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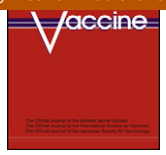

Cost-effectiveness analysis of universal childhood hepatitis A vaccination in Brazil: Regional analyses according to the endemic context

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ABSTRACT

Objective: To conduct a cost-effectiveness analysis of a universal childhood hepatitis A vaccination program in Brazil.
Methods: An age and time-dependent dynamic model was developed to estimate the incidence of hepatitis A for 24 years. The analysis was run separately according to the pattern of regional endemicity, one for South + Southeast (low endemicity) and one for the North + Northeast + Midwest (intermediate endemicity). The decision analysis model compared universal childhood vaccination with current program of vaccinating high risk individuals. Epidemiologic and cost estimates were based on data from a nationwide seroprevalence survey of viral hepatitis, primary data collection, National Health Information Systems and literature. The analysis was conducted from both the health system and societal perspectives. Costs are expressed in 2008 Brazilian currency (Real).
Results: A universal immunization program would have a significant impact on disease epidemiology in all regions, resulting in 64% reduction in the number of cases of icteric hepatitis, 59% reduction in deaths for the disease and a 62% decrease of life years lost, in a national perspective. With a vaccine price of R$16.89 (US$7.23) per dose, vaccination against hepatitis A was a cost-saving strategy in the low and intermediate endemicity regions and in Brazil as a whole from both health system and society perspective. Results were most sensitive to the frequency of icteric hepatitis, ambulatory care and vaccine costs.
Conclusions: Universal childhood vaccination program against hepatitis A could be a cost-saving strategy in all regions of Brazil. These results are useful for the Brazilian government for vaccine related decisions and for monitoring population impact if the vaccine is included in the National Immunization Program.

1. Introduction

Although the hepatitis A vaccine is effective, safe and available since the 1990s, routine childhood immunization against hepatitis A still is an underused policy.

In high endemic areas, hepatitis A occurs early in childhood and most infections are asymptomatic. Improvement of the sanitary conditions leads to a shift of the age groups affected by hepatitis A, with increasing incidence in older age groups and higher frequency of icteric and serious disease, enhancing the importance of hepatitis A as a public health problem. Higher risk of outbreaks with common source also occurs in areas in transition from high to intermediate/low endemicity [1].

The World Health Organization (WHO) recommends universal vaccination against hepatitis A in countries with intermediate endemicity [1]. Israel, USA and Argentina have implemented

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universal childhood vaccination programs against hepatitis A with great impact on the disease epidemiology [2–6].

Brazil is undergoing epidemiological transition, presenting two distinct epidemiological patterns: the North, Northeast and Midwest regions with intermediate endemicity of hepatitis A, and the South and Southeast regions with low endemicity [7–9]. Hepatitis A vaccine is available at the Brazilian public health system (Sistema Único de Saúde, SUS) only for patients at risk of serious illness, such as those with chronic liver disease, coagulopathy, hemoglobinopathy, cystic fibrosis, persons aged ≤13 years with HIV infection, carriers of hepatitis B and C virus, immunocompromised hosts, candidates for donor and transplant organs. The vaccine is also available at the private health system. This strategy results in very low vaccine coverage: <1% of children aged 1–4 years received the vaccine in 2009. According to WHO criteria, the country should consider the introduction of universal vaccination against hepatitis A [1].

We conducted a cost-effectiveness analysis of a universal childhood hepatitis A vaccination program in Brazil. Since hepatitis A seroprevalence, disease treatment costs and indirect costs differ throughout the country, cost-effectiveness of vaccination may also differ. So, the analysis was run separately according to the regional endemic context.

2. Methods

Two strategies were compared: universal childhood hepatitis A vaccination program in the second year of life and the current strategy (vaccination of high risk persons).

2.1. Model structure and parameterization

An age and time-dependent susceptible – infected/infectious – recovered – vaccinated (SIRV) compartmental dynamic model of hepatitis A transmission was developed to estimate the incidence of the disease for a period of 30 years (Appendix A) [10,11]. The model was based on data from a nationwide population survey of seroprevalence of hepatitis, conducted from 2004 to 2009, which involved persons aged 5–69 years, in the 27 Brazilian state capitals. It showed an area of intermediate endemicity of hepatitis A – the North, Northeast, and Midwest regions, where 32.8%, 52.9% and 63.2% of children and adolescents aged 5–9, 10–14 and 15–19 years had anti-hepatitis A antibodies, and an area of low endemicity – the South and Southeast regions, where 19.8%, 30.3% and 43.7% of children and adolescents of the same age had anti-hepatitis A antibodies [7–9].

The model incorporated a variable force of infection accounting for herd effects of a universal immunization program. Demographic data were obtained from Brazilian National Institute of Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE) [12]. The dynamic model predicted the numbers of hepatitis A infections by age and year for the whole Brazilian population, with the current strategy and the impact of a universal childhood immunization program. The analysis was run separately combining the North, Northeast and Midwest macro-regions, from now on called “North” area, and for the South and Southeast, from now on called “South” area.

A decision analysis model built in Microsoft Excel was used to estimate health services utilization and costs associated to hepatitis A by age group and region of residence.

The analysis was conducted using the health system perspective, including all direct medical costs (medical visits, diagnostics tests, medications and hospitalizations), and the societal perspective, incorporating nonmedical and productivity costs. The outcomes measured are cases averted, deaths averted and life-years saved (LYS). The time horizon of the economic analyses was 24 years. Future costs and outcomes were discounted at 5% [13].

