 90% to 98%) compared to placebo and reported that the first license for launching was on October 2017 for people aged at least 50 years old, because of it is safer than live attenuated zoster vaccine (Zostavax®; MSD) (Schmader, & Dworkin, 2011; Tavares-Da-Silva et al., 2020). Some reports showed a lower efficacy of 70% of the new shingles vaccine among people aged 50-59 years (95% CI: 54% to 81%). Moreover, childhood varicella vaccination helped reduce the late incidence of shingles by 51%, reducing 61% of shingles-related hospitalisation, and reducing 66% of post-herpetic neuralgia (Jeon, 2015; Schmader et al., 2012).

Modern vaccines are generally much more expensive than the previous and standard treatments; therefore, cost-effectiveness evidence is necessary for considering the incorporation or implementation of such vaccines into a national public health system. This review study aimed to collect and summarize economic value evidence of the new zoster vaccine through an economic evaluation study published worldwide for supporting health professionals' decision-making regarding the new vaccine against shingles for the elderly.

2. Objectives

To collect and summarize economic value evidence of the new herpes zoster vaccine through an economic evaluation study published worldwide. Based on data summarisation, further aims are to

find out the most impact factor to the cost-effectiveness of this vaccine and to draw a recommendation to health professionals in both developed and developing countries.

3. Methodology

3.1 Data sources and search strategy

The authors used 4 electronic databases, namely Medline, Scopus, Google Scholar, and Google search engine, for searching. The keywords used are 1) varicella, 2) herpes zoster, 3) vaccine, 4) economic evaluation, 5) pharmacoeconomics, 6) cost, and 7) cost-analysis. All results obtained from those databases in the forms of records containing title and abstract were then screened by 2 independent reviewers. The inconsistent opinion will be discussed and resolved by the third reviewer who has experience in this research field. The inclusion criteria were as follows; 1) full economic evaluation (assessing both cost and health outcomes), 2) assessing the new recombinant zoster vaccine (RZV; Shingrix®) compared with the old zoster vaccine live (ZVL; Zostavax®) or do nothing, and 3) published in the English language. Potential records of the full economic evaluation study were then read carefully so that they appraise the cost and health impact of the new and effective zoster vaccine, not the ZVL. All eligible studies were then included and extracted the crucial information from them was.

3.2 Data extraction and summarisation of included studies

The data extraction form was created based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (Husereau et al., 2013), to extract important information from all included full-text studies. The reviewers carefully read and extracted from both full-text articles and their supplementary data-of the study characteristics (setting, reporting year), important input parameters, incremental cost-effectiveness ratio (ICER), cost-effectiveness property under each study's context, the most sensitive parameter, and study's sponsor. All relevant ICERs from each study were adjusted into the US dollar using an exchange rate of each currency. Then, adjusting to the same current year using the consumer price index of each country before plotting in a graph against the cost-effectiveness threshold. This conducted research is not related to either human or animal use, thus informed consent and ethical approval are not compulsory to be approved before starting this study.

4. Results and discussion

4.1 Study selection

The search yielded a total of 771 records; after the first round of screening of titles and abstracts, 620records were excluded because they were not assessing both cost and health outcomes. The second round screened 151 records and found that 63 records were duplicated records, 47 records were economic evaluations of childhood varicella vaccine, 26 records were assessing ZVL, and 6 records were non-English articles (Figure 1). Two studies were published in the Spanish language and 4 studies were published in Russian, Chinese, Japanese, and German (see Supplementary data). Finally, 9 full-text studies regarding the economic evaluation of RZV were included for extraction and qualitative assessment of study quality.

4.2 Overall characteristics of included study

The whole overview of all included studies is shown in Table 1. Five studies were conducted in North America with 4 in the United States and 1 in Canada. Two studies were conducted in Europe (Germany and Holland) and 2 studies in Asia (Japan and Hong Kong). All settings are developed or high-income countries. 5 studies used a social perspective in cost calculation, and most of them reported a currency unit in US dollars ($). All 9 studies were model-based economic evaluations. Three were funded by the RZV vaccine manufacturing company while the other 4 studies were funded by non-profit organisations such as the Ministry of Public Health of that country. The rest 2 studies reported that their research had no sponsor support.

