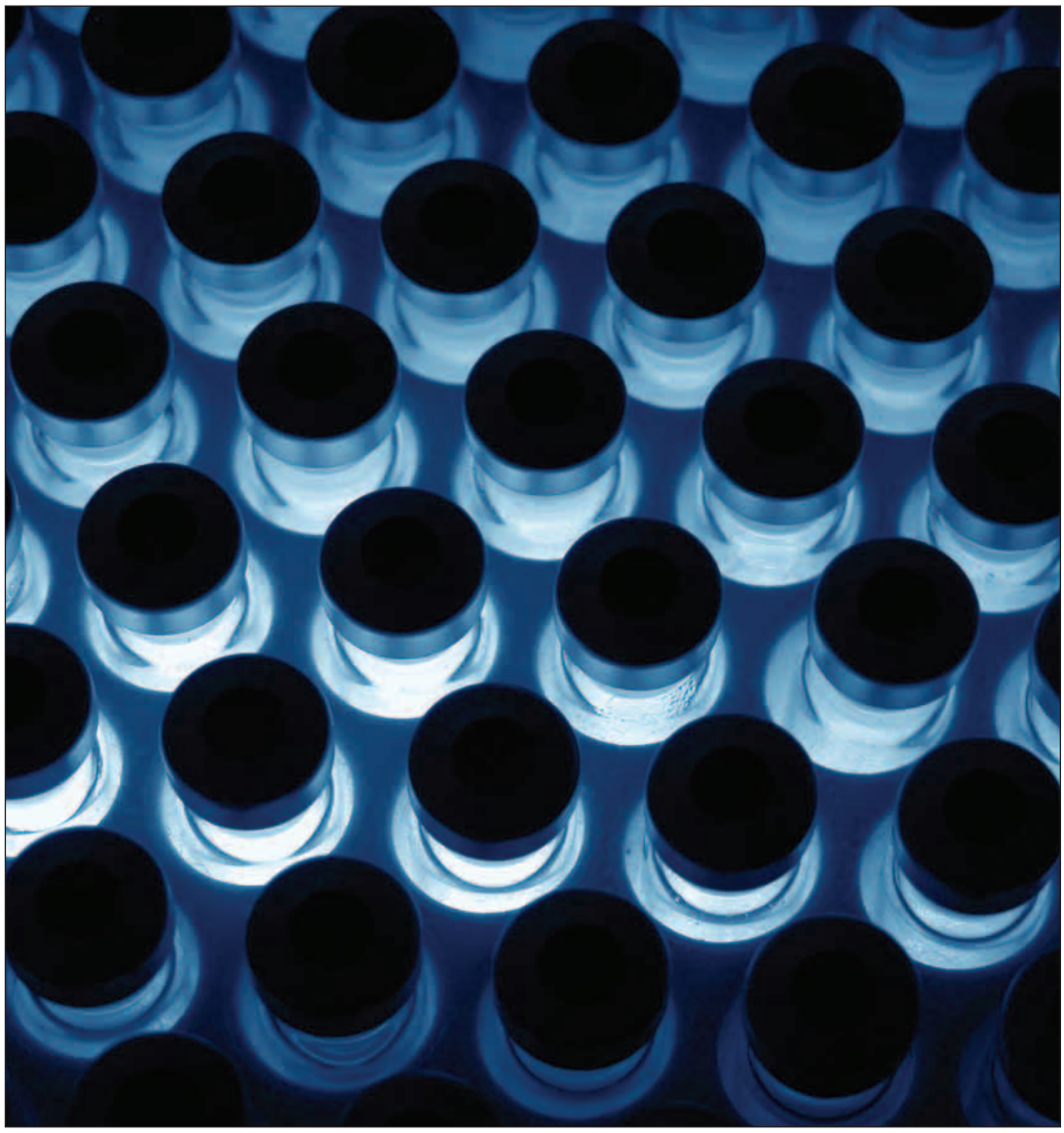
The Burden of Pneumococcal Disease and Cost-Effectiveness of a Pneumococcal Vaccine in Latin America and the Caribbean

A Review of the Evidence and a Preliminary Economic Analysis

2007



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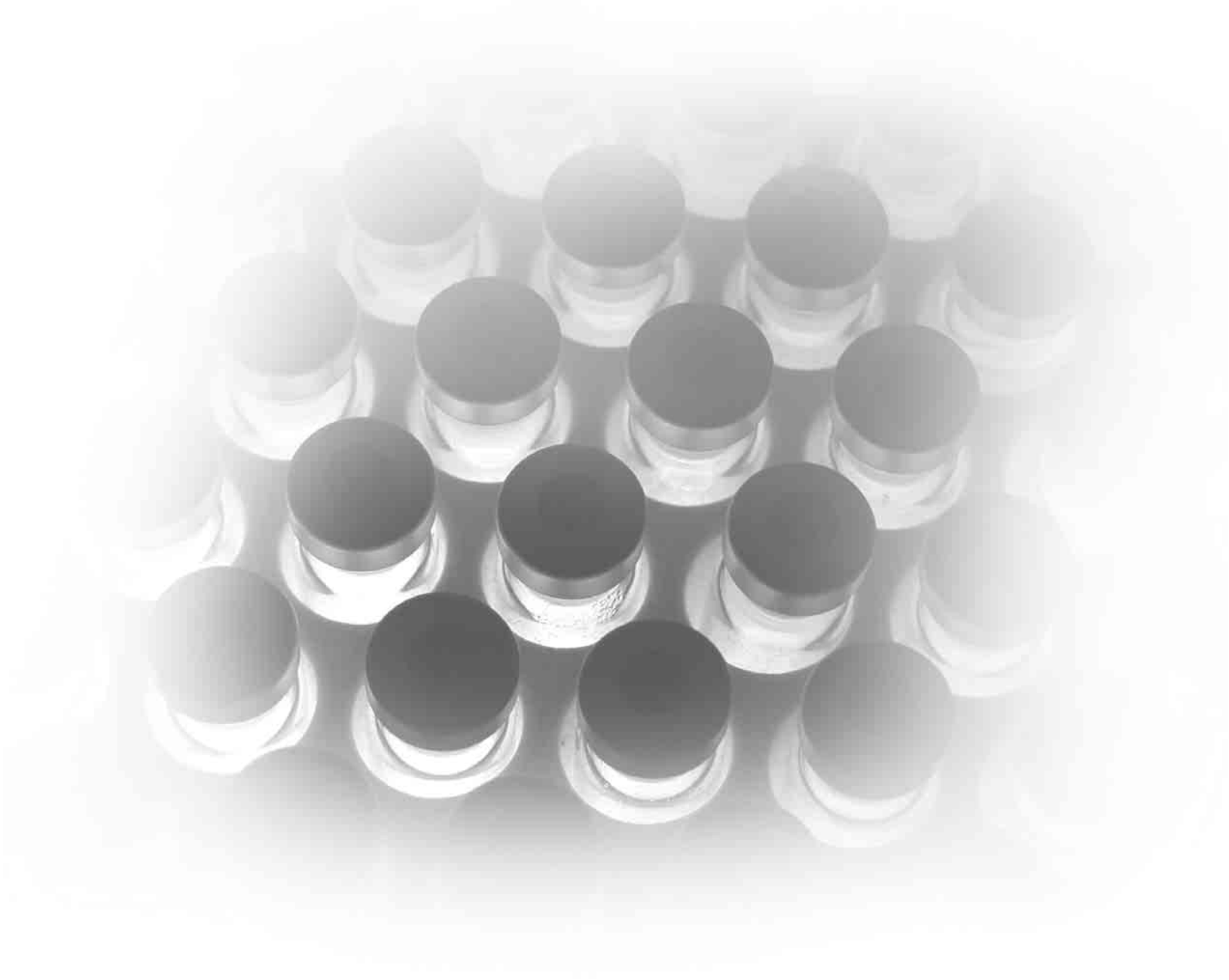

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GAVI's Pneumococcal Accelerated Development and Introduction Plan at Johns Hopkins (PneumoADIP), Baltimore, MD

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This report can be accessed at the Sabin Vaccine Institute www.sabin.org.

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EXECUTIVE SUMMARY

Background and Aim: *Streptococcus pneumoniae* (SP), or pneumococcus, causes a number of clinical conditions (including pneumonia, meningitis, bacteremia, sepsis and acute otitis media [AOM]), each of which has multiple other causes. SP is an important cause of morbidity, mortality and healthcare system costs. 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 less than five years of age. The majority of these deaths are due to pneumonia with SP as the most common agent. An effective pneumococcal conjugate vaccine exists which has been shown to reduce the likelihood of pneumococcal disease in young children, and reduce transmission from young children to adults.

The aim of this review is to estimate the burden (mortality, morbidity, and disability) and costs of pneumococcal disease in Latin America and the Caribbean. The findings will be used to inform national health authorities about the burden of pneumococcal disease and the economic value of implementing a pneumococcal conjugate vaccination program in selected countries in Latin America and the Caribbean. To achieve this aim, we conducted a review of the published and unpublished epidemiological and economic literature using the information gathered to estimate the disease and economic burden of *S. pneumoniae* and the cost-effectiveness of vaccination in Latin America and the Caribbean.

Methods: We conducted online literature searches using six electronic databases including all ages and all languages for the period 1990 to 2006 for Latin America and the Caribbean. We reviewed data from all languages, concentrating on English, Spanish, and Portuguese. We used search terms relating to pneumococcal syndromes (pneumonia, meningitis, bacteremia, and AOM) and *S. pneumoniae* . We identified 5,998 citations for review. Based on predefined inclusion and exclusion criteria, we abstracted 143 full-text peer-reviewed studies for the final epidemiological analysis. In addition, we contacted 48 pneumococcal researchers known to us in 13 countries and received 34 replies. We visited some of these researchers in Argentina, Brazil, Chile, Colombia, Dominican Republic, and Uruguay, and corresponded with others by phone or e-mail. We surveyed healthcare providers to determine criteria for hospitalization, length of stay, and cost of care. In addition, we reviewed conference abstracts and contacted all national Ministries of Health (MoH) in the region through the Pan American Health Organization (PAHO) to identify additional information on pneumococcal disease.

Using the abstracted and collected data, we estimated summary measures of disease incidence, antibiotic resistance, and serotype coverage by vaccine. For the region, the burden of pneumococcal disease was estimated for the annual birth cohort from birth until age five. We considered these diseases: all-cause acute otitis media, pneumococcal clinical pneumonia (inpatient/outpatient), pneumococcal chest x-ray confirmed pneumonia (inpatient/outpatient), pneumococcal sepsis, and pneumococcal meningitis. By incorporating cost-of-care information, we were able to also estimate the economic burden of pneumococcal disease. As a final step, we integrated our data with assumptions about vaccine-related costs and coverage to estimate the cost-effectiveness of pneumococcal conjugate vaccine in the Latin American and Caribbean region.

Findings: Pneumococcal disease is a relatively common disease with an estimated 1.3 million cases of AOM, 327,000 pneumonia cases (clinical and chest x-ray positive), 1,229 cases of sepsis, and nearly 4,000 cases of pneumococcal meningitis occurring annually in Latin America and the Caribbean. The large burden of pneumococcal AOM is a significant contributor to the substantial healthcare system costs and the broader use of antibiotics. Introduction of pneumococcal conjugate vaccines can greatly reduce the incidence of pneumococcal infections. We estimate that vaccination could prevent over half of all cases of pneumococcal disease annually in the region including 9,478 deaths. This translates into almost one life saved per 1,000 and one case prevented for every 80 children vaccinated. Cost-effectiveness analyses indicated that the vaccine program meets the criteria for "cost-effective" at a wide range of prices, suggesting that affordability rather than cost-effectiveness will be a major issue for vaccine introduction.

Surveillance Recommendations: We recommend strengthening the PAHO surveillance network to:

- Continue surveillance for pneumococcal serotype distribution and antimicrobial resistance in children,
- Identify and support population-based surveillance for invasive pneumococcal disease at suitable sites in each sub-region (especially Central America and the Caribbean) to demonstrate the impact of vaccination on *Streptococcal pneumoniae* disease after introduction,
- Collect invasive pneumococcal disease (IPD) epidemiological data on children less than two years of age, case outcome, and clinical characteristics that will facilitate more frequent publication of data,
- Establish surveillance for IPD in adults to measure the indirect effects of the vaccine,
- Support research to develop diagnostic and burden assessment tools to simplify pneumococcal disease surveillance,

  and
- Develop surveillance indicators and key parameters to be included in publications so that the quality of surveillance data can be compared across studies.

Literature Recommendation:

- Authors should present adequate data so that epidemiological studies can be assessed for quality; such data should include descriptive laboratory practices, prior antibiotic use, case definitions, and definition of numerators and denominators.

Recommendations for Future Economic Studies:

- Future research should, where possible:
  - Incorporate the indirect effects of vaccination, including herd immunity protection of unvaccinated children and adults and serotype replacement,
  - Assess the analytical-conceptual framework used in this model,
  - Perform more detailed investigation of indirect costs,
  - Examine differences in costs and cost-effectiveness across countries,
  - Include a health-related quality of life measure with longer time horizon,
  - Capture private system costs and cost of treatment in less formal settings,
- Country staff should continue to support and train in cost-effectiveness models so that policy makers will better appreciate and understand the value of vaccination. Efforts to help ensure consistent methodology across countries and vaccines, such as PAHO's Pro-Vac model, will also increase the quantity and quality of literature on the economics of vaccines in the region,
- Investigators should collect cost data alongside effectiveness trials of a pneumococcal conjugate vaccine. Effectiveness trials provide a valuable opportunity to obtain accurate estimates of both the health and economic burden of vaccine-preventable disease in real conditions,

  and
- More comprehensive guidelines are needed for the conduct, evaluation, and reporting of economic studies, and for sensitivity and uncertainty analysis to determine the validity of the cost data and cost-effectiveness results. These guidelines will ensure that cost and cost-effectiveness findings are more credible and acceptable for decision-making purposes.

ABBREVIATIONS

ABM	Acute Bacterial Meningitis
AIH	Autorización de Internación Hospitalaria (hospital admission authorization system)
AOM/OM	Acute Otitis Media/Otitis Media
APAC	Autorización de procedimientos de Alta Complejidad (Authorization System for Highly Complex medical procedures)
ATC	Anatomical Therapeutic Chemical
BIREME	PAHO Specialized Center, established in Brazil since 1967, in collaboration with Ministry of Education , São Paulo Secretary of Health and the Federal University of São Paulo
CAP	Community-Acquired Pneumonia
CBA	Cost-Benefit Analysis
CDC	Centers for Disease Control and Prevention
CE	Cost-Effectiveness
CEA	Cost-Effectiveness Analysis
CEDEPAP	Centre for the Development of Advanced Projects in Córdoba
CEPAL	Comisión Económica para América Latina y el Caribe/Economic Commission for Latin America and the Caribbean
CER	Cost-Effectiveness Ratio
CFR	Case Fatality Rate
CMA	Cost Minimization Analysis
COI	Cost of Illness Study
CP	Consolidated Pneumonia
CPI	Consumer Price Index
CRIE	Reference Center for Special Vaccine
CSF	Cerebrospinal-Fluid
CUA	Cost-Utility Analysis
CU	Cost-Utility
DALY	Disability-Adjusted Life Year
DPT	Diphtheria-Pertussis-Tetanus
DR	Dominican Republic
DRSP	Drug-Resistant *S. pneumoniae*
ENT	Ear-Nose-Throat
EPI/PAI	Expanded Program on Immunization
ER	Emergency Room
GAVI	Global Alliance for Vaccines and Immunizations
GBD	Global Burden of Disease
GDP	Growth Domestic Product
GNI	Gross National Income
GNP	Gross National Product
Hib	*Haemophilus influenzae* type B
ICD-9	International Classification of Disease - version 9
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
ILO	International Labor Organization
IMCI	Integrated Management of Childhood Illness

IPD	Invasive Pneumococcal Disease
IQR	Interquartile Range
LCR	Ligase Chain Reaction
LOS	Length of Stay
LYS/LYG	Life Years Saved/Life Years Gained
Max	Maximum
MEF	Middle Ear Fluid
MeSH	Medical Subject Headings
MIC	Minimum Inhibitory Concentration
MIN	Minimum
MoH	Ministry of Health
NA	Not available
NCKP	Northern California Kaiser Permanente
NCP	Non-Consolidated Pneumonia
OP	Obvious Pneumonia
PAHO	Pan American Health Organization
PCR	Polymerase Chain Reaction
PCV7	Seven-Valent Pneumococcal Conjugate Vaccine
PM	Pneumococcal Meningitis
PneumoADIP	GAVI's Pneumococcal Accelerated Development & Introduction Plan
PP	Pneumococal Pneumonia
PPP	Purchasing Power Parity
Pro-Vac	Promote the Implementation of Economic Analysis for Vaccine introduction in countries of Latin America and the Caribbean
QALY	Quality-Adjusted Life-Year
RSV	Respiratory Syncytial Virus
Rx	Radiology
RxC	Radiologically confirmed
SIREVA	Regional System for Vaccines
SP	*Streptococcus pneumoniae*
SVI	Sabin Vaccine Institute
US	United States of America
USD	United States Dollar
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organization
WHO-CHOICE	WHO — CHOosing Interventions that are Cost Effective
YLD	Years Lived with Disability
YLL	Years Life Lost

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CHAPTER 1 INTRODUCTION

1.1 Background

Streptococcus pneumoniae (SP), also known as pneumococcus, is an important cause of illness in children and adults. In children, it causes a number of clinical conditions, such as pneumonia, meningitis, bacteremia, sepsis and acute otitis media (AOM), but is not the unique cause of any of them. Because it is relatively common and severe, pneumococcal disease represents an important cause of morbidity, mortality, and healthcare system costs. In the past, the World Health Organization (WHO) global estimates of mortality have ranged from >700,000 to 1 million child deaths, and about 1.6 million deaths among persons of all ages annually. [1]

Diagnoses of pneumococcal disease require laboratory identification of *S. pneumoniae*. Estimating the total burden of pneumococcal disease is challenging because standard diagnostics have a low sensitivity, i.e., laboratory tests are positive in only a fraction of the children who truly have pneumococcal disease, and therefore, observational studies and surveillance systematically underestimate pneumococcal disease burden. Estimates of the true burden of *S. pneumoniae* disease are only possible with the use of vaccine probe trials to dissect out the fraction of pneumonia cases that are due to these organisms. Differences in incidence could be due to true differences in the patient population studied or differences in the operator's skill in the laboratory.

The leading cause of pneumonia deaths worldwide is SP and most pneumococcal deaths are due to pneumonia. An effective pneumococcal conjugate vaccine is available now to prevent these infections and deaths. Vaccine trials in a wide range of epidemiologic settings have shown the vaccine to be highly efficacious for preventing proven pneumococcal disease, pneumonia, otitis media, and even overall pneumonia. In February 2000, a 7-valent pneumococcal protein-polysaccharide conjugate vaccine was licensed for use in young children in the US. Conjugate vaccine was recommended for all children under two years of age and for high-risk children two to four years old. Data from the Centers for Disease Control and Prevention's (CDC) Active Bacterial Core Surveillance/Emerging Infections Program Network indicate that rates of invasive pneumococcal disease have fallen dramatically in children since the introduction of this vaccine in the high-risk group.[2] Rates of disease caused by serotypes in the conjugate vaccine have also fallen in adults, suggesting that the vaccine is interrupting transmission. In addition, antibiotic resistant infections are becoming less common. These data indicate that the vaccine is providing major benefits for reducing morbidity and mortality due to pneumococcal disease in the US.

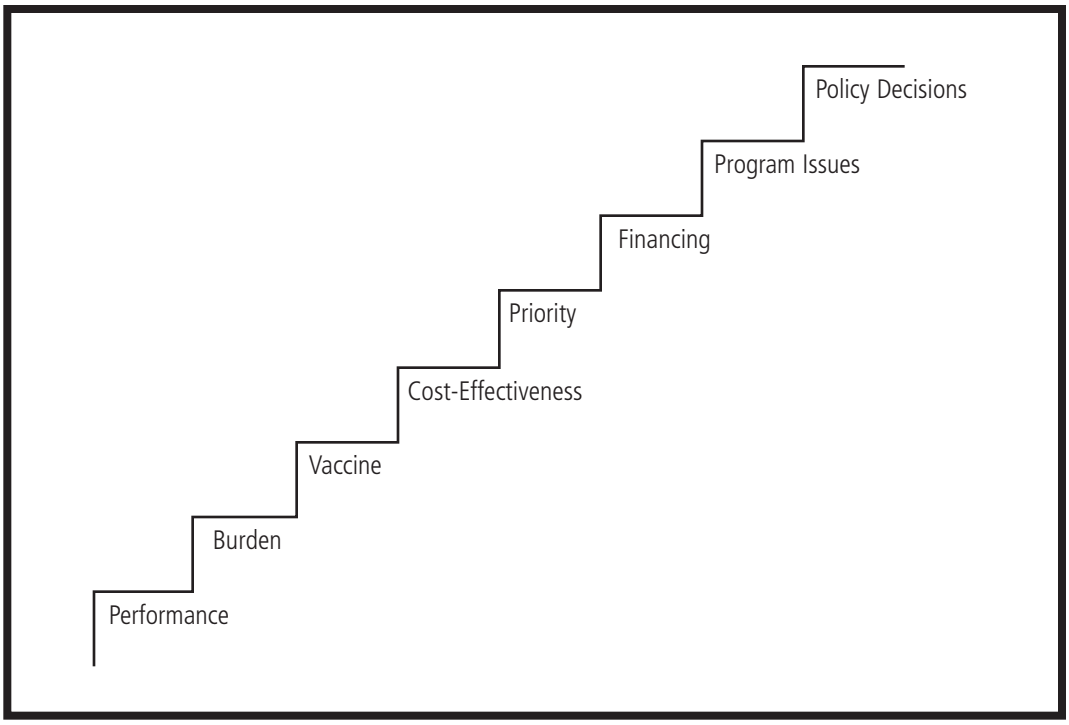
Currently the 7-valent vaccine is the only pneumococcal conjugate vaccine available and in use. Other vaccines with higher valencies (10 and 13) are undergoing clinical trials, and are estimated to be available in the next two to three years. To date, vaccine trials of various conjugate vaccines have all shown a high efficacy against invasive disease caused by the serotypes contained in the vaccines. Currently, infant pneumococcal vaccination is not a routine part of the Expanded Program of Immunization in any country in Latin America and the Caribbean. As of December 2006, its use has been limited to high risk children (e.g. Brazil, Chile, and Colombia) or in some districts (e.g., Mexico).

1.2 Vaccine Decision Making

Establishing the burden of disease and creating demand for the pneumococcal conjugate vaccine are first steps to accelerate vaccine introduction. Decisions to introduce a new vaccine may follow a process like the one shown in Figure 1, beginning with an evaluation of the performance of the immunizations system, appreciation of disease burden, availability of a safe and effective vaccine, assessment of cost-effectiveness, priority assigned to prevention of the disease, and availability of financing. Several of these critical steps are related to demonstrated need for and potential benefit from the vaccine. However, estimate of the total burden of pneumococcal disease is challenging because pneumococcus is isolated from only a fraction of

children with infection. Without recognition of the true burden of pneumococcal disease in their country, health decision makers will underestimate the value of pneumococcal vaccination and will have little incentive to spend financial and other resources necessary to introduce the vaccine.

FIGURE 1: An Aid to Decision Making: WHO Vaccine Introduction Guidelines



1.3 Surveillance for Pneumonia and Pneumococcal Disease in the Region

In 1993, coordinated pneumococcal disease surveillance for the Region of the Americas was established by the Pan American Health Organization (PAHO), through its special Program for Vaccines and Immunizations (SVI) and the regional System for Vaccines (SIREVA). SIREVA conducts surveillance for bacterial meningitis and pneumonia, and examines serotype distribution and antimicrobial resistance patterns. Surveillance started in six countries—Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay—but has recently expanded to include 300 sites in 22 countries. Surveillance is also conducted for *Haemophilus influenzae* and *Neisseria meningitidis.* The original objectives of the surveillance system, which includes children less than six years of age, were to determine the prevalence of capsular types causing invasive pneumococcal disease (IPD), to strengthen regional laboratory and epidemiological capacity for monitoring serotypes and antimicrobial resistance of pneumococcus, and to create a bank of isolates and specimens.[3] The system is currently being strengthened and will include collection of more epidemiological data including incidence data at some sites.

For the purpose of establishing burden disease estimates of likely bacterial pneumonia and estimating vaccine impact, WHO's Department of Immunization, Vaccines and Biologicals, established a working group to standardize the categorization of radiological pneumonia. The presence of significant alveolar consolidation is considered by most experts to be the most specific radiographic predictor of bacterial pneumonia available today. Three countries in Latin America (Argentina, Chile, and Uruguay) established population-based surveillance for x-ray confirmed pneumonia and data from some of these surveillance systems have recently been published.

1.4 Aim of Review

The aim of this review is to document the burden of pneumococcal disease in Latin America and the Caribbean, and to use available data to develop projections of the burden of childhood pneumococcal disease and determine the cost-effectiveness of vaccination. The scope of the review includes a description of invasive and non-invasive disease in all age groups. The review describes (1) the incidence and mortality of pneumococcal disease, and the serotype distribution and antimicrobial resistance of pneumococcal isolates; (2) the costs of pneumococcal disease, including the direct medical costs to the health system, direct medical costs due to family out-of-pocket expenses, and direct non-medical cost due to caregiver time loss; (3) the results of a preliminary cost-effectiveness study of a heptavalent pneumococcal conjugate vaccination program; and (4) the results of cost effectiveness studies that have been conducted in the region. The findings will be available to policy makers to evaluate the implementation of a pneumococcal conjugate vaccination program in their countries.

CHAPTER 2 METHODS

The methods are divided into four sections. Section 2.1 describes the literature searches for epidemiological and economic data. Section 2.2 describes the methods used in the economic analyses: cost analysis and cost-effectiveness analysis. A description of the model framework, model inputs, and sensitivity analysis are presented in this section. The gross domestic product (GDP) impact analysis is outlined in Section 2.3 and Section 2.4 describes the communications process.

2.1 Literature Review

2.1.1 Peer-reviewed Epidemiological Data

We conducted an online literature search using six electronic databases: Latin American and Caribbean Health Sciences (LILACS), Pubmed, The Cochrane Library, Embase, CAB Health Direct, and Biosis. We used search terms relating to respiratory tract infection, *Streptococcus pneumoniae*, IPD and pneumococcal syndromes (limited in this review to the syndromes of pneumonia, meningitis, bacteremia, and AOM). IPD was defined as isolation of pneumococcus from a normally sterile site. We did not include search terms related to disability caused by these syndromes. We limited our search criteria to articles from Latin American and Caribbean countries published between January 1990 and April 2006, in any language. We routinely scanned prominent journals for relevant articles published between April and October 2006. A librarian specialist developed a search strategy for each of the electronic databases according to their specific subject headings or searching structure in collaboration with the reviewers. We used Endnote (Version 9.0) to manage references. Duplicate references were deleted and we assigned a unique identification number for each citation. We checked the reference lists of published articles to identify other relevant publications. More information on the search terms and the electronic databases are provided in Appendix A.

Inclusion criteria. We included studies on IPD, bacterial and pneumococcal meningitis, pneumonia (clinical x-ray confirmed and pneumococcal bacteremic), pneumococcal sepsis and pneumococcal bacteremia, AOM (that contained information on incidence), case fatality rate (CFR), proportion of disease due to SP, serotype distribution, and antimicrobial resistance. These studies included descriptive, cohort, cross-sectional, case-control and intervention studies, and clinical trials. We included review articles only if they contained original data. We included data on all age groups and both genders. In the final analysis, we only included full-text articles published in peer-reviewed journals.

Exclusion criteria. We excluded case reports, studies on immunogenicity, molecular characterization, nosocomial disease, or special populations, such as patients with HIV/AIDS. Studies on nasopharyngeal carriage or where diagnosis of SP was done using nasopharyngeal aspirates or sputum were also excluded. Although we included search terms related to respiratory tract infections, we did not include these studies unless they had specific information on pneumonia. Policy papers and review articles with no original data were not included in the analysis, but were retained to provide background information or to provide additional articles from their reference lists. We also excluded studies where the number of pneumococcal isolates or cases of a particular syndrome was less than 30 because the distribution across a group may not be statistically valid in such situations. When analyzing the proportion of disease due to SP, we excluded studies where this proportion was 100%. Incidence data were only included if the period of data collection was for at least one year.

Data from several studies that described the serotype distribution among resistant organisms only were excluded. Studies that presented incidence data based on a retrospective data review without protocols or standards of practice in place were excluded. For example, incidence studies on meningitis required a cerebrospinal-fluid (CSF) specimen to be taken on all suspected meningitis cases. Studies on incidence of

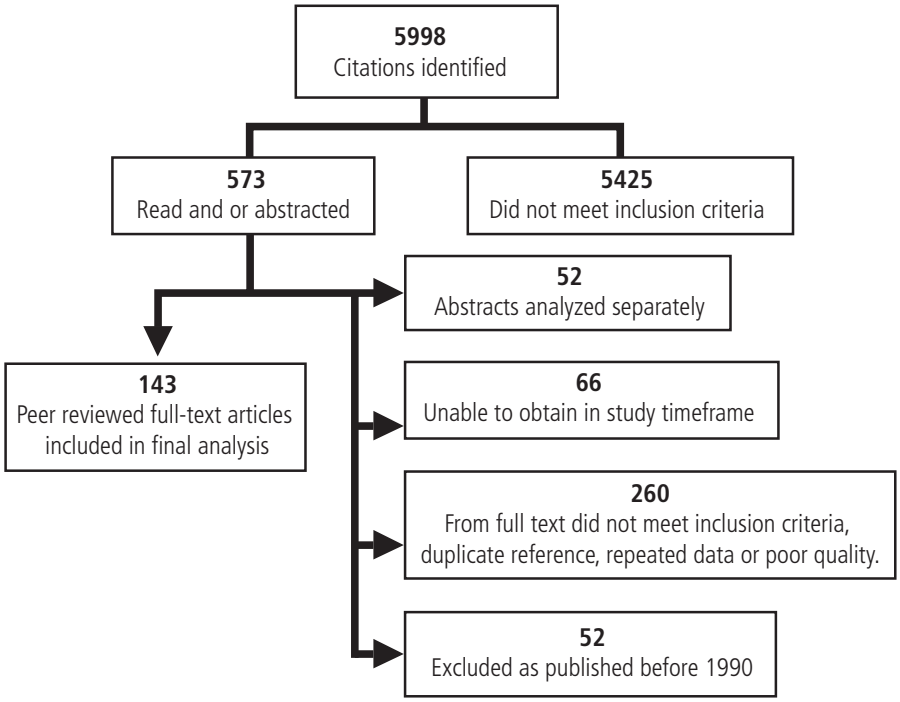
x-ray confirmed pneumonia or bacteremia required an x-ray or blood culture respectively to be taken routinely according to some predefined clinical criteria. Data using a definition for suspected cases of meningitis were excluded.

We only included articles published since 1990, although we originally searched for articles published from 1980. Restriction of papers published since 1990 helped determine the current and recent burden of pneumococcal disease. Changes in diagnostic techniques, case management, and access to care may have changed over time, so by restricting our data collection to a shorter time period, we may have reduced any bias caused by these changes.

Quality criteria. Except for the exclusion criteria mentioned above, we accepted each author's definition of meningitis, pneumonia, bacteremia, sepsis, and AOM, and their methods for identifying specific bacterial etiologies, serotyping, and assessing antimicrobial resistance. In Appendix B, we present standard case definitions for the various pneumococcal syndromes. These definitions were followed, with minor variations, for studies with data on IPD, x-ray confirmed pneumonia, and AOM. Two studies used a different technique than minimum inhibitory concentration (MIC) for measurement of antimicrobial resistance, but because their results did not differ from those that did use MIC, those studies were included. Some studies of bacterial meningitis used antigen detection in addition to isolation of an organism in their definitions. These studies were included since antigen detection is a common practice in the region. Many studies did not specify the laboratory methods used and therefore, it was not possible to assess the quality of these studies.

Screening and data extraction. The search identified 5,998 citations (titles with or without abstracts). One reviewer evaluated all citations between May and June 2006 according to the eligibility criteria. A second reviewer evaluated the citations where there was uncertainty as to whether they met the inclusion criteria. We identified 573 relevant citations for which the full text, if available, was read by one abstractor between June and August 2006. Papers which were considered relevant were abstracted. Of these, 143 unique peer-reviewed full-text articles were included in the final analysis (Figure 2). We were unable to

FIGURE 2: Flow diagram for the process of identifying and including references for the systematic review



obtain 66 articles in the timeframe of this review. These articles were mainly from Latin American journals which are not available online or through U.S. libraries.

We developed instructions on how to do the abstraction and conducted a training session (Appendix C). Where possible, we extracted raw data but if only percentages or rates were available, we included these. If data from clinical trials or case control studies were included, we abstracted data on controls only. Data presented in graphs and figures were used only if numbers (or percentages) were described in the text or labeled in the graph. In addition to details about the design and quality of studies, we abstracted the data outlined in the inclusion criteria by age, syndrome, and country.

Data processing and analysis. Data were entered in Excel spreadsheets and analyzed in Excel, EpiInfo 3.2, and SPSS version 11.5 (*SPSS Inc., Chicago, USA*). We summarized incidence and CFR data by computing the median incidence per 100,000 or median CFR for all studies combined by age and syndrome. We calculated the median percentage of disease due to SP and median percent of antimicrobial resistance by age and syndrome for all studies with these data. For each estimate, we presented the number of studies contributing to the estimate and the interquartile range (IQR). These statistics allow a judgment of the variability of the studies, particularly where there are data from only one study for a particular age group. For incidence and CFR analysis, we also presented the total number of cases in all studies combined and the countries contributing data to each estimate. For studies where data were presented by year, the data were aggregated before being summarized with other studies. Where only one study was available for a particular age and syndrome, the IQR was calculated for that study using the data across all years that were included.

We searched for studies with duplicate data by determining if the data were from the same country, facility, time period, or age group. Duplicate data occurred, for example, where separate regional and national studies presented the same data, or when a study published data at different times updating previous data. When duplicate data were found, we included the study that was considered to be of better quality or that contained information from a longer time period. We analyzed the incidence of bacterial meningitis for pre- and post-*Haemophilus influenzae* type B (Hib) vaccine introduction. The year during which vaccine was introduced was considered a pre-Hib vaccine year and the following year was considered as a post-Hib vaccine year. PAHO supplied information on year of Hib vaccine introduction by country.

