Contributions from the systematic review of economic evaluations: the case of childhood hepatitis A vaccination in Brazil

Contribuições da revisão sistemática de avaliações econômicas: o exemplo da vacinação infantil contra hepatite A no Brasil

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Abstract

The aim of this study was to present the contributions of the systematic review of economic evaluations to the development of a national study on childhood hepatitis A vaccination. A literature review was performed in EMBASE, MEDLINE, WOPEC, HealthSTAR, SciELO and LILACS from 1995 to 2010. Most of the studies (8 of 10) showed favorable cost-effectiveness results. Sensitivity analysis indicated that the most important parameters for the results were cost of the vaccine, hepatitis A incidence, and medical costs of the disease. Variability was observed in methodological characteristics and estimates of key variables among the 10 studies reviewed. It is not possible to generalize results or transfer epidemiological estimates of resource utilization and costs associated with hepatitis A to the local context. Systematic review of economic evaluation studies of hepatitis A vaccine demonstrated the need for a national analysis and provided input for the development of a new decision-making model for Brazil.

Cost-Effectiveness Evaluation; Cost-Benefit Analysis; Hepatitis A; Immunization Programs

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Introduction

In health systems with an ever-increasing demand and limited resources, economic evaluation studies have become an important tool for policy decisions on the incorporation of new health technologies.

Systematic reviews of economic studies have become an essential part of technological evaluation and public policymaking processes. Some national agencies for the appraisal of health technologies [like the National Institute for Health and Clinical Excellence (NICE), Pharmaceutical Benefits Advisory Committee (PBAC), and Canadian Agency for Drugs and Technologies in Health (CADTH)] require systematic review of the relevant economic literature for evaluation and policymaking processes in public health [1].

The methodology for summarizing the results of economic evaluations is not as well-developed as that applied to clinical evidence. The most solidly established methods for summarizing economic evaluations are: narratives summary, the cost-effectiveness plane, and permutation matrices [2].

The summary should begin with descriptive comparisons of the study questions, methods, and results. It can be useful to include tables that summarize the key information on the population, country, study perspective, comparison of interventions, outcomes, summary measures, and incremental cost-effectiveness ratios [3]. The-

oretically, a meta-analysis of economic evaluations can be performed, but in practice it is not a simple procedure [4]. The lack of details in estimates, variability in the outcomes used for effectiveness, and heterogeneity of the economic evaluations identified in the literature hinder a meta-analysis of the results [3]. In most cases, statistical "pooling" of the cost-effectiveness estimates (meta-analysis) is neither feasible, nor does it make sense [1]. Narrative synthesis has been the most widely used method.

The systematic review of economic studies has been indicated to: (1) contribute to the development of a new decision model; (2) identify one or two more relevant studies to inform a particular decision in a jurisdiction; or (3) identify the principal economic "trade-offs" in a given treatment choice or disease area [1].

In Brazil, the National Immunization Program (PNI) commissioned an economic study to estimate the cost-effectiveness of incorporating the hepatitis A vaccine. The hepatitis A vaccine has been commercially available since the early 1990s [5] and has proven safe and effective. In Israel, universal childhood vaccination has been conducted with great success since 1999 [6,7]. Argentina in 2005 [8] and the United States in 2006 [9] also implemented programs for universal childhood vaccination against hepatitis A, with a major impact on the epidemiology of the disease [10]. The pattern of hepatitis A endemicity in Brazil suggests that the introduction of a universal childhood vaccination program would be beneficial.

In this context, a systematic review of previous economic evaluations is necessary in order to verify whether a recent analysis has been performed in Brazil, with similar objectives. Two systematic reviews on the hepatitis A vaccine were published recently, approaching methodological issues related to the use of economic evaluation models [11] and the methodological quality of economic evaluations of various vaccines [12].

A systematic review is thus necessary that includes complete economic evaluation studies analyzing the use of the hepatitis A vaccine in a program for universal vaccination of children up to six years of age. This cutoff was set for the current study considering the most adequate age for vaccination in Brazil, based on the epidemiological pattern of hepatitis A in transition, with regional variation, including areas of intermediate and low endemicity [13,14].

When a new economic evaluation is justified, a review of previous economic studies can provide input for the development of a new decision model. This type of review is useful for comparing and contrasting how different researchers made their choices in relation to the methodology and the estimation of key variables and to clarify how the results of analyses can differ according to these choices [15].

A systematic review of the existing economic studies allows evaluating whether the results can be generalizable or transferable and establishes the need (or lack thereof) for developing local studies to estimate the cost-effectiveness ratio of the new vaccine to be incorporated.

The aim of this study is to present the contributions of a systematic review of economic evaluations to the development of a Brazilian national study, based on the example of childhood hepatitis A vaccination. The article discusses the importance of this review and its applicability to the design of a local economic evaluation and the definition of public policies for immunization in the country.

Methods

Literature search

On May 26, 2010, a search was conducted in six databases: EMBASE, MEDLINE, WOPEC, HealthSTAR, SciELO, and LILACS. The strategy ("economic evaluation" OR "cost" OR "cost-benefit" OR "cost-effectiveness" OR "cost-utility" OR "decision analysis") AND ("hepatitis A" OR "hepatitis A vaccines") was used in all the databases and was limited to articles published from 1995 to May 2010. On December 30, 2010, a new search was conducted, and no new publications were identified.

Inclusion/exclusion criteria

The following selection criteria were used:

- Study design: complete economic evaluation, defined as a comparative analysis of costs and consequences of two alternative healthcare interventions; including cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis;
- Type of intervention: universal childhood hepatitis A immunization program;
- Population: children up to 6 years of age.

The review excluded incomplete economic evaluations, like cost analyses, and economic evaluations of specific groups such as workers, travelers, prison inmates, university students, adolescents, hepatitis C patients, and others.

The review also excluded studies that analyzed the combined hepatitis A+B vaccine, since this vaccine, like the hepatitis A vaccine, is recommended for use starting at 12 months, and

hepatitis B vaccination is recommended soon after birth (1st dose administered in the maternity ward) [16] and is already included as routine in the Brazilian National Immunization Program.

Each study was reviewed in detail to extract and summarize information on:

- Methodological characteristics: type of study, perspective, model, herd protection, time horizon, number of cohorts, currency and year of costs, discount rate, sensitivity analysis, and parameters are varied in the sensitivity analysis;
- Estimates of key variables: epidemiological (incidence, symptomatic outcomes, and case-fatality rate); characteristics of the vaccine (vaccination scheme, coverage, efficacy, adverse events, and annual rate of waning of protection); costs (direct and indirect), and summary measures.