4.3 Cost-effectiveness summarisation

The conclusion on the cost-effectiveness results of the studies is presented in Table 2. All studies adopted a cost-utility analysis (CUA) approach. Six studies used the live-attenuated zoster vaccine and no vaccination as a comparator, while 2 studies compared with no vaccination and 1 study compared with ZVL. The herpes zoster incidence used in all models is quite high, about 500 to 1,500 cases per 100,000 population per year. The vaccine price used in the model calculation is approximately $140 per dose, and the high vaccine

efficacy of almost 100% is used as the input parameter. Most economic evaluation studies used a societal perspective with 5 out of 9 studies, 2 studies used health care system perspective, 1 used a third-party payer perspective, and 1 used both societal and healthcare provider perspectives in their evaluation. A common discount rate is 3% for both cost and health outcomes. The most sensitive input parameters were vaccine efficacy waning, vaccine price, and herpes zoster incidence. Our extracted information found that 5 studies suggested RZV as a cost-effective intervention compared with no vaccination (Prosser et al. 2019; Curran et al. 2018; Drolet et al. 2019; Van Oorschot et al. 2019), while 3 studies indicated that RZV has not been cost-effective (Figure 2) (Curran et al., 2019; Hoshi, Seposo, Shono, Okubo, & Kondo, 2019; You, Ming, Lee, Tsang, & Chan, 2018). Figure 2 is plots of incremental cost-effectiveness ratios (ICERs) from 8 studies on the cost-effectiveness plane against the threshold of $50,000 per quality-adjusted life year (QALY) gained. All 8 ICERs were adjusted to the 2019 US dollar by using the average exchange rate and the US consumer price index (Internal Revenue Service, n.d.; US Inflation, n.d.). Another 1 study was conducted to find the maximum price per dose that the vaccine is still a cost-effective intervention; thus they did not report the ICER directly (de Boer et al., 2018).

4.4 Quality assessment

All 9 included studies followed the reporting standard of the economic evaluation study and were high-quality by assessing against the CHEERS guideline. Only 1 study did not report a conflict of interest between authors and any funder (Le, & Rothberg, 2018). All of them used the RZV efficacy as an input parameter from the 2 single studies of phase-3 randomized controlled clinical trials (Cunningham et al., 2016; Lal et al., 2015).