2.2. Epidemiological estimates and health services utilization for hepatitis A

Table 1 summarizes epidemiological estimates. The age-specific proportions of icteric cases were taken from a previous study reporting the probability of developing jaundice during acute hepatitis A [14]. The number of hospitalizations for hepatitis A in the Public Health System in 2008 was retrieved from the Hospitalization Information System (Sistema de Informação Hospitalar, SIH/SUS). Because SIH/SUS registers only data for the public system, we used data from a nationwide household survey (Pesquisa Nacional por Amostra de Domicílios, PNAD), to estimate hospitalizations at the private sector [15]. PNAD-2008 showed that 74.9% of overall hospitalizations for clinical reasons were financed by SUS. From the estimated total number of hospitalizations and the number of icteric cases (estimated from the dynamic model), we estimated the hospitalization rates, by age and region of residence, for the base year.

The proportions of transplantation among hospitalized cases were based on data from the National Agency of Transplantation showing that 46% of persons who enter the transplant list for acute liver failure undergo liver transplantation. A prospective multicenter study conducted in Argentina, Brazil, Chile, Colombia, Costa Rica and Mexico, also showed 46% of patients with acute liver failure for hepatitis A were transplanted [16]. Estimates of liver failure among hospitalized hepatitis A cases, by age and region of residence, were based on the average annual number of fulminant hepatitis A cases reported to Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação, SINAN) [17] and the estimated total hospitalizations for hepatitis A. Hospital case-fatality rates before transplantation were taken from the SIH/SUS. Survival of 56.7% in the first year after transplantation was based on data from the State of São Paulo System for Transplantation [18].

2.3. Vaccination strategies, effective coverage and costs

The universal vaccination program assumed two vaccine doses administered in the second year of life. The first dose may be administered simultaneously with other vaccines already included in the childhood immunization schedule (at 12 or 15 months), but an additional visit is needed to administer the second dose of the vaccine, six months after the first dose. The current strategy was assumed to have no effects on transmission of hepatitis A, considering its low coverage.

In the base case, we assumed effective coverage of 85% (94% vaccine efficacy and 90% vaccination coverage) and wastage rate of 5% (Table 1) [1,19]. Waning immunity was not considered in the model.

The costs of the universal vaccination program included cost of vaccine dose and cost of administration. Vaccine costs were based on the price paid by the Brazilian National Immunization Program in 2008 (R$16.89 = US$7.23) plus an estimated administrative cost of R$2.33 (US$1) [20] (Table 2). As the second dose of the vaccine requires a new visit to the health center, transportation costs of this new visit were included in the model when the analysis was conducted from the society perspective.

Health care utilization and costs of adverse events following hepatitis A vaccination were not considered, since they are rare and mild, and the associated costs may be considered insignificant [21].

Table 1
Summary of epidemiological and vaccine estimates by region analysis.

Estimates	Base case			Sensitivity analysis	Source
	North	South	National All regions		
Epidemiological					
Proportion of icteric cases among infectious (%) age-group—years					[12]
<1	7.20	7.20	7.20	−50 to −90	
1–4	7.20	7.20	7.20	−50 to −90	
5–9	37.10	37.10	37.10	−50 to −90	
10–19	70.70	70.70	70.70	−50 to −90	
20–79	85.20	85.20	85.20	−50 to −90	
Proportion of hospitalization among icteric cases (%)					[Authors assumptions based on SIH/SUS and 13]
<1	2.38	0.75	1.83	−50 to −75	
1–4	1.00	0.74	0.91	−50 to −75	
5–9	0.22	0.13	0.18	−50 to −75	
10–14	0.09	0.05	0.07	−50 to −75	
15–19	0.12	0.06	0.09	−50 to −75	
20–29	0.16	0.06	0.09	−50 to −75	
30–39	0.29	0.11	0.15	−50 to −75	
40–49	0.87	0.25	0.38	−50 to −75	
50–59	2.31	0.45	0.77	−50 to −75	
60–69	3.33	1.04	1.47	−50 to −75	
70–79	19.38	2.56	4.87	−50 to −75	
Case-fatality rates among hospitalized cases before liver transplantation (%)					[Authors assumptions based on SIH/SUS]
<1	0.00	0.00	0.00		
1–4	0.41	0.65	0.47		
5–9	0.55	0.42	0.51		
10–14	0.55	0.42	0.51		
15–19	0.61	0.79	0.67		
20–29	0.99	1.11	1.03		
30–39	1.45	3.92	2.54		
40–49	4.76	4.87	4.82		
50–59	6.16	8.25	7.25		
60–69	4.02	10.30	6.87		
70–79	8.41	12.06	9.81		
Proportion of liver transplant among hospitalized cases (%)					[Authors assumption based on 14, 16]
<1–14	0.441	0.469	0.451	−50	
15–39	0.142	0.212	0.183	−50	
40–79	0.000	0.042	0.021	−50	
Survival in the first year post-transplantation (%)	56.7%	56.7	56.7%	–	[15]
Vaccine					
Efficacy (%)	94	94	94	90–95	[1]
Coverage (%)	90	90	90	84–95	[DATASUS/PNI]
Effective coverage (%)	85	85	85	75–90	
Wastage (%)	5	5	5	–	[Authors assumption based on 17]

To estimate the annual cost of the current strategy (vaccination of high risk persons), we considered the total vaccine doses (157,611) administered in Brazil in 2008.

2.4. Health care costs

Health care cost estimates, summarized in Table 2, were calculated by age group and area of residence.

Direct medical costs were estimated for outpatient care, inpatient treatment, liver transplantation and follow up post transplantation. The standard outpatient care for acute hepatitis A was based on expert opinion. The cost of health service utilization in public outpatient facilities was valued using the SUS procedures reimbursement prices in 2008, available in the Public Health Information System (Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS, SIGTAP) [22]. The costs of cases treated in the private sector were estimated based on the 2008 values recommended by the Brazilian Medical Association.

We assumed that all hospitalized cases of hepatitis A would also have outpatient care. Thus, the costs of hospital treatment include the costs of hospitalization itself plus the costs of the outpatient care (medical visits + diagnostic tests). Since values for hospitalization in the private sector were not available, we assumed the same values of the public system, taken from SIH/SUS.

As the Brazilian public health system is responsible for most transplantation, we adopted the average cost of hospitalization for liver transplantation in the SUS for both systems.

