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Cost-effectiveness of varicella vaccination

# 1 Modelling a cost-effective vaccination strategy for the 2 prevention of varicella and herpes zoster infection: A 3 systematic review

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## Abstract

**Background:** Varicella zoster virus (VZV) and its re-emergence as herpes zoster (HZ) is associated with significant morbidity and mortality. While studies show that VZV vaccination is effective in reducing VZV incidence, many decision makers have not added VZV to their vaccination schedule, largely due to uncertainty surrounding the effect of VZV vaccination on HZ incidence (exogenous boosting, EB), and the cost-effectiveness (CE) of vaccination.

**Methods:** A systematic review was conducted to identify the current published evidence of CE of VZV vaccination strategies where both VZV and HZ incidence were modelled.

**Results:** Six studies (one published in 2003 and five between 2010 to 2019), were identified with all conducting cost-utility analysis using a dynamic transmission modelling approach and assuming EB. All predicted that mass infant VZV vaccination would rapidly reduce VZV incidence, but HZ incidence would increase. Compared with no-vaccination, the CE of VZV vaccination strategies ranged from higher costs and poorer outcomes (dominated), towards CE (incremental cost-effectiveness ratios of between \$7,000 to \$61,000 USD), or lower cost and better outcomes (dominant). However, without EB, HZ incidence immediately dropped below pre-vaccination levels making VZV vaccination quickly CE and/or dominant to a no vaccination strategy.

**Conclusions:** Current models are sensitive to assumptions of EB suggesting that future studies consider an agent-based modelling approach to address the individual nature of variables that determine the infectiousness of VZV.

**Key words:** Varicella; herpes zoster; vaccination; cost-effectiveness; systematic review

## 29 Abbreviations

- 30 CADTH: Canadian Agency for Drugs and Technologies in Health
- 31 CE: cost-effectiveness
- 32 CHEERS: Consolidated Health Economic Evaluation Reporting Standards (checklist)
- 33 CUA: cost-utility analysis
- 34 DTM: dynamic transmission modelling
- 35 EB: exogenous boosting
- 36 HZ; herpes zoster
- 37 ICER: incremental cost-effectiveness ratio
- 38 INAHTA: International Network of Agencies for Health Technology Assessment
- 39 MeSH: Medical Subject Heading
- 40 MMRV: measles, mumps, rubella, varicella (vaccine)
- 41 NHS-EED: The NHS Economic Evaluation Database
- 42 NMB: net monetary benefit
- 43 PI: progressive immunity
- 44 QALY: quality adjusted life year
- 45 TI: temporary immunity
- 46 USD: United States dollars
- 47 VZV; varicella zoster virus
- 48

## 49 Introduction:

50 Varicella zoster virus (VZV or chickenpox) is a highly contagious human alpha-herpesvirus,  
51 most commonly occurring in children, with infection rates ranging from between 61% to 100 % [1].  
52 Following recovery the virus enters a latency period residing in the hosts dorsal root ganglia posing a  
53 lifetime risk of re-emergence in the form of herpes zoster (HZ or shingles) of between 23.8% and 30%  
54 [2]. This risk of HZ increases with age [3] and/or immunocompromise [4]. While considered a mild  
55 disease in children, VZV can be more severe in adults, even fatal in immunosuppressed individuals [5-  
56 7]. HZ is primarily an adult onset disease and has a significant health and quality of life impact in the  
57 majority of cases [8] with approximately 60% to 90% of patients experiencing postherpetic neuralgia  
58 (PHN) [9, 10].

59 In an unvaccinated population the direct health costs in Australia of VZV and HZ have been  
60 estimated at \$3.2 million / year [11] and \$28.2 million / year [8] respectively, with a societal burden  
61 of VZV due to lost days of work and or school attendance of approximately \$168 million per year (all  
62 in 2019 USD) [12]. Similarly, in the UK, hospital costs for VZV has been reported as over \$8 million /  
63 year [13], and over \$71 million / year to the Canadian health system [14], with societal costs in  
64 Germany of over \$326 million per year (all in 2019 USD) [15]. The annual societal cost of HZ varies by  
65 country with estimates of \$28 million in Sweden, [16], \$63 million in Italy, and \$216 million in Germany  
66 [17] (in 2019 USD). This is comparable to an estimated average of \$18.5 million / year in health care  
67 costs (in 2019 USD) spent by each of 11 audited countries to treat and control another vaccine  
68 preventable disease, measles [18]

69 With the development of the Oka varicella vaccine in 1974, VZV infections and related  
70 hospitalisations have been significantly reduced in the US and Australia [19, 20]. Use of the Oka VZV  
71 vaccine in the five-year Shingles Prevention study in 2005 (for older adults  $\geq 60$  years, mean follow-up  
72 of 3.1 years), saw the incidence of HZ and PHN reduced by 51.3% and 66.5% respectively compared  
73 with placebo treated patients [21, 22].

