Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted

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ABSTRACT

Objectives. *To investigate the cost-effectiveness of childhood vaccination against hepatitis A in the five geographic regions of Argentina, and to determine whether adding a second dose to the current one-dose schedule would provide health gains justifying its added cost.*

Methods. *A Markov model was used to consider four immunization options for the 2005 birth cohort: (1) no vaccination; (2) vaccination at 12 months of age, (3) vaccinations at 12 and 72 months of age; or (4) vaccinations at 12 and 18 months of age. Hepatitis A costs and consequences were predicted over 50 years. The cost-effectiveness of first and second vaccine doses was assessed through a range of vaccine prices and assumptions regarding the duration of vaccine protection. Costs and health gains (measured in quality-adjusted life years) were adjusted to present values using a 3% annual discount rate.*

Results. *The one-dose vaccination policy is predicted to reduce each birth cohort member's 50-year probability of overt hepatitis A from 7.2% to 4.1%. A second dose would reduce the probability to between 2.0% and 2.2%. Vaccination at 12 months of age, at 12 and 72 months, or at 12 and 18 months would reduce cases among personal contacts by 82%, 87%, and 92%, respectively. The first vaccine dose would meet accepted standards of cost-effectiveness in each region, and reduce costs in the Northeast, Central, and South regions. Adding a second dose at age 18 months would be cost-effective in each region, and further reduce costs in the Cuyo region. If the duration of protection with one dose is less than anticipated, the second dose would be more cost-effective.*

Conclusions. *Greater health gains are derived from the first than second hepatitis A vaccine dose. However, this analysis supports the cost-effectiveness of providing both first and second doses to Argentina's children.*

Key words Costs and cost analysis, hepatitis A, immunization schedule, quality-adjusted life years, vaccination, Argentina.

Hepatitis A is an important public health problem in Argentina, being a leading cause of acute liver failure and liver transplants in children (1, 2). A shortage of organs prevents transplantation for all candidates and requires use of liver reduction techniques, split livers, and related donors (3). Among children obtaining a graft, 29% die within four years (3). While few hep-

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atitis A cases require transplantation, milder cases have important implications as well. Persons infected after early childhood often experience extended morbidity (4, 5). Jaundice, fever, malaise, anorexia, nausea, and abdominal discomfort are common. Symptoms typically last for a few weeks, but may persist for several months (5, 6). Infected adults miss substantial time from employment (5). A biphasic form of hepatitis A, in which symptoms reappear after apparent recovery, may be more common in Argentina (6).

Hepatitis A infection affords lifelong immunity (7). In hyper-endemic areas, most individuals obtain natural immunity early in life without clinical illness. Thus, vaccine recommendations developed for lower endemicity regions are inappropriate (8). Hepatitis A endemicity is declining in Argentina, as in much of Latin America (9, 10). Seroprevalence among children 11 to 15 years old is 54% (9), so by adolescence, nearly half the population lacks immunity from a common disease that causes substantial medical and work loss costs (5, 11). Yet outbreaks among children still cause horrific results. In one series of 191 infected children, 20 were hospitalized, 4 developed acute liver failure, and 3 died (12).

Immunization with hepatitis A vaccine is safe and effective (13). Kinetic models of antibody decline suggest vaccine-induced immunity will persist for decades after a two-dose series (14, 15). Childhood vaccination is cost-effective in many (11, 16–20) but not all countries (8, 21). Cost-effectiveness is largely determined by the proportion of children with natural immunity and the ratio of vaccination-to-illness costs. Illness costs depend mainly on the age distribution of cases, hospitalization and liver transplant rates, medical prices, and local wages.

Argentina's Ministry of Health recently implemented universal hepatitis A vaccination with a single dose at 12 months of age. An expert panel convened by the Ministry will review disease surveillance data before recommending whether a second dose should be incorporated into the immunization schedule (22). Because hepatitis A incidence varies among Argentina's geographic regions, the cost-effectiveness of vaccination may also vary. The concern with one-dose vaccination is that long-term immunity will not be conveyed, and the average age of acquisition may be shifted to adulthood. Since hepatitis A is more severe in older individuals (4, 5), an even greater disease burden may result.

This analysis was undertaken to assess the cost-effectiveness of one- and two-dose childhood hepatitis A vaccination schedules in each of Argentina's five geographic regions. Regional estimates of health outcomes (e.g., hepatitis A cases, hepatitis A deaths) were summed to develop national estimates. Because the duration of vaccine protection (particularly with a single dose) is speculative, and the vaccine's price may change over time, these parameters were varied in sensitivity analysis.

METHODS

Four immunization options were assessed: (1) no hepatitis A vaccination; (2) hepatitis A vaccination at age 12 months only; (3) hepatitis A vaccination at ages 12 and 72 months; and (4) hepatitis A vaccination at ages 12 and 18 months. As listed, these interventions are progressively more costly. Option 3 is less costly than option 4 because second dose coverage is presumed less, and second dose costs are more heavily discounted, being incurred years in the future. It was assumed empiric vaccination would be offered (i.e., no pre-screening for immunity), and there would be no catch-up vaccination of older children or adults.

A Markov model, previously described (11, 17), was used to predict hepatitis A outcomes with and without vaccination. Markov models can be powerful tools for economic evaluation, since they allow both costs and outcomes to be predicted over extended time periods (23). The model used in the current investigation considered a single birth cohort, i.e., children born during 2005 who would be eligible for vaccination in 2006. During each of their first 50 years of life, birth cohort members were allocated to one of four health states: (1) uninfected but susceptible to hepatitis A; (2) infected with hepatitis A; (3) immune to hepatitis A; or (4) deceased. The identical model structure was used to assess hepatitis A under a no-vaccination policy and with each immunization strategy. With immunization, vaccination costs and reduced infection risks corresponding to vaccine protection were considered. When infection was predicted, the risk of disease transmission to household and other personal contacts was modeled. Infected birth cohort members were excluded from further follow-up due to presumed lifelong immunity (7). Reference case parameter estimates, described below, were applied to the hepatitis A model. Region-specific estimates are provided in Table 1, while those common to all regions are shown in Table 2.

