Economic impact of pneumococcal conjugate vaccination in Brazil, Chile, and Uruguay

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ABSTRACT

Objectives. *To evaluate the economic impact of vaccination with the pneumococcal 7-valent conjugate vaccine (PCV7) in Brazil, Chile, and Uruguay.*

Methods. *A decision analytic model was constructed to compare pneumococcal vaccination of children 0–5 years old with no vaccination in Brazil, Chile, and Uruguay. Costs and health outcomes were analyzed from the societal perspective. Vaccine, demographic, epidemiologic, and cost data were incorporated into this economic analysis.*

Results. *At the rate of diphtheria-tetanus-pertussis (DTP) vaccine coverage and a vaccine price of US$ 53 per dose, PCV7 was projected to prevent 23 474 deaths per year in children under 5 years old in the three countries studied, thus averting 884 841 disability-adjusted life years (DALYs) yearly. To vaccinate the entire birth cohort of the three countries, total vaccine costs would be US$ 613.9 million. At US$ 53 per dose, the cost per DALY averted from a societal perspective would range from US$ 664 (Brazil) to US$ 2 019 (Chile). At a cost of US$ 10 per dose, vaccine cost is lower than the overall cost of illness averted (US$ 125 050 497 versus US$ 153 965 333), making it cost effective and cost-saving.*

Conclusions. *The results of this study demonstrate that the incorporation of PCV7 vaccine at US$ 53 per dose confers health benefits at extra costs. It is unclear whether vaccination at the current price is affordable to these countries.*

Key words Cost effectiveness, vaccination, pneumococcal vaccines, *Streptococcus pneumoniae*, Brazil, Chile, Uruguay.

Pneumococcal disease can lead to multiple outcomes ranging from self-limiting illness with full recovery to sequelae resulting in death and may be an important cause of bacterial pneumonia, meningitis, sepsis, and otitis media (OM) in children under 2 years old. The World Health Organization (WHO) estimates that there are 1.6 million deaths annually due to pneumococcal disease, of which approximately 800 000 are among children under 5 years old (1). The majority of these deaths are due to pneumonia with *Streptococcus pneumoniae* as the most common agent.

Public health mortality statistics confirm that children under 2 years old living in low- and middle-income countries have a much higher rate of dying from diseases caused by this etiological agent, compared to children in high-income countries. An estimated 20%–25% of the 5 million deaths that occur each year in young infants (< 90 days) are due to the pneumococcus (2). In developing countries, this amounts to 5% of annual childhood deaths (141 per 1 000 deaths) (3).

A number of potential control strategies for pneumococcal disease

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are identified by the literature, including a range of antimicrobial agents. A considerable body of evidence suggests that these strategies alone are unlikely to have a significant impact on the increasing emergence of drug-resistant strains. Long-term effects of pneumococcal disease, rapid emergence of drug-resistant bacteria associated with *S. pneumoniae,* and substantial direct and indirect annual costs associated with this disease highlight the need for an effective vaccination program to prevent pneumococcal disease. The inclusion of a pneumococcal conjugate vaccine may significantly alter the incidence of drug-resistant strains and with it the burden of pneumococcal infection on families and society.

Currently, the pneumococcal 7-valent conjugate vaccine (PCV7) (licensed as Prevnar® by Wyeth Pharmaceuticals in the U.S. in 2000) is the only pneumococcal conjugate vaccine available and in use. Other vaccines with higher valences (10 and 13) are undergoing clinical trials, and are expected to be available in the next two to three years. To date, vaccine trials of various heptavalent conjugate vaccines have shown high efficacy against invasive disease caused by the serotypes contained in the vaccines (4, 5).

Infant pneumococcal vaccination is not currently a routine part of the Expanded Program of Immunization (EPI) in any country in Latin America and the Caribbean. However, several countries in the region are planning to introduce the vaccine into routine immunization programs. As of December 2006, its use has been limited to vaccination of high-risk children (for example, in Brazil, Chile, and Colombia) and in some districts (e.g., Mexico) (6).

Cost-effectiveness studies evaluating the pneumococcal conjugate vaccine in North America, Australia, and Europe suggest that it may be an efficacious and cost-effective strategy for reducing the health and economic burden of pneumococcal disease (7–17). While there is little doubt about the impact that this vaccine may have on health and health care in these countries, there is less agreement about whether this vaccine represents "good value for money" in low- and middle-income countries. Good value for money can be obtained in various ways: (i) where the addition of the vaccine confers health benefits and reduces total costs, thus achieving cost savings; (ii) where the addition of the vaccine confers health benefits at no extra costs; and (iii) where the addition of the vaccine confers health benefits at extra costs. The costs of these additional benefits are likely to fall beneath an agreed upon willingness-to-pay threshold.

This paper forecasts the disease burden and costs that may be averted with vaccination in three Latin American countries, and estimates the cost-effectiveness of administering PCV7 from a societal perspective. The countries included in this analysis are Brazil, Chile, and Uruguay. They were chosen because of geographic representation, the availability of epidemiological data in the countries, the potential to introduce the new vaccine into the national immunization schedule, and ability to involve local experts in the study.

MATERIALS AND METHODS

Model overview

Three decision analysis models were developed separately using published administrative and country-specific data to estimate the health and economic burden of pneumococcal disease in Brazil, Chile, and Uruguay, and to determine the cost-effectiveness of PCV7 vaccination in these three countries. The principal inputs to the models include epidemiological information on disease incidence, health care costs associated with different types of pneumococcal disease syndromes, and the effectiveness and costs of vaccination. As shown in Figure 1, each path through the decision tree represented a possible sequence of change and decision events. This sequence of events was associated with a consequence which was valued in terms of disability-adjusted life years (DALYs) averted, cases prevented, or lives saved.

