Impact of methodology on the results of economic evaluations of varicella vaccination programs: is it important for decision-making?

Impacto da metodologia nos resultados de avaliações econômicas de programas de vacinação da varicela: é importante para o processo de tomada de decisão?

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Abstract

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This study aims to review the literature on economic evaluation of childhood varicella vaccination programs and to discuss how heterogeneity in methodological aspects and estimation of parameters can affect the studies' results. After applying the inclusion criteria, 27 studies published from 1980 to 2008 were analyzed in relation to methodological differences. There was great heterogeneity in the perspective adopted, evaluation of indirect costs, type of model used, modeling of the effect on herpes zoster, and estimation of vaccine price and efficacy parameters. The factor with the greatest impact on results was the inclusion of indirect costs, followed by the perspective adopted and vaccine price. The choice of a particular methodological aspect or parameter affected the studies' results and conclusions. It is essential that authors present these choices transparently so that users of economic evaluations understand the implications of such choices and the direction in which the results of the analysis were conducted.

Cost-Effectiveness Evaluation; Costs and Cost Analysis; Immunization Programs; Chickenpox

Introduction

The exponential growth of health expenditures resulting from the development and incorporation of new technologies puts huge pressure on government budgets and has sparked increasing interest in economic evaluation studies.

Economic evaluation, as an institutionalized practice, proposes to identify, quantify, assess, and compare the costs and consequences of two technologies to be considered. The tool has contributed to greater technical and allocative efficiency in the use of resources in the health system.

Despite the potential usefulness of economic evaluation in the decision-making process, it rarely occurs, even in countries where health technology evaluation agencies provide this type of analysis to administrators. Various characteristics of the political spheres where decisions are made appear to hamper the use of cost-effectiveness analyses. The main characteristics relate to limitations in the capacity to generate, access, and interpret the information contained in economic analyses [1]. The difficulty in understanding such analyses is aggravated by the wide variation in methodologies used.

Using economic evaluations of varicella as an example, the current article points to heterogeneity in the following methodological aspects: perspective, assessment of indirect costs, type of model, modeling of the effect on herpes zoster,

and estimation of the vaccine's price and efficacy parameters.

Two previous reviews [2,3] of economic evaluations of varicella vaccination programs described the data and study methodologies with the aim of recommending the best vaccination strategies (children, health workers, and other risk groups) to policymakers.

The current study aims to review the literature on economic evaluation of childhood varicella vaccination programs, identify and discuss how the heterogeneity in the methodologies or estimates of parameters can impact the studies' results.

The article begins by reviewing the uncertainties concerning methodological aspects and estimates of parameters and how they can affect the results of analyses.

Perspective adopted in the analysis

The choice of perspective is the most important point in the analysis, since it determines which costs are included and how they are assessed [4]. The healthcare provider or payer's perspective (for example, in Brazil, the Unified National Health System or SUS) includes all the direct medical costs, such as consultations, hospitalizations, medication, and lab tests. Society's perspective includes direct medical costs, plus non-medical costs, like transportation to the health service and indirect costs or loss of productivity related to the illness, as well as family expenses. Society's perspective is more comprehensive and identifies all the costs and benefits, regardless of who covers the costs or who receives the benefits. There are strong normative arguments that favor adopting society's perspective [5]. Such arguments are related to the principles of social welfare economic theory, according to which when a change in a given policy leads to a series of effects in different individuals and groups, the overall evaluation of the policy's efficiency requires considering all of these implications [6]. Although society's point of view is generally recommended, decision-makers are more interested in the health payer's perspective, because these are the values that directly impact the health systems' budget.

Economic evaluations that adopt society's perspective favor the vaccine's cost-effectiveness.

Indirect costs

A sick child can generate numerous costs for the parents, including stress, sleep deprivation, family breakdown, and loss of income. Many of these costs, related to pain, suffering, and jeopardized quality of life, classified as intangible costs, are not monetary and are difficult to measure.

Economic analyses in health generally include two categories of costs: direct and indirect. Briefly, direct costs are defined as all the economic consequences directly related to the use of health interventions. Indirect costs are generally related to loss of productivity and family expenditures.

There are two main sources of indirect costs in immunization programs. First, loss of time at work related to the vaccination process itself (vaccine, screening and serological testing, adverse effects). Second, productivity gains due to the reduction in employees' morbidity and mortality, or in the specific case of childhood vaccination programs, the reduction in the number of workdays missed by parents to care for their sick children.

Averted losses of productivity have a major impact on the economic profile of childhood vaccination programs, where most of the savings are generated by reduction in the parents' work absenteeism. Economic evaluations that include indirect costs in their analysis favor incorporation of the vaccine.

Choice of model – static versus dynamic

The models can be divided into two main categories: static (decision trees and Markov models) and dynamic. The principal difference between these categories is that in static models, the force of infection (the rate at which susceptible individuals become infected) is a fixed parameter, constant over time, and no interactions are observed between individual and population dynamics of the disease. In dynamic models, the force of infection depends on the number of susceptible individuals in the given population [7,8].

Thus, when the possibility of change exists in the force of infection after immunization (i.e., vaccination blocks transmission of the infection and coverage is expected to be relatively high), dynamic models should be considered [9].

Dynamic models manage to include herd immunity in their analysis (i.e., indirect protection of susceptible individuals when a large proportion of the population has been vaccinated). When herd immunity is considered in the modeling, vaccination has a greater impact on effectiveness and thus on cost-effectiveness.

