January | 2017

The Evidence Base for Pneumococcal Conjugate Vaccines (PCVs):

Data for decision-making around PCV use in childhood

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Purpose and overview

The pneumococcal evidence base (EB) was developed as a reference document by Johns Hopkins' International Vaccine Access Center (IVAC) to facilitate access to and interpretation of the latest information around pneumococcal conjugate vaccines (PCV) relevant to vaccine use in routine immunization programs worldwide. National Immunization Technical Advisory Group (NITAG) members, Expanded Program on Immunization (EPI) staff, other vaccine decision-makers, international health communications and research professionals are the primary audiences for this document. The goal has been to put forth a document that may assist these groups in synthesizing the available evidence needed to formulate decisions regarding introduction or optimal use of pneumococcal conjugate vaccine (PCV) in multiple settings. The EB document was developed by IVAC in 2015 and 2016 to serve as a comprehensive resource of the highest quality information about PCVs and pneumococcal disease as is currently available. This document has been carefully vetted by a number of international pneumococcal and vaccine experts. Semi-annual updates to this document are planned beginning in mid-2017.

Important notes about this document

- Look for key messages **in black bold text** throughout the document. These points summarize the available evidence (or evidence gaps) in each chapter and subsection. The key messages from all chapters are compiled in pages 16-21 of this document.

- This draft of the EB incorporates literature search results through **December 2015**. Please see Appendix B, *Literature Search Methodology,* for an explanation of how references informing this document were compiled.

- Blue highlight boxes throughout the report indicate content areas where new evidence is expected to be available in 2017.

- Please see ***Appendix A*** for a list of resources that may be especially useful to members of NITAGs and other technical bodies.

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IVAC International Vaccine Access Center

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List of Abbreviations and Acronyms

AEFI – Adverse event following immunization
AFRO –WHO regional office for Africa
AMC – Advanced market commitment
AMRO – WHO regional office for the Americas
CAP—Community-acquired pneumonia
CBA—Cost-benefit analysis
CCR—Case:carrier ratio
CEA – Cost-effectiveness analysis
CFR—Case fatality rate
CHERG—Child Health Epidemiology Reference Group
CI – Confidence interval
CMA—Cost-minimization analysis
CP—Consolidated pneumonia
CSF – Cerebrospinal fluid
CUA—Cost-utility analysis
DALY – Disability-adjusted life year
DHS—Demographic Health Survey
DTP – Diphtheria, tetanus and pertussis vaccine
EMRO – WHO regional office for the Eastern Mediterranean
EPI—Expanded programme on immunization
EURO – WHO regional office for Europe
GAPPD – The integrated Global Action Plan for Pneumonia and Diarrhoea
Gavi – Gavi, the Vaccine Alliance
GDB – Global burden of disease study
GDP – Gross domestic product
GMC – Geometric mean concentration
GNI – Gross national income
GVAP—Global Vaccine Action Plan
HAART—Highly active antiretroviral therapy
HEU—HIV-exposed but uninfected
HUU—HIV-unexposed and uninfected
Hib- *Haemophilus influenzae* type b
IB-VPD—Invasive bacterial vaccine preventable disease
ICER – Incremental cost-effectiveness ratio
ICT—Immunochromatographic test
IFFIm – International finance facility for immunization
IgG –Immunoglobulin G
IHME—Institute of Health Metrics and Evaluation
IMCI—Integrated management of childhood illness
IPD – Invasive pneumococcal disease
ISPPD—International Symposium on Pneumococci and Pneumococcal Diseases
ITT—Intention to treat
IVAC – International Vaccine Access Center
IQR—Interquartile range
LMIC—Low- and middle-income countries

LYG—Life years gained
MCEE—Maternal Child Epidemiology Estimation group
MDG—Millennium development goal
MIC—Middle income country
MICS—Multiple indicator cluster survey
NITAG –National immunization technical advisory group
NP – Nasopharyngeal
NTHi—Non-typeable *Haemophilus influenzae*
NVT – Non-vaccine serotype
PAHO – Pan-American Health Organization
PCV – Pneumococcal conjugate vaccine
PCV7 – 7-valent pneumococcal conjugate vaccine
PCV10 – 10-valent pneumococcal conjugate vaccine
PCV13 – 13-valent pneumococcal conjugate vaccine
PIE – Post-introduction evaluation
PPV – Pneumococcal polysaccharide vaccine
QA – Quality assurance
QALY- Quality-adjusted life year
QC – Quality control
RCT—Randomized controlled trial
RED – Reach every district
ROI—Return on investment
SAARC—South Asian Association for Regional Cooperation
SAGE – Strategic Advisory Group of Experts
SD – Standard deviation
SDG—Sustainable development goal
SEARO – WHO regional office for South-East Asia
TIV—Trivalent inactivated influenza vaccine
TPP—Target product profile
U5—Under five years of age
U5MR—Under five mortality rate
UK—United Kingdom
UNICEF – United Nations International Children's Emergency Fund
US—United States of America
VAR—Vaccine attributable reduction
VE—Vaccine efficacy
VIMS – Vaccine Information Management System
VPDI—Vaccine preventable disease incidence
VT- Vaccine serotype
VT-IPD – Vaccine serotype invasive pneumococcal disease
VVM – Vaccine vial monitor
WHO – World Health Organization
WPRO – WHO regional office for the Western Pacific

Executive Summary

Burden of Pneumococcal Disease in Children

Streptococcus pneumoniae, or pneumococcus, is a gram positive diplococcus that is adapted to colonize the human nasopharynx. The bacterium has a polysaccharide capsule that helps protect it from host defenses in the absence of capsule-specific antibodies. The development of type-specific immunity helps define the over 93 different serotypes of pneumococcus. Pneumococcal nasopharyngeal (NP) colonization is relatively prevalent among children during the first few years of life and declines with age. NP colonization is a necessary precursor for pneumococcal disease in children and adults. Pneumococcus can spread from the nasopharynx by contiguous extension to cause infection in the middle ear (otitis media), or respiratory tract. Pneumococcus can also invade the bloodstream and spread to other sites in the host causing secondary, more distal infection such as meningitis, bacteremic pneumonia, or sepsis.

In 2008, the WHO estimated that more than half a million children under the age of 5 years (U5) worldwide died of pneumococcal disease, including pneumococcal pneumonia, meningitis, and other clinical manifestations of serious pneumococcal infections. Pneumococcal mortality is a significant contributor to the under 5 mortality rate worldwide. Nine percent of all deaths in children aged 1-59 months were estimated to be attributable to pneumococcus in 2008. Since that time, dozens of high-burden countries worldwide have incorporated PCVs into routine immunization programmes. (See Chapter 4 for more information on the impact of PCVs.)

Pneumonia, the most common form of serious pneumococcal disease, is the leading infectious killer of children worldwide. Pneumococcus contributes disproportionately to severe pneumonia and pneumonia mortality. Based on the vaccine probe approach, it is estimated that pneumococcus is responsible for over one-quarter (27%) to one-third (36%) of all pneumonia deaths in children U5. In 2008, the WHO estimated that 485,000 deaths (uncertainty range 354,000 to 526,000) were due to pneumococcal pneumonia in children U5.[1]

There were an estimated 120 million episodes of pneumonia in children in 2010, about 12% of which progressed to severe disease, defined as pneumonia cases requiring hospital admission. About 6% to 8% of all clinical pneumonia and 21% of severe pneumonia in children U5 is attributable to pneumococcus. For radiologically-confirmed pneumonia, a diagnosis more specific for bacterial etiology, an estimated 27% to 36% is caused by pneumococcus.

Pneumococcal meningitis is associated with a high risk of death and serious neurological sequelae in low-income, resource-poor settings. Based on 2008 estimates, meningitis accounted for about 7%, or 1 in 14, of all deaths due to pneumococcal disease in children U5.

The highest burden of serious pneumococcal disease occurs in young infants and the elderly. The childhood peak of invasive pneumococcal disease (IPD) incidence occurs earlier in developing countries compared to developed countries. Twenty percent of IPD cases in young children is found to occur in infants less than six months of age, and 50% in those under 12 months. The peak of pneumococcal meningitis is earlier than for other types of IPD, with 40% of those U5 cases occurring in infants less than six month of age, and 65% in infants under 12 months. The peak age for childhood pneumonia is slightly older and more variable by setting compared to that of IPD and meningitis.

In a systematic review of data on serotypes causing IPD in children U5, prior to the introduction of PCV, six to 11 pneumococcal serotypes accounted for over 70% of IPD. Serotype distributions vary by

[1] *New estimates of the global and regional burden of pneumococcal disease are expected in 2017.*

syndrome, disease severity and carriage prevalence. These serotype-specific factors interplay with host-specific factors, such as age and comorbidity, and put populations at risk for disease.

Pneumococcus is difficult to detect in the laboratory; newer diagnostic tests with enhanced sensitivity for detecting pneumococcus add to our understanding of the burden of disease. Laboratory surveillance for pneumococcal disease lacks sensitivity both because of the laboratory techniques available, and because not all pneumococcal disease has pneumococci present in the body fluids that are most readily accessible for testing (i.e. blood). The best tool available for determining the burden of pneumococcal disease are the PCV trials which when analyzed as a vaccine probe study, reveal the vaccine preventable disease rate from which inferences can be drawn about the total pneumococcal disease rate.

Some host-specific and socioeconomic factors put certain groups at higher risk of pneumococcal disease. HIV infection increases the risk and severity of pneumococcal disease in children. The routine use of highly active antiretroviral therapy (HAART) reduces but does not negate this risk. HIV exposure (i.e. children born to HIV infected mothers, but themselves uninfected) also confers an increased risk of pneumococcal disease. There is evidence indicating a synergistic interaction between pneumococcus and other respiratory pathogens, such as influenza, that increase individual susceptibility to upper and lower respiratory tract disease. Sickle cell disease, and the resulting functional asplenia, is another significant individual risk factor for pneumococcal disease. Other host factors associated with greater risk of pneumococcal infections include chronic lung infections, some hematologic malignancies, protein energy malnutrition, and other micronutrient deficiencies. Environmentally, crowded living conditions and chronic inhalation of smoke are risk factors. Finally, some ethnic minorities have higher rates of IPD compared to the general population, such as American Indians, Native Alaskans and Australian Aboriginals.

Interventions to Prevent and Control Pneumococcal Disease

Millennium Development Goal (MDG) 4 was to reduce the under-five mortality rate by two thirds between 1990 and 2015. While progress has been made and U5 mortality decreased 53% globally from 91 deaths per 1,000 live births in 1990 to 43 deaths in 2015, efforts need to be continued to maintain and accelerate the gains achieved.(2) In 2015, the United Nations adopted 17 Sustainable Development Goals (SDGs) to articulate and measure continued progress in human and environmental conditions. SDG 3 is to “ensure healthy lives and promote wellbeing for all at all ages”, and one SDG 3 target is to “end preventable deaths of newborns and children under 5 years age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 23 per 1,000 live births” by 2030. Progress towards SDG 3 thus needs to include strategies to reduce the incidence and mortality of pneumonia, the leading cause of death in children U5.

Strategies to prevent children from getting pneumonia include exclusive breastfeeding promotion and support, universal coverage of immunization, HIV prevention and healthy environments that reduce exposure to indoor air pollution. Children who are ill from pneumonia should be treated appropriately; this includes appropriate care seeking (i.e. ability of caregivers to recognize serious symptoms, seek care and have appropriate care available) and antibiotic treatment.

Proven strategies to reduce the burden of pneumonia are not equitably implemented between or within countries, putting children at continued risk for significant morbidity and mortality. In 2013, an estimated 59% of children with suspected pneumonia were taken to a healthcare provider based on a subset of 78 countries with available data from national surveys, Multiple Indicator Cluster Surveys (MICS) or Demographic Health Surveys (DHS), and this proportion was 49% in the least developed

countries. The disparity between the proportion of children receiving care in the least developed countries and the global estimate is likely underestimated because data is not included from many high-income countries. There is also much variation between countries and within countries in the proportion of children with pneumonia who receive antibiotic treatment. Regional average estimates of children with pneumonia symptoms receiving antibiotic treatment range from 25% in South Asia to 62% in the Middle East and North Africa based on data from 104 countries for 2009-2013.

Access to PCVs is a key strategy in the comprehensive approach to childhood pneumonia reduction. Prevention of disease through vaccination is more likely to accelerate the goals of equity than is the effort to expand access to appropriate treatment of disease, as important as those efforts are. As the WHO 2012 position paper states: "WHO recommends the inclusion of PCVs in childhood immunization programmes worldwide. In particular, countries with high childhood mortality (i.e. under 5 mortality rate of >50 deaths/1000 live births) should make the introduction of these multicomponent PCVs a high priority." In all countries, but particularly in those countries with many pneumonia and U5 deaths, preventing pneumococcal disease in the first place is more advantageous from an ethical and societal perspective than aiming to treat children once they fall ill.

Pneumococcal Conjugate Vaccine Safety and Efficacy

Licensed in 2000, PCV7 has a well-established, favorable safety profile when administered to infants and young children. Several studies from various countries demonstrate that PCV10 and PCV13 have a similar safety profile as PCV7. PCV studies have specifically demonstrated safety in HIV-infected children, children with sickle cell disease, children with recurrent otitis media, and other immunocompromised subjects.

PCVs have been tested in RCTs in a variety of settings to determine the vaccine efficacy (VE) against various disease outcomes: IPD, pneumococcal (bacteremic) pneumonia, radiologically confirmed pneumonia, clinical pneumonia, and acute otitis media (AOM). PCVs have also been studied to determine their efficacy in reducing the non-disease outcome of NP carriage. Vaccine licensure of PCV10 and PCV13 pre-dated results from VE and effectiveness studies and was based on immunological studies proving non-inferiority to PCV7. More recently, RCTs using PCV10 have been conducted looking at the outcomes of IPD, pneumonia and AOM, including a study using a schedule of two primary doses and a booster dose (2p+1). PCV13 RCTs were based on immunogenicity, not clinical endpoints. In addition, there is a growing body of evidence of the post-licensure vaccine effectiveness of both PCV10 and PCV13 (see Chapter 4).

The magnitude of PCV efficacy varies based on the outcome studied. For outcomes more specifically attributable to vaccine serotype pneumococcus, efficacy estimates are higher than those that are nonspecific for pneumococcus. In a meta-analysis of RCTs in children less than two years of age, the pooled VE of PCV7, PCV9 and PCV11 for vaccine serotype IPD (VT-IPD) was 80% (95% CI: 58%, 90%) in HIV-1 negative children. Two more recent RCTs used PCV10 (GSK) and showed high VE for VT-IPD, ranging from 92% (95% CI: 58%, 100%) for a 2p+1 schedule to 100% for 3p+1 schedules.

Estimates from RCTs that assessed PCV efficacy against pneumonia are more varied than those against IPD because the case definitions for pneumonia are multiple and vary in their specificity for pneumococcus. For radiologically-confirmed pneumonia, two meta-analyses report PCV efficacy as 27% (95% CI 15%, 36%) and 36% (95% CI 16%, 51%). VE for clinical pneumonia is estimated between 6% and 9% based on the two meta-analyses and a Latin American RCT (the COMPAS trial).

RCTs were not powered to investigate U5 mortality following PCV use. Only one RCT, from The Gambia, found a statistically significant reduction in all-cause mortality of 16% over a two-year follow period, translating to 7 deaths prevented for every 1,000 children vaccinated. Further evidence is

needed from post-licensure studies to quantify the impact of PCV use on U5 mortality in different settings.

PCV7 has a modest beneficial effect on reducing AOM in healthy infants and a more notable benefit on reducing pneumococcal AOM. PCV use in high-risk infants, toddlers and in older children with a history of recurrent AOM does not appear to prevent further infections.

PCV has been demonstrated to be efficacious in reducing VT NP carriage when administered to infants as well as children U5. There is evidence that PCV administration reduces acquisition of VT pneumococci and density of carriage but does not enhance clearance of existing carriage. Based on eight RCTs, the magnitude of the efficacy for VT carriage was reported in one review as about 50%, with individual study estimates ranging from 26%-60%. The decrease in VT NP colonization is attenuated by an increase in NVT colonization. Reducing VT NP colonization could open a niche for the NP to be replaced proportionally by NVT pneumococci, a phenomenon known as serotype replacement. As a result, PCV has shown little to no effect on overall pneumococcal colonization prevalence.

There are limited data on the duration of protection following PCV administration. The natural history of pneumococcus, with declining NP colonization prevalence after the first few years of life, and the role of natural immune system boosting following exposure to circulating serotypes complicate the interpretation of long-term follow up studies comparing immunized and unimmunized children.

Pneumococcal Conjugate Vaccine Impact

The public health impact of PCV introduction in national immunization schedules has exceeded the expected reduction in VT disease based on vaccine efficacy studies. This is because efficacy studies measure direct outcomes in a controlled, idealized setting and in a relatively small group of vaccinated persons. In real-world use, with mass vaccination, the vaccine has direct effects on NP carriage and disease burden among those who are vaccinated, and this is referred to as the vaccine effectiveness. However, what cannot be measured in RCTs are the additional indirect effects of mass vaccination on unvaccinated persons, what is known as the herd effect or indirect protection. Following PCV introduction, groups that are not themselves vaccinated have experienced a change in pneumococcal disease epidemiology due to community-level changes in the pneumococcal serotypes circulating as young children are vaccinated. When PCV has been introduced into routine use, the observed impact on disease reduction has been greater than expected from efficacy trials because of the indirect effects of the vaccine.

As PCV is introduced in more countries, including more LMICs, where the epidemiology of pneumococcal disease and carriage may vary (generally with a higher burden of disease and carriage in younger infants), it will be important to continue to monitor and survey the population-level impact of higher valency vaccines. The impact of PCV will depend on the prevailing serotypes causing disease prior to vaccine introduction, the coverage of the vaccine in groups targeted for immunization, the presence and coverage of catch-up campaigns beyond infancy, population density, and the prevalence of other risk factors, such as HIV infection.

PCV7 quickly and significantly reduced the incidence of IPD among young children in countries where it was introduced either as a 3p+1 or 2p+1 schedule. These findings were mostly from high-income countries that were early adaptors of PCV7. A 2010 WHO review included data from South Africa as well as the US, UK, Australia and Canada and found “rapid, substantial reductions (in VT-IPD) in all settings.” PCV7 use also decreased the burden of antibiotic-resistant pneumococcal disease.

The effectiveness of PCV7 on overall (i.e. all serotype) IPD was reduced, in part, by an increase in NVT IPD in some settings; this was of variable magnitude and is termed serotype replacement. While

serotype replacement with nonvaccine serotypes has been near complete in carriage, only minimal serotype replacement in pneumococcal disease has occurred because of the lower invasiveness of the replacing serotypes. Many factors affect trends in the burden of pneumococcal serotypes over time of which PCV implementation is a major factor. In all settings the increase in NVT IPD has been outweighed by the significant reduction in VT disease.

Higher valency PCV formulations were developed in part to respond to the phenomenon of serotype replacement in disease by including invasive serotypes not in PCV7. Both PCV10 and PCV13 are showing good effectiveness against most of the additional, non-PCV7 vaccine serotypes contained therein. In settings where these additional vaccine serotypes were prevalent prior to PCV10 or PCV13 use—including serotype 19A that was emergent after PCV7 introduction—there has been further decreases in VT-IPD. Data from LMICs and high-income countries is amassing on the post-licensure impact of higher valency PCVs and strengthens the assertion that the vaccines are continuing to decrease IPD burden beyond what was achieved with PCV7.

VT-IPD among adults has gradually decreased in almost all countries after a few years following PCV introduction. This indirect effect has been observed for all routinely used infant schedules, for all licensed PCV products, and in populations with high HIV-infection burden. Replacement disease with NVT pneumococci has been of variable magnitude in adults resulting in a decrease, no change or an increase in overall IPD depending on setting. The magnitude of PCV's indirect effect depends on various factors: the immunization strategy—i.e. the use of catch-up vaccination to accelerate impact—vaccine coverage rate, the population composition and density, the prevalence of VT pneumococci carried in young children, and the prevalence of VT disease prior to introduction, and of course surveillance methods that may confound the observations. When coverage rates are high, the indirect impact is consistent, while lower coverage rates yield mixed indirect impact, with some effect demonstrated starting at 40% coverage.

PCVs have had a substantial effect on pneumonia disease burden: the newer generations, high valency PCVs have reduced hospitalizations for all-cause pneumonia by 13% to 72% (n=6 studies) and for consolidated pneumonia by 20% to 45% (n=3 studies) in children U5. The magnitude of the impact on pneumonia hospitalizations must be interpreted with great care as there are methodological issues that affect the quality and comparability of the data. Factors that play a role in interpreting pneumonia data include: the case definition and ascertainment methods used, the varied pneumonia etiologies in a setting and their background incidence, access to care and health seeking behaviors, time since PCV introduction, and vaccine coverage rate. There is a limited but growing body of data on the indirect effects of higher valency PCVs on the outcome of pneumonia.

Preventing NP acquisition of vaccine serotypes, PCV implementation results in a rapid, significant decrease in VT NP carriage prevalence in children. There is replacement carriage with non-vaccine serotypes, often resulting in no net overall change in all-serotype pneumococcal colonization. However, the replacing non-vaccine serotypes are, in many cases, not as invasive and thus less likely to cause disease. Therefore reductions in all-serotype pneumococcal disease are sustained even in the face of increases in NVT colonization. Data is emerging to corroborate the significant direct and indirect effect of PCV on NP carriage in LMIC settings. Direct and indirect PCV7 impact on NP colonization was demonstrated in South Africa just two years following vaccine introduction in a 2p+1 schedule without a catch up campaign. Data from Kilifi, Kenya also demonstrate a significant direct and indirect reduction in VT NP carriage two years after PCV10 introduction using a 3p+0 schedule and catch-up campaign.

There is very limited information on the impact of PCV on mortality. Few studies have been published and they vary in the age group(s) and the outcome under study. Two studies from middle income settings suggest a direct effect of PCV use on mortality rates in young children: one study reported on the overall infant mortality rate and the other on the pneumonia mortality rate. Data from

high income countries show a reduction in IPD-related mortality rates for the general population, mainly as a result of declining VT IPD incidence rates. More studies will be needed to clarify the association between PCV use and outcome-specific mortality rates in young children and the general population.

Economic Evaluation of PCV

Economic evaluation is the process by which the costs and benefits associated with health interventions are identified, measured or modeled, and valuated in order to compare their net impact and determine whether or not the benefits of a given intervention are worth the cost. Economic evaluations provide important information for policy makers assessing the value of vaccines in the setting of finite resources that need to be allocated for maximum health impact in a target population.

Increased coverage of new and underused vaccines in Gavi-eligible countries could have significant health and economic benefits. The return on investment of meeting vaccine coverage targets in 94 LMICs in the Decade of Vaccines 2011-2020 would result in 16 times greater net cost savings than costs incurred, compared to no vaccination, for ten diseases. The return on investment for pneumococcal disease and PCV use alone is estimated as 3.13: over three times greater net cost savings than costs incurred in 94 LMICs compared to no use of PCV. Universal and high coverage (90%) with PCV in Gavi-eligible countries could avert US$24 billion in costs—mostly from productivity gains--prevent 21 million disease cases, and save 1.5 million lives between 2011-2020.

There are several types of economic evaluations. Cost-effectiveness analysis (CEA) (also called cost-utility analysis (CUA)) is the most common type of economic evaluation, where the costs are expressed in monetary units and the health effects or outcomes are measured in natural units such as life years gained (LYG), disability-adjusted life years (DALYs) which measure a health loss, or quality-adjusted life years (QALYs) which measure a health gain. According to the guidelines recommended for individual countries by the WHO Commission on Macroeconomics and Health, an intervention with an incremental cost effectiveness ratio (ICER) that is less than the per capita gross domestic product (GDP) is considered “highly cost-effective,” and an intervention with an ICER that is less than three times the per capita GDP is considered “cost-effective.”

Major components of the CEA of PCV include estimating the economic burden of disease—the cost of illness—vaccine introduction and program costs, and vaccine effectiveness in the target population. Economic burden of disease can include direct medical and non-medical costs as well as indirect costs such as productivity losses. Cost of illness is specific to a disease syndrome (e.g., pneumonia, meningitis, etc.), the level of care obtained by the patient, and the perspective (e.g. societal, public health system, etc.) of the study.

Another important cost input in the CEA model is the cost of the vaccine and the vaccination program costs. This includes the purchase price of the vaccine (commodity price) and programmatic costs associated with vaccine delivery. Worldwide, vaccine program costs are increasing as new and more expensive vaccines are added to EPI schedules and as coverage rates increase to include hard-to-reach populations. Currently, in Gavi-eligible countries the total routine immunization costs are on average $26.72 (2010 USD) to fully immunize a child, with regional variation from $23.72 (SEARO/WPRO) to $65.43 (EUR). After vaccine cost, service delivery costs are the main driver of vaccine program costs and become increasingly important with higher tiers of economic development. High-quality data on some of the CEA model inputs may be lacking in low-income countries, and so a well-conducted CEA should include an analysis of the variability in outcome based on different input scenarios (sensitivity analysis).

There is a growing body of literature on the CEA of PCVs in a variety of settings. Studies differ on key input variables—such as cost of vaccine, estimated vaccine effectiveness, perspective and inclusion of indirect effects—thus making direct comparisons of their results difficult. One study

provides a CEA of PCV7, PCV10 and PCV13 using a 3p+0 schedule compared to no vaccine in Gavi-eligible countries and concludes that PCV10 and PCV13 would be cost effective for all 72 Gavi-eligible countries (ICER<3xGDP) and highly cost-effective for all but one country (ICER<GDP). This study accounts for indirect effects, herd immunity and serotype replacement, and takes a 10-year societal perspective. Taking into account both direct and indirect effects, the ICER was estimated as $146/DALY averted (2005 US$) for PCV7, $88/DALY averted for PCV10, and $77/DALY averted for PCV13. These ICERs vary greatly by countries' U5 mortality rate. Countries with a higher mortality rate would have a lower ICER: PCV use is more cost-effective in these settings.

A study of PCV cost-effectiveness in 77 middle-income countries found PCV7 to be cost-effective for 72 countries, and PCV10 and PCV13 to be cost-effective for all countries compared to no vaccine. PCV7 would be highly cost-effective (ICER<GDP) for 53 middle-income countries, PCV10 for 68 countries and PCV13 for 71 countries. The study modeled direct and indirect effects of PCV7, PCV10 and PCV13 used in a 3p+0 schedule with a vaccine cost of $10 for lower middle-income countries and $20 for upper middle-income countries. The overall ICER was US$ 1600/DALY averted for PCV7, $1000/DALY averted for PCV10, and $900/DALY averted for PCV13.

Limitations of the economic evaluation of PCV10 vs. PCV13 are important to consider. There have been no head-to-head clinical comparisons between PCV10 and PCV13 within a single trial, so vaccine effectiveness is often assumed based on their head-to-head comparison with PCV7 or their sequential implementation in observational studies, and sometimes adjusted for serotype distribution. The indirect effects of PCV use are an influential parameter in sensitivity analyses, but many studies do not account for herd effects or serotype replacement. In addition, most evaluations use static models, meaning they assume that the probability of disease exposure and other model parameters are constant over time. For a transmissible infectious disease this is not a realistic assumption. Finally, few health economic studies look at the potential broader value of vaccines. Failing to include all value that accrues from vaccination in estimates of cost effectiveness may result in ongoing undervaluation of vaccines' impact on economic and societal well-being and risk underinvestment on the part of countries and partners. While there is a theoretical framework linking vaccine use to broader economic and behavioral effects, empirical research is needed to test these linkages and provide quantitative field based measures of their magnitude.

Implementation of PCV

Two formulations of PCV are currently WHO prequalified and available through UNICEF procurement: PCV10 and PCV13. Both preparations are administered intramuscularly by injection of 0.5 ml of liquid vaccine. Both vaccines come with a vaccine vial monitor (VVM) to provide a quality assurance of vaccine potency based on temperature stability. PCV10 (two-dose vial without preservative) and PCV13 (single dose vial) are procured by UNICEF and available to Gavi-eligible countries for a copayment as low as US$0.20 per dose (for low-income countries). PCV13 contains antigens of three additional serotypes (3, 6A and 19A) that are not in PCV10. The current formulation of PCV13 takes up 2.5 times the cold chain volume per dose as does PCV10. PCV10 is available in 100-vial cartons; each vial contains two-doses, corresponding to a volume of 4.8 cm^3 per dose. PCV13 is available in 50-vial cartons; each vial is a single-dose, corresponding 12 cm^3 per dose. The single-dose PCV13 vial reduces vaccine wastage (5% estimated) compared to a two-dose vial that, if opened and not used in the same day, must be discarded (10% estimated wastage). A preservative-free two dose vaccine has not previously been used in UN-supported programs, and so the WHO specified that post-introduction monitoring of PCV10 be conducted to assess safety and adverse events following immunization. A Kenyan study found that the risk of abscess following the second vs. first vial dose of

PCV10 was not significantly increased compared to another EPI vaccine (pentavalent vaccine), lending support to the feasibility of safely using this formulation in Africa and low-income settings.

There are two options for PCV dosing of infants that have been approved by the WHO: 3p+0 or, alternatively, 2p+1. The dosing options were systematically reviewed and results published in 2014 on the evidence for vaccine effectiveness based on the number and timing of primary doses-- including the interval between doses and the initial age to begin vaccination—and the presence or absence of a booster dose. In the 2014 review, there was little data from low-income country settings and almost no data on PCV10 or PCV13. With respect to immunogenicity, the number of primary doses (2 or 3) did not meaningfully affect geometric mean concentration (GMC) of IgG measured in the second year of life except for serotype 6B, and a booster dose significantly increases the GMCs for all serotypes regardless of the priming schedule. Older age at immunization and longer intervals between primary doses may optimize immune responses in the first year of life. One important caveat to bear in mind is that the immunological correlate of protection varies based on the outcome studied-- disease or NP carriage—and serotype. Immune response also varies significantly by geographical regions with higher IgG responses in children from Asia, Africa and Latin America compared to Europe and North America.

Differences between dosing schedules on VT-IPD are relatively small compared to the overall benefit of PCV use on this outcome with any of the commonly used schedules: 2p+1, 3p+0 and 3p+1. Similarly, differences between dosing schedules on the outcomes of clinical pneumonia and radiologically confirmed pneumonia are also hard to discern. The case definitions of clinical pneumonia, radiologically confirmed pneumonia, pneumococcal pneumonia, and empyema often vary between studies and preclude directly comparing study results.

There is evidence that three primary doses may be better than two doses for reducing VT carriage in the first year of life prior to a booster dose, but this difference is no longer discernible after the first year or following a booster dose. A 3 primary dose schedule (3p+0) is not as good as 2 primary doses and a booster (2p+1) in maintaining decreased VT NP carriage in the second year of life, indicating that the booster dose is important for continued suppression of VT carriage. The 2014 review of NP carriage was based primarily on studies of PCV7, it did not include studies using PCV10 or PCV13. Data on the 2p+1 schedule came from European studies, whereas data on the 3p+0 schedule came from clinical trials in LMICs. These countries have different epidemiological patterns of NP carriage, and these differences confound the impact of different schedules on carriage prevalence.

The WHO recommends PCV introduction in all countries, especially in countries with a high U5 mortality rate where PCV introduction is deemed a “high priority.” In making dosing decisions, policy makers should consider three fundamental questions: who is most affected, that is, what is the epidemiology of pneumococcal disease in the country; what schedule will prevent the most disease or deaths; and what schedule best fits with the current EPI schedule? Lessons learned from recent new vaccine introductions demonstrate a potential for positive and negative effects on the immunization supply chain. Constraints of the supply chain are important to assess because overburdening the system can compromise the perceived availability of all EPI vaccines. Training of health staff on the side effects of PCV is also an important part of PCV introduction planning. Health staff should also be familiar with other important key messages for parents regarding the risk of pneumonia, even with vaccination, and appropriate care seeking for signs of pneumonia. New vaccine introductions can also be an opportunity to strengthen disease surveillance systems with enhanced surveillance for diseases prevented by the new vaccines and improve awareness and reporting of adverse events following immunization (AEFIs).

In 2009 the Advanced Market Commitment (AMC) for pneumococcal vaccine was established. The AMC provides an innovative finance mechanism to incentivize the scaling up of PCV production to meet developing country needs. Both GSK (the manufacturer of PCV10) and Pfizer (the manufacturer of PCV13) have been accepted as part of the AMC. Eighty percent of eligible countries have applied for

Gavi support to obtain PCV10 or PCV13 at reduced cost. Eligibility for Gavi support and a country's vaccine co-financing contribution is based on per capita GNI. For low-income countries, those with a GNI less than US$1,045 per person, the country must co-finance US$0.20 per PCV dose. Intermediate Gavi-eligible countries, with GNI between US$1,045-US$1,580 per person, start co-financing at US$0.20 per dose with a 15% annual increase. Countries with a GNI above US$1,580 graduate from Gavi support. Graduating countries pay an additional 20% of the difference between their initial co-financing amount and the projected price of PCV in the year Gavi support ends, so that in five years they become responsible for the full cost of PCV.

Financing issues are most complicated and difficult for lower middle-income countries that are just above the Gavi-eligibility threshold. These countries are left out of the financing and AMC pricing agreements and yet are not well-resourced to finance PCV independently on the open market. This gap is evinced by the low proportion of lower middle -income countries that have introduced PCV without Gavi support.

The WHO has developed a post-introduction evaluation (PIE) tool to help conduct a systematic, qualitative assessment of vaccine introduction at multiple levels of the health system. New vaccine introduction can be a vehicle for both positive and negative impacts on the broader health system. There are principles to help guide vaccine introduction planning to maximize its beneficial impact. A immediate, quantifiable outcome measure in vaccine delivery is achieving high, equitable coverage rates all districts.

Ultimately, the measure of vaccine program performance is a reduction in the burden of preventable disease. High-quality surveillance provides valuable insight into program performance and disease epidemiology post-introduction, but the lack of a surveillance program should not be an impediment to PCV introduction. The 2012 WHO position paper on PCVs states: "high-quality surveillance should be conducted in selected countries and defined populations that represent different epidemiological profiles worldwide. Surveillance of disease incidence should begin at least 2 years prior to PCV introduction and continue for at least 5 years post-introduction." There are three tiers of surveillance. The first tier is hospital-based sentinel surveillance for all children with suspected meningitis U5 years of age. The second tier is hospital-based sentinel surveillance for all children U5 with meningitis, pneumonia or sepsis. The limitation of hospital-based sentinel surveillance is that it is not easy to assess vaccine impact, there are small numbers of cases, and the denominator (the true catchment population) is unknown so incidence of disease cannot be determined. The third tier of surveillance is active population-based surveillance that provides the most accurate method of monitoring disease trends. This type of surveillance, where the denominator (population size) from which cases are detected is known, allows incidence rates to be calculated. Quality assurance (QA) and quality control (QC) measures should be used to assess the quality of the disease surveillance system in place and the interpretation of the results as they reflect on vaccine programming.

Key Messages by Chapter

Introduction

- This evidence synthesis is to serve National Immunization Technical Advisory Groups (NITAGs) in their systematic, evidence-based consideration of PCV introduction for routine use among children in national immunization programs.
- Evidence is synthesized on the topics that inform vaccine introduction decisions, including: preventable disease burden, vaccine safety and efficacy, vaccine dosing, vaccine impact, economic impact and programmatic considerations.

Chapter 1: Burden of Pneumococcal Disease

- Pneumococcus is a natural colonizer of the human nasopharynx, particularly prevalent in young children. Pneumococcal colonization can progress to disease, diagnosed clinically or with laboratory confirmation (e.g. invasive disease).
- Over 93 pneumococcal serotypes exist, which are immunologically distinct and vary in their potential to cause disease.
- In 2008, the WHO estimated that more than half a million children under the age of 5 worldwide died of pneumococcal disease, including pneumococcal pneumonia, meningitis, and other clinical manifestations of serious pneumococcal infections.
- Pneumococcal mortality is a significant contributor to the under 5 mortality rate (U5MR) worldwide. Nine percent of all deaths in children aged 1-59 months were estimated to be attributable to pneumococcus in 2008.
- Pneumonia, the most common form of serious pneumococcal disease, is the leading infectious killer of children worldwide.
- Pneumonia killed an estimated 922,000 children under the age of 5 years in 2015, and is the leading cause of death in this age group.
- Based on the vaccine probe approach, pneumococcus is responsible for over one-quarter (27%) to one-third (36%) of all pneumonia deaths in children U5.(3-5)
- There were an estimated 120 million episodes of pneumonia in children in 2010, about 12% of which progressed to severe disease, defined as pneumonia cases requiring hospital admission.
- About 6% to 8% of all clinical pneumonia in children U5 is attributable to pneumococcus.
- Pneumococcus is the most common cause of bacterial pneumonia in children and contributes disproportionately more to severe disease.
- Pneumonia is the most common manifestation of serious pneumococcal disease.
- Pneumococcal meningitis has a high rate of death and serious neurological sequelae among bacterial causes of meningitis in children.
- Among children U5, the highest burden of serious pneumococcal disease occurs in young infants, particularly among meningitis cases and in low-income settings.
- A relatively few number of serotypes (6-11) account for over 70% of IPD worldwide.
- PCV10 serotypes account for an estimated 70% to 77% of IPD cases in children U5 in Asia, Africa, Oceania and Latin America/Caribbean. PCV13 serotypes account for 74% to 82% of IPD cases in young children from these regions.
- Serotype distributions vary by syndrome, disease severity and carriage prevalence. These serotype-specific factors interplay with host-specific factors, such as age and comorbidity, and put populations at risk for disease.

- Pneumococcus is difficult to detect in the laboratory; newer diagnostic tests with enhanced sensitivity for detecting pneumococcus add to our understanding of the burden of disease.
- HIV infection increases the risk and severity of pneumococcal disease in children. The routine use of highly active antiretroviral therapy (HAART) reduces but does not negate this risk. HIV exposure (i.e. children born to HIV infected mothers, but themselves uninfected) also confers an increased risk of pneumococcal disease.
- There is evidence indicating a synergistic interaction between pneumococcus and other respiratory pathogens, such as influenza, that increase individual susceptibility to upper and lower respiratory tract disease.
- Sickle cell disease, and the resulting functional asplenia, is another significant individual risk factor for pneumococcal disease.

Chapter 2: Interventions to Prevent and Control Pneumococcal Disease

- Reducing pneumonia mortality is a high priority to achieve a significant reduction in U5 mortality.
- Access to PCV is an integral part of reducing the burden of childhood pneumonia.
- Since 1990, the U5MR has halved to 43 per 1,000 live births worldwide in 2015. However, gains in child survival have been uneven, with the U5MR ranging from 6 deaths per 1,000 live births in2015 in high-income countries to over 100 deaths per 1,000 live births in 7 countries.
- Proven strategies to reduce the burden of pneumonia –such as appropriate care seeking and case management for children with pneumonia symptoms--are not equitably implemented between or within countries, putting children at continued risk for significant morbidity and mortality.
- Access to PCVs is a key strategy in the comprehensive approach to childhood pneumonia reduction.
- Prevention of disease through vaccination is more likely to accelerate the goals of equity than is the effort to expand access to appropriate treatment of disease, as important as those efforts are.

Chapter 3: Vaccine Safety and Efficacy

- PCVs are safe and well-tolerated in infants, young children and those with HIV infection.
- The vaccines can be administered concurrently with other EPI vaccines. There is some evidence of increased risk of transient fever and febrile seizures with the co-administration of trivalent inactivated influenza vaccine and PCV.
- PCVs are efficacious vaccines. Their use in children directly reduces the risk of IPD (including meningitis and septicemia), radiologically-confirmed pneumonia and clinical pneumonia, otitis media and nasopharyngeal carriage due to serotypes contained in the vaccine.
- PCV is highly efficacious in preventing IPD caused by vaccine serotypes.
- PCV efficacy is higher for pneumonia outcome definitions that are specific for pneumococcal etiology compared with those that are nonspecific.
- RCTs were not powered to investigate U5 mortality following PCV use.
- Only one RCT, from The Gambia, found a statistically significant reduction in all-cause mortality of 16% over a two-year follow period, translating to 7 deaths prevented for every 1,000 children vaccinated.

- Further evidence is needed from post-licensure studies to quantify the impact of PCV use on U5 mortality in different settings.
- PCV7 has a modest beneficial effect on reducing AOM in healthy infants and a more notable benefit on reducing pneumococcal AOM. PCV use in high-risk infants, toddlers and in older children with a history of recurrent AOM does not appear to prevent further infections.
- PCV directly reduces VT NP colonization by about 50% in young children.
- PCV is slightly less efficacious in HIV-infected children, but the absolute impact on disease reduction is greater in these children because they are at higher baseline risk for pneumococcal infection.
- There are limited data on the duration of protection following PCV administration.
- The natural history of pneumococcus, with declining NP colonization prevalence after the first few years of life, and the role of natural immune system boosting following exposure to circulating serotypes complicate the interpretation of long-term follow up studies comparing immunized and unimmunized children.

Chapter 4: Pneumococcal Conjugate Vaccine Impact

- Pneumococcal conjugate vaccines have been introduced in many countries and have demonstrated a greater impact than predicted from clinical trials because of the added benefit of the indirect (herd) effect.
- PCV7 quickly and significantly reduced the incidence of pneumococcal disease among young children in countries where it was introduced into the immunization schedule.
- While serotype replacement with nonvaccine serotypes has been near complete in carriage, only minimal serotype replacement in pneumococcal disease has occurred because of the lower invasiveness of the replacing serotypes.
- Pneumococcal disease burden has decreased substantially as a result of PCV use, because the magnitude of the serotype replacement with nonvaccine serotypes is small relative to the large reductions in vaccine serotype disease.
- Many factors affect trends in the burden of pneumococcal serotypes over time of which PCV implementation is a major factor. In all settings the increase in NVT IPD has been outweighed by the significant reduction in VT disease.
- With the introduction of higher valency PCVs, PCV10 and PCV13, starting in 2010, the rate of disease from the additional serotypes in these newer vaccines has fallen precipitously.
- VT-IPD among adults has gradually decreased in almost all countries within several years of PCV introduction. This indirect effect has been observed for all routinely used infant schedules, for all licensed PCV products, and in populations with high HIV-infection burden.
- Pneumonia is the most common form of serious pneumococcal disease, and so the absolute impact of PCV on pneumonia burden is greater than for the more specific clinical diagnosis of IPD.
- PCVs have had a substantial effect on pneumonia disease burden: the newer generations, high valency PCVs have reduced hospitalizations for all-cause pneumonia by 13% to 72% (n=6 studies) and for consolidated pneumonia by 20% to 45% (n=3 studies) in children U5.
- Preventing NP acquisition of vaccine serotypes, PCV implementation results in a rapid, significant decrease in VT NP carriage prevalence in children. There is replacement carriage with non-vaccine serotypes, often resulting in no net overall change in all-serotype pneumococcal colonization. However, the replacing non-vaccine serotypes are, in many cases, not as invasive

and thus less likely to cause disease. Therefore reductions in all-serotype pneumococcal disease are sustained even in the face of increases in NVT colonization.

