The burden of pneumococcal disease among Latin American and Caribbean children: review of the evidence

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ABSTRACT

Objective. *To conduct a comprehensive review of data on pneumococcal disease incidence in Latin America and the Caribbean and project the annual number of pneumococcal disease episodes and deaths among children < 5 years of age in the region.*

Methods. *We carried out a systematic review (1990 to 2006) on the burden of pneumococcal disease in children < 5 years of age in the region. We summarized annual incidence rates and case fatality ratios using medians and interquartile ranges for invasive pneumococcal disease (IPD) (including all-IPD and separately abstracting pneumococcal meningitis, pneumonia, bacteremia, and sepsis data), pneumonia (all cause and radiologically confirmed), and acute otitis media by age group: < 1 year, < 2 years, and < 5 years. We modeled age-specific cumulative incidence of disease obtained from standard Kaplan-Meier analysis and projected data to obtain regional estimates of disease burden. We adjusted burden estimates by serotype coverage, vaccination coverage, and vaccine efficacy to estimate the number of cases and deaths averted.*

Results. *Of 5 998 citations identified, 26 papers from 10 countries were included. The estimated annual burden of pneumonia, meningitis, and acute otitis media caused by pneumococcus in children < 5 years of age ranged from 980 000 to 1 500 000, 2 600 to 6 800, and 980 000 to 1 500 000, respectively. An estimated 12 000 to 28 000 deaths due to pneumococcal disease occur in the region annually. Pneumococcal conjugate vaccine could save 1 life per 1 100 and prevent 1 case per 13 children vaccinated.*

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Conclusion. *A substantial burden of pneumococcal disease in the region is potentially preventable with pneumococcal conjugate vaccines and should be considered in regional vaccine decision making. Results are limited by the very few studies, conducted in selected settings, included in this review.*

Key words *Streptococcus pneumoniae*, pneumococcal vaccines, review literature, Latin America and the Caribbean.

Streptococcus pneumoniae (pneumococcus) is a leading bacterial cause of pneumonia, meningitis, bacteremia, sepsis, and acute otitis media (AOM). Pneumococcal disease represents an important cause of morbidity and mortality in children and the elderly, resulting in substantial health care system costs to governments and society. The World Health Organization (WHO) estimates that pneumococcus causes > 700 000 to 1 million child deaths annually (1). However, the burden of pneumococcal disease in Latin American and the Caribbean is unknown. Estimates of disease burden are needed to inform use of pneumococcal conjugate vaccines in the region.

Pneumococcal polysaccharide-protein conjugate vaccines have been proven safe and effective in a variety of epidemiologic settings (2–5). Routine use of heptavalent pneumococcal conjugate vaccine (Prevnar®, Wyeth Laboratories) in the United States since 2000 has dramatically reduced the burden of pneumococcal disease (6, 7). Although countries in Latin America and the Caribbean have yet to introduce pneumococcal conjugate vaccines into the routine childhood immunization schedule, several countries—for example, Costa Rica, Guyana, Honduras, Mexico, Nicaragua, and Uruguay—are planning a national introduction in the near future. Several more have widespread use of pneumococcal vaccine in the private sector or in the public sector for certain children at high risk of pneumococcal disease, including those with immunodeficiencies and chronic diseases. Barriers to pneumococcal conjugate vaccine introduction in the region include concerns about the cost of the vaccine, concerns about coverage of pneumococcal serotypes in the region, and lack of disease burden estimates.

We conducted a comprehensive review of data on pneumococcal disease incidence in Latin America and the Caribbean and projected the annual number of pneumococcal disease episodes and deaths among children < 5 years of age in the region. Policy makers in the region can use the findings to evaluate the case of including pneumococcal conjugate vaccination in their national immunization program.

METHODS

Literature search

Literature searches of six electronic databases (Latin American and Caribbean Health Sciences, PubMed, The Cochrane Library, EMBASE, CAB Direct, and BIOSIS) identified 5 998 citations of original studies from Latin America and the Caribbean (defined as the 45 countries in the Pan American Health Organization (PAHO) region excluding the United States, Bermuda, and Canada)) published in English, Spanish, or Portuguese between 1990 and April 2006. Search terms included *Streptococcus pneumoniae*, invasive pneumococcal, pneumonia, meningitis, bacteremia, and otitis media. Additional sources of data included bibliographies of identified studies, abstracts, and proceedings from scientific conferences, unpublished reports, and contents of selected journals through December 2006. Unpublished data were included if relevant, unique, and too recent for publication.