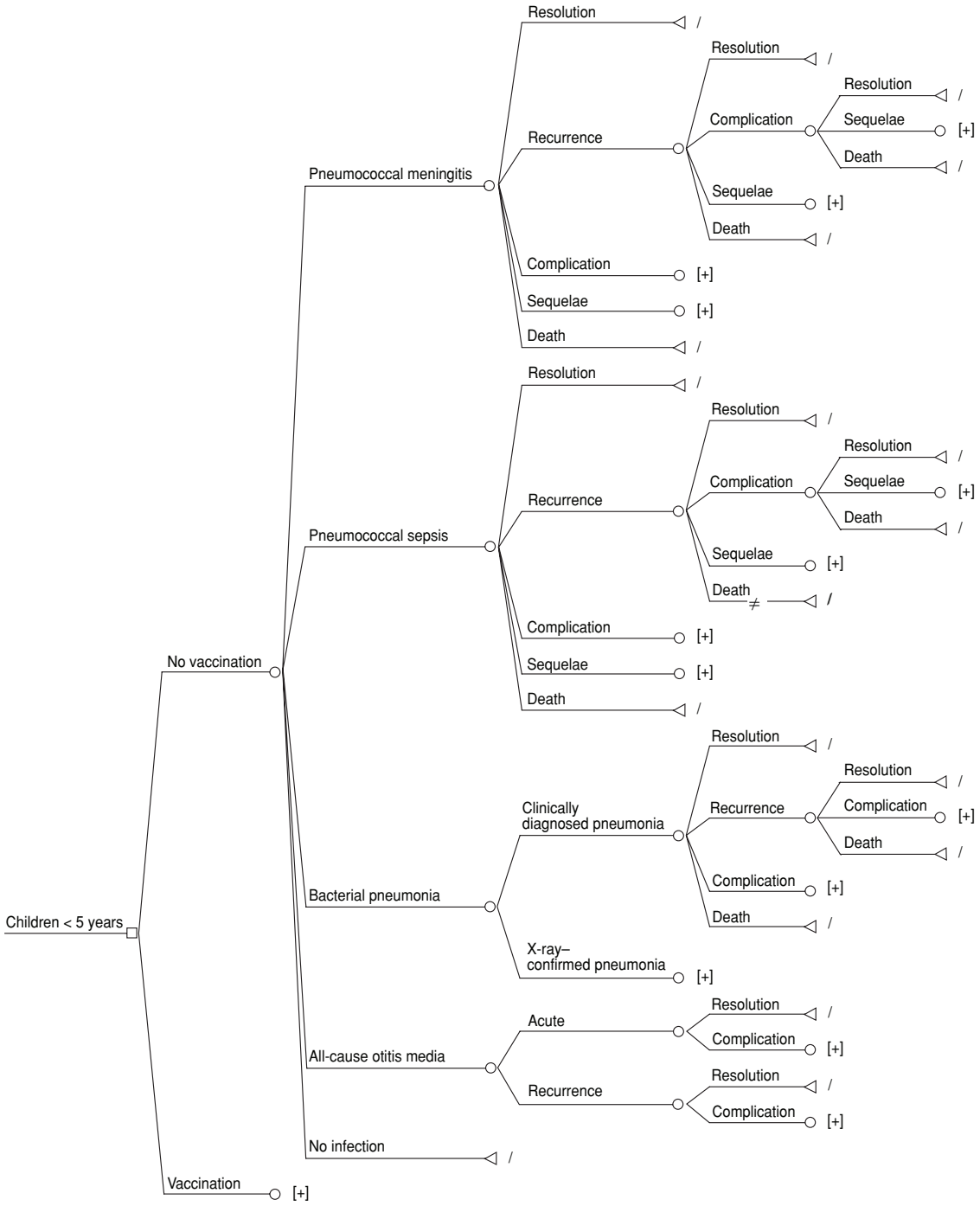
Two policy options were considered in each economic model: no vaccination or vaccination with PCV7. The models began with an annual birth cohort of healthy children under 5 years old in Brazil, Chile, and Uruguay. Children entering the models had the choice of receiving vaccination or no vaccination. Children were assumed to receive PCV7 as part of the routine immunization schedule in a three-dose schedule. Children without vaccination who were infected with pneumococcal disease were assumed to receive antibiotic therapy as standard practice. It was assumed that in the course of five years, some children would experience one or more events of uncertain outcome that were associated with pneumococcal disease. The branches emanating from the chance nodes (circles) in Figure 1 show the possible outcomes of these events. Children with pneumococcal disease either died or survived with or without a disability or complication.

Perspective and scope of analysis

The primary perspective for this analysis is society as a whole. This includes health care costs and non-health care costs in formal inpatient and outpatient settings. The model estimated the expected health outcomes and costs associated with pneumococcal disease and the events and costs that may be averted with vaccination for an annual birth cohort in each country. The period of time considered to estimate costs and benefits was five years.

For the purpose of this analysis, no economic costs were included for cases resulting in death prior to care-seeking or for those not seeking formal medical attention. Effects on lengthened hospital stay due to pneumococcal disease were also not considered. Likewise, the costs of adverse events associated with vaccination were not included because vaccine trial data suggest the safety of the vaccine to be equivalent to that of a placebo (4, 18–24). Nor does this study include

FIGURE 1. Decision tree depicting pneumococcal conjugate vaccine introduction vs. no vaccine and subsequent events that may be experienced by each child



potential indirect effects such as herd immunity because of the absence of burden of disease estimates for older children and adults in the studied countries.

Study population

The sizes of the annual birth cohorts were 3 471 000 in Brazil, 286 000 in Chile, and 57 000 in Uruguay, based on the 2005 under-five birth cohorts reported in the Pan American Health Organization (PAHO) Regional Core Health Data Initiative for Brazil, Chile, and Uruguay (25).

Choice of health outcomes

The primary outcome measures considered were the health care costs of pneumococcal disease and the disease burden and health care system costs averted by vaccination. The net cost per DALYs averted and lives saved were also calculated.