Modeling the effect of varicella vaccination on herpes zoster

The effect of introducing universal childhood varicella vaccination on the incidence of herpes zoster in the population with latent infection

with varicella zoster virus is still not clear. There are currently two opposing arguments. According to the first, re-exposure to the virus (contact with varicella) stimulates the specific immunity in individuals with latent infection, protecting them against zoster. In this case, universal varicella vaccination, decreasing the circulation of the wild virus in the population, can lead to a significant increase in the number of zoster cases in the short and medium term (as long as there are individuals with latent wild virus infection in the population). Thus, varicella immunization programs may be harmful to public health, since the gain in the reduction of varicella morbidity may be cancelled out by the increase in zoster morbidity. According to the second argument, re-exposure to the wild virus is not a decisive factor in the maintenance of specific immunity and protection against herpes zoster, and thus the incidence of herpes zoster would not be affected by a varicella vaccination program [10].

The results of models that include the impact on zoster suggest that the odds of vaccination proving cost-effective are very small. Thus, choice of the model can have a profound effect on the estimated attractiveness of varicella vaccination [11]. Although data from the modeling suggest that vaccination programs have the potential to modify the epidemiology of herpes zoster, data from the United States where a varicella vaccination program was implemented in 1995 show no evidence that such changes are occurring [12].

Price and efficacy of the vaccine

A single dose of the vaccine showed an efficacy of 70 to 90% in clinical trials [13,14,15,16,17,18]. However, a recent meta-analysis estimated less than 72.5% effectiveness (95%CI: 68.5-76.0%) in the real world [19]. There is growing evidence of decreasing immunity following vaccination (secondary failure of vaccination), which is particularly relevant to public health since it can lead to an increase in susceptibility in older age brackets, in which the risk of severe disease is greater than in childhood [19,20,21]. In 2005, in the United States, ten years after the implementation of the national varicella immunization program, the majority of cases occurred in vaccinated individuals [22]. An effectiveness of approximately 85% for one dose of the vaccine proved insufficient to prevent transmission of the wild-type virus, especially in places like schools with extensive contact. Consequently, since 2006, a second dose of the vaccine (administered to children from 4 to 6 years of age) has been indicated as part of routine immunization in the United States [23,24].

Methods

Search strategy to identify studies

A broad and exhaustive search strategy was adopted to identify all the relevant studies. The PubMed, EMBASE, Scirus, Web of Science, and LILACS databases were searched using the key words "*varicella*" or "*chickenpox*" and "*cost-effectiveness evaluation*" or "*costs and cost analysis*" in English from 1980 to December 2008.

Study selection criteria

Studies were included in the review when they met the following criteria:
• Study design: full economic evaluation, defined as a comparative analysis of the costs and consequences of two alternative health interventions, including cost-minimization, cost-effectiveness, cost-utility, and cost-benefit analyses.
• Population: children up to 6 years of age.
• Type of intervention: program for universal childhood immunization against varicella.

Results

Results of literature search

After reading the abstracts and applying the inclusion criteria, 27 studies were retrieved and analyzed in relation to the previously mentioned methodological differences. Two more articles were added [25,26] from periods studied by previous reviews [2,3], plus four articles [27,28,29,30] published in 2008.

To facilitate the comparability of study results, the monetary values were converted into PPP dollars (Purchasing Power Parity). PPP is the equivalent exchange rate for the price of a basket of goods and services identified in two countries. According to the Brazilian PPP and the exchange rate (from Brazilian *Reais* or R$ to US dollars), in 2008, US$88 could purchase the same basket of goods and services in Brazil that US$100 could purchase in the United States.

The study results' monetary values were corrected to November 2008 according to each country's inflation rates. Next, all these values were converted into current currencies and transformed into dollars, using the exchange rate presented in the World Bank report, called the ICP (International Comparison Program) available on the World Bank website [31]. Finally, the amounts in US dollars were converted into PPP dollars.

When the study failed to specify the cost year, it was assumed to be two years prior to the study's

publication. This strategy has been used previously in the literature [3].

Table 1 shows the abstracts from 27 studies [25,26,27,28,29,30,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52] listed by year of publication (from the oldest to the most recent). The table lists the authors, year of publication, country, type of economic analysis, comparative vaccination strategies, and summary measurements of the results converted into 2008 PPP dollars from the perspectives of the payer and society.

Nearly half (48%) of the studies were performed in Europe, including four in Germany [35,42,48,52], two in France [36,48], three in Spain [27,38,51], three in Italy [29,45,49], one in England and Wales [43], and one in the Slovak Republic [39]. Seven studies were performed in North America, including five in the United States [26,28,32,33,34] and two in Canada [40,41]. One study was done in New Zealand [37], one in Australia [25], two in Taiwan [44,50], one in Israel [46], and one in Brazil [30].

According to the authors, 10 studies conducted cost-benefit analyses, 9 cost-effectiveness analyses, 7 cost-benefit plus cost-effectiveness, and only one cost-utility analysis.

The majority of the studies (63%) adopted both perspectives (payer and society) [28,29,30,34,35,36,37,40,41,42,43,44,45,46,48,50,51,52], one study included the patient's perspective [44], and three did not conduct an analysis from society's perspective [25,26,41].