Modelling studies have concluded that varicella vaccination is cost-effective from a health care payer perspective with the cost per hospitalisation averted of <\$22,000 (in 2019 USD), and cost saving from societal perspective with reported benefit cost ratios of 1.3 to 3.7 [23-27]. HZ vaccination modelling studies reported that strategies could also be also cost-effective at less than \$35,000 per QALY gained (2019 USD) [14, 28, 29]. However, a number of countries do not advocate for or publicly fund a routine VZV vaccination program due to concerns surrounding the modelled shifts in VZV to older age groups and a predicted increase incidence of HZ due to a reduction in exogenous boosting (EB) [30]. EB assumes that the risk of re-activation of HZ is reduced due to a boost of immunity after re-exposure to circulating VZV [30, 31]. Given the higher morbidity and mortality associated with HZ, the effects of a VZV vaccination program on EB and resulting HZ incidence, health care costs and quality of life, could be significant and influence health policy makers decisions to recommend or fund a VZV vaccination program.

The aim of this review was to identify and summarise existing published cost-effectiveness (CE) studies that modelled the effect of VZV vaccination programs on VZV and HZ incidence, with or without the addition of a HZ vaccination program. Of particular interest was the effect of model design and inputs on the resulting CE.

## Methods:

A systematic review was conducted to identify published cost-effectiveness studies that modelled the impact of VZV and/or HZ vaccination strategies on the incidence of VZV and HZ.

### Conduct of systematic literature review

The methods of the systematic review were in accordance to PRISMA guidelines and align with Cochrane review techniques. The review strategy was developed in consultation with experts in systematic review methodology within the team.

97 *Types of studies*

98           This review considered all studies that compare the costs and benefits of providing VZV and/or  
99 HZ vaccination in one strategy (e.g. single vaccination or with booster) or form (e.g. monovalent or  
100 with MMR), to another strategy/form or to no vaccination. Studies must have considered the  
101 vaccination impact on both VZV and HZ incidence. Model design (i.e., decision tree, Markov or other)  
102 was not an exclusion criterion.

103 *Types of participants*

104           This review included studies identifying a healthy population of any age that receive a  
105 vaccination for VZV and/or HZ either as part of a study or program. Whereas studies involving  
106 immunocompromised patients at risk of VZV, such as transplant patients, were excluded, this was not  
107 an exclusion criterion for patients at risk of HZ as immunocompromise is a major risk factor for re-  
108 emergence.

109 *Interventions*

110           The method of delivery and frequency of administration were determined by the studies identified  
111 for inclusion in this review. These methods included:

- 112           • Monovalent VZV/HZ vaccination; or
- 113           • VZV/HZ vaccination as part of a multi-valent delivery (e.g. MMRV); or
- 114           • Vaccination provided at any age in any form of strategy – (e.g. once or with booster(s)).

115 *Comparator*

116           Studies were included if they evaluated a concurrent comparator such as a comparative VZV  
117 and/or HZ vaccination strategy or no vaccination strategy.

118 *Outcomes*

119           Outcomes collected in this review included any reporting of cost and effectiveness measures  
120 such as the cost per patient outcome, incremental cost-effectiveness ratios (ICER), net monetary  
121 benefit and cost per quality-adjusted life year (QALY) or other utility measures.

## Search methods for identification of studies

Key terms were identified by the researchers using both Medical Subject Headings (MeSH) and generic terms and by referencing existing systematic reviews / protocol(s). The inclusion and exclusion criteria were drafted by the authors. A structured search strategy with detailed inclusion and exclusion criteria was constructed. The review intended to identify all relevant literature through searches of electronic databases.

## Electronic searches

The following databases were searched in January 2020 to identify relevant published studies:

- Medline (Ovid) – 1946 to present;
- Embase – 1947 to present;
- Cochrane Library – searched for all years;
- EconLit – (1969 to present); and
- Economic evaluation registries and health technology assessment databases (e.g. CADTH, INAHTA, NHS EED)

Table 1 presents the key search terms included in the search strategy.