Reported rates of hepatitis A

The numbers of hepatitis A and unspecified hepatitis cases reported during 1995–2004 were obtained from Ministry of Health surveillance systems. Data were arrayed by age and geographic region, defined as follows: Northeast *(Nordeste)*, including Chaco, Corrientes, Formosa, and Misiones provinces; Central (*Centro*), including Buenos Aires City, Buenos Aires Province, Córdoba, Entre Ríos, and Santa Fe provinces; South (*Sur*), including Chubut, La Pampa, Neuquén, Río Negro, Santa Cruz, and Tierra del Fuego provinces; Cuyo, including La Rioja, Mendoza, San Juan, and San Luis provinces; and Northwest (*Noroeste*), including Catamarca, Jujuy, Salta, Santiago del Estero, and Tucumán provinces. Because 29% of hepatitis A and 60% of unspecified hepatitis case reports did not indicate patient age, they were assumed to have the identical age distributions as other cases from the region. Further, 93% of unspecified hepatitis cases age <15

TABLE 1. Parameter estimates for annual hepatitis A incidence, by age group, and daily wage rate in the five regions of Argentina

	Northeast	Central	South	Cuyo	Northwest
Reported hepatitis A incidence per 100 000 population[a]					
< 1 year	28.5	51.3	35.6	148.3	49.5
1 year	60.8	104.8	96.4	122.1	249.7
2–4 years	198.9	302.3	390.6	550.3	758.8
5–9 years	200.4	398.8	548.0	678.3	480.4
10–14 years	108.3	188.5	217.1	223.7	172.2
15–49 years	16.7	25.9	28.8	33.8	17.9
≥ 50 years	6.7	7.2	10.0	10.1	7.3
Hepatitis A infections per 100 000 population[b]					
< 1 year	407.0	733.2	508.4	2 118.8	707.8
1 year	868.2	1 496.5	1 377.3	1 744.9	3 567.4
2–4 years	2 841.5	4 318.3	5 580.3	7 861.5	10 839.6
5–9 years	541.6	1 077.8	1 481.1	1 833.2	1 298.3
10–14 years	152.5	265.5	305.8	315.0	242.5
15–49 years	22.1	34.2	38.0	44.6	23.6
≥ 50 years	7.8	8.4	11.7	11.7	8.5
Hepatitis A seroprevalence (% with immunity)[c]					
< 1 year	2%	2%	3%	10%	10%
1 year	4%	4%	6%	20%	20%
2–4 years	22%	22%	32%	72%	72%
5–9 years	28%	28%	40%	86%	86%
10–14 years	30%	30%	50%	92%	92%
15–49 years	40%	40%	60%	96%	96%
≥ 50 years	60%	60%	88%	98%	98%
Annual probability of hepatitis A infection among susceptible persons[d]					
< 1 year	0.42%	0.75%	0.52%	2.35%	0.79%
1 year	0.90%	1.56%	1.47%	2.18%	4.46%
2–4 years	3.64%	5.54%	8.21%	28.08%	38.71%
5–9 years	0.75%	1.50%	2.47%	13.09%	9.27%
10–14 years	0.22%	0.38%	0.61%	3.94%	3.03%
15–49 years	0.04%	0.06%	0.13%	1.12%	0.59%
≥ 50 years	0.02%	0.02%	0.10%	0.59%	0.43%
Secondary hepatitis A cases owing to household contact (per 100 index infections)[e]					
Index case < 6 years	19.8	19.8	11.2	2.7	2.7
Index case 6–11 years	25.2	25.2	15.2	4.0	4.0
Index case 12–17 years	23.3	23.3	12.7	2.3	2.3
Index case 18–29 years	12.8	12.8	7.2	1.7	1.7
Index case 30–39 years	15.3	15.3	9.4	2.6	2.6
Index case 40–49 years	15.3	15.3	8.7	1.9	1.9
Daily wage rate (US$)[f]	6.08	10.07	10.77	7.55	6.91

[a] Ministry of Health of Argentina and References items 1, 24, 25.
[b] Ministry of Health of Argentina and References items 1, 4, 17, 24, 25.
[c] References items 10, 26–32.
[d] Ministry of Health of Argentina and References items 1, 4, 10, 17, 24–32.
[e] References items 4, 10, 26–34.
[f] References item 39.

years (1) and 58% of older, unspecified hepatitis cases (24) were assumed to have hepatitis A rather than another form of hepatitis. Under these assumptions, 347 158 hepatitis A cases were reported over a 10-year period. Using 2001 census data as denominators (25), annual rates per 100 000 population were calculated (Table 1). Peak incidence occurred among 5- to 9-year-old children, with successively lower rates in older cohorts. Hepatitis A incidence was considerably higher in the Cuyo and Northwest regions, especially among younger children.

Hepatitis A infection rates

Hepatitis A infection is often asymptomatic, particularly in younger children. To estimate the number of infections from reported cases, two assumptions were made: (1) 100% of reported cases had overt illness; and (2) the proportions of infected individuals with overt illness are as follows: less than 5 years old, 7.0%; 5 to 9 years old, 37.0%; 10 to 14 years old, 71.0%; 15 to 49 years old, 75.7%; and 50 years and older, 86.0% (4, 17). Under these assumptions, peak infection rates occurred between ages 2 and 4 years in each region (Table 1). The rate among infants was highest in the Cuyo region, while rates among children 1 to 4 years old were highest in the Northwest region. There was considerably less regional variation among older persons.

Force of hepatitis A infection

Because no nationwide seroprevalence study has been conducted with a sample size adequate for stratification by region and age, hepatitis A seroprevalence was estimated based on reports from areas with below-average (26–28), average (10, 29, 30) and above-average (31, 32) infection rates, compared with Argentina as a whole. The Northeast and Central regions were considered to have below-average endemicity, the South region had average endemicity, and the Cuyo and Northwest regions had above-average endemicity. To estimate force of infection (the incidence of hepatitis A among susceptible persons) denominators were adjusted to reflect the number of susceptible persons by region and age (Table 2). There was wide variation by age and region, with the annual infection risk among susceptible persons ranging from 0.02% (residents of the

TABLE 2. Estimated hepatitis A hospitalization, liver transplant, and case fatality rates, by age, in the five regions of Argentina

Hepatitis A outcomes	0–14 years	15–29 years	30–39 years	> 39 years
Hospitalization rate (%)[a]	2.6%	3.6%	3.6%	3.6%
Liver transplant rate (%)[b]	0.027%	0.127%	0.127%	0.127%
Case-fatality rate (%)[c]	0.14%	0.18%	0.21%	0.36%

[a] Hospital Posadas and References item 11.
[b] References items 1, 36.
[c] References items 5, 17.