Incremental cost-effectiveness ratios (ICERs) compare the difference in cost and the difference in health outcome with and without PCV7 vaccination. For the cost-effectiveness analysis, the health care costs averted by vaccination were subtracted from the costs invested in vaccination and then divided by the health outcome. The relationship between cost and health outcome is described according to the following ratio:

$$\text{ICER} = \frac{\text{Vaccine-related costs} - \text{averted disease costs}}{\text{DALYs averted by vaccination}}$$

Burden of pneumococcal disease

For each country, the epidemiological burden of pneumococcal disease was estimated for the annual birth cohort from birth until age five. Diseases considered included: pneumococcal meningitis, pneumococcal sepsis, all-cause clinical pneumonia (inpatient/outpatient), all-cause chest X-ray–confirmed pneumonia (inpatient/outpatient), and all-cause otitis media (OM). Non-sepsis, non-meningitis invasive pneumococcal disease burden was not estimated in the current analysis. The model directly estimated numbers of cases of averted OM due to any cause, averted clinical pneumonia due to any cause, and averted chest X-ray–confirmed pneumonia due to any cause. Because of inconsistencies in case definitions for clinical and radiological pneumonia, the diagnostic processes are considered in the pneumonia branch but are not considered in any of the other branches. Only confirmed cases of pneumococcal meningitis and pneumococcal sepsis are considered. The proportion of hospitalized and outpatient cases of clinical pneumonia, chest X-ray–confirmed pneumonia, and OM are derived from a multi-center hospital-based observational study for the period 1999–2002 (26).

Disease burden was estimated as the number of disease cases and deaths based on the 2005 birth cohort size, cumulative incidences of disease, case fatality ratios (CFRs), and the estimated age distributions of each event. The annual incidence of pneumococcal meningitis and pneumococcal pneumonia was derived extracting the number of confirmed pneumococcal disease cases reported to the same observational study described above (26) and dividing it by the PAHO birth cohort estimates for each country for the same time period (25). Age-specific incidence rates were used to develop cumulative incidence estimates (ages 0 to 5) using standard Kaplan-Meier analysis. The model used one-year age bands except for children under 1 year old, who are grouped in the following age categories: 0–2 months, 3–5 months, 6–8 months, and 9–11 months.

The basis for diagnosing pneumococcal pneumonia was radiograph-confirmed, consolidated pneumonia. For pneumococcal meningitis and pneumococcal sepsis, diagnosis depended on the results of various laboratory tests. The model directly estimated the number of cases of averted OM due to any cause, averted clinical pneumonia due to any cause, and averted chest X-ray-confirmed pneumonia due to any cause. Algebraic rearrangements were used to estimate the burden of pneumococcal pneumonia and pneumococcal OM. Table 1 provides a summary of the disease risk estimates used in the model.

DALYs

In addition to estimating the number of cases and deaths caused by pneumococcal disease, the disease burden was expressed in terms of disability-adjusted life-years (DALYs). This aggregate measure allows for comparisons with other diseases and interventions by quantifying the years of healthy life lost (YLL) due to premature mortality and the years lived with disability (YLD) (3). The average country-specific life expectancy at one year of age was used to calculate DALY loss from mortality (27). YLD was calculated using default disability weights from the global burden of disease study (3) and the WHO guidelines for cost-effectiveness studies (28) and an estimated duration of 22 days (26). A discount rate of 3% and age weighting were included to ensure comparability (28).

Costs associated with pneumococcal disease

Country-specific estimates of health care costs and non-health care costs were developed for all pneumococcal events. Health care costs related to pneumococcal disease included hospital days, medical personnel time, outpatient visits, diagnostic tests, and medications. For the present analysis, cost-generating events were estimated based on data from the observational study described earlier and physician interviews reported separately (26). For hospital and ambulatory cases, these were partitioned into the cost of the visit (including facilities and personnel) and the cost of the resources used for treatment (specific tests and medications). The interview data and data from the observational study on resource utilization were combined with unit cost data from the finance departments of local hospitals, national administrative data, and national formulary data in order to derive total health care cost per case of disease. For a complete description of the methods used to calculate the costs of pneumococcal disease see Constenla (26).

Non-health care costs correspond to costs borne by the family, which include the cost of transportation to and from the medical facility and parent or caregiver time spent caring for a sick child. Country-specific estimates of non-health care costs were also developed for pneumococcal hospitalizations and ambulatory visits. These were calculated based on previous research where 60 parents of sick children were interviewed regarding

TABLE 1. Model assumptions for pneumococcal disease risk, fatality, related costs, and vaccine use for the three-country analysis