## Table 1: Search terms included (here)

## Identification of Relevant Studies

For both searches, all identified papers were pre-screened for relevance based on title and abstract by two reviewers (BH and TW) based on the pre-specified inclusion and exclusion criteria. The full text of publications identified from the previous step and those studies without abstracts was obtained. Full-text publications were independently appraised by two reviewers to ensure an acceptable level of agreement for final eligibility. Any disagreement between reviewers was adjudicated by a third reviewer (JB or PS).

## Assessment of Quality

For assessment of risk of bias in cost-effectiveness studies the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was used [32]. While not specifically designed as a critical appraisal tool this checklist consists of 24 items that must be addressed and reported for a CE study to be considered of high quality.

Two reviewers independently assessed the risk of bias (BH and TW), and a third reviewer resolved any differences (JB or PS).

## Data Management

References identified by the database searches were imported into bibliographic software (Endnote version X9). Data extraction tables (Excel Office 365, 2019), were created to facilitate and manage the information extracted from the articles and relevant data was extracted by one reviewer (BH). Data extracted included: study identification, model design, methods, outcomes, costs, and cost-effectiveness results.

## Data analyses

This review summarised the model structures presented in each publication, including model flow diagrams, strategies tested, general assumptions, perspectives, time horizons and model inputs. CE outcomes were reported and based on summary outcome measures such as incremental cost-effectiveness ratios (ICER), net monetary benefit (NMB), and quality adjusted life years (QALY). Given the heterogeneity of the studies, the results were reported in a narrative summary. All study costs were converted to 2019 United States Dollars (USD) [33].

## Results

The systematic literature search identified six publications that met the inclusion criteria (Figure 1). All six studies were conducted in European countries and five were published after 2010. Three studies modelled the effects of VZV vaccination strategies on VZV and HZ incidence [24, 34, 35],

while the remaining three studies developed models that included both VZV and HZ vaccination strategies [36-38].

**Figure 1: Selection of studies of cost-effectiveness of VZV and/or HZ vaccination strategies (here)**

CE = cost-effectiveness; HZ = herpes zoster; SR = systematic review; VZV – varicella zoster virus

**Assessment of bias in included studies**

Using the CHEERS checklist, all six studies were determined to be of high quality (>92% adherence to checklist, Table 2). Studies predominantly provided clear presentation of model design, assumptions, inputs, costs and outcomes, as well as conflicts of interest and sources of funding. Two of the six studies received funding from industry [24, 35].

**Table 2: Included studies adherence to CHEERS checklist items (here)**

**Characteristics of the evidence base**

*General study design*

While not a criterion for inclusion, all six studies used dynamic transmission modelling (DTM) to evaluate the cost-utility (CUA) of their proposed VZV and/or HZ vaccination strategies (Table 3 and Appendix Figure 2). Unlike more static models (e.g. decision tree, Markov) that assume a constant risk of infection, this method assumes that the infection risk is dependent on the number of infectious cases at a given point in time [39].

All six studies assumed the influence of exogenous boosting (EB) in their base case modelling. Five studies compared proposed VZV/HZ vaccination strategies to a no vaccination alternative [24, 34, 35, 37, 38]. Bilcke 2013 modelled a 2-dose childhood VZV vaccination program varying the timing of the second dose, with or without the assumption of EB and with or without an adult 1-dose HZ vaccination [36].

VZV vaccine coverage for the first dose was assumed to be 90% or 95% in five studies and 80% in one other [37]. One-dose HZ vaccine coverage was assumed to be lower at 60% [37] to 70% [36, 38]. Similarly, the efficacy of VZV vaccine for 1-dose was assumed to be high, between 94% and 100% [34-36] and for 2-dose vaccination between 95% and 100% [24, 34-38]. The efficacy of a 1-dose HZ vaccination was assumed to be age dependent but set at only 50% in the base case [35, 36, 38]. All studies modelled to a minimum 80-year time horizon, with two also reporting results at earlier time periods [36, 37]. Discounting of costs and outcomes was similar across studies at 3-4% with only Bilcke 2013 applying a discount of 1.5% and 3% for outcomes and costs respectively [36] and Wolfson 2019 failing to report the level of discounting of outcomes [35]. All six studies performed their analyses from a health care payer perspective, with inputs to the model of the cost of vaccination (and in two cases a separate cost of vaccine administration [36, 37]), and the direct costs of VZV and HZ infection (GP visits and/or hospitalisation). Three studies also presented results from a societal perspective where productivity losses such as parents caring for infected children are also included. [24, 34, 35].