Northeast and Central regions ≥ 50 years old) to 38.71% (Northwest region residents 2–4 years old). Even without immunization, an improving health infrastructure may partially reduce hepatitis A rates. The 10-year incidence data provided by the Ministry of Health do not cover a long enough period to predict future trends, but 25-year data are available from Chile. There, rates declined 2.9% annually among persons ≤ 4 years old, were unchanged among those aged 5–9 years, and increased 1.7% and 1.2% annually among those aged 10–14 years and ≥ 15 years, respectively (11). Weighted for the age distribution of Argentina's hepatitis A cases, these trends suggest a 0.18% annual decline could be expected without vaccination. This trend was predicted to continue during the analytic period. Thus, 2.0%, 5.4%, and 8.6% reductions in forces of infection were predicted within 10, 30, and 50 years, respectively.

Hepatitis A transmission through personal contact

A United States model of intra-household transmission (33) was adapted to Argentina to account for larger household sizes (34), higher rates of hepatitis A immunity (10, 26–32), and more recent data on age-specific probabilities that hepatitis A infections will cause overt disease (4). The model predicts the number of secondary cases resulting from personal contact with individuals infected with hepatitis A based on household size, age distribution, and age-specific probabilities of having hepatitis A immunity. In the United States, each 100 hepatitis A infections are predicted to result in 13.7 to 23.1 other intra-household cases, depending on age of the index infection (33). In Argentina, predicted rates of secondary cases are similar in low endemicity areas, but considerably less in other regions due to higher rates of immunity among household contacts (Table 1). Lacking Argentina-specific data, United States information (35) was used to estimate total hepatitis A cases due to personal contact from intra-household cases. We considered cases attributed to "household" or "sexual" contact with hepatitis A patients to represent intra-household transmission, and cases attributed to day-care center exposure or "other" contact with hepatitis A patients to represent inter-household transmission. Based on these data, 2.37 inter-household cases were predicted to occur for each intra-household case attributed to an infected person less than 15 years of age. Corresponding estimates for infected persons 15–39 years old and 40 years and older were 1.39 and 1.31 inter-household cases for each intra-household transmission case, respectively. Assuming hepatitis A immunization would continue in subsequent years, we avoided overcounting the degree of disease reduction derived from vaccination by not modeling transmission from members of the 2005 birth cohort to younger persons.

Hepatitis A outcomes

Among hepatitis A cases aged < 15 years, the hospitalization rate was determined to be 2.6%, based on a review of Hospital Posadas (Buenos Aires) patient records. Because Argentina-specific data were unavailable, the hospitalization rate for older cases was assumed to be 38% greater, as seen in Chile (11). Between 2000 and 2004, 1 030 liver transplants were performed in Argentina, of which 22% were received by persons < 15 years of age (35). Thus, 226 and 804 transplants were received by persons ≤ 14 years and > 14 years, respectively. Assuming 20% of pediatric transplants and 5% of adult transplants are caused by hepatitis A (1), and comparing these numbers with hepatitis A cases occurring during the same period, the risk of liver transplant was estimated at 0.027% for cases ≤ 14 years, and 0.127% for cases >14 years. One-third of hepatitis A cases with acute liver failure were assumed to be unable to obtain a transplant (2, 3). Age-specific case-fatality rates, derived from an expert panel review of published literature (5, 17), ranged from 0.14% for cases age ≤ 14 years to 0.36% for cases > 39 years.

Hepatitis A costs

Hepatitis A vaccine acquisition was estimated to cost US$ 8.50 per dose (based on a median price quotation, PAHO Revolving Fund solicitation, 2005). Vaccine administration was estimated to cost US$ 0.40 per dose (11). Medical costs of hepatitis A patients were determined through review of Hospital Posadas (Buenos Aires) records and national cost data (37) as follows: outpatients, US$ 44; hospitalized patients without acute liver failure, US$ 160; hospitalized patients with acute liver failure but no transplant, US$ 2 400; hospitalized patients with acute liver failure receiving a liver transplant, US$ 54 650. For liver transplant patients, this estimate includes the lifetime cost of graft maintenance, which based on United States data will cost 105% as much as the transplant procedure itself (38). We assumed that 90% of cases in those over 17 years old would be employed, and miss an average of 28 days from paid

TABLE 3. Estimated hepatitis A vaccination coverage rates, by vaccine regimen, in the five regions of Argentina

Immunization coverage[a]	No vaccination	12 months only	12+72 months	12+18 months
No doses	100.0%	5.0%	1.5%	1.0%
First dose only	0.0%	95.0%	28.5%	19.0%
Second dose only	0.0%	0.0%	3.5%	4.0%
Both doses	0.0%	0.0%	66.5%	76.0%

[a] References item 40.

employment (5, 11, 16). The value of work loss related to hepatitis A was estimated by applying region-specific wage rates (39). Work-loss costs were not applied to younger cases, and we did not consider work loss experienced by parents caring for children with disease symptoms.

Immunization coverage and protective efficacy

Based on Argentina's experience with other recommended vaccines, coverage rates of 95%, 80%, and 70% were predicted for doses scheduled at ages 12 months, 18 months, and 72 months, respectively (40). The probabilities of receiving the first and second doses were assumed to be independent, leading to the coverage estimates reported in Table 3. For the reference case, 98% of children were assumed to develop immunity with one dose (41), but 1.62% were predicted to lose protection during each of years 1 through 10, and 2.67% were predicted to lose protection annually thereafter (42). Assumptions for two doses were that 99% of children would develop immunity (41), but 0.31% would lose protection during each of years 1 through 10, and 0.62% would lose protection annually thereafter (42). Panel A of Figure 1 depicts the proportion of the birth cohort with vaccine immunity under reference case assumptions.