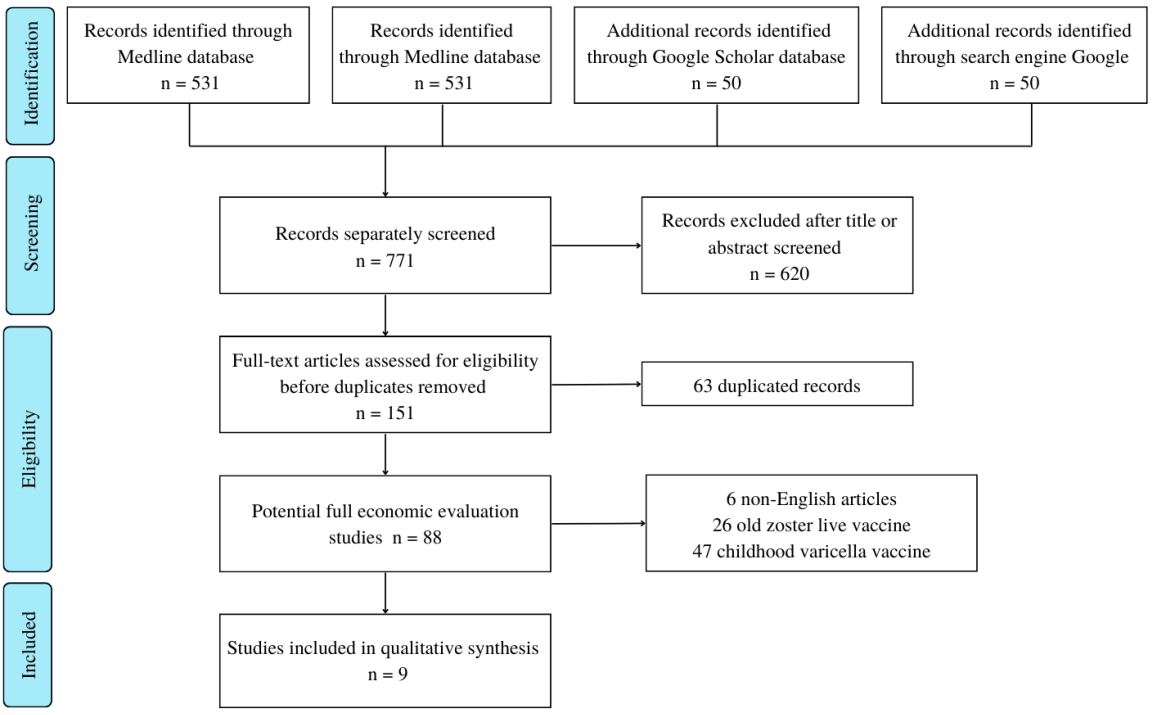

Figure 1 Flow diagram of the identified articles, the screening and inclusion process

Table 1 Characteristics of all included economic evaluation studies

Author	Publication Year	Country	Category	Perspective	Time horizon	Design	Currency, year	Funding
Drolet et al. (2019)	2019	Canada	High-income	Healthcare system	Lifetime	Model-based (decision tree)	USD, 2018	Not for-profit

Author	Publication Year	Country	Category	Perspective	Time horizon	Design	Currency, year	Funding
de Boer et al. (2018)	2018	Holland	High-income	Societal	15 years	Model-based (Markov)	EUR, 2017	No funding
Prosser et al. (2019)	2019	USA	High-income	Societal & Health care sector	Lifetime	Model-based (Markov)	USD, 2016	Not for-profit
Le and Rothberg (2018)	2018	USA	High-income	Societal	Lifetime	Model-based (Markov)	USD, 2016	No funding
Curran et al. (2018)	2018	USA	High-income	Health sector	Lifetime	Model-based (Markov)	USD, 2016	For-profit
You et al. (2018)	2018	Hong Kong	High-income	Societal	Lifetime	Model-based (Markov)	USD, 2016	Not for-profit
Curran et al. (2018)	2019	USA	High-income	Societal	Lifetime	Model-based (Markov)	USD, 2016	For-profit
Van Oorschot et al. (2019)	2019	Germany	High-income	Societal	Lifetime	Model-based (Markov)	EUR, 2017	For-profit
Hoshi et al. (2019)	2019	Japan	High-income	Payer	Lifetime	Model-based (Markov)	USD & Yen, 2017 ($1=¥110)	Not for-profit