To compare the results of the studies, the summary measures or incremental cost-effectiveness ratios (ICERs) were converted into U.S. dollars (US$) for 2005 using purchasing power parity (PPP), which is the exchange-rate equivalent of an identical basket of goods and services in two countries [17]. The monetary values of the results were corrected by the consumer price index for all annual urban consumers of healthcare in 2005 [18]. Whenever the study did not specify the year of cost, it was assumed that the year of cost was the same as that of the study's publication. This strategy had been adopted previously in the literature [12].

In addition, the research funding sources were identified in order to assess whether they influenced the studies' results.

The methodology used for summarizing economic evaluation studies was narrative synthesis. The methodological characteristics and estimates of key variables are shown in summary tables.

Results

Literature review

The initial searches identified approximately 1,047 articles. After reading the titles and/or abstracts, 20 studies were considered potentially relevant and retrieved in full text. At this stage, only one Brazilian article was selected, from the State of Paraná [19]. However, after reading the complete article it was excluded, since it turned out to be a cost analysis, or incomplete economic evaluation. The authors compared the costs of two strategies: not vaccinating and vaccinating. The non-vaccination strategy included direct medical costs with consultations, laboratory tests, serological diagnostic tests (IgM), fulminant hepatitis, transplants, and retransplantation. The vaccination strategy included the costs of vaccine doses and medical consultations due to adverse events. In order for the study to be considered a complete economic evaluation, in addition to costs it would have had to compare the health outcomes, for example hepatitis A cases averted.

After reading the full text of the 20 studies, 10 studies met the inclusion/exclusion criteria and will be discussed in the current review.

Methodological characteristics of the studies

Table 1 shows the methodological characteristics of the 10 studies [20,21,22,23,24,25,26,27,28,29] analyzed in the current review. Half of the studies were conducted in developed countries, the oldest [20] failed to specify the country but used U.S. data in its analysis, three studies were performed in the United States [21,22,23], and one in Israel [24]. Four studies were conducted in South America, including two in Chile [25,26] and two in Argentina [27,28], and one study in China [29].

As specified by the authors, four studies performed cost-effectiveness analysis, three did cost-utility analysis, two did joint cost-effectiveness and cost-utility analysis, and only one did cost-benefit analysis.

As for the perspective from which the analysis was performed, the 10 studies adopted society's perspective, which is that recommended for vaccination programs planned to improve public health, because it considers both the direct and indirect costs of the intervention. Direct costs are those directly related to the disease and are divided into medical and non-medical. Direct medical costs are those immediately related to diagnosis, treatment, and rehabilitation. They include tests, medicines, clinical or surgical procedures, etc. Meanwhile, direct non-medical costs include family costs with transportation (of the patient and accompanying person for receiving care), food (changes in the patient's normal diet), etc. Indirect costs are related to loss of income and/or productivity and disability or death of productive persons as a result of the disease. Importantly, lost productivity is not limited to the patient; costs related to the persons (caregivers) who miss work in order to care for the patient should also be taken into account.

In addition to society's perspective, four studies [22,25,26,29] also took the perspectives of the healthcare system and public payer, which are relevant for assisting decision-making in the health sector.

As for the selected model, most of the studies (7 of 10) used a Markov static model [20,21,22,23,25,28,29]. Two studies used dynamic models [26,27].

Table 1

Methodological characteristics of economic evaluations of hepatitis A immunization programs.

Study/ Country	Type of study	Perspective	Model	Herd protection	Time horizon (years)	Cohorts	Currency/ Year of Costs	Discount rate	Sensitivity rate	Parameters varied in the sensitivity analysis
Das [20]/ Developed country	CUA	Society	Static (Markov)	Not included	74.5	1	ND	Cost: 3%; Benefit: 3%	Univariate; Multivariate	Vaccination coverage; natural immunity; annual rate of waning of protection; incidence; case-fatality; costs; acute episodes of hepatitis a; doses of vaccine; serological tests; discount rate
Ginsberg et al. [24]/Israel	CBA	Society	Proxy model	Included	45	ND	US$/1997	Cost: 4%; Benefit 4%	Univariate; Break-even	Incidence; vaccine efficacy; time horizon; discount rate
Jacobs et al. [22]/USA	CUA	Healthcare system/ Society	Static (Markov)	ND	83	1	US$/2002	Cost: 3%; Benefit 3%	Univariate; Multivariate	Discount rate; incidence; annual rate of waning of protection; price of vaccine; administration fee; QALY of symptomatic infections; hospitalizations; transplants; case-fatality
Valenzuela et al. [25]/ Chile	CEA	Healthcare system/ Society	Static (Markov)	Partially included	50	1	US$/2004	Cost: 3%; Benefit 3%	Univariate	Case-fatality; annual rate of waning of protection; costs; medical; doses of vaccine; lost workdays; discount rate
Rein et al. [23]/USA	CEA	Society	Static (Markov)	Not included	95	1	US$/2005	Cost: 3%; Benefit 3%	Univariate; Multivariate; Probabilistic	Incidence; vaccination coverage in adults; annual rate of waning of protection; adverse events; QALYs; public health costs; cost of dose of vaccine; administration cost; discount rate
Armstrong et al. [21]/USA	CEA	Society	Static (Markov)	Included	95	10	US$/2005	Cost: 3%; Benefit 3%	Univariate	Incidence; vaccination coverage; annual rate of waning of protection; QALYs; cost of vaccine
Lopez et al. [27]/ Argentina	CEA	Society	Dynamic (SIR)	Included	100	100	US$/2004	Cost: 3%; Benefit: ND	Univariate	Annual reduction of force of infection; vaccination coverage; herd protection; time horizon; discount rate
Ellis et al. [28]/ Argentina	CUA	Society	Static (Markov)	ND	50	1	US$/2005	Cost: 3%; Benefit: 3%	Univariate; Multivariate	Annual rate of waning of protection; cost of dose of vaccine

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Table 1 (continued)

Study/ Country	Type of study	Perspective	Model	Herd protection	Time horizon (years)	Cohorts	Currency/ Year of Costs	Discount rate	Sensitivity rate	Various parameters in the sensitivity analysis
Quezada et al. [26]/Chile	CEA	Public payer/ Society	Dynamic (SIR)	Included	100	100	US$/2005	Cost: 3%; Benefit: 3%	Univariate; Multivariate; Best and worst-case scenarios	Annual reduction of force of infection; vaccination coverage; herd protection; costs of disease; time horizon; discount rate
Zhuang et al. [29]/China	CEA; CUA	Healthcare system/ Society	Static (Markov)	Not included	72	1	RMB Yuan/2005	Cost: 5%; Benefit 5%	Univariate; Multivariate	Vaccination coverage (1 and 2 doses); vaccine efficacy; annual rate of waning of protection; incidence; proportion of symptomatic infections; duration of symptoms; hospitalization; case-fatality; missed workdays; cost of vaccine; medical costs of hepatitis A; utility score for hepatitis A; annual growth in per capita GDP; discount rate

CBA: cost-benefit analysis; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; ND: not determined; QALY: quality-adjusted life year; GDP: gross domestic product; SIR: susceptible, infected, recovered.