### **Table 3: Model description for included studies (here)**

#### **Summary of outcomes**

#### *Effect of vaccination strategies on VZV and HZ incidence*

All models predicted a sharp decrease in VZV incidence and a rise in incidence of HZ compared to baseline after implementing an infant VZV vaccination program and assuming EB (Table 4). Van Hoek (2012), modelling provision of a 1-dose HZ vaccination only, found no change in VZV incidence but a small decrease in HZ incidence [38]. Melegaro (2018), predicted HZ incidence to naturally increase even under a no vaccination strategy [37]. When modelling was conducted without EB, HZ incidence decreased soon after initiation of an infant VZV vaccination program [35, 36].

In the longer term, all studies reported that incidence of HZ would decrease to a rate below that of pre-vaccination program values at some point during the measured time horizon, with Littlewood (2015) reporting this decrease in as little as 19 years post-program initiation [24].

**Table 4: Summary of outcomes from included studies (here)**

*Cost-effectiveness of vaccination strategies*

The included studies suggest the effects of VZV vaccination strategies on HZ incidence appear to be inversely associated with the resulting CE outcomes (Table 4). For example, studies of one [34] and two dose [36, 38] VZV vaccination strategies that predicted the incidence of HZ to be sustained above pre-vaccination levels for over 50 years that CE was unlikely to be reached before time horizons of 100 years or longer from either a health care payer [34, 36, 38] or the societal [34] perspective. However, in three later studies reporting shorter period of increase in HZ incidence (19 and 25 years), favourable CE outcomes were realised as early as five years post-initiation of a vaccination strategy from both the health care payer [24, 37] and the societal perspectives [24, 35]. Further, modelling without the EB assumption produced even more rapid positive CE outcomes [35, 36].

*Determinants of HZ incidence*

The CE outcomes of all models were highly dependent on the predicted incidence of HZ infection, which in turn was determined by the rates of VZV recovered cases becoming HZ susceptible and then HZ infected (Appendix, Figure 2). The overall rate of VZV recovered cases transitioning to an HZ susceptible state was modelled as a ratio of the waning rate ( $\omega$ ) offset by the force of infection (circulating VZV) to boost HZ susceptible cases back to a resistant state (exogenous boosting,  $k\lambda(a,t)$ ). Once in the HZ susceptible state cases could transition to the HZ infected state at a specified reactivation rate ( $\rho(a)$ ).

*Period of immunity from HZ (waning rate)*

In four of the studies the average period of immunity to HZ following recovery from VZV infection was assumed to be between 10 years [24] or 20 years [34, 36, 38]. These values were based on expert opinion only whereas, Wolfson 2019 [35] used an average period of immunity to HZ of 79.7 years based on an analysis of HZ incidence from three European countries [40]. In the Mellegaro study [37], susceptibility to HZ was modelled under two different assumptions 1) temporary immunity (TI model), or 2) progressive immunity (PI model). In the TI model as with the other four studies, cases

who recover from VZV infection attain a temporary immunity to HZ but here the average duration of immunity was set at 113.5 (95% CI 80.5, 159) years. The PI model assumes that cases recover from VZV infection over an average period of three weeks and are immediately susceptible to HZ. Under the PI assumption, incidence of HZ is always higher than predicted with the TI model at the same time horizon, and slower to become less than a no-vaccination strategy (Table 4).

#### Exogenous boosting rate

In the base case, four models assumed that exposure of an HZ susceptible case to a VZV infected person will be successfully boosted back to HZ immune status in 100% of contacts (i.e. 100% successful EB rate) [34-36, 38]. Littlewood assumed an age related EB rate using 50% of the force of infection in cases over 65 years of age [24]. In the Melegaro (2018) TI model the base case boosting rate was set at 60% [37]. However, in their PI model, HZ susceptible cases could be boosted at any age and time (with 60% success) but with the probability of reactivation of HZ reduced with each subsequent boost. In every model, the choice of boosting rates was based on expert opinion only.