Model input	Brazil Base case value [range]	Chile Base case value [range]	Uruguay Base case value [range]	Source
Birth cohort (2005)	3 471 000	286 000	57 000	(25)
Disease risk estimates (cumulative incidence)				
Probability of acute otitis media	0.9000 [0.7–1.1]	0.9000 [0.7–1.1]	0.9000 [0.7–1.1]	(29)
Probability of clinical pneumonia	0.0911 [0.1394–0.1485]	0.0911 [0.1394–0.1485]	0.0911 [0.1394–0.1485]	(30, 31)
Probability of chest X-ray–confirmed pneumonia[a]	0.1032	0.0226	0.0337	(26)
Probability of pneumococcal sepsis	0.0001 [0.00008–0.00013]	0.0001 [0.00008–0.00013]	0.0001 [0.00008–0.00013]	(32)
Probability of pneumococcal meningitis[a]	0.0265	0.0089	0.0115	(26)
Case-fatality ratios (CFR)				
CFR for clinical pneumonia	0.03 [0.019–0.055]	0.03 [0.019–0.055]	0.03 [0.019–0.055]	(33–35)
CFR for chest X-ray + pneumonia	0.05 [0.051–0.58]	0.05 [0.051–0.58]	0.05 [0.051–0.58]	(32, 36)
CFR for pneumococcal sepsis	0.35 [0.27–0.4]	0.35 [0.27–0.4]	0.35 [0.27–0.4]	(32)
CFR for pneumococcal meningitis	0.35 [0.22–0.5]	0.35 [0.22–0.5]	0.35 [0.22–0.5]	(32, 33, 37–40)
Disease-related costs, acute otitis media[b]				
Health care costs	$20 [$15–$25]	$217 [$163–$271]	$90 [$68–$113]	(26)
Costs due to out-of-pocket expenses	$174 [$131–$218]	$33 [$25–$41]	$13 [$10–$16]	(26)
Costs due to caregiver time loss	$9 [$7–$12]	$9 [$7–$12]	$9 [$7–$12]	(26)
Disease-related costs, clinical pneumonia, outpatient[b,c]				
Health care costs	$75 [$56–94]	$220 [$165–$275]	$45 [$34–$56]	(26)
Costs due to family out-of-pocket expenses	$13 [$10–17]	$35 [$26–$44]	$35 [$26–$44]	(26)
Costs due to caregiver time loss	$9 [$7–12]	$9 [$7–$12]	$9 [$7–$12]	(26)
Disease-related costs, clinical pneumonia, inpatient[b,d]				
Health care costs	$372 [$279–$465]	$3 483[$2 612–$4 354]	$1 147 [$860–$1 434]	(26)
Costs due to family out-of-pocket expenses	$15 [$11–$19]	$89 [$67–$111]	$293 [$220–$366]	(26)
Costs due to caregiver time loss	$61 [$46–$77]	$61 [$46–$77]	$61 [$46–$77]	(26)
Disease-related costs, chest X-ray–confirmed pneumonia, inpatient[b,d]				
Health care costs	$372 [$279–$465]	$3 483 [$2 612–$4 354]	$1 147 [$860–$1 434]	(26)
Costs due to family out-of-pocket expenses	$15 [$11–$19]	$89 [$67–$111]	$293 [$220–$366]	(26)
Costs due to caregiver time loss	$61 [$46–$77]	$61 [$46–$77]	$61 [$46–$77]	(26)
Disease-related costs, pneumococcal sepsis[b]				
Health care costs	$1 080 [$810–$1 350]	$5 120 [$3 840–$6 400]	$2 100 [$1 575–$2 625]	(26)
Costs due to family out-of-pocket expenses	$98 [$74–$123]	$106 [$80–$133]	$225 [$169–$281]	(26)
Non-health care costs due to caregiver time loss	$72 [$54–$90]	$72 [$54–$90]	$72 [$54–$90]	(26)
Disease-related costs, pneumococcal meningitis[b]				
Health care costs	$1 134 [$850–$1 417]	$5 436 [$4 077–$6 795]	$2 271 [$1 703–$2 839]	(26)
Costs due to family out-of-pocket expenses	$106 [$80–$133]	$153 [$115–$192]	$226 [$170–$283]	(26)
Costs due to caregiver time loss	$35 [$26–$44]	$35 [$26–$44]	$35 [$26–$44]	(26)
Vaccine estimates				
Coverage (3 doses)	96%	99%	91%	(41)
Vaccine efficacy against acute OM cases[e]	0.07 [0.04–0.10]	0.07 [0.04–0.10]	0.07 [0.04–0.10]	(4)
Vaccine efficacy against clinical pneumonia cases[e]	0.03 [–0.04–0.09]	0.03 [–0.04–0.09]	0.03 [–0.04–0.09]	(4)
Vaccine efficacy against chest X-ray–confirmed pneumonia cases[e]	0.227 [0.04–0.34]	0.227 [0.04–0.34]	0.227 [0.04–0.34]	(42)
Vaccine efficacy against vaccine-type invasive pneumococcal cases[e]	0.97 [0.83–0.99]	0.97 [0.83–0.99]	0.97 [0.83–0.99]	(4)
Vaccine program estimates				
Number of vaccine doses	3	3	3	Assumption
Wastage rate	10%	10%	10%	Assumption
Cost per dose of vaccine	$53	$53	$53	(43)
Cost of administration of one dose[f]	$1	$1	$1	Assumption
Disease-related costs, chest X-ray–confirmed pneumonia, outpatient[b,c]				
Health care costs	$75 [$56–94]	$220 [$165–$275]	$45 [$34–$56]	(26)
Costs due to family out-of-pocket expenses	$13 [$10–17]	$35 [$26–$44]	$35 [$26–$44]	(26)
Costs due to caregiver time loss	$9 [$7–12]	$9 [$7–$12]	$9 [$7–$12]	(26)

[a] These values were derived from a study that reported no range values.
[b] These cost estimates correspond to public health care costs. Costs are in 2004 U.S. dollars.
[c] The cost values for clinical pneumonia (outpatient) and chest X-ray–confirmed pneumonia (outpatient) were assumed to be the same as treatment for both syndromes was performed in the ambulatory setting.
[d] The cost values for clinical pneumonia (inpatient) and chest X-ray–confirmed pneumonia (inpatient) were assumed to be the same as treatment for both syndromes was performed in the hospital setting.
[e] Per protocol analyses. Pneumonia vaccine efficacy adjusted for regional differences in serotype distribution.
[f] Although these countries belong to different income groups [Brazil and Uruguay are considered lower- to middle-income countries and Chile is considered an upper- to middle-income country according to 2003 gross national income (GNI) per capita (44)], the same cost of administration of one dose was assumed based on interviews with local EPI managers.

money spent to transport a child or themselves to the health facility, time lost from paid work due to their child's illness, days off work, and/or income lost due to pneumococcal disease (26). The average cost of caregiver time was estimated by multiplying the mean hours lost by the mean female hourly wage for each of the countries. Further details of the cost analysis methods and results have been described elsewhere (26).

Cost estimates for children who were readmitted for complications or repeated episodes of pneumococcal infections or (long-term) sequelae were excluded from the cost-effectiveness calculations because of lack of reliable data on long-term effects of pneumococcal disease across countries. However, readmission costs were included in the cost calculations in countries where these costs were available.

All cost estimates are from the public sector because the proportion of children treated in the private sector was small across all three countries. Cost estimates are taken from standard sources, listed in Table 1. Costs were collected in local currency and were converted to 2004 U.S. dollars based on World Bank rates. All future costs were discounted at an annual rate of 3%, as recommended by the U.S. Panel of Cost-Effectiveness in Health and Medicine (45) and the World Bank Global Burden of Disease (GBD) Project (3).