Finally, one study was unable to develop a dynamic model (which the author considered the gold standard) and thus developed a "proxy model", not described clearly by the author [24].

The "dynamic" model allows projecting changes in transmission patterns, i.e., reduction in the force of infection resulting from the vaccination program. Universal vaccination programs can result in complex indirect effects known as "herd protection": unvaccinated susceptible individuals are protected from the disease by the decrease in transmission of the pathogen, which can lead to a shift in the age at infection to older age groups. Meanwhile, a "static" model does not allow incorporating change into the force of infection over time. Although theoretically the dynamic models estimate changes in the epidemiological pattern more accurately, they require larger amounts of data, which are not always available. For example, the lack of data on the annual decrease in the force of infection and seroprevalence for hepatitis A in some age groups lead authors to make assumptions that introduce uncertainties into the model. Despite the great methodological sophistication, the final results depend on the availability and quality of the data used to feed the model [26].

The inclusion of herd protection in the economic analysis can make the program more cost-effective, because it increases the number of cases averted. It was included in four studies [21,24,26,27] and partially included in one [25]. Two of these studies [21,25] included herd protection in their analysis, despite using static models. The study by Armstrong assumed a fixed proportion in the decline in infections, attributed to herd protection for persons within the vaccinated cohort and for the unvaccinated [21]. In Valenzuela et al. [25], it was not clear how this was done. It should be emphasized that static models usually fail to consider indirect effects of vaccination such as herd protection and shift in the age at infection to older age groups. Some studies using static models consider herd protection, assuming that a fixed percentage of the unvaccinated population is protected by the vaccination of the vaccinated cohort [11]. However, another characteristic of herd protection, namely an increase in the age group of infection, can lead to an increase in the frequency of symptomatic cases and consequently a change (increase) in the use of health services, not considered in static models. The inclusion of only the positive aspects of herd protection can result

Table 2

Epidemiological estimates used in economic evaluations.

Study	Incidence	Source	Symptomatic outcomes	Source	Case-fatality rate (%)	Source
Das [20]	Annual hepatitis A incidence in the unvaccinated population: 0.0001	ACIP	Episodes of acute hepatitis	ACIP	< 50 years: 0.3; > 50 years: 2.5	2 national articles
Ginsberg et al. [24]	% cases of hepatitis type A; Reported cases of hepatitis A: 54/100,000	National statistics and Ministry of Health	Mild and moderate cases: 84%; outpatient cases with relapse: 5.5%; inpatient cases with relapse: 2.7%; severe hospital cases: 7.6%; non-fatal FHF without transplant: 0.024%; fatal FHF without transplant: 0.028%; non-fatal FHF with transplant: 0.062%; fatal FHF with transplant: 0.008%	Personal communication and national data	0.0071	Ministry of Health
Jacobs et al. [22]	Hepatitis A infection rates by age and region * and national rate	SNVEDN	Symptomatic infection rate (≤ 4 years: 7%; 5-9 years: 37%; 10-17 years: 71%; 18-29 years: 73%; 30-39 years: 74%; 40-49 years: 78%; 50-59 years: 82%; 60-69 years: 86%; ≥ 70 years: 90%); hospitalization rate (≤ 14 years: 5%; 15-29 years: 10%; 30-39 years: 11%; 40-49 years: 15%; 50-59 years: 21%; 60-69 years: 26%; 70-79 years: 33%; ≥ 80 years: 43%); transplant rate (≤ 14 years: 0%; 15-39 years: 0.02%; 40-49 years: 0.05%; ≥ 50 years: 0.08%)	2 national articles; 8 national articles; 2 national articles	Case-fatality rate (≤ 14 years: 0.14%; 15-29 years: 0.18%; 30-39 years: 0.21%; 40-49 years: 0.36%; 50-59 years: 0.81%; 60-69 years: 1.49%; 70-79 years: 2.83%; ≥ 80 years: 3.85%)	7 national articles
Valenzuela et al. [25]	Reported hepatitis A infection rates per 100,000 (1-4 years: 99.1; 5-9 years: 259.7; 10-14 years: 154.0; 15-19 years: 55.8; 20-24 years: 31.0; 25-34 years: 14.7; 35-44 years: 6.9; 45-50 years: 5.6)	Ministry of Health and surveillance data	Proportion of hepatitis A cases causing overt disease (1-4 years: 7%; 5-9 years: 37%; 10-17 years: 71%; 18-29 years: 73%; 30-39 years: 74%; 40-50 years: 78%); Hospitalization rate in overt hepatitis (0-14 years: 8%; > 14 years: 11%)	3 national articles; Ministry of Health	0-14 years: 0.14%; 15-29 years: 0.18%; 30-39 years: 0.21%; 40-50 years: 0.36%	1 international article

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Table 2 (continued)