- Children are the main reservoirs of pneumococci in the community, and lower VT NP carriage prevalence in this group disrupts community circulation (transmission) of vaccine serotypes. This leads to a decrease in VT NP colonization in unvaccinated groups after PCV introduction.
- Data on the direct and indirect effect of PCV use on VT NP carriage is available from LMICs and from higher valency PCV formulations in different schedules.

Chapter 5: Economic Evaluation of PCV

- Economic evaluation is the process by which the costs and benefits associated with health interventions are identified, measured or modeled, and valuated in order to compare their net impact and determine whether or not the benefits of a given intervention are worth the cost.
- Economic evaluations provide important information for policy makers assessing the value of vaccines in the setting of finite resources that need to be allocated for maximum health impact in a target population.
- The return on investment of meeting vaccine coverage targets in 94 LMICs in the Decade of Vaccines 2011-2020 would result in 16 times greater benefits than costs incurred, compared to no vaccination, for ten diseases. The return on investment for pneumococcal disease and PCV use is 3.13.
- Universal and high coverage (90%) with PCV in Gavi-eligible countries could avert US$24 billion in costs—mostly from productivity gains--prevent 21 million disease cases and save 1.5 million lives between 2011 and 2020.
- There are several types of economic evaluations. Cost-effectiveness analysis (CEA) (also called cost-utility analysis (CUA)) is the most common type of economic evaluation, where the costs are expressed in monetary units and the health effects or outcomes are measured in natural units such as life years gained (LYG), disability-adjusted life years (DALYs) which measure a health loss, or quality-adjusted life years (QALYs) which measures a health gain. QALYs and DALYs are inverses of each other; QALYs are more commonly used in high-income countries, while DALYs are more commonly used in LMICs.
- To calculate the cost-effectiveness of PCV, it is necessary to know the total cost of the vaccine and its administration, and the total health consequences and economic costs averted through vaccination.
- According to the guidelines recommended for individual countries by the WHO Commission on Macroeconomics and Health, an intervention with an incremental cost effectiveness ratio (ICER) that is less than the per capita gross domestic product (GDP) is considered “highly cost-effective,” and an intervention with an ICER that is less than three times the per capita GDP is considered “cost-effective.”(6).
- Major components of CEA of PCV include estimating the economic burden of disease—the cost of illness—vaccine introduction and program costs, and vaccine effectiveness in the target population.
- Economic burden of disease can include direct medical and non-medical costs as well as indirect costs such as productivity losses.
- Vaccine program costs are increasing as new and more expensive vaccines are added to EPI schedules and as coverage rates increase to include hard-to-reach populations.
- Vaccine program costs are driven by vaccine price and service delivery costs, primarily labor costs.

- Since CEA is a modeling tool, it is only as good as the quality of data going into the model.
- High-quality data on some of the model inputs may be lacking in low-income countries, and so a well-conducted CEA should include an analysis of the variability in outcome based on different input scenarios (sensitivity analysis).
- Findings from CEAs/CUAs of PCV are highly dependent on the parameters of vaccine price, vaccine efficacy, disease incidence, and indirect effects used in the model.
- PCV10 and PCV13 are expected to be cost effective in all 73Gavi eligible countries (based on ICER<3xGDP) and highly cost effective in all but one country (ICER<GDP). The lowest incremental costs are in Gavi-eligible countries with the highest burden of U5 deaths.
- A study of PCV cost-effectiveness in 77 middle-income countries found PCV10 and PCV13 to be cost-effective for all countries compared to no vaccine (ICER<3xGDP). In this study, PCV10 would be highly cost-effective for 68 middle-income countries and PCV13 for 71 countries (ICER<GDP).
- While PCV13 may prevent more cases of IPD—depending on local serotype prevalence--PCV10 may prevent more cases of AOM as it has the potential benefit of reducing AOM due to non-typeable *Haemophilus influenzae (*NTHi).
- Few health economic studies look at the potential broader value of vaccines. Failing to include all value that accrues from vaccination in estimates of CE may result in ongoing undervaluation of their impact on economic and societal well-being and risk underinvestment on the part of countries and partners.
- While there is a theoretical framework linking vaccine use to broader economic and behavioral effects, empirical research is needed to test these linkages and provide quantitative field based measures of their magnitude.

Chapter 6: Implementation of PCV

- PCV13 contains antigens of three serotypes (3, 6A and 19A) that are not in PCV10. The current formulation of PCV13 takes up 2.5 times the cold chain volume per dose as does PCV10.
- The number of primary doses (2 or 3) did not meaningfully affect geometric mean concentration (GMC) of IgG measured in the second year of life except for serotype 6B.
- A booster dose significantly increases the GMCs for all serotypes regardless of the priming schedule.
- “Differences between schedules on impact on VT-IPD are difficult to discern based on available data.”(7)
- There is “strong evidence of PCV benefit against clinical and radiologically confirmed pneumonia in the age group targeted for vaccination” using 2p+1, 3p+0 and 3p+1 schedules. (8)
- There is no discernible difference in the magnitude of impact for different schedules against clinical and radiologically confirmed pneumonia based on reviewed data.
- PCV schedules of 2p+0, 2p+1, 3p+0 and 3p+1 all reduce carriage of VT pneumococcus compared to no administration of PCV.
- Most studies show no effect of PCV on overall prevalence of pneumococcal NP carriage as there is an increase in the NP carriage of NVT strains following PCV administration.(9)
- There is a significant indirect effect on reduction of VT-IPD demonstrated with all currently used PCV schedules.
- PCV introduction is recommended in all countries and is a high priority in countries with a high U5 mortality rate.
- WHO recommends a 3p+0 or, alternatively, a 2p+1 schedule for routine infant immunization.

- In choosing between schedules, countries should consider "locally relevant factors including the epidemiology of pneumococcal disease, the likely coverage, and the timeliness of the vaccine doses."(10)
- Lessons learned from recent new vaccine introductions demonstrate a potential for positive and negative effects on the immunization supply chain.
- Constraints of the supply chain are important to assess because overburdening the system can compromise the perceived availability of all EPI vaccines.
- Trained staff should communicate to caregivers that vaccinated children may still get pneumonia due to other pathogens, and if so, children need to be evaluated by an appropriate health care provider to avoid complications or death.
- Side effects following PCV administration are mild, such as soreness at the site of injection and transient fever, and serious adverse events extremely rare.
- The Pneumococcal Advanced Market Commitment (AMC) created in 2009 provides an innovative finance mechanism to incentivize the scaling up of PCV production to meet developing country needs.
- Both manufacturers of pre-qualified PCV products (Pfizer and GSK) have applied and had their products accepted as part of the AMC.
- Eighty percent of Gavi-eligible countries have applied for support to obtain PCV10 or PCV13 at reduced cost.
- Financing issues are most complicated and difficult for lower middle-income countries that are just above the Gavi-eligibility threshold. These countries are left out of the financing and AMC pricing agreements and yet are not well-resourced to finance PCV independently on the open market.(11)
- A post-introduction evaluation (PIE) is a systematic, qualitative assessment of vaccine introduction on multiple levels of a country's immunization program and can reveal important areas for improvement.
- Equitable coverage, as well as high coverage, in all districts and communities is a key intermediate goal of the vaccine program.
- New vaccine introduction can be a vehicle for both positive and negative impacts on the broader health system. There are principles to help guide vaccine introduction planning to maximize its beneficial impact.
- High-quality surveillance provides valuable insight into program performance and disease epidemiology post-introduction, but the lack of a surveillance program should not be an impediment to PCV introduction.
- There are different types (or tiers) of surveillance, and the method employed will determine the metrics that can be obtained. Limitations of the data and methodology should be considered to carefully interpret and draw conclusions on program performance and impact.

Introduction

This evidence synthesis is to serve National Immunization Technical Advisory Groups (NITAGs) in their systematic, evidence-based consideration of PCV introduction for routine use among children in national immunization programs.

Evidence has been organized around topics that inform vaccine introduction and routine immunization performance decisions, including: preventable disease burden, vaccine safety and efficacy, vaccine dosing, vaccine impact, economic impact and programmatic considerations. In general, this publication has been developed with technical decision-makers from low- and middle-income countries in mind.

In 2008, the WHO estimated that more than half a million children under the age of 5 years (U5) worldwide died of pneumococcal disease, including pneumococcal pneumonia, meningitis, and other clinical manifestations of serious pneumococcal infections. Pneumococcal mortality is a significant contributor to the under 5 mortality rate worldwide. Nine percent of all deaths in children aged 1-59 months were estimated to be attributable to pneumococcus in 2008. Pneumonia, the most common form of serious pneumococcal disease, is the leading infectious killer of children worldwide. Pneumococcus contributes disproportionately to severe pneumonia and pneumonia mortality.

There are two main types of vaccines licensed to protect against pneumococcal disease, disease caused by the bacterium *Streptococcus pneumoniae*: pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPV). Available since 1983, PPV targets 23 of the most common pneumococcal serotypes that cause disease in adults. Containing polysaccharide antigens derived from the bacterial capsule, PPV elicits a T-cell independent response and is suboptimal for inducing a protective immune response in children under two years of age.(12) In addition, PPV does not protect against nasopharyngeal (NP) carriage of pneumococcal serotypes contained in the vaccine. Consequently, pneumococcal conjugate vaccines (PCV) have been developed to protect young children from pneumococcal disease. The conjugation of a polysaccharide antigen to a protein carrier results in a T-cell dependent response, high titers of anti-polysaccharide Immunoglobulin G (IgG), and immunological memory in infants.(12) In addition, PCV protects against acquisition of vaccine serotype pneumococcal NP carriage, reducing the overall prevalence of colonization among vaccinated children. A 7-valent PCV (PCV7) was the first in class product to be licensed, which occurred in the United States (US) in 2000. From 2003-2009 the PCV Accelerated Development and Introduction Plan (PneumoADIP) project worked to establish the necessary conditions (disease burden evidence, PCV trial information, manufacturer willingness to supply, countries willing to take up vaccine) for a PCV investment case to be considered by Gavi, the Vaccine Alliance's (Gavi) Board. The 2009 inclusion of PCV in the Gavi vaccine portfolio created a funding mechanism for PCV use in eligible countries. In 2007, the WHO recommended that PCV's inclusion in routine infant immunization programs be a "priority," especially in countries with an under five mortality rate (U5MR) greater than 50 deaths per 1,000 live births.(10)(Figure 1) In 2009, the WHO prequalified PCV7 and a newer 10-valent PCV (PCV10) formulation. In that same year, Rwanda became the first country to introduce PCV with support from Gavi. In 2010, the WHO prequalified a 13-valent PCV (PCV13); and in 2012 the WHO refreshed its PCV recommendations specifying use of either PCV10 or PCV13 with either a 4-dose or 3-dose schedule.(13) For more details on the WHO recommendations, the 2012 position paper on PCV is available at: http://www.who.int/wer/2012/wer8714.pdf?ua=1.

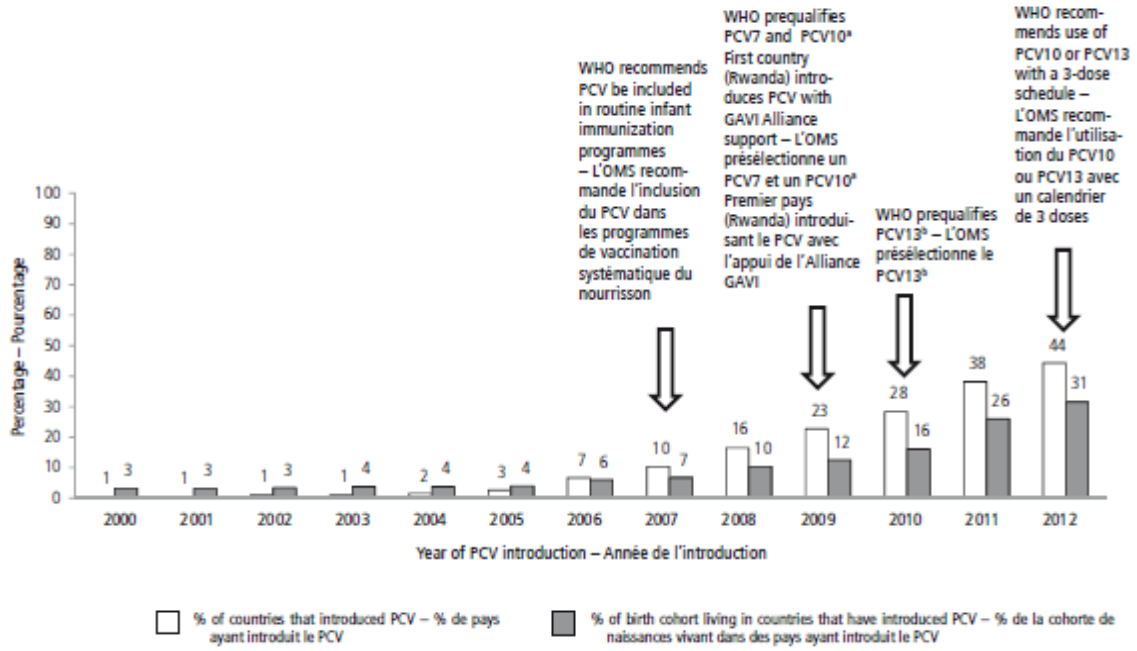


Figure 1: Percent of countries introducing PCV into routine infant immunization schedules and proportion of birth cohort living in these countries by year, 2000-2012(13)

Introduction of PCV by countries has accelerated since 2009, with support of national ministries of health and the many institutions making up the Gavi Alliance (e.g. WHO, UNICEF, academic organizations, CDC, NGO's), and yet some important inequities persist in access to PCV. As of December 2015, 134 of 194 countries (69%) have introduced PCV, including 54 out of 73 Gavi-eligible countries.(14) (Figure 2) This translates to 51% of infants worldwide living in countries or regions that have introduced PCV in 2015, up from 31% in 2012.(14) However, the proportion of infants likely to receive PCV is 44% because of incomplete vaccine coverage of the eligible population within countries, as measured by the coverage of the third dose of Diphtheria-Tetanus-Pertussis (DTP3) vaccine achieved in those countries that have introduced PCV.(14) Thus there is substantial room for improvement within countries that have adopted PCV to increase vaccine access, particularly in the poorest and socially marginalized groups, the very groups at highest risk of pneumococcal disease and death. Support and tools are also needed to make evidence-based vaccine policy decisions regarding PCV introduction in countries that have not yet adopted PCV.(15) Delays in PCV introduction exist in low- and middle-income countries (LMIC), countries in the WHO South-East Asia Regional Office (SEARO), and some countries with large birth cohorts such as India, Nigeria and Indonesia.(Figure 2)

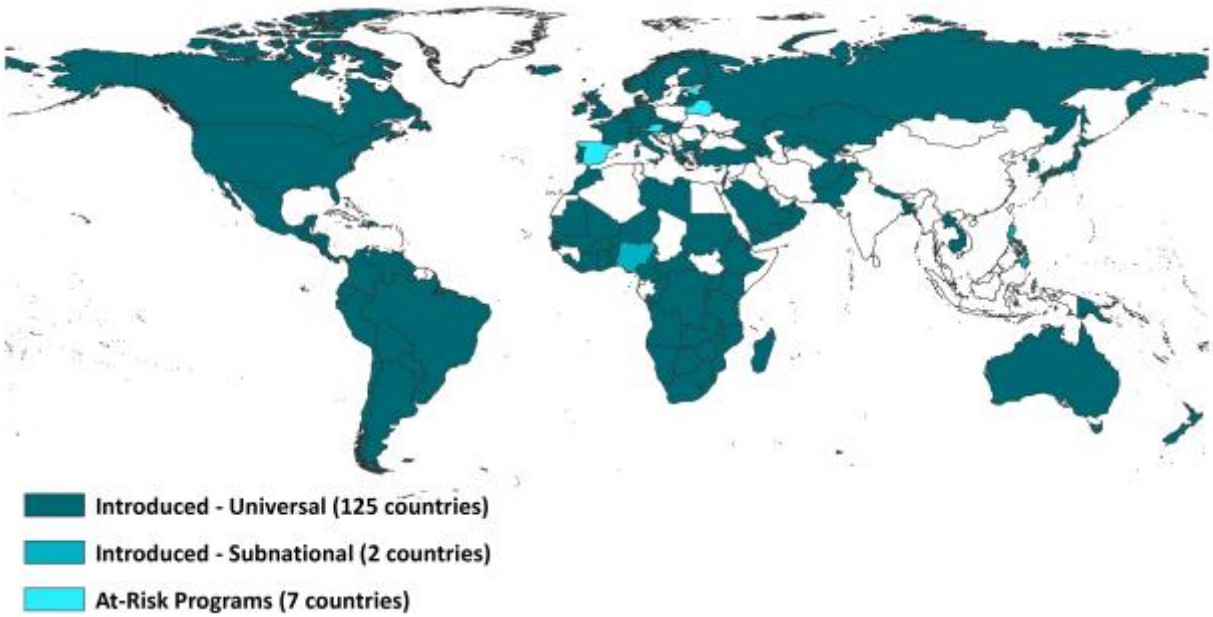


Figure 2: Map of countries that have introduced PCV, December 2015(14)

While the WHO can help critically review vaccines and establish evidence-based policies for vaccine use, individual countries need to determine priorities for their national immunization program based on a variety of epidemiological, political, and financial factors.(11) An increasing number of new vaccines put demands on countries' financial and logistical resources. For example, since 2000 PCV and rotavirus vaccines have become available for infants and human papillomavirus (HPV) vaccine and meningococcal conjugate vaccine for older children and adolescents. Some of the newer vaccines require technologically advanced manufacturing processes and thus are more expensive than traditional EPI vaccines. Increased vaccine costs, vaccine schedule crowding, and shortage of skilled health workers are among the factors that countries must weigh when considering vaccine introduction decisions.

Forming and strengthening of National Immunization Technical Advisory Groups (NITAGs) are part of the response to the increasing complexity of new vaccine introduction decision-making. In the last decade there has been a marked increase in the number of countries with NITAGs. The 2012 Global Vaccine Action Plan (GVAP) includes the specific objective that "all countries should have a functional NITAG by 2020."(16) With over 60 NITAGs created in the past decade, there are 99 countries that reported the existence of a NITAG on a legislative or administrative basis in 2012.(17, 18) However, fewer countries reported having a functional NITAG: 63 countries overall in 2012, of which 38 were developing countries, and only 9 were Gavi-eligible countries.(18) The WHO recommends countries establish a NITAG for two main reasons: "first, to empower governments to devise logical (immunization) policies without pressure from any particular outside group; and secondly, to increase the use of evidence-based decision-making for adapting global recommendations on immunization to local contexts."(18) NITAGs are generally charged with providing guidance on vaccine quality and safety, evaluating new vaccines or new immunization technologies, and in establishing immunization policies and strategies. Their credibility lies in evidence-based decision-making with technical expertise that is independent of the government, commercial, or political influence.(17) However, there is qualitative evidence that the "main drivers" of vaccine introduction decisions in practice have been primarily "availability of funding,

political prioritization . . .and burden of (preventable) disease."(19) Materials to support and strengthen the creation and function (i.e. governance and processes) of NITAGs are available through the SIVAC initiative and the NITAG resource center at http://www.sivacinitiative.org/ and http://www.nitag-resource.org/, respectively. NITAGs have a substantial need, beyond those of governance and process, for content related capacity.

This document is intended to support the systematic consideration of evidence to inform national vaccine priorities. Systematic qualitative assessments have documented some of the key factors that should be evaluated in new vaccine introduction decisions.(17, 20, 21) Theoretical frameworks have been created to conceptualize the factors that go into such decisions. Common criteria informing vaccine introduction include the following factors, which are addressed in the chapters of this evidence synthesis as it relates to PCV administration in children:

- Burden of disease—the importance of the health problem: Chapter 1
- Vaccine safety and efficacy/effectiveness: Chapter 3
- Consideration of alternative interventions: Chapter 2
- Financial/economic evaluation: Chapter 5
- Vaccine impact: Chapter 4
- Programmatic considerations—including personnel training, supply chain and logistics: Chapter 6
- Public acceptability of vaccine: not addressed in this document
- Post-introduction monitoring and vaccine program performance: Chapter 6

The compilation of evidence in this format is to serve NITAGs in their evaluation of PCV introduction and program optimization, and to facilitate evidence-informed national policy and priority-setting.

Chapter 1: Burden of Pneumococcal Disease in Children

Chapter 1 Overview

***Streptococcus pneumoniae*, or pneumococcus, is a gram positive diplococcus that is adapted to colonize the human nasopharynx. The bacterium has a polysaccharide capsule that helps protect it from host defenses in the absence of capsule-specific antibodies. The development of type-specific immunity helps define the over 93 different serotypes of pneumococcus. Pneumococcal nasopharyngeal (NP) colonization is relatively prevalent among children during the first few years of life and declines with age. NP colonization is a necessary precursor for pneumococcal disease in children and adults. Pneumococcus can spread from the nasopharynx by contiguous extension to cause infection in the middle ear (otitis media), or respiratory tract. Pneumococcus can also invade the bloodstream and spread to other sites in the host causing secondary, more distal infection such as meningitis, bacteremic pneumonia, or sepsis.**

In 2008, the WHO estimated that more than half a million children under the age of 5 years (U5) worldwide died of pneumococcal disease, including pneumococcal pneumonia, meningitis, and other clinical manifestations of serious pneumococcal infections. Pneumococcal mortality is a significant contributor to the under 5 mortality rate worldwide. Nine percent of all deaths in children aged 1-59 months were estimated to be attributable to pneumococcus in 2008.

Pneumonia, the most common form of serious pneumococcal disease, is the leading infectious killer of children worldwide. Pneumococcus contributes disproportionately to severe pneumonia and pneumonia mortality. Based on the vaccine probe approach, it is estimated that pneumococcus is responsible for over one-quarter (27%) to one-third (36%) of all pneumonia deaths in children U5. In 2008, the WHO estimated that 485,000 deaths (uncertainty range 354,000 to 526,000) were due to pneumococcal pneumonia in children U5.

There were an estimated 120 million episodes of pneumonia in children in 2010, about 12% of which progressed to severe disease, defined as pneumonia cases requiring hospital admission. About 6% to 8% of all clinical pneumonia and 21% of severe pneumonia in children U5 is attributable to pneumococcus. For radiologically-confirmed pneumonia, a diagnosis more specific for bacterial etiology, an estimated 27% to 36% is caused by pneumococcus.

Pneumococcal meningitis is associated with a high risk of death and serious neurological sequelae in low-income, resource-poor settings. Based on 2008 estimates, meningitis accounted for about 7%, or 1 in 14, of all deaths due to pneumococcal disease in children U5.

The highest burden of serious pneumococcal disease occurs in young infants and the elderly. The childhood peak of invasive pneumococcal disease (IPD) incidence occurs earlier in developing countries compared to developed countries. Twenty percent of IPD cases in young children is found to occur in infants less than six months of age, and 50% in those under 12 months. The peak of pneumococcal meningitis is earlier than for other types of IPD, with 40% of those U5 cases occurring in infants less than six month of age, and 65% in infants under 12 months. The peak age for childhood pneumonia is slightly older and more variable by setting compared to that of IPD and meningitis.

In a systematic review of data on serotypes causing IPD in children U5, prior to the introduction of PCV, six to 11 pneumococcal serotypes accounted for over 70% of IPD. Serotype distributions vary by syndrome, disease severity and carriage prevalence. These serotype-specific factors interplay with host-specific factors, such as age and comorbidity, and put populations at risk for disease.

Pneumococcus is difficult to detect in the laboratory; newer diagnostic tests with enhanced sensitivity for detecting pneumococcus add to our understanding of the burden of disease. Laboratory surveillance for pneumococcal disease lacks sensitivity both because of the laboratory techniques available, and because not all pneumococcal disease has pneumococci present in the body fluids that are most readily accessible for testing (i.e. blood). The best tool available for determining the burden of pneumococcal disease are the PCV trials which when analyzed as a vaccine probe study, reveal the vaccine preventable disease rate from which inferences can be drawn about the total pneumococcal disease rate.

There are host-specific and socioeconomic factors that put certain groups at higher risk of pneumococcal disease. HIV infection increases the risk and severity of pneumococcal disease in children. The routine use of highly active antiretroviral therapy (HAART) reduces but does not negate this risk. HIV exposure (i.e. children born to HIV infected mothers, but themselves uninfected) also confers an increased risk of pneumococcal disease. There is evidence indicating a synergistic interaction between pneumococcus and other respiratory pathogens, such as influenza, that increase individual susceptibility to upper and lower respiratory tract disease. Sickle cell disease, and the resulting functional asplenia, is another significant individual risk factor for pneumococcal disease. Other host factors associated with greater risk of pneumococcal infections include chronic lung infections, some hematologic malignancies, protein energy malnutrition, and other micronutrient deficiencies. Environmentally, crowded living conditions and chronic inhalation of smoke are risk factors. Finally, some ethnic minorities have higher rates of IPD compared to the general population, such as American Indians, Native Alaskans and Australian Aboriginals.

Clinical Spectrum of Pneumococcal Disease

Pneumococcus is a natural colonizer of the human nasopharynx, particularly prevalent in young children. Pneumococcal colonization can progress to disease, diagnosed clinically or with laboratory confirmation (e.g. invasive disease).

Over 93 pneumococcal serotypes exist, which are immunologically distinct and vary in their potential to cause disease.

Streptococcus pneumoniae, or pneumococcus, is a gram positive diplococcus that is adapted to colonize the human nasopharynx. The bacterium is surrounded by a polysaccharide capsule that protects the organism from the host's innate immune system in the absence of type specific antibody. (See Figure 3.) The capsule serves to shield underlying protein antigens on the cell surface of the organism from host antibodies and complement.

> *"The capsule is negatively charged, which helps reduce the clearing effects of sialic acid-rich mucopolysaccharides in the respiratory mucus.(22, 23) Perhaps more important, in the absence of type specific antibody, the polysaccharide capsule inhibits activation of the complement system thereby preventing opsonophagocytosis through multiple pathways. First, the capsule helps mask antibody recognition of subcapsular antigens, preventing the classical complement pathway through immunoglobulin G (IgG).(24) The capsule also prevents binding of C-reactive protein, another component of the classical complement pathway.(24) The capsule may reduce degradation of C3b to iC3b, ultimately preventing phagocytosis by neutrophils.(24)"(25)*

The host's immune system eventually produces antibodies directed against the polysaccharide capsule; this immunologically specific response helps define the over 93 distinct serotypes of pneumococcus and 46 serogroups, within which there are varying degrees of immunological cross-reactivity.

The upper respiratory tract is the primary biological niche for pneumococcus. Here, the bacterium colonizes the mucosal surfaces of the nasopharynx and can remain commensal within the host for weeks or months.(25, 26) The epidemiology of colonization varies between settings but there are some general patterns that are conserved. Colonization is relatively prevalent among children during the first few years of life. In low income settings first acquisition of carriage occurs earlier in infancy and prevalence rates are higher in children under five years (U5) and older children compared to high income settings.(27-32) In all settings colonization declines with age, and this reduction is not serotype-specific. This phenomenon is believed to be due to an immune response to non-capsular antigens, maturation of the innate immune response, or anatomical changes in the nasopharynx.(33) To a much lesser extent, pneumococcal colonization can also occur in healthy adults. Colonization duration and invasive potential of pneumococcus vary by serotype; however, the mechanisms through which such dynamics manifest are still not fully understood.(25)

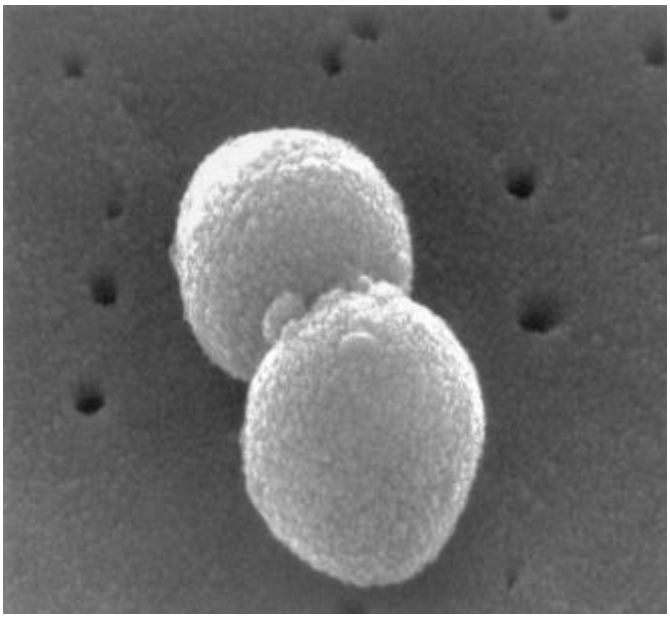


Figure 3: Scanning electron micrograph of *Streptococcus pneumoniae*, or pneumococcus, with its surrounding polysaccharide capsule (photo credit: CDC, Public Health Image Library ID#263, Dr. Richard Facklam, available at: http://phil.cdc.gov/phil/details.asp)

"Nasopharyngeal (NP) colonization is a necessary precursor for pneumococcal disease in children and adults. The first step in colonization is acquisition—when pneumococcus establishes itself within the epithelial cells of the host by attaching to host epithelial cells in the nasopharynx. The host innate and adaptive immune responses are typically sufficient to sustain pneumococcus in a commensal state. However, colonization can lead to respiratory infections or systemic disease. Specifically, host inflammation can shift the binding target of pneumococci to a platelet-activating factor.(34) This contributes to improved pneumococcal binding and is one of the first steps in invasive disease.(35)

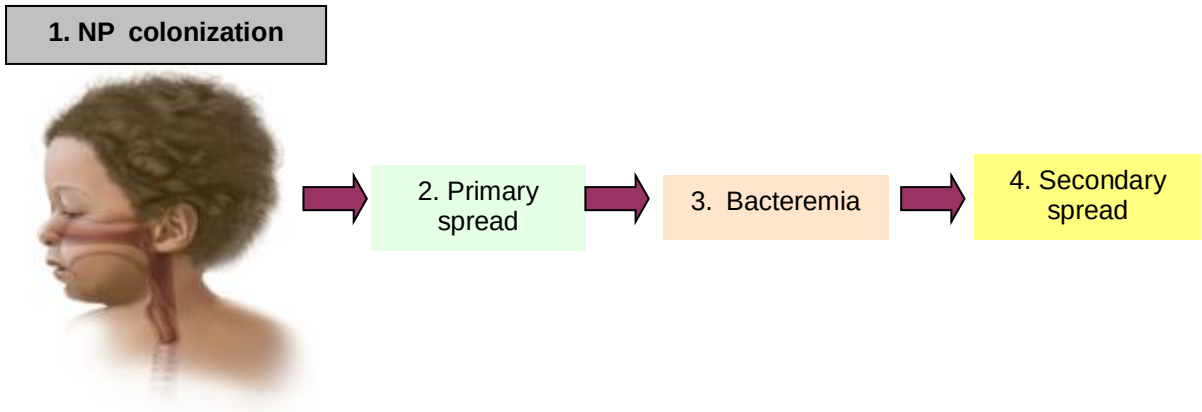
Prospective cohort studies have demonstrated the temporal relationship between colonization and disease.(35) These studies also show disease is typically associated with a newly acquired serotype.(36) The widely recognized link between colonization and invasive pneumococcal disease (IPD) is the basis for impact evaluations utilizing vaccine serotype (VT) NP colonization prevalence as an endpoint.(35)"(25)

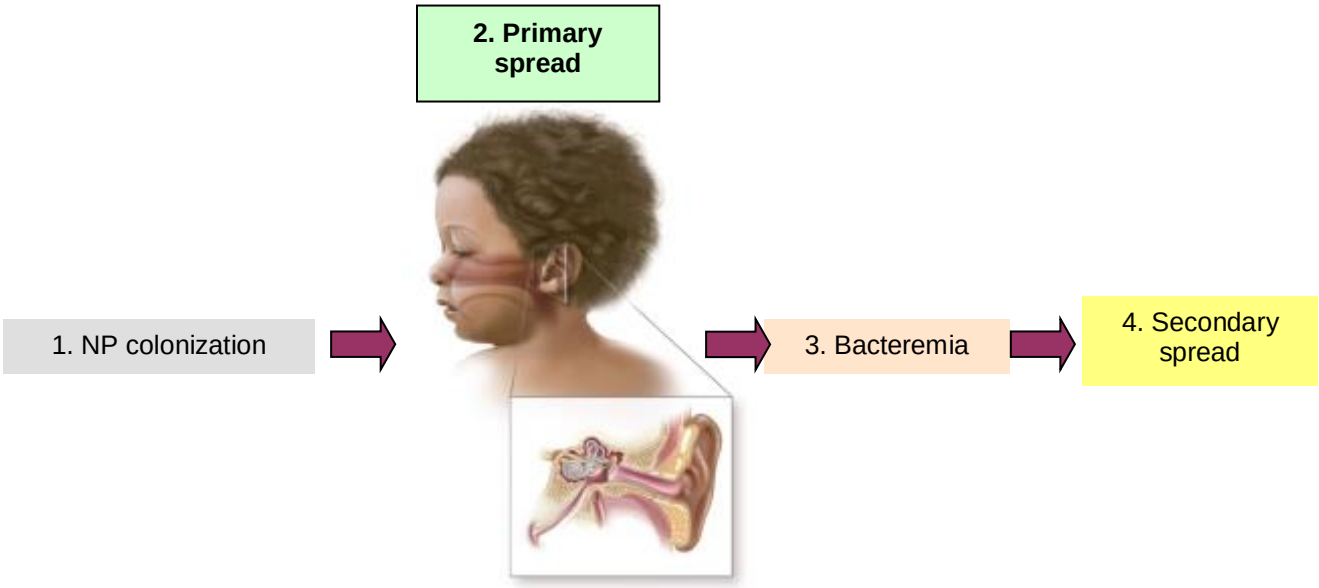
Pneumococcus can spread from the nasopharynx by contiguous extension in the respiratory tract to cause infection in the middle ear (otitis media), sinusitis or non-bacteremic pneumonia which may then become bacteremic in nature. Pneumococcus can also invade the bloodstream and spread to other sites in the host causing secondary, more distal infection such as meningitis, bacteremic pneumonia, osteomyelitis or arthritis.(Figure 4) Invasive pneumococcal disease (IPD) is defined as the isolation of pneumococcus from a normally sterile body site (such as blood, cerebrospinal fluid (CSF) or pleural fluid) and can range clinically from bacteremia with fever but no focus of infection (so-called occult bacteremia), to life-threatening infection.(37) (See Table A.) The polysaccharide capsule is an important determinant of the virulence, or invasive potential of the pneumococcus. There are serotype-specific differences in the frequency and site of disease following NP colonization wherein some serotypes are more commonly found causing bacteremic pneumonia and others more commonly found causing meningitis, for example.(38)

Table A: Invasive and noninvasive pneumococcal disease syndromes (25)

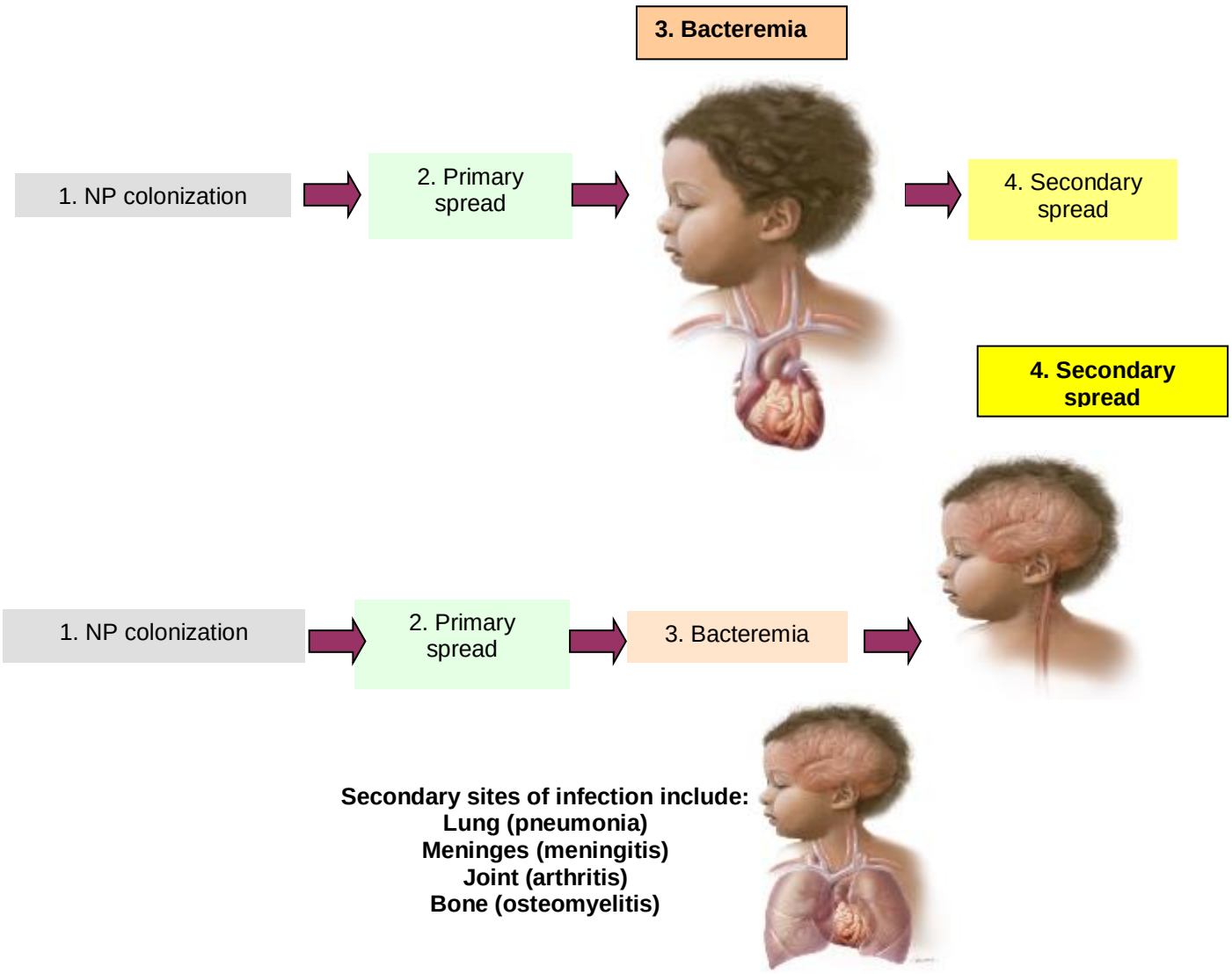
Invasive Pneumococcal Diseases	Noninvasive Pneumococcal Diseases
• Bacteremia without a clinical focus of infection • Bacteremic pneumonia • Cellulitis with bacteremia • Endocarditis • Pericarditis • Septic arthritis • Osteomyelitis • Peritonitis • Epiglottitis	• Acute otitis media • Non-bacteremic pneumonia • Bronchitis • Sinusitis • Conjunctivitis • Mastoiditis • Periorbital cellulitis

Figure4: Steps in the progression from nasopharyngeal (NP) colonization to pneumococcal disease





Sites of primary infection:
Middle ear (otitis media)
Sinus (sinusitis)
Lung (pneumonia)


3. Bacteremia
1. NP colonization
2. Primary spread
4. Secondary spread
4. Secondary spread
1. NP colonization
2. Primary spread
3. Bacteremia
Secondary sites of infection include:
Lung (pneumonia)
Meninges (meningitis)
Joint (arthritis)
Bone (osteomyelitis)

Burden of Pneumococcal Disease

In 2008, the WHO estimated that more than half a million children under the age of 5 worldwide died of pneumococcal disease, including pneumococcal pneumonia, meningitis, and other clinical manifestations of serious pneumococcal infections.(39)

Pneumococcal mortality is a significant contributor to the under 5 mortality rate (U5MR) worldwide. Nine percent of all deaths in children aged 1-59 months were estimated to be attributable to pneumococcus in 2008.(39)

In 2008, the pneumococcal mortality rate and number of deaths by region was estimated by the WHO and endorsed by the Child Health Epidemiology Reference Group (CHERG).(Table B and Figure 5) It was estimated that there were 541,000 deaths (uncertainty range 376,000 to 594,000) in children U5 worldwide, including 476,000 deaths (333,000 to 529,000) in HIV-negative children and 64,900 deaths (44,500 to 72,800) in HIV-positive children. Overall, in 2008 pneumococcal disease was estimated to cause about 9% of all deaths in children aged 1-59 months.(39)

Prior estimates of total pneumococcal mortality burden in U5 children date from 2000 and are available by region at: http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(09)61204-6.pdf. This reference also includes estimates of pneumococcal disease morbidity for 2000. **Numbers of cases and deaths due to pneumococcal disease are in the process of being updated and will become available in 2017.**

Table B: Estimated total pneumococcal deaths for children under 5 years in 2008, by WHO region(39)

	GLOBAL	AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Pneumococcal deaths	541,000 (376,000-594,000)	309,000 (208,000-336,000)	13,700 (9,400-15,900)	68,900 (49,700-75,900)	6,800 (5,000-7,800)	108,000 (79,400-119,000)	33,700 (23,900-39,400)
Deaths in HIV-positive children	64,900 (44,500-72,800)	62,300 (42,700-69,900)	400 (300-400)	600 (400-600)	<100 (<100-<100)	1,400 (1,000-1,400)	300 (200-300)
Deaths in HIV-negative children	476,000 (333,000-529,000)	247,000 (167,000-274,000)	13,400 (9,200-15,500)	68,300 (49,400-75,300)	6,800 (5,000-7,800)	107,000 (78,500-118,000)	33,400 (23,600-39,100)

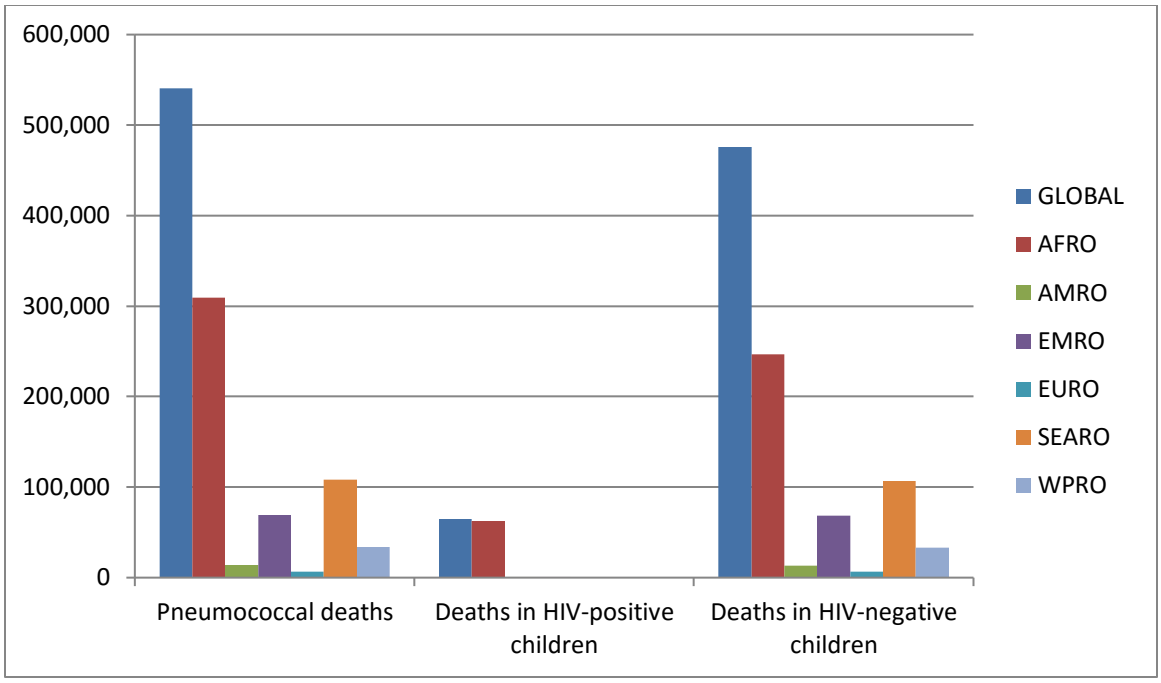


Figure 5: Estimated total pneumococcal deaths for children under 5 years in 2008, by WHO region(39)

Disease Burden of Pneumococcal Pneumonia

Pneumonia, the most common form of serious pneumococcal disease, is the leading infectious killer of children worldwide.