Considering only the values for vaccination strategies for children up to six years of age, from society's perspective, the benefit-cost ratios (BCR) varied from 1.23 [27] to 19.33 [46]. From society's perspective, the BCR represents the reduction of direct and indirect costs from the disease divided by the cost of the vaccination program. A ratio of 19.33:1 means that each dollar invested in the vaccination program saves 19.33 dollars. From the payer's perspective, the incremental cost-effectiveness ratios varied from PPP$10.70 [35] to PPP$225.60 [25] per averted case and from PPP$3,942 [34] to PPP$33,218 [41] per year of life gained.

In Table 2, of the 27 studies that were reviewed, only three [25,26,41] did not include indirect costs in the economic analysis. The magnitude of indirect costs depended on the number of days of work missed due to varicella and the unit value of workday considered in the analysis. The estimated mean number of workdays missed by parents to care for their sick children varied from 0.6 to 5 days (Table 2). The lowest value (0.6 days) was reported for the first time by Banz et al. [42], estimated from an epidemiological survey in Germany. Brisson & Edmunds [43] presented the same figure (0.6 days) based on epidemiological stud-

ies in Europe [35,36,53], and Coudeville et al. [48] and Hammerschmidt et al. [52] used the same estimate initially reported by Banz et al. [42]. The highest value (5 days) came from an assumption in the first economic evaluation study on the varicella vaccine [32], in 1994.

All the studies used the human capital model to assess missed workdays, and in most cases were based on the mean value of the female workday. The lowest value for workday missed by parents (PPP$12.70) was reported by Coudeville et al. [36] in France, followed by that reported in the Brazilian study (PPP$13.70) [30]. The values reported by other studies varied from PPP$45.60 [37] to PPP$326.40 [28].

The proportion of indirect costs in the total cost of varicella varied from 42.3% [27] to 98% [34]. The highest percentage (98%), reported by Lieu et al. [34], was explained by the inclusion of future costs related to premature death or prolonged disability related to varicella encephalitis in calculating indirect costs. Indirect costs were also heavily related to domestic policies and regulations. In the specific case of Germany, where a domestic policy requires health plans to reimburse parents for approximately 90% of the costs of workdays missed to care for sick children [52], indirect costs were also included in the health payer's perspective [42].

Table 3 summarizes the various models' characteristics. Of all the studies reviewed, 10 used dynamic models [29,30,36,40,42,43,45,48,51,52], 16 used static models [25,26,27,28,32,33,34,35,38,39,41,44,46,47,49,50], and one study used a pseudodynamic model [37]. The latter model was considered pseudodynamic because it did not incorporate the indirect effects of vaccination on the entire population, but appears to have applied reduced forces of infection to susceptible individuals in the vaccinated cohorts [2].

Most of the dynamic models [29,36,42,45,51,52] were based on the initial dynamic model developed by Halloran et al. [54], and the others [30,40,43,48] were based on similar approaches. All the dynamic models included the indirect effects of vaccination on non-vaccinated individuals (herd immunity) in the analysis. The study [44] with the Markov model succeeded in simulating the force of infection and attack rate by age bracket in the non-vaccinated group. Another study [46] with a static model reported the partial inclusion of herd immunity, but the article failed to specify its modeling methodology.

Only three studies [26,40,43] included the effect of vaccination on zoster. In the two studies by Brisson & Edmunds [40,43], the dynamic models assumed that contact with varicella would stimulate immunity against zoster for 20 years,

Table 1

Economic evaluations of universal childhood vaccination programs against varicella.

Reference/Year of publication	Country	Type of analysis *	Vaccination strategy	Payer's perspective	Society's perspective
Preblud et al. [32]/1985	USA	Cost-benefit	15 months	BCR = 0.30:1 **	BCR = 6.90:1 **
Huse et al. [33]/1994	USA	Cost-benefit	15 months	NP	NPV = 101.2 per vaccinated individual
Lieu et al. [34]/1994	USA	Cost-benefit/Cost-effectiveness	< 6 years	BCR = 0.90:1 3.3 per CA; 3,942 per LYS	BCR = 5.40:1
Beutels et al. [35]/1996	Germany	Cost-benefit	15 months	BCR = 0.82:1 23.1 per CA; 22.145 per LYS	BCR = 4.60:1
		Cost-effectiveness	15 months and catch-up	BCR = 0.92:1 10.7 per CA; 7,759 per LYS	BCR = 4.72:1
Coudeville et al. [36]/1999	France	Cost-benefit	< 6 years	NP	ANB = 374,898,339
Scuffham et al. [37]/1999	New Zealand	Cost-effectiveness	15 months	31.8 per CA	(27.6) per CA ***
Díez-Domingo et al. [38]/1999	Spain	Cost-benefit	15 months	BCR = 0.54:1 **	BCR = 1.61:1 **
Scuffham et al. [25]/1999	Australia	Cost-effectiveness	12 months	29.2 per CA	NP
			12 months and catch-up	225.6 per CA	NP
Hudeckova et al. [39]/2000	Slovak Republic	Cost-benefit/Cost-effectiveness	Newborns	BCR = 0.20:1	BCR = 1.45:1
Brisson & Edmunds [40]/2002	Canada	Cost-effectiveness	Without zoster		
			1 year	46.482 per DYLS	BCR = 5.24:1 **
			1 year and catch-up	53,128 per DYLS	BCR = 4.90:1 **
			With zoster		
			1 year	123,443 per DYLS	NP
			1 year and catch-up	156,662 per DYLS	NP
Getsios et al. [41]/2002	Canada	Cost-effectiveness	12 months	39.3 per CA; 33,218 per YLS	Economical #
Banz et al. [42]/2003	Germany	Cost-benefit/Cost-effectiveness	1-1.5 years	BCR = 1.75:1	BCR = 4.12:1
			1-1.5 years and catch-up	BCR = 1.70:1	BCR = 4.10:1
Brisson & Edmunds [43]/2003	England and Wales	Cost-utility	12-15 months	Dominated ##	Dominated ##
			12-15 months and catch-up	Dominated ##	Dominated ##
Hsu et al. [44]/2003	Taiwan	Cost-benefit	15 months	BCR = 0.34:1 **	BCR = 2.06:1 **
Coudeville et al. [45]/2004	Italy	Cost-benefit	1-2 years	BCR = 1.20:1	BCR = 3.50:1
		Cost-effectiveness	1-2 years and catch-up	NS	NS
Ginsberg & Somekh [46]/2004	Israel	Cost-effectiveness	12 months	BCR = 1.63:1	BCR = 19.33:1
			12 months and catch-up	BCR = 1.36:1	BCR = 18.80:1
Jean-Jasmin et al. [47]/2004	Singapore	Cost-benefit	15 months	NP	142.2 per CA
			15 months and catch-up		BCR = 2.25:1
Coudeville et al. [48]/2005	France and Germany	Cost-effectiveness	19 months	Cost savings #	Cost savings #
			19 months and catch-up	Cost savings #	Cost savings #
Goldman [26]/2005	USA	Cost-benefit	NS	ANC = 82.2 million	NP
Gialloreti et al. [49]/2005	Italy	Cost-effectiveness	Childhood	NP	Savings per year = 5,443,245
			Catch-up		