Study	Incidence	Source	Symptomatic outcomes	Source	Case-fatality rate (%)	Source
Rein et al. [23]	Reported annual hepatitis A incidence by age and region **	2 national articles	Infection rate without jaundice with nonspecific symptoms (0.5); Infection rate with jaundice (0-4 years: 0.076; 5-14 years: 0.512; 15-95 years:0.832); Hospitalization rate of reported cases with jaundice (0-4 years: 0.05; 5-14 years: 0.17; 15-39 years: 0.23; 40-59 years: 0.19; 60-95 years: 0.2)	Assumption; 1 national article; 1 national article	Case-fatality rate in cases with jaundice (0-4 years: 0.00030; 5-14 years: 0.00004; 15-39 years: 0.00054; 40-59 years: 0.00436; 60-95 years: 0.1276)	1 national article
Armstrong et al. [21]	Reported annual hepatitis A incidence by age and region ***	2 national articles	Infection rate without jaundice with nonspecific symptoms (0.5); Infection rate with jaundice (0-4 years: 0.076; 5-14 years: 0.512; 15-95 years: 0.832); Hospitalization rate of reported cases with jaundice (0-4 years: 0.05; 5-14 years: 0.17; 15-39 years: 0.23; 40-59 years: 0.19; 60-95 years: 0.2)	Assumption; 1 national article; 1 national article	Case-fatality rate in cases with jaundice (0-4 years: 0.00030; 5-14 years: 0.00004; 15-39 years: 0.00054; 40-59 years: 0.00436; 60-95 years: 0.1276)	1 national article
Lopez et al. [27]	Age-specific force of infection based on seroprevalence data	Published data in Latin America and Argentina	Risk of jaundice: 85.2%; Risk of FHF per symptomatic case: 0.00085; Risk of transplant per symptomatic case: 0.00072; Risk of re-transplantation per symptomatic case: 0.00014; Risk of relapse per symptomatic case: 0.15; Risk of hospitalization per symptomatic case: 0.05	Ministry of Health and 1 international article; 2 national articles; 1 international article; 2 national articles; 1 international article	Age-specific per 100,000 (≤ 14 years: 140; 15-29 years: 180; 30-39 years: 210; 40-49 years: 360; 50-59 years: 810; 60-69 years: 1,490; 70-79 years: 2,630; ≥ 80 years: 3,850)	2 international articles
Ellis et al. [28]	Reported annual hepatitis A incidence per age and region # and national rate	Ministry of Health; National statistics	Hepatitis A cases; Proportion of infection with symptoms (1-4 years: 7%; 5-9 years: 37%; 10-14 years: 71%; 15-49 years: 75.7%; ≥ 50 years: 86%); Hospitalization (0-14 years: 2.6%; 15-29 years: 3.6%; 30-39 years: 3.6%; > 39 years: 3.6%); Transplant (0-14 years: 0.027%; 15-29 years: 0.127%; 30-39 years: 0.127%; > 39 years: 0.127%)	Ministry of Health; 2 international articles; National data and 1 international article; 1 national article; National statistics	0-14 years: 0.14%; 15-29 years: 0.18%; 30-39 years: 0.21%; > 39 years: 0.36%	2 international articles

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Table 2 (continued)

Study	Incidence	Source	Symptomatic outcomes	Source	Case-fatality rate (%)	Source
Quezada et al. [26]	Age-specific force of infection based on seroprevalence data	Data published in Chile	Infected individuals with jaundice (85.2%); Hospitalization (0-14 years: 0.08; ≥ 15 years: 0.11); Transplant (0-14 years: 0.0001; ≥ 15 years: 0.0003)	2 international articles	Age-specific per 100,000 (≤ 14 years: 140; 15-29 years: 180; 30-39 years: 210; 40-49 years: 360; 50-59 years: 810; 60-69 years: 1.490; 70-79 years: 2.630; ≥ 80 years: 3.850)	2 international articles; Ministry of Health, Argentina
Zhuang et al. [29]	Annual incidence based on region-specific seroprevalence data ##	National technical document	Proportion of infections with symptoms (1-4 years: 7%; 5-9 years: 37%; 10-17 years: 71%; ≥ 18-years: 75%); Hospitalization (1-14 years: 0.08; ≥ 15 years: 0.15)	4 international articles; 2 international articles	1-4 years: 0.0030; 15-39 years: 0.00054; 40-59 years: 0.00436; ≥ 60 years: 0.1276	1 international article

ACIP: Advisory Committee on Immunization Practices (USA); FHF: fulminant hepatic failure; SNVEDN: National System for Epidemiological Surveillance of Diseases of Notification.

* 4 regions: ≥ 200% of mean national incidence, 100-199% of mean national incidence, 50-99% of mean national incidence, ≤ 50% of mean national incidence;

** 3 regions: regions 1 and 2 (incidence 1-2 times the national mean), region 3 (national mean);

*** 3 regions: region with high endemicity, region with intermediate endemicity, and region with low endemicity;

5 regions: Northeast and Central regions (incidence below the national mean), South (national mean), Cuyo and Northwest regions (incidence above the national mean);

5 regions: very low prevalence of hepatitis antibodies A (50%), low prevalence of hepatitis A antibodies (50-69%), intermediate prevalence of hepatitis A antibodies (70-79%), high prevalence of hepatitis A antibodies (80-89%), very high prevalence of hepatitis A antibodies (90%).

in overestimation of the vaccination program's beneficial effects.

The inclusion of herd protection can have a major impact on the vaccination program's predicted outcomes. For example, Ginsberg et al. [24], when modeling the potential economic and health benefits of an immunization program for children 1-2 years of age in Israel, estimated that it would take 15 years for the program to reduce symptomatic cases by 90%. However, in real life, routine immunization in Israel achieved a reduction of greater than 90% in just three years, due partially to the herd protection induced by vaccination [6].

The majority of the studies (7 of 10) used long time horizons, more than 70 years, accompanying the life expectancy of the cohorts [20,21,22,23,26,27,29]. They all used standard discount rates, from 3 to 5%, and only one study [27] failed to report the discount of benefits.

Estimates of key variables

• Epidemiological estimates

Table 2 summarizes the epidemiological estimates used in the economic evaluations.

All the studies used local data to build estimates of incidence and force of infection. Four studies [21,22,23,28] presented data on regional incidence and conducted regional and nationwide cost-effectiveness analyses. The study in China [29] conducted only regional analyses, without presenting a nationwide analysis.

The most frequently used outcomes were outpatient cases, inpatient cases, transplant cases, and deaths. To estimate the number of symptomatic cases, eight studies [21,22,23,25,26,27,28,29] used the study by Armstrong & Bell [30] which calculated the probability of developing jaundice during acute hepatitis A according to age group, utilizing data from different primary studies.

As for case-fatality, the majority of the studies used data from national studies or data furnished by the Ministry of Health to construct

their local estimate, and only four studies in Argentina [27,28], Chile [26], and China [29] used U.S. case-fatality data.

- **Characteristics of the vaccine**

Table 3 presents the vaccine's characteristics. In relation to the vaccination scheme, most studies adopted vaccination of children up to 24 months of age. Only two studies evaluated the strategy with a second dose at 54 and 72 months of age [25,28]. And only one Argentine study evaluated single-dose vaccination [28]. Argentina is the only country to have implemented a single-dose immunization program against hepatitis A [8].