Pneumonia killed an estimated 922,000 children under the age of 5 years in 2015, and is the leading cause of death in this age group.(2, 40)

Based on the vaccine probe approach, pneumococcus is responsible for over one-quarter (27%) to one-third (36%) of all pneumonia deaths in children U5.(3-5)

Pneumonia Mortality

Estimates of pneumonia mortality among children were released for 2013 from two large modeling studies, the CHERG, now known as the Maternal Child Epidemiology Estimation (MCEE) group, and the Global Burden of Disease Study (GDB) based at the Institute for Health Metrics and Evaluation (IHME). These two groups work independent of each other, so comparisons of the estimates from each modeling effort provide an important "check and balance" for either of their estimates. For pneumonia, the estimates from the two groups are strikingly similar, providing confidence in the values estimated. Both modeling efforts conclude that pneumonia is a leading killer of children under U5. The United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) has provisionally updated the estimates of pneumonia mortality for 2015.

Pneumonia accounts for 14% to 17% of all U5 deaths annually, though this burden is not spread equally across the globe. The most recent numbers from the WHO estimates that 922,000 children U5 died of

pneumonia in 2015, 15% of all U5 deaths in this year.(40) For 2015, the UN IGME estimated that 17% of the 5.9 million U5 deaths was due to pneumonia, a total of 1.0 million deaths (uncertainty range 969,000 to 1,088,000).(2) MCEE reported a similar estimate for 2013: 15% of U5 deaths were due to pneumonia, accounting for 935,000 deaths (uncertainty range 817,000 to 1,057,000) out of a total of 6,300,000 U5 deaths.(Figure 6A)(41) The GDB study estimated that 905,100 U5 deaths (95% CI 797,900 to 1,015,900) were due to lower respiratory infection, this represents 14% of the total U5 deaths of 6,300,000 for 2013.(3) Nearly 85% of all pneumonia deaths (783,000 deaths) occurred in Sub-Saharan Africa and South Asia, two regions comprising 50% of the world's U5 population.(42) Figure 6B shows the proportion of total U5 deaths due to pneumonia by country in 2015. Sixty percent of childhood pneumonia deaths were concentrated in 10 countries (Afghanistan, Angola, Chad, China, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria, and Pakistan) that represent about 50% of the world's U5 population.(42, 43)

Figure 6A: Global causes of death in children under 0-59 months in 2013 from the MCEE(41)

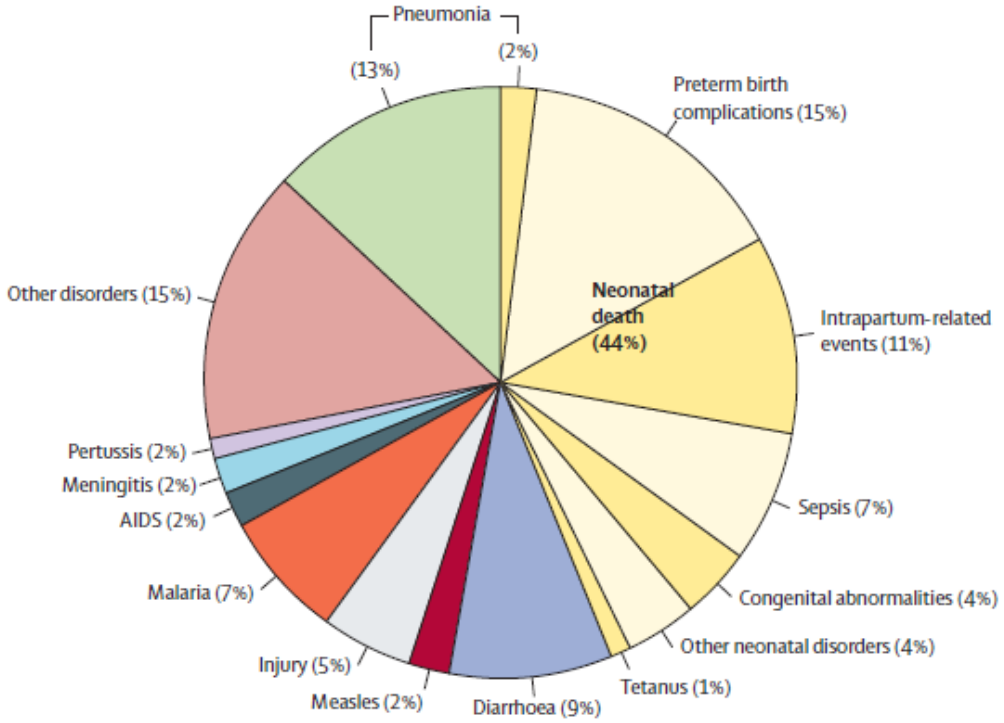
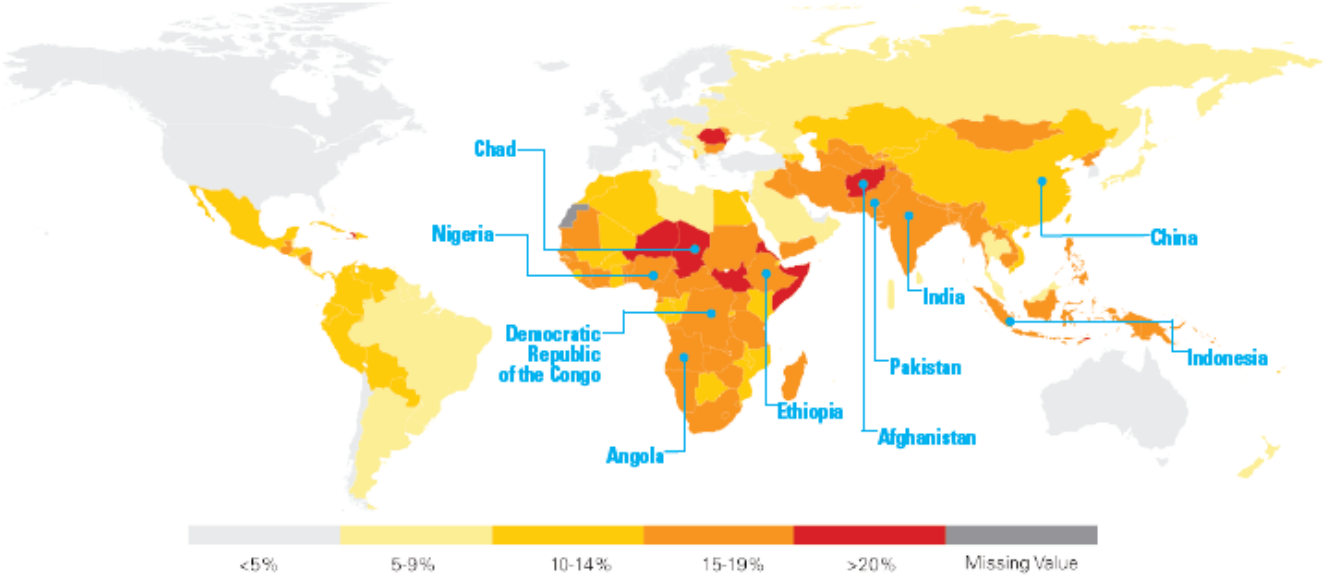


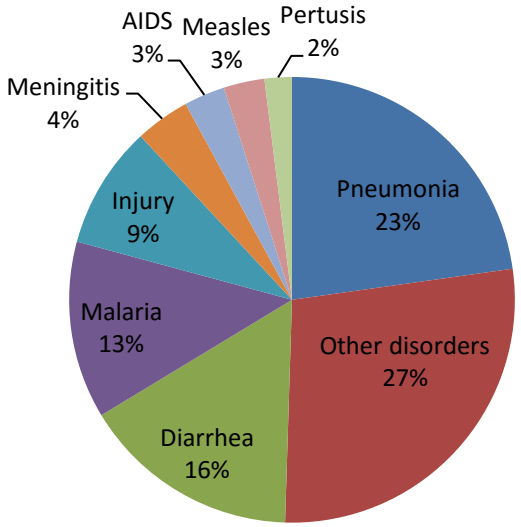
Figure 6B: Proportion of deaths among children under 5 attributable to pneumonia in 2015(43)



Pneumonia is a particularly important as a cause of child mortality beyond the neonatal period. In the first month of life, the neonatal period, preterm birth complications and intra-partum related complications are the main causes of mortality. While neonatal pneumonia is still a notable cause of death, the etiologies differ in neonates, with bacteria such as E. coli and Group B Streptococcus playing a larger role in the early neonatal period.(44) Both the MCEE study and the GDB 2013 study ranked pneumonia as the single leading cause of death in children 1-59 months, excluding the neonatal period. According to the MCEE, in 2013, pneumonia accounted for 23% of deaths in the postneonatal age group, an estimated 800,000 deaths (uncertainty range 681,000 to 923,000) out of 3,500,000 all-cause deaths.(41) (See Figure 6C.) MCEE released estimates of pneumonia deaths by Millennium Development Goal (MDG) region and by country. These estimates are available at: http://www.jhsph.edu/research/centers-and-institutes/institute-for-international-programs/_docs/maternal-newborn-and-child-cause-of-death/webappendices5-7.pdf.

Among the ten MDG regions, the proportion of child deaths due to pneumonia in the postneonatal period was 10% in the developed region and ranged between 20% (in Latin America and the Caribbean) and 27% (Southern Asia, South-eastern Asia and Caucasus/Central Asia) in developing regions.(41) The annual rate of reduction for pneumonia deaths among children U5 beyond the neonatal period was 5.0%.(41) GDB 2013 estimated that pneumonia caused 772,000 deaths (95% CI 693,000 to 850,000) out of a total of 4,039,000 deaths in 1-59 month age group, or 19%.(3)

Figure 6C: Global causes of death in children between 1-59 months in 2013 from the MCEE, 3.5 million deaths total



There are many causes of pneumonia including bacterial, viral and fungal etiologies. Pneumococcus contributes disproportionately to severe manifestations of pneumonia and pneumonia mortality. It is the most common cause of bacterial pneumonia deaths in children.(3) In 2008, the WHO estimated that 485,000 deaths (uncertainty range 354,000 to 526,000) were due to pneumococcal pneumonia.(39) The 2008 WHO estimates include a regional breakdown of pneumococcal pneumonia deaths: the highest burden of pneumococcal pneumonia deaths was in Africa.(Table C and Figure 7) Overall, pneumonia accounted for 90% of all estimated pneumococcal deaths in children U5 in 2008.. Next, the GDB study released estimates for the year 2010---these estimates suffered from serious methodologic issues and are not used. The GBD study revised their methods after consultation with the modelers who produced the WHO estimates, and released year 2013 estimates whose methods are improved. A new set of estimates from MCEE for 2015 will be available in 2016.

The vaccine probe strategy is the modeling approach to estimate the proportion of all-cause pneumonia deaths attributable to pneumococcus. The vaccine probe approach is based on the assumption that the difference in disease burden between vaccinated and unvaccinated individuals can be ascribed to the vaccine-specific pathogen.(45) Data from randomized controlled trials (RCTs) are used to estimate vaccine efficacy (VE) against a particular disease manifestation. This VE is also an estimate of the proportion of that disease manifestation that is caused by the vaccine pathogen.(45) For pneumonia, the VE of PCV against radiographically-confirmed pneumonia can be used as an estimation of pneumococcus' contribution to overall pneumonia deaths. This approximation is based on certain assumptions: all bacterial pneumonia deaths have an abnormal chest X-ray, the case fatality rate (CFR) of pneumococcal pneumonia cases with an abnormal chest X-ray is equivalent to the CFR of non-pneumococcal cases with an abnormal chest X-ray. The bias introduced with these assumptions is likely to overestimate pneumococcal deaths in high access to care settings and underestimate them in low access to care settings.(5) The published papers from PneumoADIP/WHO provide detailed descriptions

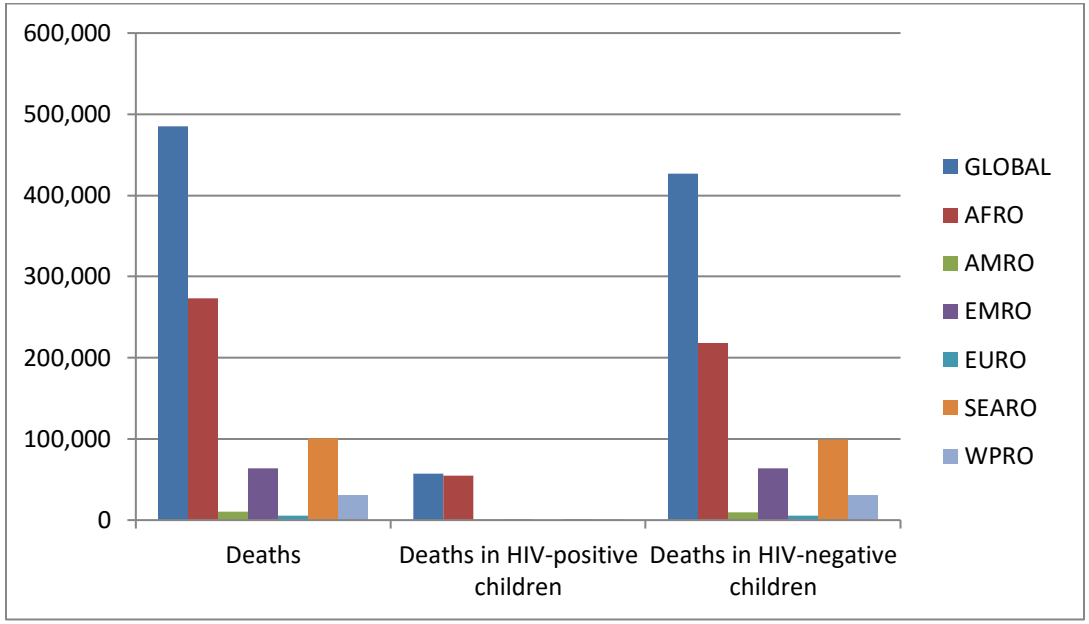
of the methodology: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61204-6/abstract.

Using the vaccine probe approach there are three estimates of pneumococcus' contribution to overall pneumonia deaths which range between 27% and 36%. All the studies analyze data from key pneumococcal conjugate vaccine (PCV) efficacy trials in the US, South Africa, The Gambia and the Philippines. The PneumoADIP/WHO 2009 paper adjusted for the proportion of pneumococcal disease caused by vaccine serotypes, VE against vaccine serotype(VT)-IPD, and the concurrent use of *Haemophilus influenzae* type b (Hib) vaccine. This review reported the pooled VE against radiologically-confirmed pneumonia as 36% (95% CI 16%, 51%) and ascribed that same proportion to pneumococcus' contribution to overall pneumonia deaths.(5) The VE against radiologically-confirmed pneumonia was also reported in the 2009 Cochrane review, and in this study it was estimated at 27% (95% CI 15%, 36%).(4) The 2013 GDB study estimated the causal fraction of lower respiratory deaths due to pneumococcus as 29.2% in children U5, resulting in 264,000 pneumococcal pneumonia deaths (95% CI 155,700 to 365,800) in 2013.(3)

Table C: Estimated pneumococcal pneumonia deaths for children under 5 years, by WHO region 2008 (uncertainty range)(39)

	GLOBAL	AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Deaths	485,000 (354,000-526,000)	273,000 (200,000-296,000)	10,300 (7,300-10,900)	64,100 (46,900-69,700)	5,700 (4,100-6,100)	101,000 (73,600-109,000)	31,200 (22,900-33,900)
Deaths in HIV-positive children	57,400 (42,000-62,400)	55,000 (40,300-59,800)	300 (200-300)	500 (400-500)	<100 (<100-<100)	1,300 (900-1,300)	300 (200-300)
Deaths in HIV-negative children	427,000 (312,000-464,000)	218,000 (159,000-237,000)	10,000 (7,100-10,500)	63,600 (46,600-69,100)	5,700 (4,100-6,000)	99,400 (72,700-108,000)	30,900 (22,600-33,600)

Figure 7: Estimated pneumococcal pneumonia deaths for children under 5 years, by WHO region 2008 (39)



Pneumonia Morbidity

There were an estimated 120 million episodes of pneumonia in children in 2010, about 12% of which progressed to severe disease, defined as pneumonia cases requiring hospital admission.(46)

About 6% to 8% of all clinical pneumonia in children U5 is attributable to pneumococcus.

Pneumococcus is the most common cause of bacterial pneumonia in children and contributes disproportionately more to severe disease.(3, 5)

Pneumonia is the most common manifestation of serious pneumococcal disease.

The contribution of pneumonia to morbidity, and not just mortality, is also substantial among children U5. There are many ways of defining pneumonia. The broadest definition is clinical pneumonia, a syndromic definition based on clinical findings alone. According to the WHO, "in children under five years of age, who have cough and/or difficult breathing, with or without fever, pneumonia is diagnosed by the presence of either fast breathing or lower chest wall indrawing where their chest moves in or retracts during inhalation."(47) Fast breathing is defined as a respiratory rate of at least 50 breaths per minute for children 2-12 months old and 40 per minute for 12-24 month olds.(48, 49) This clinical definition of pneumonia is sensitive but not specific for bacterial etiology as there are many viruses and other pathogens that can cause a similar clinical presentation. Radiologically-confirmed pneumonia is a more specific finding of bacterial pneumonia, defined by the consolidation of lung tissue or pleural fluid associated with lung infiltrate seen on X-ray.(50) Most specific—but least sensitive—for diagnosing bacterial pneumonia is the identification of a bacterial pathogen on concurrent blood culture sampling. Pneumonia associated with a positive blood cultures is called bacteremic pneumonia, and it is the gold standard test for bacterial pneumonia. However, blood culture is a very poor diagnostic test for pneumonia and the yield, even in cases of bacteremic pneumonia, is low.(51) Only 10-15% of blood cultures from children with pneumonia reveal a bacterial etiology.(52) Hence, non-bacteremic pneumonia may be cases without bacteria in the blood, pneumonia resulting from contiguous spread not invasive disease, or cases in which the bacteremia was not detected by blood culture.

"The most recent year for which pneumonia morbidity estimates are available globally is 2010. These estimates, also prepared by CHERG/MCEE partners, showed the incidence of community-acquired pneumonia in low- and middle-income countries to be 0.22 (interquartile range(IQR): 0.11, 0.51) cases per child year.(53) This estimate is based on a meta-analysis of pneumonia incidence estimates from community-based, active case finding studies. The proportion of pneumonia cases that progress to severe pneumonia was estimated to be 11.5% (IQR: 8.0%, 33.0%).(53) Country-specific estimates of pneumonia incidence were derived by adjusting the global estimate by the prevalence of seven risk factors in each country. Based on these incidence estimates, the authors estimated there were 120.4 (95% CI: 60.8, 277.0) million pneumonia cases globally and 14.1 (95% CI: 10.0, 40.0) million severe pneumonia cases in 2010.(53) Pneumonia cases have also declined in the past decade. The pneumonia incidence in 2000 was estimated to be 0.29 (IQR: 0.21, 0.71) cases per child year(54)."(25)

Pneumonia can be caused by bacteria, viruses and fungi. Bacterial etiology is associated with a higher risk of severe manifestation and mortality.(5, 55) Based on the vaccine probe approach, the contribution of pneumococcus to clinical pneumonia in children U5 is estimated to be 6% (95% 2%, 9%) to 8% (95% CI 2%, 14%), the VE of PCV against clinical pneumonia based on two separate meta-

analyses.(4, 5) The PneumoADIP/WHO 2009 review also analyzed pneumococcus' contribution to severe pneumonia and found 21% (95% CI 12%, 29%) of severe disease attributable to pneumococcus.(5) For radiologically-confirmed pneumonia, a diagnosis more specific for bacterial etiology, an estimated 27% (95% CI 15%, 36%) to 36% (95% 16%, 51%) is caused by pneumococcus.(4, 5, 45) The PERCH studies (Pneumonia Etiology Research for Child Health) are being conducted in seven Asian and African countries to apply newer diagnostic techniques and standardized case definitions to determine the contribution of different pathogens to the burden of severe pneumonia in children U5.

Results from the PERCH study are expected to be available in 2017.

Pneumonia is by far the most common manifestation of serious pneumococcal disease. Ninety-six percent of the total cases of serious pneumococcal disease in U5 children (e.g., not including otitis media or sinusitis) manifested as pneumonia in 2000.(5) Updated numbers of pneumococcal disease burden and pneumococcal pneumonia morbidity are due out for 2015.

Disease Burden of Pneumococcal Meningitis

Pneumococcal meningitis has a high rate of death and serious neurological sequelae among bacterial causes of meningitis in children.

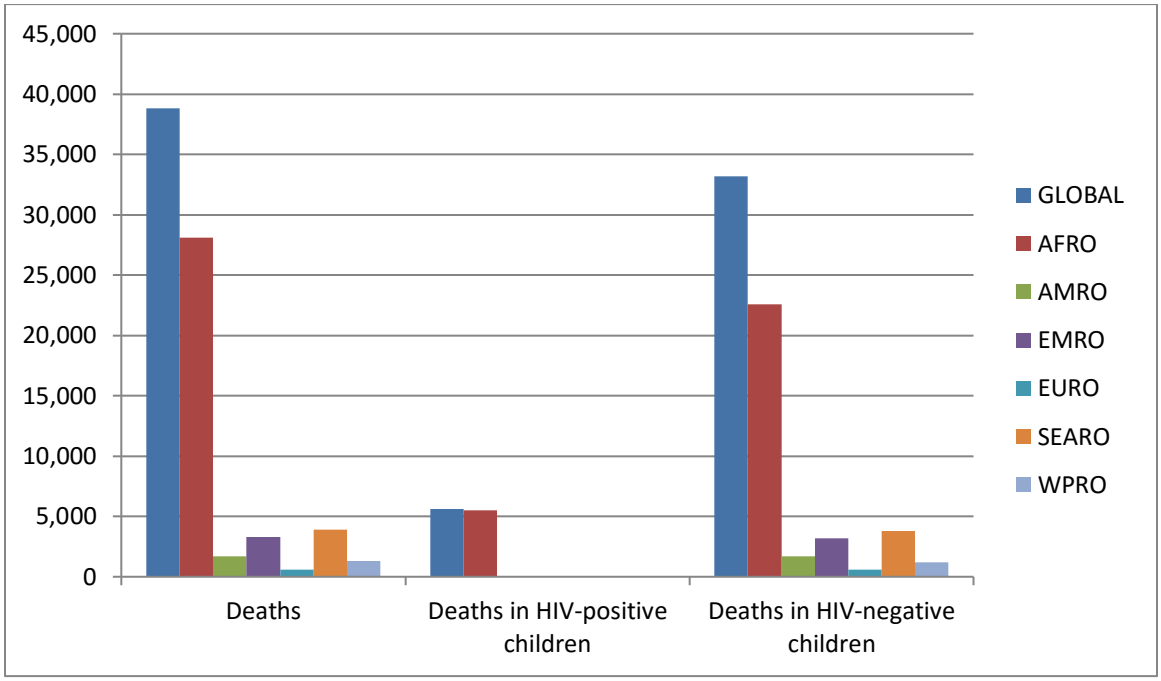
Meningitis is a serious infection that is a notable cause of death in children U5. Based on 2013 MCEE data, meningitis caused 151,000 deaths (uncertainty range 125,000 to 185,000) in children 1-59 months, representing 4% of deaths in this age group.(41) The IHME/GBD estimate for the meningitis deaths in children U5 beyond the neonatal period in 2013 was 121,400 deaths (95% CI 90,200 to 157,000), or 3% of total deaths in this age group.(3)

Pneumococcal meningitis is associated with a high risk of death and serious neurological sequelae in low-income, resource-poor settings. Based on 2008 estimates, meningitis accounted for about 7%, or 1 in 14, of all deaths due to pneumococcal disease in children U5. In 2008, there was an estimated 38,800 deaths (uncertainty range 12,900 to 43,600) in children U5 due to pneumococcal meningitis. The African region had the highest number of deaths due to pneumococcal meningitis with 28,100 (6,100 to 28,300), primarily because of the high rates of pediatric HIV infection.(39)(Table D and Figure 8)

Table D: Meningitis deaths attributed to pneumococcus in children under 5 years, by WHO region 2008 (uncertainty range)(39)

	GLOBAL	AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Deaths	38,800 (12,900-43,600)	28,100 (6,100-28,300)	1,700 (1,100-2,600)	3,300 (1,800-4,100)	600 (500-900)	3,900 (2,900-4,900)	1,300 (500-2,700)
Deaths in HIV-positive children	5,600 (1,800-7,600)	5,500 (1,700-7,400)	<100 (<100-<100)	<100 (<100-<100)	<100 (<100-<100)	<100 (<100-<100)	<100 (<100-<100)
Deaths in HIV-negative children	33,200 (12,900-43,600)	22,600 (6,100-28,300)	1,700 (1,100-2,600)	3,200 (1,800-4,200)	600 (500-900)	3,800 (2,900-4,900)	1,200 (500-2,700)

Figure 8: Meningitis deaths attributed to pneumococcus in children under 5 years, by WHO region 2008 (39)



Data on pneumococcal meningitis morbidity in children U5 was reviewed globally for the year 2000.(5) Updated numbers for 2015 are due out in 2016. In 2000, meningitis made up 0.7% of all pneumococcal cases, or 1 in 137 cases of all serious pneumococcal disease.(5) Worldwide, in 2000 there was an estimated 103,000 cases (uncertainty range 51,500 to 131,000) of pneumococcal meningitis in children U5. The overall case fatality rate (CFR), the chance of death among children with the disease, was 59% (ranging between 27% and 80% by WHO region), among the highest for bacterial causes of meningitis.(5) However, without treatment, pneumococcal meningitis can be fatal in over 70% of cases.(56) Antibiotic resistance is also of concern and complicates the treatment of pneumococcal meningitis in areas with high resistance rates. In Africa, there is some evidence that increases in

pneumococcal meningitis cases contribute to the cyclic epidemics seen during the hot, dry season in meningitis belt countries.(57-59)

Serious neurological sequelae following pediatric meningitis include hearing loss, vision loss, cognitive delay, speech/language disorder, motor delay/impairment, behavioral problems, and seizures.(60) Pneumococcal infection has the highest risk of neurological sequelae among the bacterial causes of meningitis.(61) In a global review, about 25% (IQR 16%, 35%) of pneumococcal meningitis cases resulted in major neurological sequelae.(61) Similar findings were reported in a systematic review of literature from African countries, where about one-quarter of children surviving pneumococcal meningitis had serious neurological sequelae at the time of hospital discharge.(60)

Disease Burden of Non-Pneumonia Non-Meningitis (NPNM) Pneumococcal Disease

Clinical syndromes of IPD other than pneumonia and meningitis make up the last major category of serious pneumococcal disease. These cases can be considered severe, if the child required hospitalization, or non-severe, as in the case of outpatient bacteremia. In 2008, deaths due to NPNM contributed 3% of the total number of pneumococcal disease deaths in children U5. For that year there were an estimated 17,400 deaths (uncertainty range 8,400 to 24,500), mostly from Africa (8.600 deaths) and Southeast Asia (3,700 deaths).(39)(Table E and Figure 9) NPNM disease morbidity was last reviewed globally for 2000, but updated estimates are due out in 2016.

Table E: Deaths due to NPNM disease attributable to pneumococcus in children under 5 years, by WHO region 2008 (uncertainty range)(39)

	Global	AFRO	AMRO	EMRO	EURO	SEARO	WPRO
Deaths	17,400 (8,400-24,500)	8,600 (2,600-11,500)	1,700 (1,000-2,400)	1,500 (1,000-2,100)	600 (400-800)	3,700 (2,900-4,900)	1,200 (500-2,800)
Deaths in HIV-positive children	1,900 (700-2,800)	1,800 (600-2,700)	<100 (<100-<100)	<100 (,100-<100)	<100 (<100-<100)	<100 (<100-<100)	<100 (<100-<100)
Deaths in HIV-negative children	15,500 (7,700-21,600)	6,800 (2,000-8,800)	1,700 (1,000-2,400)	1,500 (1,000-2,000)	600 (400-800)	3,700 (2,800-4,800)	1,200 (500-2,700)

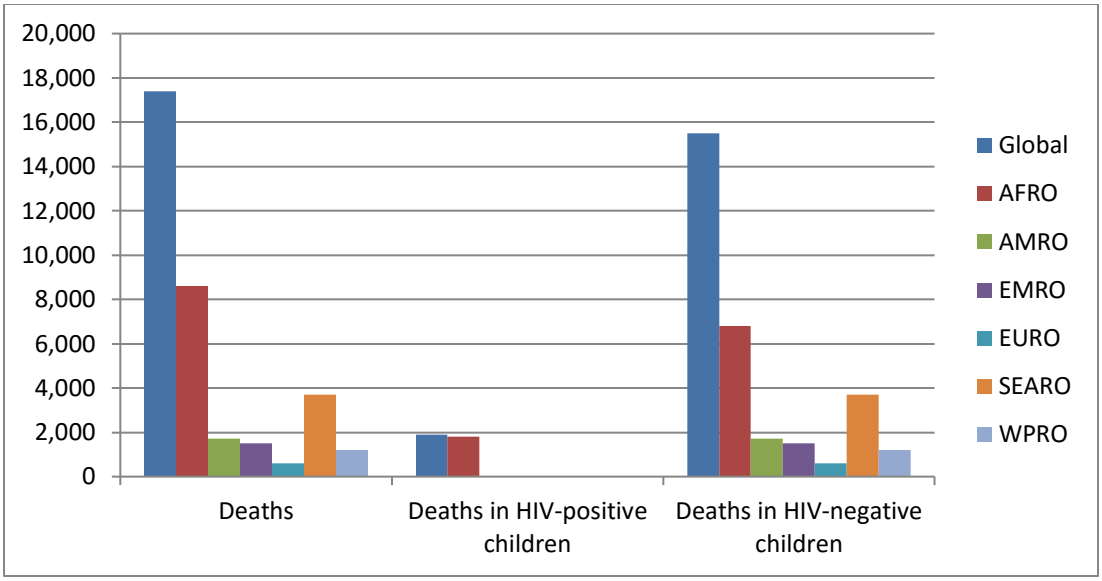


Figure 9: Deaths due to NPNM disease attributable to pneumococcus in children under 5 years, by WHO region 2008 (39)

Age Distribution of Pneumococcal Disease

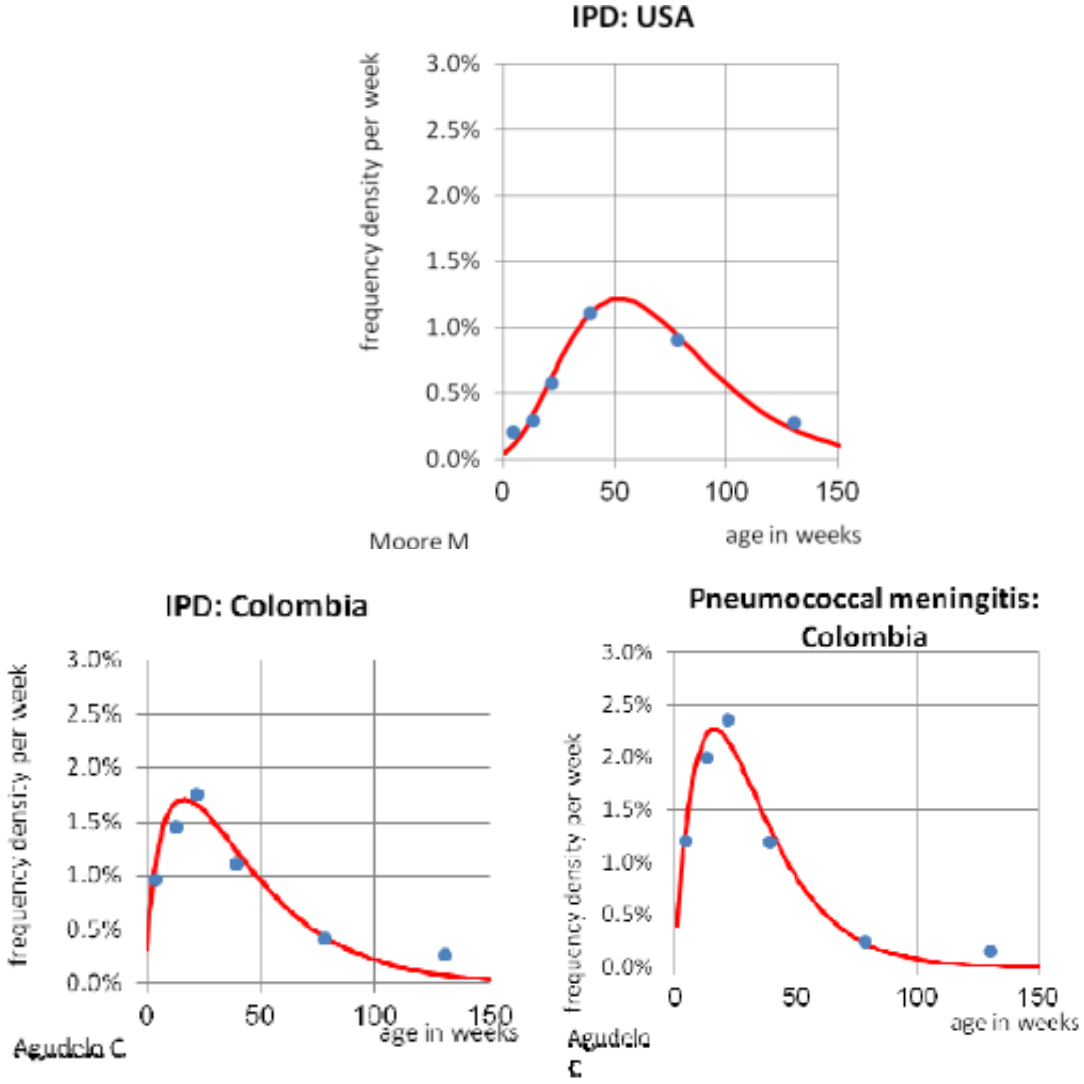
Among children U5, the highest burden of serious pneumococcal disease occurs in young infants, particularly among meningitis cases and in low-income settings.

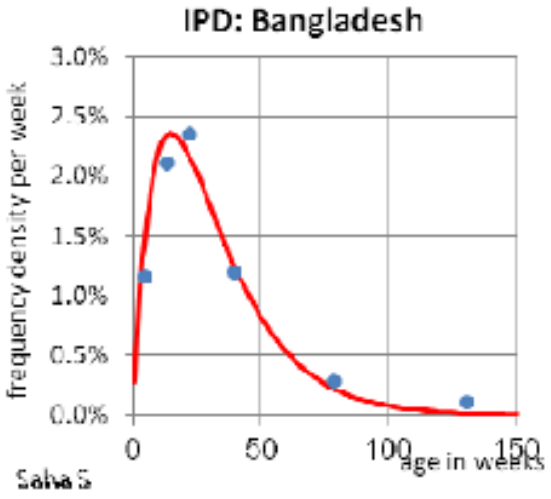
The age distribution of the pneumococcal disease rate follows a U-shaped curve with the highest burden of disease found in young infants, then in young children, and an increase found again in the elderly (62). In the US, surveillance for IPD demonstrates that the age distribution of pneumococcal mortality rate is highest among the elderly, followed by young infants (62). However, as discussed previously in this chapter, the proportionate mortality due to pneumococcus is a significant contributor to global deaths in children U5.

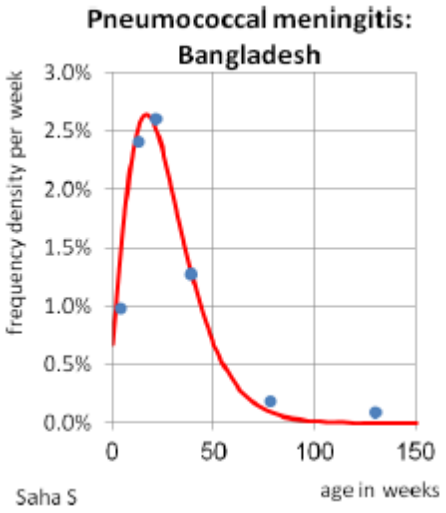
While IPD incidence rates are generally higher in developing countries in the absence of PCV, similar to developed country settings, the majority of IPD is found in younger age groups. However, the childhood peak of IPD incidence occurs earlier in developing countries compared to developed countries.(25) In a review of global data from 2011, 20% of IPD cases in the first 5 years of life was found to occur in infants less than six months of age, and 50% in those under 12 months.(63) The peak of pneumococcal meningitis is earlier than for other types of IPD, with 40% of the U5 cases occurring in infants less than six month of age, and 65% in infants under 12 months. Over half of all IPD cases in infants under two months is pneumococcal meningitis. For radiographically-confirmed pneumonia in children U5, between 9% and 52% occur in infants less than six months of age, depending on country. Between 19% and 54% of hospitalized clinical pneumonia in children occurs in infants less than six months of age. The peak age for pneumonia is slightly older and more variable by setting compared to that of IPD and meningitis.(63) The shape of age distribution curves for overall IPD and meningitis are left-skewed with a peak in early infancy that is more pronounced for low and middle income countries (LMICs) (i.e.

Colombia and Bangladesh) compared to a high-income country (i.e. U.S).(Figure 10)(63) In most settings, the incidence of pneumococcal disease declines after the second year and steadily increases again among adults older than 35 years.(25) Some of the differences in age distribution of IPD cases between countries and at the sub-national level may be due to study design, surveillance methods, access to care and health seeking behaviors.(63) To see age distribution curves for more countries included in the global review by Russell, et al, go to: http://www.who.int/immunization/sage/6_Russel_review_age_specific_epidemiology_PCV_schedules_session_nov11.pdf.

Figure 10: Age distribution for IPD and pneumococcal meningitis, 0-36 months, by country(63)







Neonatal Burden of Pneumococcal Disease

Data was limited on the burden of pneumococcal disease in the first two months of life according to the 2011 global review. There is likely a larger bias due to under-reporting in this age group with births occurring outside the hospital, higher CFR, and limited access to care. Based on the limited data available, however, it was estimated that 6% of IPD and 8% of pneumococcal meningitis cases occur in infants less than two months of age.(63)

In a 2016 systematic review of neonatal IPD, the estimate of pooled global incidence was 36.0 per 100,000 live births (95% CI 20.0, 64.7) in the pre-PCV era.(64) There was only one study with data from the least-developed country stratum (a UN designation), indicative of the limited data available on the burden of IPD in this age group: in a study from The Gambia there was an unweighted IPD incidence 369.5 per 100,000 live births (95%CI 119.2, 1138.5).

Serotype Distribution of Pneumococcal Disease

A relatively few number of serotypes (6-11) account for over 70% of IPD worldwide.

PCV10 serotypes account for an estimated 70% to 77% of IPD cases in children U5 in Asia, Africa, Oceania and Latin America/Caribbean. PCV13 serotypes account for 74% to 82% of IPD cases in young children from these regions.

