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

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Centers for Disease Control and Prevention (CDC), Atlanta, GA

Prepared by:

Dagna Constenla, Elizabeth Gomez, Fernando Pio de la Hoz, Rosalyn O'Loughlin, Anushua Sinha, Juan E. Valencia, and Maria Teresa Valenzuela

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PARTICIPANTS

Epidemiology core team	
Maria Teresa Valenzuela, MD MPH	(Team leader)**,** Profesor, Departamento de Salud Pública y Epidemiología Universidad de los Andes, Facultad de Medicina, Santiago, Chile
Elizabeth Gomez, MD MPH	Directora, Dirección General de Epidemiología, Secretaria de Estado de Salud Publica, Santo Domingo, Republica Dominicana
Fernando Pio de la Hoz MD MPH PhD	Professor, Universidad Nacional de Colombia-Facultad de Medicina, Bogota, Colombia
Rosalyn O'Loughlin, PhD	Epidemiologist, Respiratory Diseases Branch, National Center for Immunizations and Respiratory Diseases CDC, Atlanta, GA, USA
Economic core team	
Dagna Constenla, PhD MPA	Health Economist, Technical Adviser, Denver, CO, USA
Anushua Sinha, MD MPH	Assistant Professor of Preventive Medicine and Community Health, New Jersey Medical School – UMDNJ, Newark, NJ, USA
Juan E. Valencia, MD	Health Economist, Profesor Asociado, Dirección de Extensión, Universidad CES, Medellín, Colombia.
Technical advisory group	
Dr. Ciro de Quadros	President and CEO, Director of International Programs, Sabin Vaccine Institute, Washington DC, USA
Dr. Jon Andrus	Chief, Immunizations Unit, Pan American Health Organization, Washington DC, USA
Dr. Lucia Helena de Oliveria	Regional Advisor, Immunizations, Pan American Health Organization, Washington DC, USA
Dr. Orin Levine	Executive Director, GAVI's PneumoADIP, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
Farzana Muhib	Research Project Coordinator, GAVI's PneumoADIP, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
Dr. Cynthia Whitney	Medical epidemiologist, Respiratory Diseases Branch, National Center for Immunizations and Respiratory Diseases, CDC, Atlanta, GA, USA
Dr.Brendan Flannery	Epidemiologist, Respiratory Diseases Branch, National Center for Immunizations and Respiratory Diseases, CDC, Atlanta, GA, USA
Logistical support	
Ana Carvalho	Program Manager, International Programs, Sabin Vaccine Institute, Washington DC, USA

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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 SP 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 SP. 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 46 pneumococcal researchers known to us in 13 countries and received 36 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 throughout 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.
- 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.

- 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 introcuction 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 SP 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.

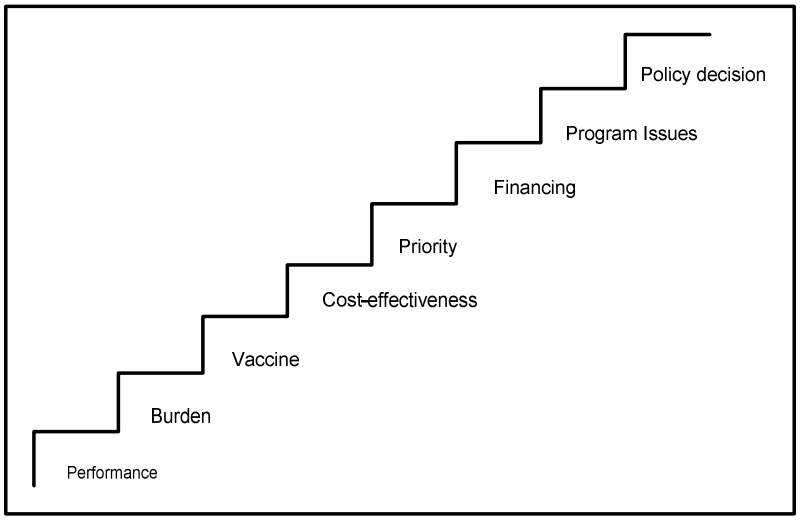

Figure 1: An aid to decision making: WHO Vaccine Introduction Guidelines

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. The first 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 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.