#### HZ reactivation rate

In HZ susceptible patients the rate at which an individual would become infected was termed the reactivation rate and was dependent upon the age of the HZ susceptible individual ( $\rho(a)$ , Appendix Figure 2). In five of the six studies, and in the TI model (Melegaro 2018), the reactivation rate was assumed to resemble a downwards parabolic curve described by the general equation:  $\omega e^{-\varphi a} + \pi a^\eta$  that is only dependent upon the age (a) of the individual [24, 34-36, 38]. Note that the first term of this equation decrease with age and the second term increases with age. However, in the PI model, Melegaro (2018) prescribes a different function to describe the reactivation rate:

$$\rho(a, \tau) = \rho_0 q^{(i-1)2} e^{\theta a (a-a_0)+} e^{\theta_\tau \tau}$$

Here, the reactivation rate that remains stable from time of recovery from VZV infection to 45 years of age ( $a_0$ ) at which time the value of the reactivation rate is a competition between the reduction in HZ due to exogenous boosting ( $\rho_0 q^{(i-1)2}$ ), and the increased risk of HZ due to age ( $e^{\theta a (a-a_0)+}$ ), and

time since last exposure to circulating VZV ( $e^{\theta_{\tau} \tau}$ ). This is the only study that incorporates a time element ( $\tau$ ) into the determination of the HZ reactivation rate.

Other differences between studies in determining of the age dependent reactivation rate were population data (prevalence data) specific to the study country of origin, the assumed period of immunity to HZ following recovery to VZV, and the boosting rate.

#### Utility weights

Finally, all studies assumed that QALY losses due to VZV infection were smaller than those associated with HZ infection resulting in a greater perceived burden associated with HZ (Table 5). Three studies [24, 37, 38] based QALY loss values due to VZV infection from Brisson 2003 [34] where values were determined from a study of 42 parents asked to rate the health of their child with chicken pox using the Health Utilities Index mark 2 (HUI-2). In Bilcke 2013, QALY loss due to VZV infection was based on estimates made by the authors [36]. The result was therefore relatively similar magnitude of QALY loss amongst the studies.

For QALY losses associated with HZ, Brisson 2003 estimated values from a weighted proportion of cases experiencing mild or extreme pain and the duration of that experience arriving at an average QALY loss per case (of any age) of 0.10 [34]. While the remaining studies also based their determination of QALY loss due to HZ on duration and severity of pain experienced, three studies assigned values to specific age categories resulting in lower QALY losses compared to Brisson 2003 in cases < 60 years of age [24, 37, 38]. In the remaining study by Bilcke 2013, HZ cases of any age received a QALY loss score based on severity of illness score (also based on severity and duration).

Three studies separated out QALY loss associated with PHN assigning values four [34] to 10-fold [24] higher than for cases not experiencing pain, whereas the third study assigned an 8% reduction in utility score [35]. In the three other studies PHN effects on QoL were included in the resulting QALY loss value [36-38].

#### Table 5: QALY inputs(here)

## Discussion

This review identified six studies that met the inclusion criteria and were of high quality according to the reporting standards required by the CHEERS checklist.

In agreement with a number of studies modelling VZV vaccination only [41-43] all six studies predicted that an infant VZV vaccination program would result in a significant decrease in the incidence of VZV. Under the assumption of EB, a reduced VZV vaccine efficacy would be expected to result in a reduction in HZ incidence. While this was observed in two studies following sensitivity analyses. [34, 35] with one exception [35] the range of base case rates for VZV vaccine efficacy modelled in the included studies were all in agreement with observed trial results and were not a main driver of the model [31]. However, under the assumption of exogenous boosting (EB), all six studies did report a concomitant rise in HZ incidence that was expected to last for decades. As HZ is associated with higher morbidity, mortality and care costs compared with VZV infection, HZ incidence has a greater influence on the resulting CE outcomes than does VZV. This review found that HZ incidence in these models was dependent upon chosen waning rates of HZ immunity after recovery from VZV infection, HZ reactivation rates, and the success of circulating VZV to boost immunity to HZ (EB). In studies with shorter waning periods (20 years), EB rates of 100%, and high rates of HZ reactivation in older age groups ( > 45 years), studies were unlikely to be cost-effective (CE) until time horizons of 100 years or more [34, 38], and in a third study only after 60 years [36]. However, in the three later studies, using longer waning periods, lower EB rates and smaller HZ reactivation rates, produced a more rapid decrease in HZ incidence and therefore returned a CE outcome well before the time horizon [24, 35, 37]. The sensitivity of these models to the EB assumption is evident, for when EB is set to 0% all vaccination strategies were CE at any time horizon [35, 36]. This is problematic given that a number of recent studies suggest that the impact of EB on HZ incidence may be overstated. While studies did report that exposure to a VZV infected close contact (e.g. within a household) does provide some protection against HZ emergence (estimated at 33%), it does not confer complete immunity