As for vaccination coverage, only three studies used more conservative coverage rates, from 69 to 89% [20,22,29].

All the studies used data on vaccine efficacy (percentage risk reduction in vaccinated individuals as observed in clinical trials). No study presented data on effectiveness (percentage risk reduction in vaccinated individuals as observed in routine use of the vaccine). Efficacy rates ranged from 91 to 98% for the first dose and from 95 to 100% for the second dose.

Data in the literature suggest that protection provided by the hepatitis A vaccine is long-lasting: persistence of antibodies or anamnestic response to a booster dose of the vaccine, or both, was demonstrated up to 12 years after the 2-dose vaccination scheme [31]. Even so, the analyses in the 10 studies assumed waning of protection over time after vaccination. Five studies [20,21,22,23,24] used estimates based on models of antibody persistence [32,33]. Three of these studies [25,28,29] used estimates constructed by an expert panel in the United States (1.62% per year in the first 10 years and 2.67% thereafter, after one dose of the vaccine, and 0.31% and 0.62% after two doses) [34]. Two studies [26,27], despite using the same expert panel cited above as the reference [34], presented an estimate of 0.58% per year, without specifying at what year after vaccination the waning of immunity was expected to occur.

- **Cost estimates**

Table 4 summarizes the elements considered in the cost estimates. All the studies included direct medical costs, costs with the vaccine, and indirect costs. In most cases, direct medical costs were related to treatment of hepatitis A in outpatients, inpatients, hepatic failure with or without subsequent transplant, and follow-up of transplant patients. All the studies used local data to estimate direct medical costs, except for Quezada et al. [26], in Chile, who used international studies, and Armstrong et al. [21], who did not specify the sources used to construct the direct cost estimates. The four studies [22,23,25,28] that included costs with follow-up of transplant patients used data from studies by Berge et al. [35] and/or Hauboldt [36], conducted in the United States.

As for costs with the vaccine, nine studies considered the values for the dose and administration, two studies included the cost of adverse events [24,26], and only one included the cost of wasted vaccines and transportation to receive the vaccine [24].

As for indirect costs, eight studies calculated lost productivity due to the disease for patients, while four studies also calculated lost productivity for caregivers. One study calculated the wage losses of spouses, assuming that they acted as caregivers [24]. Four studies [20,22,23,25] only used local data to estimate indirect costs, three [24,28,29] used international articles, and three [21,26,27] failed to specify their sources. In general, the calculation was performed using the country's median wage, adjusted for the unemployment rate. Only one study [29] used per capita GDP to construct this estimate, due to the lack of a reliable national wage estimate.

The number of lost workdays varied from 13.25 days in mild to moderate cases up to a year and a half for persons with non-fatal fulminant hepatic failure with transplant. In hospital cases this figure ranged from 33 to 71 days. Referring to the same source [35], different authors [25,28,29,34] reported different estimates of lost workdays.

Results of the analyses

Table 5 shows the summary measures presented in the results of the analyses. In general, studies funded by industry reported more favorable ICERs than the independent studies. All the studies showed favorable cost-effectiveness results, below US$ 20,000 per quality-adjusted life year (QALY) gained [37], except for two independent studies [21,23] that showed ICERs of US$ 28,000 and US$ 32,000 per QALY gained, respectively. When the latter included herd protection in the analysis, the ICER dropped from US$ 32,000 to US$ 1,000 per QALY gained.

One study [20] found that the hepatitis A vaccine was within the accepted cost-effective range, using US$ 42,000 per year of life saved as the cutoff [38]. Jacobs et al. [22] found the value of the hepatitis A vaccination program comparable to that of other immunization programs. Valenzuela et al. [25] and Zhuang et al. [29] used per capita GDP as the cost-effectiveness parameter. Rein et al. [23] found the hepatitis A immunization

Table 3

Characteristics of vaccine.

Study	Vaccination scheme	Coverage (%)		Efficacy (%)		Adverse events (%)	Annual rate of waning of protection (%)
		1st dose	2nd dose	1st dose	2nd dose		
Das [20]	2 doses (0 and 6-12 months)	80	80	ND	ND	NC	12 *
Ginsberg et al. [24]	2 doses (15 and 24 months)	95	92	94	95	Mild (1.25: 1st dose; 2.50: 2nd dose)	2 (after 10 years)
Jacobs et al. [22]	2 doses (2 years)	89	69	98	99	NC	2.3 **
Valenzuela et al. [25]	2 doses (18 and 24 months or 18 and 54 months)	96	80 (24 months); 92.2 (54 months)	98	99	ND	With 1 dose: 1.62 (1-10 years); 2.67 (after 10 years) With 2 doses: 0.31 (1-10 years); 0.62 (after 10 years)
Rein et al. [23]	2 doses (12 months)	93	87	91	100	Mild: 0.5; Severe: 0.0001	20 (1-5 years); 5 (after 5 years)
Armstrong et al. [21]	2 doses (12 months)	93	87	91	100	Mild: 0.5; Severe: 0.0001	20 (1-5 years); 5 (after 5 years)
Lopez et al. [27]	2 doses (12 and 18 months)	95	95	95	100	0.03	0.58 *
Ellis et al. [28]	1 dose (12 months) or 2 doses (12 and 18 months or 12 and 72 months)	95	76 (18 months); 66.5 (72 months)	98	99	ND	With 1 dose: 1.62 (1-10 years); 2.67 (after 10 years) With 2 doses: 0.31 (1-10 years); 0.62 (after 10 years)
Quezada et al. [26]	2 doses (12 and 18 months)	95	95	95	100	0.03	0.58 *
Zhuang et al. [29]	2 doses (12 and 18 months)	85	80	93	95	ND	With 1 dose: 1.62 (1-10 years); 2.67 (after 10 years) With 2 doses: 0.31 (1-10 years); 0.62 (after 10 years)

NC: not considered; ND: Not determined.

* Not determined at what year waning of protection begins;

** Waning of protection twice as fast in individuals that received only 1 dose of vaccine.

program cost-effective, since it was comparable to other public health interventions such as diabetes screening in patients with hypertension (US$ 34,000) and HIV screening in the general population (US$ 42,000). The other five authors [21,24,26,27,28] did not specify the cost-effectiveness criterion used when interpreting the results.