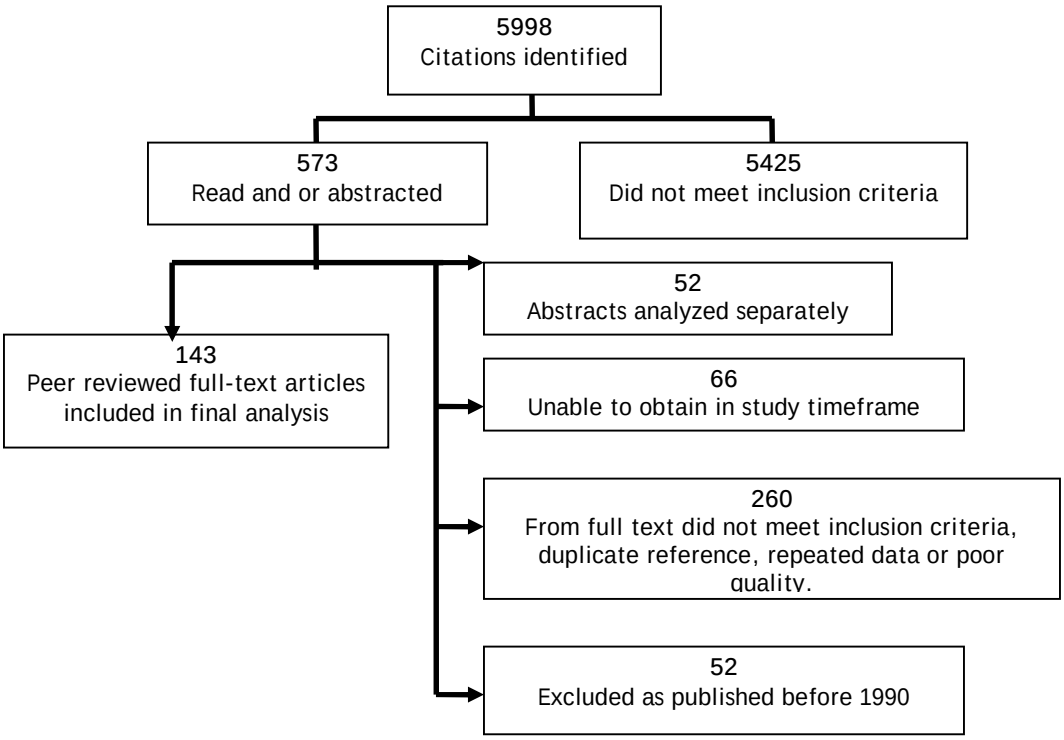

Figure 2: Flow diagram for the process of identifying and including references for the systematic review

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[1]	-	-	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.