Vaccination costs

Vaccination costs include the cost of administration, the price of each dose, the number of doses given (based on coverage level), and expected losses from waste. We assumed that PCV7 would be administered along with the current Expanded Program of Immunization (EPI) vaccines, and therefore, the incremental administration costs would be very low (US$ 1 per dose). We used the current PAHO revolving fund price of US$ 53 per dose (43) to represent the cost of PCV7. A 10% vaccine wastage rate was considered in estimating vaccine-related costs.

Vaccine efficacy and coverage

Efficacy data on PCV7 vaccine in the region are not available at present, so estimates of the effectiveness of PCV7 from the Northern California Kaiser Permanente (NCKP) trial (4) were used as this trial was considered to be most applicable to the population under consideration. Estimates of vaccine effectiveness against meningitis were adjusted for regional differences in serotype distribution. This was done by applying the vaccine's protective effect to that proportion of disease caused by vaccine-covered serotypes. Estimates of vaccine efficacy against chest X-ray–confirmed pneumonia were based on a re-analysis of the NCKP data recently performed by Hansen et al. (42). Vaccine efficacy estimates are summarized in Table 1.

Vaccine coverage was adjusted based on the ability to reach the target population. A PCV7 vaccination would occur with diphtheria-tetanus-pertussis (DTP) doses 1–3; however, standardized data were only available for coverage of the third dose. In the baseline analysis, national coverage of the third dose of DTP in 1 year-olds in 2005 in the three countries studied was estimated to be between 91% and 96% (41).

Sensitivity and uncertainty analyses

One-way sensitivity analysis was performed by calculating key outcomes for different scenarios that are likely to influence the costs of disease and the cost-effectiveness of vaccination. These scenarios included high- and low-end estimates of incidence rates, efficacy against death, health care costs, and vaccine costs. Table 1 presents the base estimate values and ranges used in the sensitivity analysis.

Monte Carlo simulation was performed to deal with multiple sources of uncertainty. A range of estimates of cost-effectiveness was created based on an assumed distribution of relevant variables. This approach was developed based on the models of pneumococcal disease and vaccination cost-effectiveness described previously (26). Individual point estimates of parameters were replaced with distributions of potential values. The process was repeated for a large number of iterations (10 000 in this case). The final product was a probability distribution of potential outcomes that described the likely range of expected results.

For national disease burden variables, distributions (ranges) were used to characterize the cumulative incidence of illness outcomes (hospitalization, ambulatory visits, and death) in each country and the proportion due to *S. pneumoniae.* Wider distributions were used for countries for which the estimates were extrapolated from foreign data. For cost variables, distributions were based on the cost estimates derived from the hospital-based observational study (26). For estimates of vaccine effectiveness, distributions were used for efficacy (in protecting against hospitalization for pneumococcal invasive disease, hospitalization for pneumococcal pneumonia, ambulatory visits for all-cause OM, and death), based on the reported confidence intervals from clinical trials. Distributions were also included for reduction in efficacy of only one dose and efficacy reduction in subsequent seasons.

Uncertainty limits (5% and 95%) were estimated for key output parameters including vaccine benefit (costs and DALYs averted) and the incremental cost-effectiveness ratio. The probability sensitivity analysis approach was also used to estimate the likelihood that vaccination would result in different levels of cost-effectiveness. In addition, variance analysis was performed to determine the contribution of the individual input parameters to the overall uncertainty regarding total societal costs and cost-effectiveness ratios.

RESULTS

Disease burden

Table 2 gives the estimated burden of all pneumococcal events in Brazil, Chile, and Uruguay. For every 1 000 children born in these three countries,

TABLE 2. Estimated burden of pneumococcal disease in Brazil, Chile, and Uruguay, per annual 2005 birth cohort (0–5 years)

Type of events	Brazil		Chile		Uruguay	
	Total events[a]	Events per 1 000 children	Total events[a]	Events per 1 000 children	Total events[a]	Events per 1 000 children
Pneumococcal disease						
Pneumococcal deaths	40 572	12	1 080	4	283	5
Pneumococcal meningitis	91 982	27	2 537	9	658	12
Pneumococcal sepsis	364	< 1	30	< 1	6	< 1
Pneumococcal otitis media	374 184	108	30 832	108	6 145	108
Pneumococcal pneumonia[b]	158 823	46	3 960	14	1 060	19
DALYs[c]	1 618 219	466	43 859	153	11 457	201
Treatment of pneumococcal disease						
Hospital care	284 295		4 302		1 183	
Outpatient care	441 058		33 056		6 686	
Total costs (2004 US$)						
Health care costs	151 450 140		27 158 183		2 680 373	
Costs borne by family[d]	90 243 644		2 148 454		518 435	
Overall total costs	241 693 783		29 306 637		3 198 808	

[a] Projected for the 2005 birth cohort during the first five years of life.
[b] Includes chest X-ray–confirmed pneumonia and other, clinically defined pneumonia.
[c] Disability-adjusted life years.
[d] Includes health care and non-health care costs borne by families.

pneumococcal disease resulted in 324 pneumococcal OM cases, 79 pneumococcal pneumonia cases, 48 pneumococcal meningitis cases, and < 1 pneumococcal sepsis case. An estimated 21 deaths per 1 000 were due to pneumococcal disease. The epidemiological burden of disease (in terms of DALY loss per 1 000 children) ranged from 153 to 466, with lower rates observed in Chile due to lower mortality. Even though duration of illness for pneumococcal disease was considered long (the observed length of stay for children with pneumococcal meningitis and pneumococcal pneumonia ranged from 5 to 9 days and 8 to 14 days, respectively), YLD contributed little to the DALY estimate. Instead, the DALY estimate was primarily based on the YLL because the majority of cases were due to premature mortality and because disability from pneumococcal disease was underreported.

Pneumococcal disease was responsible for approximately 289 780 hospitalized cases and 480 800 ambulatory cases for the three countries. The relative proportion of hospitalizations and ambulatory visits differed across countries. This is likely due to differences in access to medical care, health-seeking behaviors, and health sector structure.