(continues)

Table 1 (continued)

Reference/Year of publication	Country	Type of analysis *	Vaccination strategy	Payer's perspective	Society's perspective
Tseng et al. [50]/2005	Taiwan	Cost-benefit	12-18 months	80.8 per CA	(136.3) per CA ***
		Cost-effectiveness		BCR = 0.54:1**	BCR = 1.45:1 **
Lenne et al. [51]/2006	Spain	Cost-effectiveness	1-2 years	5,197 per LYS	NS
			1-2 years and catch-up	17,372 per LYS	11,273 per LYS
Hammerschmidt et al. [52]/2007	Germany	Cost-benefit	11-23 months and catch-up	BCR = 1.08:1 **	BCR = 2.56:1 **
Pérez-Rubio et al. [27]/2008	Spain	Cost-benefit	15 months	NP	BCR = 1.23:1
Zhou et al. [28]/2008	USA	Cost-benefit	1 dose; 12-15 months	BCR = 1:1	BCR = 4.37:1
		Cost-effectiveness	2 doses;12-15 months	BCR = 0.61:1	BCR = 2.73:1
Bonanni et al. [29]/2008	Italy	Cost-benefit	1-1.5 years	BCR = 0.67:1 **	BCR = 3.47:1 **
			1-1.5 years and catch-up	BCR = 0.64:1 **	BCR = 3.33:1 **
Valentim et al. [30]/2008	Brazil	Cost-effectiveness	12 months	28.1 per CA	31.6 per CA
				12,962 per LYS	14,573 per LYS

Note: all costs in PPP (Purchasing Power Parity) dollars for 2008.

LYS: life year saved; DLYS: discounted life year saved; NPV: net present value; ANB: actualized net benefit; CA: case averted; ANC: annual net costs; NP: not performed; NS: not specified; BCR: benefit-cost ratio.

* As reported by the author;

** This ratio included only costs, not health benefits. From the payer's perspective, it is the reduction in the direct costs of the disease divided by the cost of the vaccination program. From society's perspective, it is the reduction in the direct and indirect costs (loss of productivity) from the disease, divided by the cost of the vaccination program. A ratio of 6.9:1 means that each dollar invested in the vaccination program saves 6.9 dollars;

*** The incremental cost-effectiveness ratios (ICER) are negative because the strategies generate savings (they are cheaper than the current strategy) and generate more health benefits;

The two strategies are cost savings (they are cheaper than the current strategy) and generate more health benefits;

The two strategies are dominated (they are more expensive than the current strategy) and generate fewer health benefits.

and thus modeled the increase in the number of cases, hospitalizations, and deaths from herpes zoster resulting from vaccination.

In Goldman [26], the static model also assumed that exposure to the wild-type varicella virus would stimulate immunity, protecting against re-activation of herpes zoster, and thus vaccination against varicella would increase the incidence of herpes zoster. The model predicted the number of herpes zoster cases and the associated direct medical costs 30 years after the introduction of vaccination. Goldman calculated that after 50 years, the vaccination program would reach the break-even point, and that net medical savings would accrue from that point onward.

The vaccine prices listed in Table 4 refer only to the dose price and do not include other costs associated with vaccination, such as materials (needles and syringes), overhead, waste, and treatment of adverse events. We chose to present only the price of the vaccine, because the other components are highly subject to the organization of each country's health systems. The vaccine price per dose varied greatly, from PPP$8.31 to PPP$109.21. Ginsberg & Somekh [46] reported the lowest dose price, explained by the use of a quota for an importer of large volumes. The highest price was used in the evaluation by Gialloretti et al. [49].