Of 521 citations with potentially relevant data identified, 455 (87%) articles were obtained for full text review. Data were abstracted by one reader; data included in the final analysis were checked for accuracy by a second reader. Standardized forms were used to extract data on age-specific incidence rates, case-fatality ratios, serotype distribution, antimicrobial resistance, and health care cost. We abstracted data on invasive pneumococcal disease (IPD) (defined as isolation of pneumococcus from a normally sterile site), all-cause pneumonia (clinical and radiologically confirmed), and all-cause AOM. Studies that reported IPD but did not specify syndromes were reviewed for evidence that both blood culture and lumbar punctures were routinely performed. In studies that reported IPD and did specify syndromes, the individual syndromes (pneumococcal pneumonia, pneumococcal meningitis, pneumococcal sepsis, and pneumococcal bacteremia) were abstracted separately. Studies with fewer than 30 pneumococcal isolates or cases of a particular syndrome and incidence data for periods less than 12 months were excluded. We accepted each author's methods for identifying specific bacterial etiologies and serotyping. Final analysis included data for children < 5 years old from 24 full-text articles from peer-reviewed journals and two abstracts. Data on antimicrobial resistance and health care costs are presented elsewhere (8).

Analysis

Data stratified by age and syndrome were tabulated on spreadsheets (Excel, Microsoft). Age categories were < 1 year, < 2 years, and < 5 years. These age categories were not mutually exclusive. Serotype data obtained from PAHO's regional vaccine surveillance system included children < 6 years of age. Annual incidence rates and median values and interquartile ranges were used to summarize each syndrome. Data are presented for IPD, pneumonia, and AOM. The specific syndromes that make up IPD are also presented but are not a subset of overall IPD, as some papers presented data on only one of the syndromes, most commonly pneumococcal meningitis. Data presented by time period were aggregated for the entire period of a study.

Using the 2005 birth cohort of Latin American and Caribbean countries of 11 700 500 children (9), we projected the numbers of episodes and deaths due to pneumococcal disease using cumulative 5-year incidences or case-fatality ratios. Syndromes included in this projection were AOM, clinical pneumonia (without radiologic evidence of consolidation), radiologically confirmed pneumonia (with radiologic evidence of consolidation or pleural effusion), pneumococcal sepsis, and pneumococcal meningitis. These syndromes are mutually exclusive and therefore all-IPD and pneumococcal pneumonia were not included in the projections. Cumulative incidence was derived by using Kaplan-Meier analysis (10) from age-specific annual incidence rates and case-fatality ratios (ages 0 to 5 years) where available. Because data on the incidence of AOM were not available for the region, we used a cumulative incidence of 0.9 episode per child between birth and age 5 years derived from U.S. data (11), assuming that acute otitis media would be at least as common in Latin America and the Caribbean.

To calculate the number of vaccine-preventable episodes of each syndrome, we multiplied the estimated disease burden by the expected vaccine efficacy against specific syndromes and vaccine coverage for three doses of pneumococcal conjugate vaccine. We assumed vaccine coverage of 92%, equivalent to 2005 regional coverage for three doses of diphtheria-tetanus-pertussis vaccine (9). On the basis of the Northern California Kaiser Permanente pneumococcal conjugate vaccine trial, the expected vaccine efficacy for a heptavalent pneumococcal vaccine was 7% for all-cause AOM (2) and 4% for clinical pneumonia (12). We adjusted the 4% efficacy against clinical pneumonia downward to 3% to account for exclusion of radiologically confirmed pneumonia episodes, as we calculated that separately. Expected efficacy against radiologically confirmed pneumonia was 22.7% based on a standardized interpretation of chest x-rays from the Kaiser Permanente trial (13). Efficacy against pneumococcal pneumonia and pneumococcal sepsis was assumed to be 94%, the efficacy found against vaccine-serotype IPD in the Kaiser Permanente trial (2). We adjusted vaccine efficacies to account for differences in serotype distribution. The adjustment factor was calculated by dividing the potential PCV7 serotype coverage estimated for Latin America and the Caribbean by the coverage in the U.S. trial.

We used the model's estimated numbers of averted cases of all-cause AOM, clinical pneumonia, and chest x-ray-confirmed pneumonia and performed the following calculation to estimate numbers of pneumococcus-specific cases for each disease:

Number of pneumococcal cases of syndrome = (number of averted cases of all-cause syndrome)/
(% serotypes covered by vaccine)
× (% vaccine coverage)
× (vaccine efficacy against vaccine type invasive pneumococcal disease)

We estimated serotype coverage by syndrome for pneumococcal conjugate vaccine formulations including 7, 10, and 13 valency vaccines based on reported frequencies of these serotypes and cross-reactive serotypes from the same serogroup (with the exception of 19A, which has poor cross-reactivity (14)). The frequency of the most common serotypes was summarized by age and syndrome.