There are over 90 pneumococcal serotypes which are immunologically distinct and vary in prevalence of NP colonization, clinical disease syndromes, and geographical distribution. Immunity to pneumococci is generally serotype-specific, but there is some cross-coverage within certain serogroups.(10) Since presence in the upper respiratory tract is the necessary precondition for development of disease in an individual, the serotype distribution of colonization is of substantial interest for understanding the serotype distribution of disease-causing strains, notwithstanding the fact that the two are not directly correlated. Studies of pneumococcal NP colonization in the pre-vaccine setting reveal that not all pneumococcal carriage strains are equally abundant, that some strains are rarely found in the

colonization state in spite of their prevalence as disease-causing strains in some settings (e.g. serotype 1 and 5), that more than one strain can cause colonization at any given time, but that the frequency of multiple serotype colonization varies by community. A dominant strain is usually present and the density of colonization is an important attribute of the colonization state which varies widely between individuals and over time(65). Furthermore, the distribution of serotypes causing colonization is much broader than that of disease causing strains.(28, 66)

In a 2010 systematic review of data on serotypes causing IPD in children U5, prior to the introduction of PCV, six to 11 pneumococcal serotypes accounted for over 70% of IPD. Serotype 14 was the most common, accounting for 12% to 29% of IPD in each region. Serotype 6B ranked second in every region except Africa. Serotype 1 was a common serotype that has the unique epidemiologic feature of causing outbreaks of meningitis in the African meningitis belt. Serotype 5 was also more common outside of high-income countries. Serotypes 1, 5 and 14 together accounted for 28% to 43% of IPD in each region.(66) Figure 11 shows the proportion of IPD due to serotypes by ordered rank in Gavi-eligible countries. The seven most common serotypes in Gavi-eligible countries—serotypes 1, 5, 6A, 6B, 14, 19F and 23F—accounted for 65% of IPD in Africa and 60% in Asia.(66) The coverage of PCV10 and PCV13 is shown in Figures 12 and 13, respectively. The highest coverage was in North America and Europe. In Asia, Africa, Oceania and Latin America/Caribbean, PCV10 coverage ranged between 70% and 77%, and PCV13 coverage between 74% and 82%. Data on serotype distribution from this systematic review served as the basis for the Target Product Profile (TPP) for the procurement of PCV through the Advanced Market Commitment (AMC) used by Gavi.(25, 67) For more information on the prevalence of serotypes by region, go to http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000348 for full access to the article by Johnson, et al.

Figure 11: Serotypes causing IPD in children under 5 years, 1980-2007: data from 20 Gavi-eligible countries(66)

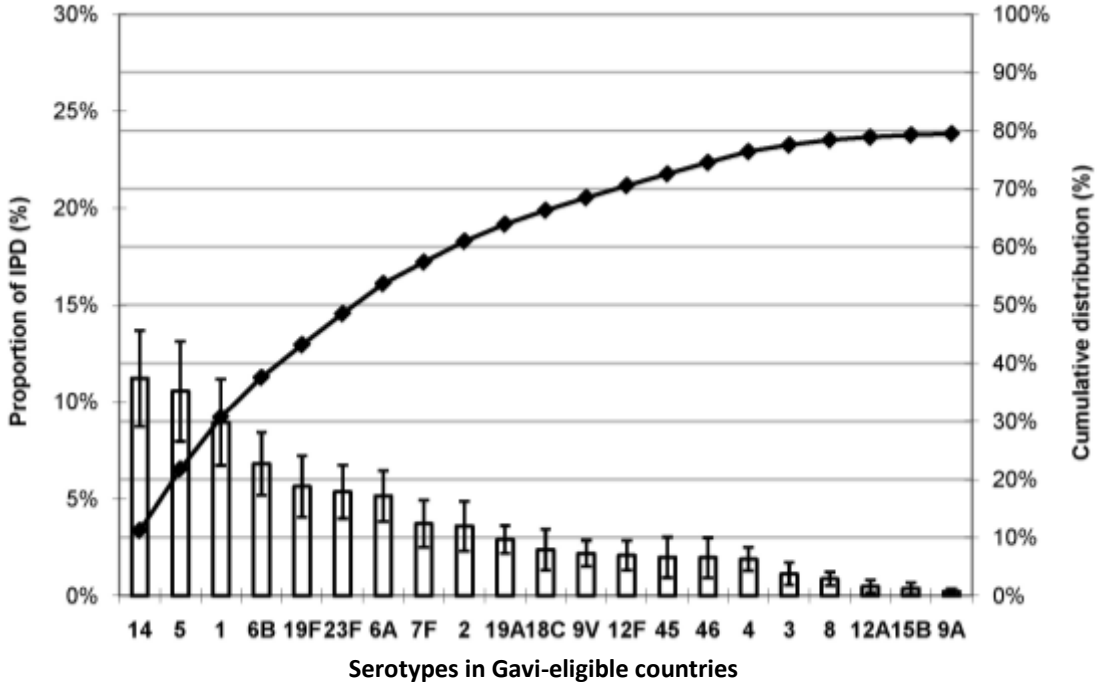


Figure 12: Proportion of IPD in children under 5 years caused by serotypes in PCV10, by region 1980-2007 (66)

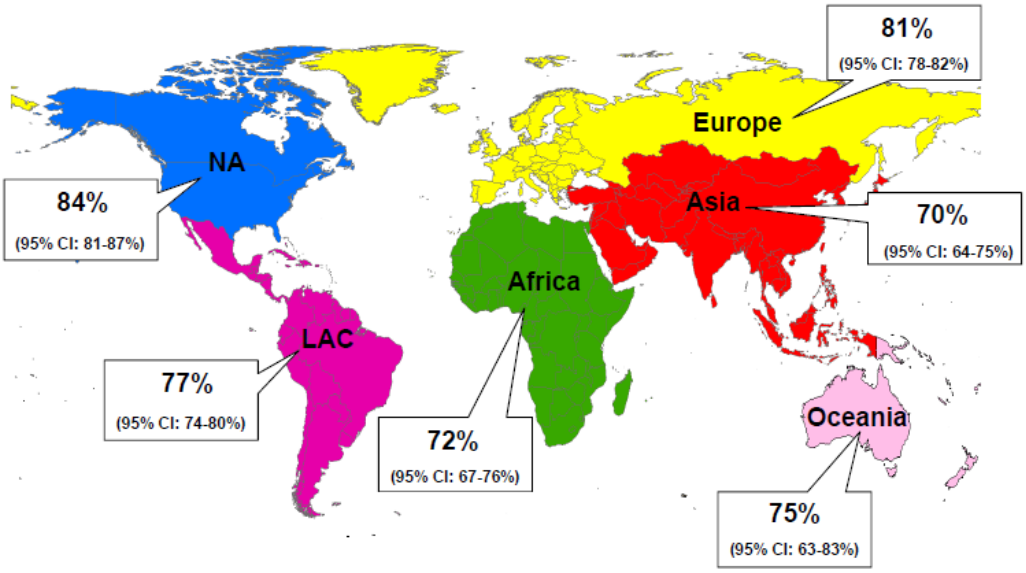
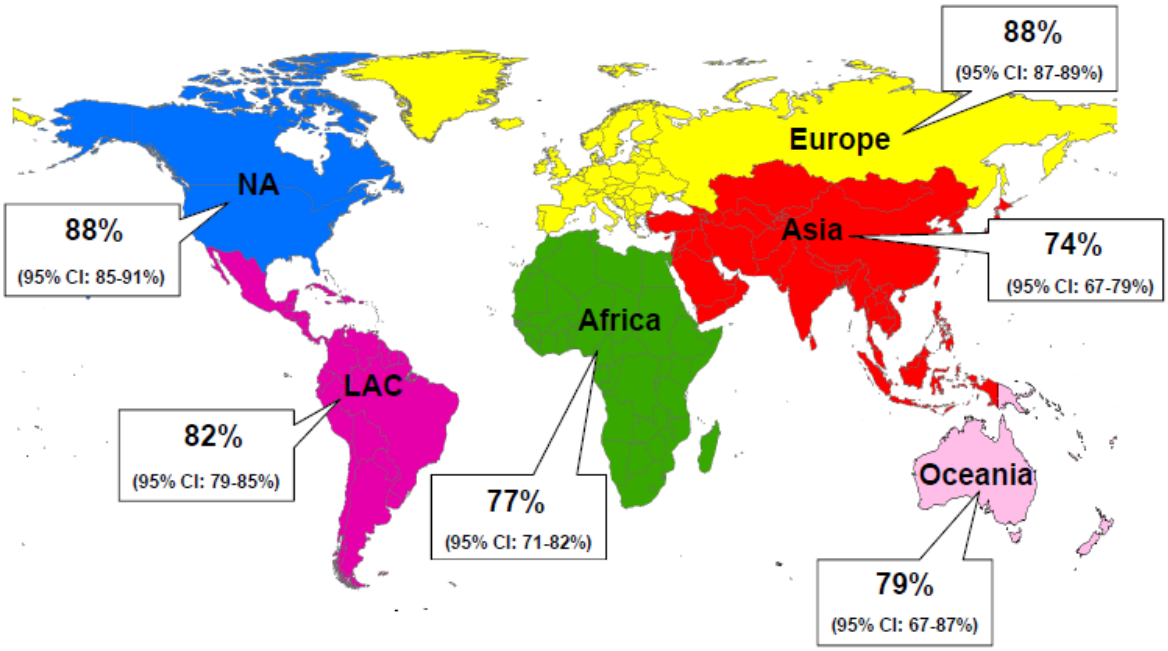


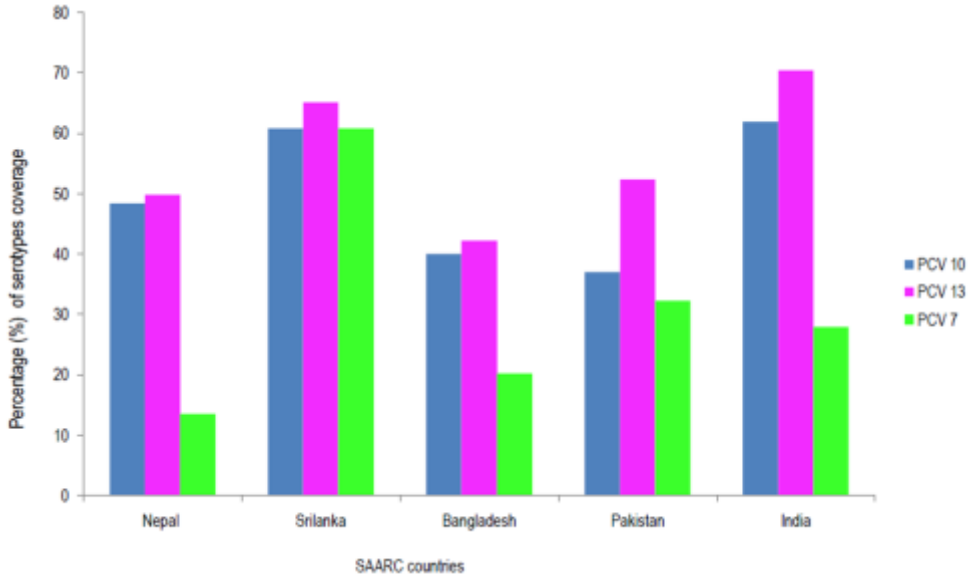
Figure 13: Proportion of IPD in children under 5 years caused by serotypes in PCV13, by region 1980-2007 (66)



At the time of the systematic review by Johnson, et al., there were limited or no data from countries with the largest populations of children U5 years of age (i.e. mainland China, India, Indonesia and Nigeria).(66) Recent publications provide some data on serotype distribution in these settings, but there are important methodological issues to bear in mind when interpreting the data. Some studies are limited by small numbers of samples and limited diagnostic techniques (i.e. culture alone versus culture plus the use of diagnostic tests such as immunochromatographic test (ICT) or polymerase chain reaction (PCR)). Antibiotic use in patients prior to specimen collection will decrease the likelihood of a positive culture, especially for infection with some serotypes of pneumococcus (i.e. those that are most likely to be antibiotic susceptible).

In a review of data on pneumococcal serotypes causing disease in children ≤12 years from South Asian Association for Regional Cooperation (SAARC) countries (India, Pakistan, Bangladesh, Sri Lanka, Nepal, Bhutan, Maldives and Afghanistan), serotypes in PCV10 accounted for an average of 50% of IPD isolates (varying from 37% in Pakistan to 62% in India), and PCV13 accounted for an average of 55% of IPD isolates (ranging from 42% in Bangladesh to 70% in India.)(68)(Figure 14) A study focusing on children U5 in Bangladesh found that PCV10 serotypes accounted for 46% of IPD isolates (annual range 29% to 57% from 2007-2013) and PCV13 serotypes 50% (annual range 37% to 64%).(69) In a review from Southeast Asia (Laos, Malaysia, Philippines, Singapore, Thailand and Vietnam), the coverage of PCV10 and PCV13 for IPD among all age groups was 53% and 65%, respectively.(70) In these studies, inclusion of older children and adults makes findings hard to compare to those from the GSP analysis since the serotype distribution of IPD varies with age. Generally, PCV serotypes are more commonly found in young children than in older children and adults, so the proportions reported from these studies that include those older than 5 years are likely underestimates of the coverage of PCV serotypes in young children.

Figure 14: Pneumococcal vaccine coverage by country, among children ≤12 years 1978-2008 (68)



Serotype distributions vary by syndrome, disease severity and carriage prevalence. These serotype-specific factors interplay with host-specific factors, such as age and comorbidity, and put populations at risk for disease.

In addition to some geographic variation, serotype prevalence also depends on the body fluid of isolation, clinical syndrome, and age of the host. Some serotypes are more able to colonize the nasopharynx and less likely to cause disease than other serotypes. Some serotypes, like serotypes 1 and 5, are rarely isolated from the nasopharynx of non-diseased individuals but are often cultured from persons with clinical disease.(71) These differences can be reflected in a serotype's case:carrier ratio(CCR) which is also referred to as the invasiveness of a strain.(72) Serotypes with more invasive potential—like types 1 and 5—have a higher CCR than those which are less invasive. These serotypes with a lower CCR ratio are relatively more common colonizers and not as virulent (i.e. less likely to cause disease, given an episode of colonization). Those serotypes with high CCRs are more likely to cause disease given an episode of colonization. The invasiveness of a serotype appears to be inherent to that serotype with those strains that are more heavily encapsulated tending to be more prevalent colonizers in young children and less likely to cause invasive disease.(73)

Serotypes also differ in their predilection for site of infection, risk of death, and antibiotic resistance.(71, 73) Serogroups 6, 10 and 23 are relatively more commonly isolated from CSF specimens than from blood, whereas serotypes 1, 4, and 14 are more commonly isolated from blood than CSF. Serotypes 1 and 3 are disproportionately represented in the subgroup of patients with severe or complicated pneumonia (i.e., with empyema).(71) In a UK study, serotypes 18C, 19F and 6B were more likely to be associated with pediatric meningitis, while serotypes 1, 3 and 19A were more likely associated with empyema.(74) In addition, serotype 1 has shown epidemic potential both for pneumonia and for meningitis; in particular type 1 has been documented in outbreaks of meningitis in the African meningitis belt countries.(57-59) In a meta-analysis of pneumococcal pneumonia cases among all age groups, serotypes 3, 6A, 6B, 9N and 19F had a higher risk ratio of death compared to serotypes 1, 7F and 8.(73) Antibiotic resistance is more common among the vaccine serotypes 6A, 6B, 9V, 14, 19A, 19F and 23F. Some clones are particularly associated with antibiotic resistance (either very high minimum inhibitory concentration or resistance to multiple antibiotics), indicating that genotype, as well as serotype, is an important factor in antibiotic resistance.(71)

Diagnosis of Pneumococcal Disease

Pneumococcus is difficult to detect in the laboratory; newer diagnostic tests with enhanced sensitivity for detecting pneumococcus add to our understanding of the burden of disease.

There are substantial limitations of the data on the burden of pneumococcal disease primarily related to the lack of sensitivity to detect pneumococcus in true cases of pneumococcal disease. This is reflected in the proportion of suspected cases of pneumococcal disease in whom pneumococcus is confirmed and in the fraction of true pneumococcal cases (as revealed through the absolute rate reduction observed in the PCV trials) that were detected by culture. The most common pneumococcal disease syndrome is 'clinically diagnosed pneumonia'. However even in these cases, most are not identified as being pneumococcal in origin either because there is no blood culture done, the blood culture does not detect bacteria present in the blood stream (false negatives), or there is no bacteremia (e.g. pneumonia from contiguous spread in the respiratory tract which is termed non-bacteremic pneumococcal pneumonia). So, laboratory surveillance for pneumococcal disease lacks sensitivity both because of the laboratory techniques available, and because not all pneumococcal disease has pneumococci present in the body fluids that are most readily accessible for testing (i.e. blood). The best tool available for determining the

burden of pneumococcal disease are the vaccine trials which when analyzed as a vaccine probe study, reveal the vaccine preventable disease rate from which inferences can be drawn about the total pneumococcal disease rate.

Pneumococcus, a fastidious bacterium, is difficult to detect through culture even when it is truly present in the body fluid specimen, particularly if samples are not processed immediately or handled properly, if an insufficient volume of the body fluid is collected, or if the patient has received antibiotics before the specimen was collected. Other diagnostic tests for pneumococcus that are not based on culture include antigen detection assays or nucleic acid detection assays both of which are useful for testing sterile site fluids such as CSF from suspected meningitis cases or pleural fluid from suspected empyema cases. Testing of urine by antigen detection in children is not helpful since antigen is shed in the urine of colonized individuals, and colonization is so prevalent in children. PCR of blood is also not routinely done or recommended since colonization also appears to result in positive results of blood PCR for pneumococcus.

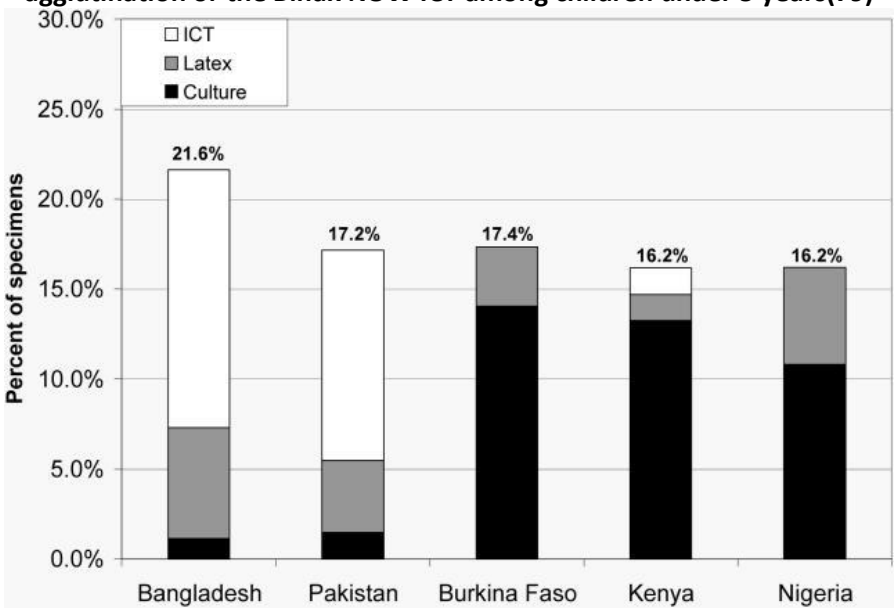
"In recent decades, new diagnostic techniques have been employed to identify pneumococcal disease. First, tests are available that can identify certain pneumococcal antigens. Those that target polysaccharide capsule antigens, including commercial latex agglutination tests, are not highly specific for pneumococcus and are therefore not believed to have much clinical relevance.(75) More reliable antigen detection tests include rapid immunochromatographic tests (ICT), tests sensitive to C polysaccharide cell wall antigen common to all pneumococci.(76) The only available ICT that identifies this antigen is manufactured by Alere and is called BinaxNOW®. It is designed to be used with urine (86% sensitivity and 94% specificity, compared to culture) and CSF (97% sensitivity and 99% specificity, compared to culture).(77) However, this test can detect pneumococcal colonization among healthy children, as pneumococcal antigens are shed in the urine. As such, it is most useful clinically in adult populations, where colonization prevalence is much lower."(25)

"Diagnostic tests based on nucleic acid amplification, such as polymerase chain reaction (PCR), are also used to identify pneumococcus and diagnose pneumococcal disease. PCR is most useful for diagnosing pneumococcal meningitis, where it has demonstrated high sensitivity (92% to100%) and high specificity (100%) compared to culture.(76) The high sensitivity and specificity of PCR on CSF is likely attributable to the low likelihood of contamination and the high concentration of pneumococcal cells found in the CSF of a patient with bacterial meningitis.(76) PCR performs less well with blood and sputum samples. For blood, PCR's sensitivity ranges from 29% to 100% in adults and 57% to 100% in children, compared to culture.(78) Pneumococcus is quickly cleared from the blood, which could lead to lower sensitivity estimates using such samples.(78) In addition, the low volume of blood (i.e., 100 µL) used for PCR reduces the probability of detecting the pathogen. Interestingly, PCR can provide positive results in seemingly healthy children, though the mechanisms through which this could possibly occur are not known. With respiratory samples, PCR also demonstrates a wide sensitivity range when compared to culture (68% to 100%).(78)"(25)

In spite of the challenges with the use of newer diagnostic tests, their careful and judicious application has helped to clarify the burden of pneumococcal disease, particularly in Asia. These diagnostic tests for CSF have been used in study settings but are only available at specific labs (i.e. reference labs) so are not widely available for routine use. In a study done in South Asian and African countries, ICT had much

better yield for identification of pneumococcus from CSF specimens, compared to CSF culture, in the South Asian sites of Bangladesh and Pakistan. (79)(Figure 15) With the additional cases detected by ICT, rates of pneumococcal meningitis from these South Asian sites were similar to global pre-vaccine rates and similar to rates from the African sites, where more specimens were positive by culture. Prior antibiotic use, the type of first-line antibiotic used, laboratory techniques, and better access to care are potential reasons for lower antigenic loads in CSF in South Asia that may have underestimated the burden of pneumococcal disease using culture alone for diagnosis.(25, 79)

Figure 15: Proportion of cerebrospinal fluid specimens positive for pneumococcus by culture, latex agglutination or the Binax NOW ICT among children under 5 years(79)



Risk Factors for Pneumococcal Disease

HIV infection increases the risk and severity of pneumococcal disease in children. The routine use of highly active antiretroviral therapy (HAART) reduces but does not negate this risk. HIV exposure (i.e. children born to HIV infected mothers, but themselves uninfected) also confers an increased risk of pneumococcal disease.

There is evidence indicating a synergistic interaction between pneumococcus and other respiratory pathogens, such as influenza, that increase individual susceptibility to upper and lower respiratory tract disease.

Sickle cell disease, and the resulting functional asplenia, is another significant individual risk factor for pneumococcal disease.

The risk of IPD in children with HIV infection has been reported in many studies from South Africa and the US. In a 2008 review, in the absence of HAART, HIV infection was associated with a 9- to 43-fold increase in IPD rate compared to rates observed in HIV-uninfected children.(80) Higher risk was reported in the studies from South Africa, where the relative risk of IPD was 36- to 43-fold higher in HIV-

infected compared to HIV-uninfected children.(80) HIV infection also increased the likelihood that children experience multiple episodes of IPD and/or severe IPD.(80)

Use of HAART in South Africa has coincided with a 50% reduction in the incidence of IPD in children with HIV.(81) Risk of IPD, however, continues to be much higher among HAART-treated, HIV-infected children compared to HIV-uninfected children. With the established use of HAART, children under two years of age with HIV infection had a 21-fold higher risk of IPD and children 2-4 years had 32-fold higher risk compared to age-matched, HIV-uninfected children.(81) There is also evidence that infants who are HIV exposed (e.g. born to HIV-positive mothers) but uninfected (HEU) still have an increased risk of IPD incidence and mortality compared to infants who are HIV-unexposed and uninfected (HUU): the incidence rate ratio of IPD was 3.1 (95% CI 2.6, 3.7) in HEU compared to HUU children.(82) The IPD CFR in HEU infants (29%) was intermediate between the CFR in HIV-infected (34%) and HUU infants (25%).(82)

Viral and bacterial pathogens have been associated with pneumococcal co-infection in the respiratory tract and likely increase a person's susceptibility to more severe disease.(83) Viral pathogens such as influenza, parainfluenza, measles, respiratory syncytial virus and human metapneumovirus have all been associated in at least some studies with increased risk of pneumococcal co-infection.(83-86) Among bacterial pathogens, *Haemophilus influenzae*, *Mycoplasma pneumoniae* and *Mycobacterium tuberculosis*, have also been more frequently associated with pneumococcal co-infection.(83, 87) These findings of viral and bacterial co-infection risk have not been widely replicated across multiple study sites and remain somewhat controversial in their magnitude and causal association. Evidence from experimental animal models, ex vivo tissue culture studies, ecological studies, observational studies and RCTs all support an interaction between respiratory viruses and pneumococcus in the pathogenesis of upper and lower respiratory tract infection.(83) For example, influenza virus predisposes individuals to pneumococcal pneumonia by: increasing the release of bacteria from the nasopharyngeal biofilm, altering physical barriers in mucosal immunity, exposing host receptors that increase bacterial adherence, dysregulating the immune system with diminished macrophage recruitment, affecting the lung repair mechanisms, and increasing density of bacterial shedding.(88, 89) Vaccine efficacy trials provide information on the proportion of pneumococcal disease associated with viral co-infection. In the South Africa 9-valent PCV (PCV9) RCT, children randomized to receive PCV were 31% less likely to be hospitalized for pneumonia in which any respiratory virus was identified compared to controls.(90) It is also in this trial that a 43% reduction in hospitalization for confirmed pulmonary tuberculosis (TB) was seen in vaccine recipients compared to controls.(87) It may be that TB was a risk factor for pneumococcal pneumonia (i.e. perturbed pulmonary tissue) rather than acting as a co-infection associated risk.

Sickle cell disease, and its resulting functional asplenia, is another established risk factor for IPD in children. In the US, the rate of IPD was 53-fold higher among persons of all ages with sickle cell disease compared to the general population prior to the introduction of PCV.(91) In a meta-analysis from Africa, the pooled odds ratio of risk of IPD was 26- to 36-fold higher in persons with sickle cell disease compared to unaffected controls.(92, 93)

"Other host factors associated with greater risk of pneumococcal infections include chronic lung infections, some hematologic malignancies, protein energy malnutrition, and other micronutrient

deficiencies (i.e., vitamin A).(94, 95) In the . . .US, some ethnic minorities (i.e., Native Americans, African American) demonstrate higher pneumococcal disease incidence rates compared to the general US population or to those identified as Caucasian.(96) Although pneumococcal disease rates in all ethnic and racial groups have declined significantly with the use of PCV, the health disparities in the residual pneumococcal disease rates persist.(97) Because individuals carrying pneumococcus are the primary source of transmission, crowded living situations are associated with increased risk of pneumococcal infections.(94) Chronic inhalation of smoke is also a risk factor.(94, 95)”(25)

Chapter 2: Interventions to Prevent and Control Pneumococcal Disease

Chapter 2 Overview

Millennium Development Goal (MDG) 4 was to reduce the under-five mortality rate by two thirds between 1990 and 2015. While progress has been made and U5 mortality decreased 53% globally from 91 deaths per 1,000 live births in 1990 to 43 deaths in 2015, efforts need to be continued to maintain and accelerate the gains achieved.(2) In 2015, the United Nations adopted 17 Sustainable Development Goals (SDGs) to articulate and measure continued progress in human and environmental conditions. SDG 3 is to "ensure healthy lives and promote wellbeing for all at all ages", and one SDG 3 target is to "end preventable deaths of newborns and children under 5 years age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 23 per 1,000 live births" by 2030. Progress towards SDG 3 thus needs to include strategies to reduce the incidence and mortality of pneumonia, the leading cause of death in children U5.

Strategies to prevent children from getting pneumonia include exclusive breastfeeding promotion and support, universal coverage of immunization, HIV prevention and healthy environments that reduce exposure to indoor air pollution. Children who are ill from pneumonia should be treated appropriately; this includes appropriate care seeking (i.e. ability of caregivers to recognize serious symptoms, seek care and have appropriate care available) and antibiotic treatment.

Proven strategies to reduce the burden of pneumonia are not equitably implemented between or within countries, putting children at continued risk for significant morbidity and mortality. In 2013, an estimated 59% of children with suspected pneumonia were taken to a healthcare provider based on a subset of 78 countries with available data from national surveys, Multiple Indicator Cluster Surveys (MICS) or Demographic Health Surveys (DHS), and this proportion was 49% in the least developed countries. The disparity between the proportion of children receiving care in the least developed countries and the global estimate is likely underestimated because data is not included from many high-income countries. There is also much variation between countries and within countries in the proportion of children with pneumonia who receive antibiotic treatment. Regional average estimates of children with pneumonia symptoms receiving antibiotic treatment range from 25% in South Asia to 62% in the Middle East and North Africa based on data from 104 countries for 2009-2013.

Access to PCVs is a key strategy in the comprehensive approach to childhood pneumonia reduction. Prevention of disease through vaccination is more likely to accelerate the goals of equity than is the effort to expand access to appropriate treatment of disease, as important as those efforts are. As the WHO 2012 position paper states: "WHO recommends the inclusion of PCVs in childhood immunization programmes worldwide. In particular, countries with high childhood mortality (i.e. under 5 mortality rate of >50 deaths/1000 live births) should make the introduction of these multicomponent PCVs a high priority." In all countries, but particularly in those countries with many pneumonia and U5 deaths, preventing pneumococcal disease in the first place is more advantageous from an ethical and societal perspective than aiming to treat children once they fall ill.

Goals for Pneumonia Prevention and Treatment

Reducing pneumonia mortality is a high priority to achieve a significant reduction in U5 mortality.

Millennium Development Goal (MDG) 4 was to reduce the under-five mortality rate by two thirds between 1990 and 2015.(98) While progress has been made and U5 mortality decreased 53% globally from 91 deaths per 1,000 live births in 1990 to 43 deaths in 2015, efforts need to be continued to maintain and accelerate the gains achieved.(2) (For country and regional data on U5 mortality rates and trends, go to: http://www.childmortality.org/.) In 2015, the United Nations adopted 17 Sustainable Development Goals (SDGs) to articulate and measure continued progress in human and environmental conditions. SDG 3 is to "ensure healthy lives and promote wellbeing for all at all ages", and one SDG 3 target is to "end preventable deaths of newborns and children under 5 years age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 23 per 1,000 live births" by 2030.(99) Pneumonia is one of the leading causes of death in children U5, accounting for 16% of all deaths in the U5 age group in 2015.(2) Progress towards SDG 3 thus needs to include strategies to reduce the incidence and mortality of pneumonia. Many countries with a high burden of pneumonia also have a high burden of diarrhea in young children—another common cause of infectious mortality U5--and some of the same risk factors predispose children to both infections. It is from this reality and pragmatic approach that UNICEF and the WHO authored the Global Action Plan for Pneumonia and Diarrhea (GAPPD). The GAPPD lays out the goals of reducing mortality from pneumonia in children U5 to fewer than 3 per 1,000 live births by 2025 and reducing the incidence of severe pneumonia by 75% compared to 2010 levels.(100)

Proven Strategies to Reduce the Burden of Pneumonia

Access to PCV is an integral part of reducing the burden of childhood pneumonia.

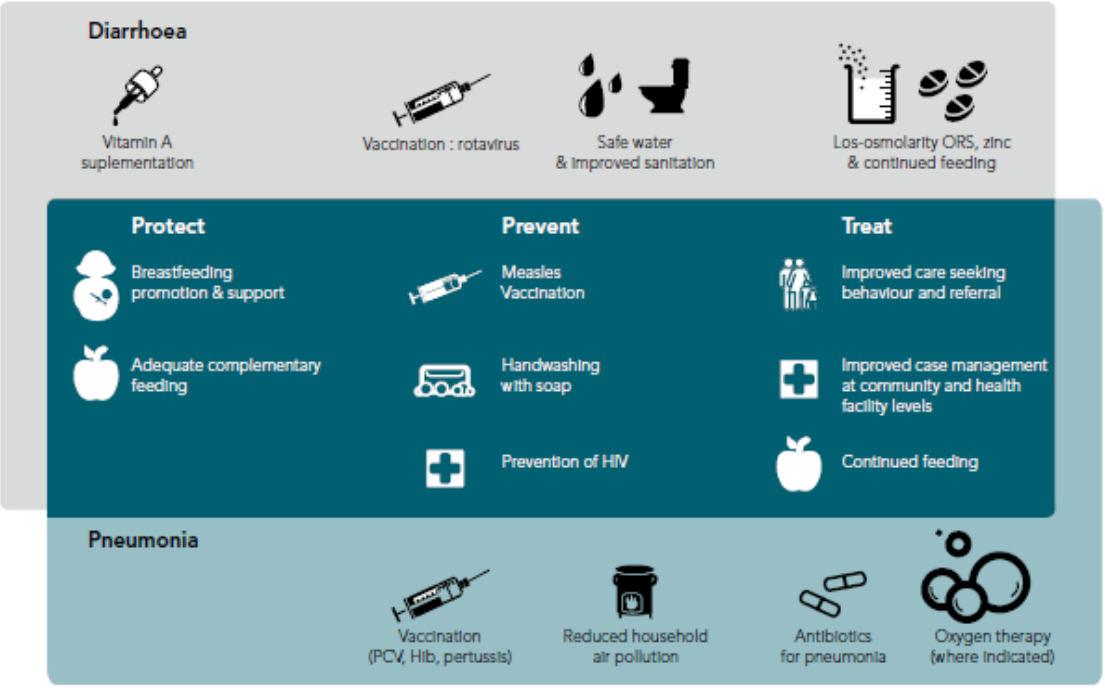
The GAPPD articulates a Protect-Prevent-Treat framework to categorize interventions that reduce the burden of pneumonia and diarrhea. Many interventions impact the risk or outcome of both diseases, while some interventions are specific to one disease. Figure 16 presents the key interventions that have been proven to reduce the burden of childhood pneumonia and/or diarrhea.

The good health practices of breastfeeding promotion and support (e.g. exclusive breastfeeding for the first six months of life) and adequate complementary feeding after six months protect children by reducing the incidence of malnutrition, an underlying risk factor that is associated with pneumonia, diarrhea and 35% of deaths in children U5.(100) One study estimated that exclusive breastfeeding for the first six months can result in a 23% reduction in pneumonia incidence.(100, 101) Another study found that infants are at a 15-fold higher risk of death from pneumonia if they are not breastfed at all in the first six months compared to infants who are exclusively breastfed.(100, 102)

Strategies to prevent children from getting pneumonia include universal coverage of immunization, HIV prevention and healthy environments. Children should have access to life-saving immunizations that target pneumonia prevention including measles containing vaccine, pertussis vaccine, Hib conjugate vaccine and PCV. As noted earlier, HIV infection can increase the risk of pneumococcal disease by 9- to 43-fold in children, thus prevention of maternal to infant HIV transmission is also critical.(80) Hand

washing with soap, reducing exposure to household air pollution and overcrowding are environmental interventions to reduce the risk of pneumonia. In one study from Guatemala, halving household air pollution exposure by use of chimney stoves reduced severe pneumonia by 33% in young children.(100, 103) The reproducibility of this study and the generalizability of its findings are not clear. In many parts of the world where indoor air pollution is severe, the contribution of improved stoves to reducing overall air pollution exposure may be minimal because of substantial air pollution from other sources. This is an area of considerable current investigation.

Figure 16: Complementarity of pneumonia and diarrhea interventions(100)



Finally, children who are ill from pneumonia should be treated appropriately; this includes appropriate care seeking (i.e. ability of caregivers to recognize serious symptoms, seek care and have appropriate care available) and antibiotic treatment. Specific strategies for treatment of children include: improved care seeking and referral, improved case management at community and health facility levels, continued feeding of children, appropriate antibiotic selection, and oxygen therapy, if indicated.(100) As stated in the GAPPD, "use of simple, standardized guidelines for the identification and treatment of pneumonia and diarrhea in the community, at first-level health facilities and at referral hospitals substantially reduces child deaths."(100) According to some studies, community case management results in a 35% reduction in child pneumonia mortality, and a 21% reduction in all-cause mortality.(100, 104)

Limited Use of Proven Strategies

Since 1990, the U5MR has halved to 43 per 1,000 live births worldwide in 2015. However, gains in child survival have been uneven, with the U5MR ranging from 6 deaths per 1,000 live births in2015 in high-income countries to over 100 deaths per 1,000 live births in 7 countries.(2)

Proven strategies to reduce the burden of pneumonia –such as appropriate care seeking and case management for children with pneumonia symptoms--are not equitably implemented between or within countries, putting children at continued risk for significant morbidity and mortality.(105)

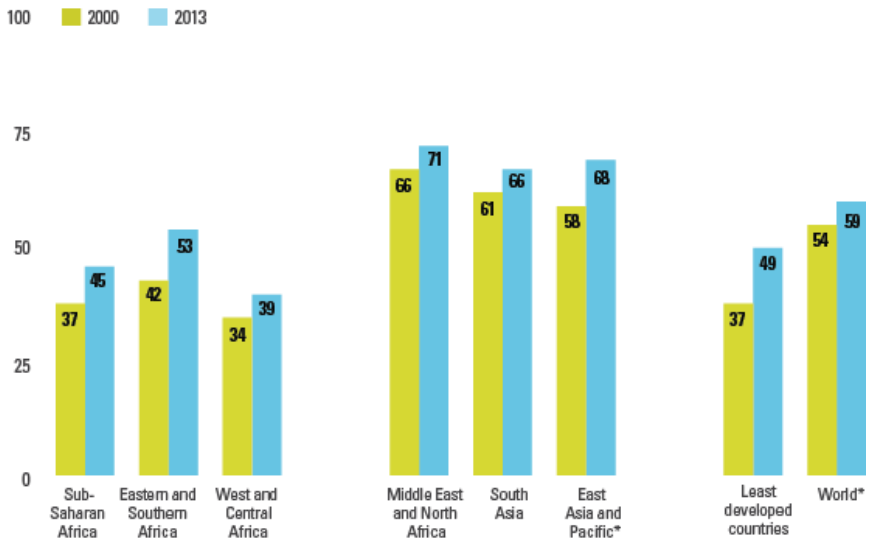
Since 1990, the U5MR has decreased globally by 53%--short of the MDG 4 goal of two thirds—to 43 per 1,000 live births worldwide in 2015.(2) Yet this average U5MR masks the large inequities between developed and developing regions. In developed regions the average U5MR was 6 deaths per 1,000 live births in 2015, compared to 47 deaths per 1,000 in developing regions, an eight-fold difference. Seven countries (all of them in sub-Saharan Africa) had a U5MR over 100 deaths per 1,000 in 2015.(2) As stated in the previous chapter, pneumonia is the single leading cause of death in children U5, causing one in six deaths in children U5 and almost one in four of deaths in children 1-59 months old.(41)

One reason for the significant inequities in child survival is that children in the poorest settings are less likely to get appropriate treatment for suspected pneumonia. Many vulnerable populations in low-income countries do not have equal access to key interventions such as appropriate healthcare seeking and case management for children with pneumonia symptoms. As stated in the GAPPD, gains in child survival have been "uneven both across and within countries," and "children are dying because services are provided piecemeal and those most at risk are not being reached."(100) In 2013, an estimated 59% of children with suspected pneumonia were taken to a healthcare provider based on a subset of 78 countries with available data from national surveys, Multiple Indicator Cluster Surveys (MICS) or Demographic Health Surveys (DHS), and this proportion was 49% in the least developed countries.(105)(Figure 17) The disparity between the proportion of children receiving care in the least developed countries and the global estimate is likely underestimated because data is not included from many high-income countries. Regional average estimates of the proportion of children with pneumonia symptoms seen by a healthcare provider ranged from 39% in West and Central Africa to 74% in East Asia and the Pacific (excluding China) for the period 2009-2013. For available country-level estimates of children with pneumonia symptoms taken to a healthcare provider, visit the UNICEF pneumonia website at: http://data.unicef.org/child-health/pneumonia.

Inequities in access to care for pneumonia within countries are driven partly by gaps between urban and rural populations and by gaps in access to care among the richest and poorest families.(105) Based on data from UNICEF on a subset of 78 countries, children in urban areas are more likely to be seen by a healthcare provider when symptoms of pneumonia arise than children in rural areas.(105)(Figure 18) Data also show large coverage gaps in care-seeking behavior among children from the richest and poorest 20% of the population as defined by families' wealth quintile. Based on estimates from 46 countries, 73% of children with suspected pneumonia from families in the richest quintile within countries are taken to a healthcare provider, compared to 52% of children with suspected pneumonia and from families in the poorest quintile in 2009-2013.(105)(Figure 19) This gap was even more pronounced in the least developed countries with 66% of children from the richest families taken to a healthcare provider versus only 38% of children from the poorest families.(105) A study on the association between distance to a health center and risk of child mortality and pneumonia in rural Gambia found that children residing over five kilometers from a larger healthcare facility had a 2.8-fold

increased risk of all-cause mortality compared to children residing within 2 kilometers of a facility but a lower risk of pneumonia.(106) The authors attributed this to lower case ascertainment, or diagnosis of pneumonia, in children living further away from a facility compared to those residing closer as they were less likely to be seen by a healthcare provider or trial staff.

Figure 17: Proportion of children under 5 years with symptoms of pneumonia who are taken to a healthcare provider, 2000 and 2013(105)

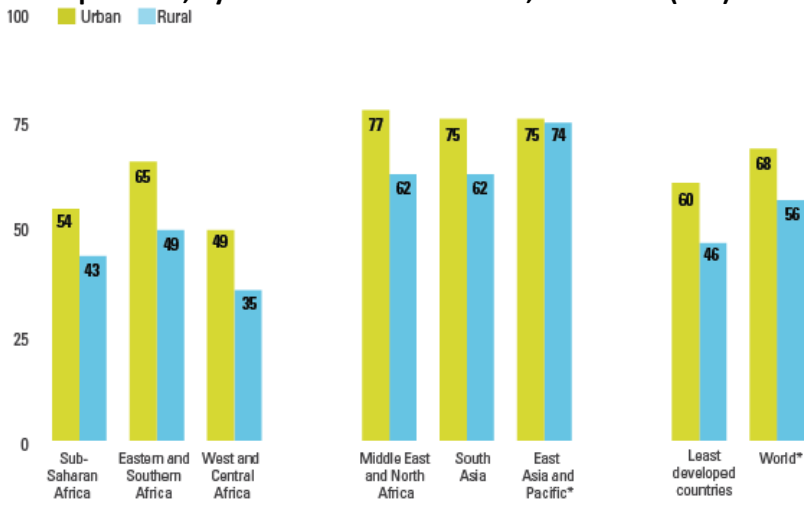


*excludes China

Notes: Estimates are based on a subset of 78 countries with available data for 2000 and 2013, covering 67% of the global population U5 (excluding China, for which comparable data are unavailable) and at least 50% of the U5 population in each region. Data coverage was insufficient to calculate the regional averages for Central and Eastern Europe and the Commonwealth of Independent States and Latin America and the Caribbean.