Most of the studies used data for the single-antigen vaccine. Only two studies [28,52] used data from the quadrivalent vaccine (MMRV) against measles, mumps, rubella, and varicella. The vast majority of the studies reported efficacy data (percentage of risk reduction in vaccinated individuals as observed in clinical trials). Very few studies [28,52] applied data on effectiveness (percentage of risk reduction in vaccinated individuals, as observed in the real world). The efficacy rates varied from 85% [30,50] to 100% [27]. The lowest effectiveness (85%) reflected the use of results

Table 2

Characteristics of indirect costs included in studies from society's perspective.

Reference/Year of publication	Number of workdays missed *	Cost per workday missed	Indirect costs as % of total cost
Preblud et al. [32]/1985	5	104.7	95.0
Huse et al. [33]/1994	3.7	156.8	75.7
Lieu et al. [34]/1994	NS	316.9	98.0
Beutels et al. [35]/1996	2.6	224.4	95.0 **
Coudeville et al. [36]/1999	3.4	12.7	NS
Scuffham et al. [37]/1999	3	45.6	75.9 **
Díez-Domingo et al. [38]/1999	1.19	64.1	69.9
Scuffham et al. [25]/1999	NI	NI	NI
Hudeckova et al. [39]/2000	NS	NS	68.9 **
Brisson & Edmunds [40]/2002	1.7-1.2 ***	81.47-69.98	86.9
Getsios et al. [41]/2002	3.7	36.1	61.9
Banz et al. [42]/2003	0.6	217.9	72.5
Brisson & Edmunds [43]/2003	0.6	54.9	43.0 **
Hsu et al. [44]/2003	1.85	103.5	72.2
Coudeville et al. [45]/2004	0.7	162.7	61.1
Ginsberg & Somekh [46]/2004	2.5	256.2 ***	92.2
Jean-Jasmin et al. [47]/2004	1.6	67.2	77.6
Coudeville et al. [48]/2005	0.7-0.6 #	202.5-222.8 #	70.5-74.0
Goldman [26]/2005	NI	NI	NI
Gialloreti et al. [49]/2005	0.6	102.2	65.0
Tseng et al. [50]/2005	3.7	76.2	42.9
Lenne et al. [51]/2006	0.97	100.7	71.5
Hammerschmidt et al. [52]/2007	0.6	217.9	51.5
Pérez-Rubio et al. [27]/2008	NS	NS	42.3
Zhou et al. [28]/2008	NS	326.4	NS
Bonanni et al. [29]/2008	0.8	163.5	81.4
Valentim et al. [30]/2008	0.27	13.7	47.3

Note: all costs in PPP (Purchasing Power Parity) dollars for 2008.

NS: not specified; NI: not included.

* Mean number of workdays missed by parents or caregivers per episode of varicella;

** Percentage of savings;

*** 1.7 for children 1-4 years of age and 1.2 for children 5-15 years of age;

0.7, 202.5, and 70.5 in Germany and 0.6, 222.8, and 74 in France.

from studies following introduction of the vaccine in the United States [55,56], while the most optimistic used data from an older clinical trial [13]. In studies that used the MMRV vaccine, Hammerschmidt et al. [52] assumed a 95% efficacy for two doses of vaccine, based on the opinion of experts. Zhou et al. [28] assumed an effectiveness of 93% for two doses of vaccine, based on the breakthrough rates (primary vaccination failure) among individuals vaccinated with 1 and 2 doses [57].

As a consequence of the U.S. recommendation of a second dose of vaccine in 2006, three more recent studies analyzed the two-dose vaccine strategy [28,29,52].

Vaccination coverage rates varied from 10% [37] to 100% [26,27,52]. The lowest coverage rate, 10%, represented private sector coverage based on the payer's perspective in the analysis [37]. Goldman [26] assumed 100% coverage, because vaccination became mandatory in many American states. The highest coverage rates were applied by those that assumed the same coverage obtained for the triple vaccine [27] or used the MMRV vaccine [52].

Of the 13 studies that reported the rate of decrease in post-vaccination immunity, seven (54%) used the 3.1% annual rate from the studies by Brisson et al. [10,58]. Four studies used the rate reported by Halloran et al. [54], where 15% of the

Table 3

Model's characteristics.

Reference/Year of publication	Type of model	Inclusion of herd immunity	Inclusion of impact of vaccination on zoster
Preblud et al. [32]/1985	Static	No	No
Huse et al. [33]/1994	Static	No	No
Lieu et al. [34]/1994	Static	Yes	No
Beutels et al. [35]/1996	Static	No	No
Coudeville et al. [36]/1999	Dynamic	Yes	No
Scuffham et al. [37]/1999	Pseudodynamic	Partially	No
Díez-Domingo et al. [38]/1999	Static	No	No
Scuffham et al. [25]/1999	Static	No	No
Hudeckova et al. [39]/2000	Static	No	No
Brisson & Edmunds [40]/2002	Dynamic	Yes	Yes
Getsios et al. [41]/2002	Static	No	No
Banz et al. [42]/2003	Dynamic	Yes	No
Brisson & Edmunds [43]/2003	Dynamic	Yes	Yes
Hsu et al. [44]/2003	Static	Yes	No
Coudeville et al. [45]/2004	Dynamic	Yes	No
Ginsberg & Somekh [46]/2004	Static	Partially	No
Jean-Jasmin et al. [47]/2004	Static	No	No
Coudeville et al. [48]/2005	Dynamic	Yes	No
Goldman [26]/2005	Static	No	Yes
Gialloreti et al. [49]/2005	Static	No	No
Tseng et al. [50]/2005	Static	No	No
Lenne et al. [51]/2006	Dynamic	Yes	No
Hammerschmidt et al. [52]/2007	Dynamic	Yes	No
Pérez-Rubio et al. [27]/2008	Static	No	No
Zhou et al. [28]/2008	Static	No	No
Bonanni et al. [29]/2008	Dynamic	Yes	No
Valentim et al. [30]/2008	Dynamic	Yes	No

successfully vaccinated individuals had lost their immunity by the end of life.