RESULTS

The 26 sources used to estimate disease burden are summarized in Table 1 (15–40) and Figure 1. They included 20 papers from South America (Brazil, 7; Chile, 5; Argentina, 4; Uruguay, 3; Peru, 1), 2 from Central America (Guatemala and Costa Rica), 1 from the Caribbean (Cuba), and 3 multicountry studies from PAHO's surveillance network. We included incidence data from 11 (42%) studies, case-fatality ratios from 15 (58%) studies, and serotype distribution from 6 (23%) studies.

Table 2 presents the annual incidence rates and case-fatality ratios of each pneumococcal disease syndrome by age. Annual incidence rates were obtained from more than two studies for only 7 of 16 (44%) syndrome and age combinations. Where incidence data were available for more than one age category (IPD, meningitis, and all pneumonia categories), the median annual incidence rate decreased with increasing age and for IPD was almost twice as high among children < 2 years of age (61/100 000) compared with children < 5 years of age (32/100 000). Case-fatality ratios were highest for pneumococcal meningitis (37%) and pneumococcal sepsis (35%) and were reported to be 0% for bacteremia (based primarily on outpatient surveillance).

Using the back-calculation outlined in the methods section, the proportion of disease due to pneumococcal infection was estimated to be 12% (n = 1.3 million episodes) for all-cause AOM, 40% (n = 270 000 episodes) for all-cause radiologically confirmed pneumonia, and 6% (n = 59 000 episodes) for all-cause clinical pneumonia without radiological evidence of consolidation. On the basis of expected vaccine efficacy, serotype distribution, and immunization coverage in the region, we estimated that approximately 54% of pneumococcal disease episodes and 53% of deaths due to pneumococcal infection among children < 5 years of age could be averted annually with introduction of heptavalent pneumococcal conjugate vaccine (Table 3). Therefore, of an estimated 10.8 million children in the birth cohort vaccinated annually, 660 000 to 1 100 000 cases of pneumococcal disease (130 000 to 270 000 cases excluding AOM), and 6 300 to 14 000 deaths could be averted.

Four papers with individual serotype data were included (Table 4). Six countries contributed data from PAHO's passive surveillance system for children < 6 years of age hospitalized with invasive bacterial disease for the time periods 1993–1999 (37) and 2000–2003 (38). Only the earlier paper presented data by syndrome. Two papers from Uruguay (30) and Argentina (39) presented data for children less than 2 years of age by syndrome. Uruguay presented data from 1994 to 2001 from hospitals participating in PAHO's surveillance network. The data from Argentina were collected as part of an active, population-based surveillance study between 1999 and 2002 and included in- and outpatients. Serotype 14 was the most common serotype (except for meningitis in children < 2 years of age, where serotype 5 was most common), making up 28% and 40% of invasive pneumococcal disease isolates from children < 2 years and < 6 years of age, respectively. An analysis of regional surveillance data among children < 6 years of age showed that 62% of IPD, 61% of pneumococcal meningitis, and 58% of pneumococcal pneumonia were caused by serotypes included in the heptavalent vaccine, including cross-reactive serotypes (Figure 2). Expected

TABLE 1. Included studies' contributing incidence, case-fatality ratio, and serotype data