We calculated the serotype coverage for the existing 7-valent pneumococcal conjugate vaccine (PCV7) and the proposed 10-valent and 13-valent preparations with and without their cross-reactive serotypes. We defined cross-reactive serotypes as all serotypes included in a serogroup that are included in the vaccine, with the exception of 19A because recent studies have shown that this is not cross reactive.[4] Our calculated coverage may differ from that presented in some papers due to different definitions of cross-reactive serotypes used. The serotypes included in the 23-valent polysaccharide pneumococcal vaccine were also calculated. Studies varied greatly in the age groups studied and in the way age categories were presented. We developed a number of age categories that are described in Table 1. These age categorizations allowed us to include as much data as possible in our analysis.

TABLE 1: Description of age categories used

AGE GROUPS	EXPLANATION	EXAMPLES OF AGE GROUPS INCLUDED
<=1 year	Age <=1y where at least 6 months (m) of the period is included.	<1y, 1-11m, 1-12m, 0-11m, 0-12m
<2 years	Age <24m excluding those in the <=1y category above. The lower age is <1y and at least 18m of the period is included.	<2y, 1-23m, 2-23m, 6-23m
<5 years	Age combinations <5y excluding those in <1y and <2y above. The lower age is <=1y and at least 3 years of the period is included.	<5y, 1m-<5y, 2m-<5y, <36m, 1-4y
<6 years	As per <5y above but including children <6y. This category only applied to data from PAHO's surveillance network.	As for <5 above and <6 years
All children	Age combinations not included in categories above where lower age is <1y and upper age is >=5y.	0-12y, 1m-14y, <18y, "children" where specific age not stated
All children (excluding infants)	Age combinations not included in categories above where lower age is >=1y but <=2y and where upper age is >5y.	2y-12y, 1y-18y
Adults	Age combinations where lower age is >=15y.	>=18, >15
Older adults	Age combinations where lower age is >=50y.	>=65, >=59, >=50
All ages	Age combinations which include children and adults.	0-90y

2.1.2 Non-Peer Reviewed Epidemiological Data

Search strategy. We defined non-peer reviewed data as data from conference proceedings and abstracts, scientific posters, unpublished reports and theses, websites, newsletters, and other grey literature. We searched books of abstracts from the last three International Symposiums on Pneumococci and Pneumococcal Diseases meetings (2002, 2004, and 2006) for relevant abstracts. Through PAHO country offices, we requested information on pneumococcal disease from the Ministries of Heath (MoH) in all countries in the region. We visited six countries—Argentina, Brazil, Chile, Colombia, Dominican Republic, Uruguay—that were chosen because we knew active pneumococcal researchers in the countries, knew their strategic importance in the region (Brazil's large birth cohort), or considered their representation of a region (Dominican Republic for the Caribbean). We were unable to visit a country representing Central America due to time constraints. In 13 countries, we contacted 48 pneumococcal researchers known to us and received 34 replies (Appendix D).

Abstraction and analysis. The same inclusion and exclusion criteria as described previously were applied to non-peer reviewed data. These data were only included in the results section if they provided new information in addition to that already obtained from the published data because it is difficult to determine data quality if study methods are not fully explained. Country visits reports are presented in Appendix E.

2.1.3 Economic Literature Search

Literature search strategy. An extensive economic literature review was conducted simultaneously with the epidemiological literature review. References with relevant economic data were included to provide a critical overview of the economic issues related to pneumococcal disease and assess the potential implications for vaccination. Relevant studies were identified, including general economic papers, "burden of illness" or "cost of illness" studies, economic evaluations, and official reports from countries in the region. The majority of these papers were published in English or Spanish from 1990 to 2005. Much of the published work and some of the completed study reports in the public domain were obtained from the Pub Med, Biosis, Cochrane Library, and Embase databases. Manual bibliographic searches revealed additional articles.

Articles that were not true economic evaluations (e.g., reviews of applied studies, commentaries, or editorials without original data) were excluded, as were some articles that substantially replicated results from other articles. Due to the limited range of published studies originating in Latin America and the Caribbean, studies containing only abstracts and emerging work in the process of being published were considered in the review.

The medical subject heading (MeSH) terms used to survey the literature on the cost of pneumococcal disease included *costs* and *cost analysis*, *cost of illness* and *cost benefit analysis*, and *SP*. Cost of illness studies require the development of country-specific models of usual care. The inputs for such models were epidemiological data and information on usual treatment patterns.

MeSH terms used to survey the literature on the economics of vaccines included *costs and cost analysis, cost of illness, hospital costs, cost control, cost-effectiveness analysis, cost-benefit analysis, cost savings, delivery of health care, drug costs, economic value of life, healthcare costs, managed care programs,* and *pneumococcal conjugate vaccine and vaccination.*

The selected studies were reviewed in terms of their country of evaluation, vaccine strategies assessed, study design, method of evaluation, cost measures, perspective and period of analysis used. Results are shown as presented in the literature. No adjustments of expenditures or savings to present value were made.

Economic papers reviewed. We identified 109 studies in the economic literature search. After abstract retrieval and review, 91 studies were excluded as not containing cost of illness, program cost, cost-minimization, cost-benefit analysis, or cost-effectiveness data related to pneumococcal disease, or pneumococcal conjugate vaccine. Of the 18 remaining papers, three were excluded because they substantially replicated results from other articles. Five other articles were excluded because they were deemed irrelevant upon full-text review; they did not contain cost of illness, program cost, cost minimization, cost-benefit analysis, or cost-effectiveness data related to pneumococcal disease or pneumococcal conjugate vaccine.

Ten studies (two cost-effectiveness and eight cost of illness) were reviewed and are summarized in Table 2. Because of concerns regarding representativeness and differences in methodology across the identified economic studies, we opted to develop an independent economic model, described in detail below.

TABLE 2: Overall results of search strategy

Search area	Argentina	Brazil	Chile	Colombia	Mexico	Uruguay	Other[a]	Total
Cost effectiveness[a]	—	—	1	—	—	—	1	2
Cost of illness	1	1	1	1	2	1	1	8
Total	1	1	2	1	2	1	2	10

[a]This includes an analysis carried out in Brazil, Chile, and Uruguay

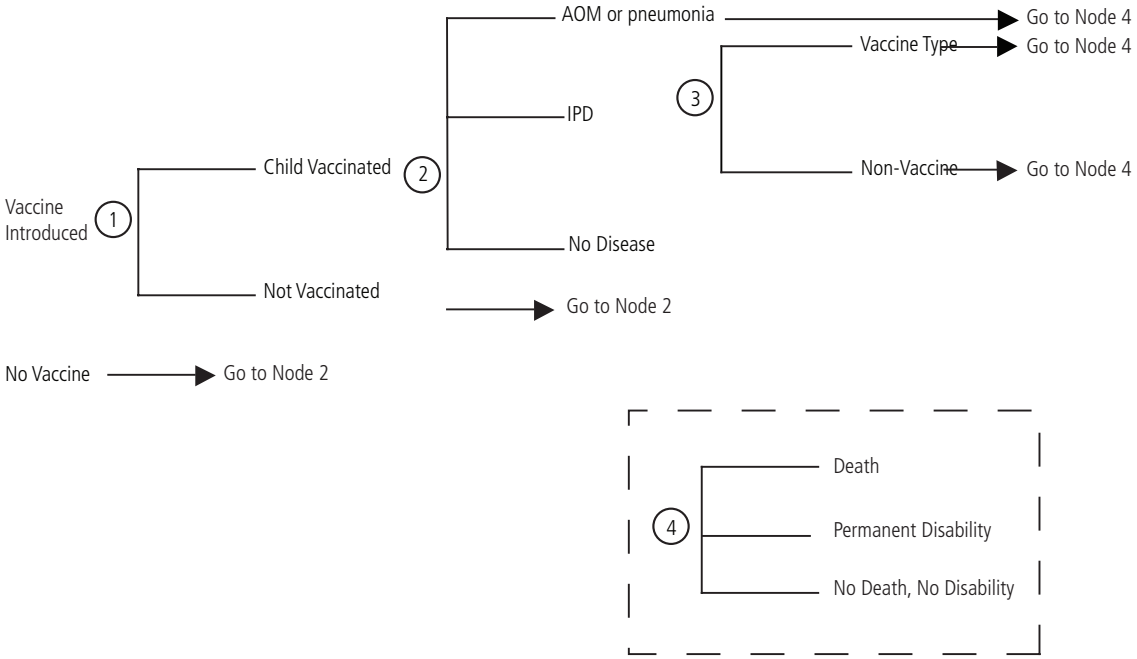
2.2 Economic Evaluation

We constructed an economic model using published and administrative epidemiological data and country-specific cost data to estimate the health and economic burden of pneumococcal disease in ten countries in Latin America and the Caribbean: Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Panama, Uruguay, and Venezuela. In addition, the model integrated the health burden estimates with economic burden estimates generated by this study to develop a regional estimate of the value for money represented by investment in the existing PCV7 vaccine (Prevnar, Wyeth Pharmaceuticals).

2.2.1 Model Overview

The principal inputs to the model include epidemiological information on disease incidence, healthcare costs associated with different types of pneumococcal disease syndromes, and the effectiveness and costs of vaccination. As shown in Figure 3, 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[1]) averted, cases prevented, or lives saved.

FIGURE 3: Schematic diagram of the model



Two policy options were considered in the economic model: no vaccination or vaccination with PCV7. The model began with an annual birth cohort of healthy children under five years of age in the Latin American and Caribbean region of 11.7 million people. Children entering the model had a choice of

[1]The Disability Adjusted Life Year extends the concept of potential years of life lost due to premature death to include equivalent years of 'healthy' life lost due to being in states of poor health or disability. The DALY combines in one measure the time lived with disability and the time lost due to premature mortality. One DALY can be thought of as one lost year of 'healthy' life.

receiving vaccination or not receiving vaccination. Children were assumed to receive PCV7 as part of the routine immunization schedule in a three-dose schedule. Children without vaccination who got 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 codes (circles numbered) were the possible outcomes of these events. Children with pneumococcal disease either died or survived with or without a disability.

Perspective and scope of the analysis. The primary perspective for this analysis is society as a whole. This includes the direct medical costs associated with medical treatment (see p. 13 — i.e., diagnostic tests, medication, supplies, facilities, and personnel) in formal inpatient and outpatient settings, direct medical costs due to family out-of-pocket costs (i.e., transportation costs to and from the medical facility), and direct non-medical cost due to caregiver time loss (caregiver productivity losses that occur as a result of the child being sick).

For the analyses, 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 etiology 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 is equivalent to that of a placebo.[5-12] We also did not include potential indirect effects such as herd immunity or serotype replacement.

2.2.2 Model Inputs

Study population. The population studied was children under five years of age. The model analyzed an annual birth cohort of 11,700,500 based on data for all Latin American and Caribbean countries reported in PAHO's 2005 Basic Health Indicators.[13] Children in the annual birth cohort are followed to age five and their disease-related costs and health consequences collected and analyzed by the model.

Choice of health outcomes. The primary outcome measures considered were the healthcare costs of pneumococcal disease and the disease burden and healthcare system costs averted by vaccination. The net cost per DALYs averted and deaths averted were also calculated. Incremental cost-effectiveness ratios (ICER) compare the difference in cost with and without PCV7 vaccination over the difference in health outcome with and without PCV7 vaccination. For the cost-effectiveness analysis, the medical 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 incremental cost-effectiveness ratio:

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

Burden of pneumococcal disease. *Cases and deaths.* For the region, the burden of pneumococcal disease was estimated for the annual birth cohort from birth until age five. Diseases considered included: all-cause AOM, all-cause clinical pneumonia (inpatient/outpatient), all-cause chest x-ray positive pneumonia (inpatient/outpatient), pneumococcal sepsis, and pneumococcal meningitis. Overall, non-sepsis, non-meningitis invasive pneumococcal disease burden was not estimated in the current analysis, although non-sepsis, non-meningitis IPD incidence, and CFR estimates are presented. The model directly estimated numbers of cases of averted otitis media due to any cause, averted clinical pneumonia due to any

cause, and averted chest x-ray positive pneumonia due to any cause. We then back-calculated the burden of pneumococcal pneumonia and pneumococcal otitis media using algebraic rearrangements of the following equations:

Averted otitis media cases = (# pneumococcal otitis media cases) * (% pneumococci that are vaccine type) * (% children receiving vaccine) * (vaccine efficacy)

Averted clinical pneumonia cases = (# pneumococcal clinical pneumonia cases) * (% pneumococci that are vaccine type) * (% children receiving vaccine) * (vaccine efficacy)

Averted chest x-ray (+) pneumonia cases = (#chest x-ray (+) pneumonia cases) * (% pneumococci that are vaccine type) * (% children receiving vaccine) * (vaccine efficacy)

Disease burden was estimated as the numbers of disease cases and deaths based on the 2005 birth cohort size, cumulative incidences of disease, case fatality ratios, and the estimated age distributions of each event. These estimates were based on the extensive literature review described previously. Age-specific annual incidences were used to develop cumulative incidence estimates (ages 0 to 5) using standard Kaplan-Meier analysis. Table 3 provides a summary of the disease risk estimates used in the model.

TABLE 3: Cumulative incidence of disease (age 0 to 5), case fatality ratios and serotype coverage by vaccine

MODEL INPUT	BASE CASE VALUE	SOURCE
Probabilities		
Disease probabilities (cumulative incidence)		
— Probability of acute otitis media	0.9000	Teele et al, 1989[14]
— Probability of clinical pneumonia	0.0911	
— Probability of chest x-ray confirmed pneumonia	0.0572	
— Probability of pneumococcal sepsis	0.0001	
— Probability of pneumococcal meningitis	0.0003	From epidemiological analysis of literature review data
Case fatality ratios		
— CFR for clinical pneumonia	0.03	
— CFR for chest x-ray confirmed pneumonia	0.05	
— CFR for sepsis	0.35	
— CFR for meningitis	0.35	
Serotype		
—Probability vaccine type (7-valent)	0.60	

DALYs. In addition to estimating numbers of cases and deaths, the disease burden was also expressed in terms of DALYs. DALYs provide a standardized measure of disease burden that allows for cross-disease comparisons of burden[15] and comparison with other diseases. The DALY estimate includes two components: Years Life Lost (YLL) due to premature mortality and Years Lived with Disability (YLD). YLL was calculated based on the average country-specific life expectancy at one year of age.[15] For the calculation of YLD, only morbidity from disease severe enough to require medical care was considered. YLD was

calculated using default disability weights from the global burden of disease study[15] and WHO's guidelines for cost-effectiveness studies.[16] We followed these standard recommendations and included a discount rate of 3% and age weighting in estimating DALYs.[16]

Costs Associated with Pneumococcal Disease. Healthcare costs. The economic burden of pneumococcal disease in the region was estimated by combining estimates of the number of each type of event with information on the costs associated with the event. Cost estimates were from the public sector regardless of the type of economic analysis. All cost estimates were collected in local currency and were converted to 2005 US dollars based on World Bank rates. All future costs were discounted at an annual rate of 3%, as recommended by the US Panel of Cost-Effectiveness in Health and Medicine[17] and the World Bank Global Burden of Disease (GBD) Project.[15]

In the cost analysis, cost generating events were estimated based on two potential sources: physician interviews in ten countries (Argentina, Brazil, Chile, Colombia, Dominican Republic, Honduras, Mexico, Panama, Uruguay, and Venezuela) and WHO — choosing Interventions that are Cost Effective (WHO-CHOICE) project.[16] Countries were divided into three income strata (low, lower- or upper-middle) (Appendix F). Countries in the low, lower-middle and upper-middle income strata were included in the cost analysis. Low and middle income countries were selected since few studies exist that have looked at the economic burden of pneumococcal disease or the cost-effectiveness of vaccination in these countries.

For the cost-effectiveness analysis, resource utilization, and cost estimates were derived from physician interviews described in the next section and were extrapolated for the region as a whole.

Unit costs based on physician interviews. In 2001, several physician interviews were done as part of a previous study to characterize the typical management of pneumococcal disease. In 2006, as part of the present study and using the same methodology, we conducted interviews in the ten participating countries. We then combined resource use data from these interviews. The majority of the physicians interviewed were pediatricians working in the public sector, but we also interviewed infectious disease specialists, neurologists, neurosurgeons, ear-nose-throat (ENT) specialists and family doctors working in the private sector. Appendix G shows the number of physicians interviewed.

Appendix H shows an example of a questionnaire (Pneumococcal Meningitis questionnaire). Similar questionnaires were used for the other syndromes (e.g., pneumococcal sepsis, all-cause clinical and x-ray positive pneumonia, and all-cause AOM). Three sets of questions were included in the questionnaires. The first set was directed at patients with acute pneumococcal disease while the second and third sets were for patients with complications or sequelae.

The unit cost for treatment was based on estimates provided by the finance departments of local hospitals and national administrative data (Appendix I). The hospital per diem cost ranged from US$65.59-US$268.70 (2005 values). The cost per stay as an inpatient was calculated by multiplying the per diem rate by the length of stay and adding the cost of diagnostics and medications. The per diem rate includes the accommodation and administration costs (cost of the bed, building, utilities, maintenance, administration, and equipment), food, and personnel. A mean hospital length of stay of 12.8 days for all-cause clinical pneumonia and x-ray positive pneumonia, 14.8 days for pneumococcal meningitis and 9.4 days for pneumococcal sepsis was derived from combined physician responses.

The cost per outpatient visit (US$5.81-US$32.93) (2005 values) was calculated as the weighted mean of the cost of visiting a pediatrician or emergency room (ER) based on the proportion seen in each of the two outpatient settings. According to physicians interviewed, 54% of patients with clinical pneumonia and x-ray positive pneumonia have an outpatient visit and all patients with all-cause AOM are treated in the outpatient setting. Based on PAHO estimates, it was assumed that 12% of office visits were private.[13] Costs for the two

types of outpatient visits in the public sector were based on the average given by the finance departments of public institutions and administrative sources described previously.

The total diagnostic cost per patient was calculated by multiplying the number of each test used by its unit cost and then summing the total cost for all the tests administered to a single patient. A mean diagnostic cost of US$11.20 was calculated for inpatient pneumonia, US$5.12 for outpatient pneumonia, US$31.84 for pneumococcal meningitis, US$25.12 for pneumococcal sepsis, and US$4.75 for all-cause AOM (2005 values).

Costs associated with medications were based on national formularies[18] and prices quoted by the finance department of the hospitals and local pharmacies. The total medication cost per patient was calculated by multiplying the cost per dose of each medication used by the number of doses administered and then summing the total cost for all the medications administered to a single patient. A mean medication cost was calculated for outpatient pneumonia (US$44.25), inpatient pneumonia (US$50.49), pneumococcal meningitis (US$82.03), pneumococcal sepsis (US$65.57), and all-cause AOM (US$27.21) (2005 values).

Appendix J, Table 3 describes in detail the use of health services associated with pneumococcal disease by income group while Appendix J, Table 4 describes the direct medical costs associated with pneumococcal disease by income group.

Costs Based on WHO-CHOICE Data. The WHO-CHOICE project developed by WHO provides estimates of the per diem cost of hospitals, outpatient visits, and health center visits for 14 epidemiological categories based on geographical region and mortality stratum. The hospital and outpatient unit cost data are specific to public hospitals and assume an 80% occupancy rate. The per diem/visit cost estimate includes such items as the cost of the facility, personnel, equipment, and food and excludes items such as medications and diagnostic tests.[19]

The per diem cost of a hospital bed day and outpatient visit are divided into three levels of care (primary, secondary, tertiary) because unit costs generally increase by increasing level of care.[19] Since the proportion of inpatients and outpatients who visit each of the three hospital levels is not known for every region and income strata, the proportions were estimated based on physician interviews. The study results demonstrate that 33%, 41%, and 26% of cases were seen at the primary-, secondary-, and tertiary-level hospitals, respectively.

Using the WHO-CHOICE data, we were able to estimate the per diem and per visit costs for each of the ten countries included in the analysis. Total cost per hospitalization was calculated by multiplying the per diem cost by the estimated length of stay reported in the physician interviews.

Since the WHO-CHOICE model was developed using 2000 international dollars, the cost estimates were inflated to 2005 international dollars using the Consumer Price Index (CPI).[20] All costs were then converted to US dollars using the 2005 purchasing power parity conversion factors and official exchange rates.[21]

The inpatient and outpatient visit costs described above estimate the costs of facilities, equipment and personnel, but did not include the cost of diagnostic tests and medications. We used information from physician interviews and finance departments of local hospitals (described previously) to estimate the additional cost of diagnostic tests, medications, and other procedures. The estimated treatment costs for pneumococcal disease based on secondary data sources (WHO-CHOICE data, Commission for Latin America and the Caribbean (CEPAL) data, and physician interviews) are summarized in Appendix J, Table 5.

Societal Costs. In addition to healthcare costs, direct non-medical costs (i.e., transportation costs and caregiver productivity losses) were calculated based on previous research where 60 parents of sick children were interviewed regarding money spent to transport a child or themselves to the health facility, time lost from paid work due to their child's illness, and days off work, or income lost due to pneumococcal disease. [22] The average

indirect cost was estimated by multiplying the mean hours lost by the mean female hourly wage for each of the countries.[23, 4, 24, 25] Appendix J, Table 2 shows the number of parent interviews completed. Appendix J, Table 6 summarizes the average direct non-medical and indirect costs of pneumococcal disease.

Vaccination Costs. Calculations of cost-effectiveness also require estimates of vaccination costs. These include the cost of administration, the price of each dose, the number of doses given (based on coverage level), and expected losses from waste. Administration costs comprise the cost of health personnel and training, cold chain, storage space, and public education. We assumed that pneumococcal conjugate vaccine would be administered along with the current Extended Program of Immunization (EPI) vaccines, and therefore, the incremental administration costs would be very low. Studies exist that estimate the cost of immunization for current EPI vaccines,[26, 27, 28, 29] however, there are no data on the incremental cost of adding a vaccine to the current EPI regimen. Based on the range of estimates found in the immunization cost studies and the assumption of low incremental costs, the model assumes an administration cost of $1.00 per dose. We used current PAHO revolving fund price (US$53 per dose) to represent the cost of PCV7. We included a 10% vaccine wastage rate in estimating vaccine-related costs.

Vaccine Efficacy. No trials of pneumococcal conjugate vaccine have been conducted in Latin America or the Caribbean, hence we used estimates of the effectiveness of PCV7 from the Northern California Kaiser Permanente (NCKP) trial 5 because this trial was considered to be most applicable to the population under consideration. Estimates of vaccine effectiveness against meningitis and sepsis were adjusted for regional differences in serotype distribution. This was done by only applying vaccine's protective effect to that proportion of disease caused by vaccine-covered serotypes. Estimates of vaccine efficacy against chest x-ray (+) pneumonia were based on a re-analysis of the NCKP data recently performed by Hansen and colleagues.[30] Vaccine efficacy estimates are summarized in Appendix J, Table 1.

Vaccine Coverage. In the baseline analysis, regional coverage with the third dose of diphtheria, pertussis, and tetanus (DPT3 ratio) at one year of age for 2005 was estimated to be 92%.[13] It was assumed that all children received the vaccine at the recommended time. The effects of partial immunization with one or two doses of vaccine were not considered. Estimates were integrated into the model by following an annual birth cohort through the age periods 0–11 months, 12–23 months, 24–35 months, 36–47 months, and 48–59 months. During each period, the number of events in the absence of vaccination was estimated. The reduction in the number of events during that period was then estimated based on the proportion of children receiving three doses of vaccine as described above. The expected number of events averted prior to age five was calculated as the sum of the events in each period.

Appendix J provides a summary of key input variables for the cost-effectiveness analysis of PCV7 program in Latin America and the Caribbean.

2.2.3 Sensitivity Analysis

The model described above requires country-specific data on the epidemiology of the disease, the economic costs associated with different outcomes, and vaccine efficacy. While some of these data are available, the quality and representativeness are limited for others. These data limitations create uncertainties regarding the final estimates of economic burden and cost-effectiveness. For this reason, we conducted a sensitivity analysis.

For the present study, one-way sensitivity analysis of key disease-related and cost inputs was performed for different scenarios that are likely to influence the cost-effectiveness of vaccination. These scenarios include high and low end estimates of vaccine price, disease incidence, and disease-related costs. Future versions of the cost-effectiveness analysis will include two-way sensitivity analyses, scenario-specific analyses, and probabilistic sensitivity analyses.

2.3 GDP Impact Analysis

The GDP of a country is defined as the market value of all final goods and services produced within a country in a given period of time. The aim of this analysis was to estimate the impact of pneumococcal disease on the GDP of Latin American and the Caribbean. All countries of the region were considered for this analysis.

The incidence and CFR estimates of pneumococcal-related diseases were based on the extensive literature review described previously. These estimates were adjusted to the general population under five years of age for the year 2005 (56,832,000). Diseases considered included: all-cause AOM, all-cause clinical pneumonia and chest x-ray positive pneumonia (inpatient/outpatient), pneumococcal sepsis, and pneumococcal meningitis. Population-weighted average medical and costs borne by families described earlier were combined with the incidence and CFR estimates to estimate the impact that pneumococcal disease has on the GDP of Latin America and the Caribbean. Future loss productivity of children with pneumococcal disease was also considered in the analysis and this was based on the mean minimal monthly wage for the region (US$162.28) assuming an eight-hour shift. [31]

2.4 Communications

The core team members held a weekly, regular scheduled conference call with additional calls as necessary for smaller groups to discuss more in-depth issues. We held four in-person meetings at the Sabin Vaccine Institute, Washington, D.C., and one meeting in São Paulo, Brazil. The economics team held two additional in-person meetings in Newark, New Jersey.

CHAPTER 3 RESULTS

The results are presented in five sections. Section 3.1 describes the epidemiological papers included in the analysis. Section 3.2 describes the epidemiological indicators associated with pneumococcal disease divided by syndrome: IPD, meningitis, pneumonia, bacteremia, and sepsis, and AOM. Incidence, CFR, proportion of disease due to SP, serotype distribution, and antimicrobial resistance pattern are presented for each syndrome where data are available. Section 3.3 summarizes the economic papers that were reviewed. Sections 3.4 and 3.5 present the results of the cost and cost-effectiveness analyses. Section 3.6 presents the results of the GDP impact analysis.

3.1 Description of epidemiological papers included in the analysis

We included 143 full-text articles from peer-reviewed journals in the final analysis. The distribution of these studies by country and sub region is presented in Table 4. Countries from South America provide 73% of studies followed by Central America with 13% and the Caribbean with 8% of all studies. Nine studies (6.3%) were multi-country studies including four from PAHO's surveillance network.

TABLE 4: Distribution of studies by country and sub-region

COUNTRY	# SUB REGION (%)	# COUNTRIES (%)
South America		**104 (72.7)**
Brazil		44 (30.8)
Chile		21 (14.7)
Argentina		16 (11.2)
Uruguay		11 (7.7)
Colombia		6 (4.2)
Venezuela		1 (0.7)
Paraguay		1 (0.7)
Peru		4 (2.8)
Central America	**19 (13.3)**	
Mexico		12 (8.4)
Costa Rica		6 (4.2)
Guatemala		1 (0.7)
Caribbean	**11 (7.7)**	
Cuba		3 (2.1)
Puerto Rico		3 (2.1)
Trinidad		2 (1.4)
Haiti		1 (0.7)
Jamaica		1 (0.7)
Dominican Republic		1 (0.7)
Multi-country	**9 (6.3)**	9 (6.3)
Total	**143 (100)**	**143 (100)**

The percent of studies with data of interest were as follows: incidence data 12% (n=18), CFR data 36% (n=51), serotype data 12% (n=18), antibiotic resistance data 49% (n=70), and data on the proportion of disease due to SP, 38% (n=55). Appendix K presents the overall distribution of included studies by syndrome and sub region, and data on the time periods during which studies were published. Appendix K also presents a comparison of the included papers with (1) those papers for which the full text was not obtained in the timeframe of this study (n=66) and (2) with papers published between 1980 and 1989, to see if these years contained additional data.

3.2 Epidemiological Data

3.2.1 Invasive pneumococcal disease (IPD)

Incidence of IPD. Only two studies, from Argentina and Chile, contributed data to the incidence of IPD (Table 5). The incidence of IPD decreased with increasing age ranging from 60.7/100,000 in hospitalized children <1 year of age to 32.3/100,000 in hospitalized children <5 five years of age.

TABLE 5: Median incidence, from studies of IPD, presented as cases per 100,000 annually, by age and inpatient or outpatient treatment with country information

AGE GROUP	INPATIENT (I) OR OUTPATIENT (O)	NUMBER OF STUDIES	MEDIAN INCIDENCE OF IPD* (25th – 75th percentile)	NUMBER OF CASES OF IPD IN ALL COMBINED STUDIES (min-max)	COUNTRY
<1 year	I	2	60.7 (58.2-63.2)	156 (26-130)	Argentina[32] Chile[33]
	O	2	80.5 (56.4-104.7)	89 (38-51)	Argentina[32] Chile[33]
<2 years	1	2	61.4 (52.1-70.7)	268 (69-199)	Argentina[32] Chile[33]
	O	2	81.0 (57.6-104.3)	190 (80-110)	Argentina[32] Chile[33]
<5 years	1	1	32.3 (31.5-33.1)	224	Chile[33]
	O	1	27	94	Chile[33]

*When the number of studies =1, the annual incidence (or the median incidence where >1 year of data are available) is presented.

IPD Case Fatality Ratio. The median CFR was highest among people of all ages at 20.3%, but this only reflects data from one study which had a small number of isolates (Table 6). The next highest median CFR was in children <2 year of age at 12.4%. Findings from a Brazilian abstract found a CFR of 12% in children less than six months of age.[34]

TABLE 6: Median case fatality ratio, from IPD studies, by age group with country information

AGE GROUP	NUMBER OF STUDIES (25th–75th percentile)	MEDIAN CFR OF IPD*	# CASES OF IPD IN ALL STUDIES COMBINED (min-max)	COUNTRIES
<2 years	2	12.4 (8.7–16.2)	157 (75–82)	Chile[35] Costa Rica[36]
<5 years`	4	10.0 (8.5–11.1)	2,592 (28–1288)	Argentina[37] Chile[33] Peru[38] Uruguay[39]
All children	5	8.8 (6.2–14.4)	1,104 (77–520)	Argentina[40] Brazil[41] Costa Rica[36] Jamaica[42] Uruguay [43]
All ages	1	20.3	64	Trinidad[44]

*When the number of studies =1 the CFR for that study is presented.

Serotype distribution of IPD. Thirteen studies from six countries provided data on serotypes for IPD with over half the studies (n=7) coming from Brazil. Two of the studies were studies from PAHO's surveillance network that included data on children <6 years of age from six countries (Argentina, Brazil, Chile, Colombia, Mexico and Uruguay). Several other studies contained serotype data which duplicated part or all of the PAHO surveillance data and were therefore excluded from this part of the analysis.

The median percentage coverage of IPD serotypes in each of three pneumococcal multi-valent conjugate vaccine preparations (available or under development) were presented by age group for the serotypes alone and with their cross-reactive serotypes (Table 7). The median percentage conjugate vaccine coverage from IPD studies was highest among children <2 years of age (64% to 92%) and lowest among older adults (35-63%) for the 7- and 13-valent vaccines, respectively with their cross-reactive serotypes. In all cases, the coverage was higher when the cross-reactive serotypes were included. Appendix L presents median coverage data from PAHO's surveillance network over time. Coverage of the 23-valent polysaccharide vaccine was 85% in adults and 68% in older adults (data not shown).

TABLE 7: Median percentage vaccine coverage from IPD studies for three pneumococcal conjugate vaccine preparations with and without cross-reactive serotypes by age and with country information

		MEDIAN % VACCINE COVERAGE EXCLUDING CROSS REACTIVE SEROTYPES (25th –75th percentile)			MEDIAN % VACCINE COVERAGE INCLUDING CROSS-REACTIVE SEROTYPES (25th – 75th percentile)			
Age group	**No. of studies**	**7-Valent**	**10- Valent**	**13- Valent**	**7- Valent**	**10- Valent**	**13- Valent**	**Countries**
<2 years	2	62 (58-66)	84 (81-87)	91 (91-92)	64 (60-69)	87 (84-90)	92 (91-93)	Argentina,[32] Uruguay [39]
<6 years*	1	59	73	84	62 (61-62)	80 (79-80)	85 (85-86)	Multi-country[45,46]
All children	6	54 (46-57)	70 (68-80)	84 (80-89)	62 (52-67)	81 (77-87)	87 (82-94)	Argentina[47] Brazil[48,49,50,51] Uruguay[43]
All ages	3	47 (46-48)	61 (56-63)	74 (71-76)	59 (54-59)	66 (66-71)	77 (75-81)	Brazil[52,53,54]
Older adults	1	31	41	63	35	45	63	Brazil[54]

*PAHO surveillance network data. Data excluding cross-reactive serotypes based on 2000-2003. Serotypes 6A and 6B were combined for 1993-1999 so this coverage could not be calculated.

We examined the frequency of serotypes by age in Table 8. Serotype 14 was most common in all age groups except for older adults where serotype 3 was the most frequent. Appendix L presents the distribution of serotypes from PAHO's surveillance network by country, and the changes in frequency over time.

TABLE 8: Median percentage frequency of most common pneumococcal serotypes, from IPD serotype studies, by age group

SEROTYPES	<6 YEARS*	<2 YEARS**	ALL CHILDREN**	ALL AGES**	OLDER ADULTS**
	%	%	%	%	%
14	27.6	41.9	25.4	17.8	7.3
6B	***13.1	8.7	8.7	7.2	4.0
5	7.9	12.0	12.6	4.9	3.3
1	7.4	6.7	6.6	5.5	3.7
23F	6.2	1.7	3.9	4.3	4.0
19F	5.0	1.8	5.6	5.7	5.5
18C	4.3	4.5	4.2	5.4	3.3
19A	3.2	1.7	4.0	2.2	0.7
9V	3.1	2.7	2.7	2.8	2.9
3	2.7	3.3	1.7	7.3	17.8
7F	2.6	3.7	1.5	2.1	3.0
4	1.6	0.6	1.7	3.4	4.4
6A	—	2.2	5.6	5.4	3.3
Total	71.6	91.5	84.2	74.0	63.2
# of studies	2[45,46]	2[32,39]	6[43,48,47,47,49,50,51]	3[52-54]	1[54]

*Data from PAHO's surveillance network. ** Data not from PAHO's surveillance network. ***Data refers to serotypes 6a and 6b combined.

Antimicrobial resistance of IPD. There were 56 studies from 11 countries that provided data on resistance to penicillin among isolates causing IPD (Table 9). The number of isolates varied from 30 to 6,470 per study. The median percentage of isolates per study that were resistant to penicillin was similar among the various child age groups. The percent of isolates that were highly resistant to penicillin ranged from 2% among those of all ages to 13% in all children. Multi-resistance was highest in children of all ages at 51%. Appendix L, Table L-1 presents data on antimicrobial resistance for IPD by country.