Adverse events were either found at what were considered low rates, ranging from 0.1% [32] to 3.6% [37], or were not considered in the analyses. Five studies [26,27,39,47,52] did not specify the adverse event rate.

Table 5 shows the most frequent factors that significantly altered the results of the analyses. The factor with the greatest impact on the results was the inclusion of indirect costs, followed by the perspective (society versus payer) and vaccine price.

Some studies reported additional factors, such as vaccine coverage [29,34,35,36,45,51,52], discount rate [25,28,29,37,40,41,42,43,46,52], health benefits discount [42], time horizon [43], and second dose of vaccine [27,30].

Discussion

According to this review, the perspective adopted in the economic evaluations affected the studies' outcome. Where society's perspective was chosen, the vaccination programs were found to be a cost-effective strategy. This confirmed the findings by Thiry et al. [2], whereby the attractiveness of childhood vaccination was also affected by the perspective adopted for analysis. According to these authors, despite the models' varying data and assumptions, the studies suggested that from society's perspective, universal vaccination at 12 or 15 months of age proved quite attractive since it generated major savings by reducing the number of workdays missed by parents. However, from the payer's point of view, vaccination did not generate savings. Likewise, Rozenbaum et al. [3] stated that from society's perspective, child-

Table 4

Vaccine assumptions in economic analyses of varicella.

Reference/Year de publication	Dose price (PPP)	Efficacy (%)	Number of doses	Vaccination coverage	Annual waning rate (%)	Adverse effects (%)
Preblud et al. [32]/1985	26.19	90.0	1	90	NC	0.1
Huse et al. [33]/1994	53.31	95.0	1	NS	NS	1.0
Lieu et al. [34]/1994	55.20	90.0	1	97	15.0 *	2.0
Beutels et al. [35]/1996	84.16	90.0	1	70	15.0 *	NC
Coudeville et al. [36]/1999	20.53	90.0	1	80	15.0 *	1.0
Scuffham et al. [37]/1999	51.38	95.0	1	10. 80 **	NC	3.6
Díez-Domingo et al. [38]/1999	40.10	90.0	1	95	NC	2.0
Scuffham et al. [25]/1999	52.49	95.0	1	80	NC	1.8
Hudeckova et al. [39]/2000	29.12	90.0	1	NS	NC	NS
Brisson & Edmunds [40]/2002	62.67 ***	90.0	1	90	3.1	NC
Getsios et al. [41]/2002	61.98	90.0	1	85	15.0 *	0.3
Banz et al. [42]/2003	73.86	86.0	1	85	0.5	2.0
Brisson & Edmunds [43]/2003	54.92	90.0	1	90	3.1	NC
Hsu et al. [44]/2003	82.11	95.0	1	95	NS	2.0
Coudeville et al. [45]/2004	50.64	97.0	1	90	3.1	1.5
Ginsberg & Somekh [46]/2004	8.31	87.6	1	94	3.1	2.0
Jean-Jasmin et al. [47]/2004	58.78	90.0	1	NS	NC	NS
Coudeville et al. [48]/2005	61.44-67.52 #	97.0	1	90	3.1	1.5
Goldman [26]/2005	NS	100.0	1	100	NS	NS
Gialloreti et al. [49]/2005	109.21	NS	1	90	NC	NC
Tseng et al. [50]/2005	43.71	85.0	1	80	NC	2.0
Lenne et al. [51]/2006	40.40	97.0	1	97	3.1	1.0
Hammerschmidt et al. [52]/2007	55.53	95.0	2	90-100 ##	0.5	NS
Pérez-Rubio et al. [27]/2008	39.49	100.0 ###	1	100	NS	NS
Zhou et al. [28]/2008	60.31-70.82 §	93.0	2	95	NC	1.0-0.5 §§
Bonanni et al. [29]/2008	45.99	90.0-93.0 §§§	2	85	3.0	2.0
Valentim et al. [30]/2008	37.96	85.0	1	80	NC	NC

NC: not considered; NS: not specified; PPP: purchasing power parity.

* 15% of successfully vaccinated individuals will have their immunity exhausted by the end of their lives;

** 10% from the consumer's perspective and 80% from society's perspective;

*** In addition to the price of the vaccine dose, administration, storage, reserve vaccines, transportation, materials, and other costs;

61.44 in France and 67.52 in Germany;

90% after first dose and 100% after second dose;

In the first year of life;

§ 60.31 for the public sector and 70.82 for the private sector;

§§ 1% after first dose and 0.5% after second dose;

§§§ 90% after first dose and 93% after second dose.

hood vaccination programs have always saved costs, with the exception of those that took the potential impact on herpes zoster into account.