Analytic methods

A cost-utility analysis was performed from the perspective of Argentina's society. Net vaccination costs were defined as those devoted to immunization minus future reductions in medical and work-loss costs. To estimate the number of quality-adjusted life years (QALYs) lost to hepatitis A, we considered each lost life-year to represent 1.0 QALY and each nonfatal hepatitis A case to represent 0.06 QALYs (43).[5] Costs and QALYs predicted to occur beyond the base year of the analysis (2006) were adjusted to present values, using a 3% annual discount rate (44).

Hepatitis A costs and outcomes were predicted under each vaccination option. Incremental costs and QALYs gained through a one-dose schedule were compared with a policy of no vaccination. The incremental costs and QALYs gained through each of the two-dose schedules were compared with the one-dose vaccination policy. In sensitivity analysis, vaccine prices and the presumed duration of vaccine protection were varied simultaneously. Because vaccine acquisition costs may change annually, we considered possible 10% and 20% price increases. Because few data are available to predict the duration of vaccine protection with a single dose, we considered the possibilities that immunity would wane at either 50% or 200% of the rates assumed in the reference case. The former assumption is depicted in panel B of Figure 1. With more sustained protection, the value of a single dose is greater, and the added value of a second dose (represented by differences between the curves) is less. The latter assumption is depicted in panel C of Figure 1. With less sustained protection, the value of a single dose is less, and the added value of a second dose is greater.

[5] For example, suppose the model indicated that in 2026, 200 nonfatal hepatitis A cases would occur with no vaccination and 50 nonfatal hepatitis A cases would occur with one-dose vaccination. The present value health gain is calculated as 150 (the number of cases prevented) multiplied by 0.06 (the number of QALYs gained by preventing each case) multiplied by 0.554 (the factor representing a 3% discount rate after 20 years), or 4.99 QALYs. Further, suppose that in 2026 the predicted number of hepatitis A fatalities among birth cohort members would decline from 0.35 to 0.10. The present value health gain is calculated as 0.25 (the number of fatalities prevented) multiplied by 56 (life expectancy at age 20 years) multiplied by 1 (QALYs assigned per life-year) multiplied by 0.554 (the factor representing a 3% discount rate after 20 years), or 7.76 QALYs. In this example, health gain attributed to one-dose vaccination in 2026 would be 4.99 QALYs plus 7.76 QALYs, or 12.75 QALYs.

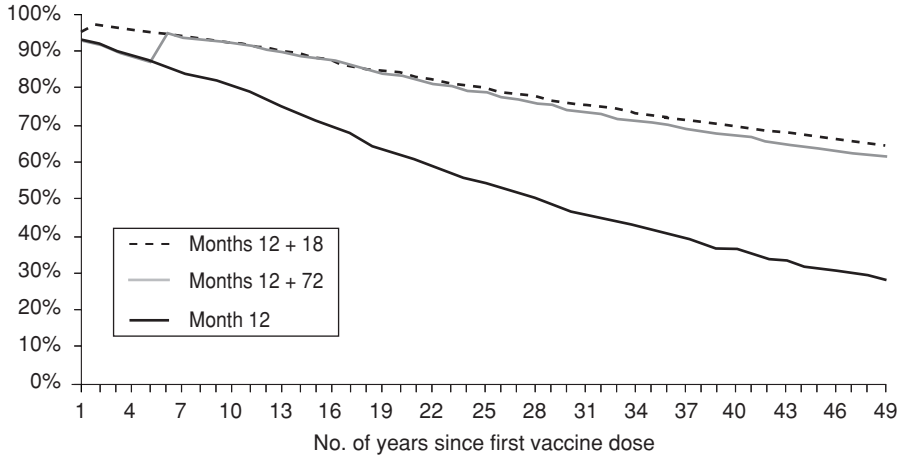
RESULTS

Hepatitis A rates among birth cohort members

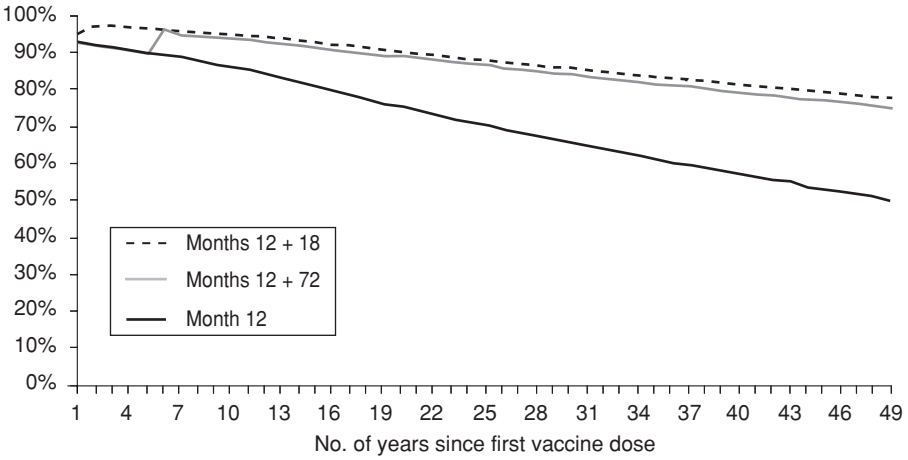
Without vaccination, our model predicts 48 493 members of the 2005 birth cohort will experience overt hepatitis A (Table 4), representing a 50-year incidence of 7.2%. Vaccination at age 12 months would reduce this number to 27 848, an incidence of 4.1%. Adding a second dose at age 72 months would nearly halve the incidence versus the one-dose schedule, to 2.2%. A second dose at age 18 months would reduce the incidence further, to 2.0%. The relative effectiveness of one- and two-dose schedules varies markedly among the regions. In the Northeast region, a single dose would be 82% as effective in reducing birth cohort cases as the two-dose 12- and 18-month schedule. Yet in Cuyo, a single dose would only be 4% as effective as the two-dose 12- and 18-month schedule. These differences reflect variation in forces of infection among the regions. Without vaccination, most children in the Cuyo and Northwest regions are infected during early childhood and thus face a low probability of symptoms. There, vaccination with a single dose will prevent infection of many birth cohort members but only delay infection for others, thus increasing the probability of symptoms. In the Northwest region a