Universal childhood hepatitis A vaccination proved to be cost-saving (costs iess and is more effective than the non-vaccination strategy) in areas with higher incidence of the disease in Argentina [28] and the United States [22,23]. In Ellis et al. [28], vaccination proved to be cost-saving in the Cuyo region (high endemicity), while in the South region (intermediate endemicity) the ICER was US$ 673 per QALY gained and in the Northeast region (low endemicity) the ICER was US$ 2,772 per QALY gained. Jacobs et al. [22] showed similar findings: the vaccination program proved to be cost-saving in regions with incidence rates ≥ 200% and 100-199% of the national average, while in regions with incidence rates 50-99% of the national average the ICER was US$ 13,800 per QALY gained and with incidence rates < 50% of the national average the ICER was US$ 63,000 per QALY gained. In Rein et al. [23], vaccination proved to be cost-saving in regions 1 and 2 (with twice the mean national incidence), and in region 3 (with the country's mean incidence) the ICER was US$ 133,000 per QALY saved.

Meanwhile, in China [29], in areas with the lowest, low, intermediate, and high prevalence of hepatitis A antibodies, the immunization program proved to be cost-saving, but in areas with extremely high prevalence of hepatitis A antibodies, the ICER was US$ 277.

Countries described their regional incidence/prevalence rates as high, intermediate, or low in relation to the national average. However, the national average differs between countries.

Table 4

Elements considered in cost estimates.

Study	Cost elements	Sources
Das [20]	Direct medical costs: acute episodes of hepatitis A	2 national articles
	Costs with vaccine: dose; administration; hepatitis A antibody tests	3 national articles
	Indirect costs: lost productivity	1 national article
Ginsberg et al. [24]	Direct medical costs: laboratory tests; prophylaxis in communicants; mild and moderate cases; outpatient cases with relapse; inpatient cases with relapse; severe hospital cases; non-fatal fulminant hepatic failure without transplan; fatal fulminant hepatic failure without transplant; non-fatal fulminant hepatic failure with transplant; fatal fulminant hepatic failure without transplant	National data
	Direct non-medical costs: transportation for outpatient consultations and hospitalization	National data
	Costs with vaccine: doses; administration; waste; adverse events; health education; transportation	National statistics
	Indirect costs *: lost productivity, patient; lost productivity, spouse (U.S. wage adjusted for unemployment rate)	2 international articles
Jacobs et al. [22]	Direct medical costs: outpatient; inpatient; transplant; transplant follow-up	2 national articles; Transplant Registry/U.S.
	Costs with vaccine: doses; administration	CDC; 1 national article
	Indirect costs: lost productivity in outpatients – 15 days; lost productivity in hospital patients – 33 days (median wage, USA)	National statistics; 1 national article
Valenzuela et al. [25]	Direct medical costs: outpatient; inpatient; transplant; transplant follow-up	Ministry of Health of Chile
	Costs with vaccine: doses; administration	CDC; Ministry of Health of Chile
	Indirect costs: lost productivity in patients 20-59 years of age – 28 days (median daily wage in Chile)	Ministry of Health of Chile; Central Bank of Chile
Rein et al. [23]	Direct medical costs: symptomatic outpatients without jaundice; unreported outpatients with jaundice; inpatients with jaundice; fulminant hepatic failure without transplant; transplant; transplant follow-up; public health costs per reported case	3 national articles
	Costs with vaccine: doses; administration	CDC
	Indirect costs: lost productivity for patients and caregivers (median expected weekly wage)	Population survey
Armstrong et al. [21]	Direct medical costs: public health costs	ND
	Costs with vaccine: dose; administration	ND
	Indirect costs: lost productivity following death from hepatitis A; lost productivity of patients; lost productivity of parents of children with hepatitis A	ND
Lopez et al. [27]	Direct costs: laboratory tests; administration of immunoglobulin M; outpatient consultations; hospital fees; fulminant hepatic failure without transplant; fulminant hepatic failure with transplant; Re-transplantation	National statistics; Abstract from Argentine study
	Costs with vaccine: doses	Abstract from Argentine study
	Indirect costs	ND
Ellis et al. [28]	Direct medical costs: outpatient; inpatients without fulminant hepatic failure; inpatients with fulminant hepatic failure without transplant; inpatients with fulminant hepatic failure with transplant; transplant follow-up	Records and data on national costs
	Costs with vaccine: doses; administration	PAHO Revolving Fund
	Indirect costs: lost productivity of patients > 17 years of age -28 days (regional wage)	3 international articles; National statistics

(continues)

Table 4 (continued)

Study	Cost elements	Sources
Quezada et al. [26]	Direct medical costs: outpatient treatment; inpatient treatment; fulminant hepatic failure with transplant	3 international articles; 2 national articles
	Costs with vaccine: doses; administration; adverse events	3 international articles; 2 national articles
	Indirect costs: lost productivity of parents of patients ≤ 15 years of age – 3 days; lost productivity of patients > 15 years -25 days	ND
Zhuang (2008) [29]	Direct medical costs: non-hospital cases; hospital cases; fatal cases	Ministry of Health
	Costs with vaccine: doses; administration	Price paid by government; U.S. CDC
	Indirect costs: lost productivity of patients 18-60 years; non-hospital cases – 16 days; hospital cases – 33 days; fatal cases – 40 days (per capita GDP/365.5)	3 international articles

CDC: Centers for Disease Control and Prevention (USA); ND: not determined; PAHO: Pan-American Health Organization; GDP: gross domestic product.
* Number of lost workdays is specific to types of cases: mild and moderate cases in adults (13.25 days); mild and moderate cases in children (9.29 days); outpatient cases with relapse (46.3 days); hospital cases with relapse (46.3 days); severe hospital cases (71 days); non-fatal fulminant hepatic failure without transplant (6 months for survivor and 6 weeks for spouse); fatal fulminant hepatic failure without transplant (10.5 days for deceased patient and 21 days for spouse); non-fatal fulminant hepatic failure with transplant (1.5 year for survivor and 1 year for spouse); fatal fulminant hepatic failure with transplant (10.5 days for deceased patient and 21 days for spouse).

While the United States has low endemicity, Argentina, Chile, and China are in transition from high to intermediate or low endemicity [14]. The severity of hepatitis A increases with age: jaundice is reported in only 7% of children less than four years of age with hepatitis A [30]. Meanwhile, more than 70% of older children and adults are symptomatic, with clinical jaundice in 40 to 70% of cases [30,39]. In countries with high endemicity, infection occurs in early childhood, and the vast majority of cases are asymptomatic. The transition from high to low endemicity can lead to an increase in age at infection, with an increase in symptomatic cases and thus greater utilization of health services, which would explain the higher cost-effectiveness ratio in areas with extremely high endemicity.