such as assumed in some of the modelling studies[20, 44-46]. Further, while the use of dynamic transmission models (DTM) attempt to account for age dependent transmission rates to determine the force of infection (on which EB is reliant), infection rates within a specified age group are assumed to be homogeneous [31, 47]. Recent work has suggested that this is unlikely proposing that for directly transmitted infectious diseases like VZV infectiousness is individual in nature and relies on a complex mixture of environmental, host and pathogen factors [48]. A preliminary report incorporating agent-based modelling to evaluate a VZV vaccination strategy showed that MMRV two-dose vaccination in a Canadian setting was cost-saving from the societal perspective and CE from the health payer perspective. While the model did not predict a substantial increase in HZ incidence following VZV vaccination, aligning with recent Canadian epidemiologic studies, if EB was assumed then VZV vaccination was never CE [49].

## Limitations

A possible limitation of this review is the use of QALY values derived from a UK population as inputs for studies in Belgium, Italy, France and Turkey. However, it could be argued that with one exception, all populations are first world European cultures and could be assumed to have similar QALY weights.

## Conclusions

This review identified six quality studies that evaluated the effect of VZV vaccination strategies with or without HZ vaccination on VZV and HZ incidence, and the resulting cost-effectiveness (CE). While the CE of mass VZV strategies was determined in all identified studies to be unlikely for a number of decades, these results were highly sensitive to the assumption of exogenous boosting (EB). This is significant as the existence or significance of EB is still under some debate. The use of dynamic transmission modelling alone cannot capture the individual nature of VZV and HZ infectiousness and disease transmission and therefore future modelling should include some aspect of agent-based modelling, to reflect the individual nature of disease infection.

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## References

- [1] Heininger U, Seward JF. Varicella. *Lancet*. 2006;368:1365-76.
- [2] Pinchinat S, Cebrian-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. *BMC Infectious Diseases*. 2013;13:170.
- [3] Keating GM. Shingles (Herpes Zoster) Vaccine (Zostavax()): A Review in the Prevention of Herpes Zoster and Postherpetic Neuralgia. *Biodrugs*. 2016;30:243-54.
- [4] Arvin AM. Varicella-zoster virus. *Clinical microbiology reviews*. 1996;9:361-81.
- [5] Amlie-Lefond C, Gilden D. Varicella Zoster Virus: A Common Cause of Stroke in Children and Adults. *Journal of Stroke & Cerebrovascular Diseases*. 2016;25:1561-9.
- [6] Macartney KK, Gidding HF, Trinh L, Wang H, McRae J, Crawford N, et al. Febrile seizures following measles and varicella vaccines in young children in Australia. *Vaccine*. 2015;33:1412-7.
- [7] Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. *Journal of Infectious Diseases*. 2000;182:383-90.
- [8] Stein AN, Britt H, Harrison C, Conway EL, Cunningham A, Macintyre CR. Herpes zoster burden of illness and health care resource utilisation in the Australian population aged 50 years and older. *Vaccine*. 2009;27:520-9.
- [9] Schmader K. Herpes zoster and postherpetic neuralgia in older adults. *Clinics in Geriatric Medicine*. 2007;23:615-32, vii-viii.
- [10] Weinberg JM. Herpes zoster: epidemiology, natural history, and common complications. *Journal of the American Academy of Dermatology*. 2007;57:S130-5.
- [11] McIntyre P, Gidding H, Gilmour R, Lawrence G, Hull B, Horby P. Vaccine preventable diseases and vaccination coverage in Australia, 1999–2000. *Communicable Diseases Intelligence* 2002;24 1-111.
- [12] Ferson MJ, Shen W, STARK A. Direct and indirect costs of chickenpox in young children. *Journal of Paediatrics and Child Health*. 1998;34:18-21.
- [13] Hobbelen PH, Stowe J, Amirthalingam G, Miller L, van Hoek AJ. The burden of hospitalisation for varicella and herpes zoster in England from 2004 to 2013. *Journal of Infection*. 2016;73:241-53.