FIGURE 1. Estimated duration of vaccine protective efficacy

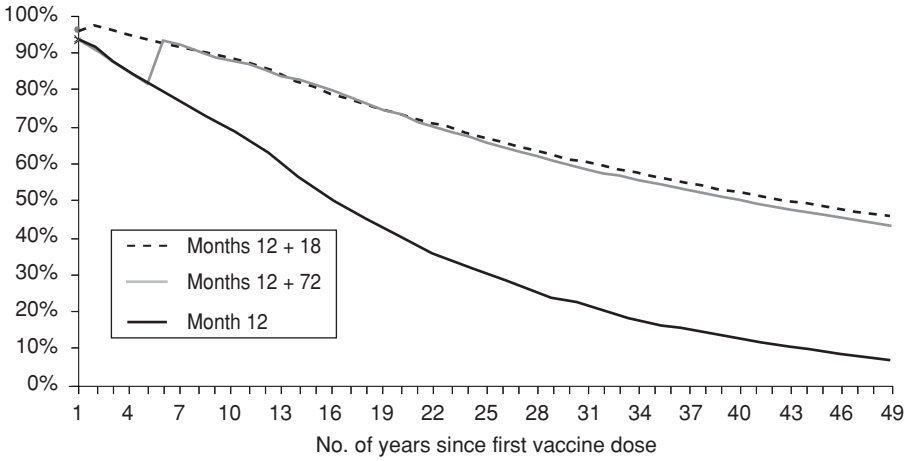
Panel A. Proportion of birth cohort members with vaccine immunity under reference case assumptions



Panel B. Proportion of birth cohort members with vaccine immunity assuming immunity wanes half as quickly as presumed in the reference case



Panel C. Proportion of birth cohort members with vaccine immunity assuming immunity wanes twice as quickly as presumed in the reference case



Note: Each panel presents the estimated proportion of the 2005 birth cohort with vaccine-induced protection. The X axis represents years elapsed since the first vaccine dose. Panel A presents reference case estimates. Panels B and C present estimates used in sensitivity analyses.

single dose will increase the median age of infection from 2 years to 7 years, and the median case age from 5 years to 17 years. Thus, while the number of infections will decline 69%, the number of cases would be reduced just 7%.

One consequence of delaying infection would be to increase the case-fatality rate. Without vaccination, 74.9 birth cohort member deaths from hepatitis A deaths are predicted from 48 493 cases, a rate of 1.5 per 1 000. With a one-dose vaccination schedule, 54.7 deaths are predicted from 27 848 cases, a rate of 2.0 per 1 000. In the Cuyo and Northwest regions, the one-dose vaccination schedule would increase numbers of hepatitis A deaths among birth cohort members by 29% and 22%, respectively. However, either two-dose regimen (vaccination at 12 and 72 months or 12 and 18 months) would reduce hepatitis A deaths among birth cohort members in each region. In terms of QALYs lost to hepatitis A by birth cohort members, one-dose vaccination would provide ≥ 70% reductions in the Northeast, Central, and South regions, with a second dose providing modest additional gains. In the Cuyo and Northwest regions, more QALYs would be gained from the second than first vaccine dose. Overall, 3 224 QALYs would be gained from one-dose vaccination. Another 1 121 to 1 344 QALYs would be gained by adding a second dose.

Hepatitis A rates among personal contacts

Due to differences among the regions in hepatitis A seroprevalence, there are important variations in the ratio of birth cohort member to personal contact cases. In the Central region, 3.2 cases are expected among personal contacts for each birth cohort member case, while in the Cuyo region, the ratio is only 0.5:1 (Table 4). Without vaccination, infections occurring among 2005 birth cohort members would be the source of 98 728 overt hepatitis A cases among their personal contacts. The effects of immunization on personal contact cases

TABLE 4. Hepatitis A outcomes in terms of hepatitis A cases, hepatitis A deaths, and quality-adjusted life years (QALYs) lost, for birth cohort and personal contacts under alternative vaccination options in the five regions of Argentina

Group/Outcome/Region(s)	No vaccination (no.)	Month 12 (no.)	Months 12+72 (no.)	Months 12+18 (no.)
Birth cohort				
Hepatitis A cases				
Northeast	2 710	770	407	339
Central	22 093	6 451	3 397	2 841
South	3 228	1 117	574	491
Cuyo	9 300	9 126	4 937	4 628
Northwest	11 162	10 384	5 570	5 031
All regions	48 493	27 848	14 885	13 330
Hepatitis A deaths				
Northeast	4.3	1.5	0.8	0.7
Central	34.4	12.1	6.4	5.5
South	5.2	2.2	1.1	1.0
Cuyo	14.4	18.6	10.4	10.0
Northwest	16.6	20.3	11.0	10.4
All regions	74.9	54.7	29.7	27.6
Lost QALYs (PV)[a]				
Northeast	305	71	40	31
Central	2 537	612	340	267
South	362	100	53	42
Cuyo	1 093	771	417	371
Northwest	1 408	927	510	426
All regions	5 705	2 481	1 360	1 137
Personal contacts				
Hepatitis A cases				
Northeast	8 828	1 393	1 069	660
Central	71 667	12 123	9 080	5 826
South	5 574	946	666	404
Cuyo	4 603	1 338	895	604
Northwest	8 056	2 062	1 510	849
All regions	98 728	17 862	13 220	8 343
Hepatitis A deaths				
Northeast	18.4	3.0	2.2	1.4
Central	149.4	25.8	18.9	12.3
South	11.1	1.9	1.3	0.8
Cuyo	8.0	2.4	1.6	1.1
Northwest	13.9	3.7	2.6	1.5
All regions	200.8	36.8	26.6	17.1
Lost QALYs (PV)[a]				
Northeast	1 223	188	150	92
Central	9 918	1 638	1 276	811
South	768	125	92	54
Cuyo	647	175	122	80
Northwest	1 159	276	209	113
All regions	13 715	2 402	1 849	1 150

[a] PV = present value.

are fairly consistent among the regions. Vaccination at 12 months, 12 and 72 months, or 12 and 18 months would reduce these secondary cases by 82%, 87%, and 92%, respectively. In each region, most of the reduction in secondary cases would be obtained with the one-dose schedule. A second dose at age 18 months would provide a greater additional reduction than a dose at age 72 months because: (a) coverage is presumed greater; and (b) vaccine protection between age 18 and 72 months, the period during which transmission is most common, is improved (Figure 1).