TABLE 9: Median percent of isolates resistant to penicillin, from IPD studies, by age

AGE GROUP	NUMBER OF STUDIES	MEDIAN NUMBER OF ISOLATES PER STUDY (Min–Max)	MEDIAN % OF ISOLATES RESISTANT PER STUDY (25^{th}-75^{th} percentile)
Overall Penicillin Resistance			
<2 years[32]	1	153	29
< 5 years[37,42,49,55,56,57-60]	9	360 (30- 6470)	27 (21-32)
All children[36,40,41,43,47,50,61-64]	10	101 (31-901)	31 (17-37)
All ages[44,65-77]	14	156 (37-1100)	23 (20-38)
High Penicillin Resistance			
<2years[32]	1	153	7
<5 years[37,42,49,55,56,57-60]	9	360 (30- 6470)	13 (3-20)
All children[36,40,43,47,61,62,64]	7	188 (56-901)	14 (7-18)
All ages[66-68,70-74,75]	9	148 (37-1100)	2 (1-8)
Resistant to Penicillin and at Least One Other Drug			
< 6 years[56,59,57]	3	NA	25 (15-31)
All children[41,47]	2	NA	51 (40-63)
All ages[68,69,72,73]	4	NA	18 (12-31)

3.2.2. Meningitis

Incidence of bacterial and pneumococcal meningitis. Most studies on bacterial meningitis were from before Hib vaccine introduction. Pre- and post-Hib vaccine comparisons were possible for children <5 years of age, all children and older adults (Table 10). Among children, the incidence was higher in the pre-Hib era than in the post-Hib era but did not change in the one study in older adults. The incidence of both bacterial and pneumococcal meningitis decreased with increasing age except among older adults. Incidence was highest in children <1 year of age at 138/100,000 for bacterial meningitis and 18.2/100,000 for pneumococcal meningitis. The incidence in children <5 years of age ranged widely between the three studies as indicated by the IQR (24.9-59.6).

TABLE 10: Median incidence, from studies of bacterial and pneumococcal meningitis, presented as cases per 100,000 annually, by age, time of Hib vaccine introduction, with country information

AGE GROUP	TIME RELATIVE TO HIB VACCINE INTRODUCTION	NUMBER OF STUDIES	MEDIAN INCIDENCE OF MENINGITIS* (25^{th} –75^{th} percentile)	NUMBER OF CASES OF MENINGITIS IN ALL STUDIES COMBINED (min-max)	COUNTRY
Bacterial Meningitis					
<1 year	Before	1	138.3	91	DR[78]
<2 years	Before	1	78.3	103	DR[78]
<5 years	Before	3	33.7 (24.9-59.6)	111***	DR[78] Cuba[79] Guatemala[80]
	After	1	7.4 (5.8-9.2)	***	Cuba[79]
All children	Before	1	7.5 (7.0-8.0)	***	Cuba[79]
	After	1	4.4 (4.0-4.9)	***	Cuba[79]
Adults**	Before	1	5.4	87	Argentina[81]
Older adults	Before	1	7.3 (7.0-7.7)	226	Cuba[82]
	After	1	7.3	117	Cuba[82]
Pneumococcal Meningitis					
<1	NA	3	18.2 (11.3-18.7)	168 (1-155)	Chile[58] DR[78], Argentina[32]
<2	NA	3	12.2 (10.1-12.2)	221 (7-198)	Chile[58] DR[78] Argentina[32]
<5	NA	6	7.9 (3.2-11.5)	88 (17-37)***	Chile[33] DR[78] Cuba[79] Brazil[53,83] Guatemala[80]
All children	NA	2	1.9 (1.4-2.3)	45***	Cuba[79] Argentina[81]
Older adults	NA	1	2.8 (2.8-2.8)	129	Cuba[82]
All ages	NA	1	1.6	140	Brazil[53]

* When the number of studies =1 the annual incidence (or the median incidence where >1 year of data are available) is presented.
**Adults — study 1988-1998, Hib vaccine introduced in 1997 so most years are pre, it is treated as pre.
***No data on number of studies for at least one study, NA — not applicable.

Bacterial and pneumococcal meningitis CFR. The highest median CFR for bacterial meningitis was among the elderly (40.2%) followed by adults (21.4%), and children <2 years of age (17.1%) (Table 11). For pneumococcal meningitis, the CFR ranged from 16.8% in children excluding infants to 43.9% in all ages. There was wide variation in the CFR between studies for some age groups as demonstrated by the IQR, for example, children <5 years of age (IQR 13.7-21.3). The CFRs for pneumococcal meningitis were approximately double that for bacterial meningitis in children but similar among adults and the elderly.

TABLE 11: Median case fatality ratio, from bacterial and pneumococcal meningitis studies, by age group with country information¥

AGE GROUP	NUMBER OF STUDIES (25th-75th Percentile)	MEDIAN CFR*	TOTAL NUMBER OF CASES OF MENINGITIS IN ALL STUDIES COMBINED (Min-Max)	COUNTRIES
Bacterial Meningitis				
<1 year	4	13.8 (12.3-17.6)	311 (51-138)**	Chile[84] Brazil[85] Cuba[86] Venezuela[87]
<2 years	3	17.1 (14.6-23.8)	402 (66-253)	Brazil[88,89] Chile[84]
<5 years	8	14.8 (13.7-21.3)	2399 (73-979) **	Brazil[83,88] Chile[84] Cuba[86] DR[78] Mexico[90] Guatemala[80] Peru[38]
All children	10	13.4 (10.9-16.3)	3567 (90-1380) **	Brazil[85,88,91-93] Chile[84,94,95] Colombia[96] Cuba[86] Venezuela[87]
Children ≥5 years	2	12.2 (10.4-14)	162**	Brazil[88] Cuba[86]
Adults	2	21.4 (20.7-22.2)	263 (87-176)	Argentina[81] Brazil[97]
Older adults	2	40.2 (32.8-47.7)	406 (63-343)	Argentina[81] Cuba[82]
Pneumococcal Meningitis				
<1 year	1	34.1	44	Brazil[98]
<2 years	3	30.3 (25.2-34.5)	160 (31-99)	Brazil[41] Chile[35] Uruguay[39]
<5 years	6	35.1 (22.3-49.7)	1587 (46-1028)	Brazil[53,83,99] Chile[33] Guatemala[80] Uruguay[39]
All children	10	27.7 (21.7-33.0)	594 (34-105)	Argentina[40,81] Brazil[51,97] [92,98,88,85] Paraguay[100] Uruguay[43]
Children (excluding <1 yr)	2	16.8 (11.8-21.9)	30**	Brazil[41] Cuba[79]
Adults	3	26.7 (19.3-29.2)	191 (45-101)	Argentina[81,101] Brazil[97]
Older adults	1	14.3	42	Argentina[101]
All ages	1	43.9	1965	Brazil[99]

*When the number of studies =1 the CFR for that study is presented.
**Total number of cases is less than actual as at least one study presented a CFR without presenting the denominator.
¥ Table 11 summarizes data from published papers only. Data from an Argentinean abstract are consistent with the CFRs presented above for bacterial meningitis in children[102] and a Haitian abstract found a lower CFR for all ages of 9%.[103] Abstracts from the Dominican Republic and Argentina reported CFRs of 27% and 20%, respectively for pneumococcal meningitis in children 0-14 years of age.[104,105]

Percentage of bacterial meningitis due to SP. Table 12 presents the percentage of bacterial meningitis due to SP. The proportion of cases due to SP was similar in all age groups at between 16% and 18% except for adults where it increased to 45%. These data are presented in Appendix L.

TABLE 12: Median percent of disease due to SP, from studies of confirmed cases of bacterial meningitis, by age with country information.

AGE GROUP	NUMBER OF STUDIES	MEDIAN % OF CONFIRMED CASES OF BACTERIAL MENINGITIS PER STUDY (25th -75th Percentile)	COUNTRY
<2 years	7	18 (17-20)	Brazil[88,106,107] Chile[84,95,108] DR[78]
<5 years	11	17 (10-22)	Brazil[83,92,107,109,110] Chile[108]
All children	14	16 (14-19)	Colombia[111,112] Mexico[90] DR[78] Peru[38] Brazil[85,88,91,92,93,107,113] Chile[84,95,108] Venezuela[87,114] Mexico[115] Uruguay[116]
Adults	3	45 (41-56)	Argentina[81] Brazil[97] Colombia[112]
All ages	6	16 (14-20)	Colombia[96,112] Brazil[110] Cuba [117] Mexico[118] Haiti[119]

Serotype distribution of pneumococcal meningitis. The median coverage in children <2 and <6 years of age ranged from 47% to 78% and from 61% to 81% for the 7- and 13-valent vaccine preparations with cross-reactive serotypes, respectively (Table 13).

TABLE 13: Median percentage vaccine serotype coverage from pneumococcal meningitis studies for three pneumococcal conjugate vaccine preparations, with and without cross-reactive serotypes by age and with country information¥

		MEDIAN % VACCINE COVERAGE EXCLUDING CROSS-REACTIVE SEROTYPES (25th -75th Percentile)			MEDIAN % VACCINE COVERAGE INCLUDING CROSS-REACTIVE SEROTYPES (25th -75th Percentile)			
Age Group	No. of Studies	7-Valent	10-Valent	13-Valent	7-Valent	10-Valent	13-Valent	Countries
<2 years	2	40 (37-43)	68 (67-70)	74 (74-74)	47 (41-53)	75 (73-76)	78 (76-79)	Brazil[120] Uruguay[39]
<6 years*	1	—	—	—	61	77	81	Multi-country[45]

*PAHO surveillance network data based on 1993-1999. Serotypes 6A and 6B were combined so percentage coverage due to vaccine types without cross-reactive serotypes cannot be calculated.

¥ Table 13 summarizes data from published papers only. An abstract describing a study of cases of pneumococcal meningitis from the Dominican Republic found similar coverage.104

Antimicrobial resistance of pneumococcal meningitis. There were only six studies on penicillin resistance among isolates causing pneumococcal meningitis (Table 14). Resistance was higher among children (22%) than among people of all ages (15%). Appendix L, Table L-4 presents these data by country.

TABLE 14: Median percent of isolates resistant to penicillin from pneumococcal meningitis studies by age

AGE GROUP	NUMBER OF STUDIES	MEDIAN NUMBER OF ISOLATES PER STUDY (Min-Max)	MEDIAN % OF ISOLATES RESISTANT TO PENICILLIN (25^{th}-75^{th} Percentile)
All children[51, 53,100, 121,122]	5	54 (38-303)	22 (9-33)
All ages[53,112]	2	172 (40-303)	15

3.2.3 Pneumonia

Incidence of pneumonia. Table 15 presents data on the incidence of clinical, x-ray confirmed, and pneumococcal pneumonia. The data on the incidence of clinical pneumonia comes from a cohort study[123] two population based surveillance studies[124,125] and a randomized controlled trial.[126] The incidence of clinical pneumonia was highest in children <18 months of age years of age (30,079/100,000). This high rate is probably because children were actively followed from birth to 18 months of age in this cohort study. Disease incidence decreased with increasing age.

Three countries (4 projects) in Latin America have established population-based surveillance for x-ray confirmed pneumonia. Data that has been published in peer-reviewed journals, from Uruguay and Córdoba, Argentina, are presented separately from the data from Chile and Buenos Aires, Argentina, that have not yet been published in peer-reviewed journals.[127,128] There were some minor differences between the studies in the inclusion criteria and the population under surveillance (outlined in Appendix L), but data by age were remarkably similar between the studies. The incidence of x-ray confirmed pneumonia decreased with increasing age and was highest in children <1year of age (2,163/100,000 and 2,328/100,000 in the published and unpublished data respectively). A study from Brazil found an incidence of x-ray confirmed pneumonia of 566/100,000 in children <5 years of age; this study is not directly comparable to the studies reported subsequently because it used a combination of active and passive surveillance.[129] The incidence of blood-cultured confirmed pneumococcal pneumonia was highest in children <2 years of age (51/100,000), higher among inpatients than outpatients, and decreased with increasing age.

Pneumonia CFR. The median CFR for clinical pneumonia was highest in older adults at 20.7% (Table 16). The median CFR among children <1 and <5 years of age was the same at 3%. As expected, the CFRs for pneumococcal pneumonia were higher than for clinical pneumonia in both children and adults. We did not find any reports of mortality among cases of x-ray confirmed pneumonia.

TABLE 15: Median incidence, from studies of clinical, x-ray confirmed, and pneumococcal pneumonia, presented as cases per 100,000 annually by age and inpatient or outpatient treatment* with country information

AGE GROUP	INPATIENT (I) OR OUTPATIENT (0) (25th -75th Percentile)	NUMBER OF STUDIES	MEDIAN INCIDENCE OF PNEUMONIA**	TOTAL NUMBER OF CASES OF PNEUMONIA FROM ALL STUDIES COMBINED (Min-Max)	COUNTRIES
Clinical Pneumonia					
<18 months		1	30,079	171	Chile[123]
<2 years		1	4,363	1,361	Uruguay[124]
<5 years		2	3,059 (2,957-3,142)	2,052 (18-2,034)	Brazil[126] Uruguay[124]
All ages		1	1,274 (1,163-1,389)	158,670	Brazil125
X-Ray Confirmed Pneumonia with Consolidation (from peer reviewed literature)					
<1 year		2	2,163 (1,963-2,364)	1,268 (253-1,015)	Argentina[32] Uruguay[124]
<2 years		2	2,132 (1,986-2,277) (519-2,112)	2,631	Argentina[32] Uruguay[124]
<5 years		1	1,174	826	Uruguay[124]
X-Ray Confirmed Pneumonia with Consolidation (from non-peer reviewed literature)					
<1 year		2	2,328 (1,998-2,657)	531 (240-291) Argentin[128]	Chile[127]
<2 years		2	1,864 (1,617-2,116)	916 (439-477)	Chile[127] Argentina[128]
<3 years		1	2,052	606	Chile[127]
<5 years		1	785	745 (328-417)	Argentina[128]
Confirmed Pneumococcal Pneumonia* **					
<2 years	1	2	51.1 (47.1-55.1)	350 (51-299)	Argentina[32] Chile[58]
	0	1	36.0	31	Argentina[32]
<5 years	1	34.1	118		Chile[33]
All children	I	1	32.8	13	Argentina[32]
	O	1	15.1	6	Argentina[32]
Adults	I&O	1	17.0	17	Argentina[101]

*For pneumococcal pneumonia only.

** When the number of studies =1 the annual incidence (or the median incidence where >1 year of data are available) is presented.

***Pneumococcal etiology confirmed by isolation from blood and or pleural fluid.

TABLE 16: Median case fatality ratio from clinical and pneumococcal pneumonia studies by age group with country information

AGE GROUP	NUMBER OF STUDIES	MEDIAN CFR* (25th-75th percentile)	TOTAL NUMBER OF CASES IN ALL COMBINED STUDIES (min-max)	COUNTRIES
Clinical Pneumonia				
<1 year	1	3.0	536	Brazil[130]
<5 years	3	3.0 (1.9-5.5)	2,476 (541-1210)	Guatemala[80] Peru[38] Uruguay[131]
All children	3	0.4 (0.2-0.8)	3,435 (510-1762)	Brazil[130,132] Uruguay[133]
Adults	3	7.6 (5.4-12.7)	774 (31-463)	Argentina[134] Chile[135,136]
Older adults	3	20.7 (16.9-24.9)	546 (100-306)	Brazil[137] Chile[138] Mexico[139]
Pneumococcal Pneumonia				
<2 years	1	8.1	37	Chile[35]
<5 years	2	5.4 (5.1-5.8)	1,949 (371-1578)	Multicenter[140] Chile[33]
All children	2	4.3 (4.1-4.6)	525 (188-337)	Argentina[40] Uruguay[43]
Adults	1	13.0	46	Chile[141]

*When the number of studies =1, the CFR for that study is presented.

Proportion of pneumonia due to Streptococcus pneumoniae. Among all pneumonias with known etiology the median percentage due to SP was 41% for all children, 23% for children <5 years of age, and 17% among adults (Table 17). More detailed tables in Appendix L present data by time of Hib vaccine introduction, suspected or bacteriologically-confirmed pneumonia, and by country.

TABLE 17: Median percent of disease due to SP from studies of bacteriologically-confirmed pneumonia, by age

AGE GROUP	NUMBER OF STUDIES	MEDIAN % OF PNEUMONIA DUE TO SP PER STUDY* (25th -75th percentile)	COUNTRIES
<5 years	5	23 (21-34)	Argentina[142] Brazil[143] Uruguay[131,144,145]
All children	6	41 (30-67)	Uruguay[116,133,146,147] Brazil[130] Peru[148]
Adults	3	17 (14-19)	Argentina134 149 Chile135

*Among those pneumonias with a known etiology

Serotypes of *pneumococcal pneumonia*. The median percentage coverage of pneumococcal pneumonia in children <2 years of age ranged from 68% to 91% and from 58% to 88% for the 7- and 13-valent vaccine preparations with cross-reactive serotypes, respectively (Table 18).

TABLE 18: Median percentage vaccine coverage for pneumococcal pneumonia studies for three pneumococcal conjugate vaccine preparations with and without cross-reactive serotypes by age and with country information

		MEDIAN % VACCINE COVERAGE EXCLUDING CROSS REACTIVE SEROTYPES (25th-75th percentile)			MEDIAN % VACCINE COVERAGE INCLUDING CROSS REACTIVE SEROTYPES (25th-75th percentile)			
AGE GROUP	# OF STUDIES	7-VALENT	10-VALENT	13-VALENT	7-VALENT	10-VALENT	13-VALENT	COUNTRIES
<2 years	2	67 (64-69)	86 (84-87)	91 (90-91)	68 (65-71)	87 (84-89)	91 (90-92)	Argentina[32] Uruguay[39]
<6 years*	1	—	—	—	58	83	88	Multi-country[45]

*PAHO surveillance network data based on 1993-1999. Serotypes 6A and 6B were combined so percentage coverage due to vaccine types without cross-reactive serotypes cannot be calculated.

Antimicrobial resistance of pneumococcal pneumonia. The median percentage of isolates resistant to penicillin was highest among children <1 year of age (79%) although this data is only from one study (Table 19). The median percentage of isolates that were highly resistant to penicillin was highest among children <5 years of age (18%). One study showed that 68% of isolates in adults were multi-resistant. Appendix L presents these data by country.

TABLE 19: Median percent of isolates resistant to penicillin from studies of pneumococcal pneumonia, by age.

AGE GROUP	NUMBER OF STUDIES	MEDIAN NUMBER OF ISOLATES RESISTANT PER STUDY* (Min-Max)	MEDIAN % OF ISOLATES PER STUDY* (25th-75th percentile)
Overall Penicillin Resistance			
<1 year[150]	1	107	79
< 5 years[133,140,151]	3	220 (51-1396)	32 (27-40)
All children[147,148,152]	3	85 (64-468)	6 (0-38)
Adults[101,135,141]	3	54 (48-101)	27 (6-12)
All ages[153,154]	2	320 (315-324)	32 (12-52)
High Penicillin Resistance			
<1 year[150]	1	107	5
< 5 years[133,140,151]	3	220 (51-430)	18 (10-22)
All children[147,148,152]	3	85 (64-468)	6 (3-22)
Adults[135,141]	2	51 (48-54)	5 (5-6)
All ages[153,154]	2	320 (315-324)	9 (3-23)
Resistant to Penicillin and at Least One Other Drug			
< 1 y[150]	1	NA	2
All children[147]	1	NA	0
Adults[101]	1	NA	68

*Where number of studies =1 the actual value rather than the median is presented
NA — not available

3.2.4 Pneumococcal Bacteremia and Sepsis

Incidence and CFR of pneumococcal bacteremia and sepsis. Two studies from Argentina and Chile instituted a standard practice of taking blood cultures on all young children with high fever. Among outpatients, the incidence of bacteremia was higher in Argentina (87/100,000) than in Chile (35/100,000) (Table 20). This may be related to the differences in case definitions used: children attending the ER with an axillary temperature of = > 39º C in Argentina and ambulatory patients with rectal temperature of 40ºC or axillary temperature of ≥39.4º C in Chile. In the study from Chile, bacteremia without focus represented 47.5% of all IPD cases. We were able to abstract data to calculate the incidence of pneumococcal sepsis from the Chile study (2.1/100,000) in children <3 years of age.

For all studies on bacteremia among children, the CFR was 0, probably due to the inclusion of bacteremia without focus. The CFR for sepsis was high in both children (35.3%) and adults (30%), and in adults with bacteremia (28%).

TABLE 20: Incidence (cases per 100,000 persons annually) and median CFR from studies of pneumococcal bacteremia and sepsis by age, inpatient or outpatient treatment, and country

AGE GROUP	PLACE OF TREATMENT	NUMBER OF STUDIES	INCIDENCE OF BACTEREMIA AND SEPSIS	CFR %	TOTAL NUMBER OF CASES OF ALL STUDIES COMBINED	COUNTRY
			Bacteremia			
<2 years	Inpatient	1	11.6	0	10	Argentina[32]
	Outpatient	1	87.0	0	75	Argentina[32]
< 2 years	Outpatient	1	34.7	—	80	Chile[33]
<36 months	Outpatient	1	31.6	0	188	Chile[33]
Adults	Inpatients	1	—	28.4	81	Argentina[134]
			Sepsis			
<36 months	Inpatients	1	2.1	35.3%	51	Chile[33]
Adults	Inpatients	1	—	30.0	40	Chile[147]
			Sepsis and Bacteremia not Differentiated			
All children	Inpatient	1	—	12.5	32	Argentina[14]

3.2.5 Acute Otitis Media (AOM)

Incidence of Acute Otitis Media. Table 21 presents the incidence of AOM from one study, a four-year passive surveillance study from the Mexican public health system.[155] The incidence was highest in children less than one year of age (1,214/100,000).

TABLE 21: Incidence of AOM presented as cases per 100,000 by age

AGE GROUP	INCIDENCE OF AOM (variation in incidence across 4 years)
<1 year	1,214 (1,125-1,349)
1-4 years	1,095 (981-1,197)
5-14 years	621 (558-694)
All ages combined	493 (454-564)

Table 22 presents data on a prospective cohort study which measured the frequency of AOM episodes in children two to 24 months of age. This three-year study from Brazil found that 68.4% of children had at least one episode of AOM by two years of age.[156]

TABLE 22: Distribution of episodes of AOM by age, Brazil, 1997-1999

AGE GROUP	NUMBER OF CHILDREN WITH NO EPISODE OF AOM (%)	NUMBER OF CHILDREN WITH 1-3 EPISODES OF AOM (%)	NUMBER OF CHILDREN WITH 4 OR MORE EPISODES OF AOM (%)	TOTAL NUMBER OF CASES
<9 months	49 (31.6)	73 (47.1)	33 (21.3)	155
10-24 months	11 (31.4)	22 (62.9)	2 (5.7)	35
Total	60 (31.6)	95 (50.0)	35 (18.4)	190

The data from these two studies were considered to be underestimates of the region as a whole since data from more developed countries have shown a higher number of episodes per child. For the economic model, we used a cumulative probability of AOM up to age five of 0.9. This probability came from two studies. The first, a seven-year prospective cohort, showed that the average number of episodes of AOM in children under two was 0.9 to 1.2. 14 The second study, carried out in Finland, measured the cumulative incidence of the first episodes of AOM in children up to 24 months of age, and found the average number of episodes in the two first years of life was 0.93 (0.90-0.96).[157]

Proportion of AOM due to *Streptococcus pneumoniae*. SP was the etiological agent most frequently isolated (46.8%) from 12 studies which routinely examined middle ear fluid on all children. A higher rate is noted for children <1 year of age (61.4%) (Table 23).

TABLE 23: Median percent of disease due to SP from studies of bacteriologically confirmed AOM by age with country information

AGE GROUP	NUMBER OF STUDIES	MEDIAN % OF BACTERIOLOGICALLY CONFIRMED AOM STUDY	COUNTRY
<1 year	1	61.4	Costa Rica[158]
< 5years	6	39.0	Brazil,[159] Costa Rica[160,161] Multicenter[162,163] Argentina[164]
All children	5	47.1	Costa Rica[165,166,167] Chile[168] Multicenter[169]
Overall median	12	46.8	

*Where number of studies =1 actual value rather than median is presented

Serotypes of Acute Otitis Media. Two published studies were included in Table 24 with data on serotype distribution. MEF was routinely taken from children in these studies. The median vaccine coverage for AOM ranged from 68% to 78% for the 7- and 13-valent vaccine including cross-reactive serotypes, respectively (Table 24). A study among older children, aged 18m to 13y, from Argentina found similar vaccine coverage (69% to 84%).[170]

TABLE 24: Median percentage vaccine coverage from AOM studies for three pneumococcal conjugate vaccine preparations with and without cross-reactive serotypes by age and with country information

		MEDIAN % VACCINE COVERAGE EXCLUDING CROSS REACTIVE SEROTYPES (25th -75th percentile)			MEDIAN % VACCINE COVERAGE INCLUDING CROSS REACTIVE SEROTYPES (25th -75th percentile)			
AGE GROUP	# OF STUDIES	7-VALENT	10-VALENT	13-VALENT	7-VALENT	10-VALENT	13-VALENT	COUNTRIES
<5 years	2	58 (54-61)	58 (54-63)	70 (66-74)	68 (65-71)	69 (66-72)	78 (77-80)	Brazil[159] Costa Rica[161]

Distribution of serotypes among children <5 years of age with AOM varies from the distribution found in IPD, with 19F (22.4%) and 6B (13.5%) the most frequent serotypes (Table 25). Data from 1999-2001 in Costa Rica found 19F to be the most frequent serotype (75%) in children 4m to 12y. 161 However, 19F was considered to be an outbreak serotype so these data were not included in Table 24. In the study from Argentina, serotype 14 was the most frequent (53%).[170]

TABLE 25: Median percentage frequency of the 12 most common serotypes from AOM serotype studies for children <5 years of age

SEROTYPES	14	6B	5	1	23F	19F	18C	19A	9V	3	7F	4	6A	TOTAL
%	2.9	13.5	0	0.7	6	22.4	4.6	6.3	7.5	2.9	0	0.7	2.9	70.4

Antimicrobial resistance of Acute Otitis Media. As shown in Table 26, overall proportion of pneumococcal isolates that were penicillin resistant was higher among all children than for children under six years of age. Conversely, the median percentage of isolates highly resistant to penicillin was higher in children <6 years than for all children. However, only one study had data on high-level resistance to penicillin among children < 6 years. Appendix L, Table L-10 presents data on antimicrobial resistance for IPD by country.

TABLE 26: Median percent of acute otitis media isolates resistant and highly resistant to penicillin by age

AGE GROUP	NUMBER OF STUDIES	MEDIAN NUMBER OF ISOLATES PER STUDY (Min-Max)	MEDIAN % OF ISOLATES RESISTANT TO PENICILLIN (25^{th}-75^{th} Percentile)
Overall Penicillin Resistance			
<6 years[161,159,160,162,163]	5	74 (48-229)	30 (23-40)
All children[158,108,170,168,165]	5	63 (38-187)	40 (33-52)
High Penicillin Resistance			
<6 years[160]	1	11	8.1
All Children[158,108,168,165]	4	20 (9-41)	3 (2-16)

3.3 Description of Economic Papers Reviewed

Of 109 studies identified in the economic literature search, two studies with cost-effectiveness data and eight studies with cost of illness data were reviewed. Appendix M presents more detailed information on these ten papers.

In the published literature, sources of cost data were generally methodologically deficient, not generalizable to other populations, and did not reflect the true economic costs of pneumococcal disease. Results from two methodologically rigorous cost-effectiveness analyses performed in Chile and in a three-country study suggest that the economic burden of pneumococcal disease is substantial.[171,172] These two studies also indicate that the targeted conjugate vaccination program may be cost-saving for reducing the incidence of pneumococcal disease in healthy infants and young children if vaccine price were reduced by more than half the current listed price.

In these two analyses, potential cost-effectiveness of pneumococcal vaccine depended on several factors, including vaccine coverage, vaccination costs, vaccine efficacy and effectiveness, disease incidence (including incidence of penicillin resistance), serotype distribution, length of vaccine protection, time since vaccination, age of vaccinated group, and lost future wages from children who die of pneumococcal diseases. The majority of the remaining eight studies reinforced the importance of performing economic evaluations on the basis of local settings. Factors limiting the accuracy of these economic studies included lack of understanding the healthcare system in each country, publication bias, and validity of data used to determine the values of key variables. These studies did not include estimates of herd effects. Because of these limitations, no data from these studies were used in the current analysis.

3.4 Cost analysis

The results presented here provide insight into the cost of pneumococcal disease by country income group (low income, lower-middle income, and upper-middle income). These costs are considered to be the best available estimates for the countries studied.

3.4.1 Costs of Pneumococcal Disease-Associated Events

Estimates of total costs per case associated with pneumococcal disease are provided in Table 27. These costs are presented by income group using physician interviews (Appendix G) and parent interviews[171]. The total

direct medical cost per case for all-cause clinical pneumonia and chest X-ray positive pneumonia (inpatient) ranged from US$804.46 to US$1,076.89 per patient, with higher cost incurred by upper-middle income countries due to higher treatment costs. In all countries (except for low income countries), the majority (71%) of these costs resulted from hospital stay (per diem x length of stay). For pneumococcal meningitis, the total cost per case was between US$1,030.54 to US$2,453.26 per patient and here again the majority (73%-88%) was attributed to the cost of hospital stay. The direct medical cost per case for pneumococcal sepsis ranged from US$1,053.03 to US$1,354.62 per patient, with higher cost in upper-middle income countries. Fifty-seven percent and 89% of these costs were attributed to hospital stay, respectively in low vs. upper middle income countries. The direct medical cost per case for all-cause clinical pneumonia and chest x-ray positive pneumonia (outpatient) was between US$64.15 and US$142.06 per patient. For all-cause AOM, the direct medical cost per case ranged from US$77.03 to US$91.52 per patient, with higher cost in upper-middle income countries. The majority of these costs were attributed to outpatient visits. Overall, direct medical costs accounted for 54-97% of the total costs in these countries.

TABLE 27: Total costs associated with pneumococcal disease by income group using physician and parent interviews[a]

	LOW INCOME (US$2,130 or Less)[b]	LOWER-MIDDLE INCOME (US$2,131-US$3,820)[b]	UPPER-MIDDLE INCOME (US$ 3,821 or more)[b]
All-cause chest x-ray positive pneumonia or clinical pneumonia, inpatient			
Total direct medical costs	804.46	824.69	1,076.89
Total direct non-medical costs (transport)	11.82	13.85	55.84
Indirect costs	50.64	47.40	192.56
Total cost per patient	866.92	885.94	1,325.29
All-cause chest x-ray positive pneumonia or clinical pneumonia, outpatient			
Total direct medical costs	64.15	77.80	142.06
Total direct non-medical costs (transport)	7.35	8.13	32.98
Indirect costs	6.32	6.64	45.55
Total cost per patient	77.82	92.57	220.59
Pneumococcal Meningitis			
Total direct medical costs	1,030.54	1,220.36	2,453.26
Total direct non-medical costs (transport)	11.82	13.85	55.84
Indirect costs	16.88	69.52	252.32
Total cost per patient	1,059.24	1,303.73	2,761.42
All-cause acute otitis media			
Total direct medical costs	77.03	79.19	91.52
Total direct non-medical costs (transport)	7.35	8.13	32.98
Indirect costs	6.32	6.64	45.55
Total cost per patient	90.70	93.96	170.05
Pneumococcal sepsis			
Total direct medical costs	1,053.03	—	1,354.62
Total direct non-medical costs (transport)	11.82	13.85	55.84
Indirect costs	67.52	58.46	132.80
Total cost per patient	1,132.37	[c]	1,543.26

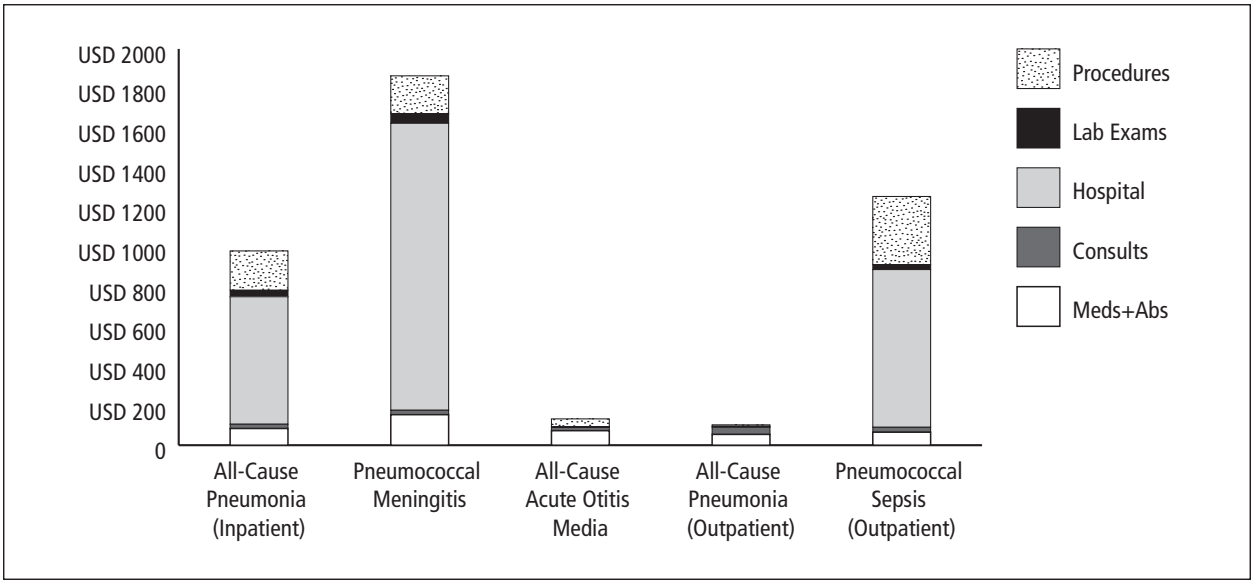
[a]Income groups are divided according to 2003 gross national income (GNI) per capita (Atlas method, US$, 2003). The groups are low-income: $2,130 or less (Colombia, Dominican Republic, Honduras); lower-middle income: $2,131 - $3,820 (Argentina, Brazil, Venezuela, Uruguay); and upper-middle income: $3,821 or more (Chile, Mexico, Panama). The high income group is not included in the present analysis. Values are based on US$2005.

[b]This represents the population weighted average (US$, 2005). However, the cost of pneumococcal sepsis for upper-middle income countries is only an average cost based on responses from Chilean physicians.

[c]Unable to calculate the total cost per patient with a pneumococcal sepsis.

Figure 4 shows the variations in total medical costs by type of disease from a regional perspective. Direct medical costs comprised cost of hospitalization, outpatient visits, use of antibiotics and other medications, diagnostics, radiography, and other procedures. Across the region, the highest costs per case of disease were attributed to pneumococcal meningitis, followed by pneumococcal sepsis, and all-cause inpatient pneumonia.