Sensitivity analyses (Table 1) showed that the parameters with the greatest impact on the results of economic evaluations were cost of the vaccine dose and administration, followed by incidence and medical costs of the disease. Four [26,27,28,29] of the 10 studies presented robust results in favor of vaccination, which did not change with variations in the parameters for sensitivity analyses.

Discussion

This systematic review of economic studies on childhood hepatitis A vaccination showed that this type of study can contribute to the development of a national decision-making model. The review pointed to some important issues to be considered when using the methodology and estimates of key variables in the published studies, especially in relation to the transferability of data and generalizability of results.

We observed variability among the studies under review in relation to the methodological characteristics and estimates of key variables. Methodological characteristics accounted for some differences in the studies' results, particularly the perspective and type of model used.

The type of perspective adopted by the study is a methodological choice. Many experts recommend society's perspective, because it is more comprehensive [15]. In this review, when three studies [22,23,25] took society's perspective, the results were very different from those obtained using the healthcare system's perspective (Table 5). Although all the studies took society's perspective (considering direct and indirect costs), in the Brazilian case it is also recommendable to conduct the study from the healthcare system's perspective, because it provides results that only consider the amounts reimbursed by the Unified National Health System and can assist public managers in the decision making process.

As for the type of model, although most of the studies (7 of 10) used a Markov static model [20,21,22,23,25,28,29], the review suggests the development of a dynamic transmission model as the best option for evaluating the country's universal childhood immunization program. This methodological choice will require a larger amount of local data, for example data on hepatitis A sero-

Table 5

Summary measures presented in results according to the perspective of the analysis and funding source.

Funding Source	Perspective	
	Society	Healthcare system
Independent		
Das [20]	US$ 14,948 per QALY gained	ND
Ginsberg et al.[24]	Cost-benefit ratio *: 3.07:1	Cost-benefit ratio **: 2.17:1
Rein et al. [23]	US$ 284 per averted infection	ND
	US$ 199,000 per year of life gained	ND
	US$ 28,000 per QALY gained	US$ 40,000 per QALY gained
Armstrong et al. [21]	US$ 32,000 per QALY gained (without considering herd protection)	ND
	US$ 1,000 per QALY gained (considering herd protection)	
Zhuang et al. [29]	< 0 ***: US$ 3,633 per year of life gained	< 0 ***: US$ 2,680 per year of life gained
	< 0 ***: US$ 277 per QALY gained	< 0 ***: US$ 204 per QALY gained
Industry		
Jacobs et al. [22]	US$ 2,382 per year of life gained	US$ 15,265 per year of life gained #
	US$ 1,516 per QALY gained	US$ 9,852 per QALY gained #
Valenzuela et al. [25]	< 0 ## per year of life gained	US$ 475-US$ 911 per year of life gained
	< 0 ## per QALY gained	US$ 290-US$ 520 per QALY gained
Lopez et al. [27]	US$ 3,542 per year of life gained	ND
Ellis et al. [28]	< 0 ###: US$ 234 per QALY gained (1 dose of vaccine)	ND
	< 0 §: US$ 2,772 per QALY gained (2 doses of vaccine)	
Quezada et al. [26]	US$ 4,984 per year of life gained	ND

ND: not determined; QALY: quality-adjusted life year.

* US$ 1 invested in vaccination produces a savings of US$ 3.07;

** US$ 1 invested in vaccination produces a savings of US$ 2.17;

*** Incremental ratio was negative in regions with low, medium, intermediate, and high endemicity and was US$ 3,633 per year of life gained in the region
with extremely high endemicity; incremental ratio was negative in regions with low, medium, intermediate, and high endemicity and was US$ 277 per QALY gained in the region with extremely high endemicity; incremental ratio was negative in regions with low, medium, intermediate, and high endemicity and was US$ 2,680 per year of life gained in the region with extremely high endemicity; incremental ratio was negative in regions with low, medium, intermediate, and high endemicity and was US$ 204 per QALY gained in the region with extremely high endemicity;

Health service's perspective;

Negative incremental ratio means that the vaccination strategy is "cost-saving", cost less and is more effective;

Incremental ratio was negative in Argentina as a whole and US$ 234 per QALY gained in the Cuyo region;

§ Incremental ratio was negative in the Cuyo region and US$ 2,772 per QALY gained in the Northeast region.

prevalence in Brazil. Data from the recent *National Hepatitis Survey* allow feeding a dynamic model for hepatitis A.

The Brazilian dynamic model should consider both the positive aspects of herd protection such as the increase in averted cases of the disease and the negative aspects like the change in age at infection and proportion of symptomatic cases and use of health services, in order to avoid overestimating the beneficial effects of the vaccination program with more favorable cost-effectiveness results.

Estimates of the key variables also accounted for differences in the results in the studies reviewed here.

Incidence was one of the factors with the greatest impact on the cost-effectiveness of universal hepatitis A vaccination programs. Cost-effectiveness ratios in areas with low incidence of the infection are heavily influenced by the

cost of the vaccine and the inclusion of social costs. Cost-effectiveness in high-incidence areas proved more robust to changes in the cost of the vaccine or other costs [12]. Data from epidemiological estimates are considered to have low transferability in economic evaluations. Measures of clinical events can be misleading if there are differences in the underlying epidemiological estimates. The "guidelines" recommend the use of specific country data [40]. In the absence of local data, it is recommended that data from countries with similar endemicity be used. Despite the existence of studies in Chile [25,26] and Argentina [27,28] with similar epidemiological profiles, the results are not transferable due to the differences in the organization of healthcare and coverage in the respective health systems.

In the Brazilian case, the preference should be for regional analyses based on different patterns of endemicity, in addition to a nationwide analysis. To conduct a nationwide analysis, the most important issue would be the availability of reliable data on incidence of the infection, number of symptomatic cases, and deaths from hepatitis A. The data on probability of symptomatic infection (jaundice) may be transferable from other studies, because in this specific case there is no reason for the natural history of the disease to differ between countries. Studies in Argentina [27,28], Chile [25,26], and China [29] used the proportion of symptomatic individuals among the infected, provided by Armstrong & Bell [30], a study conducted in the United States. The Brazilian national study could repeat this approach. As for case-fatality, although some studies in the review used international data, the Brazilian study should use national data. Guidelines suggest that this estimate should only be transferred from similar locations in the absence of data on case-fatality in the country itself, but that the estimate should be validated by expert panels.