Economic burden

Table 2 also shows the estimated health care costs and costs borne by families due to pneumococcal-related events in each country. From the health care system perspective, the average cost of health care ranged from US$ 44 to US$ 95 per child, with higher costs in Chile due to higher income. In all countries except Brazil, the majority (64%–73%) of these costs resulted from ambulatory visits. From the societal perspective, total costs of pneumococcal disease ranged from US$ 56 to US$ 102 per child. Overall, health care accounted for 63%–92% of the total costs in the three countries.

Benefits of vaccination

Table 3 shows the expected pneumococcal-related events with and without vaccination in Brazil, Chile, and Uruguay. It was projected that for each annual birth cohort vaccinated, PCV7 would prevent 53%–58% of pneumococcal cases and deaths and 50%–55% of DALYs. Table 3 also shows the projected reduction in the economic burden, averting 29%, 16%, and 17% of the health care costs associated with pneumococcal disease treatment in Brazil, Chile, and Uruguay, respectively. Projections for these three countries indicate that vaccination would prevent US$ 48.7 million in health care treatment costs and US$ 56.2 million in total costs.

Cost-effectiveness of vaccination

Table 4 shows the estimated annual costs, net costs, and cost-effectiveness of pneumococcal conjugate vaccination from the societal perspective in Brazil, Chile, and Uruguay. The vaccine-related costs ranged from US$ 8.7 million to US$ 557.8 million annually, assuming a vaccine cost of US$ 53 per dose and vaccine coverage of 91%–99% (42). The cost per DALY ranged from US$ 664 to US$ 2 019 and the cost per life saved was from US$ 847 to US$ 2 555, assuming the same vaccine cost of US$ 53 per dose. At a vaccine price of US$ 5 per dose, these annual costs would be less, with the cost per DALY ranging from US$ 74 to US$ 224 and the cost per life saved from US$ 94 to US$ 284.

An alternative way to view these cost-effectiveness results is using cost-acceptability curves, based on the cumulative distribution of the estimated

TABLE 3. Estimated burden of pneumococcal disease with and without vaccination, per annual 2005 birth cohort (0–5 years old) in Brazil, Chile, and Uruguay

Type of events	No vaccination	With vaccination	Averted with vaccination[a]	% averted
Brazil				
Pneumococcal deaths	40 572	17 873	22 699	56
Pneumococcal meningitis	91 982	40 378	51 604	56
Pneumococcal sepsis	364	160	204	56
Pneumococcal otitis media	374 184	164 258	209 926	56
Pneumococcal pneumonia[b]	158 823	69 720	89 104	56
DALYs[c]	1 618 219	763 010	855 209	53
Total health care costs[d]	US$ 151 450 140	US$ 107 529 599	US$ 43 920 541	29
Costs borne by families[d,e]	US$ 90 243 644	US$ 83 024 152	US$ 7 219 492	8
Overall total costs[d]	US$ 241 693 783	US$ 205 439 716	US$ 51 140 033	
Chile				
Pneumococcal deaths	1 080	456	625	58
Pneumococcal meningitis	2 537	1 069	1 468	58
Pneumococcal sepsis	30	13	17	58
Pneumococcal otitis media	30 832	12 994	17 838	58
Pneumococcal pneumonia[b]	3 960	1 669	2 291	58
DALYs[c]	43 859	19 948	23 911	55
Total health care costs[d]	US$ 27 158 183	US$ 22 812 874	US$ 4 345 309	16
Costs borne by families[d,e]	US$ 2 148 454	US$ 1 955 093	US$ 193 361	9
Overall total costs[d]	US$ 29 306 637	US$ 24 910 641	US$ 4 538 670	
Uruguay				
Pneumococcal deaths	283	133	150	53
Pneumococcal meningitis	658	308	350	53
Pneumococcal sepsis	6	3	3	53
Pneumococcal otitis media	6 145	2 877	3 268	53
Pneumococcal pneumonia[b]	1 060	496	564	53
DALYs[c]	11 457	5 736	5 721	50
Total health care costs[d]	US$ 2 680 373	US$ 2 224 710	US$ 455 663	17
Costs borne by families[d,e]	US$ 518 435	US$ 451 038	US$ 67 397	13
Overall total costs[d]	US$ 3 198 808	US$ 2 686 999	US$ 523 060	

[a] Based on vaccine effectiveness, which incorporates information on vaccine efficacy and coverage.
[b] Includes chest X-ray–confirmed pneumonia and other, clinically defined pneumonia.
[c] Disability-adjusted life years.
[d] Based on 2004 US$ estimates.
[e] Includes non-health care costs and productivity losses.

incremental cost-effectiveness ratio (ICER) from the Monte Carlo analysis (Figure 2). To estimate the likelihood that vaccination meets the standard of very cost-effective (ICER < gross domestic product [GDP] per capita) in a given country, a vertical line is extended from the horizontal axis at the country's per capita GDP until it reaches the curve for that country. The value along the vertical axis at this point would be the likelihood of it meeting this standard. For Brazil and Uruguay, the chance that vaccination will be considered very cost-effective (ICER < GDP per capita) is more than 95%. Chile has a greater than 85% chance of being considered cost-effective (based on the standard of ICER < 3 times GDP per capita).

Sensitivity and uncertainty analyses

The sensitivity analysis evaluated the impact of different values for specific variables on the health care cost of treating pneumococcal disease and the cost-effectiveness estimates. The health care cost per child was affected by the incidence of pneumococcal disease and the cost of treatment. The variables that had the largest impact on the cost-effectiveness estimates were mortality, vaccine efficacy against mortality, and vaccine price.