FIGURE 4: Variations in total direct medical costs per case by disease syndrome, regional perspective.



The variations in structure of direct medical costs by disease are illustrated in Figure 5. Again, hospital stay took up the biggest proportion (63%-81%) of the total cost of all-cause pneumonia (inpatient), pneumococcal meningitis, and pneumococcal sepsis. Nearly 45% and 31% of the total cost of all-cause AOM were attributed to procedures and medication, respectively. For all-cause clinical pneumonia and X-ray positive pneumonia (outpatient), 51% of the total medical costs were attributed to medication and 36% to ambulatory visits.

FIGURE 5: Variations in structure of direct medical costs by disease, regional perspective

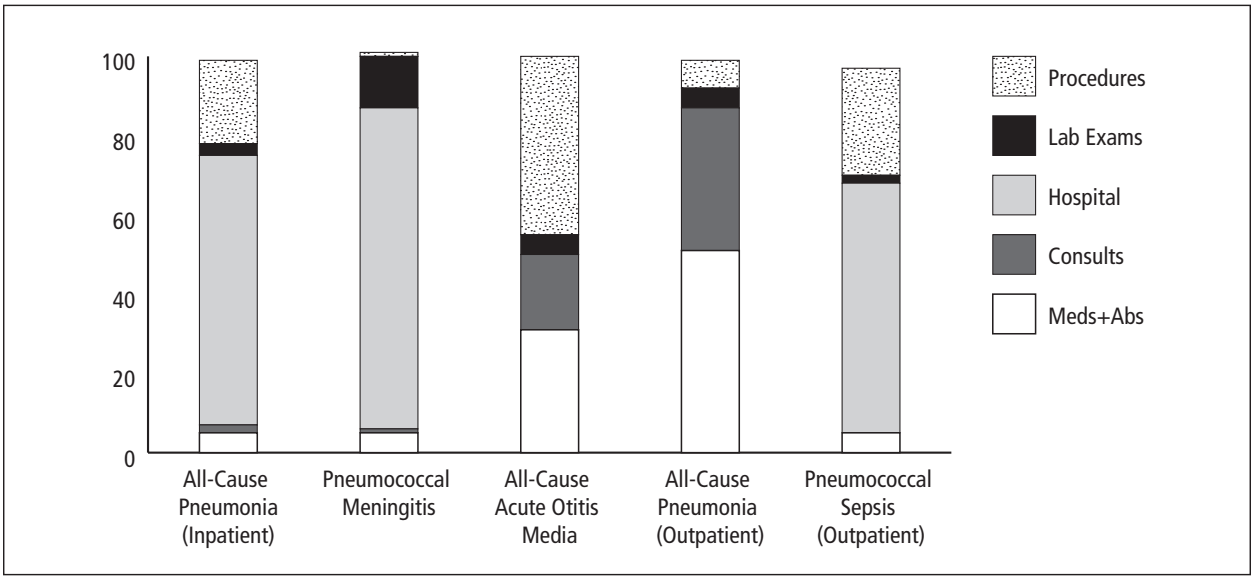


Table 28 provides estimates of direct non-medical costs for patients with pneumococcal disease. Direct non-medical cost associated with transportation for upper-middle income countries was more than the cost for low income countries. For all caregivers, the average cost to transport a child with chest x-ray positive/clinical pneumonia (inpatient), pneumococcal meningitis and pneumococcal sepsis to the hospital ranged from US$11.82 to US$55.84. The average cost to transport a child with chest x-ray positive/clinical pneumonia (outpatient) and all-cause AOM to the outpatient clinic ranged from US$7.35 to $32.98. Seventy percent of caregivers also reported a cost associated with visiting their child at the hospital.

The direct, non-medical costs associated with lost wages for caregivers of patients who require hospitalization (clinical pneumonia/chest x-ray positive pneumonia, pneumococcal meningitis and pneumococcal sepsis) were much higher than that for patients treated as outpatients (clinical pneumonia/chest x-ray positive, all-cause AOM) (Table 28). This is because more caregivers of inpatients lost time from work (72% versus 34%) and on average, caregivers of inpatients lost more time from work than caregivers of outpatients (average value 6.4 days versus 3.2 days, respectively).

TABLE 28: Direct non-medical costs of pneumococcal disease

	DIRECT NON-MEDICAL COSTS	
SYNDROME	TRANSPORTATION AND OTHER (Average US$, 2005)	PRODUCTIVITY COSTS FOR CAREGIVERS (Average US$, 2005)
Pneumococcal meningitis	15.15	35.32
Pneumococcal sepsis	15.15	72.28
Pneumonia (inpatient)[a]	15.15	61.23
Pneumonia (outpatient)[a]	9.28	9.27
AOM	9.28	9.27

[a]This includes all-cause clinical pneumonia and x-ray positive pneumonia.

3.4.2 Comparison of direct medical costs using alternative sources

Table 29 compares the costs of treating pneumococcal disease using physician interviews and WHO-CHOICE/CEPAL data (option 1) to physician interviews and country-specific data (option 2). With the exception of pneumococcal sepsis and pneumococcal meningitis, the costs of treating pneumococcal disease using WHO-CHOICE/CEPAL and physician interviews are higher than the costs using physician interviews and country data. For the cost-effectiveness study, resource utilization, and cost estimates were based on physician interviews and country-specific data as these were considered the most reliable estimates for the region.

TABLE 29: Comparison of direct medical costs of treating pneumococcal disease using physician interviews and WHO-CHOICE/CEPAL data (regional estimate) or physician interviews and country specific data

	WHO/CEPAL AND PHYSICIAN SURVEY[a]	COUNTRY-SPECIFIC DATA AND PHYSICIAN SURVEY[a]
Chest x-ray positive pneumonia or clinical pneumonia, inpatient		
Total direct medical costs/event	1,333.88	940.43
Chest x-ray positive pneumonia or clinical pneumonia, outpatient		
Total direct medical costs/event	152.25	98.68
Pneumococcal meningitis		
Total direct medical cost/event	1,569.17	1,792.08
All-cause acute otitis media		
Total direct medical cost/event	130.31	82.29
Pneumococcal sepsis		
Total direct medical cost/event	1,244.51	1,256.97

[a]Values are based on a regional estimate using population weighted average of cost per event (US$, 2005).

3.5 Economic Evaluation

In this section, we make projections of the burden of childhood pneumococcal disease and the cost-effectiveness of vaccination.

3.5.1 Disease Burden

Estimation of proportion of AOM and pneumonia caused by pneumococcal disease. The median proportion of AOM due to pneumococcal disease among children less than five years was 40% based on six relevant studies. However, the majority of these studies were clinical trials where MEF was taken systematically for suspected bacterial pathogens and therefore may not be reflective of all cause AOM. Therefore we did not use this figure in our calculation. Using a back calculation outlined in table 30 we calculated the proportion of all cause AOM due to pneumococcal disease as 12% (n = 1,261,348). We also reviewed the proportion of pneumonia due to pneumococcal disease and found that it was 23% based on five studies. These were mainly studies that isolated pneumococcus from the blood of patients ill with pneumonia. For our purposes we were interested in the proportion of all cause pneumonia and x-ray confirmed pneumonia due to pneumococcal disease and not just bacteremic pneumonia. Therefore we used the calculations in Table 30 to calculate indirectly the proportion of pneumonia due to pneumococcal disease. We found 25% (n = 268,432) of x-ray confirmed pneumonia cases, and 9% (n = 58,793) of clinical pneumonia (excluding x-ray confirmed pneumonia) are due to pneumococcal disease.

TABLE 30: Estimated proportion of AOM and pneumonia caused by pneumococcal disease

SYNDROME	ESTIMATED NUMBER OF CASES IN THE REGION*	PCV VACCINE EFFICACY	ESTIMATED NUMBER OF EVENTS AVERTED FROM VACCINATION	ESTIMATED % OF PNEUMOCOCCAL DISEASE AVERTED (BASED ON SEROTYPE DISTRIBUTION AND VACCINE COVERAGE)***	NUMBER (%) OF CASES OF EACH SYNDROME ESTIMATED TO BE DUE TO PNEUMOCOCCAL DISEASE
All cause AOM	10,530,450*	7%[5]	678,161	54%	1,261,348 (12%)
All cause x-ray confirmed pneumonia	669,351**	22.7%[30]	144,322	54%	268,432 (40%)
All cause clinical pneumonia (excluding x-ray confirmed)	1,065,386***	3%**[5]	31,610	54%	58,793 (6%)

* We used a cumulative probabilities in table 3
** The vaccine efficacy from the Kaiser Permanente trial was adjusted downwards to account for the exclusion of the x-ray confirmed component of all cause clinical pneumonia
***We used under-five IPD serotype coverage with cross-reactive serotypes of 60%[30] and vaccine coverage of 92%[13] as found in the literature review

Estimated cases (sepsis, meningitis), deaths, and DALYs attributed to pneumococcal disease. Table 31 provides estimates of the number of epidemiological events attributed to pneumococcal disease in Latin American and Caribbean countries per annual birth cohort (0 to five years). Overall, we estimated that pneumococcal disease results in 1.3 million pneumococcal AOM cases, 327,225 pneumonia cases (x-ray positive and other clinically defined estimated to be caused by pneumonia), 1,229 cases of pneumococcal sepsis cases, and 3,918 cases of pneumococcal meningitis. The epidemiological burden of disease (in terms of DALY loss per children) is 617,261 and is proportional to income level. We estimated that 18,068 deaths are due to pneumococcal disease.

TABLE 31: Estimated health burden (cases, deaths, and DALYs) of pneumococcal disease[a] in Latin American and Caribbean countries, per annual birth cohort, age 0 to 5

	TOTAL EVENTS ANNUALLY	NUMBER OF EVENTS ANNUALLY PER 1,000 CHILDREN
Pneumococcal acute otitis media	1,261,348	108
Pneumococcal pneumonia		
Chest x-ray positive	268,432	23
Other, clinically defined[a]	58,793	5
Pneumococcal sepsis	1,229	<1
Pneumococcal meningitis	3,918	<1
Total cases annually	1,593,720	136
Deaths due to *S. pneumoniae*	18,068	2
DALYs	617,261	53

[a]Not including chest x-ray (+) pneumonia.

3.5.2 Economic Burden

Estimates of the economic burden of pneumococcal disease per annual birth cohort (0 to five years) are described in Table 32. Overall, the direct medical costs of pneumococcal disease borne by the healthcare system are US$293 million which represents US$25 for each child born in the region annually. While the health burden of pneumococcal disease is greater in lower income countries, the economic burden (in terms of cost per child) is high in the higher income countries.

TABLE 32: Estimated economic burden of pneumococcal disease in Latin American and Caribbean countries, per annual birth cohort, age 0 to 5

CASES OF PNEUMOCOCCAL DISEASE	TOTAL EVENTS ANNUALLY	COST US$ PER CHILD	TOTAL COSTS (2005 US$)
Hospitalized	181,880	15	174,771,120
Treated as outpatients	1,411,840	10	118,642,469
Health system cost*	**1,593,720**	**25**	**293,413,589**
Costs borne by families**		3	39,993,931
Overall total costs		**28**	**333,407,520**

*Direct medical costs to health care system. ** Direct medical and non-medical costs borne by families.

3.5.3 Benefits of Vaccination

Table 33 shows that vaccination with PCV7 would prevent a total of 678,161 cases of AOM, 175,932 cases of pneumonia (clinical pneumonia and chest x-ray positive pneumonia), and 2,768 cases of pneumococcal sepsis and meningitis. Annually, 9,478 deaths could be averted by pneumococcal conjugate vaccination. Overall, 0.9 lives may be saved per 1,000 children vaccinated and one case of pneumococcal disease could be averted for every 80 children vaccinated. These saved lives, as well as averted cases of deafness, motor deficit, and seizure, result in 321,876 DALYs being averted annually. By applying the mean percentage disease averted from Table 33 (54%) to the overall disease costs of US$333 million from Table 31, we estimated that the costs averted due to vaccination are US$180 million.

TABLE 33: Potential impact of pneumococcal conjugate vaccination on health burden (cases, deaths, and DALYs) of pneumococcal disease

PNEUMOCOCCAL DISEASE EVENT	NO. OF CASES WITHOUT VACCINATION	NO. OF CASES WITH VACCINATION	EVENTS AVERTED	% PNEUMOCOCCAL DISEASE AVERTED*
Pneumococcal acute otitis media	1,261,348	583,187	678,161	54%
Pneumococcal pneumonia				
Chest x-ray positive	268,432	124,110	144,322	54%
Other, clinically defineda	58,793	27,183	31,610	54%
Pneumococcal sepsis	1,229	568	661	54%
Pneumococcal meningitis	3,918	1,812	2,107	54%
Deaths due to *S. pneumoniae*	18,068	8,590	9,478	52%
DALYs	617,261	295,385	321,876	52%

[a] Not including chest x-ray (+) pneumonia.
*% serotype distribution (60%) and vaccine coverage (92%) was not varied by syndrome

3.5.4 Cost-Effectiveness of Vaccination

If vaccine cost the current PAHO revolving fund price of US$53 per dose and vaccine coverage for all children across the Latin American and Caribbean region were the same as for the diphtheria-pertussis-tetanus vaccine (92% coverage[13]), then vaccine-related costs would amount to slightly over US$1.8 billion annually and the cost per DALY and life saved from a societal perspective would be US$5,039 and US$171,130, respectively (Table 34). At lower costs of US$30, US$20, US$10, and US$5 per dose, these annual costs would be lower with the cost per DALY and life saved dropping to US$62 and US$2,110, respectively, at a vaccine price of US$5 per dose.

TABLE 34: Estimated annual vaccine program costs, net costs and cost-effectiveness of a pneumococcal conjugate vaccination program in Latin America and the Caribbean (US$, 2005)

			US$ PER DALY AVERTED		US$ PER LIFE SAVED
DOSE COST	VACCINE COSTS (MILLIONS)[a]	NET COSTS (MILLIONS)[a]	HEALTHCARE PERSPECTIVE[b]	SOCIETAL PERSPECTIVE[b]	SOCIETAL PERSPECTIVE
$53	1,802	1,650	5,106	5,039	171,130
$40	1,368	1,216	3,758	3,691	125,343
$30	1,034	882	2,720	2,653	90,103
$20	701	549	1,686	1,619	54,969
$10	367	215	648	581	19,730
$5	200	48	129	62	2,110

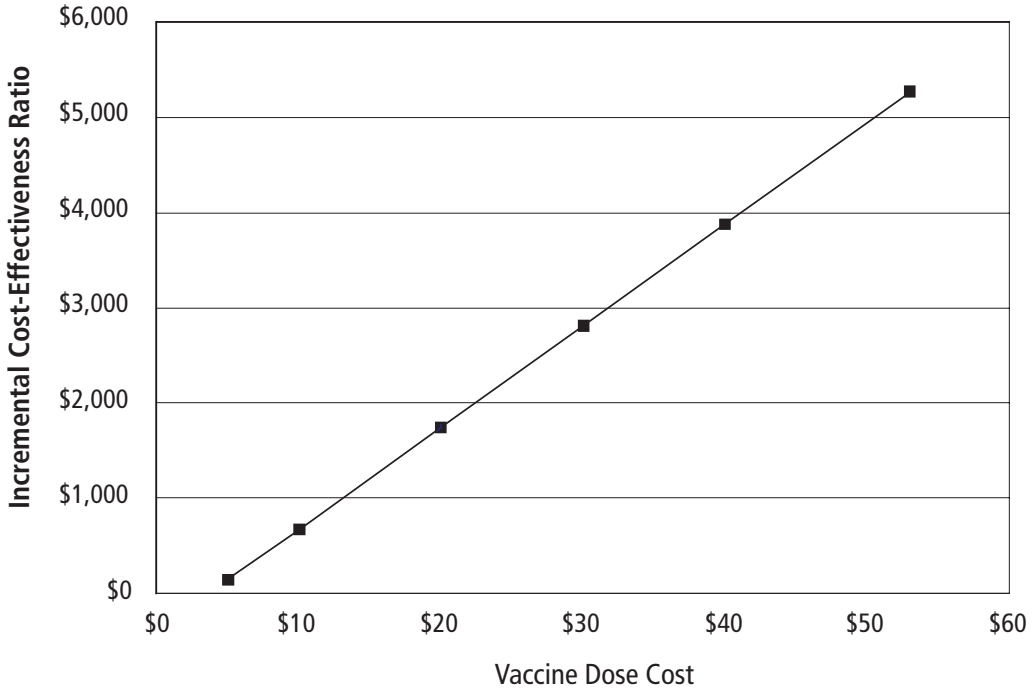
[a]Undiscounted costs.
[b]Using discounted costs and health benefits.

3.5.5 Sensitivity Analysis

The sensitivity analysis evaluated the impact of specific variables (cumulative incidence estimates, CFRs, serotype coverage, and direct medical costs borne by the healthcare system) on the cost-effectiveness of vaccination. We performed sensitivity analysis using the current dose price of US$53. In sensitivity analysis using the high and low estimates for direct medical and non-medical costs, cost per DALY averted ranged from US$2,988 to US$8,234. Addition of a booster dose (fourth dose) would increase the incremental cost-effectiveness ratio to US$7,102 per DALY averted and US$241,000 per life saved. Use of the proposed 13-valent vaccine would decrease the cost per DALY and life saved to US$3,571 and US$121,000, respectively. We did not include any indirect effects of the vaccine. Further sensitivity analysis will be performed for the number of cases and deaths from pneumococcal disease and averted due to the vaccine.

Incremental cost-effectiveness ratios are very sensitive to changes in estimates around vaccine dose costs. A change in the vaccine dose costs results in a change in the cost-effectiveness ratio (Figure 6). At lower costs of US$30, US$20, US$10 and US$5 per dose, these annual costs would be US$1.03 billion, US$700.8 million, US$367.1 million, and US$200.2 million, respectively. The break-even cost per dose (the dose cost where net costs equal zero) is less than US$4 per dose.

FIGURE 6: Effect of vaccine dose cost on cost-effectiveness of pneumococcal conjugate



3.6 GDP Impact Analysis

For 2005, total health expenditures of pneumococcal disease in the Latin American and Caribbean region were estimated to be US$1,186 million. The GDP in Latin America and the Caribbean was estimated at US$2,455,621 in 2005.[173] Based on these estimates, healthcare spending for pneumococcal disease in Latin America and the Caribbean region as a percentage of GDP was estimated at 0.05%, compared to the reported 8-10% of GDP spent on healthcare overall in the region.[174] Fifteen percent of the health expenditures for pneumococcal disease were attributed to health service costs related to hospitalized pneumococcal disease, while 10% was due to health services for ambulatory pneumococcal disease. Four percent was due to costs borne by families. The remaining 71% of these expenditures were due to long term lost productivity over the course of their lifetimes of children with pneumococcal disease.

CHAPTER 4 DISCUSSION

4.1 Main Findings

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. Many of these infections, approximately 400,000, are serious and may lead to hospitalization, permanent disability, and death. The large burden of pneumococcal AOM (1.2 million cases per year) is a significant contributor to the substantial healthcare system costs and broader use of antibiotics. Introduction of pneumococcal conjugate vaccines can greatly reduce the incidence of pneumococcal infections. Using a benchmark of 3 times per capita gross national income as the threshold for cost-effective interventions[175] these cost-effectiveness analyses suggest that, from a regional perspective, 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 7-valent formulation could prevent over half of all cases and deaths due to pneumococcal disease annually in the Latin America and the Caribbean region, including 9,478 deaths. This translates into almost one life saved per 1,000 and one case of pneumococcal disease prevented per 80 children vaccinated. 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 the region should consider these data in their decision-making as they introduce new vaccines, determine affordability, and weigh competing priorities.

We estimated that US$180 million in direct medical and non-medical costs would be averted by introduction of a vaccine. To vaccinate the entire birth cohort of all countries in the region, total vaccine costs would be US$1.8 billion at US$53 per dose and US$200 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 programmatic capacity and sustainability. 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 it would appear in this analysis. At a cost of US$5 per dose, vaccine cost is only slightly higher than the cost of illness averted (US$200 million versus US$180 million) making it very cost-effective, and nearly cost-saving.

4.2 Global Context

This analysis supports the conclusion that pneumococcal disease poses a sizable burden in the Latin American and Caribbean region and results in nearly 10,000 early childhood deaths in the region annually. Establishing the burden of disease is a first step to accelerate vaccine introduction. Several recent events globally are contributing to improved awareness of pneumococcal disease and are setting the stage for more widespread use of the vaccine. In January 2007, the WHO Strategic Advisory Group of Experts recommended the introduction of pneumococcal vaccine in developing countries. This has been followed by a WHO position paper calling for introduction of pneumococcal vaccine in developing countries.[176] In November 2006, the Global Alliance on Vaccines and Immunizations (GAVI) pledged money to support the introduction of pneumococcal and rotavirus vaccines in the poorest countries of the world including six in

Latin America and the Caribbean. Establishing the burden of disease and creating demand for the pneumococcal conjugate vaccine are first steps to accelerating its introduction. The findings of this report, showing the burden of pneumococcal disease in Latin America and the Caribbean, were presented at the Second Regional Pneumococcal Symposium in December 2006 in Brazil. During this meeting, there was a call for action to reduce the burden of pneumococcal disease in the region.

WHO, together with GAVI's PneumoADIP and Hib Initiative, have recently conducted a comprehensive global review of the available data on pneumococcal (and Hib) disease burden. The WHO process incorporated an evaluation of data quality and employed meta-analytic methods and modeling techniques to generate country, sub-regional, regional, and global level estimates of the burden of pneumococcal disease in children. These estimates are expected to be published in mid to late 2007. Our review differed from the WHO global disease burden project in several respects. Our scope was broader in that we provided a comprehensive description of invasive and non-invasive pneumococcal disease in the region for all age groups, and included a description of antimicrobial resistance and serotype distribution.

Due to our limited timeframe, we had a shorter data abstraction sheet and did not conduct an explicit assessment of study quality. We included published papers from 1990 (as opposed to 1980 forward in the global analysis) and included an economic analysis. Additionally, we incorporated key disease experts who have local knowledge of disease burden that may not be published in the literature. Our review is complimentary to the global disease project estimates because it provides more detailed information about the Latin American and Caribbean region. Although the results from the two reviews may differ due to some of the reasons stated previously, the reports should be viewed as complimentary.

4.3 Epidemiological Data

The presentation of the IQR allows an assessment of the variability between studies. In some cases this variability is quite large and could reflect true variability in disease or mortality rates or it could be related to differences in study design and case definitions. We did not conduct any meta-analysis due to the wide variability in study types, the paucity of studies relating to incidence, and difficulties in assessing study quality. We had planned to stratify our findings by subregion but, the majority of our data came from the south region so there were insufficient data from other regions to stratify for incidence, CFR, or serotype distribution.

While assessment of quality of the studies was difficult, our inclusion and exclusion criteria were well defined and they allowed us to retain good quality studies that were likely to be more generalizable. For example, we excluded studies with a small sample size, and incidence studies without 12 months of continuous data collection. As expected, we observed that the incidence of pneumococcal disease was highest in the youngest age groups and decreased with increasing age. The same declines by age were seen in mortality rates among children. However, when we looked at data for all ages, including adults or the elderly, the picture was not always consistent with what we expected. For example, for IPD we observed that the CFR for all ages (20.3%) was higher than that among children less <2 (12.4%) and <5 (10.0%) years of age. This may be due to the scarce data in some age groups or because of a very high CFR among older adults who account for a higher proportion of the total population. Where good surveillance exists, a decrease should be observed in the incidence of bacterial meningitis before and after vaccine introduction. In children <5 years of age, we observed a decline in the post-Hib era, suggesting that the surveillance data included were sensitive enough to measure this type of intervention. Nonetheless, most surveillance studies may not have captured the total disease burden because of limited use of diagnostic tests. A study in Chile, which obtained blood cultures from all young children presenting with high fever to the emergency room, found that this process doubled the incidence of SP bacteremia, demonstrating that routine data underestimates the burden of SP bacteremia. It is likely therefore, that the clinical threshold for obtaining a blood culture, largely determines the incidence of SP bacteremia.[33]

The currently available 7-valent conjugate vaccine preparation with cross-reactive serotypes would provide protection to 64% of children less than two years of age and 60% of children less than six years of age with coverage increasing for the higher valency vaccines. Since higher valency vaccines will not be available for a few years, our economic analysis focused on the cost-effectiveness of the 7-valent vaccine.

4.4 Limitation of the epidemiological data

Burden Estimates are Minimum Estimates

- Incidence data on pneumococcal syndromes were limited to a few studies in a few countries, sometimes necessitating extrapolation to the region based on one study. There have been no pneumococcal vaccine trials in the region so incidence data mainly came from hospital-based retrospective and prospective surveillance studies.
- Limited studies on adults and the elderly made it difficult to determine the burden of pneumococcal disease in these age groups.
- Estimates resulting from studies in healthcare facilities (particularly tertiary hospitals) are very dependent on access to care, care-seeking behavior, and quality of medical care. This may result in overestimates or underestimates of events, particularly as criteria for hospitalization varies significantly from country to country. For example, in hospital-based studies because the sickest children are likely to be those admitted to hospital, CFRs are likely to be higher.
- Although we attempted to identify all published and unpublished data from the region, we acknowledge that we were unlikely to have found studies published in non-indexed journals or not published at all. We tried to minimize this by contacting all MoHs, several local researchers, and reviewing relevant conference abstracts. We believe that we included the most relevant information from the region.
- We were unable to obtain the full text of 66 studies in the timeframe of this study. We reviewed the abstracts of these studies and found only four that reported the incidence of pneumococcal disease. For three of these we had more recent incidence data from the same country, and the fourth study reported incidence data from the 1960s and 1970s from several countries. The 66 studies mainly came from those countries from which we already had other data so we consider it unlikely that they biased this review. It is also likely, based on our experience from reviewing other studies, that the majority of these 66 studies would have been excluded on reading the full text.
- We did not adjust any study findings for potential underestimates resulting from limited access to care, presence of private hospitals, or a lack of pathogen-specific diagnosis for probable bacterial meningitis cases. For the latter, we presented data both on pneumococcal meningitis and probable bacterial meningitis to allow the reader to see the incidence and CFR for both and the proportion of disease due to SP for the probable bacterial meningitis cases.

Difficulty in Assessing the Quality of Many Studies

- No surveillance indicators exist for surveillance of pneumococcal syndromes with the exception of standards for classification of X-rays, making assessment of data quality difficult.
- We did not use a specific scoring system to assess the quality of papers. We were unable to identify any validated method of evaluating the quality of the wide variety of studies that we included (for example retrospective reviews, observational studies, cases series, or surveillance studies).

- The incidence of SP may have been underestimated due to lack of collection of blood cultures, poor yield of culture techniques, variation in laboratory practice (including hours of operation), prior antibiotic use, poor or non-uniformly applied case definitions, poor definition of numerators and denominators, and death before diagnostic testing. In several cases, inadequate information was provided in the study to evaluate these factors. Even when case ascertainment and laboratory methods are of high quality, the burden of SP may be underestimated, as clearly shown by pneumococcal vaccine probe trials where SP vaccine prevented a larger proportion of disease than expected based on serotype distribution and incidence rates. [177,178]

Other limitations of Epidemiological Data

- Studies that included only neonates were excluded but we did not exclude studies that included neonates as part of a larger age group. Inclusion of neonates may have overestimated our stated vaccine benefits but the contribution of neonatal cases would be relatively small compared to all cases in children <2 years or < 5 years of age.
- We aggregated data on antimicrobial resistance from several studies without accounting for differences in sample size, geography, or population. As the prevalence of resistance varies geographically, this is likely inaccurate.
- We assumed that the pneumococcal serotype distribution for pneumococcal pneumonia was similar to the serotype distribution for clinical and x-ray confirmed pneumonia since we had no data on the serotypes distribution in these groups. A different serotype distribution may over or underestimate our stated vaccine benefits.
- Many studies did not present the frequency of all serotypes but just presented the most common ones. Typically, this corresponded with the ones in the vaccine-making calculation of coverage possible. However, our calculation of coverage for cross-reactive serotypes may have been underestimated because some cross-reactive serotypes were not reported.

4.5 Limitations of the economic study

Vaccination Inputs

- We used vaccine efficacy data from the Kaiser Permanente clinical trial of PCV7. 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 may be relevant only to the specific setting and timeframe of the trial. Because this trial was conducted in the US, the vaccine efficacy data may not be generalizable to Latin America and the Caribbean. Nonetheless, studies of PCV7 among Native Americans and PCV9 in Africa also showed high efficacy.
- We assumed that all children were fully vaccinated at levels of coverage with three doses of DPT 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 DPT. 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.

Cost Inputs

- The disease burden estimates are considered to be underestimates for the reasons stated earlier. Using these estimates in the cost-effectiveness model also underestimates the cost-effectiveness of the vaccine.

These limitations have important implications for the results, particularly when these are expressed as cost per DALY averted.

- Our estimates of resource use, medical treatment costs, and indirect costs were developed using physician and caregiver interviews and data from selected facilities in each of ten countries and referred to public system costs only. These estimates could be improved with patient-level data and larger samples. Results of the sensitivity analysis showed that cost-effectiveness was sensitive to disease-related direct medical costs.
- 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).
- We used an assumption for the cost of adding an additional vaccine to the immunization program because no standard cost exists.

Other limitations of the Economic Model

- 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, as well as prevent disease in non-targeted populations, and improve the cost-effectiveness of a heptavalent pneumococcal conjugate vaccination program.

4.6 Vaccine Introduction/Surveillance

Regardless of whether or when a country decides to introduce pneumococcal vaccine, surveillance for pneumococcal disease will remain important. For countries that decide not to introduce or who have not made the decision to introduce the vaccine, strengthening national level surveillance for pneumococcal disease will help determine the burden of disease and allow assessment of the potential benefits of the vaccine. For countries that do introduce the vaccine, surveillance to monitor the impact of the vaccine will be extremely important to show the benefit of the vaccine and to justify its introduction and continued use. Such surveillance is very challenging.

The optimal method for demonstrating vaccine impact may be measurement of the impact on X-ray consolidated pneumonia using WHO standardized definitions.[179, 180] However, such surveillance is not feasible in most countries so evidence of vaccine effectiveness may be generated regionally rather than nationally or by using modified pneumonia case definitions. Surveillance for invasive disease, which would better allow assessment of changes in pneumococcal serotypes will also be important. PAHO's surveillance network may take on a more important role after vaccine introduction by monitoring the distribution of serotypes to provide data on serotype replacement, a phenomena that has been shown to a limited extent in the U.S., and that has the potential to reduce vaccine efficacy over time.[181] PAHO is currently strengthening this network by improving collection of clinical data from cases of pneumonia, including recording of radiological findings. It is not possible to estimate disease incidence from this surveillance network, but it may be possible to see a reduction in the number of pneumococcal isolates following introduction of pneumococcal vaccine. Some sites in Latin America are conducting population-based surveillance for invasive or radiologically-confirmed pneumonia but we did not find any data from the Caribbean or Central America with population-based surveillance; establishing more population-based surveillance sites would add to our ability to assess pneumococcal disease burden and vaccine impact in Latin America and the Caribbean.

CHAPTER 5 CONCLUSION

Pneumococcal disease results in significant morbidity, as well as economic burden in the Latin American and Caribbean region, resulting in 1.6 million cases of disease and 18,068 deaths annually. Vaccination provides an effective opportunity for improving child health in this region. 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. These results emphasize the importance of pneumococcal conjugate vaccination as a cost-effective intervention for preventing childhood death and disability.

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APPENDIX A ELECTRONIC DATABASES AND SEARCH TERMS

Electronic Databases

- **LILACS,** Latin American and Caribbean Health Sciences, is a Regional Medicine Library (BIREME) cooperative database which covers literature related to the health sciences and since 1982, has been published in countries of the Latin American and Caribbean region. It contains articles from about 6,700 of the most well-known journals in the field of medicine, covering more than 150,000 records and other documents, such as: theses, theses chapters, books, book chapters, congressional and conference proceedings, technical and scientific reports, and governmental publications.

- **PubMed** is available via the NCBI Entrez retrieval system. It was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM), located at the US National Institutes of Health (NIH). PubMed provides access to MEDLINE, the International Database for Medical Literature which is produced by the NLM. MEDLINE gathers bibliographic references and summaries of more than 4,800 biomedical journals published in the United States and 70 other countries. Since 1966, there are approximately 14 million records or citations on biomedical literature covering medicine, nursing, odontology, veterinary, and preclinical sciences. Coverage is worldwide, but most records are from English-language sources or have English abstracts. Updating is done on a monthly basis.

- **The Cochrane Library** consists of a regularly updated collection of evidence-based medicine databases, including The Cochrane Database of Systematic Reviews. This database is evidence-based systematic reviews prepared by the Cochrane Collaboration which provide high quality information to people providing and receiving care and those responsible for research, teaching, funding, and administration at all levels.

- **Embase** (**Excerpta Medica**) is a comprehensive bibliographic database that covers the worldwide literature on biomedical and pharmaceutical fields. It is produced by Elsevier B.V., the world's largest publisher of scientific information.

- **CAB Health Direct** provides access to key resources directly from CABI Publishing, incorporating two databases: CAB Abstracts and Global Health. CAB has over four million records dating back to 1973, and directly covers research and development literature in the fields of agriculture, forestry, human health, human nutrition, animal health, and the management and conservation of natural resources. The database is international, with literature from over 125 countries and dozens of originating languages. Literature is selected from the following sources: peer-reviewed journals, academic books, technical reports, bulletins, and conference proceedings.

- **Biosis** is a database on life sciences information which is part of Thompson Scientific.