Study reference	Publication type	Language	Year of publication	Country	Study design	Data included in analysis[a]			
						Epidemiological indicator: syndrome[b]	Years of surveillance	No. of SP isolates	Age
(15)	International	English	2006	Argentina	Active ambulatory and hospitalized population-based surveliance	Incidence: IPD, XRC pneumonia, Pnc pneumonia, Pnc bacteremia CFR: Pnc bacteremia	3 y	179	2–23 mo
(16)	International	English	2002	Chile	Active ambulatory and hospitalized population-based surveillance	Incidence: IPD, Pnc meningitis, Pnc pneumonia, Pnc sepsis CFR: IPD, Pnc meningitis, Pnc pneumonia	3 y	442	< 36 mo
(17)	National	Spanish	2001	Chile	Population-based hospital surveillance (9 hospitals)	Incidence: Pnc meningitis, Pnc pneumonia	7 y	846	< 5 y
(18)	International	English	2005	Cuba	National population-based surveillance	Incidence: Pnc meningitis	6 y	Not stated	1–5 y
(19)	International	English	2002	Brazil	Statewide active population-based surveillance	Incidence: Pnc meningitis CFR: Pnc meningitis	4 y	305	< 5 y
(20)	Regional	English	2003	Guatemala	Population-based hospital surveillance (3 hospitals)	Incidence: Pnc meningitis CFR: Pnc meningitis, clinical pneumonia	2 y 4 mo	77	1–59 mo
(21)	Regional	Spanish	1996	Chile	Prospective cohort study	Incidence: clinical pneumonia	1 y 6 mo	n/a	≤ 18 mo
(22)	International	English	2006	Uruguay	Population-based hospital surveillance (4 hospitals)	Incidence: clinical & XRC pneumonia	3 y	n/a	< 5 y
(23)	International	English	1994	Brazil	Randomized, double-blind, placebo-controlled community trial	Incidence: clinical pneumonia	1 y	n/a	6–48 mo
(24)	Abstract[c]	English	2005	Argentina	Population-based hospital surveillance (2 hospitals)	Incidence: XRC pneumonia	2 y	n/a	< 5 y
(25)	Abstract[c]	English	2006	Chile	Population-based hospital surveillance (3 hospitals)	Incidence: XRC pneumonia	2 y	n/a	1–35 mo
(26)	International	English	1998	Chile	Retrospective laboratory-based review (5 y) and prospective laboratory and hospital surveillance (3 y)	CFR: IPD. Pnc meningitis, Pnc pneumonia	8 y	274	< 2 y
(27)	International	English	2003	Costa Rica	Retrospective hospital review	CFR: IPD	7 y	99	< 5 y
(28)	National	Spanish	2002	Argentina	Laboratory- and hospital-based surveillance, part of PAHO surveillance system (19 hospitals)	CFR: IPD	3 y 6 mo	1 390	< 6 y
(29)	National	Spanish	2003	Peru	Sentinel surveillance (5 hospitals)	CFR: IPD, clinical pneumonia	1 y 3 mo	28	< 5 y
(30)	International	English	2003	Uruguay	Laboratory- and hospital-based surveillance, part of PAHO surveillance system	CFR: IPD, Pnc meningitis, serotype: IPD, Pnc meningitis, Pnc pneumonia	8 y	506	< 6 y
(31)	National	Portuguese	1990	Brazil	Sentinel surveillance (1 hospital)	CFR: Pnc meningitis	10	44	1–11 mo
(32)	International	English	1996	Brazil	Sentinel surveillance (2 hospitals)	CFR: Pnc meningitis	4	58	< 2 y
(33)	National	Portuguese	1990	Brazil	Retrospective chart review (28 hospitals)	CFR: Pnc meningitis	17	1 028	< 5 y
(34)	National	English	2002	Brazil	Prospective cohort study (2 hospitals)	CFR: Clinical pneumonia	1 y 2 mo	n/a	< 6 y
(35)	Regional	English	1994	Uruguay	Etiology study (1 hospital)	CFR: Clinical pneumonia	4	48	1 mo–5 y
(36)	Regional	Spanish	2000	Multicountry	PAHO laboratory-based surveillance network	CFR: Pnc pneumonia	6	1 409	< 6 y
(37)	International	English	2001	Multicountry	PAHO laboratory-based surveillance network	Serotype: IPD, Pnc meningitis, Pnc pneumonia	6	4 105	< 6 y
(38)	Regional	English	2006	Multicountry	PAHO laboratory-based surveillance network	Serotype: IPD	3	3 264	< 6 y
(39)	National	Spanish	2006	Argentina	Active population-based surveillance (ambulatory and 4 hospitals)	Serotype: IPD, Pnc pneumonia	3	179	2–23 mo
(40)	Regional	Portuguese	1990	Brazil	Laboratory-based surveillance	Serotype: Pnc meningitis	12	308	≤ 2 y

[a] Papers may include more data or more age groups but only data used in burden estimates listed here.
[b] XRC, radiologically confirmed; Pnc, pneumococcal; IPD, invasive pneumococcal disease; CFR, case-fatality ratio; y, year; mo, month; n/a, not applicable.
[c] Additional information obtained from authors.

FIGURE 1. Distribution of studies used in burden of disease analysis, by subregion and country

serotype coverage was higher for proposed vaccine formulations including 10 and 13 serotypes.

DISCUSSION

This review and synthesis of existing evidence of pneumococcal disease in Latin American and Caribbean countries provide estimates of the annual number of episodes and deaths that could be prevented with universal introduction of pneumococcal conjugate vaccines for young children. Vaccination with a heptavalent pneumococcal conjugate vaccine could prevent more than half of all episodes of pneumococcal disease and related deaths among children < 5 years of age in the region. This value translates into 1 life saved per 1 100 children vaccinated, 1 case prevented per 60 children vaccinated excluding AOM, and 1 case prevented per 13 children vaccinated including AOM. Vaccine formulations that include additional serotypes could cover a larger proportion of pneumococcal serotypes causing invasive disease in the region. Active surveillance is needed to determine with better precision the burden of pneumococcal diseases, increase awareness of this burden, monitor the introduction of pneumococcal vaccines, and evaluate the impact of the vaccine including changes in disease burden, serotype distribution, antimicrobial resistance patterns, and herd effects.