In addition, detailed data are necessary on access to health services, healthcare patterns, and use of resources in outpatient, inpatient, and transplant cases, as well as on post-transplant follow-up. The studies reviewed here do not provide details on the methodology used for the identification and measurement of resources used in treatment of the previously cited cases. Data on use of resources are considered to have intermediate transferability. The guidelines from pharmacoeconomics recommend obtaining data on the use of resources from the location where the evaluation is being performed. Differences in clinical practices, payment systems, and incentives are generally cited as the principal reasons for variation in the use of resources between one location and another. When there are no local data and it becomes necessary to transfer data from elsewhere, an expert panel is recommended for reviewing the data and evaluating whether the treatment patterns are similar, in order to produce more relevant estimates for the local context [40]. The Brazilian case requires obtaining the pattern of care practiced in local health services in order to determine the resources (medical consultations, hospitalizations, tests, drugs, etc.) and the amounts used in outpatient, inpatient, and transplant cases and post-transplant follow-up.

Most studies (8 of 10) used local data to estimate direct medical costs. Data from cost estimates are considered to have low transferability. The guidelines are very strict and do not allow transferring these data under any circumstances. Cost unit estimates must be specific to the context being evaluated, due to differences in absolute and relative prices between countries [40]. Thus, in the Brazilian case, direct medical costs for outpatient and inpatient treatment of hepatitis A, hepatic failure with or without subsequent liver transplant, and post-transplant follow-up, as well as the costs of the vaccine, must necessarily use local data.

The inclusion of indirect costs related to lost productivity was important in determining the attractiveness of the immunization program (Table 5). Value assessment of lost work time depends on the country's wage and employment levels. Four studies [20,22,23,25] used only local data to estimate indirect costs, indicating greater difficulty in obtaining local data for this estimate. In the Brazilian national study, additional efforts should be made to accurately document the real number of lost workdays related to the disease locally, since indirect costs of the disease can have an important impact on the results of the analysis.

Data on the effect of treatment are considered highly transferable [40]. The vaccine's efficacy, obtained from randomized controlled clinical trials conducted in other countries, can be used in the local study. The vaccination scheme should be adjusted to the prevailing national childhood immunization calendar, with two doses administered in the second year of life. Considering resource limitations, single-dose vaccination may be explored, as in the Argentine experience. Vaccination coverage should be estimated, based on the coverage of other vaccines already incorporated into the National Immunization Program and which are administered during the same period (measles-mumps-rubella, administered at 12 months, or the DTP booster, administered at 15 months).

Summary of Recommendations for a Brazilian National Model

Based on the information obtained from the articles in this review, it is possible to summarize some methodological characteristics and estimates of key variables to be used in the Brazilian national model:

- Adopt the society and healthcare system perspectives;
- Develop a dynamic transmission model;
- In addition to the national analysis, conduct regional analyses according to different patterns of endemicity;
- Use national data on incidence, force of infection, and case-fatality;
- Use national data on access to health services, patterns of care, and use of resources in outpatient, inpatient, and transplant cases;
- As a comparative strategy, adopt a vaccination scheme adjusted to the prevailing national childhood immunization calendar;
- Use local data to estimate direct medical costs;
- Use local data on coverage and cost of the vaccine;
- Consider international data on vaccine efficacy if local data on effectiveness are not available;
- Use local data to estimate indirect costs related to lost productivity;
- Discount costs and benefits at a 5% standard rate;
- Conduct sensitivity analysis for the estimates of incidence, cost of dose, and administration of the vaccine and medical costs of the disease.

Final remarks

Economic evaluations can benefit from systematic reviews of the clinical literature. However, prior review of the literature is not sufficient to guarantee a good economic evaluation [41]. Some authors have questioned the contributions of systematic reviews and raised concerns about generalizing the results of economic evaluation studies. Unlike systematic reviews of treatment effects in randomized controlled clinical trials, the cost-effectiveness results of new interventions are more context-dependent than the clinical efficacy results. The cost-effectiveness of a particular intervention is heavily influenced by the use of resources and the costs associated with the intervention, which vary between countries, regions, or types of services, as well as over time [42,43,44].

Economic evaluations in health make use of epidemiological data and data on access and use of health services, treatment patterns, and costs associated with the disease, which vary greatly between countries, making it very difficult to generalize and/or transfer the results to different contexts. The systematic review of economic evaluation studies for the hepatitis A vaccine showed that it is not possible to generalize the results to the Brazilian context, and confirmed the need to develop a local study to estimate the cost-effectiveness ratio of the new vaccine to be incorporated.

The discussion of methodological characteristics and estimates of key variables and the summary of recommendations provided elements for the development of a new decision-making model for Brazil.

Resumo

O objetivo deste estudo foi apresentar as contribuições da revisão sistemática de avaliações econômicas para o desenvolvimento de um estudo nacional, o caso da vacinação infantil contra hepatite A. Foi realizada revisão da literatura nas bases de dados EMBASE, MEDLINE, WOPEC, HealthSTAR, SciELO e LILACS, no período de 1995 a 2010. A maioria dos estudos (8 em 10) mostrou resultados favoráveis de custo-efetividade. As análises de sensibilidade indicaram como parâmetros mais importantes para os resultados os custos da vacina, incidência de hepatite A e custos médicos da doença. Foi observada variabilidade nas características metodológicas e estimativas de variáveis-chaves dos 10 estudos revisados. Não é possível generalização dos resultados e transferibilidade de estimativas epidemiológicas, de usos de recursos e custos associados à hepatite A para o contexto local. A revisão sistemática dos estudos de avaliação econômica da vacina contra hepatite A demonstrou a necessidade de uma análise nacional e forneceu elementos para o desenvolvimento de um novo modelo de decisão para o Brasil.

Avaliação de Custo-Efetividade; Análise Custo-Benefício; Hepatite A; Programas de Imunização

Contributors

P. C. De Soárez participated in the design and planning, data analysis and interpretation, elaboration of the draft, and approval of the final version of the article. A. M. C. Sartori participated in the design and planning, elaboration of the draft, critical review of the content, and approval of the final version of the article. A. Santos participated in the design and planning, critical review of the content, and approval of the final version of the article. A. Itria participated in the data analysis and interpretation, critical review of the content, and approval of the final version of the article. H. M. D. Novaes participated in the design and planning, critical review of the content, and approval of the final version of the article. C. M. T. Martelli participated in the design and planning, critical review of the content, and approval of the final version of the article.

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