Despite the important debate in the literature on the most appropriate method (human capital versus friction cost) for assessing social losses resulting from the disease [59], all the studies used the human capital method to assess the workday value. The variability in the value of the workday lost by parents, from PPP$12.70 to PPP$326.40 [28], highlights the wide variation in wage scales between the different countries studied.

Although PPP supposedly corrects these differences in price levels, it fails to completely cancel out these disparities. Thus, in the more economically developed countries, where wages are higher, the analyses are more favorable to introduction of the vaccine, because the amount

Table 5

Impact of methodology and parameters on the results of economic analyses for varicella.

Reference/Year de publication	Perspective	Indirect costs	Model	Herpes zoster	Vaccine price	Vaccine efficacy
Preblud et al. [32]/1985	Yes	Yes			Yes	
Huse et al. [33]/1994		Yes				
Lieu et al. [34]/1994	Yes	Yes			Yes	
Beutels et al. [35]/1996	Yes	Yes				Yes
Coudeville et al. [36]/1999	Yes	Yes	Yes			
Scuffham et al. [37]/1999	Yes	Yes			Yes	Yes
Díez-Domingo et al. [38]/1999	Yes	Yes				
Scuffham et al. [25]/1999					Yes	
Hudeckova et al. [39]/2000		Yes				
Brisson & Edmunds [40]/2002	Yes	Yes	Yes	Yes	Yes	Yes
Getsios et al. [41]/2002					Yes	
Banz et al. [42]/2003		Yes	Yes		Yes	
Brisson & Edmunds [43]/2003			Yes	Yes		Yes
Hsu et al. [44]/2003	Yes	Yes			Yes	
Coudeville et al. [45]/2004			Yes		Yes	
Ginsberg & Somekh [46]/2004		Yes			Yes	
Jean-Jasmin et al. [47]/2004		Yes				
Coudeville et al. [48]/2005	Alteration of all the parameters did not modify the result of the analysis					
Goldman [26]/2005					Yes	
Gialloreti et al. [49]/2005	Did not analyze sensitivity of the parameters.					
Tseng et al. [50]/2005	Yes	Yes				
Lenne et al. [51]/2006	Yes	Yes	Yes			
Hammerschmidt et al. [52]/2007		Yes	Yes			
Pérez-Rubio et al. [27]/2008	Yes	Yes				
Zhou et al. [28]/2008	Yes				Yes	
Bonanni et al. [29]/2008	Yes	Yes	Yes		Yes	
Valentim et al. [30]/2008			Yes		Yes	

of indirect costs saved is higher, thus underscoring one of the main critiques of the human capital method, which assesses productivity based on income. The vaccine proved more attractive where wages are higher, because according to the human capital method, persons are worth what they produce for society.

To determine the impact of indirect costs on total cost of varicella, indirect costs as a proportion of the total cost of the disease were presented. The results should be interpreted with caution, because the definition of indirect costs differed somewhat between studies and because the measurement and assessment of indirect costs varied greatly. While some studies only included losses of productivity in the form of workdays lost by parents to care for their children, others also included the cost of death or prolonged disability resulting from the disease.

Estimation of the number of workdays lost also varied between studies. While some authors [48,52] repeated the value (0.6 days) initially reported by Banz et al. [42] or presented the same value [43] as in epidemiological studies conducted in Europe [35,36,53], others assumed a higher figure (5 days). It was not surprising that the highest percentage of indirect costs in the total cost of varicella (98%) [34] was associated with the second highest cost of a workday (PPP$316.90). Overestimation of these data biases the results of the analysis in favor of the vaccine.

The definition of indirect cost determines which values will be included in its calculation. Together with the value of the workday, they can have a huge impact on the results of the analysis. All evaluations that included indirect costs in their calculation favored the vaccination program, and the higher the value attributed to in-

direct costs, the more favorable the incremental cost-effectiveness ratio (ICER).

All the economic evaluations that employed dynamic models included herd immunity in the analysis and favored the vaccination program.

Due to the complexity of developing dynamic models, various authors tend to use the same model in different contexts. Several authors have used the dynamic model designed by Halloran et al. [54] to evaluate the cost-effectiveness of their vaccination programs.

This model indicated that vaccination of children at 12 months reduced both varicella incidence and hospitalization in the United States. However, the study investigated a small number of vaccination policies and coverage rates, assumed optimistic vaccine efficacy rates, adopted an age structure that did not reflect varicella epidemiology precisely, and did not conduct a sensitivity analysis in the "Who Acquires Infection from Whom" matrix (WAIFW) [36].

In addition, this model focused mainly on the change in varicella incidence and morbidity due to changes in the age at infection, and failed to explore the possible effects of vaccination on zoster epidemiology.

These issues emphasize the importance of clarity in the models' methodology and assumptions, as well as a justification for the choices and discussion of the possibility of using the same model in different contexts. Taking the WAIFW as an example, can a single matrix represent the age structure and contact pattern in different countries?

The three studies [26,40,43] that included the effect of vaccination on zoster assumed that contact with varicella would stimulate immunity against zoster, and thus modeled the increase in incidence, mortality, and use of resources related to zoster treatment.

The model [10] adopted in the two studies by Brisson & Edmunds [40,43] predicted an increase in post-vaccination zoster incidence for a period of 60 years [10,40,43,60]. However, they recognized the lack of knowledge on the mechanisms that trigger zoster and the model's structure, and the estimated parameters are speculative and probably oversimplified.