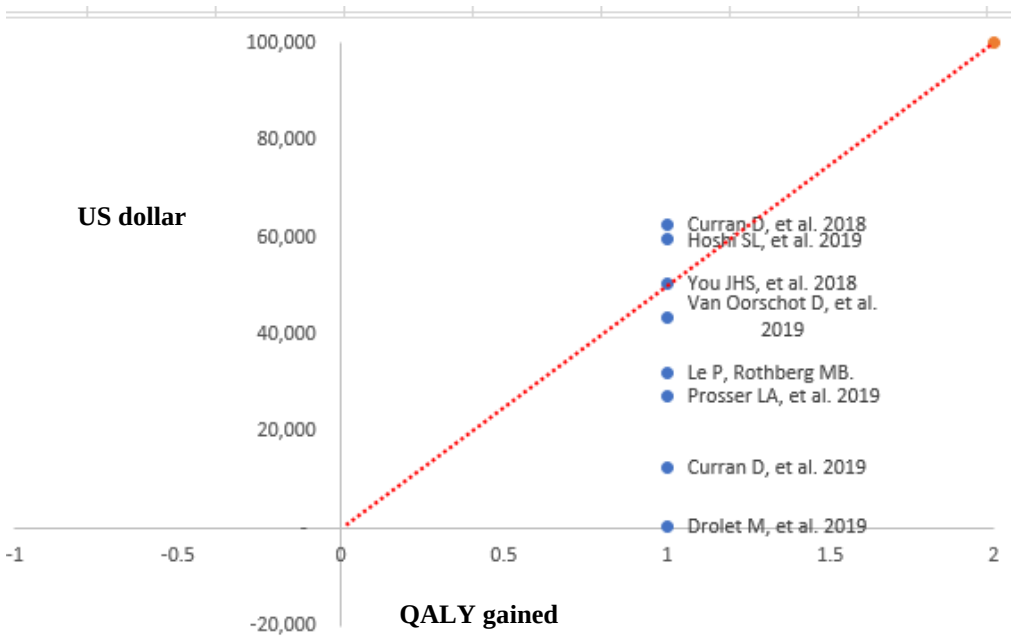

Figure 2 Incremental cost-effectiveness ratios from 8 included studies plotted on the cost-effectiveness plane

Table 2 Cost-effectiveness result and conclusion of all included economic evaluation studies

Author	Intervention	Comparator	Perspective	Discount rate	Incidence (/100,000)	Price/ dose	Vaccine efficacy	ICER	Sensitivity analysis	Sensitive parameter	Conclusion
Drolet et al. (2019)	RZV	ZVL & no vaccination	Healthcare system	3%	380–990	$100 – 200	97.2% (93.7-99.0)	$404 /QALY	DSA, PSA	HZ incidence	Cost-effective
de Boer et al. (2018)	RZV	ZVL	Societal	4% cost & 1.5% QALY	591–1,481	Varied	98.1% (90.4-100.0)	RZV ≤ €104.30 per dose	DSA, PSA	RZV waning	Cost-effective if not > threshold price
Prosser et al. (2019)	RZV	ZVL & no vaccination	Societal & Health care sector	3%	500–1,500	$140	97.0% (92.0-100.0)	$25,683 /QALY	DSA, PSA, Scenario analyses	Vaccine efficacy	Cost-effective
Le and Rothberg (2018)	RZV	ZVL & no vaccination	Societal	3%	890–1,650	$140	99.5%	$30,084 /QALY	DSA, PSA	RZV waning	Cost-effective
Curran et al. (2018)	RZV	ZVL & no vaccination	Health sector	3%	674–1,278	$140	97.2% (93.7-99.0)	$11,863 /QALY	DSA, PSA	RZV waning	Cost-effective
You et al. (2018)	RZV	No vaccination	Societal	3%	720–1,250	$104	100%	$47,442 /QALY	DSA, PSA	Vaccine price	Cost-ineffective
Curran et al. (2018)	RZV	ZVL & no vaccination	Societal	3%	932–1,278	$140	97.2% (93.7-99.0)	$58,793 /QALY	DSA, PSA, Threshold	RZV waning	Cost-ineffective
Van Oorschot et al. (2019)	RZV	No vaccination	Societal	3%	1,000–1,390	€110	97.2% (93.7-99.0)	€37,025/QALY gained	DSA, PSA, Threshold analyses	HZ incidence	Cost-effective
Hoshi et al. (2019)	RZV	ZVL & no vaccination	Payer	3%	300–800	¥8,000	97.2% (93.7-99.0)	¥6,278,557 /QALY	DSA, PSA	Vaccine price	Cost-ineffective

ICER = Incremental cost-effectiveness ratio, QALY = Quality-adjusted life year, DSA = Deterministic sensitivity analysis (1-way or 2-way), PSA = Probabilistic sensitivity analysis

4.5 Discussion

This systematic review study was conducted to collect and summarize economic value evidence of the novel recombinant zoster vaccine from economic evaluation studies published worldwide. Researchers did not include the old live-attenuated zoster vaccine in this qualitative analysis, because it is based on the health technology assessment (HTA) principle that HTA has many dimensions including clinical efficacy/effectiveness, economic value, and ethical aspects for appraising a health technology (Fattore, Maniadakis, Mantovani, & Boriani, 2011) such as new drug and new vaccine. Because the efficacy of ZVL for herpes zoster compared to placebo has not passed the clinical value, based on the recent systematic review and meta-analysis studies (McGirr et al., 2019; Tricco et al., 2018); therefore, the authors do not need to further assess its economic value. We found the interesting findings that no study has been conducted in the context of developing countries; all are conducted in high-income countries and most of the included studies indicated that RZV is a cost-effective intervention. This phenomenon may imply that the incidence of shingles among elderly people in developed