Considering the effect of childhood vaccination on fatal hepatitis A among personal contacts, one-dose vaccination would reduce the number of deaths from 200.8 to 36.8. A second dose at age 72 months would prevent an additional 10.2 deaths, while a second dose at age 18 months would prevent an additional 19.7 deaths. The effect of vaccination on QALYs lost by personal contacts follows a similar pattern. A single dose would prevent the loss of 11 313 QALYs, while a second dose would prevent the loss of an additional 553 to 1 252 QALYs.

Economic costs of immunization

Vaccinating the 2005 birth cohort would cost US$ 5.6 million under the one-dose, month 12 schedule (Table 5). In return, the present value of hepatitis A medical costs would be reduced by US$ 8.6 million, while the present value of hepatitis A work-loss costs would decline US$ 12.3 million. Thus, one-dose vaccination would save Argentina's society US$ 15.3 million while producing substantial health gains. However, the one-dose schedule would increase the present value of birth cohort member work-loss costs by 47%, the result of shifting disease acquisition from childhood to adulthood. On a regional basis, one-dose vaccination would reduce the present value of hepatitis A costs (including immunization expenses) in the Northeast, Central, and South regions, while increasing them by 15% in Cuyo and 5% in the Northwest region.

Nationally, the additional present value cost of a second vaccine dose would be US$ 3.5 million if scheduled for 72 months of age, or US$ 4.7 million if scheduled for 18 months of age. However, when reduced medical and work-loss costs are considered, the two-dose 12- and 18-month schedule would be slightly less costly. Compared with the one-dose schedule, vaccinations at the ages of 12 and18 months would reduce the present value of medical costs by US$ 1.5 million, and the present value of work-loss costs by US$ 1.8 million. Thus, the net additional present value cost of the second dose would total US$ 1.4 million.

TABLE 5. Hepatitis A costs for the birth cohort and for personal contacts under alternative vaccination options in the five regions of Argentina[a]

Region/type of cost	No vaccination (US$ 000)	Month 12 (US$ 000)	Months 12+72 (US$ 000)	Months 12+18 (US$ 000)
Northeast (birth cohort = 79 000)				
Vaccination	0	649	1 060	1 195
Medical—birth cohort	136	36	20	16
Medical—personal contacts	822	126	102	62
Work loss—birth cohort	34	21	10	10
Work loss—personal contacts	936	142	118	70
Total	1 928	974	1 308	1 352
Central (birth cohort = 405 000)				
Vaccination	0	3 325	5 432	6 124
Medical—birth cohort	1 111	306	165	135
Medical—personal contacts	6 651	1 097	862	546
Work loss—birth cohort	383	257	126	120
Work loss—personal contacts	12 481	2 034	1 644	1 026
Total	20 625	7 019	8 230	7 951
South (birth cohort = 39 000)				
Vaccination	0	320	523	590
Medical—birth cohort	162	52	27	23
Medical—personal contacts	489	79	59	35
Work loss—birth cohort	73	56	28	27
Work loss—personal contacts	894	142	109	63
Total	1 617	650	746	736
Cuyo (birth cohort = 56 000)				
Vaccination	0	460	751	847
Medical—birth cohort	477	425	229	212
Medical—personal contacts	343	94	66	43
Work loss—birth cohort	124	371	203	205
Work loss—personal contacts	299	80	58	37
Total	1 244	1 430	1 307	1 344
Northwest (birth cohort = 98 000)				
Vaccination	0	804	1 314	1 482
Medical—birth cohort	590	486	263	232
Medical—personal contacts	617	147	112	61
Work loss—birth cohort	91	333	175	179
Work loss—personal contacts	503	116	91	48
Total	1 801	1 887	1 955	2 002
Argentina total (birth cohort = 677 000)				
Vaccination	0	5 558	9 080	10 238
Medical—birth cohort	2 476	1 305	704	618
Medical—personal contacts	8 922	1 543	1 201	747
Work loss—birth cohort	705	1 038	542	541
Work loss—personal contacts	15 113	2 514	2 020	1 244
Total	27 216	11 958	13 547	13 388

[a] Costs are presented as present values (3% discount rate) in thousands of 2005 U.S. dollars.

Cost-effectiveness ratios

In each region, one-dose vaccination would provide health gains (as measured in QALYs) over no vaccination, and each two-dose schedule would provide health gains over the one-dose schedule. To examine costs per QALY, incremental cost-effectiveness ratios were calculated by region and vaccination policy (Table 6). Cost-effectiveness ratios for the first vaccine dose are < US$ 0 in the Northeast, Central, and South regions, indicating vaccination is both less expensive and more effective than no vaccination. In the Cuyo and Northwest regions, one-dose vaccination costs US$ 234 and US$ 63 per QALY gained, respectively. The cost-effectiveness of the second vaccine dose would range from < US$ 0 to US$ 4 829 per QALY gained. In each region, a second dose at age 18 months would be more cost-effective than a second dose at age 72 months. Nationally, a second dose at age 18 months would cost US$ 551 per added QALY gained. In Cuyo, adding a second dose at age 18 months would reduce costs, while in other regions it would cost between US$ 173 and US$ 2 772 per additional QALY gained.

Cost-effectiveness ratios are fairly stable throughout the range of alternative assumptions considered (Table 7). Importantly, the first vaccine dose would yield cost reduction even if the price were to increase 20%, vaccine protection were to wane at twice the reference case estimate, or both of these conditions were to occur. Under each scenario, more favorable cost-effectiveness is obtained with a second dose at age 18 months compared with age 72 months. If vaccine protection wanes more quickly, a second dose would prevent additional hepatitis A infections. Thus, at the reference case price of US$ 8.50 per dose, the incremental cost-effectiveness of a two-dose series would improve to US$ 159 per QALY gained. If a single vaccine dose provides more sustained protection, fewer hepatitis A infections would remain, and incremental cost-effectiveness would increase to US$ 1 038 per QALY gained.