Given the complexity and unpredictable interactions between childhood varicella vaccination and herpes zoster incidence, the safest options for vaccination programs would be: (1) vaccination targeting adolescents, adults, and other high-risk susceptible groups. In this case, only a limited proportion of the population is vaccinated, and there is no impact on either virus transmission in the community or herpes zoster incidence; (2) vaccination against varicella in childhood and vaccination against zoster for individuals at increased risk of reactivation of the varicella zoster virus. However, there are no economic evaluation studies on the concurrent introduction of the two vaccines in a population. Besides, the decrease in varicella transmission could result in a change in the age bracket at risk of herpes zoster. However, it is extremely important to monitor and analyze these two diseases, which exert a substantial impact on public health, in order to guarantee that vaccination programs are producing the expected benefits [12].

Any economic analysis that assumes an increase in zoster incidence after varicella vaccination will present unfavorable results for inclusion of the vaccine. Taking Brisson & Edmunds [40] as an example, the WAIFW nearly tripled with the inclusion of zoster. In the strategy based on vaccination of children at one year of age, the values ranged from PPP$46,482 to PPP$123,443, and in the strategy with vaccination of children at one year of age plus catch-up they varied from PPP$53,128 to PPP$156,662.

The second dose of vaccine against varicella is expected to reduce the number of vaccine failures and thus reduce the number of vaccinated individuals that remain susceptible after one dose of the vaccine [61]. However, two doses of the vaccine nearly double the total cost of vaccination. If this cost increase is not compensated for by a reduction in the cost of vaccine failures, it may negatively impact the vaccination program's cost-effectiveness [3].

Conclusions

In most of the studies reviewed, universal childhood vaccination programs against varicella proved to be cost-saving (i.e., generated savings) from society's perspective. According to five studies [42,45,46,48,52] they were cost-saving from the perspectives of both society and the payer. Three of these studies [42,48,52] were done in Germany, where productivity costs are also assessed from the payer's perspective.

The only studies in which childhood vaccination was not considered a cost-effective strategy were those that considered the increase in cases of post-varicella vaccination zoster [26,40,43]. However, the relationship between vaccination against varicella in childhood and zoster incidence in the population with latent varicella zoster infection has still not been completely elucidated, and the results of these modeling studies are considered speculative. It is crucially important to conduct studies on the process of zoster reactivation and

herpes zoster surveillance following introduction of the varicella vaccine.

In the case of varicella, the indirect costs from absenteeism and loss of associated productivity are more important than the direct costs of treating the disease. Thus, indirect costs should be defined, measured, and assessed better, because the introduction of a universal childhood vaccination program may represent a preventive strategy with major social and economic impact.

Due to the complexity of varicella epidemiology, dynamic models are recommended for analyzing childhood vaccination programs, since they are the only ones capable of modeling the indirect effects of vaccination, which are so important in determining the programs' cost-effectiveness.

The programs' cost-effectiveness was heavily related to the price of the vaccine used. The emerging concept of the need for a second dose of vaccine will require better negotiation efforts. It is possible that larger discounts on the vaccine price will be achieved with large purchase volumes or competition between vaccine manufacturers, which may thus lead to a price drop.

Since the vaccine's efficacy also played an important role in the programs' cost-effectiveness, it is recommended to use effectiveness data from post-vaccination studies, since they are more realistic than efficacy data based on clinical trials.

In conclusion, we observed a wide heterogeneity in the perspectives, assessment of indirect costs, type of model, modeling of the effect on herpes zoster, and estimation of the vaccine price and efficacy parameters. The choice of a given methodological aspect or parameter affected the studies' results and conclusions. It is crucial for the authors to present these choices transparently, and that readers and users of economic evaluations understand the repercussions of these choices, i.e., in which direction (for or against) the results were conducted. Since Brazil is currently reviewing its decision on whether or not universal childhood vaccination against varicella should be adopted, we have the chance to benefit from the experience of countries that have already introduced the vaccine, as well as the results of various published economic evaluation studies.

Resumo

O presente trabalho tem por objetivo rever a literatura sobre avaliação econômica de programas de vacinação infantil contra varicela, e discutir como a heterogeneidade em aspectos metodológicos e na estimativa dos parâmetros pode afetar os resultados dos estudos. Após aplicação dos critérios de inclusão, 27 estudos do período de 1980 a 2008 foram analisados com relação às diferenças metodológicas. Observou-se grande heterogeneidade na perspectiva adotada, valoração dos custos indiretos, tipo de modelo empregado, modelagem do efeito no herpes zoster, e na estimativa dos parâmetros de preço e eficácia da vacina. O fator que mais impactou os resultados foi a inclusão dos custos indiretos seguido da perspectiva e preço de vacina adotados. A escolha de um determinado aspecto metodológico ou parâmetro afetou os resultados e conclusões dos estudos. É de fundamental importância que os autores apresentem essas escolhas com transparência para que os usuários das avaliações econômicas compreendam as repercussões dessas escolhas, e em qual direção os resultados das análises foram conduzidos.

Avaliação de Custo-Efetividade; Custos e Análise de Custo; Programas de Imunização; Varicela

Contributors

P. C. de Soárez participated in the data analysis and interpretation and writing and critical revision of the article. H. M. D. Novaes critically revised the article. A. M. C. Sartori participated in the data analysis and interpretation and critically revised the article. All the authors approved the final version for publication.

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