Due to lack of data for the costs of outpatient follow up post transplantation, primary data was collected in the Digestive System Organ Transplantation Service of the Hospital das Clinicas, the academic hospital of the University of Sao Paulo School of Medicine, in Sao Paulo, Brazil. The direct costs of transporting patients to receive care were included when the analysis was performed from the society perspective.

Indirect costs refer to lost productivity due to hepatitis A by the patient or caregivers (we assumed the mother) of children aged <15 years. We used the human capital approach to calculate indirect costs. Lost productivity was calculated by multiplying the estimated number of working days lost by the national average wage for women. We assumed mean duration of 15 days for hepatitis

Table 2
Summary of input cost parameters by region analysis (in 2008 Brazilian currency, Real, R$2.33 = US$1).

Costs[a] parameters	Base case						Sensitivity analysis	Source
	North		South		National	All regions		
	Health system perspective	Society perspective	Health care system perspective	Society perspective	Health care system perspective	Society perspective		
Vaccine dose	16.89	16.89	16.89	16.89	16.89	16.89	+50 to +150%	[CGPNI]
Administration	2.33	2.33	2.33	2.33	2.33	2.33	–	[17]
Outpatient treatment[a]								[Authors assumptions]
<1 year	103.53	405.65	120.21	468.75	111.70	417.19	−50 to −75%	
1–4 years	103.53	405.65	120.21	468.75	111.70	417.19	−50 to −75%	
5–9 years	97.26	399.37	112.32	460.87	104.69	410.19	−50 to −75%	
10–14 years	101.72	411.36	111.17	467.83	104.69	417.71	−50 to −75%	
15–19 years	171.36	270.64	189.70	334.58	179.29	298.04	−50 to −75%	
20–29 years	181.09	468.18	202.79	600.99	189.50	524.76	−50 to −75%	
30–39 years	181.87	601.03	199.57	749.02	189.95	667.33	−50 to −75%	
40–49 years	182.31	675.53	188.75	787.82	188.75	733.19	−50 to −75%	
50–59 years	179.61	636.33	188.86	714.42	184.60	677.28	−50 to −75%	
60–69 years	176.95	427.57	190.16	494.57	184.83	463.58	−50 to −75%	
70–79 years	185.30	284.52	201.27	311.53	194.04	298.69	−50 to −75%	
Inpatient treatment[b]								[SIH/SUS]
<1 year	326.15	1141.89	370.79	1372.06	337.85	1169.26	–	
1–4 years	317.14	1133.27	435.00	1384.30	352.30	1179.34	–	
5–9 years	313.79	1124.81	331.11	1264.98	321.82	1141.51	–	
10–14 years	312.00	1132.11	381.99	1331.24	334.64	1165.03	–	
15–19 years	389.29	656.18	410.19	796.90	398.08	716.10	–	
20–29 years	388.77	1152.79	419.92	1484.18	400.69	1293.77	–	
30–39 years	393.11	1524.55	454.56	1953.61	422.17	1716.80	–	
40–49 years	401.86	1744.76	513.21	2174.62	458.63	1957.92	–	
50–59 years	491.85	1728.62	484.64	2026.76	489.09	1875.48	–	
60–69 years	398.28	1072.21	713.65	1587.32	569.83	1346.36	–	
70–79 years	425.78	698.22	788.12	1103.57	573.78	865.71	–	
Transplantation[c]								[DATASUS]
<39 years	53,703.16	61,183.45	53,703.16	62,402.86	53,703.16	65,611.34	−50%	
40–49 years	53,703.16	55,882.38	53,703.16	57,028.67	53,703.16	67,309.46	−50%	
50–59 years	53,703.16	60,759.75	53,703.16	63,614.45	53,703.16	65,998.77	−50%	
60–69 years	53,703.16	64,087.78	53,703.16	67,452.36	53,703.16	60,581.87	−50%	
70–79 years	53,703.16	65,954.20	53,703.16	68,711.88	53,703.16	56,173.70	−50%	
Follow up post transplantation[d]								
1 year				34,364.24				
2 years				15,923.79				
3 years				9889.13				
4 years				7436.03				
5–23 years				5761.42				
Discount rate				0			+5%, +10%	

[a] Outpatient treatment costs include two medical visits and diagnostic tests, in the health care system perspective. In the society perspective, they also include transportation and indirect costs related to lost productivity from the patient and caregivers of children under-15 years of age.
[b] Inpatient treatment costs include hospitalization in the health care system perspective. In the society perspective, they also include transportation and indirect costs related to lost productivity from the patient and caregivers of children under-15 years of age.
[c] Transplantation costs include the procedure cost, in the health care system perspective. In the society perspective, they also include transportation and indirect costs related to lost productivity from the patient and caregivers of children under-15 years of age.
[d] Follow up post transplantation direct medical costs include medication, diagnostic tests, medical visits, and hospitalization. The same value was used in both regions and perspectives.

A outpatients [23]. For inpatients, estimates of duration of disease were based on the specific average hospital stay by age group and region of residence, retrieved from SIH/SUS, to which we added 10 days before the admission and 10 days after the discharge. The duration of inpatient disease ranged from 24 to 30 days.

2.5. Sensitivity analysis

Because of uncertainty in our baseline estimates, we conducted univariate and bivariate sensitivity analysis on key parameters, such as the frequency of icteric cases, rates of hospitalization, proportions of liver transplantation, vaccine price and outpatient care costs. A reduction of 1% a year in the incidence of hepatitis A due to improvement in sanitary conditions was also considered in the sensitivity analyzes.

3. Results

3.1. Model estimates

Hepatitis A seroprevalence data from the nationwide population survey [7–9], provided the following fitting parameters: $k_1 = (0.01762 \pm 0.00096)\,\mathrm{yr}^{-2}$ and $k_2 = (0.0699 \pm 0.0048)\,\mathrm{yr}^{-1}$ for the "North" area and $k_1 = (0.00815 \pm 0.00018)\,\mathrm{yr}^{-2}$ and $k_2 = (0.0485 \pm 0.0031)\,\mathrm{yr}^{-1}$ for the "South" area. Those parameters were used to estimate the force of infection for each area (Fig. 1).