This study is limited by the number of studies reporting incidence data and the quality of the studies, which led us to exclude several. We extrapolated information to the whole region based on data from studies in only a few countries and in some cases based on only one study. This procedure likely underestimated disease burden as most studies that met our inclusion criteria came from the more developed countries in the region, which are likely to have lower disease burden and better access to care. Because of the very limited number of studies included overall and the predominance of studies from Brazil and the Southern Cone, we were unable to stratify our findings by subregion. Most data came from studies in health care facilities, particularly tertiary hospitals, making the results very dependent on access to care, care-seeking behavior, and quality of medical care. As we did not adjust for access to care, our results may have over- or underestimated the number of events, particularly since criteria for hospitalization vary significantly from country to country and case-fatality ratios for hospitalized children may be higher.

Our findings show that the incidence of pneumococcal meningitis was roughly a third of the incidence of IPD, and about half of all isolates from PAHO's regional surveillance network are meningitis. This finding is in contrast to 4% to 5% of total IPD obtained from U.S. population-based surveillance in children < 2 years and 2% to 3% for children 2 to 4 years old (41). This likely reflects the variation in the rate of taking blood cultures. In the United States, blood cultures are performed more frequently than in other parts of the world (42) and higher rates of blood culture sampling have been associated with a higher incidence of invasive pneumococcal disease (43). This review used a vaccine coverage rate of 92% based on three doses of diphtheria-tetanus-pertussis vaccine. The vaccine efficacy estimates that we used for PCV7 are based on trials using a three-dose infant schedule with a booster in the second year of life. Although a study in the United States showed that three infant doses of PCV7 with a booster (100%) were more protective against vaccine-type disease than were three infant doses alone (95%) (14), we do not expect that this has greatly changed our burden estimates, as the effectiveness of PCV7 was still found to be very high with only three doses.

An additional reason that our projections may be underestimates is the difficulty of diagnosing pneumococcal infection, particularly when there has been previous antibiotic use. Clinical trials have shown that pneumococcal conjugate vaccines prevent a much larger number of noninvasive episodes than invasive disease, and overall impact has been greater than expected based on serotype distribution and incidence rates of invasive pneumococcal disease (3, 4). For example, introduction of pneumococcal conjugate vaccine in the United States was temporally associated with a 39% reduction in pneumonia hospitalizations among children < 2 years of age (44). Pneumococcal conjugate vaccines reduce nasopharyngeal carriage of vaccine serotypes, resulting in decreased community transmission and "herd pro-

TABLE 2. Median annual incidence and case-fatality ratios (CFR) of pneumococcal disease by age and syndrome

Age group[a]	No. of studies with incidence data (reference)	No. of cases in all studies combined (minimum–maximum)[b]	Median annual incidence/100 000 (25th–75th percentile)[c]	No. of studies with CFR data (reference)	Median CFR (25th–75th percentile)[b]
Invasive pneumococcal disease[d]					
< 1 year	2 (15, 16)	156 (26–130)	61 (58–63)	. . .[e]	. . .
< 2 years	2 (15, 16)	268 (69–199)	61 (52–71)	2 (26, 27)	12 (9–16)
< 5 years	1 (16)	224	32 (32–33)	4 (16, 28, 29, 30)	10 (9–11)
Pneumococcal meningitis					
< 1 year	1 (17)	155	19	1 (31)	34
< 2 years	1 (17)	198	12	3 (26, 30, 32)	30 (25–35)
< 5 years	4 (16, 18–20)	37[f]	11 (9–15)	5 (16, 19, 20, 30, 33)	37 (33–54)
All-cause clinical pneumonia (includes radiologically confirmed pneumonia)					
< 1 year	1 (21)	29	7 651[g]	1 (34)	3
< 2 years	1 (22)	2 022	7 173[g]	. . .	. . .
< 5 years	2 (22, 23)	1 802 (35–1 767)	2 834 (2 673–2 995)	3 (20, 29, 35)	3 (2–6)
All-cause radiologically confirmed pneumonia					
< 1 year	4 (15, 22, 24, 25)	1 983 (240–1 015)	2 163 (1 744–2 670)	. . .	. . .
< 2 years	4 (15, 22, 24, 25)	3 830 (439–2 112)	2 100 (1 723–2 375)	. . .	. . .
< 5 years	3 (22, 24, 25)	2 564 (606–1 132)	1 174 (980–1 613)	. . .	. . .
Pneumococcal pneumonia[h]					
< 2 years	2 (15, 17)	350 (51–299)	51 (47–55)	1 (26)	8
< 5 years	1 (16)	118	34	2 (16, 36)	5 (5–6)
Pneumococcal bacteremia[i]					
< 2 years	1 (15)	10	12	1 (15)	0[j]
Pneumococcal sepsis					
< 3 years	1 (16)	51	2	1 (16)	35