DISCUSSION

Medical interventions are conventionally considered acceptably cost-effective if their net costs per QALY gained do not exceed an economy's annual per-capita gross domestic product (GDP) (45). In terms of purchasing power parity, Argentina's 2004 per-capita GDP was US$ 12 468, or US$ 3 915 in nominal dollars (46). Thus, medical interventions with cost-effectiveness ratios < US$ 3 915 may be considered appropriate uses of Argentina's public health expenditures. Our results indicate that providing the first and second doses of hepatitis A vaccine to Argentina's

TABLE 6. Incremental cost-effectiveness of first and second hepatitis A vaccine doses in Argentina, by region[a]

Region	First dose at age 12 months (US$)	Second dose at age 72 months (US$)	Second dose at age 18 months (US$)
Northeast	< 0	4 829	2 772
Central	< 0	1 908	796
South	< 0	1 204	673
Cuyo	234	< 0	< 0
Northwest	63	142	173
Argentina total	< 0	949	551

[a] Incremental cost-effectiveness is presented as the additional net cost (in 2005 U.S. dollars) per additional quality-adjusted life year gained.

TABLE 7. Incremental cost-effectiveness of first and second hepatitis A vaccine doses in Argentina under various scenarios; by duration of vaccine protection and vaccine price[a]

Long-term protection/vaccine price	First dose at age 12 months (US$)	Second dose at age 72 months (US$)	Second dose at age 18 months (US$)
Protection wanes at rates presumed by reference case			
Reference case vaccine price (US$ 8.50 per dose)	< 0	949	551
10% higher vaccine price (US$ 9.35 per dose)	< 0	1 149	722
20% higher vaccine price (US$ 10.20 per dose)	< 0	1 350	894
Protection wanes half as quickly as presumed by reference case			
Reference case vaccine price (US$ 8.50 per dose)	< 0	1 790	1 038
10% higher vaccine price (US$ 9.35 per dose)	< 0	2 072	1 258
20% higher vaccine price (US$ 10.20 per dose)	< 0	2 353	1 477
Protection wanes twice as quickly as presumed by reference case			
Reference case vaccine price (US$ 8.50 per dose)	< 0	394	159
10% higher vaccine price (US$ 9.35 per dose)	< 0	523	291
20% higher vaccine price (US$ 10.20 per dose)	< 0	682	423

[a] Incremental cost-effectiveness is presented as the additional net cost (in 2005 U.S. dollars) per additional quality-adjusted life year gained.

children meets this standard of cost-effectiveness. Compared with no vaccination, the one-dose schedule would save US$ 15.3 million and produce 14 537 QALYs, while the 12- and 18-month schedule would save US$ 13.8 million and produce 17 133 QALYs. The incremental cost-effectiveness of a second dose at age 18 months is US$ 551 per QALY gained, or 14% of the per-capita GDP.

Argentina recently enacted a one-dose hepatitis A vaccination schedule, and plans to review disease surveillance data before recommending whether, and at what age, a second dose should be added (22). This analysis indicates that a second dose would be more effective if scheduled at age 18 months. A second dose at either 18 or 72 months would provide roughly equivalent disease reduction among birth cohort members, with the modest advantage of the 12- and 18-month regimen resulting from a presumed higher coverage rate (40). However, the 12- and 18-month regimen would offer approximately twice the reduction in cases, deaths, and lost QALYs among personal contacts. This is entirely due to increased vaccine protection between ages 18 and 71 months, when viral transmission most commonly occurs (33).

Regional variation in vaccination cost-effectiveness is evident from this analysis, with the first dose providing greater health gains in lower endemicity regions and the second dose providing greater health gains in higher endemicity regions. The Central region would obtain US$ 5.09 in cost reduction for each US$ 1 invested in the first vaccine dose. There, vaccination would reduce costs even at a vaccine price of US$ 43 per dose. In Cuyo, the vaccine price would need to decline to US$ 4.75 before cost reduction would occur through a one-dose vaccination schedule. Variation in hepatitis A seroprevalence largely accounts for these differences. More adults in the Central region are susceptible to hepatitis A, and thus reduced infections in children would play a greater role in arresting disease transmission. A second vaccine dose will be most important in the Cuyo and Northwest regions. There, a one-dose vaccination schedule would actually increase the risk of fatal hepatitis A among birth cohort members by shifting the average age of infection to adulthood. Yet either two-dose schedule would reduce hepatitis A fatalities versus a policy of no vaccination.

Nationally, vaccination of the 2005 birth cohort would provide substantially greater health gains for today's adults than for birth cohort members. With one-dose vaccination, only 20% of the reduction in hepatitis A cases and 11% of the reduction in hepatitis A deaths would accrue to the birth cohort. With the two-dose 12- and 18-month schedule, the birth cohort would represent 28% and 20% of reduced cases and deaths, respectively. The health gains of personal contacts would occur quickly, while birth cohort member health gains would accrue slowly over time. In the Central region, 71% of the reduction in secondary cases from a 12- and 18-month schedule would occur within five

years, while only 33% of the reduction in birth cohort cases would be seen within this time period.

The cost-effectiveness estimates reported herein may be conservative for several reasons. First, we did not consider public health costs of hepatitis A outbreaks, including surveillance activities and immune globulin. Second, we were unable to quantify certain nonmedical costs, including transportation required for clinic visits and work time missed by parents nursing sick children. Third, we assumed hepatitis A case-fatality rates would range from 1.4 to 3.6 per 1 000, although higher rates have been reported (47). Fourth, we did not consider reduced life expectancy and quality of life for persons receiving hepatitis A liver transplants. Fifth, we assumed overt hepatitis A causes the loss of 0.06 QALYs per case (43), while other studies assume 0.08 to 0.22 QALYs are lost per case (48, 49). Sixth, we may have underestimated disease rates. Calculations were based on cases detected by Ministry of Health surveillance. More overt infections likely occurred but were either unrecognized, or recognized but not reported. In other countries, surveillance systems identify only 24% to 61% of hepatitis A cases (4, 11, 16). Finally, while we considered transmission from birth cohort members to their personal contacts, we did not consider further disease spread (i.e., from the personal contacts to other susceptible persons). This probably explains why the identical Markov model, applied in the United States (17), seems to have underestimated the degree of disease reduction (50).