We ran a simulation of the SIRV model without vaccination to estimate the proportion of infectious $\Psi(a, t)$ (Appendix A). This proportion was then converted to number of new infections per 100,000 inhabitants (Fig. 2). The next step was simulating different vaccination scenarios: with 75% effective coverage (vaccine efficacy of 90% and coverage rate of 84%), 85% effective coverage (94% and

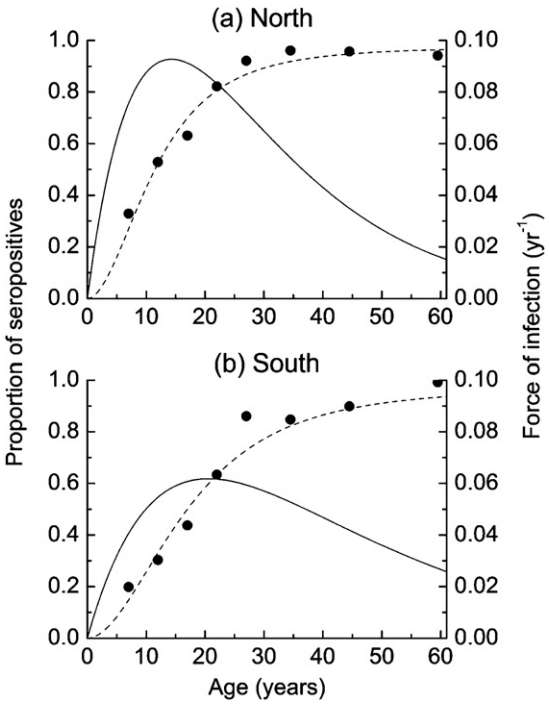

Fig. 1. Seroprevalence data, the corresponding fitted curve (dashed line and left-hand scale), and the age-dependent force of infection (thick line and right-hand scale) of hepatitis A in "North" (North + Northeast + Midwest regions) and "South" (South + Southeast regions) areas, Brazil, 2008.

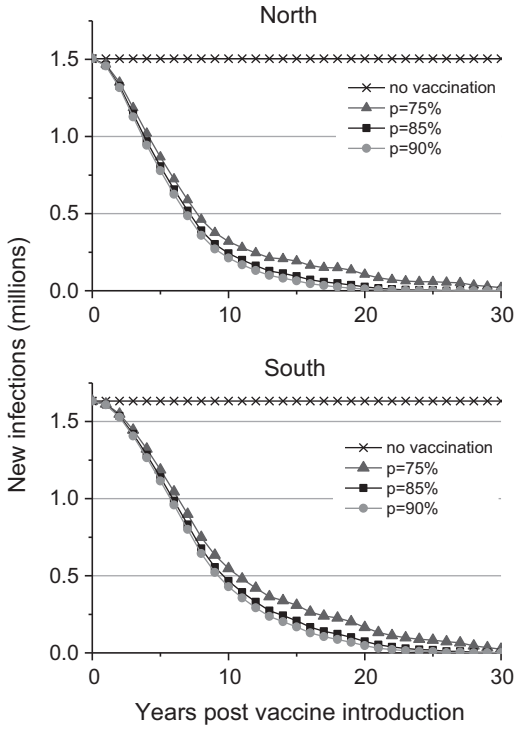

Fig. 2. Number of new hepatitis A infections estimated by the dynamic model in the North and South areas in the absence of vaccination and for three different effective coverage (vaccine efficacy × vaccination coverage): 90% (95% × 95%); 85% (94% × 90%), and 75% (90% × 84%).

90%), and 90% effective coverage (95% and 95%) for both areas separately. These proportions were also converted to number of new infections per 100,000 inhabitants (Fig. 2). The numbers of new infections in both areas by age and year of occurrence were added up to run the national analysis.

3.2. Disease impact and cost-effectiveness ratios

Tables 3 and 4 summarize disease impact, costs and cost-effectiveness ratios of the analyses of the two areas and the national. Under the base case assumptions (two dose vaccination schedule, vaccine efficacy of 94% and coverage of 90%) a universal childhood immunization program would have a significant impact on disease epidemiology, resulting in 64% reduction in the number of icteric cases, 59% reduction in deaths and 62% decrease of life years lost, in a nationwide perspective. The reduction of the icteric cases would be slightly larger in the "North" (68%) than in the "South" (61%), as well as the reduction in deaths, "North" (65%) and "South" (57%). The universal program brings incremental costs that are compensated for lower disease treatment costs (Table 3). Hepatitis A vaccination was a cost-saving (more effective and less expensive) strategy in the "North" (intermediate endemicity), in the "South" (low endemicity), and in Brazil as a whole from both health system and society perspective, without and with 5% discount of cost and benefits.

3.3. Sensitivity analysis

Universal childhood hepatitis A vaccination program was a cost-effective strategy in most variations of the key estimates (Table 4). The incremental cost-effectiveness ratios (ICERs) were more sensible to variations in the proportion of icteric cases, vaccine costs and outpatient care costs. Reduction of 1% a year in the incidence of the infection due to improvement in sanitary conditions did not impact on the ICERs. Variations in hospital and liver transplantation costs had no impact on the ICER either. Despite their high costs, these procedures are rare, and the large number of outpatients had greater impact on the ICER.

4. Discussion

Results showed that a universal childhood vaccination program against hepatitis A would have an important impact on the epidemiology of the disease.