Search Terms

Search terms varied slightly for the databases used:

- **Set1**

Pneumonia, infectious diseases, lower respiratory tract infections, acute lower respiratory tract disease, respiratory diseases, bacterial pneumonia, streptococcaceae, community-acquired pneumonia, bacterial meningitis, lobar pneumonia

- **Set2**

Streptococcus pneumoniae, *Diplococcus pneumoniae*, pneumococcus S. pneumoniae, pneumococci, pneumococcus vaccine, pneumococcus polysaccharide, pneumococcal conjugate, Pneumovax 23, Prevnar, pneumococcal heptavalent conjugate, Pnu-Imune 23.7-valent PncOMPC vaccine, seven-valent pneumococcal PS, meningococcal OMPC conjugate vaccine, PNCRM7 or Mnc-CRM197, MnCC, Pneumococcal Polysaccharide Vaccine, or Pneumovax, Pnu-Imune Vaccine

- **Set3**

Streptococcus pneumoniae meningitis, pneumococcal meningitis, pneumococcal meningitis, pneumococcal pneumonia, pneumococcal bacteraemia, invasive NEAR/2 pneumoccal, pneumococcal mortal* or pneumococcal w/5 pneumonia or pneumococcal w/5 meningitis or pneumococcal w/5 bacteraemia or pneumococcal w/5 invasive

- **Set4**

(otitis media):de OR bacterial otitis media OR ([ear diseases]:de AND [infections]:de)

- **Set5**

(South America):bt OR (Central America):bt OR (Latin America):bt OR (Caribbean):bt OR (Virgin Islands):bt OR (Bermuda):gl

APPENDIX B CLINICAL AND ECONOMIC DEFINITIONS

Clinical Definitions

1) INVASIVE PNEUMOCOCCAL DISEASE

Pneumonia, meningitis or bloodstream infections (Bacteraemia) in which the *Streptococcus pneumonia* (also called pneumococcus) bacteria is isolated from a normally sterile site (i.e., blood, cerebral spinal fluid, or pleural fluid).

a. Bacteremia: Isolation of *S. pneumoniae* from blood or another normally sterile fluid; for cases with a positive blood culture results but the child did not fulfill the Severe Disease, Meningitis or Pneumonia Clinical Syndrome definitions.

b. Septicemia or **Sepsis**: The presence of bacteria in the blood (i.e. bacteremia) associated with serious clinical symptomatology. Septicemia may progress to septic shock. Signs and symptoms of sepsis include spiking fever and chills, rapid breathing and heart rate, looking very ill or toxic, and a feeling of impending doom. For young children, signs and symptoms can include inability to drink or breastfeed, vomiting, convulsions, lethargy, and unconsciousness (not meningitis).[1]

c. Other Invasive Diseases: Other diseases include septic arthritis, peritonitis, pericarditis, and cellulitis.

2) PNEUMONIA

a. Clinical Pneumonia: A child presenting with a history of cough or difficult breathing (tachypnea) with elevated respiratory rate (based on counting breaths in one minute) according to the following age categories:

>50 breaths/minute if 2 months to < 12 months
>40 breaths/minute if child 12 months to < 5 years
AND no chest indrawing, no general danger signs.

b. Chest X-ray confirmed Pneumonia: Chest radiograph performed and read to have an infiltrate consistent with pneumonia (using WHO standardized definition for primary end point pneumonia - "A dense fluffy consolidation [alveolar infiltrate] of a portion of a lobe or entire lung. This often contains air bronchograms, and may be associated with a pleural effusion.") [2]

c. Pleural effusion: Presence of fluid in the lateral pleural space between the lung and chest wall; in most cases, this will be seen at the costophrenic angle or as a layer of fluid adjacent to the lateral chest wall; this does not include fluid seen in the horizontal or oblique fissures. [3]

c.1 Consolidated Pneumonia (CP): Refers specifically to the presence of consolidation, infiltrates, or effusion. A dense or fluffy opacity that occupies a portion or whole of a lobe or of the entire lung that may or may not contain air-bronchograms. The presence of significant alveolar consolidation is considered by most authorities to be the most specific radiographic predictor of bacterial.

c.2 Pneumonia with infiltrates (Non-Consolidated Pneumonia, NCP): Linear and patchy densities (interstitial infiltrate) in a lacy pattern involving both lungs, featuring peribronchial thickening and

multiple areas of atelectasis, and small areas of atelectasis which in children may be difficult to distinguish from consolidation.

d. Pneumococcal pneumonia: Clinical signs and symptoms of pneumonia presence of *Streptococcus pneumoniae* in blood or pleural fluid.

3) MENINGITIS[4]

a. Clinical Meningitis: Sudden onset of fever, headache, AND at least one of the following:

- Stiff neck
- Altered consciousness/Reduced level of consciousness
- Other meningeal signs.

b. Pneumococcal Meningitis: Clinical signs of meningitis with cerebral spinal fluid (CSF) culture positive for *Streptococcus pneumonia* (also called pneumococcus) bacteria OR

Clinical signs of meningitis with positive CSF findings (purulent meningitis) plus either blood culture positive or CSF antigen positive for *Streptococcus pneumonia.*

c. Bacterial Meningitis: Clinical symptoms of meningitis with isolation of any bacteria from CSF or abnormal CSF findings such as Turbidity, Leukocytosis (>100calls/mm3), Luekocytosis (10-1-calls/mm3 AND EITHER elevated protein (>100mg/dl) OR decreased glucose (<40mg/dl).

4) ACUTE OTITIS MEDIA (AOM):

An inflammation of the middle ear, usually occurs with an upper respiratory infection. Symptoms may include earache, high fever, nausea, vomiting and diarrhea. AOM is defined as signs and symptoms of OM for <72hrs.

5) OTHER DEFINITIONS

a. Penicillin Resistance: In the case of S. pneumoniae, isolates with a penicillin minimum inhibitory concentration (MIC) of <0.125 mg/l were considered susceptible, isolates with an MIC between 0.125 and 1.0 mg. were considered intermediately resistant to penicillin and those with an MIC >1.0 mg/l were defined as highly penicillin resistant. [5, 6]

b. Multi-drug resistance: Resistance to penicillin and at least one other antibiotic.,

Health Economic Definitions

Average cost: Total treatment or program cost divided by total quantity of treatment units provided (see also marginal cost).

Benefits: The positive impacts of a healthcare intervention including health outcomes, productivity gains, and non-health related effects on well-being.

Breakeven price: The price at which the cost of the intervention would offset the cost of the disease; when the total cost of vaccine introduction equals the costs saved.

CEPAL (Comisión Económica para América Latina y el Caribe/Economic Commission for Latin America and The Caribbean) is a subsidiary body of the Economic and Social Council of the United Nations and cooperates with other specialized bodies of the United Nations and with international financial institutions. It also collaborates with regional organizations such as the BID, OEA, OLADE and universities, academic institutions, and labor unions.

Consumer price index: Measures inflation experienced by consumers in their day-to-day living expenses. Represents changes in prices of all goods and services purchased for consumption by urban households.

Cost-benefit analysis (CBA): Measurement of costs and benefits in pecuniary units to compute a net monetary gain/loss or a cost-benefit ratio. The monetary measure is obtained by estimating what an individual is willing to pay for life-saving or health-improving interventions - a measure that favors the wealthy over the poor.

Cost-effectiveness (CE): Efficient use of (scarce) resources.

Cost-effectiveness analysis (CEA): Measure of efficiency in the production of health. It compares drugs or programs having a common health outcome (e.g. reduction of blood pressure; life-years saved) and computes a cost/effectiveness ratio for comparison purposes. CEA relates the net cost; such as the cost of delivering a standard set of antigens through routine infant immunization in fixed-site clinics minus the treatment and other costs not incurred because of the beneficial effects of immunization to a desired health outcome, such as the reduction of illness or death from the vaccine-preventable diseases.

Cost-effectiveness ratio (CER): Ratio of the total costs of a program divided by the health benefit gained (e.g. cost per life year gained) or disease burden averted (e.g. cost per DALY averted).

Cost of illness (COI): The direct and sometimes indirect and intangible costs of a particular disease or risk factor (e.g. smoking or alcohol consumption).

Cost-minimization analysis (CMA): The least costly program among those shown or assumed to be of equal benefit.

Cost per QALY (quality-adjusted life years) gained: An expression of cost-utility analysis (CUA) used to assist in comparisons among programs; expressed as monetary cost per unit of outcome.

Cost saving: Interventions that result in reduced treatment costs that exceed the cost of the intervention itself. Such interventions are uncommon.

Cost-utility analysis (CUA): Type of economic evaluation that measures therapeutic consequences in utilities (e.g. QALYs) rather than physical units and computes a cost/utility- ratio for comparison purposes.

Decision analysis: A systematic approach to decision making to determine costs and outcomes with different clinical strategies and over different timeframes. This is an explicit quantitative approach for sharing decisions under conditions of uncertainty.

Decision tree: A framework for representing the alternatives used in decision analysis.

Direct medical costs: Fixed and variable costs associated directly with a healthcare intervention, including the cost of medical personnel, facilities, medications and diagnostic procedures.

Direct non-medical costs: Non-medical costs associated with provision of medical services, including travel, and childcare costs.

Disability-adjusted life year (DALYs): A common measure of illness that captures years of life lost due to premature mortality and years lived with disability. Also used as a measure of effectiveness in cost-effectiveness analyses. The morbidity-adjustment weight for each health state is multiplied by the time in the state (which may be discounted) and then summed to calculate number of DALYs. It can capture gains from reduced morbidity (disability gains) and reduced mortality (quantity gains).

Discounting: Conversion of future costs and benefits into a present value to facilitate comparison between these costs and benefits. The discounted value of a **cash flow** is determined by reducing its value by the appropriate **discount rate** for each unit of time between the time when the cash flow is to be valued to the time of the cash flow. Most often the discount rate is expressed as an annual rate. To calculate the **net present value** of a single cash flow, divide by one plus the interest rate for each period of time that will pass. This is expressed mathematically as raising the divisor to the power of the number of units of time.

Discount rate: Rate of discount used to convert future costs and benefits into equivalent present values; typically 2 to 6% per annum. A default rate of 3% per year is typically used in economic evaluations of health interventions.

Economic evaluation: Identification, measurement, and valuation of the costs and benefits of alternative healthcare interventions, to provide evidence regarding technical or allocative efficiency and aid decision making for resource allocation.

Economies of scale: A more efficient use of fixed costs, where costs and doses reduce as volumes increase.

Gross domestic product (GDP): The total value of final goods and services produced within a territory during a specified period (or, if not specified, annually. **GDP** is the total value of final goods and services produced within a country's borders in a year. GDP differs from **gross national product** (GNP) in excluding inter-country income transfers, in effect attributing to a territory the product generated within it rather than the incomes received in it.

Gross national product (GNP): The market value of all final goods and services produced in a given time period (usually one year) by the nationals of a country residing either in the country or abroad.

Gross national income (GNI): Previously known as GNP, GNI comprises the total value of goods and services produced within a country (i.e. its **GDP**), together with its income received from other countries (notably **interest** and **dividends**), less similar payments made to other countries.

Incremental cost: Difference between the cost of a program (treatment) and the cost of a comparison program.

Incremental cost-effectiveness ratio (ICER): Represents the extra cost per unit outcome obtained when comparing one intervention to another; a value judgment is required to assess whether the extra unit of outcome is worthwhile. It is used in cost effectiveness analysis to compare the net cost and net health benefit of interventions. It is used in economic evaluations to choose between programs.

Indirect cost: Cost of reduced productivity or lost time from paid employment resulting from illness or treatment.

Inflation: An increase in the general level of prices of a given kind. General inflation is caused by a fall in the **market value** (**value** of a **firm**'s outstanding **common shares**) or **purchasing power** (refers to the amount of goods and services a given amount of **money** — or, more generally, **liquid assets** — can buy) of **money** within an economy, as compared to **currency devaluation** which is the fall of the market value of a currency between economies. General inflation is referred to as a rise in the general level of prices. The former applies to the value of the currency within the national region of use, whereas the latter applies to the external value on international markets. The extent to which these two phenomena are related is open to economic debate. If money income stays the same, but the price of most goods go up, the effective purchasing power of that income falls. Falling purchasing power can thus be part of **inflation**. However, inflation does not always imply falling purchasing power of one's income, since one's money income may rise faster than inflation.

International Dollars: Results of WHO-CHOICE analyses are presented in current international dollars of 2000. An international dollar has the same purchasing power as the US dollar in the United States. Costs in local currency units are converted to international dollars using purchasing power parity (PPP) exchange rates. An international dollar is, therefore, a hypothetical currency that is used as a means of translating and comparing costs from one country to the other using a common reference point, the US dollar.

Marginal cost: The extra cost of one extra unit of product or service delivered (usually differs from average cost).

Net cost: The total cost of the intervention minus the total cost of treating the illness that would occur in the absence of the intervention.

Opportunity cost: The cost of using resources for some purpose, measured as their value in their next best alternative use.

Purchasing power parity (PPP): Rates of currency conversion that equalize the same basket of goods and services in all countries, reflecting only differences in the volume of goods and services purchased, and eliminating the differences in price levels among countries.

Quality-adjusted life-year (QALY): A measure of health outcome that incorporates the effect of an intervention on both length and quality of life. This measure is based on the utility associated with particular health states on a scale from 0 to 1, where 0 is the utility of death, and 1 is the utility of perfect health. If a treatment raises utility form 0.2 to 0.4 for a period of 10 years, then it has produced 0.2 x 10 = 2 QALYs. Alternatively, a treatment might extend life for 5 years, in each of which utility would be 0.4. Then again the treatment produces 0.4 x 5 = 2 QALYs. Although the 'outputs' of the two treatments are very different, they are worth the same in terms of QALYs. This measure combines mortality and QOL gains (outcome of a treatment measured as the number of years of life saved; adjusted for quality).

Sensitivity analysis: A method of dealing with uncertainty; determines how and/or whether plausible changes in uncertain clinical or costing variables affect the main results of the analysis. Assessment of the robustness of study results through systematic variation of key variables.

APPENDIX C DATA ABSTRACTION INSTRUCTIONS

C.1: Screening question for titles and abstracts

1. Does the title or abstract include data on one or more of the following: acute lower respiratory infection, acute otitis media, pneumonia, meningitis, bacterial infection, bacteremia, chest x-ray documented pneumonia, Pneumococcal invasive disease, Pneumococcal acute otitis media, Pneumococcal bacteremic, Pneumococcal meningitis, Pneumococcal pneumonia, antibiotic resistance? **Yes/No**

2. Does the title or abstract refer to data collected after 1990? **Yes/No**

3. Does the title or abstract refer to data on LA and Caribbean countries? **Yes/No**

4. Are the numbers of cases in each study greater than 30? **Yes/No**

If answer to any of the above questions is **No**, exclude study.

C.2: Instructions for full-text screening

STUDY DESIGN AND QUALITY				
	ANALYSIS CATEGORY	**MAIN DATABASE STRUCTURE**	**INSTRUCTIONS**	**STANDARDIZATION CATEGORIES**
1	Article Identification	abstractor ID	Enter initials of name	
2	Article Identification	study ID	Enter study ID of article; for several country data in the same article use the study ID followed by country name.	Open
3	Article Identification	author	Last name of first author	Open
4	Article Identification	journal name	Journal name as shown in article	Journal name
5	Article Identification	year of publication	Enter year of publication	yyyy
6	Article Identification	volume-number	Enter volume number	Volume number
7	Study Population	countries (list)	Enter all countries with study subjects	Country name
8	Study Population	geographic area	Enter nation, region, province/department, or city name for which data can be generalized followed by designation of community type	nation, region, province; rural, urban, periurban, mixed, unknown
9	Study Population	service	Catchment area of study subjects	outpatient=o, hospitalized=h, both=b
10	Study Population	start year of data collection	Specify day, month and year in a given format	dd/mm/yyyy
11	Study Population	end year of data collection	Specify day, month and year in a given format	dd/mm/yyyy
12	Study Population	total number of study years	formula = (end year)-(start year)	Number of years
13	Study Population	lower age of subjects	Specified age (number) and m (month) or y (year)	E.g. 5y = 5 years old; 1m = 1 month old
14	Study Population	upper age of subjects	Specified age (number) and m (month) or y (year)	E.g. 5y = 5 years old; 1m = 1 month old
15	Case Definition	Disease measured	Enter all syndromes or clinical forms from the given list	acute lower respiratory infection, acute otitis media, pneumonia, meningitis, bacterial infection, bacteriemia, chest x-ray documented pneumonia, Pneumococcal invasive disease, Pneumococcal acute otitis media, Pneumococcal bacteremic, Pneumococcal meningitis, Pneumococcal pneumonia
16	Case Definition	Confirmed Case Definition	Specify the criteria used to confirm cases and list all	blood by culture, csf by culture, csf by non-culture method, other sterile fluid by culture, PCR, other sterile fluid by non-culture, x-ray confirmed pneumonia, AIEPI definition
17	Case Definition	Antimicrobial resistant test	Enter yes or no depending whether or not	yes/no antibiotic resistance test was performed
18	Study Design	Study's temporal relation with the data collection	Chose one category from the list (mutually exclusive)	retroprospective, prospective, cross sectional, other, unknown/no clear

19	Study Design	Type of study	Choose one category from the list (mutually exclusive). If in doubt, type in study design exactly as described by authors.	Longitudinal Study Population based (incidence data); Surveillance system (incidence data), Evaluate intervention vaccine, evaluate intervention case management, Epi/clinical characteristics of ALRI, Epi/clinical characteristics of bacterial invasive/non invasive disease, Etiology of disease, Other
20	Quality Assessment	Numerator: Case ascertainment: catchment area	Select one only	— All pediatric hospitals in study area included — Some pediatric hospitals in study area not included, results adjusted accordingly —Some not included, authors state the effect was not significant — Some not included, authors state the effect may have been significant — Some not included, no discussion of the effect — No hospital-based case-ascertainment used — Unable to determine/no information provided by authors — NON INCIDENCE STUDY — external validity not specify
21	Quality Assessment	Numerator: Case ascertainment: — potential problems	Enter any bias describe by authors or base on your own judgment relate with case ascertainment	Open
22	Quality Assessment	Denominator: Population data	Mention source of reference population	census, national population estimates, other (specify)
23	Quality Assessment	Other factors affecting study result accuracy	Enter any other potential bias in study	Open
24	Quality Assessment	Relevant references	Specify number of relevant references that source identifies	Open
25	Quality Assessment	Eligibility of the study for analysis	Specify reason if not eligible	Yes/No (specify)
26	Economic Information	Cost of care	Indicate whether cost data is reported in study	Yes/No
27	Observations	Comments/ additional information	Enter comments or additional information	Open

EPIDEMIOLOGICAL DATA ABSTRACTION			
	MAIN DATABASE STRUCTURE	**INSTRUCTIONS**	**STANDARDIZATION CATEGORIES**
1	Study id	Enter the study id used in "design and quality" section	Study ID
2	Indicator	Use one row for each indicator reported. Note that the same indicator e.g. annual incidence may have data for several syndromes, age groups and/or year. Use one row for each variation of these 3 variables. Select one option from the list	Annual incidence per 100,000 pop., Case fatality rate %, Proportion due to *S pneumo*, proportion clinical form
3	Disease syndrome	Choose the syndrome or clinical form to which the indicator in the previous field refers.	acute lower respiratory infection, acute otitis media, pneumonia, meningitis, bacterial infection, bacteriemia, chest x-ray documented pneumonia, Pneumococcal invasive disease, Pneumococcal acute otitis, Pneumococcal bacteremic, Pneumococcal meningitis, Pneumococcal pneumonia
4	Denominator	The # entered here represents the denominator of the population under study	Absolute number
5	<2	In a specific row, these columns are mutually exclusive. The number entered here represents case in the numerator for given age.	Absolute number
6	<5		Absolute number
7	Other age		Absolute number
8	ALL ages		Absolute number
9	Formula	Formula based on number in columns for numerator and denominators provided in the article. If these two pieces of data are not provided, enter indicator data as reported in the article.	=n/d*100,000 (4 decimal points)
10	Year	Enter time period (in years) and number of years	# year or yyyy — yyyy
11	Observations	Enter any comment of particular interest	Open

SEROTYPE DATA ABSTRACTION

	MAIN DATABASE STRUCTURE	INSTRUCTIONS	STANDARDIZATION CATEGORIES
1	Study ID	Enter the study ID used in "design and quality" section.	study ID
2	Total isolates serotyped	Enter total number of isolates reported in the study.	Absolute number
3	Fluid type	Enter fluid type reported in study. Select options from the list.	blood, CSF, Pleural fluid, Lung aspirate, ear fluid, mixture
4	Serotype	Specify serotype.	Open
5	Number of isolates for given serotype	Enter number of isolates for the serotype entered in "serotype" row.	Absolute number
6	Percent (%) serotype isolated	Formula base on number in columns for numerator and denominators available in the article. If these two pieces of data are not provided, enter % of serotype given in the article.	=n/d*100 (1 decimal point)
7	Observations	Enter any comment of particular interest	Open

ANTIMICROBIAL RESISTANCE DATA ABSTRACTION

	MAIN DATABASE STRUCTURE	INSTRUCTIONS	STANDARDIZATION CATEGORIES
1	Study ID	Enter the study ID used in "design and quality" section.	study ID
2	Total pneumococcal isolates tested	Enter the total number of isolates tested. Use a different row for each serotype tested and reported.	Absolute number
3	% overall penicillin non-susceptible	Enter data reported in study.	%
4	% overall penicillin susceptible	Enter data reported in study.	%
5	% overall penicillin non-susceptible (intermediate level)	Enter data reported in study.	%
6	% overall penicillin non-susceptible (Highly resistant)	Enter data reported in study.	%
7	% non-susceptible to two or more drugs	Enter data reported in study.	%
8	Observations	Enter any comment of particular interest.	Open

APPENDIX D LIST OF RESEARCHERS CONTACTED AND INTERVIEWED FOR EPIDEMIOLOGICAL SECTION

TABLE D.1: Number of researchers contacted and replied, by country

COUNTRY	NUMBER OF RESEARCHERS CONTACTED	NUMBER OF REPLIES RECEIVED
Argentina	7	4
Chile	7	4
Uruguay	3	2
Perú	2	2
Colombia	4	3
Brazil	7	6
Guatemala	1	0
Costa Rica	2	1
México	6	3
República Dominicana	3	2
Venezuela	2	3
Ecuador	1	1
PAHO	3	3
Total	**48**	**34**

TABLE D.2: Name and affiliation of researchers interviewed by country

INVESTIGADOR	INSTITUTION	COUNTRY
Dra. Angela Gentile	Coordinadora de estudios sobre neumococo, SIREVA	Argentina
Dr. Miguel Tregnaghi	Centro de Estudios Avanzados en Pediatría	Argentina
Dr. Raúl Ruvinsky	Coordinador de estudios sobre neumococo, SIREVA	Argentina
Silvia Ayala Gonzalez	Mar del Plata	Argentina
Dra. Rosanna Lagos	CVD- Chile	Chile
Dr. Andrés Rosenblüt	Otorrinolaringólogo Hospital Dr Sótero del Río	Chile
Dra. M Elena Santolaya	Directora de Investigaciones, Hospital LC Mackenna	Chile
Dr. Rodrigo Vergara	Universidad de Valparaíso	Chile
Dra. María Hortal	Encargada de estudios sobre neumococo de PAHO	Uruguay
Dra. Teresa Camou	Laboratorio de Referencia	Uruguay
Dr. Claudio Lanata	Instituto de Investigación Nutricional	Peru
Theresa Ochoa	Universidad Peruana Cayetano Heredia, Depto de Pediatría e Inst. de Medicina Tropical, Lima, Perú	Peru
Dra. Elizabeth Castañeda	Laboratorio de Referencia	Colombia
Dr. Gustavo Aristizabal	Medico Pediatra y Neurologo. Programa de Vigilancia de ERA.	Colombia
Dr. Joao Cassio de Moraes	Ministerio de Salud	Brazil
Dra. Marta Velandia	Jefe PAI, MINSAL	Colombia
Dra. M Cristina Brandileone	Jefe Bacteriología	Brazil
Dra. Joice Neves		Brazil
Dra. M Regina Cardoso	Faculdade Saúde Pública	Brazil
Dra. Cristiana Nascimento Carvalho	Departamento de Pediatria	Brazil
Dr. Adriano Arguedas	Director Programas Internacionales	Costa Rica
Dra. Gabriela Echaniz Aviles	Departamento de Epidemiología y Diagnóstico del Centro para Investigaciones de Enfermedades Infecciosas	Mexico
Demostenes Gomez Barreto	Hospital General "Dr. Manuel Gea González" Secretaria de Salud del Gobierno Mexicano	Mexico
Dr. Napoleón González G	Vigilancia Epidemiológica de Infecciones Invasivas	Mexico
Dr. Jesús Feris Iglesias	Jefe Departamento de Enfermedades Infecciosas	Dominican Republic
Dra. Jacqueline Sánchez	Laboratorio Microbiología, Departamento Enferm. Infecciosas	Dominican Republic
Dra. Beatriz del Nogal	Escuela de Medicina Jose Maria Vargas	Venezuela
JH de Waard	Escuela de Medicina Jose Maria Vargas	Venezuela
AJ Gonzalez Mata		Venezuela
Dra. Nancy Vasconez	Coordinadora Nacional del Programa de Inmunizaciones	Ecuador
Dr. Albert I Ko	Académico Salvador Ciudad Salvador	Brazil
Dr. J Gabasteau	PAHO	
Dr. Salvador García	PAHO	Argentina
Dr. José Luis di Fabio	PAHO	Washington, USA

APPENDIX E COUNTRY VISIT REPORTS

CÓRDOBA, ARGENTINA

LEADER	DATE(S) OF VISIT
Maria Teresa Valenzuela	August 3 – 4, 2006

Objective The Centre for the Development of Advanced Projects in Córdoba (CEDEPAP) has carried out numerous studies on pneumococcal disease, some of which have not been published. Since their work has been cited in the review, we conducted a site visit to better understand their research methodology and findings.

Information Collected Arranged by Events and Age Groups Surveillance of Consolidated Pneumonia

CEDEPAP's criteria for inclusion and exclusion differed from studies carried out in Uruguay and Chile. Here, only children up to two months old were included and x-rays were taken only if there were signs or symptoms of pneumonia. This classification differed from WHO recommendations; however, the study was initially interpreted by two specialists (a radiologist and a pediatrician) who used a gold standard to settle disagreements. Only consolidated pneumonia cases were registered and classified as "Obvious Pneumonia" (criteria used before 2001). This is the same criteria utilized by Black et al in a study on the efficacy of the heptavalent vaccine. *(Black S, Shinefield H, Fireman B, Lewis EL, Ray P, Hansen JR, et al. Northern California Kaiser Permanent Vaccine Study Center group. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 41:63-6)*:

a) Pneumococcal Pneumonia (PP) is a case with a dense consolidation of > 2.5 cm without atelectasis involving a segment, lobe or lung on chest roentgenogram and isolation of S. pneumoniae from blood or pleural fluid.

b) Obvious pneumonia (OP) is a case with a dense consolidation > 2.5 cm without atelectasis involving a segment, lobe or lung on chest roentgenogram, but without etiologic diagnosis.

The incidence of OP (equivalent to Consolidated Pneumonia), was $2{,}112*10^5$ in children under 24 months. Results of this surveillance were included in Tregnaghi-2006, *Pediatr Infect Dis J* 2006; 25: 370.

TABLE E.1: Consolidated Pneumonia: Incidence per 100,000 children under 24 months. Córdoba

AGE	POPULATION	NUMBER OF CASES	INCIDENCE $*10^5$
2-5m	15,675	323	2,060.6
6-11m	23,512	692	2,943.2
12-23m	47,024	1,073	2,281.8
Total	**86,211**	**2,112**	**2,449.8**

Community-Acquired Pneumonia with agent isolation: 66.3% of the cases were hospitalized and 33.7% were treated as outpatients. On the other hand, 59.3% of the cases of pneumonia without agent isolation were treated as outpatients.

Surveillance of Bacteremia Without Focus

CEDEPAP has been conducting bacteraemic surveillance without focus for 11 years. Surveillance is carried out on children under 36 months old with temperatures >39ºC seeking medical attention at the Emergency Services. 82.05% of bacteraemia cases are treated as outpatients

TABLE E. 2: Incidence of bacteraemia without focus in children under 24 months, Córdoba

AGE GROUP (months)	INCIDENCE *10^5
2-5	74.4
6-11	163.4
12-17	75.9
18-24	49.6

Abstract: Congreso SLIPE-Veracruz 2005.

Invasive Disease

In a surveillance group of 86,211 children between two and 23 months old, 179 cases were diagnosed during a three-year study.

TABLE E.3: Incidence of IPD in different age groups * [7]

AGE GROUP (months)	INCIDENCE *100,000
2-5	114.9
6-11	246.7
12-17	238.2
18-24	199.9
Total	206.8

Information on Resistance [7]

Information on Serotypes [7]

Other Relevant Information

Acute Bacterial Otitis Media: No population-based information available.

Conclusions

CEDEPAP is staffed by a team of multidisciplinary professionals with vast experience in epidemiological investigation of population-based transmittable diseases. The visit was extremely valuable because it allowed considerably more data than that published to be collected and the difference between the surveillances carried out in different parts of the region to be evaluated.

Researchers and Authorities Interviewed

Dr. Miguel Tregnaghi, *Director of CEDEPAP*
Dr. Ana Ceballos, *Pediatric Infectious Disease Specialist*
Dr. Pablo Tregnaghi, *Pediatrician*

BUENOS AIRES, ARGENTINA

LEADER	DATE(S) OF VISIT
Maria Teresa Valenzuela	August 17 – 18, 2006

Objective While the researcher's team on pneumococcal diseases has presented several poster sessions to Scientific Congresses during the last three years, very few of these data have been published. It was therefore necessary to review the data of the surveillance studies being carried out and clarify certain questions about abstracts and determine current progress.

Information Presented By Event and Age Group

Surveillance of Consolidated Pneumonia (CP) in the community for three regions (Pilar, Concordia, and Paraná) over three consecutive periods from November 2002 through 2005 is provided. Data for 2005 is not shown because it is still being analyzed.

All suspected cases of acute bacterial pneumonia in children under five are identified by pediatricians who attend only outpatients and are especially trained for this purpose. The x-rays of these patients are blindly interpreted by the pediatricians, and subsequently by a specialized radiologist. In the most recent period, a third control element — a radiologist from a country which has been designated as a point of reference — was added (Pilar). Outcomes of the surveillance studies for the first two periods of the investigation are shown in Tables 1, 2, and 3 below.

Pilar

Between November 2002 and October 2004, 821 lower-respiratory infection cases were reported. 732 (89%) were examined with chest x-rays. Of those, 417/732 (57%) resulted in CPs or probable Bacterial Pneumonias. There was total congruence between the pediatrician's interpretation and that of the reference radiologist.

Of 417 probable Bacterial Pneumonias, 13 cases (3%) were confirmed by isolating the pathogen. The most important was *S. pneumoniae* confirmed by culture (53.8%), then *S. aureus* (30.8%), and *S. beta hemolytic* (15.4%).

TABLE E.4: Number and Rate of CP 2002-2003 and 2003-2004 in Pilar

AGE	NUMBER OF CHILDREN	CP	RATE OF CP *10^5 2002-2003	CP	RATE OF CP *10^5 2003-2004
<1y	5,324	119	2,235.2	68	1277.2
12m-23m	5,046	77	1,526.0	24	475.6
24m-48m	16,839	90	534.5	39	231.6
Total <5y	27,209	286	1,051.1	131	481.5

Concordia and Paraná

Between November 2002 and October 2004, 1,456 children under age five were examined for acute respiratory infections. Of these, 715 (49.1%) were x-ray confirmed CP or probable Bacterial Pneumonia. The congruence between the local level and the reference radiologist was 77%, for a Kappa index of 0.52. The interpretation classifying images as pathological radiology (Rx) and normal Rx was 90%.

Of the 715 cases of probable bacterial pneumonia, 31 (4.3%) were confirmed as being bacterial by isolating the pathogen: *S. pneumoniae* was the most important, 24, 77.4 %, (19, 79.2% per culture and 5, 20.8% by latex). In second place was S. aureus, 2, 6.4%

TABLE E.5: Number and Rate of CP 2002-2003 and 2003-2004 in Concordia

AGE	NUMBER OF CHILDREN	CP	RATE OF CP *2002-2003	CP	RATE OF CP *100,000 2003-2004
<1y	3,203	62	1,935.7	42	1,311.3
12m-23m	3,068	55	1,792.7	30	977.8
24m-48m	9,877	74	749.2	65	658.1
Total <5y	16,148	191	1,182.8	137	848.4

TABLE E.6: Number and Rate of CP 2002-2003 and 2003-2004 Paraná

AGE	NUMBER OF CHILDREN	CP	RATE OF CP *10^5 2002-2003	CP	RATE OF CP *10^5 2003-2004
<1y	5,714	102	1,785.1	82	1,435.1
12m-23m	5,412	50	923.9	49	905.4
24m-48m	17,613	56	317.9	48	272.5
Total <5y	28,739	208	723.8	179	622.8

The variation in the incidence from one year to the next may be explained by the Respiratory Syncitial Virus epidemic affecting the 2002-2003 period.

Possible bias: The system may not have detected all outpatient cases. These are representative studies of the cases that require hospitalization. It is estimated that **40%** of the cases studied received **outpatient** treatment.

When dealing with outpatients, hemoculture tests are discarded since the efficiency of this procedure is no higher that 5-10%, (the latter percentage being under optimal diagnostic conditions). Pneumonia caused by *H. influenzae* type B has virtually disappeared since Hib vaccine introduction thus, *S. pneumoniae* can be identified as the principal agent responsible for consolidated pneumonia, although some viruses such as respiratory syncytial virus (RSV) can also cause CP.

Surveillance of Invasive diseases caused by Streptococcus pneumoniae, Argentina, SIREVA. Data provided by Dr. Ruvinsky.

TABLE E.7: Cases of IPD investigated in laboratories by age (months)

AGE	NUMBER	PERCENT
0-11	752	43.0
12-23	414	23.7
24-35	222	12.7
36-47	120	6.9
48-59	104	5.8
>60	138	7.9
Total	1,750	100.0

Information on the localization of the infection is available in 1,643 of the 1,750 cases studied. The most important is pneumonia (59.3%), followed by meningitis (24.7%), then sepsis: 8.5% and bacteremic without focus: 3.3%. Other localizations are infrequent.

Regarding the serotype, 14 was identified as the most prevalent strain in invasive disease in both children under and over two years old, representing an incidence of nearly 40% in the former. Distribution by age group is different, which concurs with information available from different countries. The presence of serotypes 14, 6A/B is very significant in children under two and the relative importance of 5 and 1 increases as they grow older.

TABLE E.8: Prevalent serotypes by age groups, under two years old and over two

SEROTYPES	<2 YEARS N°	%	>2 YEARS N°	%
14	451	39.1	139	24.8
5	125	10.9	119	21.2
1	53	4.6	99	17.6
6A/B	123	10.7	29	5.2
7F	57	4.9	21	3.7
9V	34	3.0	17	3.0
23F	40	3.5	10	1.8
18C	30	2.6	16	2.9
19A	36	3.1	10	1.8
19F	32	2.8	12	2.1
9N	22	1.9	9	1.6
3	11	1.0	9	1.6
12F	11	1.0	8	1.4
16F	8	0.7	5	0.9
4	10	0.9	2	0.4
Others	109	9.5	56	10.0
Total	**1,152**		**561**	

Argentina has a good bacterial meningitis surveillance system. Table 7 shows the trend between 1994 and 2005 for children under 15 years of age. Pneumococcal meningitis has remained relatively stable during the period, fluctuating at around 400 cases per year.