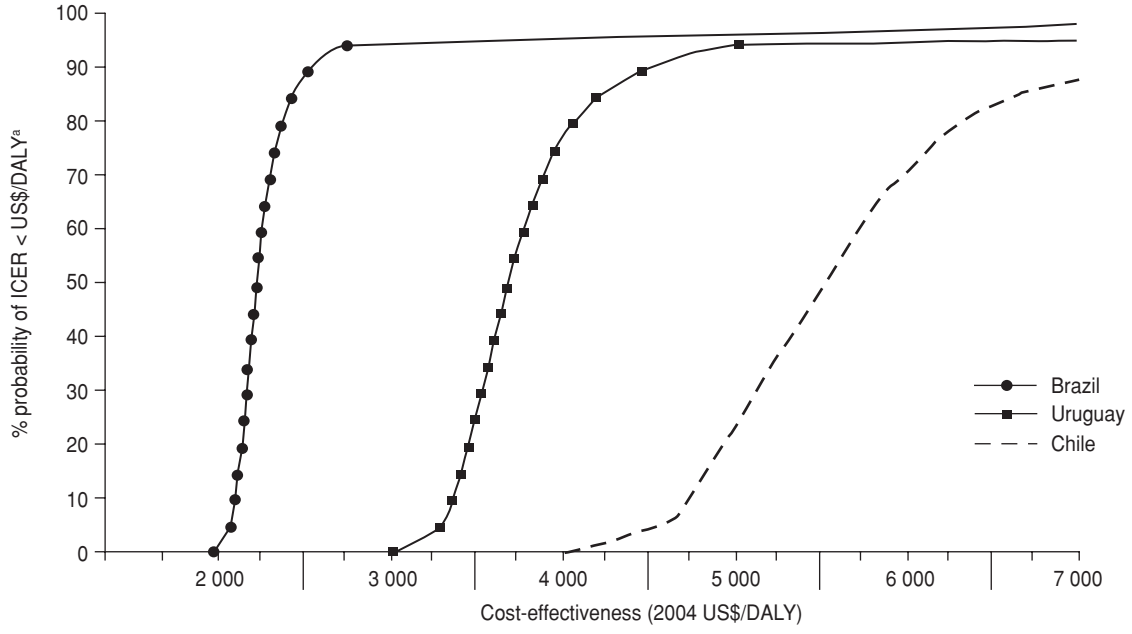
In the contribution to variance analysis, the contribution of each variable to overall uncertainty differed between the countries, depending on the relative quality of the epidemiological data and the relative importance of hospital and ambulatory events. Uncertainty in pneumococcal OM contributed over 9% of overall uncertainty in each country, and it was much higher in Brazil and Uruguay. Incidence of pneumococcal meningitis was most important in Brazil where it accounted for 17% of uncertainty. The uncertainty limits were smallest where country-specific epidemiological data were available. Health care costs were relatively more important sources of variability in countries with more certain country-specific epidemiological inputs (e.g., hospitalization in Brazil and Chile). Uncertainty in non-health care costs for hospitalizations contributed a small fraction of overall uncertainty, however these costs for ambulatory visits contributed to 18% overall uncertainty in

TABLE 4. Estimated annual costs, net costs, and cost-effectiveness of pneumococcal conjugate vaccination in Brazil, Chile, and Uruguay (2004 US$)

Cost per dose (US$)	Vaccine costs (US$)[a]	Net costs (US$)[a]	US$ per DALY[b] averted[c]	US$ per life saved[c]
Brazil				
53	557 803 584	474 675 648	664	847
40	423 517 536	340 389 600	505	643
30	320 220 576	237 092 640	381	486
20	216 923 616	133 795 680	258	329
10	113 626 656	30 498 720	135	173
5	61 978 176	Cost-saving	74	94
Chile				
53	47 397 636	31 996 265	2 019	2 555
40	35 987 094	20 585 723	1 533	1 940
30	27 209 754	11 808 383	1 159	1 467
20	18 432 414	3 031 043	785	994
10	9 655 074	Cost-saving	411	520
5	5 266 404	Cost-saving	224	284
Uruguay				
53	8 683 038	7 294 435	1 546	1 959
40	6 592 677	5 204 074	1 174	1 488
30	4 984 707	3 596 104	887	1 125
20	3 376 737	1 988 134	601	762
10	1 768 767	380 164	315	399
5	964 782	Cost-saving	172	218

[a] Vaccination cost includes the discounted cost of the vaccine and discounted cost of administering the vaccine.
[b] Disability-adjusted life years.
[c] Using discounted costs and health benefits.

FIGURE 2. Cost acceptability curve for pneumococcal conjugate vaccination in Brazil, Chile, and Uruguay



[a] ICER: incremental cost-effectiveness ratio; DALY: disability-adjusted life years.

Brazil. The uncertainty limits were smallest where country-specific data were available and were more reliable for estimating key epidemiological parameters (Brazil, Chile).

In all three countries, the primary sources of uncertainty in cost-effectiveness estimates were overall mortality (accounting for 43%–52%) and vaccine efficacy against mortality (accounting for 12%–16%). These findings were consistent with earlier study findings, which showed that cost-effectiveness ratios were sensitive to variation in the incidence of pneumo-

coccal death (14). Similarly, a 25% increase or decrease in vaccine efficacy against mortality resulted in a 20%–32% change in the incremental cost-effectiveness ratio.

DISCUSSION

Pneumococcal disease is a relatively common disease with an estimated 1.6 million children in Latin America and the Caribbean having an episode of pneumococcal disease annually. An estimated 400 000 of these infections are serious and may lead to hospitalization, permanent disability, and death. Pneumococcal otitis media (411 161 cases per year) is a significant contributor to the substantial health care system costs and broader use of antibiotics in Brazil, Chile, and Uruguay. Introduction of pneumococcal conjugate vaccines can greatly reduce the incidence of pneumococcal infections. Using a benchmark of three times GDP per capita as the threshold for cost-effective interventions (46), these cost-effectiveness analyses suggest that, from the perspective of these three countries, the vaccine program meets the criteria for cost-effective at a wide range of prices, suggesting that affordability rather than cost-effectiveness may be a major issue for vaccine introduction.

We estimated that vaccination using the currently available heptavalent formulation could prevent over half of all cases and deaths due to pneumococcal disease annually in the three countries studied. Even greater reductions in pneumococcal disease are possible using vaccine formulations that include additional serotypes or provide additional cross-protection against serotypes not included in the vaccine. Policy makers in these countries should consider these data as they introduce new vaccines, determine affordability, and weigh competing priorities.