The incremental cost-effectiveness ratios (ICERs) showed our base case scenario of universal vaccination as a cost-saving strategy in the intermediate and low endemic areas, and in Brazil as a whole, from both health system and society perspective. Among the cost-effectiveness studies of new vaccines (rotavirus, varicella, pneumococcal conjugate, and meningococcal C conjugate) we conducted for the Brazilian Ministry of Health, only hepatitis A vaccine proved to be a cost-saving intervention [11,24–26].

In the sensitivity analysis, results were more sensitive to variations in the proportions of icteric infection, vaccine costs and outpatient care costs (Table 4). However, only with large variations in these parameters, universal vaccination becomes not cost-effective in both perspectives. Since there is no Brazilian standard of cost-effectiveness, we use WHO criteria, that considers an intervention "very cost-effective" when the cost of averting one disability-adjusted life-year (DALY) is less than the gross domestic product (GDP) per capita; an intervention is considered "cost-effective" if the cost per DALY averted is from 1 to 3 times the GDP per capita; and an intervention is "not cost-effective" if the cost per DALY averted is >3 times the GDP per capita. 2008 Brazilian GDP = R$15,240 (US$6541).

Table 3
Predicted outcomes under two vaccination strategies by area analyzed.

Outcomes	Base case					
	North		South		National All regions	
	Current strategy[a]	Universal vaccination	Current strategy[a]	Universal vaccination	Current strategy[a]	Universal vaccination
Disease impact						
Number of icteric cases	19,362,612	6,242,236	25,566,782	10,095,236	44,929,394	16,337,472
Number of avoided cases		13,120,376		15,471,546		28,591,922
Reduction in the number of icteric cases (%)		68		61		64
Number of deaths	819	288	1040	449	1787	732
Number of avoided deaths		532		591		1055
Reduction in the number of deaths (%)		65		57		59
Number of life years lost	21,217	6954	21,669	9010	42,275	16,122
Number of life years gained		14,263		12,659		26,153
Reduction in the number of life years lost (%)		67		58		62
Costs[b]			**Society perspective**			
Disease treatment cost[c]	7,994,666,912	4,146,691,719	13,863,427,939	7,082,620,447	20,858,463,895	10,793,846,069
Treatment cost avoided		3,847,975,193		6,780,807,492		10,064,617,826
Reduction in the treatment costs (%)		48		49		48
Intervention cost[d]	13,449,071	1,563,205,826	62,496,666	1,512,334,409	75,945,737	3,055,278,919
Incremental cost of universal vaccination		1,539,756,756		1,449,837,743		2,979,333,182

[a] Current strategy: vaccination of high risk group.
[b] In 2008 Brazilian currency (real), R$2.33 = US$1.
[c] In the perspective of society, it includes costs of hospital treatment, transplantation, follow up post transplantation, medical visits, diagnostic tests and medication, family transportation costs and indirect costs (lost productivity of the caregiver and patient).
[d] Intervention cost in the universal vaccination strategy includes the cost of two doses of vaccine, administration cost (R$2.33 = US$1 per dose) and 5% of vaccine wastage, assuming 94% of vaccine coverage and that all children that initiate vaccination scheme received two recommended doses.

Hepatitis A seroprevalence data used in the dynamic model was taken from a nationwide population survey conducted in all state capitals covering all regions, the best available evidence for Brazil. Data from state capitals were generalized to the entire country. Possible differences in seroprevalence of hepatitis A between the capitals, usually with better sanitary conditions, and smaller towns, villages and rural areas were not considered in the model. However, 2010 Brazilian census showed that 84% of Brazilian population lives in urban areas. A National Sanitation Survey, conducted in 2008, showed that safe water supply reaches 99.4% of Brazilian municipalities, solid waste management (including scavenging and garbage collection) 100%, and sewage collection 55.2% [27].

The proportion of icteric cases and the components and costs of outpatient care have a large impact on the ICER, as shown by sensitivity analysis (Table 4).

The numbers of icteric hepatitis A cases are difficult to estimate due to variations in clinical assessment and underreporting. The proportion of icteric cases among all infections is not well known. Literature review found only one study reporting the frequency of jaundice by age group [14], which was also used in economic studies of hepatitis A vaccine in Argentina and Chile [28–31]. The sensitivity analysis showed the proportion of icteric cases impact the ICER; however, even with a reduction of 50% of the base case values, universal vaccination remained a cost-saving strategy in the society perspective and was cost-effective in the health system perspective. A reduction of 75% over the base case makes universal vaccination not cost-effective from the health system perspective, although cost-effective in the North and still cost-saving in South and in the whole country from the society perspective. Only with extreme values (90% reduction over the base case), very unlikely, universal vaccination becomes not cost-effective from the society perspective (Table 4).

Hepatitis A is mainly treated in outpatient settings. Data on health services utilization and procedures of the outpatients care are quite scarce in Brazil. The ambulatory (SIA/SUS) and primary health care (SIAB/SUS) public health information systems do not provide data according to diagnosis. We established a “minimum care package” of outpatients care and costs, a decision which may have underestimated these costs, particularly in the specialized clinics and in the private sector. Sensitivity analysis showed that outpatient costs impact the ICER. With a 50% reduction in outpatient costs, the program continued cost-saving from society perspective, and cost-effective from health system perspective. Only with reduction of 75% of outpatient costs (very unlikely) the intervention became not cost effective in the health system perspective, although it became cost-effective in North and remained cost-saving in South and National from society perspective (Table 4).

The vaccine cost also has great impact on the ICER. The price of R$24.35 (US$10.45) per dose (50% higher of our base case), paid by the Ministry of Health in 2010, makes the universal childhood vaccination program cost-effective in North from the perspective of the health system, but it remained a cost-saving strategy in the perspective of the Society; and in South and National in both perspectives.

Waning immunity has not been considered in our model. There is evidence that the inactivated hepatitis A vaccine provides protection for up to 14 years, as defined by currently accepted correlates of protection [32]. Mathematical models suggested duration of protection for 50 years, with 95% of vaccinees keeping protection for more than 35 years, if the cut-off of protection is established at 10 mIU/ml, or for more than 30 years if the cut-off is established at 20 mIU/ml [33]. This is longer than the temporal horizon of our study (24 years). Furthermore, herd protection has been demonstrated for hepatitis A vaccination, with reduction in

Table 4
Sensitivity analysis by perspective and area analyzed.