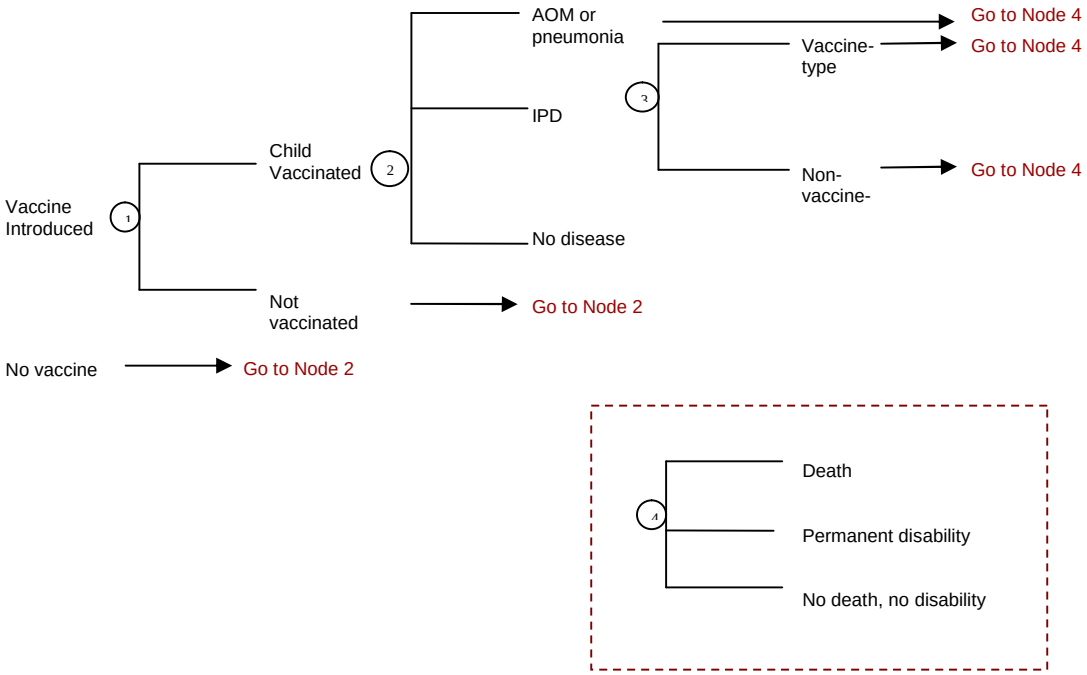

Figure 3: Schematic diagram of the model

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 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 (e.g., diagnostic tests, medication, supplies, facilities, and personnel) in formal inpatient and outpatient settings, direct medical costs due to family out-of-pocket costs (e.g., transportation costs to and from the medical facility), and direct non-

[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.

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* (25^{th} -75^{th} percentile)	Number of cases of IPD in all studies combined (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	I	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	I	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	Median CFR of IPD* (25^{th}-75^{th} percentile)	# 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 (25^{th} -75^{th} percentile)			**Median % vaccine coverage including cross-reactive serotypes (25^{th} -75^{th} 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 (25th-75th 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	Median CFR* (25^{th}-75^{th} percentile)	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 (25^{th} -75^{th} 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] Colombia [111 112] Mexico [90] DR [78] Peru [38]
All children	14	16 (14-19)	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 (25^{th} -75^{th} percentile)			Median % vaccine coverage including cross-reactive serotypes (25^{th} -75^{th} 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 (25th-75th 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 (2163/100,000 and 2328/100,000 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)	Number of studies	Median incidence of pneumonia** (25^{th} -75^{th} percentile)	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	4363	1361	Uruguay[124]
<5 years		2	3059 (2957-3142)	2052 (18-2034)	Brazil [126] Uruguay[124]
All ages		1	1274 (1163-1389)	158,670	Brazil [125]
X-ray confirmed pneumonia with consolidation (from peer reviewed literature)					
<1 year		2	2163 (1963-2364)	1268 (253-1015)	Argentina[32], Uruguay[124]
<2 years		2	2132 (1986-2277)	2631 (519-2112)	Argentina [32], Uruguay [124]
<5 years		1	1174	826	Uruguay[124]
X-ray confirmed pneumonia with consolidation (from non-peer reviewed literature)					
<1 year		2	2328 (1998-2657)	531 (240-291)	Chile[127] Argentina[128]
<2 years		2	1864 (1617-2116)	916 (439-477)	Chile[127] Argentina[128]
<3 years		1	2052	606	Chile[127]
<5 years		1	785	745 (328-417)	Argentina[128]
Confirmed pneumococcal pneumonia* **					
<2 years	I	2	51.1 (47.1-55.1)	350 (51-299)	Argentina [32], Chile [58]
	O	1	36.0	31	Argentina [32]
<5 years	I	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* (25^{th}-75^{th} percentile)	Total number of cases in all studies combined (min-max)	Countries
Clinical pneumonia				
<1 year	1	3.0	536	Brazil [130]
<5 years	3	3.0 (1.9-5.5)	2476 (541-1210)	Guatemala [80] Peru [38] Uruguay [131]
All children	3	0.4 (0.2-0.8)	3435 (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)	1949 (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* (25^{th} -75^{th} percentile)	Country
<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)	Argentina[134 149] Chile[135]