TABLE E.9: Cases of Acute Bacterial and Pneumococcal Meningitis and rate per 100,000 children under 15 years old, Argentina 1994-2005

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
ABM Cases (#)	2,710	2,502	2,701	2,792	1,923	1,736	1,415	1,534	1,505	1,571	1,278	1,192
ABM Rate *100000	7.47	6.9	7.45	7.7	5.3	4.79	3.9	4.23	4.15	4.33	3.52	3.3
PM Cases (#)	379	412	415	404	304	359	321	347	372	467	378	306
PM Cases (%)	14.0	16.5	15.4	14.5	15.8	20.7	22.7	22.6	24.7	29.7	29.6	25.7
PM rate * 10^5	1.05	1.14	1.14	1.11	0.84	0.99	0.89	0.96	1	1.29	1.04	0.84

ABM—acute bacterial meningitis, PM — pneumococcal meningitis.

Antimicrobial Resistance Information

Of the cases studied, 132 (13.8%) out of the 954 strains of pneumonia cases showed intermediate resistance and 40 (4.2%) showed high resistance. A total resistance of 18% was seen for penicillin and 5.1% for cefotaxime. For meningitis cases, 68 (17.1%) out of the 398 strains studied showed intermediate resistance 30 (7.5%) high resistance (7.5%), yielding in total 24.6% resistance to penicillin and 14.8% to cefotaxime.

Other Relevant Information

Acute Bacterial Otitis Media—No population-based information is available. Dr. Claudia Hernández from the Hosp. Nacional de Pediatría Garrahan, has provided partial data demonstrating that *S. pneumonia* has a relative importance of 40%, and non-capsulated *H. influenzae* has one of 30-40%. For children previously treated with antibiotics, 35% of the strains are resistant to penicillin.

Conclusions

- All experts interviewed agreed that the prevention of pneumococcal diseases is an urgent problem.
- The heptavalent pneumococcal conjugate vaccine is not considered to be the ideal vaccine for all invasive diseases, although its merits are recognized when focused on pneumonia. The coverage of serotypes in children under two averages 63%.
- The principal barrier for its introduction in mass immunization programs is cost; each dose of the vaccine costs US$90.
- It is not easy to conclude that the effectiveness of the vaccine is only related to the serotype immunization coverage — the effect of herd immunity should also be taken into account. Perhaps the best way of appreciating the real impact of an intervention is in those places where population-based vaccination has taken place: Uruguay (Paysandú and Salto), Chile: Región Metropolitana, Córdoba, Goiania, and Buenos Aires. These countries have observed a reduction of invasive disease particularly of pneumonia cases.

Researchers and Authorities Interviewed.

Dr. Angela Gentile, *Pediatric Infectious Diseases Specialist, Head of Epidemiology Department, Niños R Gutiérrez Children's Hospital*

Dr. Raúl Ruvinsky, *Pediatric Infectious Diseases Specialist, Consultant of OPS-SIREVA Argentina*

Dr. Salvador García, *Consultant in Expanded Program Immunization and Childhood Diseases, OPS/OMS Argentina.*

SÃO PAULO, BRAZIL

LEADER	DATE(S) OF VISIT
Juan Esteban Valencia and Fernando de la Hoz	August 14-17, 2006

Objective Collect information of pneumococcal disease in São Paulo.

Information collected by events, by age group

Dr. José Cássio de Moraes. Santa Casa Hospital. Former Director of Respiratory Infections Surveillance at the São Paulo Health Secretary. Member of the Brazilian committee for vaccine programs evaluation and monitoring.

Dr. de Moraes gave details about the quality of surveillance data and introduction of vaccines in the Brazilian EPI schemes. Brazil has a regular surveillance system for meningitis since 1986 in some places and a national system since approximately 1998, but no similar system is in place for pneumonia. Meningitis surveillance includes diagnosis for bacterial agents but proportions of bacteriological confirmations range widely between states (30% to 60%), being better in São Paulo than the Northern states. It is correlated with the economical level. Dr. Cassio de Moraes is author of "*O Livro da Meningite — Uma doença sob a luz da cidade*," in which he describes the history and epidemiology of meningitis in São Paulo.

Brazil seems to have a higher average CFR for pneumococcal meningitis than other Latin American countries that may be attributed to factors such as under diagnosis and poor clinical management.

The most reliable information on pneumonia occurrence in Brazil comes from studies in the state of Goias where good population-based surveillance has been in place for the last three to four years. A new study, financed by industry, aims to estimate the frequency of bacteraemia by *S. pneumoniae* in children.

It is not possible to generalize the Goias's situation to other places in Brazil, because of difference of climatic patterns this influences occurrence of ARI syndromes. The northern part of the country probably has less incidence of pneumonia than the south. Regarding the distribution of serotypes in Brazil generated by SIREVA data, there is some bias since most of the serotype samples are isolated from meningitis cases. Serotype distribution for meningitis can be easier to generalize since there is better surveillance of that syndrome. However, some caution still should be taken since a large proportion of CSF is still not cultured across Brazil.

It likely that Brazil will obtain high coverage with S. pneumoniae conjugated vaccines once the decision to introduce is made. Despite the addition of more shots to the immunization schedule, Hib vaccine achieved > 80% coverage in its first year of introduction. The increasing number of injections is not a deterrent to Brazilian mothers. This may be due to the fear of meningitis, an endemic threat in Brazil that has been widely publicized in the past due to several outbreaks of meningococcal disease. One of the most important limitations is the high cost of vaccine and scarcity of studies on cost-effectiveness. S. pneumoniae vaccines rank at the bottom of this list.

The MoH recently commissioned Dr. Maria Novaes to conduct a pharmacoeconomy study on S. pneumoniae to make a better assessment of the potential benefit of universal vaccination with conjugated vaccines. It will include herd immunity and take its potential benefits into account, as well as consider the cost of disability caused by meningitis. Even though the Brazilian MoH does not directly finance medical care for meningitis disability, it is an important consideration. Despite this, Brazil does vaccinate its high risk population with heptavalent conjugate vaccine. The MoH buys 30 to 40 thousand doses yearly through PAHO's revolving fund. This vaccine is administered through special health centers known as CRIE (Special Immunological Centres).

Relevant epidemiological and demographical information for Brazil is available for free in the web pages of the MoH (www.datasus.gov.br www.saude.gov.br/svs www.saude.sp.gov.br). These sites have data such as hospital discharges, cost of disease, causes of mortality, and mandatory reportable diseases.

Dr. Maria Cristina Brandileone, Head of the reference laboratory for Streptococcus pneumoniae. Instituto Adolfo Lutz; Dr Vera Simonssen Head of the bacteriology branch, Instituto Adolfo Lutz, Dr Telma Carvalhana, Head of the surveillance system for ARI at the São Paulo Secretary of Health.

Dr. Brandileone at the lead the Brazilian reference laboratory is a center for *S. pneumoniae* collection of samples. The laboratory based surveillance on *S. pneumoniae* does not include data on ambulatory pneumonia. Hospitalized pneumonia data should also be analyzed cautiously since this data come mainly from São Paulo.

The serotype distribution of pneumonia cannot be easily extrapolated because new clones are constantly introduced in Brazil due to human migration from different parts of the world. Some serotypes such as 14 are increasing in their proportion of invasive disease.

The high CFR of meningitis in Brazil may be due to the persistent use of penicillin as a first-line drug for meningitis whereas third-generation cephalosporin is more commonly used in other countries.

Vaccine introduction for *S. pneumoniae* is probably not a priority for the Brazilian government. Meningococcus is perceived as a more pressing issue. The fear is that *S. pneumoniae* vaccine will only have a marginal impact on the global occurrence of pneumonias and meningitis as was observed after introduction of influenza vaccine for people aged 60 and older.

Dr. Carlos Fortaleza. Head of the Coordenadoria de Controle de Doenças da Secretaria de Estado de Saúde do Governo do Estado de São Paulo.

Dr. Fortaleza is in charge of the epidemiological surveillance and control programs for most communicable and non-communicable diseases in the state of São Paulo (44 million people).

The quality of surveillance data for meningitis in Brazil is good enough to make a decision (which is not the case with pneumonia). Data from www.datasus.gov.br can be used to partially validate our estimates from the systematic review; however, it is important to consider underestimating and sometimes incorrect diagnoses in the database. Dr. Fortaleza has epidemiological data that is more specific, and of higher quality than national data that we could use as another source of validation to estimate the pneumonia burden review.

He believes that *S. pneumoniae* vaccines may be introduced in São Paulo if epidemiological and economical data are strong enough. However, we feel that pneumococcal vaccination for the elderly is regarded as more pressing for him.

Reference Center for Special Vaccine (CRIE). Dr. Marta Lopez, Head of the CRIE. Dr. Pasesa Quispe Torres, Dr. Melissa Mascherette, and Dr. Tania Chaves.

This is the center in charge of delivering special *S. pneumoniae* conjugate vaccines to high risk children under two years of age. Limitations: (a) They cannot perform follow-up of patients to evaluate vaccine effectiveness; (b) They do not have data on costs. The cost of a heptavalent dose ranges from US$100 to US$200 for individuals outside the governmental system; and (c) 7-valent is not adequate for all patients since it misses several important serotypes. Vaccine uptake has increased greatly - from 167 doses administered per month in January 2000 to a total of 8,334 doses through April 2005. The schedule utilized for 7-valent is: 2-6m-3 plus booster, 7-11m-2 plus booster, 12-23m-2 plus booster, and >24m-2 plus booster. Consideration is being made to expand vaccination to children under five.

As a participant in the National Advisory Committee for Immunizations, she acknowledged that they have introduced rotavirus and are studying the introduction for chicken pox and meningococcal vaccines. A decision for pnemococcus will be made following a decision these two vaccines.

Dr. Sueli Gonsales Saes - Asesor Técnico de Gabinete, Dr. Antonio Lucarelli - Asistencia Médica e Nefrologia. Secretaria de Estado de Saúde, Health Economy Unit.

Unique Health System's main objective is the equitable provision of health services. One of the interesting topics is health economy studies and several health secretaries at the state level have created a unit on health

economy. One of the first to organize such study groups has been the São Paulo health secretary. They are working mainly in outcome research on primary health evaluation, management models evaluation, and new technology evaluation.

Augusto Guerra and Emerson Ricciardi, who are in charge of the Price Bank (Banco de precios) at the MoH, have offered to provide advice about the accuracy of the costs displayed in www.datasus.gov.br., including prices of medical drugs and cost of medical care.

The MoH website posts economic information under the following databases:

- Sistema de Autorización de Internación Hospitalaria (hospital admission authorization system) AIH
- Sistema de Autorización de procedimientos de Alta Complejidad (Authorization System for Highly Complex medical procedures)= APAC

They support the methodology of our study.

Dr. Maria Navaez, Pediatrician and Health Economist. School of Medicine, University of São Paulo - USP.

Dr. Navaez led the cost-effectiveness study for the introduction of the rotavirus vaccine carried out in Brazil with funding from the MoH. Today, she is leading the cost-effectiveness of the conjugate *S. pneumoniae* vaccine for Brazil.

She suggested using: (a) the median (average) salary instead of minimal salary to calculate loss of productivity due to premature deaths or other adverse outcomes; and (b) cost data from DATASUS so that the study will increase its acceptability for health authorities.

Information About Resistance

Dr. Regina Cardoso. Professor, Public Health School. University of São Paulo — USP.

She is participating in two studies: (a) To evaluate the impact of *S. pneumoniae* resistance on outcomes of children with pneumonia treated with penicillin in Brazil, Dominican Republic, and Argentina. So far, they have evaluated 2,800 children with pneumonia, of which 257 had blood isolation with *S. pneumoniae.* Resistance was highest in the Dominican Republic (40%), and less in Argentina (20%) and Brazil (9%). Twenty percent of children with *S. pneumoniae* had treatment failure for penicillin but no difference was observed between those with a resistant or sensitive strain. Results of this study have not been published yet but she is willing to share the main results with us; and (b) To estimate the frequency of different agents (viral and bacterial) in the etiology of pneumonia in Salvador.

She said that in-vitro resistance does not necessarily imply that a clinical prognosis is worse and that the clinical meaning of resistance may have been overplayed. With respect to information from www.datasus.gov.br, she has the same concern which is the underestimation of diseases.

Conclusions

Brazil is a big country with a lot of information in the web page www.datasus.gov.br. There is no good data for AOM in Brazil because there are no population-based studies in this area.

List of the Researchers and Authorities Interviewed in Brazil

Dr. Carlos Fortaleza,*Head of the Coordinadoria de Controle de Doenças da Secretaria de Estado de Saúde do Governo do Estado de São Paulo*

Dr. Regina Cardoso, *Professor, School of Public Health. University of São Paulo — USP*

Dr. Jose Cassio de Moraes, Santa Casa Hospital. *Former director of Respiratory Infections Surveillance at the São Paulo Health Secretary. Member of the Brazilian committee for vaccine programs evaluation and monitoring*

Dr. Sueli Gonsales Saes, *Asesor Técnico de Gabinete. sgaes@saude.sp.gov.br. Dr. Antonio Lucarelli — Asistencia Médica e Nefrologia. Secretaria de Estado de Saúde. Health Economy Unit*

Reference Center for Special Vaccines - CRIE

Dr. Marta Lopez, *Head of CRIE*

Dr. Pasesa Quispe Torres

Dr. Melissa Mascherette

Dr. Tania Chaves

Dr. Maria Cristina Brandileone, *Head of the reference laboratory for Streptococcus pneumoniae. Adolfo Lutz Institute*

Dr Vera Simonssen, *Head of the bacteriology branch. Instituto Adolfo Lutz*

Dr Tema Carvalhanas, *Head of the surveillance system for ARI at the São Paulo Secretary of Health*

Dr. Maria Navaez, *Paediatrician and Health Economist, School of Medicine, University of São Paulo — USP*

Future Contacts

Dr. Moisés Goldbaum, *Secretaria Nacional de Ciencia Tecnología e insumos estratégicos.* He was contacted by phone and referred us to Sueli Saez.

Dr. Elias Antonio Jorge, *Departmento de economia de saude*

Emerson Ricciardi, emerson.ricciardi@saude.gov.br

Augusto Guerra, augustoguerra@medicina.ufmg.br

Portal Nacional de Información en Economia de la Salud. BVS-ECO http://economia.saude.bvs.br

Dr. Marcos Bosi Ferraz. *Universidad Federal de São Paulo — UNIFESP. CPES - Centro Paulista de Economia de Saude.* marcos.ferraz@cpes.org.br

CHILE

LEADER	DATE(S) OF VISIT
Maria Teresa Valenzuela	September 1, 2006

Objective Vaccine Development Centre (CVD-Chile) is one of the regional centers which since 1994, has consistently conducted hospital-based surveillance studies on invasive diseases caused by S. pneumoniae and studies on bacteraemia without focus in metropolitan Children's Hospital ERs. Between December 2003 and 2005, CVD-Chile participated as a WHO reference center for the interpretation of the digitized Rx reading of pneumonia cases. They developed the study "Population-Based for Surveillance Suspected (s) and Rx confirmed (RxC) Community-Acquired Pneumonia (CAP) in children 1-35 months in six municipalities of the metropolitan region. Results for part of these studies were presented in poster sessions at Scientific Congress and were included in the analysis section. For that reason, it was necessary to obtain more precise information on this work.

Information Collected by Events, by Age Group

The serotype analysis by small age groups presents some of the most interesting data.

Table 1 shows the isolated serotypes of pneumococcal invasive diseases. In the 0-5 months age-group, 61 strains were typified; in the 6-11 months group, 146 strains; in the 12 -17 months, 143; in the 18-23 months, 63. Total number of strains typified, 413. From 6 months up Serotype 14 has the highest relative significance—almost a third of the strains belong to this serotype. In children 0-5 months old, the most significant serotype was 5 (16.4%) although serotype 13 is also high in this age-group (14.8%).

TABLE E.10: Relative importance of vaccine serotypes in Chilean infants below 24 months old, corresponding to invasive diseases

SEROTYPES	0-5M NUMBER ISOLATES	%	6-11M NUMBER ISOLATES	%	12-17M NUMBER ISOLATES	%	18-23M NUMBER ISOLATES	%	0-23M NUMBER ISOLATES	%
1	1	1.6	0	0	4	2.8	1	1.6	6	1.5
4	3	4.9	6	4.1	7	4.9	3	4.8	19	4.6
5	10	16.4	10	6.8	8	5.6	7	11.1	35	8.5
6b	2	3.3	12	8.2	10	7.0	4	6.3	28	6.8
7f	3	4.9	4	2.7	5	3.5	4	6.3	16	3.9
9v	1	1.6	4	2.7	1	0.7	2	3.2	8	1.9
14	9	14.8	60	41.1	45	31.5	22	34.9	136	32.9
18c	2	3.3	12	8.2	14	9.8	8	12.7	36	8.7
19f	8	13.1	4	2.7	5	3.5	2	3.2	19	4.6
23f	1	1.6	4	2.7	6	4.2	1	1.6	12	2.9
Total 10Valent	40	65.6	116	79.5	105	73.4	54	85.7	315	76.3
4	3	4.9	6	4.1	7	4.9	3	4.8	19	4.6
6b	2	3.3	12	8.2	10	7.0	4	6.3	28	6.8
9v	1	1.6	4	2.7	1	0.7	2	3.2	8	1.9
14	9	14.8	60	41.1	45	31.5	22	34.9	136	32.9
18c	2	3.3	12	8.2	14	9.8	8	12.7	36	8.7
19f	8	13.1	4	2.7	5	3.5	2	3.2	19	4.6
23f	1	1.6	4	2.7	6	4.2	1	1.6	12	2.9
Total heptavalent	26	42.6	102	69.9	88	61.5	42	66.7	258	62.5
Total serotyped	61		146		143		63		413	

DOMINICAN REPUBLIC

LEADER	DATE(S) OF VISIT
Elizabeth Gomez	August , 2006

Objective Contact MoH personnel to assess pneumococcal disease burden, and to identify information about pneumococcal disease from local researchers, local medical journals, conferences, newsletters, university theses, and unpublished reports. This included meeting officials involved with epidemiology activity at central level or in specific units, such as childhood surveillance or communicable diseases (particularly pneumonia and meningitis) and laboratory surveillance systems. Additionally, we attempted to identify who will most likely be involved in the decision to adopt pneumococcal vaccination and its subsequent implementation.

If the officials in the MoH were unable to provide some of the required data, they directed us to pertinent literature, national health statistics and other relevant sources of information, such as, ministry web pages, to obtain official country information and statistical reports. We also contacted experts and medical practitioners affiliated with specialized medical societies.

Information Collected

1) National Surveillance System

TABLE E.11: Number and rates of probable cases of probable bacterial meningitis by age group, Dominican Republic 2005

AGE GROUP	# CASES	POPULATION	RATE/100,000 POPULATION
<1 year	21	220,224	9.5
1-4 years	7	813,556	0.9
5-9 years	4	1,032,871	0.4
10-19 years	4	1,910,128	0.2
20-54 years	14	4,143,314	0.3
>=55 years	2	980,089	0.2

2) Robert Reid Referral Pediatric Hospital

Between 2000 and 2005, 496 IPD isolates were obtained; 84% (n=415) of these were from children <6 years of age. Table X presents the distribution of isolates by age and illness. Table E.13 presents data on serotype distribution among children < 6 years.

TABLE E.12: Number of IPD isolates by age and illness

ILLNESS	AGE GROUP	NUMBER OF ISOLATES 2000–2005
Pneumonia	<6	239
	6-14	24
	15-60	5
Meningitis	<6	167
	6-14	32
	15-60	10
Sepsis/bacteremia	<6	9
	6-14	1
	15-60	0
	Total	487

TABLE E.13: Distribution of serotypes among children <6 years

SEROTYPE	NUMBER OF ISOLATES 2000–2005
1	23
3	12
4	8
5	13
6A	19
6B	42
7F	3
9V	6
14	171
18C	12
19A	7
19F	16
23F	23
Others	39
No serotype	21
Total	415

Researchers and Authorities Interviewed and Contacted

Zacarias Garib, *Director, Immunizations Program, Department of Public Health*

Jesús Feris, *Director, Department of Infectious Disease, Robert Reid Cabral Children's Hospital (national reference)*

Jacqueline Sanchez, *Manager, Microbiology Laboratory, Department of Infectious Disease, Robert Reid Cabral Children's Hospital; (national reference) and SIREVA Coordinator*

Mercedes Jimenez, *Coordinator, Nacional epidemiology surveillance system, Department of Public Health*

Carlos Rodriguez, *President, Infectious Disease Society, ONG*

MONTEVIDEO, URUGUAY

LEADER	DATE(S) OF VISIT
Maria Teresa Valenzuela	July 27- 28, 2006

Objective Uruguay has been one of the collaborative centers of SIREVA since its inception. Contacting researchers and obtaining details about their research, including changes in serotypes and resistance to antibiotics over time (from 1993 to present) was a priority for this study of the burden of pneumococcal disease.

Information Collected by Events, by Age Group

Uruguay has a network of bacteriology laboratories coordinated by the National Reference Laboratory of Bacteriology located in Montevideo, and has been a collaborator of SIREVA since 1993. This network is composed of 18 laboratories, one for each region of the country where there is a large hospital and an auxiliary site.

In addition, SIREVA/OPS which has promoted the vigilance of invasive illnesses for *S. pneumoniae*, *H. influenzae Type B*, and *N. meningitidis*, has also encouraged surveillance studies on radiology of pneumonia in children younger than five years old with a hospital-based population. Salto and Paysandú, two cities that meet the WHO-Pneumonia Working Group criteria in terms of the under-five population, the classification criteria for pneumonias, and the number of readings and quality control for the reference center, participated in the study. The results are included in the reviewed articles, the last of them: *Hortal M, Estevan M, Iraola I, De Mucio B. A population-based assessment of the disease burden of consolidated pneumonia in hospitalized children under five years of age. Int J Infect Dis 2006. [Epub ahead of print]*

The pediatric center with the greatest number of patients is the Pediatric Hospital Pereira Rosell which has a complexity level of 3. Annually, this hospital attends an average of 59,000 pediatric consultations in the ER. Thirty one percent (31%) of these consultations are for ARI. Of these, 80% are due to upper respiratory tract infections and 20% to lower respiratory tract infections. That is, 3,658 consultations on average per year. Practically 90% of these are for pneumonias. **40% of the pneumonias require hospitalization**. Combining Salto and Paysandú, 2,034 children younger than five are attended for lower respiratory tract symptoms, of which 40.6% correspond to CP, 46.3% to non-consolidated pneumonia (NCP) and only 13.1% to non pneumonias. (This data is very similar to that obtained in the Pediatric Hospital Rosell).

Studies Performed in the Reference Laboratory.

Of 400 cases of CP, *S. pneumoniae* was isolated in 4.5%.
Of 189 cases of NCP, *S. pneumoniae* was isolated in 1.1%.

Information About Resistance

Given that this laboratory has a 12-year involvement in these studies, they have been able to observe an increasing tendency of bacterial resistance to beta-lactamases with 80% of the resistance being contributed by serotype 14. They have also observed resistance to trimetropin (serotypes 5 y 14) and to erythromycin. Resistance to *S. pneumoniae* in adults is no more than 10%.

Information About Serotypes

The serotypes most frequently isolated have been the 14, 5, and 1, with the first of these constant in the distinct age groups, the second more frequent in those under one year, and the third in those older than one year of age. This laboratory also has adult serotype information available with respect to adults which differs from those found in children with a greater frequency of 7F.

Conclusions

In the opinion of the experts who were interviewed, the burden of pneumococcal disease is most relevant in the child population. Because markers are not available that have the sensitivity to reflect the real magnitude of the problem, the only way of knowing the impact of the pneumococcal conjugate vaccine in our environment would be through the performance of effectiveness studies in places where epidemiologic surveillance has been systematic. If the US has been able to observe the impact of the heptavalent conjugate vaccine in the decrease of pneumococcal disease in adults, there is no doubt that the impact would be even greater here, given the conditions of life in our senior citizen population and the greater social contact between adults and children, among other factors.

Researchers and Authorities Interviewed

Dr. María Hortal, *Pediatrician and microbiologist, Studies Coordinator SIREVA*

Dr. Teresa Camou, *Chief of National Reference Laboratory of Bacteriology*

Dr. Gabriela García, *National System of Laboratories*

COLOMBIA

LEADER	DATE(S) OF VISIT
Juan Esteban Valencia	August 2006

Objective: Contact several people from the institutions listed below to present the project, discuss the methodology from an economic point of view, and discuss the expected results from the review. The principal goal of this effort is to obtain information on costs related to pneumococcal disease.

Susalud — hmo (health maintenance organization) *An Insurer Health Company, that offers obligatory health plans, prepaid medicine and private health policies; with a wide national health course.* Susalud had 1 million affiliates. We obtained information about the affiliates, clinics costs for those under contract with the HMO, health tendencies of patient population, and the impact of pneumococcal disease.

Health services provider institution — universidad de antioquia
We contacted the health economics unit and gathered the estimation of the attention cost for pneumococcal diseases.

Ces Clinic
Third level attention clinic with 130 hospital beds; it was made a pneumococcal diseases patient handle poll (pneumonia, bacterium, and meningitis). Also, we got the hospitals attention costs of pneumococcal diseases.

General hospital in Medellin
Fourth level hospital with 400 beds; treating patients with pneumococcal disease (pneumonia, bacterium, meningitis and otitis)

Otorhinolaryngology clinic
We presented the project to pediatricians specializing in otorhinolaryngology.

Santa Ana Children's Clinic
Second level attention clinic with 35 beds dedicated to pediatrics attention were made pneumococcal diseases patient handle poll (pneumonia, bacterium, and meningitis).

Social Protection Ministry
We presented the project to the immunizations unit of the ministry; not too much information about pneumococcal diseases. They just have information related to other vaccines.

Pan American Health Organization (PAHO) — Colombia
We presented the project to a PAHO immunizations representative; there is not too much information about pneumococcal diseases. They just have information related to other vaccines.

APPENDIX F PARTICIPATING COUNTRIES ACCORDING TO INCOME CATEGORY

TABLE F.1: Participating countries listed according to GNI per capita, 2003

LOW INCOME (US$2,130 or less)	LOWER-MIDDLE INCOME (US$2,131-US$3,820)[1]	UPPER-MIDDLE INCOME (US$ 3,821 or more)[1]
Colombia	Argentina	Chile
Dominican Republic	Brazil	Mexico
Honduras	Uruguay	Panama
	Venezuela	

[1]Income groups are divided according to 2003 gross national income (GNI) per capita (Atlas method, USD, 2003). The groups are low-income: $2,130 or less; lower-middle income: $2,131 - $3,820; and upper-middle income: $3,821 or more. The high income group is not included in the present analysis.

APPENDIX G PHYSICIAN INTERVIEW LIST BY COUNTRY

PHYSICIAN	INTERVIEW DATE	AFFILIATION
ARGENTINA		
Dra. A Gentile	30/09/2006	Hospital de Niños
Dr. J M Galdeano	24/09/2006	Hospital de Niños Juan C. Navarro
BRAZIL		
Dr. S Rassi Dafico	31/05/2001	Universidade Federal de Goiânia
Dr. MSN Da Costa	04/06/2001	Hospital Pronto Socorro
Dr. E T Alonso	05/06/2001	Hospital das Clinicas
Dr. D M Ferreira	04/06/2001	Universidade Federal de Goiás
Dr. L L P Simões	29/05/2001	Hospital de Doenças Tropicais
Dr. M W de Carvalho	30/05/2001	Universidade Federal de Goiás
Dr. L de S Mazie	31/05/2001	Clinica Roberto Carlos Marie
Dr. S Brea	21/06/2001	Universidade Federal de Goiás
Dr. A Santos	27/09/2001	Hospital de Doenças Tropicais
CHILE		
Dr. I Royne	06/07/2001	Hospital Calvo Mackenna
Dr. W Ledermann	12/07/2001	Hospital Calvo Mackenna
Dr. A Reyes	14/08/2001	Hospital Calvo Mackenna
Dr. C Perret	08/11/2001	Hospital Universidad Católica
Dr. C Derr	08/11/2001	Clínica Universidad Católica
Dr. Tejias	17/12/2001	Clínica Las Condes
Dr. Concha	17/12/2001	Clínica Las Condes
Dra. ME Santolaya	18/11/2006	Hospital Roberto del Rio
Dr. R Vergara	20/11/2006	Hospital de Valpaiso
COLOMBIA		
Dr. JP González	02/10/2006	Clínica Infantil Santa Ana
Dr. JP González	24/10/2006	Clínica Infantil Santa Ana
Dr. JD Londoño	24/10/2006	Hospital General de Medellín
Dr. JD Londoño	26/10/2006	Hospital General de Medellín
Dra. C Rodríguez	21/09/2006	Hospital General de Medellín
Dra. C Rodríguez	26/10/2006	Hospital General de Medellín
Dr. R Posada	21/09/2006	Clínica CES
Dr. CA Cortes	26/09/2006	Clínica Materno Infantil
Dr. A Uribe	25/09/2006	Clínica Bolivariana
Dr. GJ Cano	26/09/2006	Clínica Bolivariana
Dra. LC Pubiano	14/09/2006	Clínica Materno Infantil
Dra. D Guarneros	26/10/2006	Clínica Materno Infantil
DOMINICAN REPUBLIC		
Dr. B Veras	10/11/2006	Hospital J. M. Cabral y Baez
Dr. J Pérez	10/11/2006	Hospital J. M. Cabral y Baez
Dra. M Santana	10/11/2006	Hospital Dr. Arturo Grullon
Dra. M Vargas	08/11/2006	Hospital J. M. Cabral y Baez
Dra. A Pichardo	08/11/2006	Hospital J. M. Cabral y Baez
Dra. F Pena	08/11/2006	Hospital J. M. Cabral y Baez
Dr. J Cruz	10/11/2006	Hospital Dr. Arturo Grullon
Dr. J Feriz	25/09/2006	Hospital Robert Reid Cabral

PHYSICIAN	INTERVIEW DATE	AFFILIATION
HONDURAS		
Dr. M Rivera	18/09/2006	Hospital Escuela
Dr. F Rodríguez	27/09/2006	Instituto Hondureño de Seguro Social
MEXICO		
Dra. M Macías	26/09/2006	Instituto Nacional de Pediatría
Dr. M Guarneros	02/10/2006	Instituto Nacional de Pediatría
Dr. F Solórzano	07/10/2006	Instituto Nacional de Pediatría
PANAMA		
Dr. X Sáez-Llorenz	14/09/2006	Hospital del Niño
Dra. T De León	01/10/2006	Hospital José Domingo de Obaldía
URUGUAY		
Prof. E San Julian	04/10/2001	Centro Hosp. Pereira Rossell
Dr. A Galiana	15/06/2001	Centro Hosp. Pereira Rossell
Dr. G Bellinzona	13/06/2001	Sanatorio Pedro Larghero
Dr. Fernández	21/06/2001	Centro Hosp. Pereira Rossell
Dr. M Zamorra	19/06/2001	Policlínico Giordano
Dr. MA Pujadas	12/06/2001	Centro Hosp. Pereira Rossell
Dr. T Pais	13/06/2001	Consultorio J Enrique Rodo 2214
Dr. A Lofredo	14/06/2001	Centro Hosp. Pereira Rossell
Dr. M Santos	15/06/2001	Policlínico Giordano
VENEZUELA		
Dr. B del Nogal	28/09/2006	Escuela de Medicina José Maria Vargas
Dr. F Valery	15/09/2006	Hospital Elias Toro

APPENDIX H SAMPLE PHYSICIAN INTERVIEW FORM

Resource use form — pneumococcal meningitis (Spanish version)

ENCUESTA A MÉDICOS SOBRE EL MANEJO DE MENINGITIS AGUDA BACTERIANA EN NIÑOS < 5 AÑOS

La Meningitis constituye una de las principales causas de enfermedad y muerte en niños menores de 5 años, lo que representa un alto costo económico aún en países desarrollados.

La siguiente encuesta contiene algunas preguntas sobre el manejo estándar de meningitis aguda bacteriana. La definición de meningitis aguda bacteriana estará basada en la presencia de los siguientes síntomas: síntomas de irritación de meninges (irritabilidad paradojal, y rigidez del cuello y columna, y signos de Kernig y Brudzinsky), síntomas de hipertensión endocraneana (vómito, abombamiento del bregma, convulsiones, edema cerebral o compromiso de conciencia). Además se considerarán los siguientes exámenes de laboratorio: punción lumbar; histoquímica; gram; cultivo; glicemia en sangre o en LCR, albuminia (100 mg/dL), y celularidad (100 celulas/dL; 80% polimorfos nucleares).

La información que le estamos solicitando nos permitirá conocer lo siguiente:
1) El comportamiento de meningitis aguda bacteriana en niños menores de 5 años.
2) Medidas que adopta el médico o especialista con meningitis aguda bacteriana.
3) Los tratamientos aplicados a estos niños.

Ud., médico o especialista, ha sido seleccionado para contestar una encuesta breve, que le tomará aproximadamente 45-60 minutos. Agradeceremos responder a esta encuesta de una manera que refleje su práctica y experiencia médica. En el caso de recurrir a literatura publicada, haga el favor de citar sus fuentes. De igual forma se le agradecerá anotar debajo o en una hoja aparte sugerencias y comentarios sobre el manejo estándar de meningitis aguda bacteriana.

Los resultados obtenidos con esta encuesta serán aplicados a un estudio económico de una nueva vacuna que permitirá proteger a los niños de estas enfermedades. Su contribución será de indudable valor.

Responder a esta encuesta es voluntario y si no lo desea no está obligado a hacerlo.

Dr. Dagna Constenla

ECONOMISTA EN SALUD **MÉDICO / ESPECIALISTA**

Antes de dar vuelta la hoja, responda a la siguiente pregunta.

¿Cuántos niños < 5 años con meningitis aguda bacteriana atienden mensualmente?

¿Meningitis aguda bacteriana? _____ Niños/mes.

Completado por: _____ Fecha: _____/_____/_____
Nombre (Área de Especialidad)

DIAGNOSTICO DE MENINGITIS AGUDA BACTERIANA

Las siguientes preguntas aluden al diagnostico de meningitis aguda bacteriana.

1. ¿Cuáles son los signos y síntomas más frecuente que detecta en niños con meningitis aguda bacteriana? Ponga abajo un "✓" correspondiente a su respuesta.

a. Síntomas de irritación meninge

- ❑ Irritabilidad paradojal
- ❑ Rigidez del cuello o columna
- ❑ Convulsiones
- ❑ Signos Kernig y Brudzinsky
- ❑ Otro (Especificar): _____

b. Síntomas de hipertensión endocraneana

- ❑ Vómito
- ❑ Abombamiento del bregma
- ❑ Edema cerebral
- ❑ Otro (Especificar): _____
- ❑ Otro (Especificar): _____

2. ¿Qué criterio usa para el diagnostico de meningitis aguda bacteriana?

- ❑ Clínica
- ❑ Clínica + Exámenes de laboratorio
- ❑ Solo Exámenes de laboratorio
- ❑ Otro (Especificar): _____

Observaciones: _____

3. ¿Qué porcentaje (%) de niños con meningitis es diagnosticado con este criterio? % _____

4. Haga el favor de enumerar los exámenes de diagnostico, estimar el porcentaje (%) de niños diagnosticados de acuerdo a cada examen, el promedio (frecuencia) de exámenes por niño, y el lugar de atención.