Sensitivity analysis	Cost per life year saved[a]					
	North		South		National All regions	
	Health care system perspective	Society perspective	Health care system perspective	Society perspective	Health care system perspective	Society perspective
Univariate						
Reduction in the incidence of hepatitis A infection due to improvement in sanitary conditions						
Low (−1% per year)	<0	<0	<0	<0	<0	<0
Base case	<0	<0	<0	<0	<0	<0
% of symptomatic infection						
Extremely low (−90%)	85,294	68,350	82,479	48,012	86,689	62,354
Much lower (−80%)	72,938	30,779	62,122	<0	70,342	12,667
Very low (−75%)	66,761	11,993	51,943	<0	62,168	<0
Low (−50%)	35,872	<0	1050	<0	21,299	<0
Base case	<0	<0	<0	<0	<0	<0
% of hospitalization[b]						
Very low (−75%)	<0	<0	<0	<0	<0	<0
Low (−50%)	<0	<0	<0	<0	<0	<0
Base case	<0	<0	<0	<0	<0	<0
% of transplantation[b]						
Very low (−75%)	<0	<0	<0	<0	<0	<0
Low (−50%)	<0	<0	<0	<0	<0	<0
Base case	<0	<0	<0	<0	<0	<0
Vaccine price per dose						
Base case	<0	<0	<0	<0	<0	<0
R$24.35[c] (+50%)	12,543	<0	<0	<0	<0	<0
Very high (+100%)	61,250	<0	26,882	<0	31,385	<0
Extremely high (+150%)	148,405	<0	118,395	<0	123,209	<0
Outpatient costs						
Very low (−75%)	66,761	11,993	60,970	<0	62,168	<0
Low (−50%)	35,872	<0	19,103	<0	21,299	<0
Base case	<0	<0	<0	<0	<0	<0
Discount rate[d]						
Base case 0%	<0	<0	<0	<0	<0	<0
3%	<0	<0	<0	<0	<0	<0
5%	<0	<0	<0	<0	<0	<0
10%	<0	<0	<0	<0	<0	<0
Bivariate						
Effective coverage[e]						
Low (75%)	<0	<0	<0	<0	<0	<0
Base case (85%)	<0	<0	<0	<0	<0	<0
High (90%)	<0	<0	<0	<0	<0	<0
Costs of transplantation and follow-up post-transplantation						
Low (−50%)	<0	<0	<0	<0	<0	<0
Base case	<0	<0	<0	<0	<0	<0

[a] In 2008 Brazilian currency (real) R$2.33 = US$1.
[b] The rates of all age groups are varied simultaneously.
[c] Current vaccine price.
[d] Discount of costs and benefits.
[e] Effective coverage is the product of multiplication of two factors (vaccine efficacy and vaccine coverage). Low: 75% (84% and 90%). Base case: 85% (90% and 94%). High: 90% (95% and 95%).

disease incidence in non-vaccinated groups after the introduction of universal vaccination in children [2,5]. Even if the antibodies decreases, herd protection may keep transmission of hepatitis A under control. However, there is no data in the literature on the impact of hepatitis A universal vaccination program for such long time. The oldest programs have been implemented in the late 1990s [2,5]. In case of decline of protection over time, a shift in the age of new infections to older age groups, which may have more severe illness, may occur. In other economic studies, varying the rates of waning immunity in the sensitivity analysis had no impact on cost-effectiveness ratio [34].

The hepatitis A vaccine is commercially available in single-dose vials, which reduces waste, but it occupies more space in the cold chain than vaccines presented in multi-dose vials. Additionally, due to recent introductions into the national childhood immunization schedule, of the 10-valent pneumococcal conjugate and meningococcal C conjugate vaccines, both also available in single dose vials, the cold chain is currently already under great stress. The introduction of a new vaccine in the program requires a preliminary assessment of the cold chain capacity and the required adjustments and investments, which were not considered in our analyses.

The first dose of the vaccine was assumed to be administered simultaneously to other vaccines already incorporated by the National Immunization Program and would not require a new visit to the Vaccination Clinic, but the second dose would require a specific visit. The transportation cost to the health center to receive the second dose of the vaccine was considered when the analysis is carried out from the society perspective. Indirect costs related to the vaccination process were not included in the analyses considering that the Brazilian Ministry of Health provides standing orders for routine children vaccination, which is administered by nurses in health centers near the families' home; a pre-vaccination medical visit is not required and not usual; and the vaccination process is quick. Therefore, parents do not usually lose a workday to vaccinate their children.

Most economic studies of hepatitis A vaccine showed favorable cost-effectiveness results. Universal childhood vaccination against hepatitis A was shown a cost-saving strategy in areas of higher incidence of disease in Argentina [29] and USA [35,36]. In China, the immunization program has proved to be cost-saving in areas of lowest, low, intermediate and high endemicity of hepatitis A [37].

In other contexts, the parameters that mostly influenced the results of economic evaluations were administration cost and cost per vaccine dose, followed by the incidence of disease and medical costs, as in this study.

The regional analysis showed some differences in the impact of a universal hepatitis A vaccination program in Brazil. Greater reduction in the number of icteric cases and deaths are expected in the "North" area. The results of the South model were more robust than the North and national models.

Although the producers of the hepatitis A vaccine recommend two-dose schedule to ensure long-term efficacy, immunogenicity studies have shown that >90% of children have protective antibody titers after a single dose. There is evidence of seroprotection for up to 10 years after a single dose of hepatitis A vaccine [38]. Argentina observed a significant reduction in the incidence (80%) and hospitalizations (88%) for hepatitis A after introducing a single dose of the vaccine in routine immunization of 12-month children with high vaccination coverage (95%) [5,6]. Six years after implementing the single-dose program, no cases of hepatitis A have been observed in vaccinees, although hepatitis A continued occurring in non-vaccinated persons [38]. The WHO Strategic Advisory Group of Experts has recently concluded that National Immunization Programs may consider the introduction of a single-dose of hepatitis A in their immunization schedules [39]. A single-dose schedule saves costs with the vaccine, being attractive particularly for countries with economic constraints.