countries is high enough to compensate for the expensive vaccine price per dose in those countries. Besides, the number of cases has attracted the attention of vaccine manufacturer companies to serve this demand, which is the reason why the authors found only an economic evaluation study of RZV from rich countries. However, the herpes zoster incidence in developing countries may be much lower than in developed countries, thus the vaccine price should be reduced when marketing in low-income countries, or an economic evaluation exercise should be conducted under the resource-limited context before implementing the national subsidiary or reimbursement using a public budget of new recombinant zoster vaccine into their health system.

The appropriate comparator for the new RZV should be the do nothing or no vaccine provision policy option since recent systematic review and meta-analysis studies suggested that the ZVL has no statistical significance in preventing herpes zoster incidence among the elderly compared with the placebo (McGirr et al., 2019; Tricco et al., 2018). For this reason, the authors plotted the adjusted incremental cost-effectiveness ratios of RZV compared with no vaccination from these included studies (Figure 2) against the $50,000 per QALY gained as the cost-effectiveness threshold. The authors found that 3 out of 8 studies showed that RZV is not a cost-effective intervention (Curran et al., 2019; Hoshi et al., 2019; You et al., 2018). One study did not report an ICER directly; instead reported the maximum price per dose that the RZV is still a cost-effective intervention (de Boer et al., 2018).

The most sensitive input parameters that affect the ICERs are the most-are efficacy waning of the vaccine, the vaccine's price per dose, and herpes zoster incidence, which is reasonable since the current evidence shows that the efficacy of RZV is much higher than that of ZVL (McGirr et al., 2019; Tricco et al., 2018). Therefore, if the waning efficacy is high, the new vaccine tends to be not cost-effective. Long-term data on a new vaccine efficacy is still needed to ensure a cost-effectiveness property of the new zoster vaccine. Moreover, herd immunity or indirect effect was not considered in all included studies. If it was incorporated into the economic evaluation, the incremental cost-effectiveness ratio would be lower, which means the tendency to be more cost-effective toward the new recombinant zoster vaccine.

All efficacy input parameters for all 9 model-based economic evaluations were obtained from 2 single phase-3 randomized controlled clinical trials of RZV (Cunningham et al., 2016; Lal et al., 2015), which is not the best evidence compared to a systematic review and meta-analysis of vaccine efficacy. Future economic evaluations should use the vaccine effectiveness from meta-analysis studies as an input parameter. Our review has updated information from the previous systematic review searched until March 2018 that included both ZVL and RZV with the main focus on the use of long-term efficacy data (Chiyaka et al., 2019). It seems not to be relevant now, similar to other systematic review studies including economic evaluation studies before the first launch of RZV in October 2017 (Damm et al., 2015; Szucs, & Pfeil, 2013) since the above-mentioned meta-analyses suggested that the ZVL has no efficacy compared with the placebo, while the RZV has more substantial efficacy. This review has some limitations calling for careful interpretation of the results. A heterogeneity was encountered due to the differences between included studies on cost components, comparators of the new herpes zoster vaccine, and the age of participants enrolled. Furthermore, the authors did not find any economic evaluation study conducted in developing countries; therefore, the review's results presented in this report should be considered carefully when applying to the context of low- and middle-income countries, which still need their vaccine price negotiation and own economic evaluation exercise.

5. Conclusion

The new vaccine is likely to be a cost-effective intervention in high-income countries, where herpes zoster incidence is quite high compared with in developing counties. However, although the RZV has more efficacious than the old live-attenuated, its price is also much higher. Therefore, before implementation in developing countries with the low herpes zoster incidence expected, an economic evaluation of the new zoster vaccine should be conducted to find out an optimal price per dose which the vaccine is still a cost-effective intervention. Under the context of developed countries, the new herpes zoster vaccine is a cost-effective intervention or it offers a good value for money. However, in developing countries

such as Thailand and Vietnam, this vaccine needs to lower its price to be a cost-effective intervention. Health professionals can use these findings for supporting their decision on this vaccine implementation for their own country.

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