Source: UNICEF global databases, 2014, based on MICS, DHS and other national surveys.

Figure 18: Proportion of children under 5 with symptoms of pneumonia taken to a healthcare provider, by urban or rural residence, 2009-2013(105)

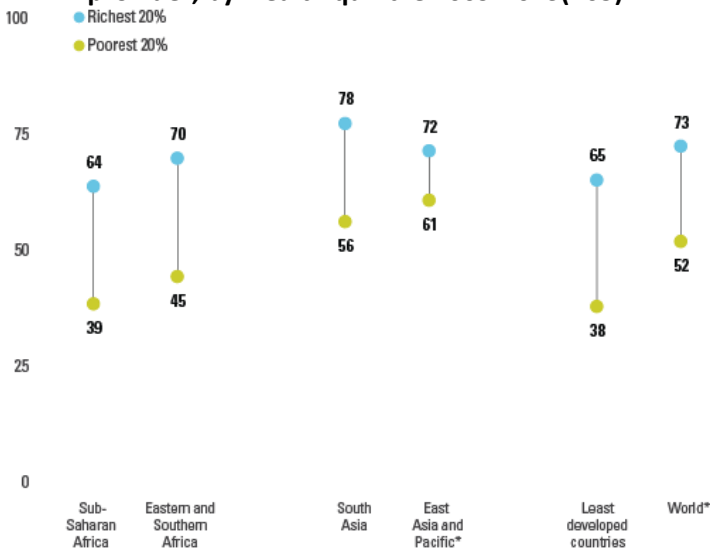


*excludes China

Notes: Estimates are based on a subset of 78 countries with available urban and rural data for 2009-2013, covering at least 50% of the U5 population in each region included in the analysis. Data coverage was insufficient to calculate a global average as well as the regional averages for the Commonwealth of Independent States and Latin America and the Caribbean.

Source: UNICEF global databases 2014, based on MICS, DHS and other national surveys.

Figure 19: Proportion of children under 5 with symptoms of pneumonia taken to a healthcare provider, by wealth quintile 2009-2013(105)



*excludes China

Notes: Estimates are based on a subset of 46 countries with available data for 2009-2013, covering at least 50% of the U5 population in each region shown. Data coverage was insufficient to calculate a global average as well as the regional averages for the Commonwealth of Independent States, Latin America and the Caribbean, the Middle East and North Africa and West and Central Africa.

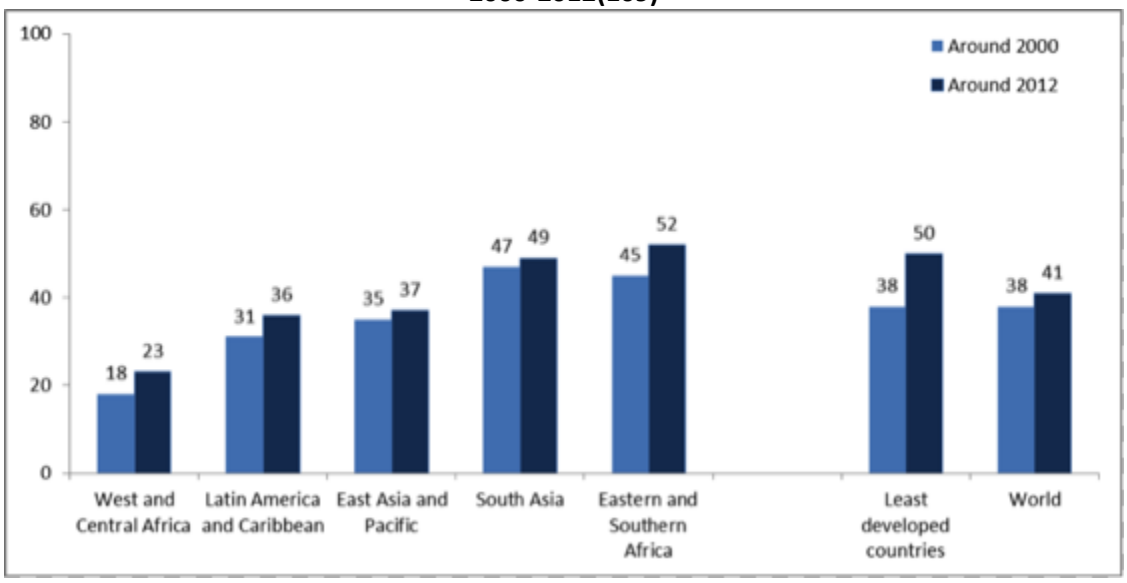
Sources: UNICEF global databases 2014, based on MICS, DHS and other national surveys.

If a child has pneumonia, death can be prevented through "prompt, cost-effective and life-saving treatment" such as antibiotics for bacterial pneumonia. (105) In the 1980's the WHO and UNICEF

formulated an approach for pneumonia diagnosis and treatment in low-resource settings. These efforts led to the creation of the Integrated Management of Childhood Illness (IMCI) guidelines, an approach to the main causes of childhood morbidity and mortality in which community-based healthcare workers could triage sick children and provide treatment or make referrals when appropriate (105) Pneumonia was originally classified in three categories of variable severity. In 2014 the WHO published revised classification guidelines for pneumonia which reduced the categories to two. The first category is pneumonia with fast breathing (previously "pneumonia") and/or chest indrawing (previously "severe pneumonia") which can be treated with oral amoxicillin on an outpatient basis. The second category is severe pneumonia (previously "very severe pneumonia") which is pneumonia accompanied by a danger sign--such as inability to drink, persistent vomiting, convulsions, lethargy or unconsciousness, stridor in a calm child or severe malnutrition —which requires hospital admission and injectable antibiotic therapy.(107) There is much variation between countries and within countries in the proportion of children with pneumonia who receive antibiotic treatment. Regional average estimates of children with pneumonia symptoms receiving antibiotic treatment range from 25% in South Asia to 62% in the Middle East and North Africa based on data from 104 countries for 2009-2013.(105) For available country-level estimates of children with pneumonia symptoms who receive antibiotic treatment, visit the UNICEF pneumonia website at: http://data.unicef.org/child-health/pneumonia.

Other factors associated with children's risk of developing pneumonia are appropriate breastfeeding (a protective factor) and indoor air pollution (a risk factor). Around 2012, 50% of infants in the least developed countries and 41% of infants from 62 countries were exclusively breastfed for the first six months of life.(108)(Figure 20) While gains have been made in the least developed countries from 2000-2012, there is still room for improvement as 50%-60% infants worldwide are on formula or mixed feedings and, hence, are at increased risk for disease and malnutrition. Non-breastfed infants may be exposed to more water-borne and food-borne pathogens at an early age when their immune systems are still immature, and they are not receiving the full benefit of maternal antibodies present in breastmilk that help protect against disease in early infancy. Many children from low-income settings are also exposed chronically to indoor air pollution as a large portion of the world's population—3 billion people—still rely on inefficient, polluting solid fuels for cooking and heating.(100)

Figure 20: Proportion of infants aged 0-5 months that are exclusively breastfed by region, around 2000-2012(109)



Notes: Estimates are based on a subset of 62 countries with available trend data (excludes Brazil and China due to the lack of trend data). Regional aggregates are presented where adequate population coverage is reached. Rates for around 2012 may be different from those presented as "current regional/global estimates" since the trend analysis is based on a subset of countries.

Source: UNICEF global databases 2014, based on MICS, DHS and other nationally representative surveys.

Pneumococcal Vaccination—A Global Priority

Access to PCVs is a key strategy in the comprehensive approach to childhood pneumonia reduction.

Prevention of disease through vaccination is more likely to accelerate the goals of equity than is the effort to expand access to appropriate treatment of disease, as important as those efforts are.

While increasing the proportion of children with pneumonia symptoms who are seen by a healthcare provider and receive appropriate case management is an important aspect of pneumonia control and child survival, prevention of the most common cause of bacterial pneumonia through introduction of PCV is a complimentary and key strategy. As the WHO 2012 position paper states:

> **"WHO recommends the inclusion of PCVs in childhood immunization programmes worldwide. In particular, countries with high childhood mortality (i.e. under 5 mortality rate of >50 deaths/1000 live births) should make the introduction of these multicomponent PCVs a high priority."(10)**

The GAPPD sets coverage targets of "90% full-dose coverage of each relevant vaccine (with 80% coverage in every district)."(100) While the number of countries introducing PCV is high at 134 as of December 2015—including 54 of the 73 Gavi countries—this number masks the in-country inequities in access to full immunization.(14) As of December 2015, 76.3 million infants, 56% of the world's infants, do not have access to PCV because either their country has not yet introduced the vaccine or because they are not receiving routine immunizations, as indicated by DTP3 coverage. Forty-nine percent of infants globally (66.6 million infants) live in countries that have not yet introduced PCV, including

countries not eligible for Gavi support.(14) Among infants born in Gavi countries, 47.1 million (59%) do not have access to PCV because either their country has not yet introduced the vaccine or they are not receiving routine immunizations, as indicated by DTP3 coverage. Forty-nine percent of infants in Gavi countries (39.6 million) live in countries that have not yet introduced PCV as of December 2015.(14) UNICEF estimates that coverage of infants with a third dose of PCV (PCV3) has increased worldwide from 11% in 2000 to 31% in 2014, including 53% PCV3 coverage in sub-Saharan Africa in 2014 in large part due to Gavi support.(43)

Prevention of disease through vaccination is more likely to accelerate the goals of equity than is the effort to expand access to appropriate treatment of disease, as important as those efforts are. Every severe disease episode impacts a child's immune system and nutritional balance. In the case of IPD, even with appropriate treatment, some infected children will die (global CFR was 5.7% in 2000 in the pre-PCV era).(5) In the case of pneumococcal meningitis, a significant proportion (about 25%) of treated children will have major neurological sequelae that can affect their long-term ability to learn and function.(61) Caring for a sick child also can cause a family to incur substantial economic costs from paying for medical care to lost caregiver wages or productivity. The families least able to bear this economic burden are also the most at risk for having malnourished or undernourished children, compounding the cost of pneumococcal disease in this population. Also, many countries—such as in the South and Southeast Asian region—have the highest absolute burden of IPD and pneumonia and have not yet introduced PCV. The potential impact in these countries could very likely exceed the impact observed in countries that have already introduced PCV and had a lower pre-vaccine burden of disease. In all countries, but particularly in those countries with many pneumonia and U5 deaths, preventing pneumococcal disease in the first place is more advantageous from an ethical and societal perspective than aiming to treat children once they fall ill.

Chapter 3: Vaccine Safety and Efficacy

Chapter 3 Overview

Licensed in 2000, PCV7 has a well-established, favorable safety profile when administered to infants and young children. Several studies from various countries demonstrate that PCV10 and PCV13 have a similar safety profile as PCV7. PCV studies have specifically demonstrated safety in HIV-infected children, children with sickle cell disease, children with recurrent otitis media, and other immunocompromised subjects.

PCVs have been tested in RCTs in a variety of settings to determine the vaccine efficacy (VE) against various disease outcomes: IPD, pneumococcal (bacteremic) pneumonia, radiologically confirmed pneumonia, clinical pneumonia, and acute otitis media (AOM). PCVs have also been studied to determine their efficacy in reducing the non-disease outcome of NP carriage. Vaccine licensure of PCV10 and PCV13 pre-dated results from VE and effectiveness studies and was based on immunological studies proving non-inferiority to PCV7. More recently, RCTs using PCV10 have been conducted looking at the outcomes of IPD, pneumonia and AOM, including a study using a schedule of two primary doses and a booster dose (2p+1). PCV13 RCTs were based on immunogenicity, not clinical endpoints. In addition, there is a growing body of evidence of the post-licensure vaccine effectiveness of both PCV10 and PCV13 (see Chapter 4).

The magnitude of PCV efficacy varies based on the outcome studied. For outcomes more specifically attributable to vaccine serotype pneumococcus, efficacy estimates are higher than those that are nonspecific for pneumococcus. In a meta-analysis of RCTs in children less than two years of age, the pooled VE of PCV7, PCV9 and PCV11 for vaccine serotype IPD (VT-IPD) was 80% (95% CI: 58%, 90%) in HIV-1 negative children. Two more recent RCTs used PCV10 (GSK) and showed high VE for VT-IPD, ranging from 92% (95% CI: 58%, 100%) for a 2p+1 schedule to 100% for 3p+1 schedules.

Estimates from RCTs that assessed PCV efficacy against pneumonia are more varied than those against IPD because the case definitions for pneumonia are multiple and vary in their specificity for pneumococcus. For radiologically-confirmed pneumonia, two meta-analyses report PCV efficacy as 27% (95% CI 15%, 36%) and 36% (95% CI 16%, 51%). VE for clinical pneumonia is estimated between 6% and 9% based on the two meta-analyses and a Latin American RCT (the COMPAS trial).

RCTs were not powered to investigate U5 mortality following PCV use. Only one RCT, from The Gambia, found a statistically significant reduction in all-cause mortality of 16% over a two-year follow period, translating to 7 deaths prevented for every 1,000 children vaccinated. Further evidence is needed from post-licensure studies to quantify the impact of PCV use on U5 mortality in different settings.

PCV7 has a modest beneficial effect on reducing AOM in healthy infants and a more notable benefit on reducing pneumococcal AOM. PCV use in high-risk infants, toddlers and in older children with a history of recurrent AOM does not appear to prevent further infections.

PCV has been demonstrated to be efficacious in reducing VT NP carriage when administered to infants as well as children U5. There is evidence that PCV administration reduces acquisition of VT pneumococci and density of carriage but does not enhance clearance of existing carriage. Based on eight RCTs, the magnitude of the efficacy for VT carriage was reported in one review as about 50%, with individual study estimates ranging from 26%-60%. The decrease in VT NP colonization is attenuated by an increase in NVT colonization. Reducing VT NP colonization could open a niche for the NP to be replaced proportionally by NVT pneumococci, a phenomenon known as serotype

replacement. As a result, PCV has shown little to no effect on overall pneumococcal colonization prevalence.

There are limited data on the duration of protection following PCV administration. The natural history of pneumococcus, with declining NP colonization prevalence after the first few years of life, and the role of natural immune system boosting following exposure to circulating serotypes complicate the interpretation of long-term follow up studies comparing immunized and unimmunized children.

PCV Safety

PCVs are safe and well-tolerated in infants, young children and those with HIV infection.

The vaccines can be administered concurrently with other EPI vaccines. There is some evidence of increased risk of transient fever and febrile seizures with the co-administration of trivalent inactivated influenza vaccine and PCV.

Licensed in 2000, PCV7 has a well-established, favorable safety profile when administered to infants and young children.(110, 111) The side effects of PCV are usually mild and include soreness at the injection site and transient fever in fewer than 5% of vaccinees. Other side effects include local reactions that have been reported in 10-20% of vaccinees, only about 3%, however, were considered severe, such as "tenderness that interferes with arm or leg movement."(112, 113) Several studies from various countries demonstrate that PCV10 and PCV13 have a similar safety profile as PCV7.(10, 114, 115) PCV studies have specifically assessed safety in HIV-infected children, children with sickle cell disease, children with recurrent otitis media, hematopoietic transplant recipients and solid organ transplant recipients.(80, 116-118) The WHO states that "PCVs are considered safe in all target groups for vaccination, (including) . . . immunocompromised individuals."(10)

PCVs are safe to co-administer with other EPI vaccines. However, there is some indication that the co-administration of trivalent inactivated influenza vaccine (TIV) and PCV13 can increase the short-term risk of fever and febrile seizures in young children. This finding was reported in one season (2010-2011) in Australia, where there was an increased risk of febrile seizures associated with one formulation of TIV coadministrated with PCV13.(119) In the 2011-2012 flu season in New York City, another study reported higher risk of fever in day 0-1 following vaccination with TIV and PCV13 compared to administration of either vaccine alone.(120)

PCV Immunogenicity

An update to a comprehensive "PCV Dosing Landscape" study previously published (7-9, 227, 367, 370, 374-5) **is expected in 2017 and will include immunogenicity as an outcome for the first time. The updated review, called PRIME (PCV Review of Impact Evidence) will be a full analysis of PCV Impact studies. An overview of PRIME is available in Appendix A at the end of this document.**

PCV Efficacy

PCVs are efficacious vaccines. Their use in children directly reduces the risk of IPD (including meningitis and septicemia), radiologically-confirmed pneumonia and clinical pneumonia, otitis media and nasopharyngeal carriage due to serotypes contained in the vaccine.

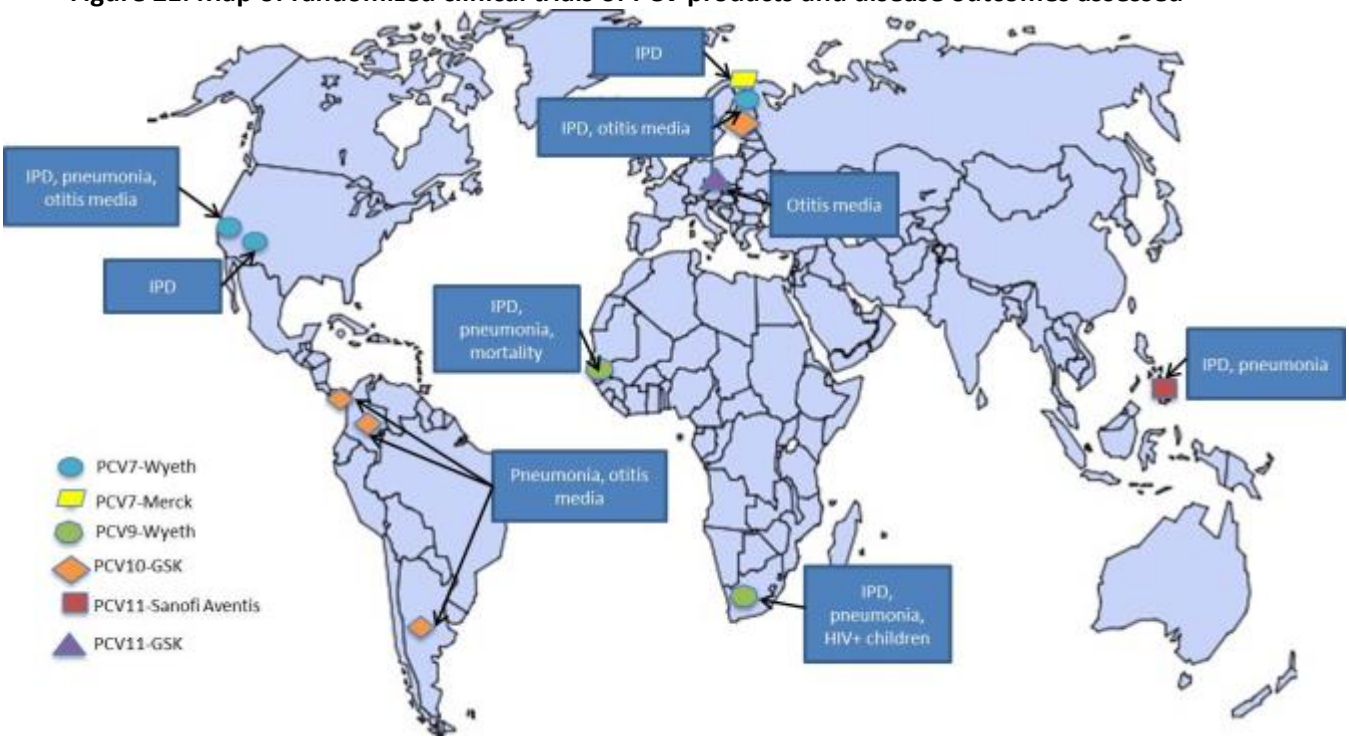
Vaccine efficacy is the proportionate reduction in disease incidence in an unvaccinated group compared to a vaccinated group. Ideally, vaccine efficacy is based on data from double-blind, randomized controlled trials (RCT) that represent the "best case scenario" of vaccine protection under controlled conditions. In an RCT, the intervention (vaccine) can be controlled, the disease incidence closely studied, and confounding factors reduced by the randomization process.(121) However, RCTs usually include exclusion criteria and may not therefore accurately represent the effectiveness of the intervention in the general population or under "real world" scenarios.

PCVs have been tested in RCTs in a variety of settings to determine the vaccine efficacy against various disease outcomes: IPD, pneumococcal (bacteremic) pneumonia, radiologically confirmed pneumonia, clinical pneumonia, and acute otitis media (AOM). PCVs have also been studied to determine their efficacy in reducing the non-disease outcome of NP carriage.

Clinical trials of PCV efficacy in young children began in the late 1990's and were conducted by several vaccine manufacturers using different PCV formulations including PCV7 (Pfizer and Merck), PCV10 (GlaxoSmithKline (GSK)), PCV9 (Pfizer) and PCV11 (GSK and Sanofi Pasteur); the latter two products did not proceed to licensure. Randomized controlled trials of PCV7 given in three primary doses and one booster dose (3p+1 schedule) were conducted in high-income countries. In low or middle-income countries, the investigational PCV9 or PCV11 vaccines were studied using three primary doses without a booster dose (3p+0 schedule). Figure 21 shows a map of the location, PCV product and outcome studied in RCTs.

Vaccine licensure of PCV10 and PCV13 pre-dated results from vaccine efficacy and effectiveness studies and was based on immunological studies proving non-inferiority to PCV7.(10) More recently, RCTs using PCV10 have been conducted looking at the outcomes of IPD, pneumonia and AOM, including a study using a schedule of two primary doses and a booster dose (2p+1) (Figure 13). PCV13 RCTs were based on immunogenicity, not clinical endpoints. In addition, there is a growing body of evidence of the post-licensure vaccine effectiveness of both PCV10 and PCV13 (see Chapter 4 on PCV vaccine impact).

Figure 21: Map of randomized clinical trials of PCV products and disease outcomes assessed



The magnitude of PCV efficacy varies based on the outcome studied. For outcomes more specifically attributable to vaccine serotype pneumococcus, efficacy estimates are higher than those that are nonspecific for pneumococcus. Vaccine induced immune protection for pneumococcus is serotype-specific, and PCVs largely only protect against those serotypes contained within the vaccine, though some cross-protection between related serotypes (such as 6B from PCV7 protecting against 6A and 19F of PCV10 providing some protection against 19A in vaccinated children) can occur.(10, 122, 123) For outcomes based on clinical syndrome rather than microbiologically confirmed pneumococcal diagnoses, vaccine efficacy is lower because pneumococcus is one among several etiological agents for a given clinical syndrome, such as pneumonia or otitis media. A discussion of the estimates for PCV efficacy is presented below by specific disease outcomes and for NP carriage.

Vaccine Efficacy for IPD

PCV is highly efficacious in preventing IPD caused by vaccine serotypes.

RCTs have established the vaccine efficacy of PCV for vaccine serotype IPD (VT-IPD), and for all serotype IPD. The latter includes IPD caused by vaccine serotypes (VT), non-vaccine serotypes (NVT) and vaccine-related (VR) serotypes so the quantitative value of efficacy is directly influenced by the fraction of IPD caused by VT strains in the observed population. In a 2009 meta-analysis of RCTs in children less than two years of age, the pooled vaccine efficacy of PCV7, PCV9 and PCV11 for VT-IPD was 80% (95% CI: 58%, 90%) in HIV-1 negative children.(Figure 22)(4) The vaccine efficacy for all serotype IPD was 58%

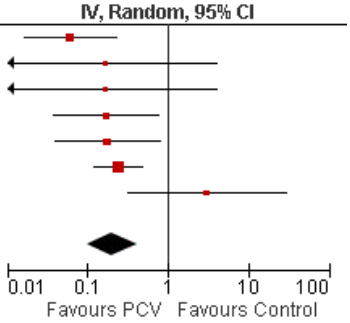
(95% CI: 29%, 75%). The pooled vaccine efficacy for NVT IPD was 8% (95% CI: -117%, 61%, not significant).(4) The meta-analysis was based on seven phase III studies conducted in Africa (118, 124), the US (125, 126), the Philippines (127) and Finland (128, 129) and enrolling about 57,000 children receiving PCV and a similar number receiving placebo or another vaccine. Inclusion of HIV-infected children from the South Africa trial(118) slightly reduced the pooled vaccine efficacy for VT-IPD to 77% (95% CI: 58%, 88%). The lowest vaccine efficacy point estimate was reported in the Philippines trial; this is also the only RCT that used PCV11, however this should not be interpreted necessarily to mean that the product was truly less efficacious.(127) There may have been some reason for this 11-valent formulation of PCV not being as efficacious as the PCV7 or PCV9 products, both of which had risk ratios with a narrower range between 0.06 to 0.24. Hence, the inclusion of the Philippines trial (PCV11) estimate may lead to an underestimation of the true efficacy of PCV7 and PCV9 as reported in the 2009 meta-analysis.

Overall, the quality of evidence on the outcome of VT-IPD was graded high in the 2009 Cochrane review.(4) The vaccine attributable rate reduction (VAR), the number of cases of VT-IPD prevented per 1,000 children vaccinated, varies based on the underlying incidence of VT-IPD in a population and is reported in the 2009 review. In populations with a moderate risk of VT-IPD (baseline rate of 0.2%), the estimated absolute effect of PCV use is 2 cases of VT-IPD prevented per 1,000 children. In populations with a high risk of VT-IPD (baseline rate of 0.5%), the absolute reduction is estimated at 4 cases of VT-IPD prevented per 1,000 children. (4)

Figure 22: Forest plot of comparison: HIV-1 negative and <24 months children, outcome VT-IPD, Intention to treat (ITT), random-effects model (4)

Study or Subgroup	log[Risk Ratio]	SE	Treatment Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Black 2000	-2.7969	0.6658	18927	18941	18.6%	0.06 [0.02, 0.22]
Kilpi 2003 (1)	-1.7952	1.6311	835	416	4.7%	0.17 [0.01, 4.06]
Eskola 2001 (2)	-1.7904	1.6323	831	416	4.7%	0.17 [0.01, 4.09]
Klugman 2003	-1.772	0.7684	18633	18626	15.5%	0.17 [0.04, 0.77]
O'Brien 2003	-1.7487	0.7662	2974	2818	15.6%	0.17 [0.04, 0.78]
Cutts 2005 (3)	-1.4159	0.3525	8718	8719	32.5%	0.24 [0.12, 0.48]
Lucero 2009	1.0953	1.1545	6097	6094	8.5%	2.99 [0.31, 28.73]
Total (95% CI)			**57015**	**56030**	**100.0%**	**0.20 [0.10, 0.42]**

Heterogeneity: Tau² = 0.30; Chi² = 9.07, df = 6 (P = 0.17); I² = 34%
Test for overall effect: Z = 4.31 (P < 0.0001)



(1) The software could not accept entry of 415.5 so we had to enter a whole number of 416. Actual number of controls in Finnish studies is
(2) The software could not accept entry of 415.5 so we had to enter a whole number of 416. Actual number of controls in Finnish studies is
(3) Treatment and control totals included children < 29 months of age because investigators of the Gambian trial could not provide us with

Two additional RCTs were conducted since the meta-analysis was published. These trials used PCV10 (GSK) and showed high vaccine efficacy for VT-IPD. In the 2014 COMPAS trial conducted in Argentina, Panama and Colombia, intention-to-treat analysis of PCV10 efficacy was 100% (95% CI: 77%, 100%) for VT-IPD and 67% (95% CI: 22%, 86%) for all serotype IPD.(130) In the 2013 FinIP trial, the vaccine efficacy of PCV10 for VT-IPD was 100% (95% CI: 83%, 100%) for a 3p+1 schedule (three primary doses given a minimum of four weeks apart plus a booster), and 92% (95% CI: 58%, 100%) for a 2p+1 schedule (two primary doses given a minimum of eight weeks apart plus a booster).(131) The FinIP trial was significant insofar as it was the first clinical trial evaluating the efficacy of a 2p+1 schedule in young infants.

Vaccine Efficacy for Pneumonia

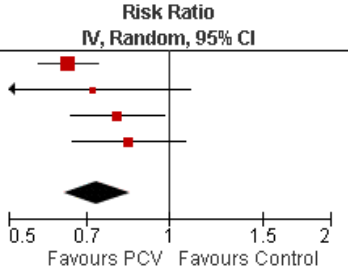
PCV efficacy is higher for pneumonia outcome definitions that are specific for pneumococcal etiology compared with those that are nonspecific.

Estimates from RCTs that assessed PCV efficacy against pneumonia are more varied than those for IPD because the case definitions for pneumonia are multiple and vary in their specificity for pneumococcus. Clinical pneumonia and radiologically-confirmed pneumonia (based on WHO radiographic criteria) are two of the common definitions used in RCTs, with the latter being more specific for bacterial pneumonia and therefore for pneumococcal pneumonia. In the 2009 Cochrane meta-analysis, PCV pooled efficacy for radiologically-confirmed pneumonia was 27% (95% CI 15%, 36%) (Figure 23)(4). In the 2009 systematic literature review by O'Brien et al., the researchers adjusted vaccine efficacy for pneumonia endpoints from the same four RCTs analyzed in the Cochrane review by three factors: the proportion of pneumococcal disease caused by vaccine serotypes, vaccine efficacy for VT pneumococcal disease, and the concurrent use of Hib vaccine to estimate the fraction of radiographically defined pneumonia that was likely attributable to pneumococcus.(5) The estimated value was 36%. In the COMPAS trial (conducted in three upper middle income countries using Hib vaccine routinely), PCV10 efficacy for radiologically-confirmed pneumonia was 22% (95% CI 8%, 34%).(130)

Figure 23: Forest plot of comparison: HIV-1 negative and <24 months children, outcome: X-ray defined pneumonia ITT (Random-effects model); excludes the outlier result of the PCV effect against X-ray defined pneumonia among American Indian children (4)

Study or Subgroup	log[Risk Ratio]	SE	Treatment Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Cutts 2005 (1)	-0.4368	0.0666	8718	8719	40.8%	0.65 [0.57, 0.74]
Hansen 2006 (2)	-0.3299	0.2149	8396	8382	9.8%	0.72 [0.47, 1.10]
Klugman 2003	-0.2231	0.1047	18633	18626	27.3%	0.80 [0.65, 0.98]
Lucero 2009	-0.1744	0.1247	6097	6094	22.1%	0.84 [0.66, 1.07]
Total (95% CI)			**41844**	**41821**	**100.0%**	**0.73 [0.64, 0.85]**

Heterogeneity: Tau² = 0.01; Chi² = 5.12, df = 3 (P = 0.16); I² = 41%
Test for overall effect: Z = 4.23 (P < 0.0001)



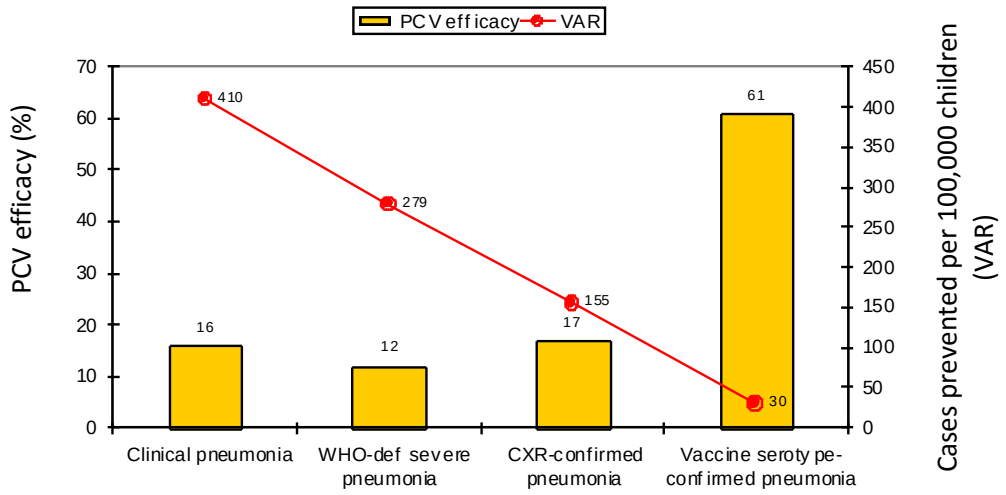
(1) Treatment and control totals included children < 29 months of age because investigators of the Gambian trial could not provide us with t
(2) Treatment and control totals are in person-years

For the case definition of clinical pneumonia, a diagnosis based on symptomatic presentation and not confirmed by X-ray, PCV efficacy was 6% (95% CI 2%, 9%) in the 2009 Cochrane meta-analysis. This case definition is likely to include many clinical illnesses that are not pneumonia at all, pneumonia cases caused by pathogens other than pneumococcus, and pneumococcal pneumonias that are not vaccine serotype. PCV would not be expected to have as large an effect on this syndrome as it would on radiologically confirmed pneumonia because of the reduced specificity for pneumococcus. In the 2009 O'Brien paper, the authors similarly estimated the fraction of clinical pneumonia likely to be attributable to pneumococcus bases on the vaccine efficacy findings; they estimated that 8% of clinical pneumonia were likely pneumococcal in origin.(5) In the Latin America COMPAS study, the efficacy of PCV10 for community-acquired pneumonia was 9% (95% 4%, 13%).(130)

The varying case definitions for pneumonia outcomes illustrate an interesting point. While vaccine efficacy is higher for pneumococcal-specific outcomes, the absolute impact of vaccine use on disease reduction (cases prevented per 1,000 children vaccinated or the VAR, vaccine attributable reduction) is higher for more non-specific outcomes. This is best understood by considering that a small reduction in a very common disease can account for a larger number of cases prevented than a large reduction in a rare disease. Specifically, the incidence of non-specific disease outcomes, such as clinical pneumonia, in young children is very common, while bacteremic pneumonia is much less common. Even though PCV efficacy for clinical pneumonia is lower than it is for pneumococcal (bacteremic) pneumonia, the net benefit (i.e. cases of clinical pneumonia prevented) is greater because clinical pneumonia is much more common than bacteremic pneumonia. Also, because of the synergistic effect between respiratory pathogens (viral and bacterial), reducing pneumococcal pneumonia may also reduce the risk of subsequent disease and/or severity of disease.

A large RCT from South Africa clearly demonstrated this inverse relationship between specificity of pneumococcal disease outcome and absolute disease reduction, the total number of cases prevented (Figure 24). The burden of preventable disease, or cases prevented per 100,000 children, is referred to as the vaccine attributable reduction (VAR) and is dependent on the background incidence of disease. As shown in Figure 24, while PCV efficacy for the non-specific endpoint of clinical pneumonia was only 16%, the use of PCV9 in the study population was estimated to prevent 410 cases of clinical pneumonia per 100,000 children vaccinated. For VT pneumococcal pneumonia, PCV9 efficacy was higher at 61%, but as this is a less common outcome, the VAR was estimated as 30 cases prevented per 100,000 vaccinated children. All children in this RCT were given Hib vaccine though it was not part of South Africa's EPI at the time of the trial.

Figure 24: Inverse relationship between PCV efficacy and vaccine attributable reduction (VAR), the burden of preventable disease (132)



Even though the outcome of clinical pneumonia is less specific for pneumococcal disease, since it is a more common disease in children, PCV's absolute reduction of disease burden is greater. Based on the 2009 Cochrane meta-analysis, in low-risk populations, (baseline rate of clinical pneumonia 5.9% in control groups) PCV use is estimated to prevent 4 cases of clinical pneumonia per 1,000 children vaccinated. In high-risk populations (baseline rate 31.5%), the absolute reduction from PCV use is estimated to be 19 cases of clinical pneumonia prevented per 1,000 children vaccinated.(4) In populations with low risk of radiologically-confirmed pneumonia (baseline rate of 0.3% in the control group), PCV use is estimated to have an absolute reduction of 1 case per 1,000 children. In high-risk populations (baseline rate of 6.3%), the absolute reduction from PCV use is estimated to be 17 fewer cases per 1,000 children.(4)

Vaccine Efficacy for Under 5 Mortality

RCTs were not powered to investigate U5 mortality following PCV use.

Only one RCT, from The Gambia, found a statistically significant reduction in all-cause mortality of 16% over a two-year follow up period, translating to 7 deaths prevented for every 1,000 children vaccinated.(124)

Further evidence is needed from post-licensure studies to quantify the impact of PCV use on U5 mortality in different settings.

Five RCTs provide data on the effect of PCV on all-cause mortality among children U5. In a pooled analysis, the vaccine efficacy for mortality in children under two years was 11% (95% CI: -1%, 21%).(4)(Figure 25) However, the effect did not reach statistical significance as none of the trials were powered to investigate mortality as an outcome.(4) In a sub-group analysis including all HIV-1 negative

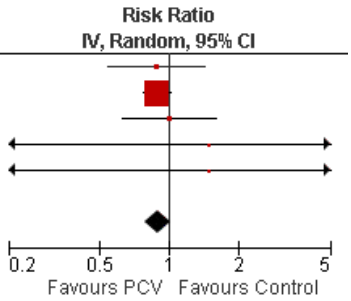
children under 29 months of age, the vaccine efficacy for all-cause mortality reached statistical significance at 13% (95% CI: 2%, 23%).(4)(9)(Figure 26)

The only RCT with a statistically significant reduction in all-cause mortality was conducted in The Gambia using PCV9. In this study, all-cause mortality was reduced by 16% (95% CI 2%, 38%) in the vaccinated group compared to the control group over a two-year follow up period. This translates to 7 deaths prevented for every 1,000 children vaccinated in the study.(124) More information is needed from post-licensure studies to quantify the impact of PCV on all-cause mortality in early childhood.

Figure 25: Forest plot of comparison: 1 HIV-1 negative and <24 months children, outcome: All-cause mortality, ITT (Random-effects model)(4)

Study or Subgroup	log[Risk Ratio]	SE	Treatment Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Lucero 2009	-0.1294	0.2505	6097	6094	6.6%	0.88 [0.54, 1.44]
Cutts 2005 (1)	-0.1233	0.0698	8718	8719	85.5%	0.88 [0.77, 1.01]
Klugman 2003	-0.0004	0.2355	18633	18626	7.5%	1.00 [0.63, 1.59]
Kilpi 2003 (2)	0.4019	1.6319	835	416	0.2%	1.49 [0.06, 36.61]
Eskola 2001 (3)	0.4067	1.6319	831	416	0.2%	1.50 [0.06, 36.79]
Total (95% CI)			**35114**	**34271**	**100.0%**	**0.89 [0.79, 1.01]**

Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 4 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.75 (P = 0.08)



(1) Treatment and control totals included children < 29 months of age because investigators of the Gambian trial could not provide us with t
(2) The software could not accept entry of 415.5 so we had to enter a whole number of 416. Actual number of controls in Finnish studies is
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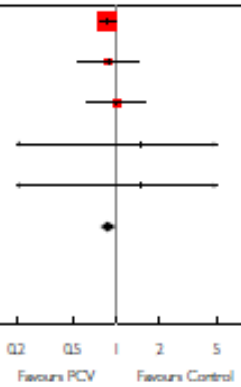
Figure 26: Forest plot of comparison: 1 HIV-1 negative and <29 months children, outcome: All-cause mortality, ITT (Random-effects model)(4)

Study or subgroup	Treatment N	Control N	log [Risk Ratio] (SE)	Weight	Risk Ratio IV,Random,95% CI
Cutts 2005	8718	8719	-0.1508 (0.0649)	87.2 %	0.86 [0.76, 0.98]
Lucero 2009	6097	6094	-0.1294 (0.2505)	5.9 %	0.88 [0.54, 1.44]
Klugman 2003	18633	18626	0 (0.2355)	6.6 %	1.00 [0.63, 1.59]
Kilpi 2003	835	416	0.4019 (1.6319)	0.1 %	1.49 [0.06, 36.61]
Eskola 2001	831	416	0.4067 (1.6319)	0.1 %	1.50 [0.06, 36.79]
Total (95% CI)				**100.0 %**	**0.87 [0.77, 0.98]**

Heterogeneity: Tau² = 0.0; Chi² = 0.60, df = 4 (P = 0.96); I² =0.0%
Test for overall effect: Z = 2.28 (P = 0.023)



Vaccine Efficacy for Otitis Media

PCV7 has a modest beneficial effect on reducing AOM in healthy infants and a more notable benefit on reducing pneumococcal AOM. PCV use in high-risk infants, toddlers and in older children with a history of recurrent AOM does not appear to prevent further infections.

In a 2014 meta-analysis, 9 RCTs were reviewed that looked at the effect of PCV7, PCV9 and PCV11 on AOM in children under 12 years of age.(133) Four trials studied the effect of PCV7 on all-cause AOM when administered to young infants and found no relative reduction with vaccine use (128, 129, 134) or a modest reduction (7%, 95% CI: 4%, 10%).(126, 135) The POET (Pneumococcal Otitis Efficacy Trial) study using PCV11, conjugated to *Haemophilus influenzae* protein D carrier protein, found a 34% reduction (95% CI: 21%, 44%) in all-cause AOM in infants; part of the effect may have been related to the protein D carrier which was demonstrated to reduce AOM caused by non-typeable *Haemophilus influenzae.*(136) The Latin American COMPAS trial investigating the use of PCV10, again with the *H. influenzae* protein D carrier, also found a significant reduction in all cause AOM of 19% (95% CI: 4%, 31%).(130) After early infancy, PCV use did not result in a significant reduction in AOM episodes, either in healthy toddlers or in older children with a history of recurrent AOM.(137-139) A secondary outcome of the FinIP trial evaluated PCV10 effectiveness on tympanostomy tube placements (TTP). Vaccine effectiveness for reducing TTP was 13% (95% CI: -2%, 26%) for the 2p+1 and 3p+1 schedules combined.(140)

Vaccine efficacy was significant when limited to the outcome of pneumococcal AOM. In early infancy, PCV7 administration reduced pneumococcal AOM by 20% and 34% in two RCTs.(128, 129, 141) PCV11 and PCV 10 reduced pneumococcal AOM by 52% (95% CI: 37%, 63%) and 70% (95% CI: 30%, 87%), respectively.(130, 136)

Vaccine Efficacy for Nasopharyngeal Colonization

PCV directly reduces VT NP colonization by about 50% in young children.