Regardless of schedule used, the incorporation of hepatitis A vaccine into the routine must be accompanied by intensification of surveillance and monitoring program impact.

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Appendix A.

We have implemented an age- and time-dependent compartmental model, dividing the population into four compartments: susceptible, infected/infectious, recovered from natural infection, and vaccinated individuals (SIRV model). A full description of the SIRV model and the parameters estimation procedure may be found elsewhere [11]. We briefly describe below the main steps of the modeling approach.

From the model, we have estimated the force of infection, $\lambda(a, t)$, the per capita rate at which individuals with age a acquire infection at time t. The calculation of the force of infection depends on a contact rate function $\beta(a, a')$, given by the number of potentially infectious contacts a person with age between a and $a + da$ makes with all persons with age between a' and $a' + da'$ per unit time.

We assumed a constant vaccination rate, related to a given proportion p of the population covered by the routine immunization program, delivered between 1 and 2 years of age.

An estimate of the function $S^+(a)$, the proportion of seropositive individuals for hepatitis A with age a, resulted from fitting the serological data to [40]:

$$S^+(a) = 1 - \exp\left\{\frac{k_1}{k_2^2}[(k_2 a + 1)e^{-k_2 a} - 1]\right\}, \quad (1)$$

where k_1 and k_2 are the fitting parameters, estimated by the maximum likelihood method for the North and South areas.

In the absence of vaccination, the force of infection $\lambda_0(a)$ was estimated from the seroprevalence data by the equation below [11]:

$$\lambda_0(a) = k_1 a e^{-k_2 a}. \quad (2)$$

For the contact function, we have chosen the following form [10]:

$$\beta(a, a') = b_1(a + a')e^{-b_2(a+a')}e^{-(a'-a)^2/[b_3+b_4(a+a')]^2}e^{\mu a}, \quad (3)$$

where μ is the mortality rate, and b_1, b_2, b_3 and b_4 are parameters to be determined.

The parameters of the contact function $\beta(a, a')$ were estimated so that the resulting force of infection $\lambda(a)$, in the absence of vaccination, agreed with $\lambda_0(a)$ given by Eq. (2). A more detailed description of the numerical solution may be found in another publication [10].

The mortality rate was estimated as the inverse of the life expectancy at birth, taken as $\mu = 0.0135\,\mathrm{yr}^{-1}$ (life expectancy of 74 years) and $\mu = 0.0139\,\mathrm{yr}^{-1}$ (life expectancy of 72 years) for the South and North areas, respectively. The recovery rate γ was taken to be $8.1\,\mathrm{yr}^{-1}$, corresponding to an infectious period of 45 days.

The proportion of new infections, $\Psi(a, t)$, was estimated by

$$\Psi(a, t) = r(a, t) - r(a - \Delta t, t - \Delta t) \quad (4)$$

where $r(a, t)$ is the proportion of recovered individuals with age a at time t, and Δt is a time interval. In Eq. (4), we assumed that the increment in the proportion of recovered individuals, $r(a, t)$, during a time interval Δt is directly related to the proportion of new infections.

References

[1] Hepatitis A vaccines. Wkly Epidemiol Rec 2000;75:38–44.
[2] Chodick G, Heymann AD, Ashkenazi S, Kokia E, Shalev V. Long-term trends in hepatitis A incidence following the inclusion of Hepatitis A vaccine in the routine nationwide immunization program. J Viral Hepat 2008;15(Suppl. 2):62–5.
[3] Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. JAMA 2005;294:202–10.
[4] Vogt TM, Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. J Infect Dis 2008;197:1282–8.
[5] Hendrickx G, Van Herck K, Vorsters A, Wiersma S, Shapiro C, Andrus JK, et al. Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology. J Viral Hepat 2008;15(Suppl. 2):1–15.
[6] Vacchino MN. Incidence of hepatitis A in Argentina after vaccination. J Viral Hepat 2008;15(Suppl. 2):47–50.
[7] de Alencar Ximenes RA, Martelli CM, Merchán-Hamann E, Montarroyos UR, Braga MC, de Lima ML, et al. Multilevel analysis of hepatitis A infection in children and adolescents: a household survey in the Northeast and Central-west regions of Brazil. Int J Epidemiol 2008;37:852–61.
[8] Ximenes RA, Pereira LM, Martelli CM, Merchán-Hamann E, Stein AT, Figueiredo GM, et al. Methodology of a nationwide cross-sectional survey of prevalence and epidemiological patterns of hepatitis A, B and C infection in Brazil. Cad Saude Publ 2010;26:1693–704.
[9] Ministério da Saúde Estudo de prevalência de base populacional das infecções pelos vírus das hepatites A, B e C nas capitais do Brasil; 2010.
[10] Amaku M, Coutinho FA, Azevedo RS, Burattini MN, Lopez LF, Massad E. Vaccination against rubella: analysis of the temporal evolution of the age-dependent force of infection and the effects of different contact patterns. Phys Rev E Stat Nonlin Soft Matter Phys 2003;67:051907.