Tipo de Examen *Ejemplo: LCR*	**% Pacientes** *65%*	**Frecuencia** *1*	**Lugar de Atención** *Ambulatorio*

MANEJO DEL TRATAMIENTO DE MENINGITIS AGUDA BACTERIANA

Las siguientes preguntas aluden al tratamiento aplicado para meningitis aguda bacteriana que evoluciona sin complicaciones, ni secuela.

4. ¿Cuál es su conducta terapéutica en niños con meningitis aguda bacteriana? Es posible que niños reciban más de un tratamiento y por consiguiente el porcentaje sea mayor a 100%.

a. Manejo general _____ %
   i. Alimentación especial _____ %
   ii. Manejo vía aérea, apoyo ventilatorio _____ %
   iii. Hidratación _____ %
   iv. Manejo de fiebre _____ %

a. Tratamiento farmacológico _____ %
   i. Antibiótico _____ %
   ii. Oxigenoterapia _____ %
   iii. Otro (Especificar): _____ _____ %
c. Derivación a especialista (Especificar): _____ _____ %
d. Ningún tratamiento _____ %
e. Otro (Especificar): _____ _____ %

6. Si su conducta terapéutica considera tratamiento general, ¿En qué momento lo indica? (Ej.: Cuando los síntomas aparecen; cuando los síntomas empeoran; cuando otras medidas no han dado resultado; en forma complementaria a otras medidas).

_____

_____

7. Haga el favor de describir en la próxima página el manejo general (Ej. NaCl) que administra en forma habitual para la meningitis aguda bacteriana, y describa su dosis diaria, frecuencia, duración, vía, y lugar de atención.

Manejo General *Ej. Dipirona*	**Dosis Diaria** *0.05 ml/k/d*	**Frecuencia** *6 in 6 hrs.*	**Duración** *2–3 d*	**Vía** *OV*	**Lugar de Atención** *Ambulatorio*

8. Si su conducta terapéutica considera tratamiento farmacológico (Ej. Cefotaxime), ¿En qué momento lo indica? (Ej.: Cuando los síntomas aparecen; cuando los síntomas empeoran; cuando otras medidas no han dado resultado; en forma complementaria a otras medidas).

_____

_____

9. Haga el favor de enumerar en la tabla de abajo los antibióticos u otros medicamentos que administra habitualmente para la meningitis aguda bacteriana y describa su dosis diaria, frecuencia, duración, vía, y lugar de atención.

Antibiótico/Otro *Ej. Cefotaxime*	**Dosis Diaria** *150 mg/k/d*	**Frecuencia** *6 in 6 hrs.*	**Duración** *9 d*	**Vía** *EV*	**Lugar de Atención** *Enfermería*

10. ¿Qué porcentaje (%) de niños presenta efectos adversos a causa de este tratamiento? ____ %

11. ¿Qué tipo de tratamiento le ofrece a niños que presentan estos efectos adversos? En caso de requerir tratamiento farmacológico, haga el favor de describir el tipo de efecto adverso, medicamento para el manejo de este efecto adverso, y estime la dosis diaria, frecuencia, duración, vía, y lugar de atención.

Efecto Adverso *Ej. Alergia*	**Medicamento** *Dexametasona*	**Dosis Diaria** *0,6 Mg/K/D*	**Frecuencia** *4 X D*	**Duración** *4 Dias*	**Vía** *EV*	**Lugar de Atención** *Infeccioso*

12. Qué porcentaje (%) de niños con meningitis aguda bacteriana refiere Ud. al especialista? _____ %

13. Especifique:_____

14. Motivo de derivación al especialista:

- ❑ Complicación
- ❑ Gravedad al cuadro clínico
- ❑ *No respuesta a tratamiento*
- ❑ Edad
- ❑ Condiciones sociales
- ❑ *Otro(especificar):* _____

15. ¿A QUÉ SALA DE HOSPITAL LLEGAN NIÑOS CON MENINGITIS AGUDA BACTERIANA HABITUALMENTE?

_____

_____

16. Indique el número de días cama de niños con meningitis aguda bacteriana: _____ Días.

MANEJO DEL TRATAMIENTO DE MENINGITIS AGUDA BACTERIANA CON ALGUNA COMPLICACIÓN / SECUELA

Las siguientes preguntas aluden al tratamiento de meningitis aguda bacteriana que evoluciona a alguna complicación / secuela. Se entiende por complicación cuando un cuadro no evoluciona de la forma esperada, y por secuela cuando hay una disminución de la función parcial o total.

17. ¿Qué porcentaje (%) de meningitis aguda bacteriana evoluciona a alguna:

a. Complicación? _____ % b. Secuela? _____%

18. Especifique tipo de complicación / secuela.

Tipo de complicación: _____

_____

Tipo de secuela: _____

19. ¿Cuál es su conducta terapéutica en niños con meningitis aguda bacteriana que evoluciona a alguna complicación / secuela?

	Complicación	**Secuela**
a. Manejo general	_____ %	_____ %
b. Tratamiento farmacológico	_____ %	_____ %
c. Intervención quirúrgica	_____ %	_____ %
d. Ningún tratamiento	_____ %	_____ %
e. Derivación a especialista	_____ %	_____ %
f. Otro (Especificar):	_____ %	_____ %

***Las preguntas que aparecen a continuación están dirigidas al especialista (utiólogo, intensivista, infectólogo, neurólogo, neurocirujano pediatra). Si Ud. es un pediatra o médico general / integral, sirva no responder estas pregunta**

PARA EL ESPECIALISTA
MANEJO DEL TRATAMIENTO DE MENINGITIS AGUDA BACTERIANA
CON ALGUNA COMPLICACION

Las siguientes preguntas aluden al tratamiento de meningitis aguda bacteriana que evoluciona a alguna complicación.

20. ¿Cuáles son los signos y / o síntomas más frecuente que detecta en niños con meningitis aguda bacteriana que evoluciona a alguna complicación?

21. Si su conducta terapéutica considera tratamiento general/farmacológico para meningitis aguda bacteriana que evoluciona a alguna complicación, ¿En qué momento lo indica? (Ej.: Cuando los síntomas aparecen; cuando los síntomas empeoran; cuando otras medidas no han dado resultado; en forma complementaria a otras medidas).

_____

_____

22. Haga el favor de describir en la tabla de abajo el tratamiento general / farmacológico que se realice para meningitis aguda bacteriana que evoluciona a alguna complicación, y estima dosis diaria, frecuencia, duración, vía, y lugar de atención.

_____

_____

Tratamiento *Ej. Ceftriaxona*	**Dosis Diaria** *100 mg/k/d*	**Frecuencia** *2 X D*	**Duración** *10-14 d*	**Vía** *EV*	**Lugar de Atención** *Enfermería*

25. Si su conducta terapéutica considera intervención quirúrgica para el manejo de meningitis aguda bacteriana que evoluciona a alguna complicación, ¿En qué momento la indica? (Ej.: Cuando los síntomas aparecen; cuando los síntomas empeoran; cuando otras medidas no han dado resultado; en forma complementaria a otras medidas).

_____

_____

26. Haga el favor de anotar en la tabla de abajo las intervenciones quirúrgicas que realiza para meningitis aguda bacteriana que evoluciona a alguna complicación, y anote el especialista que realizó la intervención, duración (incluyendo el tiempo de la intervención + el número de días de hospitalización post intervención), y lugar de atención (durante y post intervención).

Tipo de Intervención *Ej. Drenaje de empiema*	**Tipo de Especialista** *Neurocirujano pediatra*	**Duración** *1 hr.*	**Lugar de Atención** *Centro Quirúrgico*

27. ¿Qué porcentaje (%) de niños con meningitis aguda bacteriana que evoluciona a alguna complicación presenta efectos adversos a causa de este tratamiento? _____%

28. ¿Qué tipo de tratamiento le ofrece a niños que presentan estos efectos adversos? En caso de requerir tratamiento farmacológico, haga el favor de describir en la siguiente página el tipo de efecto adverso, medicamento, dosis diaria, frecuencia, duración, vía, y lugar de atención.

Efecto Adverso *Infección Hosp*	**Medicamento** *Vancomicin*	**Dosis Diaria** *40 mg/k/d*	**Frecuencia** *6 en 6 hrs.*	**Duración** *10-20 d*	**Vía** *VO*	**Lugar de Atención** *Infeccioso*

29. ¿Cuál es el total de días cama en un niño con meningitis aguda bacteriana que ha evolucionado a alguna complicación? _____ Días. Especificar:

_____

_____

30. ¿Cuántas consultas médicas (controles) realiza en un niño con meningitis aguda bacteriana que ha evolucionado a alguna complicación? _____ Controles. Especificar:

_____

_____

31. Haga el favor de enumerar abajo los exámenes médicos que realiza a causa de la meningitis aguda bacteriana que evoluciona a alguna complicación, el porcentaje (%) de niños por examen, el promedio (frecuencia) de exámenes por niño, y lugar de atención.

Tipo de Examen *Ej. Tomografía computarizada*	**% Pacientes** *70%*	**Frecuencia** *2x*	**Lugar de Atención** *Centro de radiografía*

MANEJO DEL TRATAMIENTO DE MENINGITIS AGUDA BACTERIANA CON SECUELA

Las siguientes preguntas aluden al tratamiento de meningitis aguda bacteriana que evoluciona a alguna secuela.

32. ¿Cuáles son los signos y / o síntomas más frecuente que detecta en niños con meningitis aguda bacteriana que evoluciona a alguna secuela?

_____

_____

33. Si su conducta terapéutica considera tratamiento general / farmacológico para meningitis aguda bacteriana que evoluciona a alguna secuela, ¿En qué momento lo indica? (Ej.: Cuando los síntomas aparecen; cuando los síntomas empeoran; cuando otras medidas no han dado resultado; en forma complementaria a otras medidas).

_____

_____

34. Haga el favor de describir en la tabla de abajo el tratamiento general / farmacológico que se realice para meningitis aguda bacteriana que evoluciona a alguna secuela, y estime dosis diaria, frecuencia, duración, vía, y lugar de atención.

Tratamiento *Ej. Diamoxina*	**Dosis Diaria** *0,25 compr.*	**Frecuencia** *3-4 x d*	**Duración** *Indef.*	**Vía** *VO*	**Lugar de Atención** *Domicilio*

35. ¿Qué porcentaje (%) de niños con meningitis aguda bacteriana que evoluciona a alguna secuela presenta efectos adversos a causa de este tratamiento? _____%

36. ¿Qué tipo de tratamiento le ofrece a niños que presentan estos efectos adversos? En caso de requerir tratamiento farmacológico, haga el favor de describir en la siguiente página el tipo de efecto adverso, medicamento, dosis diaria, frecuencia, duración, vía, y lugar de atención.

Efecto Adverso *Infección Hosp*	**Medicamento** *Vancomicin*	**Dosis Diaria** *40 mg/k/d*	**Frecuencia** *6 en 6 hrs.*	**Duración** *10-20 d*	**Vía** *VO*	**Lugar de Atención** *Infeccioso*

37. Si su conducta terapéutica considera intervención quirúrgica para el manejo de meningitis aguda bacteriana que evoluciona a alguna secuela, ¿En qué momento la indica? (Ej.: Cuando los síntomas aparecen; cuando los síntomas empeoran; cuando otras medidas no han dado resultado; en forma complementaria a otras medidas).

_____

_____

38. Haga el favor de anotar en la tabla de abajo las intervenciones quirúrgicas que realiza para meningitis aguda bacteriana que evoluciona a alguna secuela, y anote el especialista que realizó la intervención, duración (incluyendo el tiempo de la intervención + el número de días de hospitalización post intervención), y lugar de atención (durante y post intervención).

Tipo de Intervención *Ej. Atroca de valvula*	**Tipo de Especialista** *Neurocirujano pediatra*	**Duración** *30–40 min*	**Lugar de Atención** *Centro Quirúrgico*

39. ¿Qué porcentaje (%) de niños con meningitis aguda bacteriana que evoluciona a alguna secuela presenta efectos adversos a causa de esta intervención? _____%

40. ¿Qué tipo de tratamiento le ofrece a niños que presentan estos efectos adversos? En caso de requerir tratamiento farmacológico, haga el favor de describir en la siguiente página el tipo de efecto adverso, medicamento, dosis diaria, frecuencia, duración, vía, y lugar de atención.

Efecto Adverso *Infección Hosp*	**Medicamento** *Vancomicin*	**Dosis Diaria** *40 mg/k/d*	**Frecuencia** *6 en 6 hrs.*	**Duración** *10-20 d*	**Vía** *VO*	**Lugar de Atención** *Infeccioso*

41. ¿Cuál es el total de días cama en un niño con meningitis aguda bacteriana que ha evolucionado a alguna secuela? _____ Días. Especificar:

_____

42. ¿Cuántas consultas médicas (controles) realiza en un niño con meningitis aguda bacteriana que ha evolucionado a alguna secuela? _____ Controles. Especificar:

_____

43. Haga el favor de enumerar abajo los exámenes médicos que realiza a causa de la meningitis aguda bacteriana que evoluciona a alguna secuela, el porcentaje (%) de niños por examen, el promedio (frecuencia) de exámenes por niño, y lugar de atención.

Tipo de Examen *Ej. Audiometría*	**% Pacientes** *100%*	**Frecuencia** *1x*	**Lugar de Atención** *Consultorio*

Agradecemos su colaboración en esta encuesta.

APPENDIX I SOURCE OF UNIT COST DATA BY COUNTRY

Country	Information Source
Argentina	Formulario Terapeutico Provincial, Buenos Aires, 2005. Listado de precios (Cordoba City). Listado de Precios — Medicamentos Genéricos; In: farmacia@mutualsentimiento.org.ar Price given by the health insurance (IOMA). División Compras del Hospital de Niños "R Gutiérrez". Hospital de Niños accounting department, Córdoba, 2005. Hospital Sor. Maria Ludovica accounting department, Ciudad de La Plata, 2005. Hospital Humberto Notti accounting department, Mendoza, 2005. Módulo Nomenclador de Prestaciones de Salud, Gob. de la Ciudad de Buenos Aires, 2005.
Brazil	Tabela de Procedimentos do Sistema Ambulatorial do Sistema Único de Saúde (SIA / SUS), Abril 2004. RGM do Brasil. Internet: http://www.rgmnet.net Tabela de Procedimentos do Sistema Hospitalario do Sistema Único de Saúde (SIH / SUS), Abril 2004. RGM do Brasil. Internet: http://www.rgmnet.net Dicionario de Medicamentos Genéricos. A. C. Basile, A.C. Zanini. SUS. Secretaria de Saúde do Estado de Goias e Cidade de Goiânia. 1999. (2 Edition. IPEX Comercial Edidora Ltda. Internet: http//:www.guiamed.com. E-mail: suporte@guiamed.com. Dicionario de Especialidades Farmaceuticas. DEF 99/2000. Jornal Brasileiro de Medicina. Editora de Publicações Cientificas (EPUC) Ltda. Ministério da Saúde, Secretaria de Gestão de Investimentos en Saúde. Internet: www.saude.gov.br/banco/index.htm (Banco de Precos en Saude, Pesquisados em 20/09/01. Laboratório Teuto Brasileiro Ltda. Internet: www.teuto.com.br Agência Nacional de Vigilância Sanitaria. Internet: www.anvisa.gov.br Drugstore: http://www.novacosmeticos.com.br/drogaria_D_F.asp Drugstore: http://www.farmaciaprincesa.com.br/f.html
Chile	Hospital Exequiel González Cortés accounting department, 2005. Hospital Luis Calvo Mackenna accounting department, 2005. Hospital Roberto del Río accounting department, 2005. Central Supply Clearinghouse (CENABAS), 2005.
Colombia	Hospital Materno-Infantil, Cali, accounting department, 2005
Dominican Republic	Hospital Robert Reid Cabral, accounting department, 2005. Hospital José María Cabral y Báez, accounting department, 2005. Hospital Infantil Dr. Arturo Grullón, accounting department, 2005.
Honduras	Erminia Suazo, Jefe de Relaciones Públicas, Hospital Centro Médico Hondureño, 2004. Roberto Bhaday & Ramón Gonzalez, Hospital Escuela accounting department, 2004.
Mexico	Edmundo Vega Mendoza, Subdirector Administrativo from Hospital General de Tlalnepantla, 2005.
Panama	Centro de Salud Amelia Denis Icaza accounting department, 2005. Hospital de José Domingo Obaldía accounting department, 2005. FarmaEnvios; In: http://farmaenvios.com
Uruguay	Dirección Administrativa, CHPR/ CASMU, 2005. Dirección Administrativa, Mutualismo, 2005.
Venezuela	Centro Médico Docente La Trinidad, accounting department, 2005. Hospital Metropolitano del Norte, accounting department, 2005. INSALUD accounting system, 2005.

APPENDIX J ECONOMIC MODELING METHODS TABLES

TABLE J.1: Input Variables: General, disease-related, and healthcare-related variables

MODEL INPUT	BASE CASE	PLAUSIBLE RANGE		SOURCE
	VALUE	LOW VALUE	HIGH VALUE	
Demographics				
Birth cohort	11,700,500	—	—	PAHO regional data
Life expectancy at age 1	72.3	—	—	PAHO regional data
Discounting				
— discount rate for costs	3%	0%	6%	Gold M et al, 1996 [8]
— discount rate for health benefits	3%	0%	6%	Gold M et al, 1996 [8]
Probabilities				
Disease probabilities (cumulative incidence)				
— Probability of acute otitis media	0.9000			Teele et al, 1989 [9]
— Probability of clinical pneumonia	0.0911			Current analysis
— Probability of chest x-ray confirmed pneumonia	0.0572			Current analysis
— Probability of pneumococcal sepsis	0.0001			Current analysis
— Probability of pneumococcal meningitis	0.0003			Current analysis
Case fatality ratios				
— CFR for clinical pneumonia	0.03			Current analysis
— CFR for chest x-ray confirmed pneumonia	0.05			Current analysis
— CFR for sepsis	0.35			Current analysis
— CFR for meningitis	0.35			Current analysis
Serotype				
—Probability vaccine type (7-valent)	0.60			Current analysis
Healthcare-related				
— Probability that clinical pneumonia is hospitalized	0.08			Constenla D. Personal communication.
— Probability that chest x-ray confirmed pneumonia is hospitalized	0.64			Constenla D. Personal communication.
Disability related				
— Probability of deafness due to acute otitis media	0.0			Constenla D. Personal communication.
— Probability of deafness due to pneumococcal meningitis	0.13			Constenla D. Personal communication.
— Probability of seizure disorder due to pneumococcal meningitis	0.17			Constenla D. Personal communication.
— Probability of motor disorder due to pneumococcal meningitis	0.16			Constenla D. Personal communication.

TABLE J.1: Input Variables *(continued)*

MODEL INPUT	BASE CASE	PLAUSIBLE RANGE		SOURCE
	VALUE	LOW VALUE	HIGH VALUE	
Duration of illness (in days)				
— acute otitis media	8			Current analysis
— clinical pneumonia (inpatient/outpatient)	15/7			Current analysis
— chest x-ray confirmed pneumonia (inpatient/outpatient)	17/11			Current analysis
— pneumococcal sepsis	10			Current analysis
— pneumococcal meningitis	15			Current analysis
Vaccine-related inputs				
Vaccination coverage rate	92%			PAHO
Vaccine efficacy				
— against acute otitis media	0.07	0.04	0.10	
— against clinical pneumonia	0.04	-0.04	0.12	
— against chest x-ray confirmed pneumonia	0.23	0.04	0.34	
— against vaccine type invasive pneumococcal disease (sepsis or meningitis)	0.97	0.83	1.00	
Vaccine program				
— number of vaccine doses	3			
— wastage rate	10%			
— cost per dose of vaccine	$53	$5	$53	
— cost for administration of one dose	$1.00	$0.50	$1.50	
Costs				
Disease-related costs, acute otitis media				
— direct medical costs for acute otitis media, health system	$82	$65	$155	10 physician interviews
— direct medical costs due to family out-of-pocket costs	$9	$7	$33	60 parent interviews in 3 countries
— direct non-medical cost due to caregiver time loss	$9	$6	$46	60 parent interviews in 3 countries
— other direct non-medical costs	$0	$0	$0	
Disease-related costs, clinical pneumonia, outpatient				
— direct medical costs for clinical pneumonia, health system	$99	$66	$157	18 physician interviews
— direct medical costs due to family out-of-pocket costs	$9	$7	$33	60 parent interviews in 3 countries
— direct non-medical cost due to caregiver time loss	$9	$6	$46	60 parent interviews in 3 countries
— other direct non-medical costs	$0	$0	$0	

TABLE J.1: Input Variables *(continued)*

MODEL INPUT	BASE CASE	PLAUSIBLE RANGE		SOURCE
	VALUE	LOW VALUE	HIGH VALUE	
Disease-related costs, clinical pneumonia, inpatient				
— direct medical costs for clinical pneumonia, health system	$940	$512	$1,925	18 physician interviews
— direct medical costs due to family out-of-pocket costs	$15	$12	$56	60 parent interviews in 3 countries
— direct non-medical cost due to caregiver time loss	$61	$47	$193	60 parent interviews in 3 countries
— other direct non-medical costs	$0	$0	$0	
Disease-related costs, chest x-ray positive pneumonia, outpatient				
— direct medical costs for clinical pneumonia, health system	$99	$66	$157	18 physician interviews
— direct medical costs due to family out-of-pocket costs	$9	$7	$33	60 parent interviews in 3 countries
— direct non-medical cost due to caregiver time loss	$9	$6	$46	60 parent interviews in 3 countries
— other direct non-medical costs	$0	$0	$0	
Disease-related costs, chest x-ray positive pneumonia, inpatient				
— direct medical costs for clinical pneumonia, health system	$940	$512	$1,925	18 physician interviews
— direct medical costs due to family out-of-pocket costs	$15	$12	$56	60 parent interviews in 3 countries
— direct non-medical cost due to caregiver time loss	$61	$47	$193	60 parent interviews in 3 countries
— other direct non-medical costs	$0	$0	$0	
Disease-related costs, pneumococcal sepsis				
— direct medical costs for pneumococcal sepsis, health	$1,257	$844	$1,355	11 physician interviews
System	$15	$12	$56	60 parent interviews in 3 countries
— direct medical costs due to family out-of-pocket costs				
— direct non-medical cost due to caregiver time loss	$72	$58	$133	60 parent interviews in 3 countries
— other direct non-medical costs	$0	$0	$0	
Disease-related costs, pneumococcal meningitis				
— direct medical costs for pneumococcal meningitis, health system	$1,792	$652	$2,494	18 physician interviews
— direct medical costs due to family out-of-pocket costs	$15	$12	$56	60 parent interviews in 3 countries
— direct non-medical cost due to caregiver time loss	$35	$17	$252	60 parent interviews in 3 countries
— other direct non-medical costs	$0	$0	$0	

Table J.2: Forms completed and parent interviews conducted

	Resource use forms completed				
COUNTRY	PNEUMONIA[a]	PNEUMOCOCCAL MENINGITIS	PNEUMOCOCCAL SEPSIS	ACUTE OTITIS MEDIA	PARENTS INTERVIEWS CONDUCTED
Argentina	1	—	—	1	
Brazil	3	4	—	2	20
Chile	—	5	2	2	20
Colombia	5	1	3	3	—
Dominican Republic	—	1	7	—	—
Honduras	1	1	—	—	—
Mexico	2	1	—	—	—
Panama	1	1	—	—	—
Uruguay	4	4	—	1	20
Venezuela	1	—	—	1	—
Total	18	18	11	10	60

[a] Includes all-cause clinical and x-ray positive pneumonia (inpatient/outpatient).

TABLE J.3: Use of health services associated with pneumococcal disease by income group

INCOME GROUP	DIAGNOSTICS	ANTIBIOTICS	OTHER MEDICATIONS	OUTPATIENT VISITS	HOSPITALIZATION (in days)[a]	RADIOGRAPHY	OXYGEN THERAPY	PHYSIOTHERAPY	SURGERY
	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]
Chest x-ray positive pneumonia or clinical pneumonia, inpatient									
Low income (US$2,130 or less)									
Colombia	1.3 (55%)	2.8 (100%)	1.5 (21%)	4 (10%)	13.5 (68%)	1 (98%)	1 (43%)	1 (10%)	1 (73%)
DR	—	—	—	—	—	—	—	—	—
Honduras	1 (70%)	2 (100%)	1 (50%)	4 (60%)	12.5 (80%)	1 (95%)	1 (60%)	2 (50%)	1 (1%)
Lower-middle income (US$2,131-US$3,820)									
Argentina	1 (10%)	2 (100%)	3 (7%)	2 (100%)	12.5 (65%)	2 (100%)	—	2 (25%)	1 (10%)
Brazil	1.5 (97%)	4 (56%)	1 (50%)	2 (50%)	16 (60%)	1.6 (58%)	1 (25%)	2 (100%)	1 (2%)
Venezuela	2.3 (60%)	2 (100%)	2 (65%)	2 (40%)	10.5 (50%)	2 (90%)	—	3 (50%)	2 (40%)
Uruguay	1.5 (97%)	4 (56%)	1 (50%)	2 (50%)	14.5 (60%)	1.6 (58%)	1 (25%)	2 (100%)	1 (2%)
Upper-middle income (US$ 3,821 or more)									
Chile	—	—	—	—	—	—	—	—	—
Mexico	1 (90%)	2 (100%)	1 (60%)	3 (60%)	10.5 (65%)	1 (100%)	1 (60%)	6 (60%)	1 (5%)
Panama	1.8 (92%)	5 (100%)	2 (10%)	2 (60%)	12.5 (65%)	2 (100%)	—	2 (100%)	2 (30%)
Pneumococcal meningitis									
Low income (US$2,130 or less)									
Colombia	2 (100%)	2 (100%)	2 (100%)	—	11 (100%)	—		—	1 (5%)
DR	1 (72%)	1 (100%)	3 (30%)	—	11 (100%)	—	1 (30%)	—	1 (10%)
Honduras	1.9 (94%)	1 (100%)	2 (100%)	—	14.5 (100%)	—	1 (20%)	—	1 (5%)
Lower-middle income (US$2,131-US$3,820)									
Argentina	—	—	—	—	—	—	—	—	—
Brazil	1.6 (95%)	4 (86%)	2 (100%)	—	21.5 (100%)	1 (58%)	4 (45%)	—	1 (8%)
Venezuela	—	—	—	—	—	—	—	—	—
Uruguay	1.6 (95%)	4 (86%)	1 (100%)	—	17.5 (100%)	1 (58%)	1 (45%)	—	1 (8%)
Upper-middle income (US$ 3,821 or more)									
Chile	2.4 (98%)	2 (100%)	1 (54%)	—	14.5 (100%)	—	1 (45%)	—	1 (8%)
Mexico	1 (97%)	3 (100%)	2.5 (60%)	4 (60%)	15.5 (100%)	1 (95%)	1 (85%)	—	1 (5%)
Panama	1.5 (95%)	5 (100%)	1 (35%)	—	13 (83%)	—	1 (25%)	—	1 (5%)
All-cause acute otitis media									
Low income (US$2,130 or less)									
Colombia	1 (90%)	3 (87%)	2 (12%)	1 (100%)	—	—	—	—	1 (43%)
DR	—	—	—	—	—	—	—	—	—
Honduras	—	—	—	—	—	—	—	—	—
Lower-middle income (US$2,131-US$3,820)									
Argentina	1.5 (10%)	2 (100%)	2 (50%)	3 (100%)	—	—	—	—-	
Brazil	1 (100%)	2 (67%)	1 (67%)	3 (100%)	—	—	—	—-	
Venezuela	1 (100%)	1 (80%)	1 (20%)	2 (100%)	—	—	—	—-	1 (5%)
Uruguay	1 (100%)	2 (67%)	1 (67%)	3 (100%)	—	—	—	—-	
Upper-middle income (US$ 3,821 or more)									
Chile	3 (100%)	2 (100%)	1 (100%)	2 (100%)				1 (25%)	
Mexico	—	—	—	—	—	—	—	—	—
Panama	—	—	—	—	—	—	—	—	—

TABLE J.3: Use of health services associated with pneumococcal disease by income group *(continued)*

INCOME GROUP	DIAGNOSTICS	ANTIBIOTICS	OTHER MEDICATIONS	OUTPATIENT VISITS	HOSPITALIZATION (in days)[a]	RADIOGRAPHY	OXYGEN THERAPY	PHYSIOTHERAPY	SURGERY
	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]	Frequency[b] (% used)[c]
Chest x-ray positive pneumonia or clinical pneumonia, outpatient									
Low income (US$2,130 or less)									
Colombia	1.3 (40%)	2.8 (100%)	2 (50%)	5 (100%)	—	—	1 (25%)	—	—
DR	—	—	—	—	—	—	—	—	—
Honduras	1 (70%)	2 (100%)	1 (50%)	4 (100%)	—	—	—	1 (20%)	—
Lower-middle income (US$2,131-US$3,820)									
Argentina	1.5 (100%)	3 (100%)	3 (7%)	2 (100%)	—	—	—	5 (25%)	—
Brazil	1 (95%)	2 (100%)	2 (65%)	2 (100%)	—	—	—	1 (20%)	—
Venezuela	2 (80%)	2 (100%)	2 (65%)	3 (100%)	—	—	—	3 (50%)	—
Uruguay	1 (95%)	2 (100%)	2 (65%)	2 (100%)	—	—	—	1 (20%)	—
Upper-middle income (US$ 3,821 or more)									
Chile	—	—	—	—	—	—	—	—	—
Mexico	1 (90%)	2 (100%)	1 (60%)	3 (100%)	—	—	—	6 (60%)	—
Panama	2 (100%)	3 (100%)	2 (10%)	5 (100%)	—	—	—	2 (100%)	—
Pneumococcal sepsis									
Low income (US$2,130 or less)									
Colombia	1 (73%)	1.7 (100%)	1.7 (48%)	3 (100%)	12 (100%)	1 (10%)	1 (45%)	—	1 (50%)
DR	1.6 (65%)	3.5 (100%)	2 (48%)	3 (100%)	8.3 (100%)	1 (25%)	1.5 (76%)	—	1 (26%)
Honduras	—	—	—	—	—	—	—	—	—
Lower-middle income (US$2,131-US$3,820)									
Argentina	—	—	—	—	—	—	—	—	—
Brazil	—	—	—	—	—	—	—	—	—
Venezuela	—	—	—	—	—	—	—	—	—
Uruguay	—	—	—	—	—	—	—	—	—
Upper-middle income (US$ 3,821 or more)									
Chile	1 (63.3%)	3 (100%)	2 (80%)	2 (60%)	8 (100%)	—	1 (30%)	—	—
Mexico	—	—	—	—	—	—	—	—	—
Panama	—	—	—	—	—	—	—	—	—

a This includes pediatric/infectious disease ward and intensive care unit (ICU).
[b] Average number of events (visits, diagnostics, antibiotics) occurring during the acute phase of the illness based on physician interviews in the public sector (n = 57) (e.g., the average length of stay in the hospital is 3.5 days; an average of 2.5 blood count tests are performed in patients with meningitis).
[c] Proportion of treatment-related events (visits, diagnostics, medications) occurring (e.g., 100% pneumonia patients are admitted to pediatric ward; 20% otitis media patients are seen by their pediatrician; 20% meningitis patients receive blood count tests).

TABLE J.4: Direct medical costs associated with pneumococcal disease by income group[a]

	LOW INCOME (US$2,130 or less)[b]	LOWER-MIDDLE INCOME (US$2,131-US$3,820)[b]	UPPER-MIDDLE INCOME (US$ 3,821 or more)[b]
Chest x-ray positive pneumonia or clinical pneumonia, inpatient			
Diagnostics			
Polymerase chain reaction (PCR)	3.95	0.97	0.47
Blood test	2.14	11.12	2.31
Bacteriology	2.98	2.75	0.14
Antibiotics	34.04	33.90	33.70
Other meds	3.69	11.04	4.56
Outpatient visits	4.00	9.37	52.13
Hospitalization			
Pediatric ward	268.55	561.65	767.79
ICU	11.94	36.28	51.35
Radiography	13.82	16.98	30.51
Surgery	453.26	131.87	110.74
Oxygen therapy	4.36	1.46	8.77
Physiotherapy	1.74	7.31	14.43
Total cost per event	804.46	824.69	1,076.89
Chest x-ray positive pneumonia or clinical pneumonia, outpatient			
Diagnostics			
Blood test	2.80	6.57	2.20
Bacteriology	0.00	0.15	—
Antibiotics	22.14	35.52	32.69
Other meds	9.89	21.93	4.56
Outpatient visits	27.46	9.40	88.18
Physiotherapy	1.87	4.23	14.43
Total cost per event	64.15	77.80	142.06
Pneumococcal meningitis			
Diagnostics			
Blood test	37.39	3.97	0.65
Bacteriology	0.00	2.53	1.13
Lumbar puncture	0.00	5.61	1.41
CSF	0.00	15.42	0.64
Ligase chain reaction (LCR)	1.28	—	5.24
Latex	1.14	—	—
Chemistry	0.62	—	10.30
Antibiotics	36.46	43.21	56.24
Other meds	34.39	26.95	13.75
Outpatient visits	0.00	—	68.81
Hospitalization			
Pediatric ward	721.81	847.94	2,111.29
ICU	30.77	68.82	57.23
Oxygen therapy	0.87	10.39	12.81
Radiography	0.00	11.18	28.56
Surgery	165.81	184.38	85.18
Total cost per event	1,030.54	1,220.36	2,453.26

TABLE J.4: Direct medical costs associated with pneumococcal disease by income group[a] *(continued)*

	LOW INCOME (US$2,130 or less)[b]	LOWER-MIDDLE INCOME (US$2,131-US$3,820)[b]	UPPER-MIDDLE INCOME (US$ 3,821 or more)[b]
All-cause acute otitis media			
Diagnostics	3.41	6.10	1.85
Antibiotics	23.37	22.84	5.10
Other meds	2.21	12.09	2.27
Outpatient visits	4.80	24.39	2.83
Surgery	43.24	13.77	79.47
Total cost per event	77.03	79.19	91.52
Pneumococcal sepsis			
Diagnostics			
Blood test	7.63	—	1.35
PCR	3.43	—	8.17
LCR	10.83	—	—
Blood culture	0.49	—	—
Urine culture	1.81	2.78	
Venereal disease research Laboratory (VDRL)	1.11	—	—
Antibiotics	34.43	—	75.72
Other meds	13.00	—	35.92
Outpatient visits	22.59	—	16.81
Hospitalization			
Pediatric	217.12	—	1,060.86
ICU	384.59	—	151.42
Oxygen therapy	4.42	1.59	
Radiography	1.77	—	—
Surgery	349.82	—	—
Total cost per event	1,053.03	—	1,354.62

[a] Income groups are divided according to 2003 GDP per capita (Atlas method, USD, 2003). The groups are low-income: $2,130 or less; lower-middle income: $2,131 - $3,820; and upper-middle income: $3,821 or more. The high income group is not included in the present analysis.