Many studies have evaluated the effect of PCV administration on VT NP colonization, and all have shown a reduction in VT carriage.(142) NP carriage is an important and required step in the pathophysiology of pneumococcus in an individual host as the nasopharynx is the entry point for pneumococcus, as well as a reservoir and source of pneumococcal transmission between individuals. The risk of progression from pneumococcal carriage to disease depends on the invasive potential of the colonizing strain and host risk factors.(143)

PCV has been demonstrated to be efficacious in reducing VT carriage when administered to infants as well as children U5. There is evidence that PCV administration reduces acquisition of VT pneumococci and density of carriage but does not enhance clearance of existing carriage.(142) Based on eight RCTs, the magnitude of the efficacy against carriage was reported in one review as about 50%, with individual study estimates ranging from 26%-60%.(143-145) (Table F) In a separate meta-analysis of four studies done in sub-Saharan Africa, there was an 81% reduction in VT carriage in children less than two years immunized with either PCV5 (one study) or PCV9 (three studies).(146) A 2013 randomized study comparing PCV13 to PCV7 in Israeli children reported reduced rates of NP acquisition of five additional

serotypes in PCV13 (serotypes 1, 6A, 6C, 7F and 19A) as well as 19F, a common serotype in both PCV13 and PCV7, in the PCV13 group.(147) Serotype 3 elicited the lowest immune response, and its acquisition was not different between the PCV13 and PCV7 groups. There were too few acquisition episodes of serotype 5 to draw inferences in this study.(147) Another RCT looked at the efficacy of PCV10 administered to children 12-59 months old (two doses given either two or six months apart).(148) PCV10 significantly reduced VT carriage in the vaccinated groups after the first and second doses (prevalence 16-21%) compared to the control group (prevalence 30-31%).(148)

"The decrease in VT NP colonization is attenuated by an increase in NVT colonization of up to 67% in some studies.(144) Reducing VT NP colonization could open a niche for the NP to be replaced proportionally by NVT pneumococci, a phenomenon known as serotype replacement. As a result, PCV showed little to no effect on colonization for pneumococcus of any serotype."(25) In the sub-Sahara African meta-analysis, NVT carriage increased by 15% in immunized children under two years compared to controls, and overall pneumococcal carriage was similar.(146)

Table F: PCV randomized trials with data on direct vaccine effect on colonization
Effect size reported as percent (%) protection, relative risk (RR) or odds ratio (OR) (95% CI)
(Source: Simell, et al. (35))(25)

Trial site, population, vaccine	Vaccine schedule	Time of testing	Effect size	Reference
South Africa, HIV-infected and uninfected, PCV-9	6, 10, 14 weeks	9 months	VT: vaccinated 18%, unvaccinated 36% (p< 0.001); NVT: vaccinated 36%, unvaccinated 25% (p=0.007)	(149)
The Gambia, PCV-9	3 doses starting at 6–51 weeks	9-15 months	VT: RR 0.56 (0.49, 0.65); NVT: RR 1.59 (1.41, 1.79)	(150)
US, American Indians, PCV-7	3 doses starting at 6 weeks to 7 months, a booster at 12–15 months catch-up cluster randomized	7 months	VT: OR 0.40 (0.23, 0.67); NVT: OR 0.72 (0.43, 1.23)	(144)
		12 months	VT: OR 0.51 (0.34, 0.78); NVT: OR 1.02 (0.61, 1.72)	
		18 months	VT: OR 0.81 (0.51, 1.31); NVT: OR 1.67 (1.02, 2.78)	
Czech Republic and Slovakia, PCV-11	2, 4, 6, 12 months	After booster	VT: 42.8% (16.7%, 71.9%); NVT: 15.3% (-78.9%, 59.7%)	(151)
Finland, PCV-7	2, 4, 6, 12 months	12 months	VT: 17% (not significant)	(152)
		18 months	VT: p < 0.001; NVT increase: p=0.02	
The Philippines, PCV-11	6, 10, 14 weeks	24 months	VT: 35% (8%, 54%); NVT: no effect	(153)
Argentina, Panama, Colombia, PCV-10	2, 4, 6 and 15–18 months	7 months	VT: 18% (-7%, 37%); NVT: -15.2% (-55%, 14%)	(145)
		12 months	VT: 28% (5%, 48%); NVT: 3% (-32%, 29%)	
		3 months after booster	VT: 28% (2%, 57%); NVT: -28% (-78%, 7%)	
		9 months after booster	VT: 29% (-0.2%, 49%); NVT: -22% (-74%, 15%)	
		Any visit	VT: 26% (13%, 37%); NVT: -6% (-25%, 10%)	
Israel, day care attendees, PCV-9	2 doses for children <1 year, 1 dose for older	1 month after booster	VT: OR 0.50 (0.3, 0.66); NVT: OR 1.59 (1.28, 1.96)	(154)

Vaccine Efficacy in HIV-infected Children

PCV is slightly less efficacious in HIV-infected children, but the absolute impact on disease reduction is greater in these children because they are at higher baseline risk for pneumococcal infection.

Only one phase III RCT in South Africa measured PCV efficacy in HIV-infected children. Among this group, PCV9 efficacy for VT-IPD was 65% (95% CI: 24%, 86%), which was lower than the measured efficacy in HIV-uninfected children of 83% (95% CI: 39, 72%).(118) PCV efficacy for all serotype IPD in HIV-infected children was reported as 53% (95% CI: 21%, 73%), efficacy was 13% (95% CI: -7, 29%) for radiologically-confirmed pneumonia, and 15% (95% CI: 6%, 24%) for clinical lower respiratory tract infection.(118)

In a five-year follow up of the South African study, vaccine efficacy diminished more rapidly in HIV-infected children compared to HIV-uninfected children for VT-IPD. In the HIV-infected group, PCV efficacy for VT-IPD was 39% (95% CI -8%, 65%) in the six years of follow up, while PCV efficacy was 78% (95% CI 34%, 92%) in the HIV-uninfected group over the same follow up period.(155) However, the absolute rate reduction of VT-IPD over the six years was higher in the HIV-infected group (940 cases per 100,000 child-years) compared to the HIV-uninfected group (75 cases per 100,000 child-years), because of the higher burden of disease in the HIV-infected group.(155)

Duration of Protection

There are limited data on the duration of protection following PCV administration.

The natural history of pneumococcus, with declining NP colonization prevalence after the first few years of life, and the role of natural immune system boosting following exposure to circulating serotypes complicate the interpretation of long-term follow up studies comparing immunized and unimmunized children.

There are limited data on the duration of protection following PCV administration, with some evidence of a more rapid decline in protection among HIV-infected children. Some studies have found persistence of higher antibody responses in children immunized in infancy, but the role of natural boosting following exposure to circulating pneumococcal serotypes may play a role in maintaining antibody levels.(156) In a follow up study to the South African RCT using PCV9 in a 3p+0 schedule, vaccine efficacy remained significant against VT IPD after six years.(157) Immunogenicity data also showed that specific antibody concentrations were above the assumed protective thresholds for HIV-uninfected children. In contrast, HIV-infected children had evidence of waning immunity after about 2 years with IgG concentrations below the 0.35 mcg/ml protective threshold.(10, 157) Follow up of a Finnish otitis media RCT also found significantly higher antibody levels and functional response in previously immunized children compared to unimmunized controls four years after the last PCV7 dose.(158)

In contrast, other follow up studies have not demonstrated much difference between previously immunized and unimmunized children. Confounding the elucidation of the duration of protection from PCV administration is the natural history of pneumococcus in humans: a trend of decreasing colonization prevalence after the first few years of life. Prior colonization or disease episodes that elicit and then boost the host's immune response, maturation of the innate immune response, and/or anatomical changes in the nasopharynx may all contribute to the declining prevalence of pneumococcus as a colonizer and potential pathogen in childhood.(159) As children age, the expected difference between previously immunized and unimmunized groups would be smaller and thus more difficult to detect. Follow up of the Gambian PCV9 RCT showed long-term increases in only 3 out of the 9 vaccine serotype antibodies at almost four years post-vaccine.(160) Compared to controls, children previously immunized with PCV9 had significantly higher anti-6B, 14 and 23F concentrations; this may be the result of natural boosting or occult infection as two of these three serotypes are considered prevalent in Gambian children.(160, 161) Overall 75% of previously vaccinated children and 66% of controls had antibody concentrations >0.35 mcg/ml (the correlate of protection), with considerable variation by vaccine serotype. There were no significant differences in NP carriage of VT between the previously vaccinated and control groups, but the study was inadequately powered to detect a difference based on the low prevalence of VT carriage in both groups.(160) A small study among American Indian children

(n=36) four years following routine infant immunization found comparable serotype-specific antibody levels between immunized and unimmunized children. Only serotype 14 antibodies were higher in the previously immunized group.(156) As follow up to a US RCT, another study looked at ten years post-PCV7 infant immunization and found little difference between IgG antibody levels and functional response in immunized versus unimmunized children.(162)

Chapter 4: Pneumococcal Conjugate Vaccine Impact

Chapter 4 Overview

The public health impact of PCV introduction in national immunization schedules has exceeded the expected reduction in VT disease based on vaccine efficacy studies. This is because efficacy studies measure direct outcomes in a controlled, idealized setting and in a relatively small group of vaccinated persons. In real-world use, with mass vaccination, the vaccine has direct effects on NP carriage and disease burden among those who are vaccinated, and this is referred to as the vaccine effectiveness. However, what cannot be measured in RCTs are the additional indirect effects of mass vaccination on unvaccinated persons, what is known as the herd effect or indirect protection. Following PCV introduction, groups that are not themselves vaccinated have experienced a change in pneumococcal disease epidemiology due to community-level changes in the pneumococcal serotypes circulating as young children are vaccinated. When PCV has been introduced into routine use, the observed impact on disease reduction has been greater than expected from efficacy trials because of the indirect effects of the vaccine.

As PCV is introduced in more countries, including more LMICs, where the epidemiology of pneumococcal disease and carriage may vary (generally with a higher burden of disease and carriage in younger infants), it will be important to continue to monitor and survey the population-level impact of higher valency vaccines. The impact of PCV will depend on the prevailing serotypes causing disease prior to vaccine introduction, the coverage of the vaccine in groups targeted for immunization, the presence and coverage of catch-up campaigns beyond infancy, population density, and the prevalence of other risk factors, such as HIV infection.

PCV7 quickly and significantly reduced the incidence of IPD among young children in countries where it was introduced either as a 3p+1 or 2p+1 schedule. These findings were mostly from high-income countries that were early adaptors of PCV7. A 2010 WHO review included data from South Africa as well as the US, UK, Australia and Canada and found "rapid, substantial reductions (in VT-IPD) in all settings." PCV7 use also decreased the burden of antibiotic-resistant pneumococcal disease.

The effectiveness of PCV7 on overall (i.e. all serotype) IPD was reduced, in part, by an increase in NVT IPD in some settings; this was of variable magnitude and is termed serotype replacement. While serotype replacement with nonvaccine serotypes has been near complete in carriage, only minimal serotype replacement in pneumococcal disease has occurred because of the lower invasiveness of the replacing serotypes. Many factors affect trends in the burden of pneumococcal serotypes over time of which PCV implementation is a major factor. In all settings the increase in NVT IPD has been outweighed by the significant reduction in VT disease.

Higher valency PCV formulations were developed in part to respond to the phenomenon of serotype replacement in disease by including invasive serotypes not in PCV7. Both PCV10 and PCV13 are showing good effectiveness against most of the additional, non-PCV7 vaccine serotypes contained therein. In settings where these additional vaccine serotypes were prevalent prior to PCV10 or PCV13 use—including serotype 19A that was emergent after PCV7 introduction—there has been further decreases in VT-IPD. Data from LMICs and high-income countries is amassing on the post-licensure impact of higher valency PCVs and strengthens the assertion that the vaccines are continuing to decrease IPD burden beyond what was achieved with PCV7.

VT-IPD among adults has gradually decreased in almost all countries after a few years following PCV introduction. This indirect effect has been observed for all routinely used infant schedules, for all licensed PCV products, and in populations with high HIV-infection burden. Replacement disease with NVT pneumococci has been of variable magnitude in adults resulting in a

decrease, no change or an increase in overall IPD depending on setting. The magnitude of PCV's indirect effect depends on various factors: the immunization strategy—i.e. the use of catch-up vaccination to accelerate impact—vaccine coverage rate, the population composition and density, the prevalence of VT pneumococci carried in young children, and the prevalence of VT disease prior to introduction, and of course surveillance methods that may confound the observations. When coverage rates are high, the indirect impact is consistent, while lower coverage rates yield mixed indirect impact, with some effect demonstrated starting at 40% coverage.

PCVs have had a substantial effect on pneumonia disease burden: the newer generations, high valency PCVs have reduced hospitalizations for all-cause pneumonia by 13% to 72% (n=6 studies) and for consolidated pneumonia by 20% to 45% (n=3 studies) in children U5. The magnitude of the impact on pneumonia hospitalizations must be interpreted with great care as there are methodological issues that affect the quality and comparability of the data. Factors that play a role in interpreting pneumonia data include: the case definition and ascertainment methods used, the varied pneumonia etiologies in a setting and their background incidence, access to care and health seeking behaviors, time since PCV introduction, and vaccine coverage rate. There is a limited but growing body of data on the indirect effects of higher valency PCVs on the outcome of pneumonia.

Preventing NP acquisition of vaccine serotypes, PCV implementation results in a rapid, significant decrease in VT NP carriage prevalence in children. There is replacement carriage with non-vaccine serotypes, often resulting in no net overall change in all-serotype pneumococcal colonization. However, the replacing non-vaccine serotypes are, in many cases, not as invasive and thus less likely to cause disease. Therefore reductions in all-serotype pneumococcal disease are sustained even in the face of increases in NVT colonization. Data is emerging to corroborate the significant direct and indirect effect of PCV on NP carriage in LMIC settings. Direct and indirect PCV7 impact on NP colonization was demonstrated in South Africa just two years following vaccine introduction in a 2p+1 schedule without a catch up campaign. Data from Kilifi, Kenya also demonstrate a significant direct and indirect reduction in VT NP carriage two years after PCV10 introduction using a 3p+0 schedule and catch-up campaign.

There is very limited information on the impact of PCV on mortality. Few studies have been published and they vary in the age group(s) and the outcome under study. Two studies from middle income settings suggest a direct effect of PCV use on mortality rates in young children: one study reported on the overall infant mortality rate and the other on the pneumonia mortality rate. Data from high income countries show a reduction in IPD-related mortality rates for the general population, mainly as a result of declining VT IPD incidence rates. More studies will be needed to clarify the association between PCV use and outcome-specific mortality rates in young children and the general population.

An update to a comprehensive "PCV Dosing Landscape" study previously published (7-9, 227, 367, 370, 374-5) **is expected in 2017 and will include an updated comprehensive analysis of PCV impact evidence. An overview of this forthcoming review, called PRIME (PCV Review of Impact Evidence), is available in Appendix A at the end of this document.**

In 2017, the VIEW-Hub tool (www.view-hub.org) **will launch a PCV Impact Study module which will allow users to search, filter and link to completed and ongoing PCV impact studies worldwide through the interactive online tool, based on a comprehensive, curated database of PCV impact studies maintained by Johns Hopkins' IVAC.**

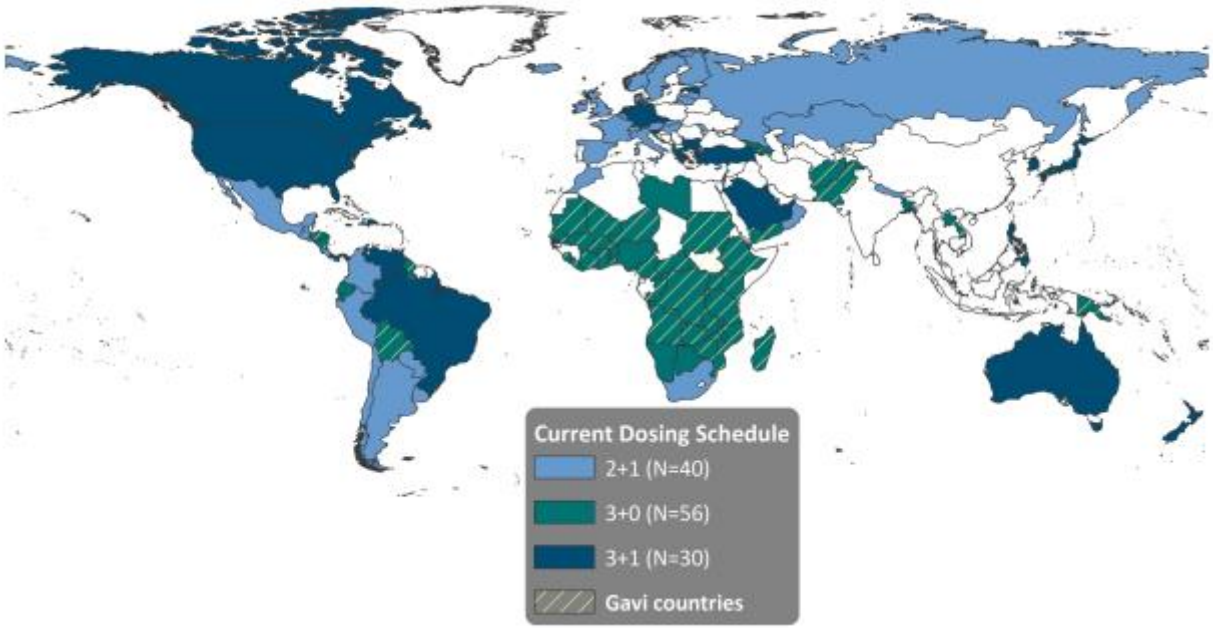
Pneumococcal conjugate vaccines have been introduced in many countries and have demonstrated a greater impact than predicted from clinical trials because of the added benefit of the indirect (herd) effect.

PCVs are administered routinely to infants through national immunization programs in 134 countries in 2015. As of December 2014, 28 countries were using a 3p+1 schedule, 49 countries—including 41 Gavi-eligible countries—were using a 3p+0 schedule, 39 countries—including two Gavi-eligible countries (Moldova and Nepal)—were using a 2p+1 schedule.(Figure 27) The public health impact of PCV introduction in national immunization schedules has exceeded the expected reduction in VT disease based on vaccine efficacy studies. This is because efficacy studies measure direct outcomes in a controlled, idealized setting and in a relatively small group of vaccinated persons. In real-world use, with mass vaccination, the vaccine has direct effects on NP carriage and disease burden among those who are vaccinated, and this is referred to as the vaccine effectiveness. However, what cannot be measured in RCTs are the additional indirect effects of mass vaccination on unvaccinated persons, what is known as the herd effect or indirect protection. Following PCV introduction, groups that are not themselves vaccinated have experienced a change in pneumococcal disease epidemiology due to community-level changes in the pneumococcal serotypes circulating as young children are vaccinated. When PCV has been introduced into routine use, the observed impact on disease reduction has been greater than expected from efficacy trials because of these indirect effects of the vaccine.(163)

In considering the mechanisms of action of PCV, carriage of pneumococcus by young children is an important driver of transmission of pneumococcus in the community and risk of disease.(9) PCV acts through several mechanisms to reduce disease at the population level. First, PCV decreases VT NP carriage in vaccinated individuals, thereby reducing their individual risk of disease. Second, PCV provides systemic immunity in vaccinated individuals reducing their likelihood of disease even in the event of colonization. Third, with reduced VT NP carriage in vaccinated individuals, there is reduced transmission to, and carriage among, unvaccinated persons, and thus their risk of pneumococcal disease is also decreased. Lastly, vaccinated individuals also benefit from the indirect effect of less VT pneumococcus circulating in the community and thus have less chance of exposure and acquisition even if their individual immunity wanes over time.(164)

As PCV is introduced in more countries, including more LMICs, where the epidemiology of pneumococcal disease and carriage may vary (generally with a higher burden of disease and carriage in younger infants), it will be important to continue to monitor and survey the population-level impact of higher valency vaccines. The impact of PCV will depend on the prevailing serotypes causing disease prior to vaccine introduction, the coverage of the vaccine in groups targeted for immunization, the presence and coverage of catch-up campaigns beyond infancy, population density, and the prevalence of other risk factors, such as HIV infection.(165)

Figure 27: Map of countries currently using PCVs, by dosing schedule and Gavi status



Source: IVAC, reduced dose analysis presentation slides, July 2015

PCV7 Impact on Invasive Disease—Young Children

PCV7 quickly and significantly reduced the incidence of pneumococcal disease among young children in countries where it was introduced into the immunization schedule.

Countries in North America and Europe were the first to introduce PCV7 and measure the post-licensure impact of the vaccine. In a meta-analysis of multiple IPD surveillance sites in high-income countries, the routine use if PCV7 resulted in a rapid, 45% decrease in overall IPD in children U5 within the first year after introduction (observed: expected disease rate ratio of 0.55). Vaccine coverage in the first year varied widely by site from 7%-94%, based on the proportion of children receiving the full infant dose by 12 months. The reduction in all serotype IPD was sustained through year 7 after introduction (rate ratio of 0.49), despite increases in NVT IPD.(166) The incidence of VT-IPD rapidly decreased through year 3 post-introduction by 91% (95% CI: 86%, 94%), with a slower rate of decline afterwards through year 7.(Figure 28)(166) Data from the US, the first country that implemented PCV7 in 2000, similarly showed a rapid decrease in PCV7-IPD incidence in the first three years after vaccine from a rate of about 80 cases per 100,000 children U5 to <1 case per 100,000 in 2007.(Figure 29)(167) In another systematic review of PCV7 dosing schedules, countries implementing either a 2p+1 or 3p+1 schedule had VT-IPD reductions of up to 100% (95% CI: 15%, 100% and 94%, 100%, respectively).(7) The WHO stated that there are “rapid, substantial reductions in all settings” in VT-IPD following introduction of PCV7 based on a review of data from Australia, Canada, the U.K, the US and South Africa.(168)

Figure 28: Observed: expected disease rate ratios by age group and year post-PCV7 introduction (166)

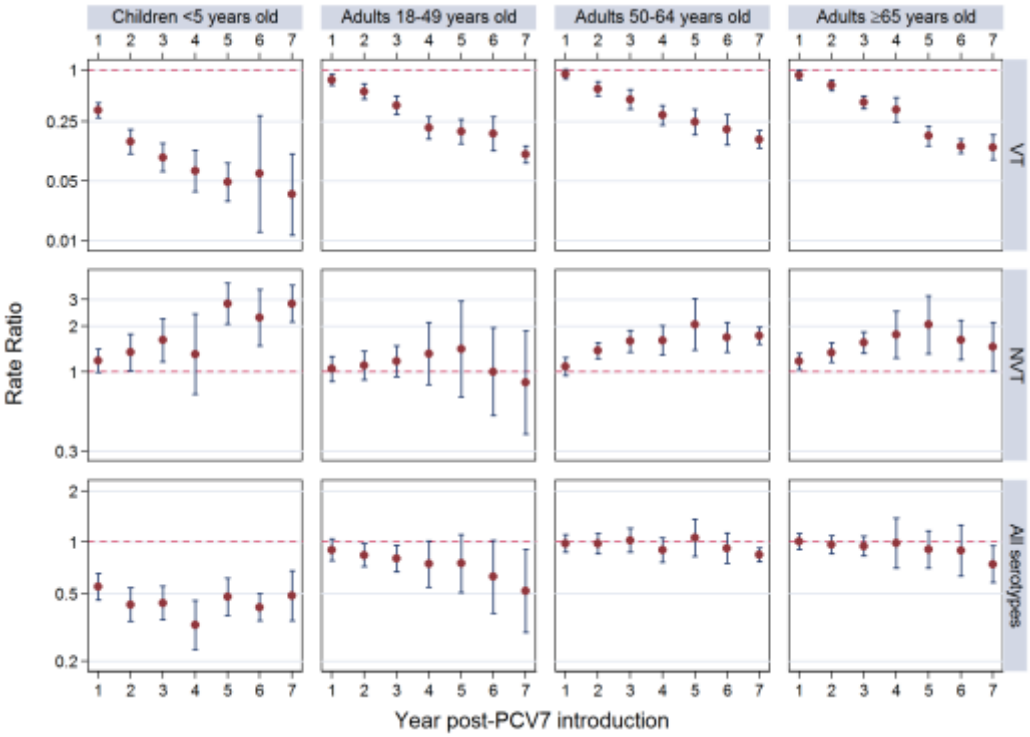
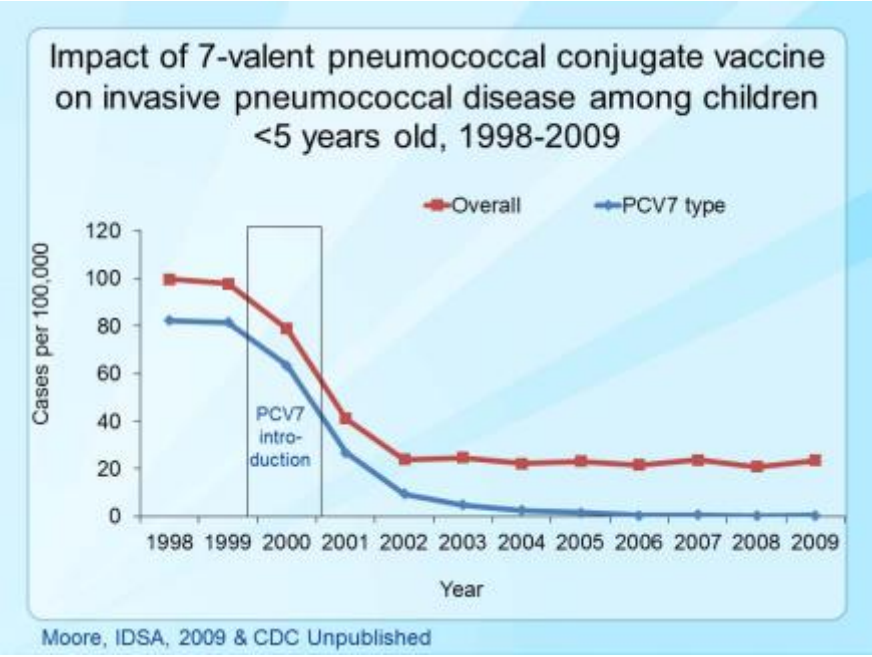


Figure 29: Impact of 7-valent pneumococcal conjugate vaccine on IPD among children in the US (167)

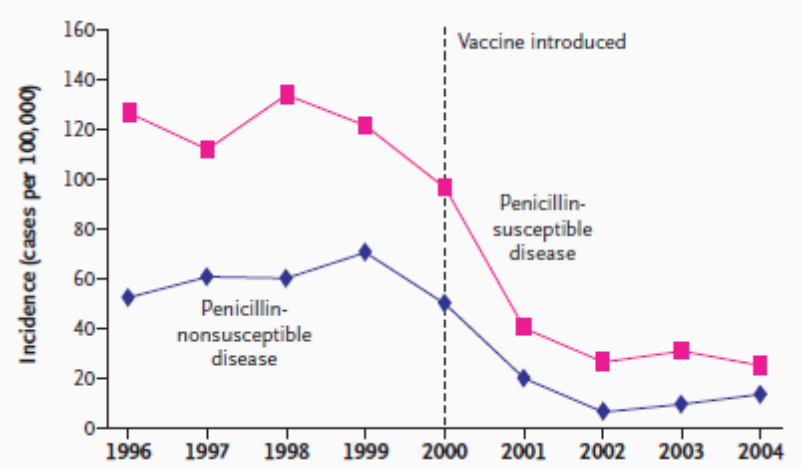


PCV7 impact data was also available from South Africa, a middle-income country. IPD surveillance in South Africa demonstrated that there was an 89% reduction in PCV7 VT disease among children <2 years after three years of PCV implementation using a 2p+1 schedule and no catch-up campaign. VT-IPD incidence declined similarly in HIV-uninfected and HIV-infected young children <2 years by 85% (95% CI:

79%, 89%) and 86% (95% CI: 78%, 91%), respectively. The authors of this study state, "among HIV-infected children younger than 2 years of age, we observed declines in disease caused by PCV serotypes and by nonvaccine serotypes (31% decrease), most likely reflecting the combined effects of PCV7, ART, and improvements in the prevention of mother-to child transmission of HIV".(169) However, the rate of IPD remained 25 times higher among HIV-infected children compared to HIV-uninfected children.(169)

PCV7 use decreased the burden of antibiotic-resistant pneumococcal disease. In the US, four years after PCV7 introduction, penicillin-nonsusceptible disease incidence had declined by 81% (95% CI 80%, 82%) in children <2 years.(Figure 30)(170) This was largely a result of a decrease in PCV7-sertoype disease, which accounted for 78% of penicillin-nonsusceptible strains in the US prior to PCV introduction in 1998.(170) Eight years after PCV7 introduction (2008), penicillin-nonsusceptible IPD rates had declined 64% for children U5 and 45% for adults over 65 years in the US. Over three-quarters of penicillin-nonsusceptible IPD remaining was due to PCV13-non PCV7 serotypes, thus likely to be positively impacted by the subsequent introduction of PCV13.(171) In South Africa, two years after PCV7 introduction, vaccine effectiveness against all-serotype multidrug-resistant IPD was 96% (95% CI 62%, 100%) among HIV-uninfected children.(172) After three years of PCV use, penicillin-nonsusceptible IPD rates had declined by 47% (95% CI: 38%, 55%) in South African children <2 years, this was "predominately due to declines in the proportion of penicillin-nonsusceptible PCV7 serotypes from 70% of isolates in 2009 to 47% of isolates in 2012."(169)

Figure 30: Annual incidence of IPD caused by penicillin-susceptible and penicillin-nonsusceptible strains among children under two years of age, 1996 to 2004, US (170)



Serotype Replacement following PCV7 Implementation

While serotype replacement with nonvaccine serotypes has been near complete in carriage, only minimal serotype replacement in pneumococcal disease has occurred because of the lower invasiveness of the replacing serotypes.

Pneumococcal disease burden has decreased substantially as a result of PCV use, because the magnitude of the serotype replacement with nonvaccine serotypes is small relative to the large reductions in vaccine serotype disease.

Many factors affect trends in the burden of pneumococcal serotypes over time of which PCV implementation is a major factor. In all settings the increase in NVT IPD has been outweighed by the significant reduction in VT disease.

The effectiveness of PCV7 on overall (i.e. all serotype) IPD was reduced, in part, by an increase in NVT IPD in some settings; this has been of variable magnitude and is termed serotype replacement.(168) Serotype replacement in NP carriage is defined as "an increase in the proportion of individuals in a population who harbor NVTs in their nasopharynx after vaccine introduction."(173) Pneumococcal disease serotype replacement can also occur and is defined as an "increase in the incidence of IPD caused by NVTs after vaccine introduction." PCV introduction reduces the risk of VT colonization but increases the risk of NVT colonization by opening up a biological niche in the nasopharynx. There has been a "discrepancy between the near-complete replacement in (pneumococcal) carriage and partial replacement in disease."(173) A key reason for this is that the replacing NVT serotypes are less invasive than the VT strains, with the exception of serotypes 1 and 5 (that are included in higher valency vaccines but not PCV7). Thus, even with an increase in NVT carriage, there was minimal increase in NVT disease, and therefore the decrease in the overall IPD burden resulting from PCV7 use has been preserved.(173)

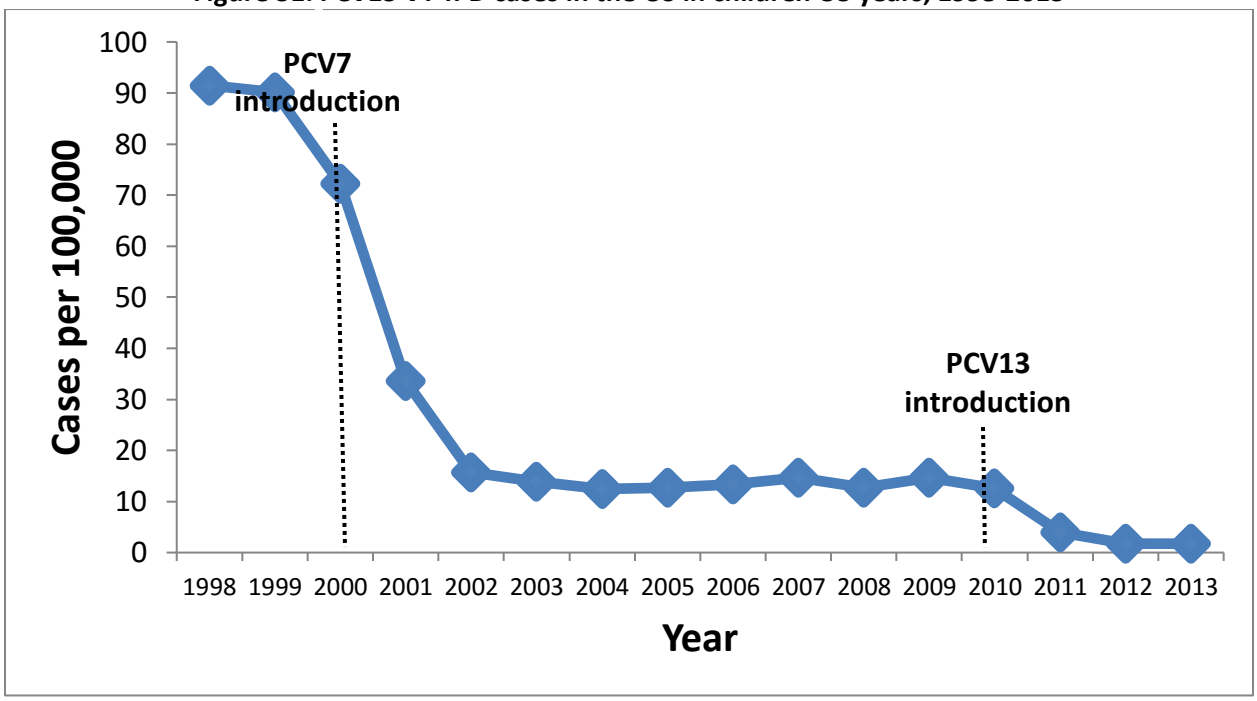
The magnitude of the measured NVT IPD increases have been "minimal to substantial," depending on setting; the variability in the magnitude of the measured replacement may be a result of multiple interacting factors in addition to PCV use and invasive potential of the replacing strains. (168) Unmasking, or increased detection of NVT carriage after PCV use, changes in the sensitivity of disease detection surveillance systems, secular trends in serotype distribution, patterns of antibiotic use and serotype-specific population immunity can also affect trends in serotype prevalence in carriage and disease absent PCV use.(165, 168) Therefore analyses of trends over time in any of these outcomes must interpret any changes observed relative to changes in these factors in addition to the change in PCV use in the population. In a systematic analysis of IPD data from multiple surveillance sites, there was an increase in NVT IPD over the first four years following PCV7 introduction, plateauing between the fifth and seventh year with the observed rate of NVT diseases 2.3-2.8 fold higher than the expected, albeit low, rate.(Figure 28)(166) The serotypes causing replacement disease have varied. In many countries, the greatest increase in NVT disease following PCV7 introduction has been due to increasing prevalence of serotype 19A.(165) In the US, the increased incidence of serotype 19A following PCV7 introduction accounted for 70% of the total rise in NVT IPD.(174) "It should be noted that in every setting, the increase in NVT IPD has been far outweighed by the reduction in VT IPD", especially in young children, the group at highest risk for disease.(25)

Vaccine Impact of PCV10 and PCV13 on IPD in Children, Trends since 2010

With the introduction of higher valency PCVs, PCV10 and PCV13, starting in 2010, the rate of disease from the additional serotypes in these newer vaccines has fallen precipitously.

Higher valency PCV formulations were developed in part to respond to the phenomenon of serotype replacement in disease by including invasive serotypes not in PCV7. Both PCV10 and PCV13 are showing good effectiveness against most of the additional, non-PCV7 vaccine serotypes contained therein. In settings where these additional vaccine serotypes were prevalent prior to PCV10 or PCV13 use—including serotype 19A that was emergent after PCV7 introduction—there has been further decreases in VT-IPD. PCV13 has decreased the risk of serotype 19A IPD, one of the serotypes contained in the vaccine, and PCV10's 19F seems to evoke some cross-protection against 19A IPD.(123, 175, 176) In the US, the incidence of PCV13 VT IPD fell after PCV7 introduction and further decreased to near elimination after PCV13 introduction. (Figure 31) Private hospital discharge data from the US was used to model national estimates for the impact of PCV13 two years after introduction and showed a 64% (95% CI: 47%, 75%) reduction in seasonal IPD admissions among children <2 years based on 54% vaccine coverage compared to the PCV7 period.(177) There was also a 55% (95% CI: 16%, 75%) reduction in IPD admissions among children two to four years of age.(177)

Figure 31: PCV13 VT-IPD cases in the US in children U5 years, 1998-2013



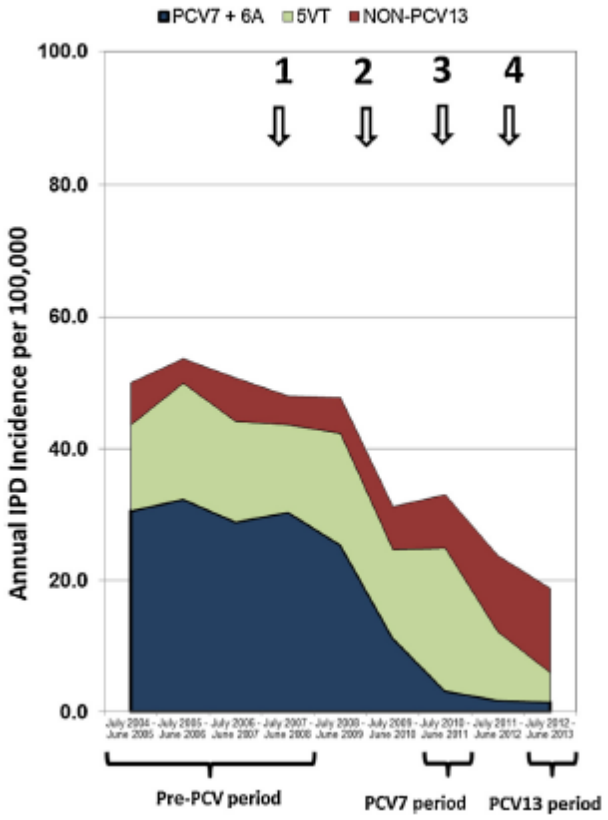
Source: CDC, Emerging Infections Program, Active Core Bacterial Surveillance, unpublished data September 2014 (Courtesy of M. Moore)

European countries have also reported decreasing trends in the rate of VT IPD after the introduction of PCV13. Data from the European *Streptococcus pneumoniae* Invasive Disease network (SpIDnet) have shown PCV13 to be over 94% effective against the additional vaccine serotypes 1, 14, 19A, and 19F. The

effectiveness of PCV13 against serotype 3, however, is lower at 34%. The higher valency PCVs are equally effective as PCV7 against the seven common vaccine serotypes.(178) In an indirect cohort study from the UK, PCV13 effectiveness after two doses in infancy or one dose after 12 months of age was 75% (95% CI: 58%, 84%) against VT IPD. Vaccine effectiveness was 90% (95% CI: 34%, 98%) for thePCV7 serotypes and 73% (95% CI: 55%, 84%) for the six additional serotypes included in PCV13. Vaccine effectiveness against serotype 3 was not significant.(179) This study also estimated the serotype-specific correlates of protection and found the threshold for protection to be higher than 0.35 mcg/ml for serotypes 1, 3, 7F, 9V, 19A, 14 and 19F, and lower than 0.35 mcg/ml for serotypes 6A, 6B, 18C and 23F. The aggregate correlate of protection for PCV13 serotypes plus serotype 6C was 0.98 mcg/ml.(179)

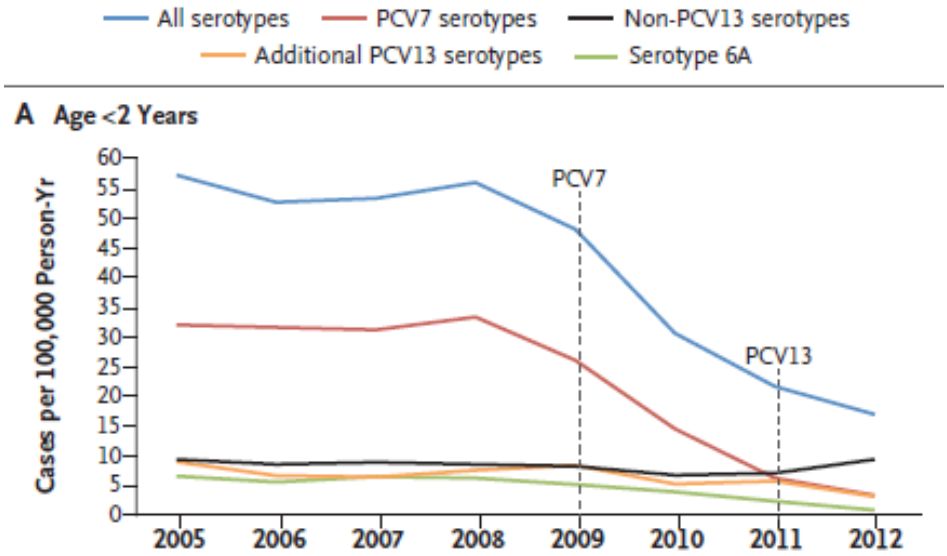
Data from other countries is amassing on the post-licensure impact of higher valency PCVs and strengthens the assertion that the vaccines are continuing to decrease IPD burden beyond what was achieved with PCV7. In Israel, nationwide active surveillance revealed a 47% increase in IPD in children U5 caused by the five additional PCV13-non PCV7 serotypes (1, 3, 5, 7F and 19A) one year after PCV7 introduction compared to the pre-PCV7 period.(Figure 32)(180) This trend was reversed with the introduction of PCV13, after which there was a 79% decrease in IPD due to these five additional serotypes. While NVT IPD increased 2.4 times over the study period among children U5, the overall rate of IPD decreased by 63% in the PCV13 period compared to the pre-PCV period.(180)

Figure 32: Annual IPD rates for PCV13, five PCV13-non PCV7 serotypes (5VT) and non-PCV13 serotypes in Israeli children U5. Arrows: (1) PCV7 introduction in private market; (2) PCV7 introduction in national program; (3) PCV13 introduction in national program; (4) over 70% of children 12-23 months old received 2+ doses of PCV13(180)



In South Africa, sequential introduction of PCV7 and PCV13 using a 2p+1 schedule and no catch-up campaign resulted in a 69% decrease (95% CI: 65%, 72%) in overall IPD one year after the PCV13 switch compared to the pre-PCV7 baseline in children <2 years.(Figure 33)(169) PCV7 VT IPD decreased 89% (95% CI: 86%, 92%) and PCV13-nonPCV7 disease decreased 57% (95% CI: 42%, 68%).(169)

Figure 33: Changes in the incidence of IPD in children <2 years in South Africa, 2005-2012. Vaccine coverage estimates for 3 doses of PCV in infancy were 10% for 2009, 64% for 2010, 72% for 2011 and 81% for 2012.(169)



In Brazil, the vaccine effectiveness of PCV10 against VT-IPD has been about 85% in vaccinated children based on a 3p+1 schedule.(181, 182) The catch-up schedule of one dose for 12-23 month olds has also been shown to be 68% effective against VT-IPD.(181) Table G summarizes data on the impact of PCV10 and PCV13 implementation on IPD from recent publications and from poster presentations at the International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-9) held in Hyderabad, India in March 2014.