[11] Valentim J, Sartori AM, de Soárez PC, Amaku M, Azevedo RS, Novaes HM. Cost-effectiveness analysis of universal childhood vaccination against varicella in Brazil. Vaccine 2008;26:6281–91.
[12] IBGE (Instituto Brasileiro de Geografia); 2008. Available from: http://www.ibge.gov.br/english/#sub_populacao
[13] Diretrizes Metodológicas: estudos de avaliação econômica de tecnologias em saúde. Brasília; 2009. Available from: http://www.ispor.org/PEguidelines/source/Economic-Evaluation-Guidelines-in-Brazil-Final-Version-2009.pdf
[14] Armstrong GL, Hepatitis Bell BP. A virus infections in the United States: model-based estimates and implications for childhood immunization. Pediatrics 2002;109:839–45.
[15] Instituto Brasileiro de Geografia. Pesquisa Nacional de Amostra por Domicílios; 2008. Available from: http://www.ibge.gov.br/home/estatistica/populacao/panorama_saude_brasil_2003_2008/PNAD_2008_saude.pdf[05.01.12].
[16] Ciocca M, Moreira-Silva SF, Alegría S, Galoppo MC, Ruttiman R, Porta G, et al. Hepatitis A as an etiologic agent of acute liver failure in Latin America. Pediatr Infect Dis J 2007;26:711–5.
[17] SINAN. Sistema de Informação de Agravos de Notificação; 2007–2009. Available from: http://dtr2004.saude.gov.br/sinanweb/index.php
[18] Pereira L, Coria S, Monteiro F, Scandiuzzi M. Transplantation system in the State of São Paulo: history, results, and future prospects. Rev Admin Saúde 2006;8:7–24.
[19] WHO. Projected vaccine wastage. http://www.who.int/immunization_delivery/systems_policy/logistics_projected_wastage/en/index.html [accessed in 03.06.10].
[20] Podewils LJ, Antil L, Hummelman E, Bresee J, Parashar UD, Rheingans R. Projected cost-effectiveness of rotavirus vaccination for children in Asia. J Infect Dis 2005;192(Suppl. 1):S133–45.
[21] Das A. An economic analysis of different strategies of immunization against hepatitis A virus in developed countries. Hepatology 1999;29:548–52.
[22] SIGTAP. Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS; 2008. Available from: http://sigtap.datasus.gov.br/tabela-unificada/app/sec/inicio.jsp
[23] Berge JJ, Drennan DP, Jacobs RJ, Jakins A, Meyerhoff AS, Stubblefield W, et al. The cost of hepatitis A infections in American adolescents and adults in 1997. Hepatology 2000;31:469–73.
[24] de Soárez PC, Valentim J, Sartori AM, Novaes HM. Cost-effectiveness analysis of routine rotavirus vaccination in Brazil. Rev Panam Salud Publ 2008;23:221–30.
[25] Sartori AM, de Soárez PC, Novaes HM. Cost-effectiveness of introducing the 10-valent pneumococcal conjugate vaccine into the universal immunisation of infants in Brazil. J Epidemiol Community Health 2012;66:210–7.
[26] de Soarez PC, Sartori AM, de Andrade Lagoa Nóbrega L, Itria A, Novaes HM. Cost-effectiveness analysis of a universal infant immunization program with meningococcal C conjugate vaccine in Brazil. Value Health 2011;14:1019–27.
[27] IBGE (Instituto Brasileiro de Geografia e Estatistica). Pesquisa Nacional de Saneamento Básico; 2008. Available from: http://www.ibge.gov.br/home/presidencia/noticias/noticia_visualiza.php?id_noticia=1691&id_pagina=1 [22.09.12].
[28] Lopez E, Debbag R, Coudeville L, Baron-Papillon F, Armoni J. The cost-effectiveness of universal vaccination of children against hepatitis A in Argentina: results of a dynamic health-economic analysis. J Gastroenterol 2007;42:152–60.
[29] Ellis A, Rüttimann RW, Jacobs RJ, Meyerhoff AS, Innis BL. Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted. Rev Panam Salud Publ 2007;21:345–56.
[30] Valenzuela MT, Jacobs RJ, Arteaga O, Navarrete MS, Meyerhoff AS, Innis BL. Cost-effectiveness of universal childhood hepatitis A vaccination in Chile. Vaccine 2005;23:4110–9.
[31] Quezada A, Baron-Papillon F, Coudeville L, Maggi L. Universal vaccination of children against hepatitis A in Chile: a cost-effectiveness study. Rev Panam Salud Publ 2008;23:303–12.
[32] Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines. A systematic review. Vaccine 2012, http://dx.doi.org/10.1016/j.vaccine.2012.04.104.
[33] Bovier PA, Bock J, Ebengo TF, Frosner G, Glaus J, Herzog C, et al. Predicted 30-year protection after vaccination with an aluminum-free virosomal hepatitis A vaccine. J Med Virol 2010;82:1629–34.
[34] De Soarez PC, Sartori AM, Santos A, Itria A, Novaes HM, Martelli CM. Contributions from the systematic review of economic evaluations: the case of childhood hepatitis A vaccination in Brazil. Cad Saude Publ 2012;28:211–28.
[35] Jacobs RJ, Greenberg DP, Koff RS, Saab S, Meyerhoff AS. Regional variation in the cost effectiveness of childhood hepatitis A immunization. Pediatr Infect Dis J 2003;22:904–14.
[36] Rein DB, Hicks KA, Wirth KE, Billah K, Finelli L, Fiore AE, et al. Cost-effectiveness of routine childhood vaccination for hepatitis A in the United States. Pediatrics 2007;119:e12–21.
[37] Zhuang GH, Pan XJ, Wang XL. A cost-effectiveness analysis of universal childhood hepatitis A vaccination in China. Vaccine 2008;26:4608–16.
[38] WHO position paper on hepatitis A vaccines—June 2012. Wkly Epidemiol Rec 2012;87:176–261.
[39] Meeting of the Strategic Advisory Group of Experts on immunization, April 2012—conclusions and recommendations. Wkly Epidemiol Rec 2012;87:201–16.
[40] de Almeida LM, Amaku M, Azevedo RS, Cairncross S, Massad E. The intensity of transmission of hepatitis A and heterogeneities in socio-environmental risk factors in Rio de Janeiro, Brazil. Trans R Soc Trop Med Hyg 2002;96:605–10.