This study indicates that US$56.2 million in health care and non-health care costs would be averted by introduction of a vaccine. To vaccinate the entire birth cohort of all three countries studied, total vaccine costs would be US$ 613.9 million at US$ 53 per dose and US$ 68.2 million at US$ 5 per dose. When compared to WHO benchmarks for cost-effectiveness, vaccination meets the criteria at this range of vaccine prices. Clearly, decision makers faced with many cost-effective interventions will also need to consider the issue of affordability given national financial constraints, as well as the capacity and sustainability of vaccination programs. While averted treatment costs can be used to partially offset the costs of vaccination, we acknowledge that in some health systems the distributions of costs and savings may not be equitable, and hence, the impact of averted treatment costs on affordability may be less than would appear in this analysis.

Pneumococcal disease results in significant disease burden and costs in each of the three countries studied. From a public health perspective, the concern was mainly on deaths and hospitalization of invasive disease cases. However, from an economic perspective, ambulatory visits generated a large portion of the costs of pneumococcal disease in the form of OM cases. The pattern of burden differed among countries. As expected, the greatest disease burden was in the lower-middle income country, Brazil. In contrast, the greatest economic burden was in Chile, due to higher treatment costs per child.

This is the first study to assess the likely cost-effectiveness of a program of immunization with a heptavalent pneumococcal conjugate vaccine in countries of this region. More work on the cost-effectiveness and affordability of new vaccination programs needs to be done in this region, where there is currently dire paucity of literature in this area.

The evaluation presented here is conservative in a number of ways. Although we adjusted for key variables influencing the cost-effectiveness ratio (i.e., vaccine coverage, serotype coverage, age at vaccination, and disease burden), the vaccine efficacy data, derived from the Kaiser Permanente clinical trial of PCV7, may be relevant only to the specific setting and time frame of that trial. Because the Kaiser Permanente trial was conducted in the United States, the vaccine efficacy data may not be the most applicable to the populations under consideration. We assumed that all children were fully vaccinated at levels of coverage with three doses of DTP vaccine and did not adjust for potential protection provided by incomplete vaccination (e.g., receiving only one or two doses of PCV7). Such protective effects would have increased vaccine cost-effectiveness. Our vaccine coverage estimate was based on coverage of the third dose of DTP. We assumed that all groups within a country would have equal likelihood of vaccination and would be vaccinated at the recommended time. If high-risk populations are missed or vaccination is delayed, the effectiveness may be reduced.

In terms of cost inputs, we did not consider costs borne by families for treatment of pneumococcal disease in less formal settings (i.e., treatment at home or by traditional healers). Since the price for the PCV7 vaccine for different countries is still not established, and the associated vaccination programmatic and support costs are uncertain, we used the PAHO revolving fund price of US$ 53 per dose. Future studies should focus on the cost of PCV7 vaccination programs, particularly the cost of the vaccine itself as this is likely to be a major determinant of the cost and affordability of any vaccine program.

In addition to these limitations, we did not consider potential quality of life benefits of the vaccine for complications or sequelae that are prevented or reduced either within or beyond the first five years of life. Due to methodological difficulties and time constraints, we did not consider the potential indirect protective effect of herd immunity on people who are not vaccinated. Herd immunity could offset gaps in delivery of full course, on-time vaccination, prevent disease in non-targeted populations, and improve the cost-effectiveness of a heptavalent pneumococcal conjugate vaccination program.

The focus of the evaluation was on only four conditions for which the efficacy of PCV7 has been established. It is likely that the vaccine will also have an impact on other pneumococcal diseases. In addition, pneumococcal disease in

high-risk children was not considered despite the higher costs that this subgroup may incur to health services. This was due to lack of reliable data on the efficacy against pneumococcal disease in this population. Loss in quality of life resulting from disease morbidity was also not considered because of the many conceptual and methodological problems with utility measurement.

CONCLUSION

Pneumococcal disease results in significant morbidity, as well as economic burden in the three countries studied. Vaccination provides an effective opportunity for improving child health in these countries. The cost-effectiveness of vaccination compared to other interventions directed at reducing pneumococcal mortality will depend on vaccine price and the ability of vaccination programs to reach vulnerable children at the highest risk of death and to be affordable. These results emphasize the importance of pneumococcal conjugate vaccination as a cost-effective intervention for preventing childhood death and disability.

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RESUMEN

Impacto económico de la vacuna antineumocócica conjugada en Brasil, Chile y Uruguay

Objetivos. Evaluar el impacto económico de la aplicación de la vacuna antineumocócica conjugada heptavalente (PCV7) en Brasil, Chile y Uruguay.

Métodos. Se elaboró un modelo analítico de decisiones para comparar la vacunación antineumocócica de los niños de 0-5 años de edad con la no vacunación, en Brasil, Chile y Uruguay. Los costos y los desenlaces para la salud se analizaron desde el punto de vista de la sociedad. Al análisis económico se incorporaron los costos y los datos demográficos, epidemiológicos y de la vacuna.

Resultados. Con una cobertura como la de la vacuna contra la difteria, el tétanos y la tos ferina (DTP) y un precio de US$ 53,00 por dosis, la vacuna PCV7 podría evitar 23 474 muertes anuales en niños menores de 5 años en los tres países estudiados, con lo que se evitarían anualmente 884 841 años de vida ajustados por discapacidad (AVAD). Para vacunar toda la cohorte de recién nacidos de los tres países, el costo total de la vacuna sería de US$ 613,9 millones. A US$ 53,00 por dosis, el costo por AVAD evitado desde la perspectiva de la sociedad variaría entre US$ 664,00 (en Brasil) y US$ 2 019,00 (en Chile). A US$ 10,00 por dosis, el costo de la vacuna sería menor que el costo total de la enfermedad evitada (US$ 125 050 497 frente a US$ 153 965 333), lo que sería efectivo en función del costo y representaría un ahorro.

Conclusiones. Estos resultados demuestran que la incorporación de la vacuna PCV7 a US$ 53,00 por dosis ofrece beneficios con un costo adicional. No queda claro si estos países pueden costear la vacunación a los precios actuales.

Palabras clave Análisis costo-beneficio, vacunación, vacunas neumocócicas, Brasil, Chile, Uruguay.