Table G: Evidence on the impact of PCV10 and PCV13 use on IPD, updated through January 16,2016

Country	PCV product	Findings	Ref
Argentina	PCV13	One year post-PCV13: hospitalizations of children <60 months for IPD decreased 43% and consolidated pneumonia hospitalizations decreased 43% in this multicenter, prospective study.	(183)
Australia	PCV13	One year post PCV-13: data on IPD incidence rate ratios for PCV13-nonPCV7 serotypes compared to same period post-PCV7. There was a 54% reduction in incidence rate ratio for children U5 but an increase for PCV13-nonPCV7 in 15-49 year olds and no change in other age groups.	(184)
Brazil	PCV10	Vaccine effectiveness for the age-appropriate PCV10 schedule was 84% for VT-IPD in children and 78% for vaccine-related IPD. Serotype-specific effectiveness for IPD presented for serotypes 14, 6B and 19A. For ST19A, effectiveness was estimated as 82% (95% CI: 11%, 96%). One-dose catch up in children 12-23 months was 68% effective against VT-IPD.	(181)
Brazil	PCV10	Two years post-PCV10: PCV10-IPD rates had decreased significantly in all age groups up to 65 years old. Vaccine effectiveness for PCV10-IPD shown by age group. For under 2 year olds (direct effect) effectiveness was 85%. For 2-5 year olds, effectiveness was 50%, for 5-49 year olds, effectiveness was 40%, and for 50-64 year olds effectiveness was 47%.	(182)
Brazil	PCV10	Serotype and antibiotic resistance of IPD isolates in the first two years after PCV10 introduction showed that PCV10 covered 49% of isolates and antibiotic resistance was particularly associated with ST 19A. 159 isolates were studied from patients admitted at three hospitals.	(185)
Brazil	PCV10	Using an indirect cohort method, this study estimated the effectiveness of PCV10 for VT-IPD and vaccine related (VR)-IPD in young children. The adjusted effectiveness of ≥1 dose for VT-IPD was 73% (95% CI: 44%, 87%) and for VR-IPD 61% (95% CI: 15%, 83%). PCV10 was also effective against specific VT 14, 6B, 23F, and 18C and the vaccine-related ST19A.	(186)

Brazil (Sao Paulo)	PCV10	Based on hospital sentinel surveillance, overall IPD incidence in children <2 years and PCV10 IPD incidence decreased in the 2 years following PCV10 introduction compared to 4 years pre-PCV10. Data on antibiotic resistance among STs also presented.	(187)
Canada	PCV13	PCV7 implementation resulted in a decrease in IPD among children U5 from 36.5 to 15.0 cases per 100,000 population between 2002 and 2006. IPD increased slightly to 20.3 cases per 100,000 in children U5 by 2009. Incidence of overall IPD in children U5 declined from 18.0 to 14.2 cases per 100,000 between 2010 and 2012. Incidence in persons ≥5 years was relatively unchanged over the same time period. The proportion of PCV13-IPD decreased in both age groups, from 66% to 41% in U5 and 54% to 43% in over 5 year olds. There was a decrease in 19A and 7F, but a slight increase in serotype 3.	(188)
Canada	PCV7, PCV10 and PCV13	Data from the PCV7 period was compared to the PCV10 and PCV13 period (2008-2010). Incidence of IPD increased significantly for adults ≥65 years. Among persons eligible for PCV7, there was a 77% decrease in VT-IPD rate between 2008 and 2010, and a 60% decrease in VT-IPD among persons not eligible for PCV7.	(189)
Canada	PCV7 and PCV10	IPD rates were significantly lower in the birth cohorts exposed to PCV10 (35 per 100,000 person-years) as compared with those exposed to PCV7 (64 per 100,000 person-years).	(190)
Canada	PCV13	Overall incidence of IPD has been relatively constant between 2008 and 2012 at 9.7 cases per 100,000, except in <1 year old and 2-4 year olds, in which groups the incidence has decreased. In infants <1 year old, the incidence of IPD has decreased from 29.3 to 17.6 cases per 100,000, and in 2-4 year olds from 16.5 to 13.3 cases, between 2008 and 2012. The six additional serotypes in PCV13 are decreasing except serotype 3, which has been relatively unchanged since 2010, accounting for 8% IPD cases tested. Multidrug resistance is highest in serotypes 15A and 19A.	(191)
Canada (Quebec)	PCV7 and PCV10	IPD incidence in children U5 was 67 per 100,000 in 2001-2004 (pre-PCV) and decreased to 32 per 100,000 in 2007-2009, 3-5 years after PCV7 introduction. A further decrease to 24 per 100,000 was observed 1 year after the switch to PCV10. There was a reversal of	(192)

		the trend of increasing prevalence of 19A after the switch to PCV10. PCV7 serotypes represented 82% of the total IPD cases before PCV and were eliminated in 2011, 7 years after the vaccination program was implemented. Some data from adults show that serotype replacement eroded benefits with IPD rates increasing 3-4 years after PCV7.	
Denmark	PCV7 and PCV13	Overall there was a 17% reduction in total incidence of IPD post-PCV13. In children under 2 years, there was an 85% reduction in PCV13-nonPCV7-IPD and 74% reduction in all IPD. There was a 28% reduction in IPD-attributable 30-day mortality from 3.4 deaths to 3.1 and 2.4 deaths in the PCV7 and PCV13 periods, respectively. The mortality decline was observed in all age groups, but mainly in the unvaccinated population.	(77)
Denmark	PCV7 and PCV13	IPD incidence among children U5 nearly halved after the introduction of PCV7. This study presents data from post-PCV7 through transition to PCV13.	(193)
European countries (n=8)	PCV10 and PCV13	In children 2 months - 4 years, adjusted vaccine effectiveness was 94.6% against PCV7 IPD and 87.1% against PCV13-nonPCV7 IPD. Vaccine effectiveness was also given for serotype-specific IPD and was lowest for serotype 3 at 48.5%.	(178)
Finland	PCV10	Five years of national IPD surveillance—including the first year post-PCV10 introduction—show that PCV10 serotypes decreased. Penicillin nonsusceptibility increased over the study period, mainly associated with serotypes 19A, 19F and 14.	(194)
Finland	PCV10	Overall IPD rate among vaccine-eligible children (direct effect) was reduced by 80% (95% CI: 72%, 85%), driven by a 92% (95% CI: 86%, 95%) decrease in PCV10 IPD. There was also a 48% (95% CI: 18%, 69%) decrease in IPD among unvaccinated children 2-5 years old (indirect effect). There was a reduction in VR IPD, including ST6A and 19A, of 62% (95% CI: 20% 85%) in vaccine-eligible children. There was a nonsignificant increase in NVT IPD.	(176)
France	PCV13	This multicenter, retrospective cohort study looked at pneumococcal meningitis in children aged <18 years in northern France. There was a decrease in the corrected pneumococcal meningitis incidence, but it	(195)

		was only significant among children <2 years, in whom the incidence rate decreased from 11.9 per 100,000 in 2008 to 1.9 in 2013.	
The Gambia	PCV7 and PCV13	Three years after the introduction of PCV13, the incidence of all cause IPD decreased by 55% (95% CI 30%, 71%) in 2-23 month olds, with an 82% (95% CI 64%, 91%) reduction in PCV13-type IPD, compared to baseline. In 2-4 year olds, the incidence of all cause IPD decreased by 56% (95% CI 25%, 75%), with a 68% reduction (95% CI 39%, 83%) in PCV13 IPD. There was an upward trend in non-PCV13 IPD in children 2-59: 47% increase (95% CI -21%, 275%).	(196)
Israel	PCV7 and PCV13	In Israel, nationwide active surveillance revealed a 47% increase in IPD in children U5 caused by five additional PCV13-non PCV7 serotypes (1, 3, 5, 7F and 19A) one year after PCV7 introduction compared to the pre-PCV7 period.(Figure 32) This trend was reversed with the introduction of PCV13, after which there was a 79% decrease in IPD due to these five additional serotypes. While NVT IPD increased 2.4 times over the study period among children U5, the overall rate of IPD decreased by 63% in the PCV13 period compared to the pre-PCV period.	(180)
Israel	PCV7 and PCV13	In children U5: overall IPD incidence decreased by 63%. PCV7+6A IPD decreased by ≥91% and IPD caused by the 5 additional serotypes in PCV13 decreased by 70%. Non-PCV13 IPD rates increased by 140%.	(197)
Italy (Apulia)	PCV7 and PCV13	PCV effectiveness was 84.3% for hospitalization in children U5. The reasons for hospitalization were not specified in the abstract.	(198)
Kenya	PCV10	One year after PCV10 introduction, vaccine effectiveness for VT-IPD was estimated to be 72% (95% CI 34%, 88%) in children U5.	(199)
Kuwait	PCV7 and PCV13	Data is presented from 2006 to 2011, post-PCV7 period through the transition to PCV13 (one year after introduction). Pre-PCV data for comparison is not in this paper but the authors referenced other published findings for comparison. There was an increase in the incidence of non-PCV7 PCV13 serotypes 1, 3 and 6A. Coverage was low-moderate with 35%-62% of children <2 years vaccinated.	(200)
Netherlands	PCV7 and PCV10	PCV7-IPD incidence declined by 95% in 0-4 year olds and 71% in ≥65 year olds in 2009-2011 (post-PCV7) and by 95% and 87% in 2011-2013 for those same age groups. NVT-IPD incidence is also provided.	(201)

		Trends in IPD did not change substantially after introduction of PCV10 due to low numbers of serotypes 1, 5 and 7F cases.	
Netherlands	PCV7 and PCV10	Three years after the introduction of PCV10, there was an observed decrease in IPD incidence caused by the serotypes 1, 5 and 7F. The data do not support or exclude cross-protection against ST19A.	(202)
Norway	PCV7 and PCV13	The incidence of VT IPD decreased in children U5 and persons ≥5 since PCV7 introduction and further decreased in the year following PCV13 introduction. There was a lag phase for the indirect effects of PCV7, suggesting that the indirect protection from PCV13 will increase in the coming years. NVT incidence, especially STs 23B and 15A, increased after PCV13 intro. There was an increased diversity of serotypes causing disease in young children.	(203)
Portugal	PCV10 and PCV13	IPD incidence in children <18 years decreased from 8.19 per 100,000 in 2008-2009 to 4.52 per 100,000 in 2011-2012. This was due to reduction of the additional serotypes in PCV10 and PCV13. The decrease in 19A before vaccination was likely not triggered by introduction of PCV13. Likewise, the decrease in ST1 in all age groups concomitant with PCV10 introduction is also unlikely triggered by vaccination. PCV13 serotypes account for 63% of isolates recovered in 2011-2012. PCV is available through the private sector, not through the national immunization program. Coverage ranged between 63% and 75%. Indirect effect was seen in 5-17 year olds.	(204)
Portugal	PCV10 and PCV13	IPD incidence in persons <18 years decreased from 8.19 cases per 100,000 in 2008-09 (PCV7 period, right before PCV10 introduction) to 4.52 cases per 100,000 in 2011-12 (1 year after PCV13 introduction). This decrease was a result of a decline in iPD due to additional serotypes in PCV10 and PCV13. The ST19A and ST1 decrease was not likely due to vaccine introduction.	(205)
Saudi Arabia	PCV7 and PCV13	Data is presented from pre- and post-PCV7 and through right after switch to PCV13. There was a significant rise in ST19A over the years in children U5 and a notable decrease in ST18C.	(206)
South Africa	PCV7 and PCV13	Sequential introduction of PCV7 and PCV13 using a 2p+1 schedule and no catch-up campaign resulted in a 69% decrease (95% CI: 65%, 72%) in overall IPD one year after the PCV13 switch compared to the pre-	(169)

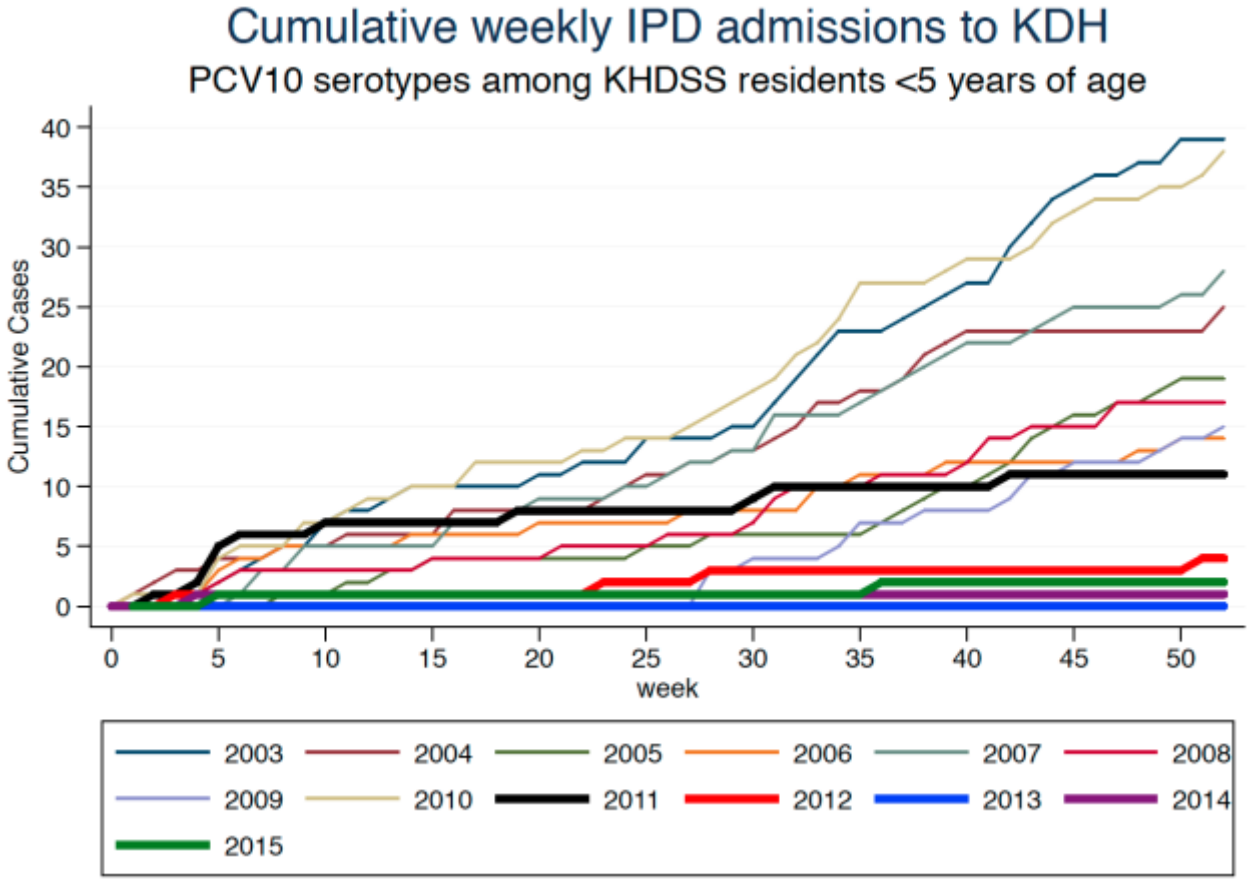
		PCV7 baseline in children <2 years.(Figure 33) PCV7 VT IPD decreased 89% (95% CI: 86%, 92%) and PCV13-nonPCV7 disease decreased 57% (95% CI: 42%, 68%).	
Spain	PCV13	Incidence rate of IPD decreased overall from 17.09 (PCV7 period) to 7.70 (PCV13 period) cases per 100,000 persons <15 years. Incidence rate of bacteremic pneumonia, empyema and meningitis reported separately as are rates for serotypes 1, 5 and 19A. IPD caused by non-PCV13 did not increase.	(207)
Spain	PCV7 and PCV13	Data is presented from the period post-PCV7 through PCV13 transition. Incidence of IPD in children decreased in 2010-2011, during the early PCV13 switch over, and was driven by a decrease among children <24 months. The incidence of PCV13-IPD was significantly lower in 2010-2011 than in previous years.	(208)
Spain (Navarre)	PCV7 and PCV13	Between 2004-2009 (PCV7 period) and 2010-2013 (0-3 years after PCV13 introduction in private market), IPD incidence declined by 69% in children U5, 34% in persons 5-64 years old, and 23% in those >65 yrs. The incidence of PCV13 IPD declined by 81% in children U5 and 2% in the whole population.	(209)
Spain	PCV7 and PCV13	In a region with intermediate vaccine uptake (estimated infant coverage of 50% in 2006), there have been significant declines in adult VT IPD incidence rates, both in the general and immunosuppressed adult population. Overall IPD incidence decreased by 60% in the adult population, mostly driven by a decrease in PCV7 serotypes and to a lesser extent PCV13 serotypes.	(210)
Sweden (Stockholm)	PCV7 and PCV13	In a hospital-based retrospective study, positive blood cultures for pneumococcus decreased by 42% (from 5.6 to 3.2 per 100,000) in previously healthy children <17 years, and by 62% (24.2 to 9.2 per 100,000) in previously healthy children <36 months. Two time periods were compared: 2002-2007 (pre-PCV) and 2008-2013 (PCV7 then PCV13 introduced).	(211)
Taiwan	PCV7, PCV10 and PCV13	The 12 year-trend of annual incidence of IPD admissions at one hospital is presented. The annual incidence of IPD admissions (in all ages) decreased significantly from 9.8 per 1000 in 2000 to 2.1 in 2012.	(212)
Turkey	PCV7 and PCV13	Data from 22 hospitals covering 65% of the population showed a	(213)

		decreased in VT-IPD in children between 2008 and 2014. PCV7 serotypes decreased from 58% to 37% and PCV13 from 77% to 61%. NVT IPD increased from 27% to 38%.	
UK	PCV7 and PCV13	Correlates of protection against VT IPD vary by serotype, with concentrations higher than 0.35 mcg/ml needed for serotypes 1, 3, 7F, 19A and 19F, and lower concentrations for serotypes 6A, 6B, 18C and 23F. PCV13 effectiveness for 2 doses before age 12 months or one dose after age 12 months was 75%. Vaccine effectiveness was 73% for the 6 additional serotypes in PCV13.	(179)
UK	PCV13	PCV13-nonPCV7 IPD vaccine effectiveness was 78% in vaccine-eligible children within a year post-PCV13. Website has graphs of direct and indirect cumulative cases.	(214)
UK (England, Oxfordshire)	PCV7 and PCV13	The incidence of PCV7 IPD decreased in all ages 1-2 years after PCV7 introduction, whereas the incidence of PCV6+ IPD and NVT IPD increased in children ≥2 years after PCV7 introduction. PCV6+ IPD incidence decreased significantly 3 years after PCV13 intro in all age groups, and the incidence of NVT IPD declined significantly in children≥2.	(215)
US	PCV13	Data from the PCV13 period is compared to the PCV7 period. IPD decreased 42% overall and 53% for children <24 months in 2011 compared with 2007-2009. PCV13 serotypes decreased 57% in this time period.	(216)
US	PCV7 and PCV13	Following the introduction of PCV7, annual IPD incidence in children U5 decreased from 547 per 100,00o in 1996-2000 to 148 per 100,000 in 2001-2004. The annual incidence increased to 426 per 100,000 in 2005-2007 due to NVT disease. Following the introduction of PCV13, the IPD incidence decreased to 399 per 100,000 in 2005-2008 and to 106.7 per 100,000 in 2009-Aug 2011.	(217)
US	PCV13	Post-PCV13, overall and PCV5 (PCV13-nonPCV7) IPD rates decreased by 59% and 88%, respectively, in children U5. Some serotype-specific data is also presented.	(218)
US	PCV13	After PCV13 use, antimicrobial resistance due to 19A/ST320 complex decreased. The strain contributing most to remaining beta-lactam resistance was 35B/ST558. PCV13 decreased all VT clones and strain	(219)

		subsets with resistance and/or adherence features (pilus types) conducive for successful carriage.	
US	PCV13	Private hospital discharge data from the US was used to model national estimates for the impact of PCV13 two years after introduction and showed a 64% (95% CI: 47%, 75%) reduction in seasonal IPD admissions among children <2 years based on 54% vaccine coverage compared to the PCV7 period. There was also a 55% (95% CI: 16%, 75%) reduction in IPD admissions among children 2-4 years of age.	(177)
US (Alaska)	PCV13	45 months after PCV13 introduction, state-wide surveillance found a decrease in overall IPD and VT-IPD rates in children U5 of 58% and 83%, respectively, between the pre-PCV13 period of 2005-2008 and post-PCV13 period of 2010-2013. There was also evidence of indirect effects with a 39% decline in the IPD rate in persons 18-44 years.	(220)
US (Massachusetts)	PCV13	IPD due to PCV13 serotypes declined by 18% in the first 2 years after PCV13 use.	(221)
US (Tennessee)	PCV13	In children <2 years, IPD rates declined by 70% in the post-PCV13 period compared to the early PCV7 period. There were also declines in IPD rates in children 2-4 years and 5-17 years. In the late PCV7 period, IPD rates in Black children <2 years was higher than in White children of the same age. These racial differences were no longer significant post-PCV13.	(222)
US	PCV7 and PCV13	Prevalence of PCV7 serotypes decreased from 64% of invasive and 50% of noninvasive isolates in 1999-2000 to 3.8% and 4.2%, respectively, in 2010-2011.	(223)
US	PCV13	This hospital-based study of pneumococcal meningitis in children found a significant decrease in PCV13 serotypes causing meningitis although the overall number of pneumococcal cases did not change in the 3 years after PCV13 use compared to the 3 years prior. ST19A continued to be the most common serotype in the post-PCV13 period. Antibiotic resistance decreased significantly.	(224)

In Kilifi District, Kenya, PCV10 was introduced in January 2011. The catch up campaign and high coverage rates, about 65% of U5 children vaccinated in the first 10-12 weeks of PCV rollout, has meant that the impact of PCV is accelerated and impact results are available earlier than they would have been without a catch-up campaign in this low-income setting. The Pneumococcal Conjugate Vaccine Impact Study (PCVIS) is an ongoing surveillance project to determine the effectiveness of PCV10 in this setting and follows the outcomes of IPD, pneumonia and NP colonization. One year after PCV10 introduction, coverage of one and two doses of PCV10 in children U5 was estimated to be 65% and 33%, respectively, and effectiveness for VT IPD was 70% (95% CI: 30%, 91%).(225) As shown in the cumulative case count in Figure 34, by year two after introduction, there was an impressive drop in IPD admissions to Kilifi District Hospital (KDH). Since serotype 1 has different epidemiology with the potential to cause outbreaks, continued monitoring to ascertain the inter-epidemic interval will be important to determine the impact of vaccine against this particular serotype.(226)

Figure 34: Impact of PCV introduction on IPD hospital admissions in one Kenyan district

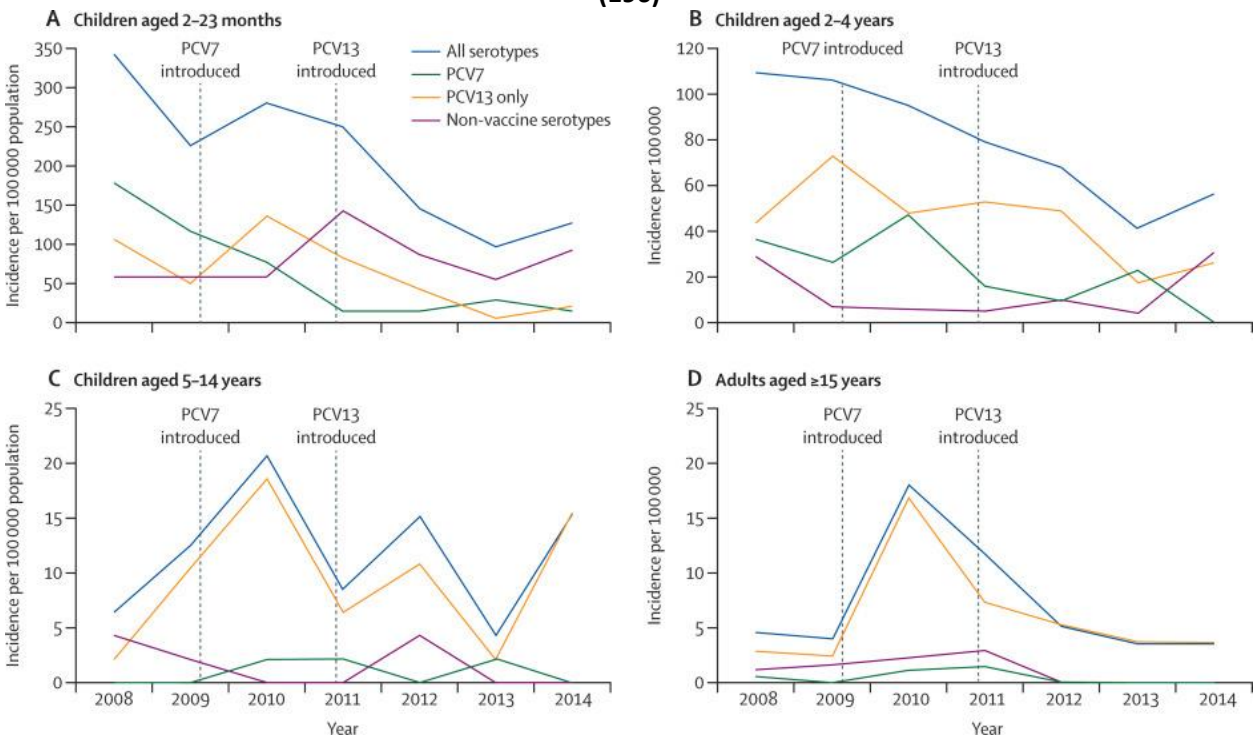


Accessed from KEMRI Wellcome Trust: Pneumococcal Conjugate Vaccine Impact Study at http://www.kemri-wellcome.org/index.php/en/studies_inner/75, last updated on January 15, 2016 and downloaded on January 25, 2016.

Data from population-based surveillance in the Upper River Region, The Gambia, is available showing the impact of the transition to PCV13 from PCV7 on IPD.(196) Three years after the introduction of PCV13, the vaccine coverage of at least two doses of PCV before 12 months of age has increased to 94%.

In the post-PCV period compared to the baseline period, there have been significant reductions in all cause IPD and PCV13 IPD in children 2-23 months old and 2-4 years old. In the 2-23 month olds, all cause IPD has decreased 55% (95% CI: 30%, 71%) and PCV13 IPD has decreased 82% (95% CI: 64%, 91%). Among 2-4 year olds, all cause IPD has decreased 56% (95% CI: 25%, 75%) and PCV13 IPD has decreased 68% (95% CI: 39%, 83%).(196) There has been a concomitant increase of 47% (95% CI: -21%, 275%) in non-PCV13 IPD in young children 2-59 months old. (See Figure 35.)

Figure 35: Adjusted annual incidence of IPD from 2008-2014, by age group and serotype, The Gambia. (196)



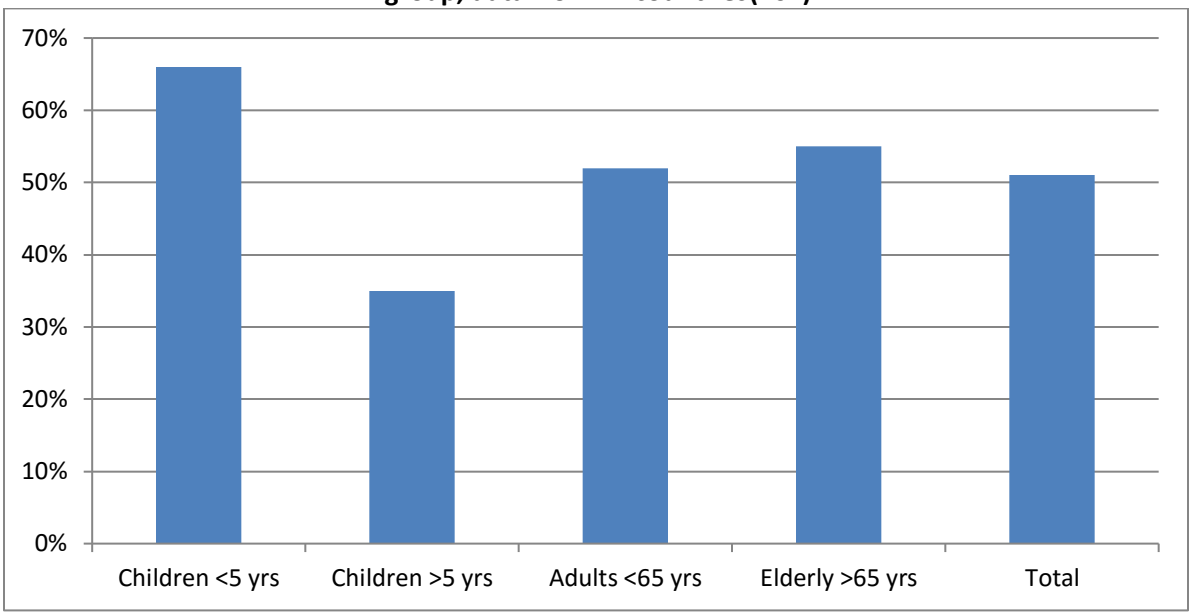
Indirect Impact of PCV Use on IPD

VT-IPD among adults has gradually decreased in almost all countries within several years of PCV introduction. This indirect effect has been observed for all routinely used infant schedules, for all licensed PCV products, and in populations with high HIV-infection burden.

PCV implementation into national immunization programs has impacted the rate and serotype distribution of pneumococcal disease in age groups beyond the ages targeted for vaccination. There have been reductions in VT-IPD in individuals not directly vaccinated with PCV due to reduced transmission of VT pneumococci from young children who are vaccinated. However, there has been replacement disease with NVT pneumococci. The relative magnitude of the two effects--herd immunity and serotype replacement--has varied across studies/populations and resulted in observed IPD rates among unvaccinated groups that have decreased, remain unchanged or increased depending on setting.(168) The observed magnitude of PCV's indirect effect depends on various factors: the immunization strategy—i.e. the use of catch-up vaccination to accelerate impact—vaccine coverage rate, the population composition and density, the prevalence of VT pneumococci carried in young children, the prevalence of VT disease prior to introduction, and of course surveillance methods that may confound the observations.(10)

In a systematic review of data on the indirect effect of PCV use in 14 countries, VT-IPD consistently decreased after PCV introduction, though the magnitude of the reduction varied in the age groups spanning from U5 to >65 years.(164) The indirect effect on VT-IPD has been found in countries implementing any of the common infant schedules: 3p+1, 3p+0 and 2p+1.(227) The magnitude of the decrease among unimmunized adults grew over the first seven years after PCV introduction, the duration for which data were available. For the general population, the median percent decrease in VT-IPD was 57% (interquartile range (IQR) 40% to 77%).(Figure 36) For aboriginal populations, the median percent decrease was 67% (IQR 40% to 85%).(164) The indirect effect was dependent on vaccine coverage rates: when coverage rates were high, the indirect impact was consistent, while lower coverage rates yielded mixed indirect impact, with some reductions in disease demonstrated starting at 40% coverage.(164)

Figure 36: Impact of herd protection as demonstrated by the percent reduction in VT IPD by age group, data from 14 countries(164)



Adapted from Davis SM, et al. "Impact of pneumococcal conjugate vaccines on nasopharyngeal carriage and invasive disease among unvaccinated people: review of evidence on indirect effects." Vaccine 2013; 32: 133-145.

From the pooled results of high-income setting surveillance, VT-IPD decreased significantly for all adult age groups by the second year after PCV7 introduction.(166) The rate of decrease was more gradual than that in young children (the group targeted for vaccination). After the fourth year following PCV7 introduction, the magnitude of the decrease in adults was on par with the decrease in children U5 seen in the first year after PCV7 use.(Figure 28)(166) Among adults 50-64 years, there was a more modest decrease in VT-IPD and no change in the overall IPD rate due to the increase in NVT disease.(166)

Data from the US have shown that the absolute impact of PCV's indirect effect is greater than that of the direct effect. While the relative magnitude of the reduction in VT-IPD is lower in adults, because they make up a larger portion of the total population, the actual number of IPD cases prevented among adults is greater. In the US, it was estimated that over twice as many cases of VT-IPD were prevented in adults in 2003 (n=20,459) compared to cases prevented in vaccinated children U5 (n=9,140).(228) Another estimate of the absolute reduction in IPD cases in the US also shows a greater number of cases prevented in adults through the indirect effect of vaccination strategy, 2,500-29,000 VT-IPD cases per year, compared to the reduction in vaccinated children (direct effect), among whom 2,700- 14,000 cases were prevented per year.(174)

Extrapolation from the US experience to LMICs needs to proceed with caution. The age structure of low-income countries is more heavily weighted to children and young adults, so there is not as much opportunity for indirect protection. For example, if the US had the population structure of a low-income country, it was estimated that only 5,805 cases of IPD would have been indirectly prevented in 2003 and 13,417 cases prevented in children U5.(50) Furthermore, the contribution of older children and adults to the transmission dynamics of VT pneumococcal carriage is greater in some low income settings so the magnitude and timing of the indirect effect of vaccinating infants is still not quite clear. The effect of the

age structure of low-income countries is countered by the higher burden of IPD and pneumonia even among older children and adults in such settings. So the potential impact on absolute number of cases prevented in older children and adults may still be high.

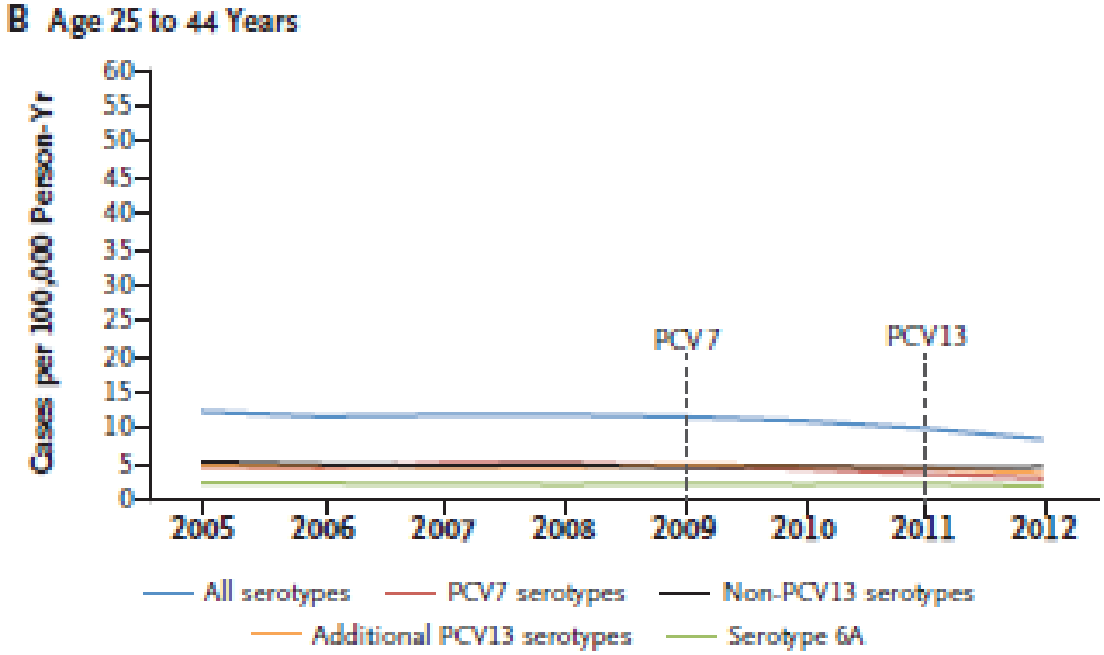
The opportunity for indirect protection also depends on the serotypes causing pneumococcal disease in older children and adults. Overall, a lower proportion of vaccine serotypes cause disease in older age groups compared to young children.(229) The Adult Global Estimation of Disease Burden and Distribution (AGEDD) study is a systematic review of data on serotypes causing serious pneumococcal disease in older children and adults in the pre-PCV era and helps assess the potential indirect impact of PCV use in different countries. Findings from the AGEDD study show that in the pre-PCV period, PCV10 and PCV13 serotypes accounted for over 50% of IPD in children over five years of age and adults in every region, though data was limited in Africa and Asia.(230) PCV10 serotypes plus 6A accounted for 52% to 62% of IPD in each region; and PCV13 serotypes accounted for 60-75% of IPD. The authors of the study conclude: "if current and future PCV products induce indirect effects for IPD among adults as has been observed for PCV7, we expect there to be no more than a 50% reduction in IPD rates" among those persons aged five and older.(230)

Evidence is emerging on the indirect effect following introduction of the higher valency products PCV10 and PCV13. After PCV13 introduction in the US, IPD caused by the five additional PCV13-nonPCV7 serotypes (1, 3, 5, 7F and 19A) declined by 65% in adults 18-49 years, 54% in 50-64 year olds, and 47% in adults over 65 years. Non-PCV13 IPD incidence did not change.(231) In Brazil, there has been a 40% reduction in VT-IPD in persons 5-49 years old and a 47% reduction in 50-64 year olds two years after PCV10 introduction, based on national laboratory surveillance.(182) In Finland, PCV10 use was followed by a 41% reduction in VT-IPD rates in 18-49 year olds, a 24% reduction in 50-64 year olds, and a 41% reduction in persons over 65 years.(232) In Israel, sequential introduction of PCV7 and then PCV13 has coincided with a 69% reduction (95% CI 56%, 79%) in PCV7 serotypes and a 55% reduction (95% CI 45%, 63%) in PCV13 serotypes causing IPD in adults. NVT IPD has increased by 47% (95% CI 19%, 81%), but overall IPD has decreased 22% (95% CI 10%, 32%).(233)

In South Africa, national surveillance has demonstrated significant reductions in IPD in adults 25 to 44 years of age in the first three years following sequential introduction of PCV7 and PCV13. (169) In a population with an HIV prevalence of 30% among pregnant women that remained stable over the study period (2005-2012), PCV introduction resulted in a 34% decrease in all IPD (95 CI 29%, 39%) in adults 25 to 44 years.(Figure 37) PCV7 VT IPD decreased 57% (95% CI 50%, 63%). IPD caused by the six additional serotypes in PCV13 decreased 32% (95% CI 22%, 40%). There was no significant change in the rate of NVT IPD.(169)

In The Gambia, population-based surveillance in the third year after PCV13 implementation, in a setting that effectively did not have a catch up campaign, has not yet demonstrated a significant change in all cause IPD or PCV13 IPD in the age groups 5-14 years and adults.(196) Seventy-seven of the 320 cases of IPD identified in the seven years of surveillance occurred in persons over the age of 5 years. All cause IPD was found to have decreased by 16% (95% CI -125%, 69%) in 5-14 year olds and 59% (95% CI -3, 84%) in adults over 15 years old. PCV13 IPD had decreased by 50% (95% CI -32%, 81%) in adults but had not decreased in the 5-14 year old age group.(196)(Figure 35)

Figure 37: Changes in the incidence of IPD in adults 25 to 44 years old following sequential introduction of PCV7 and PCV13, South Africa 2005-2012(169)



PCV implementation has indirectly reduced the burden of VT-IPD among HIV-infected adults. Pooled results of the indirect impact of PCV revealed that the median reduction in VT-IPD for HIV-positive populations was 30% (IQR 13% to 46%).(164) In the US, there was a 91% reduction in VT-IPD incidence among HIV-infected adults between 1998/1999 (pre-vaccine) and seven years post-PCV7 (2007).(234) In Spain there was a 67% reduction in disease among HIV-infected adults at a Barcelona hospital six years after PCV7 introduction.(235)

Neonates and infants too young to be immunized with PCV have also benefited from the routine use of PCV, however, replacement disease has occurred to some extent. In the UK, following PCV7 introduction there has been an 83% decline in VT-IPD among infants younger than 90 days and a declining trend in overall IPD.(236) In the US state of Utah, PCV7-IPD decreased by 74% in infants younger than 90 days, and NVT-IPD increased by 57%.(237) In Denmark, while there have been no cases of VT-IPD after two years of PCV use, the overall rate of all-serotype IPD has not changed in infants younger than 90 days.(238)

Vaccine Post-introduction Impact on Pneumonia

Pneumonia is the most common form of serious pneumococcal disease, and so the absolute impact of PCV on pneumonia burden is greater than for the more specific clinical diagnosis of IPD.