[a] Age groups are not mutually exclusive.
[b] Studies with < 30 pneumococcal isolates or < 30 cases of a particular syndrome were excluded. However, where subanalysis resulted in fewer than 30 isolates or cases these data were included.
[c] When number of studies = 1, annual incidence is presented.
[d] Inpatient rate shown. Outpatient median annual incidence of IPD in children < 1 year 80.5/100 000 (56.4–104.7) (15, 16), children < 2 years 81.0/100 000 (57.6–104.3) (15, 16), children < 5 years 27/100 000(16).
[e] . . . , no data.
[f] Only two studies gave denominators.
[g] Inpatient rate.
[h] Inpatient rate shown. Outpatient pneumococcal pneumonia annual incidence among children < 1 year was 36/100 000 (15).
[i] Inpatient rate shown. Outpatient bacteremia annual incidence among children < 2 years was 87/100 000 in Argentina (15), 34.7/100 000 in Chile (16), and 31.6/100 000 among children < 3 years in Chile (16).
[j] 88% of bacteremia cases were ambulatory (15).

tection" of unvaccinated children and adults. We did not adjust for potential herd effects in our study. Minimal data on the burden of pneumococcal disease in adults were available, making assumptions difficult. The impact of pneumococcal vaccine is expected to be higher due to herd effects and was estimated to cause an 8% to 36% reduction in U.S. adults (7).

No quality indicators currently exist for pneumonia and invasive disease surveillance data. A review of *Haemophilus influenzae* studies showed insufficient data to determine the sensitivity of case ascertainment in 44 papers with incidence data (45). Our strict inclusion criteria captured the highest-quality studies, but to facilitate a more formal assessment of data, we recommend that quality indicators be developed for pneumonia and invasive disease surveillance. These could include indicators to allow some assessment of microbiological capacity and quality, such as the proportion of cerebrospinal fluid and blood cultures with a bacterial pathogen identified, and, to assess access to care and clinical practice, the proportion of children admitted who had a lumbar puncture or blood cultures performed.

Better disease burden estimates are needed. WHO, together with GAVI's PneumoADIP, is conducting a comprehensive global review and modeling exercise of the available data on pneumococcal disease burden with estimates by country, subregion, region, and globally expected in late 2008. Our data will be complementary to the WHO disease burden project since they provide more detailed information about the Latin

TABLE 3. Projected annual burden of pneumococcal disease and number of events averted with 7-valent pneumococcal conjugate vaccine (PCV7) in Latin America and the Caribbean in children < 5 years of age[a]

Syndrome	Projected burden of disease using cumulative 5-year incidence[b] (sensitivity analysis)[c]	Number (%) of cases of each syndrome estimated to be caused by pneumococcus[d] (sensitivity analysis)[c]	Pneumococcal events averted by PCV7 vaccine (%)[e] (sensitivity analysis)[c]
Acute otitis media	10 500 000 (8 200 000–12 900 000)	1 300 000 (12) (980 000–1 500 000)	680 000 (52) (530 000–830 000)
All-cause clinical pneumonia	1 700 000 (1 300 000–2 170 000)	330 000 (19) (250 000–410 000)	180 000 (53) (130 000–220 000)
All-cause radiologically confirmed pneumonia	670 000 (510 000–840 000)	270 000 (40) (200 000–340 000)	140 000 (53) (110 000–180 000)
All-cause clinical pneumonia excluding radiologically confirmed pneumonia	1 070 000 (800 000–1 300 000)	59 000 (6) (44 000–73 000)	32 000 (54) (24 000–40 000)
Pneumococcal sepsis	1 200 (900–1 500)	n/a[f]	660 (55) (500–800)
Pneumococcal meningitis	3 900 (2 600–6 800)	n/a	2 100 (54) (1 400–3 600)
Pneumococcal deaths	18 000 (12 000–28 000)	n/a	9 500 (53) (6 300–14 000)

[a] Projections rounded to nearest 10 for numbers 100–999, 100 for numbers 1 000–9 999, 1 000 for numbers 10 000–99 000, 10 000 for numbers 100 000–999 999, and 100 000 for ≥ 1 000 000.
[b] Probability of each syndrome calculated from Kaplan-Meier analysis and projected by using the regional birth cohort of 11.7 million.
[c] Sensitivity analysis varies cumulative 5-year incidence rates, case-fatality ratios, and vaccine efficacy estimates.
[d] Events of all-cause disease averted calculated as follows: no. of pneumococcal cases of syndrome = (no. of averted cases of all-cause syndrome)/((% serotypes covered by vaccine × (% vaccine coverage) × (vaccine efficacy against vaccine type invasive pneumococcal disease)).
[e] Cumulative 5-year incidence adjusted for vaccine efficacy, vaccine coverage, and serotype coverage. Percentage is proportion of pneumococcal cases of a syndrome that are averted.
[f] n/a = not applicable.