- [14] Brisson M, Pellissier JM, Camden S, Quach C, De Wals P. The potential cost-effectiveness of vaccination against herpes zoster and post-herpetic neuralgia. *Human vaccines*. 2008;4:238-45.
- [15] Banz K, Wagenpfeil S, Neiss A, Hammerschmidt T, Wutzler P. The burden of varicella in Germany. Potential risks and economic impact. *European Journal of Health Economics*. 2004;5:46-53.
- [16] Nilsson J, Cassel T, Lindquist L. Burden of herpes zoster and post-herpetic neuralgia in Sweden. *BMC Infectious Diseases*. 2015;15:215.
- [17] Ultsch B, Koster I, Reinhold T, Siedler A, Krause G, Icks A, et al. Epidemiology and cost of herpes zoster and postherpetic neuralgia in Germany. *European Journal of Health Economics*. 2013;14:1015-26.
- [18] Carabin H, Edmunds WJ, Gyldmark M, Beutels P, Lévy-Bruhl D, Salo H, et al. The cost of measles in industrialised countries. *Vaccine*. 2003;21:4167-77.
- [19] Davis MM, Patel MS, Gebremariam A. Decline in varicella-related hospitalizations and expenditures for children and adults after introduction of varicella vaccine in the United States. *Pediatrics*. 2004;114:786-92.
- [20] Heywood AE, Wang H, Macartney KK, McIntyre P. Varicella and herpes zoster hospitalizations before and after implementation of one-dose varicella vaccination in Australia: an ecological study. *Bulletin of the World Health Organization*. 2014;92:593-604.
- [21] Sanford M, Keating GM. Zoster vaccine (Zostavax): a review of its use in preventing herpes zoster and postherpetic neuralgia in older adults. *Drugs & Aging*. 2010;27:159-76.
- [22] Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. *Clinical Infectious Diseases*. 2012;55:1320-8.
- [23] Lenne X, Diez DJ, Gil A, Ridao M, Lluch JA, Dervaux B. Economic evaluation of varicella vaccination in Spain: results from a dynamic model (Structured abstract). *Vaccine* 2006. p. 6980-9.
- [24] Littlewood KJ, Ouwers MJ, Sauboin C, Tehard B, Alain S, Denis F. Cost-effectiveness of routine varicella vaccination using the measles, mumps, rubella and varicella vaccine in France: an economic

analysis based on a dynamic transmission model for varicella and herpes zoster. *Clinical therapeutics*. 2015;37:830-41.e7.

[25] Scuffham P, Devlin N, Eberhart-Phillips J, Wilson-Salt R. The cost-effectiveness of introducing a varicella vaccine to the New Zealand immunisation schedule. *Social Science & Medicine*. 1999;49:763-79.

[26] Scuffham PA, Lowin AV, Burgess MA. The cost-effectiveness of varicella vaccine programs for Australia (Structured abstract). *Vaccine*2000. p. 407-15.

[27] Valentim J, Sartori A, Soares P, Amaku M, Azevedo R, Novaes H. Cost-effectiveness analysis of universal childhood vaccination against varicella in Brazil (Structured abstract). *Vaccine*2008. p. 6281-91.

[28] Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine*. 2001;19:3076-90.

[29] Pellissier JM, Brisson M, Levin MJ. Evaluation of the cost-effectiveness in the United States of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *Vaccine*. 2007;25:8326-37.

[30] Hope-Simpson RE. The Nature of Herpes Zoster: A Long-Term Study and a New Hypothesis. *Proceedings of the Royal Society of Medicine*. 1965;58:9-20.

[31] Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. *Epidemiology and infection*. 2000;125:651-69.

[32] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value in Health*. 2013;16:231-50.

[33] The Campbell and Cochrane Economics Methods Group (CCEMG). CCEMG - EPPI-Centre Cost Converter v1.6. 2019.

- [34] Brisson M, Edmunds WJ. Varicella vaccination in England and Wales: cost-utility analysis. Archives of disease in childhood. 2003;88:862-9.
- [35] Wolfson LJ, Daniels VJ, Pillsbury M, Kurugöl Z, Yardimci C, Kyle J, et al. Cost-effectiveness analysis of universal varicella vaccination in Turkey using a dynamic transmission model. PLoS ONE. 2019;14.
- [36] Bilcke J, Hoek A, Beutels P. Childhood varicella-zoster virus vaccination in Belgium: cost-effective only in the long run or without exogenous boosting? (Provisional abstract). Human Vaccines and Immunotherapeutics2013. p. 812-22.
- [37] Melegaro A, Marziano V, Del Fava E, Poletti P, Tirani M, Rizzo C, et al. The impact of demographic changes, exogenous boosting and new vaccination policies on varicella and herpes zoster in Italy: A modelling and cost-effectiveness study. BMC Medicine. 2018;16.
- [38] van Hoek A, Melegaro A, Gay N, Bilcke J, Edmunds W. The cost-effectiveness of varicella and combined varicella and herpes zoster vaccination programmes in the United Kingdom (Structured abstract). Vaccine2012. p. 1225-34.
- [39] Pitman R, Fisman D, Zaric GS, Postma M, Kretzschmar M, Edmunds J, et al. Dynamic Transmission Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group—5. Medical Decision Making. 2012;32:712-21.
- [40] Poletti P, Melegaro A, Ajelli M, Del Fava E, Guzzetta G, Faustini L, et al. Perspectives on the impact of varicella immunization on herpes zoster. A model-based evaluation from three European countries. PLoS ONE [Electronic Resource]. 2013;8:e60732.
- [41] Brisson M, Edmunds WJ. The cost-effectiveness of varicella vaccination in Canada (Structured abstract). Vaccine2002. p. 1113-25.
- [42] Beutels P, Clara R, Tormans G, Doorslaer E, Damme P. Costs and benefits of routine varicella vaccination in German children (Structured abstract). Journal of Infectious Diseases1996. p. S335-s41.
- [43] Lieu TA, Cochi SL, Black SB, Halloran ME, Shinefield HR, Holmes SJ, et al. Cost-effectiveness of a routine varicella vaccination program for US children. Jama. 1994;271:375-81.