[b] This represents the population weighted average (US$, 2005). However, the cost of pneumococcal sepsis for upper-middle income countries is only an average cost based on responses from Chilean physicians.

TABLE J.5: Estimated treatment costs for pneumococcal disease based on secondary data sources

PNEUMOCOCCAL DISEASE	US$, 2005[d]
All-cause clinical pneumonia and x-ray positive pneumonia (inpatient)	
Hospitalization[a] (WHO-CHOICE data (WHO, 2000)) & CEPAL	964.46
Diagnostics/medication (Physician interviews/country-specific sources)	296.94
Outpatient visit (WHO-CHOICE data (WHO, 2000)) & CEPAL	72.48
All-cause clinical pneumonia and x-ray positive pneumonia (outpatient)	
Outpatient visit (WHO-CHOICE data (WHO, 2000)) & CEPAL	89.57
Diagnostics/medication (Physician interviews/country-specific sources)	62.68
All-cause acute otitis media	
Outpatient visit (WHO-CHOICE data (WHO, 2000)) & CEPAL	64.21
Diagnostics/medication (Physician interviews/country-specific sources)	66.10
Pneumococcal meningitis	
Hospitalization[b] (WHO-CHOICE data (WHO, 2000)) & CEPAL	1,115.04
Diagnostics/medication (Physician interviews/country-specific sources)	343.89
Outpatient visit (WHO-CHOICE data (WHO, 2000)) & CEPAL	110.24
Pneumococcal sepsis	
Hospitalization[c] (WHO-CHOICE data (WHO, 2000)) & CEPAL	709.98
Diagnostics/medication (Physician interviews/country-specific sources)	460.94
Outpatient visit (WHO-CHOICE data (WHO, 2000)) & CEPAL	73.59
Diagnostics/medication (Physician interviews/country-specific sources)	

[a]Hospitalization cost assumes an average stay of 12.81 days based on physician interviews.
[b]Hospitalization cost assumes an average stay of 14.81 days based on physician interviews.
[c]Hospitalization cost assumes an average stay of 9.43 days based on physician interviews.
[d]Values are based on a regional estimate using population weighted average of cost per event (US$, 2005).

Table J.6: Direct non-medical and indirect costs of pneumococcal disease

	NON-MEDICAL COSTS (average US$, 2005)	INDIRECT COSTS (average US$, 2005)
Pneumococcal meningitis	15.15	35.32
Pneumococcal sepsis	15.15	72.28
Pneumonia (inpatient)[a]	15.15	61.23
Pneumonia (outpatient)[a]	9.28	9.27
OMA	9.28	9.27

[a] This includes all-cause clinical pneumonia and x-ray positive pneumonia.

APPENDIX K EPIDEMIOLOGY RESULTS SECTION 3.1

TABLE K.1: Time periods during which studies were published or during which data collection commenced, by sub-region

TIME – PERIOD	CENTRAL AMERICA	CARIBBEAN	SOUTH AMERICA	MULTI-COUNTRY STUDY	TOTAL
Years of study publication, Number (%)					
1990-1995	5 (25.0)	0 (0)	14 (70.0)	1 (5.0)	20 (14.0)
1996-2000	8 (19.0)	3 (7.1)	27 (64.3)	4 (9.5)	42 (29.4)
2001-2006	6 (7.4)	8 (9.9)	63 (77.8)	4 (4.9)	81 (54.6)
Total	19 (13.3)	11 (7.7)	104 (72.7)	9 (6.3)	143 (100)
First year of data collection, Number (%)					
Before 1980			3 (100.0)		3 (2.1)
1980-1989	2 (10.0)		18 (90.0)		20 (14.0)
1990-1999	13 (13.0)	8 (8.0)	74 (74)	5 (5)	100 (69.9)
2000-2006	2 (13.3)	3 (20.0)	7 (46.7)	3 (20)	15 (10.5)
Unknown	2 (40.0)		2 (40.0)	1 (20)	5 (3.5)
Total	19 (13.3)	11 (7.7)	104 (72.7)	9 (6.3)	143 (100)

TABLE K.2: Distribution of studies by syndrome by sub-region

SYNDROME	CENTRAL AMERICA	CARIBBEAN	SOUTH AMERICA	MULTI-COUNTRY	TOTAL*
IPD	4	6	42	5	57 (39.8)
Pneumococcal Pneumonia	2	0	32	2	36 (25.2)
Bacterial Meningitis	4	5	25	0	34 (23.8)
Pneumococcal Meningitis	3	2	22	1	28 (19.6)
Clinical Pneumonia	2	0	13	0	15 (10.5)
Acute Otitis Media	6	0	5	3	14 (9.8)
Pneumococcal Bacteremia	0	0	5	0	5 (3.5)
X-ray Confirmed Pneumonia	0	0	4	0	4 (2.8)

*Total does not add to 100% as one study could have data from several syndromes

TABLE K.3: Comparison of studies included in analysis, studies not found and studies published before 1990

SYNDROME	INCLUDED PAPERS N=143*	PAPERS NOT FOUND N=66*	PUBLISHED BEFORE 1990 N=52*
Distribution by subregion		N=61**	
South America	104 (72.7)	56 (91.8)	30 (57.7)
Central America	19 (13.3)	1 (1.6)	9(17.3)
Caribbean	11 (7.7)	4 (6.6)	8 (15.4)
Countries not represented in included papers			
South America	—	Bolivia x1 Ecuador x1	
Central America	—	Panama x1	El Salvador x1 Honduras x1 Panama x1
Caribbean	—	Barbados x1	Bahamas x1 Barbados x1
Time period of publication		N=61	
1990-1995	20 (14.0)	23 (37.7)	—
1996-2000	42 (29.4)	25 (41.0)	—
2001-2006	81 (56.6)	13 (21.3)	—
Distribution by syndrome			
IPD	57 (39.8)	11 (16.7)	1(1.9)
Pneumococcal Pneumonia	36 (25.2)	3 (4.6)	0 (0.0)
Bacterial Meningitis	34 (23.8)	14 (21.2)	18 (34.6)
Pneumococcal Meningitis	28 (19.6)	0 (0.0)	0 (0)
Clinical Pneumonia	15 (10.5)	23 (34.8)	10 (19.3)
Acute Otitis Media	14 (9.8)	3 (4.6)	2 (3.8)
Pneumococcal Bacteremia	5 (3.5)	0 (0.0)	1 (1.9)
X-ray Confirmed Pneumonia	4 (2.8)	3 (4.6)	0 (0.0)
Distribution by type of data		N=30	N=38
Annual Incidente	18 (12.6)	3 (10)	9 (23.7)
Case Fatality Rate	51 (31.6)	13 (43.3)	14 (36.8)
Serotype Data	18 (12.6)	13 (43.3)	3 (7.9)
Antibiotic Resistance	70 (49.0)	18 (60.0)	7 (18.4)
% of Disease Due to *S. Pneumoniae*	55 (38.4)	18 (60.0)	23 (60.5)

*Totals may not add 100% for syndrome and type of data as one study could have several types of data from several syndromes.

*Data not presented in 5 abstracts.

APPENDIX L EPIDEMIOLOGY RESULTS SECTION 3.2

INVASIVE PNEUMOCOCCAL DISEASE

Serotypes

TABLE L.1: Vaccine coverage for IPD for three conjugate vaccine preparations with cross-reactive serotypes by country and time period among children less than six years of age

COUNTRY	YEARS	NUMBER OF ISOLATES*	% VACCINE COVERAGE INCLUDING CROSS REACTIVE SEROTYPES		
			7-VALENT	10- VALENT	13- VALENT
Argentina	2000-2003	549	59	83	87
Argentina	1993-1999	1,006	57	84	88
Brazil	2000-2003	1,588	64	76	83
Brazil	1993-1999	1,203	65	82	88
Chile	2000-2003	34	74	94	100
Chile	1993-1999	495	42	72	78
Colombia	2000-2003	411	69	84	89
Colombia	1993-1999	623	70	87	89
Mexico	2000-2003	369	63	66	73
Mexico	1993-1999	426	62	68	76
Uruguay	2000-2003	313	54	80	89
Uruguay	1993-1999	352	52	85	93
All 6 countries	2000-2003	3,264	63	78	84
All 6 countries	1993-1999	4,071	60	81	86

*The sum of countries > than total as 4,071of 4,105 isolates were available for typing but information on number of isolates available by country was not available. So country denominator was used providing a slight underestimate.

TABLE L.2: Distribution (percentage) of serotypes for IPD by country in children less than six years old from SIREVA data, 1993-2003 [10 11]

SEROTYPE	ARGENTINA %	BRAZIL %	CHILE %	COLOMBIA %	MEXICO %	URUGUAY %	TOTAL %
14	34.2	27.8	15.0	27.9	10.5	34.9	25.0
6A/6B	8.9	14.8	10.2	16.9	16.5	7.0	12.4
5	13.3	5.4	5.9	7.1	1.3	13.3	7.7
1	7.7	7.5	15.5	7.0	1.8	11.5	8.5
23F	3.4	5.1	5.2	10.2	15.6	2.0	6.9
19F	3.0	4.5	15.8	5.3	12.1	2.7	7.2
18C	3.2	6.2	4.4	4.3	2.5	2.1	3.8
19[a]	2.8	3.5	3.2	0.4	5.5	3.8	3.2
9V	3.2	3.5	0.5	3.0	3.5	2.9	2.8
7F	4.5	1.6	3.8	1.8	1.1	4.0	2.8
3	1.1	2.7	2.9	3.2	2.0	5.3	2.9
4	0.9	1.8	6.4	1.6	1.9	1.3	2.3
Total	86.1	84.4	88.7	88.6	74.3	90.8	85.5
No of isolates*	**1,555**	**2,791**	**529**	**1,034**	**795**	**665**	**7,335**

*Total number of isolates for countries does not sum to overall total due to denominator differences between isolates and isolates available for serotyping in data from 1993-1999.

TABLE L.3: Absolute percentage difference between percentage serotype frequency 1993-1999[10] and 2000-2003[11] for IPD by country for children less than six years from SIREVA data*

SEROTYPE	ARGENTINA %	BRAZIL %	CHILE %	COLOMBIA %	MEXICO %	URUGUAY %	TOTAL %
14	3.1	-10.8	5.8	-12.5	-6.4	15.3	3.1
6a/6b	0.1	6.4	-1.0	-2.8	-2.7	6.9	0.1
5	-1.5	-5.9	-2.5	7.5	-11.7	7.9	-1.5
1	-0.5	2.3	-4.7	8.2	4.3	-10.9	-0.5
23f	0.4	1.6	-0.2	-0.4	1.3	5.0	0.4
19f	-0.1	1.6	0.0	-2.3	27.2	-22.0	-0.1
18c	2.0	3.2	-2.4	-2.0	2.9	-1.4	2.0
19A	-0.5	0.9	0.0	-0.1	-0.5	-2.3	-0.5
9v	-0.2	1.3	-1.8	-1.6	-1.0	1.8	-0.2
7f	-1.3	-3.1	1.8	2.1	-1.7	-0.7	-1.3
3	0.8	0.5	1.5	-0.7	0.1	-1.9	0.8
4	0.0	0.6	0.5	-1.0	10.8	-9.6	0.0

*Data represents % serotype frequency in 2000-2003 minus 1993-1999.

Antimicrobial Resistance

TABLE L.4: Median percent of invasive pneumococcal disease isolates resistant and highly resistant to penicillin and multiresistant, by country

COUNTRIES	NUMBER OF STUDIES	MEDIAN NUMBER OF ISOLATES PER STUDY (Min-Max)	MEDIAN % OF ISOLATES RESISTANT (25^{th}-75^{th} percentile)
Overall Penicillin Resistance			
Argentina [7,12-15,16,17]	7	188 (101- 1288)	29 (22-32)
Brazil [18,19,20,21,17,22-31]	15	237 (31- 6470)	21 (19-23)
Mexico [21,17,32]	3	253 (220-285)	47 (41-48)
Uruguay [33,34]	2	354 (184-520)	54 (42-65)
Chile [17,35,36,37-42]	9	128 (67-901)	31 (26-36)
Puerto Rico [43,44,45]	3	53 (38-56)	48 (48-55)
Colombia [21,46]	2	764	26 (12-40)
Peru [47,48]	2	88 (30-146)	21 (15-27)
Trinidad [49,50]	2	37	10 (5-15)
Multicenter* [51]	1	1100	24
Jamaica [52]	1	117	14
West Indies [17]	1	84	7
All countries combined	**62**	**160 (30-6470)**	**24 (20-34)**
High Penicillin Resistance			
Argentina [7,12-14]	4	274 (101-1288)	18 (14-19)
Brazil [53,20-30]	12	300 (31-6470)	2 (1-3)
Mexico [21,32]	2	220 (220-220)	22 (21-22)
Uruguay [33]	1	520	14
Chile [39,35-38,40-42]	8	151 (78-567)	10 (2-13)
Puerto Rico [43,45]	2	47 (38-56)	35 (29-42)
Colombia [46]	1	764	13
Perú [48]	1	30	27
Trinidad [49]	1	37	0
Multicenter* [51]	1	1100	7
Costa Rica [54]	1	84	4
Jamaica [52]	1	117	0
All Countries Combined	**37**	**247 (30-1288)**	**7 (2-16)**
Resistant to Penicillin and at Least One Other Drug			
Argentina [14]	1	NA	40
Brazil [18,22,23,25,28,55]	6	NA	17 (5-35)
Uruguay [34]	1	NA	9
Colombia [46]	1	NA	6
Peru [48]	1	NA	37
Multicenter* [51]	1	NA	18
All countries combined	**12**	**NA**	**17.5 (9-38)**

MENINGITIS

Proportion of disease due to Streptococcus pneumoniae

TABLE L.5: Median percentage of confirmed cases of bacterial meningitis due to *S. pneumoniae* by country

COUNTRY	NUMBER OF STUDIES	MEDIAN %	25th -75th PERCENTILE	Min-Max %
Brazil[56-58,56,59-61,62-65]	11	17	11-29	3-40
Chile[66-68]	3	21	17-23	15-43
Colombia[69, 70,71]	3	11	10-24	6-45
Cuba[72,73]	2	27	26-27	26-28
Mexico[74,75]	2	19	15-17	14-19
Dominican R[76]	1	15		
Venezuela[77,78]	2	12	11-13	11-13
Uruguay[79]	1	26	--	--
Peru[80]	1	24	--	--
Haiti[81]	1	17	--	--
Argentina[82]	1	66	--	--

Antimicrobial Resistance

TABLE L.6: Median percent of meningitis pneumococcal isolates resistant and highly resistant to penicillin by country and age

COUNTRIES	NUMBER OF STUDIES	MEDIAN NUMBER OF ISOLATES PER STUDY (Min-Max)	MEDIAN % OF ISOLATES RESISTANT PER STUDY (25th-75th percentile)
Brazil[83,84]	2	179 (55-303)	15 (15-36)
Mexico[85]	1	38	29
Colombia[71]	1	40	20
Paraguay[86]	1	52	2
All countries combined	5	46 (38-303)	17.5 (12-22)

PNEUMONIA

Characteristics Of Surveillance Systems

TABLE L.7: Characteristics of surveillance systems for x-ray confirmed pneumonia in South America by site

CHARACTERISTIC	URUGUAY	ARGENTINA - CORDOBA	ARGENTINA - BUENOS AIRES	CHILE
Published in peer reviewed journal	Yes	Yes	No- conference abstract	No- conference abstract
Inclusion of very young children	All children <5 years included	Children <2 month excluded	All children <5 years included	Children <1 month excluded
Ambulatory or hospitalized children	Hospitalized only	Ambulatory and hospitalized children	Ambulatory and Hospitalized children	Ambulatory and hospitalized children
X-ray diagnosis	WHO standardized radiological criteria	Description similar to WHO standardized radiological criteria	WHO standardized radiological criteria—quality control in ones site	WHO standardized radiological criteria with quality control
Coverage the public service	Public and private hospitals included in the study	~60%	~60%	~75%

Proportion of Disease Due to Streptococcus Pneumoniae

TABLE L.8 Proportion of pneumonia due to *S. pneumoniae* by age and by whether pneumonia was suspected or bacteriological confirmed

AGE GROUP	SYNDROME	TIME TO HIB VACCINE INTRODUCTION	NUMBER OF STUDIES	MEDIAN % 25th -75th percentile)
<5	Suspected	Pre introduction	5 [55,87-90]	6 (6-8)
	Bacteriologically confirmed	Pre introduction	5 [55,87-90]	23 (19-44)
All children	Suspected	Pre introduction	3 [27, 79, 91]	7(4-48)
	Suspected	Post introduction	3 [92-94]	11 (9-11)
	Bacteriologically confirmed	Pre introduction	3 [27,79,91]	41 (30-65)
	Bacteriologically confirmed	Post introduction	3 Pirez, 2001 #163][93,94]	94 (92-96)
Adults	Suspected	Post introduction	3[95-97]	5 (4-9)
	Bacteriologically confirmed	Post introduction	3 [95-97]	17 (13-19)

TABLE L.9: Proportion of bacteriologically confirmed pneumonia due to *Streptococcus pneumoniae* by country

COUNTRY	NUMBER OF STUDIES	MEDIAN % (25th-75th percentile)
Uruguay[55,79,87,88,92,93,94]	7	88 (52-92)
Argentina [95,90,97]	3	18 (12-31)
Chile[96]	1	21
Brazil [27,89]	2	32 (28-36)
Peru [91]	1	19

Antimicrobial resistance

TABLE L.10: Median percent of pneumococcal pneumonia isolates resistant and highly resistant to penicillin by country

COUNTRIES	NUMBER OF STUDIES	MEDIAN NUMBER OF ISOLATES PER STUDY (Min-Max)	MEDIAN % OF ISOLATES RESISTANT PER STUDY (25th-75th percentile)
Overall Penicillin Resistance			
Argentina[95,98-101]	5	107 (35-468)	35 (28-38)
Brazil[99,102-104]	4	304 (153-364)	23 (19-25)
Mexico[99,105,106]	3	220 (192-315)	50 (48-52)
Uruguay[92,94,99]	3	64 (51-205)	21 (6-42)
Chile[96,107]	2	51 (48-54)	12 (9-15)
Colombia[99,108]	2	274 (224-324)	16 (12-20)
Peru	1	85	0
All Countries Combined	**20**	**198 (35-468)**	**23 (14-39)**
High Penicillin Resistance			
Argentina[95,99-101]	4	269 (35-468)	14 (7-24
Brazil[99,103,104]	3	345 (153-354)	4 (2-7)
Mexico[99,105,106]	3	220 (192-315)	22 (21-23)
Uruguay[92,94,99]	3	64 (51-205)	10 (0-18)
Chile[96,107]	2	51 (48-54)	5 (5-6)
Colombia[99,108]	2	274 (224-324)	7 (3-11)
All Countries Combined	**17**	**245 (35-468)**	**9 (5-19)**
Resistant to Penicillin and at Least One Other Drug			
Argentina[95,100,98]	3	NA	3 (2-68)
Brazil[102]	1	NA	34
Uruguay[94]	1	NA	0
All Countries Combined	**5**	**NA**	**3 (2-35)**

NA — not available

ACUTE OTITIS MEDIA

Antimicrobial resistance

TABLE L.11: Median percent of Acute Otitis Media pneumococcal isolates resistant and highly resistant to penicillin by country

COUNTRIES	NUMBER OF STUDIES	MEDIAN NUMBER OF ISOLATES PER STUDY (Min-Max)	MEDIAN % OF ISOLATES RESISTANT PER STUDY (25^{th}-75^{th} percentile)
Overall Penicillin Resistance			
Argentina[109]	1	86	80
Brazil[110]	1	48	56
Costa Rica[111,112,113,114]	5 Arguedas-A	58 (38-197)	21 (19-23)
Chile[68,115]	2	125 (63-187)	38
Multicenter* [116,117]	2	144 (60-229)	40 (30-47)
All Countries Combined	**11**	**69 (38-229)**	**38 (23-41)**
High Penicillin Resistance			
Costa Rica[112-114]	3	58 (38-197)	3 (2-4)
Chile[68,115]	2	125 (63-187)	17 (16-17)
All Countries Combined	**5**	**63 (38-197)**	**8 (3-16)**

*Includes data from 7 countries

SUMMARIZED ANTIMICROBIAL DATA

TABLE L.12: Median percentage of pneumococcal isolates resistant or highly resistant to penicillin by time and syndrome

RANGE OF YEARS DURING WHICH ALL OR PART OF DATA COLLECTION TOOK PLACE		MEDIAN (Min-Max)	NUMBER OF STUDIES
Penicillin Resistance	**All Pneumococcal Disease**		
Overall Resistance	1985-1990	23 (2-64)	8
	1991-1995	30 (0-83)	46
	1996-2001	24 (6-81)	43
High Resistance	1985-1990	2 (2-3)	2
	1991-1995	12 (0-30)	34
	1996-2001	7 (0-42)	29
	Invasive infections		
Overall Resistance	1985-1990	24 (9-64)	4
	1991-1995	31 (0-83)	26
	1996-2001	24 (0-87)	29
High Resistance	1985-1990	2 (2-3)	2
	1991-1995	11 (0-22)	20
	1996-2001	7 (2-42)	16
	Pneumonia		
Overall Resistance	1985-1990	27	1
	1991-1995	35 (0-79)	13
	1996-2001	18 (6-28)	6
High Resistance	1991-1995	18 (2-30)	10
	1996-2001	6 (0-10)	6
	Meningitis		
Overall Resistance	1985-1990	2	1
	1991-1995	22 (15-36)	4
High Resistance	1991-1995	6 (0-11)	2

TABLE L.13: Median percentage of pneumococcal isolates resistant or highly resistant to penicillin by time and country

		OVERALL RESISTANCE		HIGH RESISTANCE	
	COUNTRIES	MEDIAN (Min-Max) %	NUMBER OF STUDIES	MEDIAN (Min-Max) %	NUMBER OF STUDIES
Argentina	91-95	32 (3-79)	10	18 (5-19)	7
	96-01	28 (16-39)	6	7 (2-21)	5
Brazil	85-90	27	1		
	91-95	21 (15-36)	10	1 (0-4)	9
	96-01	23 (11-42)	14	3 (2-8)	10
Chile	85-90	25 (23-26)	2	2 (2-3)	2
	91-95	33 (0-71)	4	12 (0-16)	4
	96-01	30 (9-38)	7	11 (4,6-27)	6
Colombia	91-95	20 (12-40)	3	11 (10-13)	3
Mexico	91-95	48 (29-52)	7	21 (11-23)	7
	96-01	42 (41-43)	2	23	1
Uruguay	85-90	33 (3-64)	2		
	91-95	64 (31-83)	5	16 (14-18)	2
	96-01	51 (6-81)	4	5 (0-10)	2
Peru	91-95	0	1		
	96-01	21 (15-27)	2	13	1

APPENDIX M ECONOMIC LITERATURE

Cost of Illness Studies

Out of ten economic studies identified from a search of publications from 1990-2005, eight COI studies that addressed pneumococcal-related diseases were undertaken in the Latin American region. Four of these studies were published as full articles: Brazil,[118] Mexico,[119] Uruguay,[120] and Colombia[121]. One study in Argentina was published only as an abstract [122] and there were two official reports published by the MoH in Chile[123] and by the National Institute of Public Health in Mexico[124]. An additional study was undertaken in Brazil, Chile and Uruguay[125].

Four of the COI studies identified in this review used the prevalence approach to "cost of illness" analysis[118,120,125,124]. The only study that used the incidence approach was the one published by [123]. In some of these studies it was not possible to identify the study approach[118,122,121].

Two of the COI studies focused only on direct medical costs [119,118]. Both of these studies estimated the total direct medical costs attributable to pneumonia: one from Brazil[118], and another from Mexico[119]. However, their focus was very different. The first study evaluated the direct costs per case management of pneumonia episodes, whereas the latter two studies evaluated the annual costs of managing pneumonia. In all studies except for [118] the base year for which costs were estimated is known.

The authors from Brazil [118] estimated the direct costs of pneumonia at approximately US$1,056 per case management per episode (base year of cost unknown). The average case management per episode included a first time medical visit and follow-up visits, five days of hospitalization, laboratory and diagnostic studies. The authors concluded that human resources (44%) incurred the majority of the costs. It was unclear what items under this category were the true cost drivers.

The study by Arredondo 119 estimated the cost of pneumonia in Mexican children. Public and private sector treatment costs ranged from N$546 - N$1,755 and N$ 3,419 -N$3,500 respectively (in 1994 Mexican pesos).

Indirect costs are generally related to loss of productivity that can arise from reduced productivity of working parents of children who have pneumococcal disease. Commonly, this important component is omitted in the calculation of morbidity costs because it is more difficult to calculate than production losses. Several authors included direct non-medical costs or indirect costs it in their evaluations [120,123,121,122, 124,125]. Three of the 8 studies in this review did not estimate the indirect costs because of difficulties in measuring and valuing them.

The order of magnitude of the direct costs for the studies varied widely. Some differences may be accounted for by differences in setting and variables that were considered such as AOM, pneumonia, and sinusitis. It is possible that by including a greater diversity of data sets, the average cost of pneumococcal diseases was reduced due to larger cost discrepancies. Alternatively, the difference could be attributable to the exclusion of all direct non-medical costs and possible exclusion of important direct medical costs.

TABLE M1: Summary of cost of illness studies

REFERENCE (country of analysis)	PERIOD ANALYSIS	STUDY TYPE (economic evaluation)	PERSPECTIVE	POPULATION	COST ELEMENTS	OUTCOMES MEASURED	RESULTS
Arrendondo et al., 1995 (Brazil) [118]	Not known	Cost of illness	Health service perspective	Children < 5 years	Direct medical costs	Direct costs	Pneumonia at US$1,056 per episode. Human resources (44%) incurred the majority of the costs. It was unclear what items under this category were the true cost drivers. Surgical procedures represented 5% of the costs, laboratory and diagnostic studies with 4% and drugs with 1% of the total costs of pneumonia.
Arredondo, 1995 (Mexico) [119]	1994	Cost of illness	Health service perspective	Not Known	Costs of inpatient care	Direct medical costs	Cost of pneumonia. Public sector M$ 546 to M$1,755 (Mexican peso); private sector M$ 3,419 to M$ 3,500; and bank insurance at M$2,720 to M$ 5,200 exchange rate: M$3.20 = US$1.00 (year 1994).
CVI & INSP, (Mexico)[124]	1999	Cost of illness	Societal perspective	Children 0-5 years with pneumonia, diarrhea, meningitis (n = 1,134)	Direct and indirect costs	Direct and indirect costs	Costs of pneumonia by health care settings and level of care similar to the cost of diarrhea (estimate not reported). However, higher costs are incurred in the ambulatory-urban setting with respect to the rural setting (US $60 per event [rural setting] versus US$70-US$105 [urban setting]). A significant difference is observed between hospital costs of the private and public sectors tertiary level) (estimate not reported). Cost of meningitis (US$4,476 per event), transport costs (US$44 per event), productivity loss (US$176 per event).
Concha-Barrientos et al., 1999 (Chile)[123]	1998	Cost of illness	Societal perspective	Birth cohort < 5 years, elderly (105,340)	Inpatient and outpatient care costs and indirect	DALYs, direct medical costs	Total cost of ambulatory care for ALRI was $20,103 (in 1998 Chilean pesos). Seventy-three percent ($ 14,678) of the total cost of ambulatory care was attributable to direct medical costs and 27% ($5,426 in indirect costs). ALRI stood at number 12 in order of magnitude of costs incurred to the National Health Service in Chile.
Constenla, 2007 Brazil, Chile, Uruguay[125]	2004	Cost of illness	Societal perspective	Children < 5 years from Brazil, Chile and Uruguay	Direct costs, out-of-pocket expenses, productivity loss	Direct costs, parent costs	Pneumococcal meningitis generated up to US$5,435/child. The treatment costs of pneumococcal pneumonia were lower (US$372/child to US$3,483/child). Treatment of AOM cost between US$20/child and US$217/child. The societal cost rose up to US$3,572/child for pneumonia, US$5,589/child for meningitis, and US$250/child for AOM.
Guzmán et al., 2005 (Colombia)[121]	2001 - 2003	Cost of illness	Health service and parent perspective	128 cases of pneumonia (< 2 years)	Direct and out-of-pocket expenses	Direct medical and parents cost	Costs of pneumonia 611.50 USD (in 2002 prices) and viral pneumonia 472.20 USD (in 2002 prices).
López et al., 2001 (abstract) (Argentina) [122]	Not known	Cost of illness	Societal perspective	140 cases of meningitis and 14,553 of pneumonia (< 1 year)	Costs associated with the treatment of pneumococcal meningitis and pneumonia and with productivity loss	Direct and indirect costs; disability-adjusted life years (DALYs)	Estimated 909 DALYs, 907 YLLs by meningitis, and 5,460 YLLs by pneumonia. Pneumococcal associated diseases were estimated to cost $12,778,155 in direct medical costs, $6,416,201 in work-loss, $ 73,671,127 in YLLs and $10,520,943 in DALYs.

Economic evaluations of pneumococcal vaccination

A search of the economic literature from 1990 to 2005 identified only 2 full economic evaluations of pneumococcal vaccines. [126,127]Both of these papers are part of the emerging literature and are in the process of being published. Discussions with the author were conducted to confirm study methods and results.

One of the studies was undertaken in Chile [126] and the other study was undertaken in Brazil, Chile and Uruguay. [127] Both studies projected the economic impact of pneumococcal vaccination of healthy infants and young children less than 5 years of age. In terms of vaccine preparation, both studies evaluated the heptavalent pneumococcal conjugate vaccination program and compared it with standard care.

Both were modeling studies that incorporated a decision analysis approach. These studies were carried out prior to the implementation of an immunization program so it is understandable that most of them were modeling studies.

Moreover, both studies used a cost-effectiveness analysis (CEAs) approach and disability-adjusted life-year and cost per (healthy) life year saved (LYS) or gained (LYG) as their primary cost-effectiveness measures. Other cost-effectiveness measures used included cost per infections avoided or cases prevented, deaths prevented and ambulatory visits prevented. The review did not identify any other studies based on cost-utility analysis, cost-benefit analysis, cost consequences and cost analysis.

The first study estimated direct medical costs only.[126] The most common direct medical costs considered were hospitalization costs and vaccine administration costs (vaccine cost, syringe cost, administration cost and the cost associated with adverse reactions) and the costs of treatments (ambulatory and hospital treatment including cost of hospitalization per day and physician visits). One study considered both direct and indirect costs.[125] The most common indirect costs considered were productivity losses associated with the disease as loss of income due to working days of parents of sick children, and lost of future earnings for children who died of pneumococcal diseases. This paper also estimated direct medical and non-medical costs125. The most common direct non-medical cost considered was mortality costs, long-term morbidity costs, and disability costs or costs of sequelae. Disability costs considered the different types of care used (institutionalization, consultation, home care, specialized education centers). Other direct non-medical costs included the costs of transportation to the hospital, and the cost of dying.

The period of analysis (or analytic horizon) was clearly stated in both cost-effectiveness studies. and extended up to 5 years for a pneumococcal conjugate vaccination program. Parameter estimates used in the studies were generally based on the medical literature and best-judgment estimates by experts in the field and, and as such, resulted in a degree of uncertainty. Sensitivity analysis was conducted in both studies to account for this uncertainty. By varying study estimates or by varying two or more estimates simultaneously, sensitivity analysis was used to determine the effects of changes in parameter estimates on decision results.

The second paper paper pneumococcal vaccination at the rate of DPT vaccine coverage was projected to prevent 2,111 deaths per year (46%) in children < 5 years; averting 70,442 (discounted) DALYs yearly. [127] At a vaccine cost of US$7.50 per dose, vaccination would have a net cost of US$33.4 million, a cost of US$1,003 per DALY averted. If the price of the vaccine was reduced between US$1.50 and US$3.70 per dose, pneumococcal vaccine was projected to substantially reduce childhood mortality and offset the costs of treatment in these Latin American countries.

The 2006 paper by Constenla and Valenzuela[126] estimated that the pneumococcal conjugate vaccine would result in an annual US$17.1 million (17%) reduction in direct medical costs. If indirect costs were included, the costs would be reduced by 12% (or US$20.2 million yearly). From the health service perspective, vaccination would result in US$8.951 per DALY and US$306.455 per death averted. From the societal perspective, vaccination would result in US$8.554 per DALYs.

Several variables were found to have a determining influence upon the results of the cost-effectiveness and cost-savings studies. Evaluations were relatively sensitive to variations in the following factors: incidence of pneumococcal disease, case-fatality rate, age of vaccinated group, treatment cost of pneumococcal disease, hospital admission rates, number of vaccine doses needed, vaccination costs, discount rate, inclusion of indirect costs, study perspective, and vaccine efficacy and effectiveness.

Factors that produced more favorable cost-effectiveness ratios included increasing case-fatality, older or younger age, high incidence of pneumococcal pneumonia, low vaccination costs, inclusion of indirect costs. Factors for less favorable cost-effectiveness outcomes included low incidence of pneumococcal pneumonia, low treatment costs of pneumococcal pneumonia, and low vaccine effectiveness.

TABLE M.2: Summary of economic evaluations

REFERENCE (country of analysis)	PERIOD ANALYSIS	STUDY TYPE (economic evaluation)	PERSPECTIVE	POPULATION	COST ELEMENTS	OUTCOMES MEASURED	RESULTS
Constenla and Valenzuela 2006[126]	2004 - 2005	Cost - effectiveness analysis	Health service perspectiva	238,000 birth cohort (< 5 years)	Costs of treatment of pneumococcal disease and cost of vaccination program	DALYs, deaths averted, life years saved, hospitalizations averted, outpatient visits averted	Saving from vaccine estimated at US$16.9 million. The relations cost effectiveness was US$8.5951 per DALYs and US$306.455 per death avoided. The vaccine is cost effectiveness when price of vaccine is reduced.
Constenla, 2007 Brazil, Chile, Uruguay[127]	2005	Cost - effectiveness of a pneumococcal conjugate vaccination program		554.372 ambulatory visits, 95,175 hospitalizations. Under five years	Cost - effectiveness of a pneumococcal conjugate vaccination program. Costs of meningitis, pneumonia and otitis media.	Healthcare System and social Costs. DALYs	The total cost of treatment in the three countries was US$116.5 millions for every birth cohort. For Brazil and Uruguay the vaccination program will be considered very cost- effective at a reduced cost; the cost per DALY averted in Brazil was US$1,221 and Uruguay 1,373. In Chile is considered cost-effective.

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