American and Caribbean region despite different methods used. The burden of pneumococcal disease in Latin America and the Caribbean is lower than estimates from other regions such as the United States and Africa. Our results are likely underestimates for the reasons explained above, and the true burden is likely to be closer to, or above, the burden in the United States during the prevaccine era. The incidence of invasive pneumococcal disease in children < 5 years of age ranges from 111 to 436 per 100 000 in Africa (46) and was reported to be 96 per 100 000 in children < 5 years in the United States in the prevaccine era (7). In our review, the incidence of invasive pneumococcal disease in children < 5 years was 32 per 100 000. However, these data come from one study in a more developed country (Chile). It demonstrated that, as the clinical threshold for obtaining a blood culture decreased, the ability to detect the true incidence increased, indicating that reported disease rates can be affected by clinical practice (16).

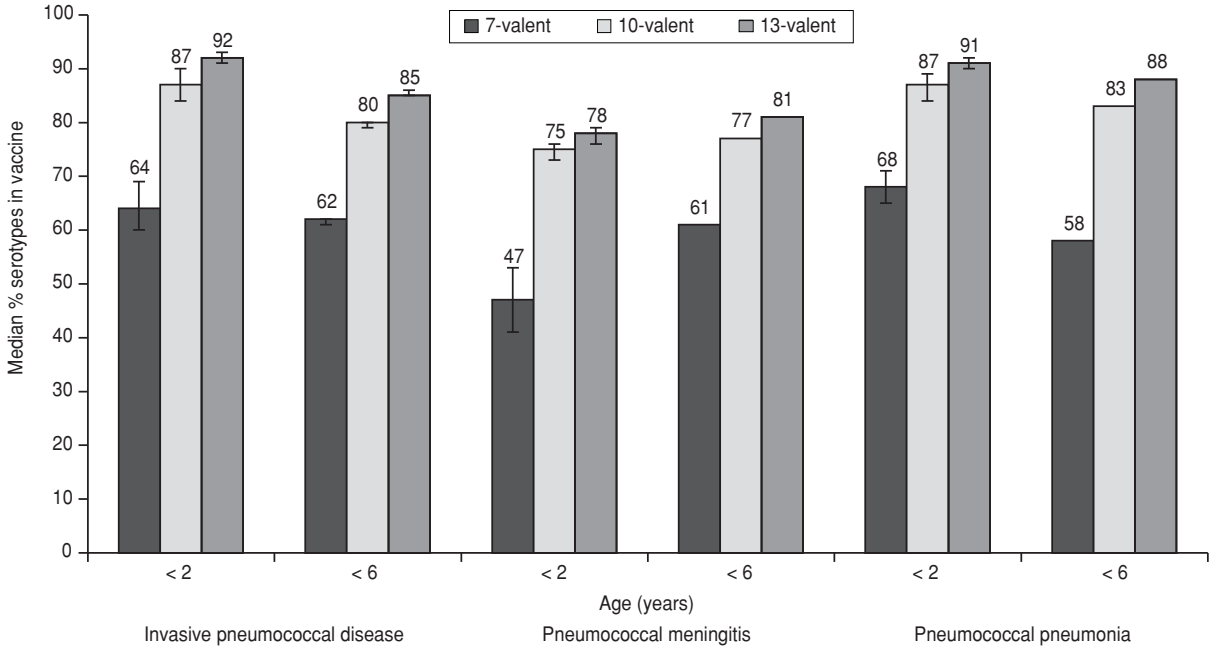
A major challenge facing regional pneumococcal introduction is the issue of vaccine financing. At $53 per dose and