[44] Forbes H, Douglas I, Finn A, Breuer J, Bhaskaran K, Smeeth L, et al. Risk of herpes zoster after exposure to varicella to explore the exogenous boosting hypothesis: self controlled case series study using UK electronic healthcare data. *BMJ*. 2020;368:l6987.

[45] Harder T, Siedler A. Systematic Review and Meta-analysis of Chickenpox Vaccination and Risk of Herpes Zoster: A Quantitative View on the “Exogenous Boosting Hypothesis”. *Clinical Infectious Diseases*. 2018;69:1329-38.

[46] Harpaz R. Do varicella vaccination programs change the epidemiology of herpes zoster? A comprehensive review, with focus on the United States. *Expert Review of Vaccines*. 2019;18:793-811.

[47] Halloran ME, Watelet L, Struchiner CJ. Epidemiologic effects of vaccines with complex direct effects in an age-structured population. *Mathematical Biosciences*. 1994;121:193-225.

[48] Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. *Nature*. 2005;438:355-9.

[49] Rafferty E, McDonald W, Osgood N, Doroshenko A, Farag M. What we know now: Revisiting the cost-effectiveness of chickenpox vaccination using an agent-based model. *Value in Health*. 2019;22:S652.

## Appendix

### Dynamic transmission models (DTM)

All studies identified in this review employed a DTM model similar to the general model presented in Figure 2 below [47], where ordinary differential equations were used to determine rates of change from one health state to another.

In general, the models assumed the following structure:

In an unvaccinated population, newborns are initially protected from a particular disease by maternal antibodies (in previously VZV infected and recovered mothers), that wanes at a rate  $\delta$ , rendering them susceptible to infection. Depending on the force of infection ( $\lambda(a,t)$ , the incidence or hazard rate) of a given disease, susceptibles, in an age and time dependent rate, can become infected and enter a non-infectious latent phase. Movement from the latent phase to the infectious phase occurs at a rate  $\sigma$ . Recovery with immunity occurs at a rate  $v$ .

In a population with the ability to vaccinate against the disease, newborns can again be protected by maternal antibodies or not. Susceptibles can be vaccinated with complete protection at an age and time dependent rate  $s(a,t)$  or remain susceptible at an age and time dependent rate  $f(a,t)$  due to the failure of the vaccine. As with unvaccinated susceptibles, vaccinated susceptibles can become infected and enter the latent phase, then the infectious phase and finally recover with immunity occurring at rates of  $b\lambda(a,t)$ ,  $\sigma'$ , and  $v'$  respectively. Vaccination imparted immunity can wane at a rate of  $\tau$  but with re-exposure to the disease (exogenous boosting) at a rate of  $k\lambda(a,t)$  can maintain immunity, whereas vaccinated susceptible population can also experience exogenous boosting at a rate of  $k'\lambda(a,t)$  to attain disease resistance.

In VZV infected/vaccine failure and recovered population, cases are susceptible to HZ at a rate of  $\omega$ . That can be countered by exogenous boosting again equal to the force of infection  $k\lambda(a,t)$ . HZ

490 susceptible cases can express HZ infection at an age dependent rate  $\rho$  and recover (and become HZ  
491 immune) at a rate of  $\alpha$ .

492

493 **Figure 2: Basic dynamic transmission model flow diagram [47]**

494

## 495 Conflicts of interest

496 The authors declare that they have no known competing financial interests or personal relationships  
497 that could have appeared to influence the work reported in this paper.

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