*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 (25^{th} -75^{th} percentile)			Median % vaccine coverage including cross reactive serotypes (25^{th} -75^{th} 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 per study* (Min-Max)**	**Median % of isolates resistant 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	1214 (1125-1349)
1-4 years	1095 (981-1197)
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 per 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 (25^{th} -75^{th} percentile)			**Median % vaccine coverage including cross reactive serotypes (25^{th} -75^{th} 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 per study (25th-75th 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.

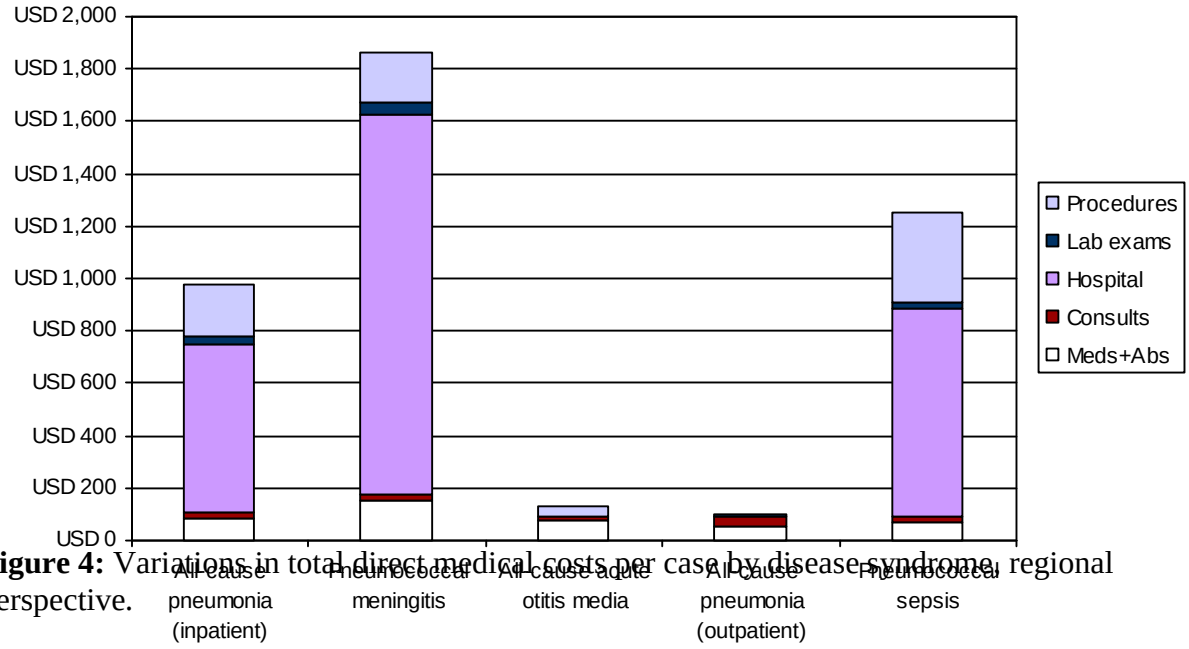

Figure 4: Variations in total direct medical costs per case by disease syndrome, regional perspective.

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.