TABLE 4. Most common pneumococcal serotypes by age and syndrome

	Number (%) of IPD[a] pneumococcal serotypes					
	< 6 years[b]			< 2 years		
Serotype	All IPD	Pneumococcal pneumonia	Pneumococcal meningitis	All IPD	Pneumococcal pneumonia	Pneumococcal meningitis
14	2 008 (28)	565 (33)	318 (20)	194 (40)	138 (52)	15 (15)
6A/6B	959 (13)	180 (11)	234 (15)	41 (9)	17 (6)	11 (11)
5	590 (8)	192 (11)	133 (8)	64 (13)	29 (11)	24 (25)
1	555 (7)	205 (12)	86 (5)	29 (6)	13 (5)	3 (3)
23F	454 (6)	75 (4)	113 (7)	10 (2)	3 (1)	3 (3)
19F	363 (5)	51 (3)	83 (5)	6 (1)	2 (1)	2 (2)
18C	312 (4)	21 (1)	125 (8)	17 (4)	1 (0)	4 (4)
19A	236 (3)	63 (4)	41 (3)	. . .[c]	. . .	. . .
9V	224 (3)	55 (3)	43 (3)	13 (3)	9 (3)	0 (0)
3	189 (3)	31 (2)	24 (2)	21 (4)	15 (6)	3 (3)
7F	189 (3)	34 (2)	46 (3)	20 (4)	9 (3)	8 (8)
4	114 (2)	21 (1)	24 (2)	3 (1)	1 (0)	1 (1)
Other	1 075 (15)	214 (13)	323 (20)	63 (13)	26 (10)	23 (24)
Total	7 335 (100)	1 707 (100)	1 593 (100)	481 (100)	263 (100)	0
No. of studies	2	1	1	2	2	2
References	(37, 38)	(37)	(37)	(30, 39)	(30, 39)	(30, 39)

[a] IPD, invasive pneumococcal disease.
[b] Data from PAHO's surveillance network.
[c] . . . , no data.

FIGURE 2. Median percentage of invasive pneumococcal disease, meningitis, and pneumococcal pneumonia caused by serotypes included in the vaccine with interquartile range[a] for three pneumococcal conjugate vaccine preparations, by age (years); coverage includes vaccine serotypes and related serotypes, with the exception of 19A



[a] Interquartile range presented when > 1 study was analyzed.

assuming a four-dose schedule, the cost to fully vaccinate one child against pneumococcal disease is more than the cost of vaccinating a child with all routine vaccines combined. Sustainable vaccine financing for developing countries is being achieved through the GAVI Alliance, Advanced Market Commitments, and the International Financing Facility for Immunizations (www.pneumoadip.org). However, only six countries in the region qualify for this support. In other countries, governments pay the bulk of costs of vaccination programs. A very successful revolving fund for bulk purchasing of vaccines has contributed to the lead this region has taken in adopting new and underutilized vaccines, including *H. influenzae* type b vaccine. Despite the high cost, there is strong public support for public immunization programs in the region. Countries are moving to comply with the WHO recommendation to introduce pneumococcal vaccine (1), and prevention of pneumonia is a public health priority for many governments. Strong surveillance systems are essential to monitor the impact of more expensive vaccines and to guide policy, and they cost only a fraction of the vaccine price.

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La carga de enfermedad neumocócica en niños de América Latina y el Caribe: revisión de la información científica

RESUMEN

Objetivo. Realizar una revisión amplia de los datos sobre la incidencia de la enfermedad neumocócica en América Latina y el Caribe y proyectar el número anual de episodios de la enfermedad y de defunciones entre niños menores de 5 años de edad en la región.

Métodos. Se llevó a cabo una revisión sistemática (1990–2006) sobre la carga de la enfermedad neumocócica en niños < 5 años en la región. Las incidencias anuales y las tasas de letalidad se compendiaron mediante las medianas y los rangos intercuartiles de la enfermedad neumocócica invasiva (en su conjunto y por separado para meningitis, neumonía, bacteremia y sepsis neumocócicas), la neumonía (todos los casos confirmados mediante radiología) y la otitis media aguda, por grupos de edad: < 1 año, < 2 años y < 5 años. Se modeló la incidencia acumulada de la enfermedad específica para la edad mediante el análisis estándar de Kaplan-Meier y se proyectaron los datos para obtener estimados regionales de la carga de la enfermedad. Para estimar el número de casos y muertes evitados se ajustaron los estimados de la carga según la cobertura de los serotipos bacterianos, la cobertura de la vacunación y la eficacia de la vacuna.

Resultados. De las 5 998 referencias identificadas se seleccionaron 26 artículos de 10 países. La carga anual estimada de neumonía, meningitis y otitis media aguda causadas por neumococos en niños < 5 años varió entre 980 000 y 1 500 000, 2 600 y 6 800, y 980 000 y 1 500 000, respectivamente. Se estimó que en la región podrían morir anualmente entre 12 000 y 28 000 niños debido a la enfermedad neumocócica. La vacuna antineumocócica conjugada podría salvar una vida por cada 1 100 niños vacunados y evitar un caso de enfermedad por cada 13.

Conclusiones. Se podría evitar una parte substancial de la carga de enfermedad neumocócica en la región mediante la aplicación de vacunas antineumocócicas conjugadas y esto se debe tener en cuenta al tomar decisiones sobre la vacunación en la región. Estos resultados están limitados por los pocos estudios —realizados en ubicaciones específicas— analizados en esta revisión.

Palabras clave *Streptococcus pneumoniae*, vacunas neumocócicas, revisión, América Latina, región del Caribe.