While we considered the net costs of hepatitis A vaccination to Argentina's society, other perspectives may be of interest. Some economic analyses consider net costs to the health system, i.e., excluding effects on work absenteeism. In the United States (17) and Chile (11), health system costs of a two-dose childhood hepatitis A schedule are US$ 9 100 and US$ 281 per QALY gained, respectively. Our model indicates that in Argentina, the one-dose, 12-month schedule would cost the health system < US$ 0 per QALY gained, while the two-dose 12- and 18-month schedule would cost US$ 12 per QALY gained. To our knowledge, only in India (8) and Thailand (21) has childhood hepatitis A vaccination been found to have an unacceptably high cost from the health system perspective. Another perspective is gained by calculating the number of vaccine doses needed to achieve a specific health improvement. In Argentina, one hepatitis death would be averted for each 3 500 to 5 100 vaccine doses, depending on the vaccination schedule. Prior studies using the identical Markov model provide comparative information. In Chile, 7 100 vaccine doses are required to prevent one hepatitis A death (11), while in the United States, 39 900 doses are required (17). Since Argentina is the only country to implement childhood hepatitis A vaccination with a single dose, it is reasonable to consider whether the amount saved by withholding the second dose is worth the projected health consequences. In the reference case, savings of US$ 1.4 million come at the cost of 47 additional hepatitis A deaths.

The cost-effectiveness of childhood hepatitis A vaccination, and in particular the incremental cost-effectiveness of the second dose, is strongly influenced by the duration of vaccine protection. The World Health Organization calls for two vaccine doses administered 6 to 18 months apart when childhood immunization is recommended (51). Citing long-term antibody persistence and evidence that immune memory persists after loss of detectable antibody, an expert panel concludes there is no evidence to support booster vaccination in healthy individuals after a two-dose series (52). The same panel calls for studies exploring long-term protection after a single dose, concluding it is currently not established (52). Our reference case assumptions regarding duration of protection are based on another expert panel's opinion (42). Because these estimates are speculative, sensitivity analyses were conducted with wide variation in reference case assumptions. Under the "best case" scenario, 76% of the birth cohort would remain protected for 20 years after a single dose, and 52% would be protected after 50 years. Under the "worst case" scenario, only 41% and 8% would be protected after 20 and 50 years, respectively. While results are moderately affected by changes in this important parameter, conclusions are not. The cost-effectiveness of a second vaccine dose at age 18 months ranges from US$ 159 to US$ 1 038 per QALY gained, or from 4% to 27% of Argentina's per-capita GDP. Other cost-effectiveness assessments of hepatitis A vaccination have made more pessimistic assumptions regarding duration of protection (17, 49). Had they been used in the current analysis, second dose cost-effectiveness would appear substantially improved.

Childhood vaccines typically prevent disease that would otherwise occur in the children vaccinated. The current analysis indicates that the greatest beneficiaries of childhood hepatitis A in Argentina will be today's adults. However, in the higher endemicity regions of Argentina a one-dose vaccination schedule is predicted to increase the risk of fatal hepatitis A among birth cohort members by shifting the age of disease acquisition to adulthood. This unintended result would not occur for decades. It would therefore present an important problem in terms of reinitiating vaccination in susceptible adults. Both one- and two-dose vaccination schedules would reduce morbidity and mortality and quickly pay for themselves through reduced medical and work-loss costs. Importantly, the addition of a second dose would easily meet accepted standards of cost-effectiveness. In summary, this analysis supports the expansion of Argentina's hepatitis A vaccination program, preferably with the two-dose 12- and 18- month schedule.

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RESUMEN

Efectividad en función del costo de la vacunación infantil contra la hepatitis A en Argentina: se justifica una segunda dosis

Objetivos. Investigar la efectividad en función del costo de la vacunación infantil contra la hepatitis A en las cinco regiones de Argentina y determinar si la adición de una segunda dosis al esquema actual de una dosis aumentaría los beneficios a la salud y si estos justificarían el costo adicional.

Métodos. Se empleó el modelo de Markov para valorar cuatro opciones de vacunación para la cohorte nacida en el año 2005: 1) no vacunar; 2) vacunar a los 12 meses de edad; 3) vacunar a los 12 y a los 72 meses; y 4) vacunar a los 12 y a los 18 meses de edad. Se estimaron el costo y las consecuencias de la enfermedad a 50 años. La efectividad en función del costo de la primera y la segunda dosis de la vacuna se calculó a partir de varios precios de la vacuna e hipótesis acerca de la duración de la protección. Los costos y los beneficios para la salud (medidos en años de vida ajustados por la calidad de vida) se ajustaron por los valores actuales utilizando una tasa de descuento anual de 3%.

Resultados. Se estima que la política de vacunación con una dosis reduciría la probabilidad de cada miembro de la cohorte de padecer hepatitis A sintomática en 50 años de 7,2% a 4,1%. Una segunda dosis reduciría esa probabilidad a 2,0%-2,2%. La vacunación a los 12 meses de edad, a los 12 y a los 72 meses, o a los 12 y a los 18 meses reduciría el número de casos entre los contactos personales en 82%, 87% y 92%, respectivamente. La primera dosis de la vacuna satisfaría los estándares aceptados de efectividad en función del costo en todas las regiones del país y reduciría los costos en las regiones Nordeste, Central y Sur. La aplicación de una segunda dosis a los 18 meses resultaría efectiva en función del costo en todas las regiones y reduciría adicionalmente los costos en la región de Cuyo. Si la duración de la protección con una dosis fuera menor de la esperada, la segunda dosis tendría una mayor efectividad en función del costo.

Conclusiones. La primera dosis de la vacuna contra la hepatitis A genera mayores beneficios a la salud que la segunda. Sin embargo, este análisis sustenta la efectividad en función del costo de aplicar ambas dosis a los niños en Argentina.

Palabras clave Costos y análisis de costo, hepatitis A, esquema de inmunización, años de vida ajustados por calidad de vida, vacunación, Argentina.