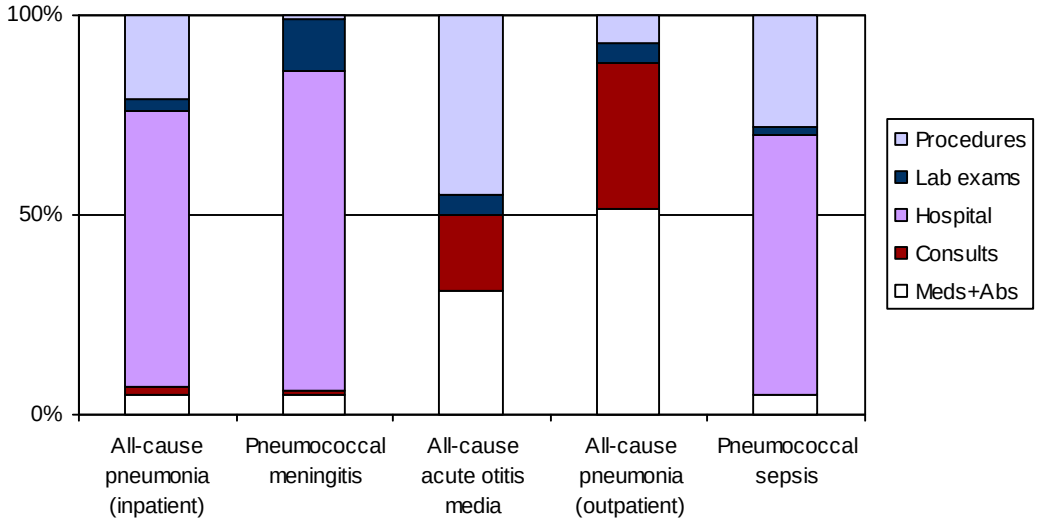

Figure 5: Variations in structure of direct medical costs by disease, regional perspective

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 defined[a]	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.

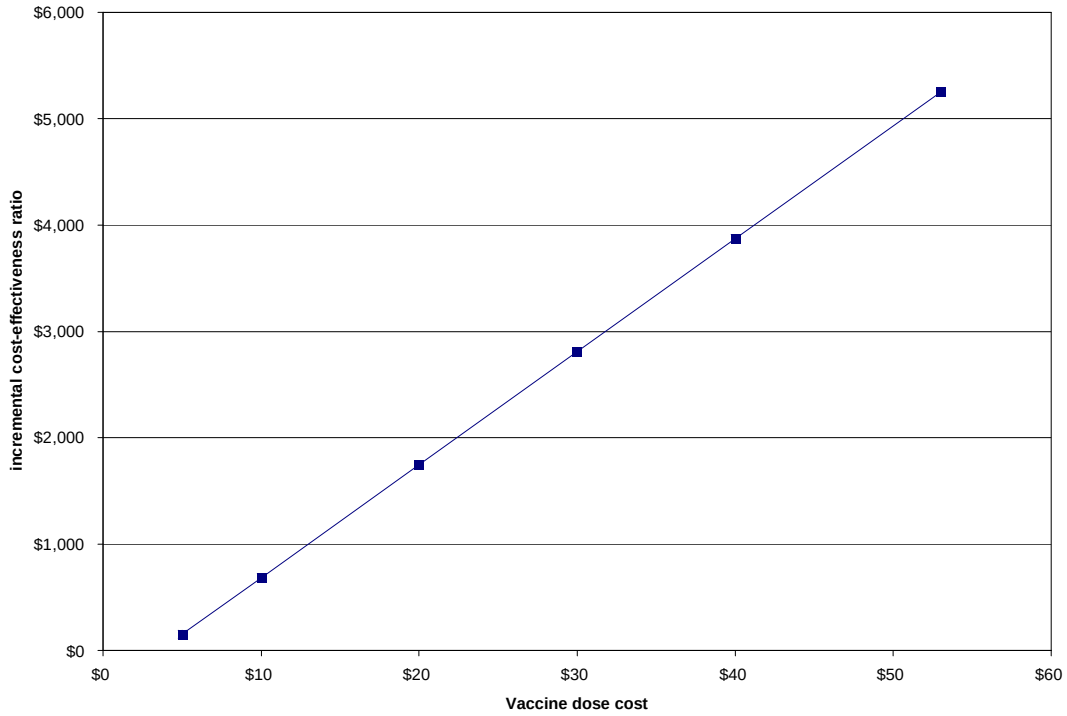

Figure 6: Effect of vaccine dose cost on cost-effectiveness of pneumococcal conjugate

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 million 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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