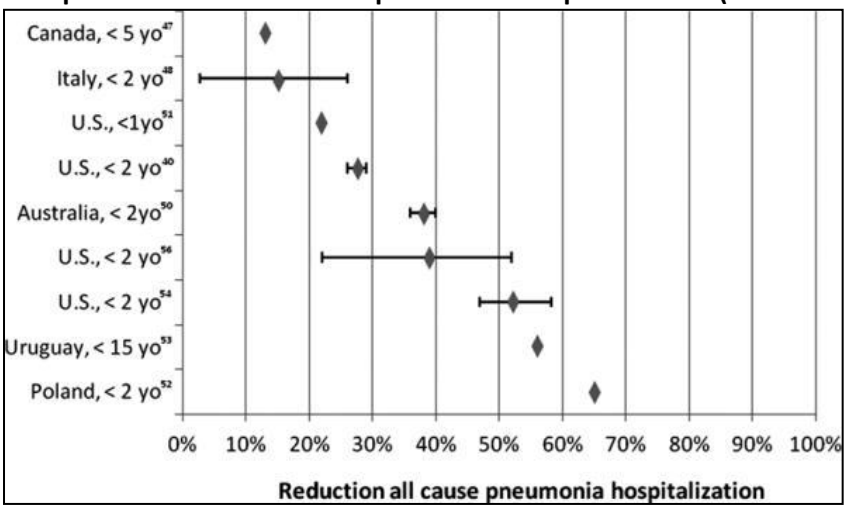
PCVs have had a substantial effect on pneumonia disease burden: the newer generations, high valency PCVs have reduced hospitalizations for all-cause pneumonia by 13% to 72% (n=6 studies) and for consolidated pneumonia by 20% to 45% (n=3 studies) in children U5.

Pneumonia is the most common form of serious pneumococcal disease and the leading cause of death in children U5.(2, 5, 39, 41) Clinical pneumonia is difficult to attribute to a particular etiology because blood culture is not a sensitive diagnostic tool (see Chapter 1, "Diagnosis of Pneumococcal Disease"). However, vaccine probe studies and PCV effectiveness against clinical and radiologically confirmed pneumonia help provide estimates of the total burden of pneumonia due to pneumococcus. A vaccine probe strategy estimates the relative burden of pneumococcal disease manifesting as non-bacteremic or culture-negative pneumonia by determining the reduction in the incidence of the disease endpoint in the vaccinated group in a vaccine efficacy trial compared to the control group. This approach confirms that IPD is only a "small fraction of all pneumococcal disease most of which manifests as non-bacteraemic pneumonia."(50) In The Gambia PCV9 trial, for example, there were 15 cases of radiologically confirmed pneumonia prevented by vaccine for every two cases of IPD prevented.(50, 124)

In countries that have introduced PCV, there has been a "dramatic effect on hospitalization due to pneumonia" among children, including hospitalizations associated with community-acquired pneumonia and radiologically confirmed pneumonia.(165) The magnitude of the PCV impact on pneumonia hospitalizations has varied by country due to variability in serotypes causing pneumonia, the etiology of pneumonia, the background incidence of pneumonia, access to care and health seeking behaviors, time since PCV introduction, and vaccine coverage rate. PCV7 was estimated to reduce pediatric hospitalizations due to all-cause pneumonia by between 13% and 65%, by study and country.(Figure 38)(165) Some of these values seem implausibly high, given that any reduction is only attributable to the serotypes in the PCV product in use. There are substantial analytic, methodologic concerns about how to analyze the administrative time-series data on pneumonia admissions, so any such reports should be interpreted with great care.

In the PCV dosing landscape analysis review, there was consistent evidence that all commonly used PCV7 schedules—3p+1, 3p+0 and 2p+1—were effective in reducing clinical and radiologically confirmed pneumonia incidence in vaccinated children.(8) Sixty percent of studies (12 out 20) found a statistically significant reduction in clinical pneumonia, and 55% (6 out of 11) found a statistically significant reduction in radiologically confirmed pneumonia. The evidence on impact against pneumococcal pneumonia is more variable for all schedules, but 44% of studies (7 out of 16) did show a statistically significant reduction.(8) The mixed results for pneumococcal pneumonia are complicated by the difficulty in diagnosing a particular etiology for pneumonia and indicative of the low sensitivity of blood culture for detecting the etiology.(165)

Figure 38: Impact of PCV7 on all-cause pneumonia hospitalizations (with 95% CI)(165)



References: Canada(239), Italy(240), US(241-244), Australia(245), Uruguay(246), Poland(247)

In the US, reductions in all-cause pneumonia hospitalizations were sustained in young children for the nine years following PCV7 introduction.(248) Comparing the pre-PCV years of 1998-1999 to 2007-2009, there was a 43% reduction in pneumonia hospitalizations among children <2 years of age, and a 10.5% reduction in pneumonia hospitalizations over all age groups. Again the magnitude (43%) of the effect in the age group targeted for immunization is far greater than expected. If 90% of pneumococcal pneumonia events in the pre-vaccine era were from PCV7 VT strains and if the vaccine was 100% effective against these cases, this implies that 50% of all pneumonia hospitalizations are from pneumococcus. Assessing the trends in hospitalization rates prior to vaccination and accounting for these in the analyses are critical components of time series analyses.

The indirect effect of PCV7 on US adult pneumonia hospitalizations was more gradual, modest and variable by age group, with the largest reduction seen in those adults 75-84 years old (13%) and over 85 years (23%). The authors also report that there was no "compensatory" increase in outpatient visits for pneumonia, but rather there was a decrease in outpatient visits as well. There was also noted to be a stable length of stay for admissions, suggesting no major increases in admission thresholds for the diagnosis of pneumonia.(248) Of note, only 2%-8% of pneumonia hospitalizations in the US sample included a code specific for pneumococcal disease, possibly due to the difficulty in establishing a definitive pneumonia etiology or incomplete coding practices.(248)

Another study supports the indirect effect of PCV7 on pneumonia burden in US adults. Six years after the introduction of PCV7 in the US, the hospitalization rate for all-cause pneumonia was 32% lower (95% CI 30%, 33%) in 18-39 year olds, 8% lower (95% CI 7%, 9%) in 40-64 year olds, and 12% lower (95% CI 11%, 13%) in persons 65 years and older compared to pre-PCV.(241) In the US setting with an older population composition and higher frequency of VT disease, modeled data demonstrate that 90%-95% of the reduction in pneumococcal pneumonia is due to PCV's indirect effect in persons over 18 years of age.(241)

Long-term surveillance in Australia presents a slightly different picture for the stability of PCV7 impact on pneumonia. In Australia, reductions in all pneumonia hospitalizations were still significantly reduced for children <4 years of age after 6.5 years of PCV use. The reductions were 32% in those <2 years and

20% in 2-4 year olds. For persons over five years of age, however, the reduction in pneumonia hospitalization was no longer significant and ranged from 6% lower to 5% higher, compared to pre-PCV years.(249, 250)

Additional evidence on the indirect effect of PCV7 implementation on pneumonia hospitalizations is very limited. In Poland, based on hospitalized and outpatient cases five years post-PCV7, there was a 40%-44% reduction in pneumonia in persons 50 years and older.(251) In Taiwan, there was no significant reduction in clinical pneumonia in 5-64 year olds, but there was a 64% reduction in those over 65 years, a group that also experienced increased use of PPV23.(252) In Spain, while there was a 27% decrease in VT pneumococcal pneumonia in adults, there was an overall increase in pneumococcal pneumonia (39%) due to the increase in NVT cases.(253)

Evidence is accumulating of the beneficial effect of higher valency PCV products on pneumonia burden. PCV10 and PCV13 have reduced or continued to reduce pneumonia hospitalizations in countries where they have been implemented. In the US, two years after the switch to PCV13, all-cause pneumonia admissions were estimated to be 21% lower (95% CI 14%, 28%) in children <2 years and 17% lower (95% CI 7%, 27%) in children two to four years old compared to the PCV7 period.(177) This translates to about 14,000 and 8,600 fewer seasonal hospital admissions for pneumonia compared to the PCV7 period and based on a PCV13 coverage rate of 54%.(177) Among adults, the only age group for which the US study model predicted a significant reduction in all-cause pneumonia admissions was the 18 to 39 year olds: in this age group, there was estimated to be a 12% reduction in pneumonia admissions (95% CI 6%, 17%) or 9,500 fewer seasonal admissions in 2012 compared to the PCV7 period.(177)

Table H presents data from recent publications on the effect of new generation PCV products on pneumonia. Reduction in all-cause pneumonia admissions range from 13% to 72% in children U5, based on results from 6 different studies. Reduction in consolidated pneumonia admissions in children U5 range from 20% to 45%, based on 3 studies. Comparisons between studies need to be made with caution as there is variability in the age groups under study, the case definition of pneumonia, and the number of years post-PCV introduction.

Table H: PCV10 and PCV13 impact on pneumonia, updated as of January 16, 2016

Country	PCV product	Age group	Outcome	Percent reduction	Ref
Argentina	PCV13	<5 years	Hospitalization for probable bacterial pneumonia, 1 year post-PCV	41% (95% CI 16%, 67%)	(254)
Argentina	PCV13	<5 years	Hospitalization for consolidated pneumonia (CP) and non-viral consolidated pneumonia	CP: 29% (95% CI 19%, 30%), Non-viral CP: 37% (95% CI 29%, 43%)	(255)
Argentina	PCV13	<5 years	Hospitalization for radiologically-confirmed (RC) CP, time series 2001-2013	RCCP: 20% Non-viral RCCP: 28% Viral RCCP: 4.8%	(256)
Argentina (Pilar)	PCV13	<5 years, <1 year, 12-23 months	CP incidence, 2 years post-PCV13 introduction	<5 years: 40% (95% CI 25%, 51%) <1 year: 45% 12-23 months: 58%	(257, 258)
Argentina	PCV13	<12 and 13-23 months	National surveillance for clinical pneumonia	<12 months: 28% 13-23 months: 30%	(259)
Brazil	PCV10	0-4 years	Hospitalizations for pneumonia, adjusted for seasonality and secular trends, 2 years after PCV10 introduction	12.7%	(260)
Brazil	PCV10	2-24 months	Hospitalization for all-cause pneumonia in 5 cities	3 cities with high PCV coverage (>95%) had significant decline in hospitalizations, between 23% and 29%. Two cities with lower vaccine coverage (about 80% to 85%) did not	(261)

				have significant decline.	
France	PCV13	<15 years, <1 year	Emergency room cases of community-acquired pneumonia (CAP)	<15 years: CAP 16%, pneumococcal CAP 63% <1 year: CAP 32%	(262)
Israel (Southern)	PCV7 and PCV13	<5 years	Annual incidence of radiologically-confirmed pneumonia	13% in PCV7 period (vs. pre-PCV) 47% in PCV13 period (vs. pre-PCV)	(263)
Italy (Apulia)	PCV7 and PCV13	<5 years	Hospitalization for pneumococcal pneumonia	57% (95% CI 10%, 79%)	(198)
Nicaragua	PCV13	<1 year, 12-23 months	Hospitalization for all-cause pneumonia	<1 year: 33% (95% CI 25%, 41%), 12-23 months: 26% (95% CI 19%, 33%)	(264)
Poland (Kielce)	PCV7 and PCV13	Indirect effects in adults 30-49 years, 50-64 years, 65+ years	Incidence of pneumonia based on ICD codes	30-49 years: 31% decline in pneumonia incidence from 2005-2012; 50-64 years: 57% decrease; 65+ years: 67% decrease	(265)
South Africa	PCV7 and PCV13	≥8 weeks, 16-103 weeks	Hospitalization for presumed bacterial pneumonia in HIV-uninfected children	≥8 weeks: 20% (95% CI -9%, 42%), 16-103 weeks: 39% (95% CI 8%, 60%)	(266, 267)
Sweden (Stockholm County)	PCV7 and PCV13	0-<2 years, 2-<5 years	Hospitalizations for pneumonia, 4 years before and after PCV	19% in 0-<2 years (p<.001) 15% in 2-<5years (p=.002)	(268)
UK (England)	PCV7 and PCV13	<16 years, <2 years	Hospitalizations for all-cause pneumonia, hospitalization for empyema	No added benefit of PCV13 over PCV7 for all-cause pneumonia in <16 years; Empyema <2 years: PCV13 period RR 0.58 (95% CI: 0.34, 0.99) vs. PCV7 period	(269)
US	PCV13	<2 years, 2-4 years	Hospitalization for all-cause pneumonia, 2 years post-PCV13	<2 years: 21% (95% CI 14%, 28%), 2-4 years: 17% (95% CI 7%, 27%)	(270)

US	PCV13	Adults >18 years	Respiratory infections (mostly sputum samples), 2009-2012	PCV13 serotypes identified in 28.2% of samples from 2012 vs. 33.7% to 35.5% of samples in 2009-2011; Proportion due to 19A remained stable; NVT increased, especially 35B	(271)
US (Tennessee)	PCV7 and PCV13	<2 years	All-cause pneumonia hospitalizations, hospital discharge data	27% additional reduction relative to PCV7 period, 72% reduction since pre-PCV7	(272)
Uruguay	PCV7 and PCV13	0-14 years	Annual hospitalization rates for CAP and bacterial-confirmed CAP	CAP hospitalization rate decreased 78% Pneumococcal CAP rate decreased 92%	(273)
Uruguay	PCV7 and PCV13	12-23 months	Hospitalization for consolidated pneumonia	45%	(274)

Vaccine Impact on Nasopharyngeal Colonization

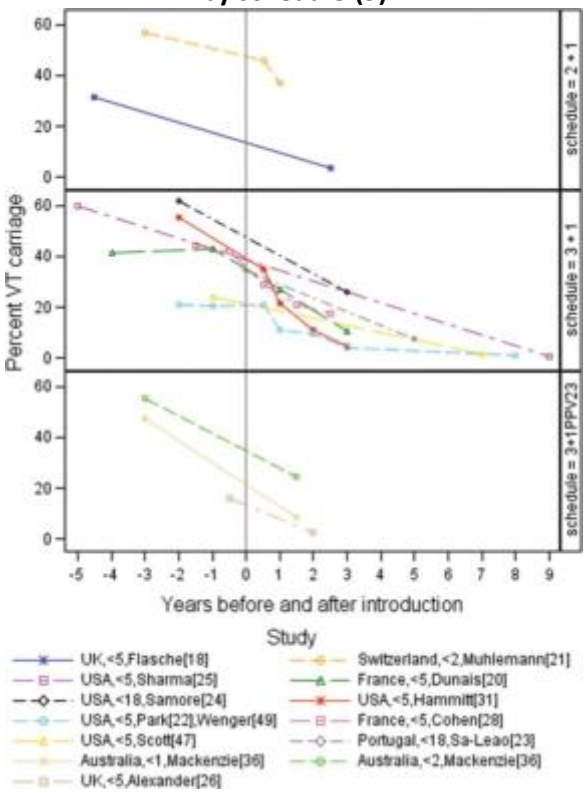
Preventing NP acquisition of vaccine serotypes, PCV implementation results in a rapid, significant decrease in VT NP carriage prevalence in children. There is replacement carriage with non-vaccine serotypes, often resulting in no net overall change in all-serotype pneumococcal colonization. However, the replacing non-vaccine serotypes are, in many cases, not as invasive and thus less likely to cause disease. Therefore reductions in all-serotype pneumococcal disease are sustained even in the face of increases in NVT colonization.

Children are the main reservoirs of pneumococci in the community, and lower VT NP carriage prevalence in this group disrupts community circulation (transmission) of vaccine serotypes. This leads to a decrease in VT NP colonization in unvaccinated groups after PCV introduction.

Data on the direct and indirect effect of PCV use on VT NP carriage is available from LMICs and from higher valency PCV formulations in different schedules.

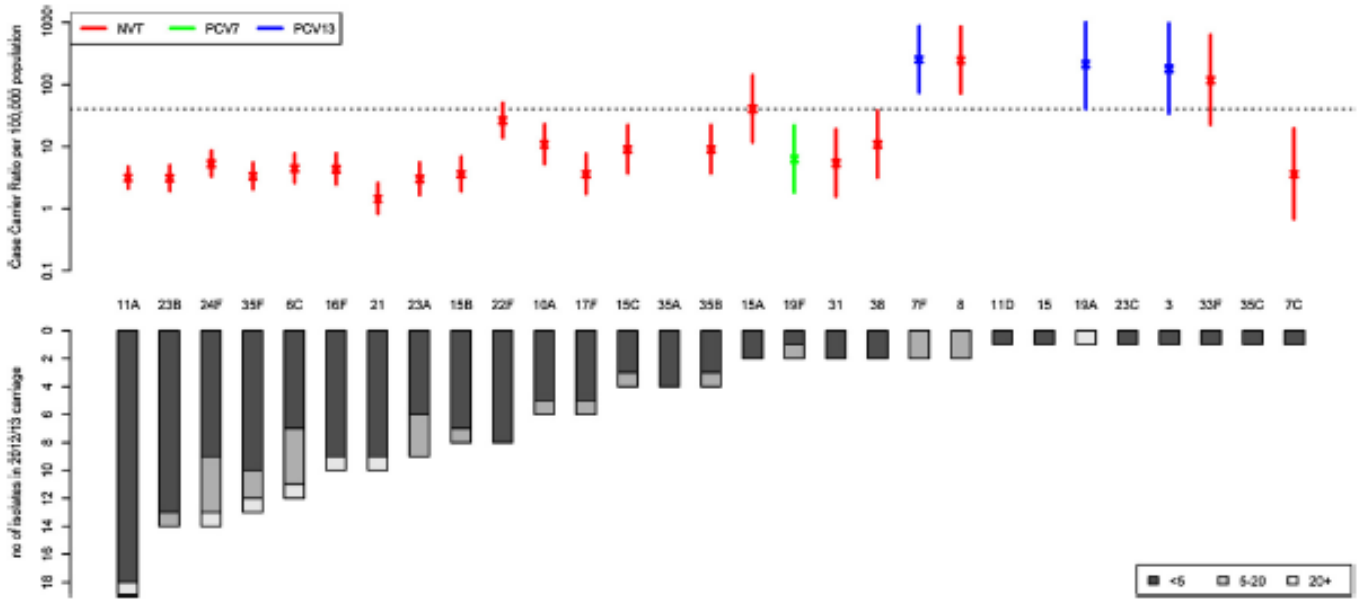
NP colonization is a necessary but not sufficient precursor to pneumococcal disease as most carriage episodes do not result in clinical disease. Pneumococcal serotypes differ in their propensity to be colonizers of the nasopharynx and in their invasive potential. More studies are revealing the complex, interplay of factors and organisms (including the microbiome) that contribute to colonization of the human nasopharynx. Introduction of PCV results in a decrease in NP colonization by VT pneumococci in vaccinated children by preventing acquisition of vaccine serotypes not by reducing the duration of carriage of serotypes already established in the nasopharynx. In one review, the range of reduction in VT colonization was 48%-92%, based on four studies from high-income countries and following PCV7 introduction.(165) Similarly, UK studies have found a 69%-94% decrease in VT colonization in children two to three years following PCV7 introduction.(72, 275) The decrease in NP colonization due to vaccine serotypes is seen with all commonly used PCV dosing schedules: 2p+1, 3p+0 and 3p+1.(Figure 39)(9)

Figure 39: Percent VT carriage in children from observational studies pre- and post-PCV7 introduction, by schedule.(9)



Most PCV studies show that the overall proportion of children colonized with pneumococcus (all-serotype) does not change significantly after vaccine introduction. With the decrease in VT colonization, there is, in most settings, an increase in NVT colonization resulting in almost complete replacement in carriage.(9, 72, 173, 275, 276) The relation between pneumococcal colonization and disease is described by the case:carrier ratio, the ratio between the number of cases of disease due to a specific serotype and the number of carriers of that specific serotype. Conceptually this case:carrier ratio expresses the number of cases of a serotype that occur for each colonization event. For most NVT pneumococci, the case: carrier ratio is lower than for VT strains, meaning the non-vaccine serotypes are less virulent than the vaccine serotypes they are replacing.(Figure 40)(72, 173, 277) The invasive potential of a pneumococcal serotype—which is in largely due to the characteristics of its polysaccharide capsule--does not appear to change over time, geography or following vaccine introduction.(9, 72, 173, 278, 279)

Figure 40: Case:carrier ratios of pneumococcal serotypes, estimated from UK carriage and IPD data two years after PCV13 implementation, 2012-2013(280)



Top figure—serotype-specific case:carrier ratio per 100,000 population (95% CI).
Lower figure—number of samples of each particular serotype in persons under 60 years of age.

Data is emerging on the significant direct and indirect effect of PCV on NP carriage in LMIC settings. PCV7 impact on NP colonization has been demonstrated in South Africa just two years following vaccine introduction in a 2p+1 schedule without a catch up campaign. Based on two cross-sectional surveys in a rural South African community with high HIV prevalence, there was a 50% reduction in VT colonization seen in children <2 years of age and a 64% reduction in adults. The prevalence of NVT colonization increased 35% among children <2 years but did not increase among adolescents and adults.(281) Replacing serotypes were predominately serogroup 15 and serotypes 16F and 11A in children. The authors from this study conclude: "despite a high prevalence of vaccine serotype colonization among older children in resource poor, rural settings, children <2 years of age are likely the primary source of transmission of vaccine serotypes in the community and . . . an indirect effect of PCV immunization can be realized within 2 years of initiating the PCV immunization program, even without a catch-up campaign of older children and with a fairly modest level of vaccine coverage of the target population (about 50%)."(281)

Results from the first Gavi-eligible country to report on vaccine effectiveness against NP colonization come from Kenya, where PCV10 was introduced in 2011 resulting in a substantial direct and indirect effect of vaccine. PCV10 was implemented using a 3p+0 schedule, and in Kilifi—unlike the rest of Kenya--there was catch up vaccination for children U5 years. Catch up campaigns increase the pace of herd protection by more quickly increasing coverage in young children, who are the main reservoirs of pneumococci in the community and drive transmission. From annual cross-sectional community surveys covering two years pre- and two years post-PCV10 introduction, there has been a 64% reduction in VT colonization in children U5 years and a 66% reduction in persons over 5 years.(282) There was a concomitant increase in the prevalence of NVT colonization that was significant in children U5 years, but not significant for those over 5 years.(282) In Nairobi, Kenya, the impact of PCV10 use on VT NP

colonization was measurable one year after implementation even in the absence of a catch up campaign: PCV10 VT carriage decreased by 57% in infants <12 months and by 59% in children 1-4 years old, including unvaccinated children 1-4 years old in whom PCV10 reduction was 61%.(283)

A study from The Gambia done one year after the transition from PCV7 to PCV13 reveals significant decrease in NP carriage of the six additional serotypes in PCV13 in infants fully immunized with PCV13.(284) While overall pneumococcal carriage did not change significantly among infants 6-11 months fully immunized with three doses of PCV13 compared to an earlier survey of infants fully immunized with PCV7, VT NP carriage was significantly reduced for PCV7, PCV13 and PCV13-nonPCV7 serotypes in the PCV13 group. Mothers of the infants enrolled were also assessed. There was no significant change in mothers' overall carriage of pneumococcus or VT carriage.(284)

As found in South Africa and Kenya, there is a significant indirect effect of PCV use on VT NP colonization among older children and adults reported in other studies. In the four populations where VT colonization and IPD have been studied together, there has been a contemporaneous decrease in both carriage and IPD rates due to VT pneumococcus.(164) After a decade of PCV7 use in Native American communities, there was virtual elimination of VT NP carriage among adults (0.1% prevalence) and only a modest increase in NVT NP carriage.(279) Other studies from the US, Australia and Portugal provide an estimate of the percent decrease in VT carriage among older children and adults ranging between 45% and 87%.(285-288)

Data from recently published or presented studies is adding to the evidence base for the NP colonization effect of PCV10 and PCV13.(Table I) The data indicate that PCV10 and PCV13 have a significant direct and indirect effect reducing VT NP colonization. As of 2016, there are 13 countries that have studied or are continuing to monitor serotype-specific IPD and carriage, so more data on the correlation between NP carriage and IPD changes will likely be forthcoming.

Table I: Data on PCV10 and PCV13 impact on pneumococcal NP colonization, updated as of January 16, 2016

Country	PCV product	Findings	Ref
Brazil (Goiania)	PCV10	Cross-sectional household survey of NPC in children aged 7-11 and 15-18 months was done in the year of PCV10 introduction. Children who had received 2 or 3 primary doses of PCV10 had a significant reduction in VT NPC, with PCV10 effectiveness estimated to be 36% and 44%, respectively. For children who had received one catch-up dose, no significant effectiveness was detected. ST6A and 19A were found in slightly higher proportions.	(289)
Canada (Calgary)	PCV13	Study presents results of annual cross-sectional surveys of Spn NPC in healthy children 12 and 18 months and 4.5 yrs old. In the first two years after PCV13 introduction, the proportion of children colonized with Spn decreased to 13% from the PCV7 period (20%). Vaccination with two or more doses of PCV7 or PCV13, older age and recent antibiotic use reduced the odds of Spn NPC. Two years after PCV13 introduction, 94% of all isolates were NVT.	(290)
France	PCV7 and PCV13	Children with AOM who had received at least 1 dose of PCV13 had lower prevalence of overall pneumococcal carriage and carriage of the PCV13-nonPCV7 serotypes compared to children who only received PCV7, including reduced carriage of serotype 19A.	(291)
France	PCV7 and PCV13	NPC was assessed in children 6-24 months presenting to clinics and diagnosed with AOM. Overall pneumococcal carriage decreased from 71% to 56% between 2001 and 2014. The carriage of the 6 additional PCV13-non PCV7 serotypes increased after PCV7 introduction but decreased after the switch to PCV13. The proportion of ST19A carriage increased from 8.6% to 15.8% from 2001-2010 then decreased to 1.2% in 2014. After PCV13 introduction, the most frequently carried NVTs were 15B/C, 11A, 15A and 35B. Penicillin nonsusceptible strains decreased over this time period.	(292)
The Gambia	PCV7 and PCV13	Replacing PCV7 by PCV13 resulted in decreased prevalence of VT NP carriage in Gambian infants one year after the transition to PCV13 but not in their mothers. While the overall carriage of pneumococcus was similar in the PCV7 and PCV13 groups (infants 6-11 months fully immunized with 3	(284, 293)

		doses of PCV), the latter infant group had lower prevalence of PCV7 and PCV13 VT carriage. There was a decrease in carriage of the 6 additional serotypes in PCV13, namely a reduction in 6A and 19F carriage in infants.	
Israel	PCV7 and PCV13	NPC in children U5 was assessed by prospective, population-based, active surveillance from 2009 to 2014. In this time period, overall pneumococcal carriage rates decreased significantly by 10%. PCV7 serotype, 6A and additional PCV13 serotype carriage rates decreased by 76%, 90% and 66%, respectively. Non-PCV13 serotypes increased in carriage prevalence by 71%.	(294)
Kenya	PCV10	From annual cross-sectional community surveys covering two years pre- and two years post-PCV10 introduction, there has been a 64% reduction in VT colonization in children U5 years and a 66% reduction in persons over 5 years. There was no effect on the vaccine related serotypes 6A or 19A. There was a concomitant increase in the prevalence of NVT colonization that was significant in children U5 years, but not significant for those over 5 years.	(282)
Kenya	PCV10	NP carriage was studied in children less than 5 years old in a Nairobi slum. Overall pneumococcal carriage prevalence was similar pre- and post-PCV10 (90% and 92%, respectively). PCV10 VT was present in 38% and 17% of children pre- and post-PCV10 use. PCV10 VT carriage decreased by 57% in infants under 12 months and by 59% in children 1-4 years, including unvaccinated children 1-4 years old in whom PCV10 reduction was 61%.	(283)
The Netherlands	PCV7 and PCV10	Carriage was studied in PCV10-vaccinated 11-mo old infants and 24-mo old PCV7-vaccinated toddlers and compared to previous cross-sectional NP studies conducted in the pre-PCV, and post-PCV7 periods. VT carriage has almost completely disappeared <2% since PCV7 introduction. Carriage of the additional 3 serotypes in PCV10 was also very low (<2%) since PCV7 introduction. NVT carriage has almost doubled since PCV7 introduction. ST19A is still the most frequently carried serotype: its prevalence has declined significantly in PCV7-vaccinated 24-month-olds (from 14% to 8%) but less in PCV10-vaccinated 11-month-olds (12% to 9%).	(295)
South Africa (Soweto)	PCV7 and PCV13	This study assessed NPC in HIV-infected and HIV-uninfected mother-child pairs in 2010-2011 (PCV7 period) and 2012-2013 (PCV13 period). In children <12 years, PCV13 NPC decreased in HIV-uninfected (adjusted OR	(296)

		0.32, 95% CI: 0.25, 0.40) and HIV-infected (adjusted OR 0.37, 95% CI: 0.28, 0.49) children. There was an increase in NVT NPC. Decreases in PCV13 VT carriage was also observed in HIV-uninfected women, with a similar trend in HIV-infected women, who nonetheless had a higher prevalence of overall NPC and VT NPC over the time period.	
UK	PCV13	Carriage of PCV7 serotypes has continued to decline and PCV13-nonPCV7 serotypes have rapidly reduced since the introduction of PCV13. Case:carrier ratios are stable for all serotypes.	(297)
US	PCV13	Two years post-PCV13, there was evidence of direct and indirect effect with reduction in NP carriage for the 6 additional serotypes in PCV13 in children under 5 years and adults at least 18 years old. Overall pneumococcal NP colonization prevalence was stable.	(298)
US	PCV13	VT colonization prevalence in vaccinated children decreased from 12% to 4% with PCV13 introduction. VT NP carriage was not significantly different in persons over 5 years.	(299)
US (Alaska)	PCV13	Overall Spn NP colonization prevalence remained stable in rural (66%) and urban (35%) children <5 yrs and adults >=18 yrs (14%) from 2008-2012 (2 yrs pre and post PCV13 intro). Colonization by PCV6+ STs declined significantly in children <5yrs (rural 25% to 5%, urban 22% to 9%) and adults (22% to 6%).	(300)
US (Navajo and White Mountain Apache)	PCV13	A decline in PCV13 serotypes (1 ,3, 5,6A,19A) and related ST6C carriage among children aged <5 years was observed 9 and 15 months after PCV13 introduction, respectively. Among underimmunized children, a decline in PCV13-specific carriage was observed 11 months after PCV13 introduction, when coverage in the community reached 58%. In Year 2 of PCV13 use, PCV13-specific and 6C carriage were reduced by 60% and 70%, respectively, among children U5. The reduction in PCV13-specific carriage among those aged 5-<8 years and 18+ years in Year 2 of PCV13 use was not statistically significant.	(301)
US (Massachusetts)	PCV13	In the first two years of PCV13 introduction, there was a 74% reduction in PCV13 NPC in immune children compared to nonimmune children. There was a 50% or more decline in PCV13 carriage in nonimmune children as well, so that over the study period, the difference in PCV13 NPC prevalence between nonimmune and immune children disappeared.	(302)

US (Atlanta, Georgia)	PCV13	NPC was evaluated in an ER setting from 2010-2013. 32% of subjects had pneumococcal carriage. The proportion with overall pneumococcal carriage remained stable, but PCV13 serotype carriage decreased significantly from 29% to 3%, predominantly due to a decline in ST19A from 26% to 3%. NVT carriage (excluding 6C) increased from 68% to 97%. ST35B increased significantly from 9% to 25%. Ceftriaxone and penicillin nonsusceptibility declined.	(303)

There is conflicting evidence on the effect of PCV use on the prevalence of other bacterial species, particularly *Staphylococcus aureus*, in the nasopharynx. *S. aureus* has been of interest because it too is a cause of invasive disease in children. Some reports have suggested an inverse relationship between carriage of pneumococcus and *S. aureus*, with *S. aureus* increasing in prevalence following PCV administration.(276, 304-306) However, this finding has not been demonstrated in other studies.(282, 307-309)

The co-colonization between *S. pneumoniae, H. influenzae* and *M. cattarhalis* has been described, though the reasons for this positive association are not well understood.(310) Mixed species biofilm may facilitate colonization by some bacteria, but it is hard to tease out all the potential factors (bacterial and host-specific) involved. There is some evidence that the nature of the associations may vary in health and in the presence of symptomatic upper respiratory tract infection.(310) There may also be differences in the nature of these commensal interactions based on pneumococcal serotype.(311) PCV introduction has had mixed results on *H. influenzae* colonization as reported in different study settings, including the Netherlands and Kenya.(276, 282, 295, 312) Because carriage is expected to be in flux for a few years after PCV introduction, long-term surveillance of NP carriage will be essential to understand the trends in carriage of NVT pneumococci and other nasopharyngeal bacteria and the implications for disease.(282)

Vaccine Impact on Mortality and Case Fatality Rates

As summarized in Chapter 3 in the section "Vaccine Efficacy for Under 5 Mortality", there is some data from clinical trials that suggested PCV's effect on reducing U5 mortality. The main study that indicated this effect was the PCV9 trial in The Gambia which found a statistically significant reduction in all-cause mortality of 16% (95% CI 2%, 38%) over a two-year follow up period in vaccinated subjects compared to controls.(124) Four other RCTs provided data on PCV's effect on all-cause U5 mortality, however the RCTs were not powered to investigate this outcome, and so in the Cochrane review, the pooled analysis did not reach statistical significance for children under 2 years. In a sub-group analysis including all HIV-1 negative children under 29 months of age, the vaccine efficacy for all-cause mortality was significant at 13% (95% CI 2%, 23%).(Table Ja)(4) Please see chapter 3, Figures 25 and 26 for more details.

There is limited information on the impact of PCV on child mortality following vaccine introduction. Few studies have been published and they vary in the age group(s) and outcome reported. The mortality rate (for which the denominator is the total population of persons of a defined age group) has been reported for all causes of death, IPD, and pneumonia. Two studies from middle income settings suggest a direct effect of PCV use on mortality rates in young children. A study from Nicaragua found a 33% reduction (95% CI 20%, 43%) in the adjusted incidence rate ratio for infant mortality in the early post-PCV13 period compared to the pre-vaccine period.(264) The infant mortality rate was 138 deaths per 10,000 infant-years (95% CI 133,144) in the pre-vaccine period compared to 93 deaths (95% CI 79, 109) in the PCV13 period.(264) In Brazil, there has been a 16% (95% CI -38%, 7%) reduction in pneumonia mortality rate among children 2-23 months old three years post-PCV10. Mortality rates due to other respiratory causes increased slightly in this same time period. No significant decrease in pneumonia mortality was observed in other age groups.(313) In such studies, there may be confounding as changes in mortality rates may also be due to changes in antibiotic use or case management, not only due to vaccine introduction.

Data from high income countries show a reduction in IPD mortality rates for the general population, mainly as a result of declining VT IPD incidence rates. In a study from Denmark, the IPD-related mortality rate in the general population decreased after the introduction of PCV7 and PCV13, mainly driven by incidence and mortality rate reductions in the unvaccinated adult population. The 30-day IPD-related mortality decreased by 28% in the PCV13 period compared to the pre-PCV period, from 3.4 deaths (95% CI 3.2, 3.6) per 100,000 population to 2.4 deaths (95% CI 2.2, 2.7).(77) Though there was a trend towards lower IPD-related mortality in children <2 years, because of the low number of deaths, this finding did not reach statistical significance.(77, 314) The 30-day case fatality ratios for IPD did not change significantly over the study period, and ranged between 15% and 17% for the general population.(77) Similarly, in the Netherlands, the IPD mortality rate for the general population decreased from 2.4 deaths per 100,000 persons to 1.6 deaths following PCV7 introduction, mainly due to a decrease in the incidence rate of VT IPD.(315) In the US, one study reported a significant association between the increase in PCV7 coverage and reduction in hospital mortality for IPD, pneumococcal pneumonia and all-cause pneumonia cases. The estimated number of deaths prevented was greatest for the group aged 65 years and older, based on modeled data.(241) Another US study, however, did not find an association between PCV7 vaccination and pneumococcal mortality among those over 65 years beyond what was expected based on the historical pace of decline.(316)

Table Jb summarizes the findings with respect to PCV impact on mortality rates. More studies will be needed to clarify the association between PCV use and the outcome-specific mortality rates in young children and the general population.

Table Ja: Data on PCV efficacy on all-cause mortality in children <29 months from RCTs, intention to treat analysis, adapted from a Cochrane review (4)

Country	PCV Product	Findings (Risk Ratio)	Ref
Finland	PCV7	1.49 (95%CI: 0.06, 36,61)	(129)
Finland	PCV7	1.50 (95% CI: 0.06, 36.79)	(128)
The Gambia	PCV9	0.86 (95% CI: 0.76, 0.98)	(124)
The Philippines	PCV11	0.88 (95% CI: 0.54, 1.44)	(127)
South Africa	PCV9	1.00 (95% CI: 0.63, 1.59)	(118)
Pooled analysis (random effects model)		**0.87 (95% CI: 0.77, 0.98)**	**(4)**

Table Jb: Data on PCV impact on mortality, updated as of January 16, 2016

Country	PCV product	Findings	Ref
Brazil	PCV10	There has been a 16% (95% CI -38%, 7%) reduction in pneumonia mortality rates among children 2-23 months old three years post-PCV10. Mortality rates due to other respiratory causes increased slightly in this same time period. No significant decrease in pneumonia mortality was observed in other age groups.	(313)
Denmark	PCV7 and PCV13	The 30-day IPD-related mortality decreased by 28% in the PCV13 period compared to the pre-PCV period, from 3.4 deaths (95% CI 3.2, 3.6) per 100,000 population to 2.4 deaths (95% CI 2.2, 2.7). This decrease was mainly driven by incidence and mortality rate reductions in the	(314)

		unvaccinated adult population.	
Netherlands	PCV7	The IPD (all serotypes) mortality rate for the general population decreased from 2.4 deaths per 100,000 to 1.6 deaths following PCV7 introduction, mainly due to a decrease in the incidence of VT IPD. The mortality rate of VT IPD decreased from 1.1 deaths per 100,000 to 0.5 deaths over the study period. There was also a slight decrease in the case fatality ratio of NVT IPD.	(315)
Nicaragua	PCV13	There was a 33% reduction in the adjusted incidence rate ratio for infant mortality in the early post-PCV13 period compared to the pre-vaccine period. The infant mortality rate was 138 deaths per 10,000 infant-years (95% CI: 133,144) in the pre-vaccine period compared to 93 deaths (95% CI: 79, 109) in the PCV13 period.	(264)
US	PCV7	The study reports a significant association between the increase in PCV7 coverage and reduction in hospital mortality for IPD, pneumococcal pneumonia and all-cause pneumonia cases. The absolute number of US deaths prevented was greatest for the group aged 65 years and older based on modeled data.	(241)
US	PCV7	This study did not find an association between PCV7 vaccination and pneumococcal mortality among those over 65 years beyond what was expected based on the historical pace of decline.	(316)

Chapter 5: Economic Evaluation of PCV

Chapter 5 Overview

Economic evaluation is the process by which the costs and benefits associated with health interventions are identified, measured or modeled, and valuated in order to compare their net impact and determine whether or not the benefits of a given intervention are worth the cost. Economic evaluations provide important information for policy makers assessing the value of vaccines in the setting of finite resources that need to be allocated for maximum health impact in a target population.

Increased coverage of new and underused vaccines in Gavi-eligible countries could have significant health and economic benefits. The return on investment of meeting vaccine coverage targets in 94 LMICs in the Decade of Vaccines 2011-2020 would result in 16 times greater net cost savings than costs incurred, compared to no vaccination, for ten diseases. The return on investment for pneumococcal disease and PCV use alone is estimated as 3.13: over three times greater net cost savings than costs incurred in 94 LMICs compared to no use of PCV. Universal and high coverage (90%) with PCV in Gavi-eligible countries could avert US$24 billion in costs—mostly from productivity gains--prevent 21 million disease cases, and save 1.5 million lives between 2011-2020.

There are several types of economic evaluations. Cost-effectiveness analysis (CEA) (also called cost-utility analysis (CUA)) is the most common type of economic evaluation, where the costs are expressed in monetary units and the health effects or outcomes are measured in natural units such as life years gained (LYG), disability-adjusted life years (DALYs) which measure a health loss, or quality-adjusted life years (QALYs) which measure a health gain. According to the guidelines recommended for individual countries by the WHO Commission on Macroeconomics and Health, an intervention with an incremental cost effectiveness ratio (ICER) that is less than the per capita gross domestic product (GDP) is considered "highly cost-effective," and an intervention with an ICER that is less than three times the per capita GDP is considered "cost-effective."

Major components of the CEA of PCV include estimating the economic burden of disease—the cost of illness—vaccine introduction and program costs, and vaccine effectiveness in the target population. Economic burden of disease can include direct medical and non-medical costs as well as indirect costs such as productivity losses. Cost of illness is specific to a disease syndrome (e.g., pneumonia, meningitis, etc.), the level of care obtained by the patient, and the perspective (e.g. societal, public health system, etc.) of the study.

Another important cost input in the CEA model is the cost of the vaccine and the vaccination program costs. This includes the purchase price of the vaccine (commodity price) and programmatic costs associated with vaccine delivery. Worldwide, vaccine program costs are increasing as new and more expensive vaccines are added to EPI schedules and as coverage rates increase to include hard-to-reach populations. Currently, in Gavi-eligible countries the total routine immunization costs are on average $26.72 (2010 USD) to fully immunize a child, with regional variation from $23.72 (SEARO/WPRO) to $65.43 (EUR). After vaccine cost, service delivery costs are the main driver of vaccine program costs and become increasingly important with higher tiers of economic development. High-quality data on some of the CEA model inputs may be lacking in low-income countries, and so a well-conducted CEA should include an analysis of the variability in outcome based on different input scenarios (sensitivity analysis).

There is a growing body of literature on the CEA of PCVs in a variety of settings. Studies differ on key input variables—such as cost of vaccine, estimated vaccine effectiveness, perspective and inclusion of indirect effects—thus making direct comparisons of their results difficult. One study provides a CEA of PCV7, PCV10 and PCV13 using a 3p+0 schedule compared to no vaccine in Gavi-eligible countries and concludes that PCV10 and PCV13 would be cost effective for all 72 Gavi-eligible countries (ICER<3xGDP) and highly cost-effective for all but one country (ICER<GDP). This study accounts for indirect effects, herd immunity and serotype replacement, and takes a 10-year societal perspective. Taking into account both direct and indirect effects, the ICER was estimated as $146/DALY averted (2005 US$) for PCV7, $88/DALY averted for PCV10, and $77/DALY averted for PCV13. These ICERs vary greatly by countries' U5 mortality rate. Countries with a higher mortality rate would have a lower ICER: PCV use is more cost-effective in these settings.

A study of PCV cost-effectiveness in 77 middle-income countries found PCV7 to be cost-effective for 72 countries, and PCV10 and PCV13 to be cost-effective for all countries compared to no vaccine. PCV7 would be highly cost-effective (ICER<GDP) for 53 middle-income countries, PCV10 for 68 countries and PCV13 for 71 countries. The study modeled direct and indirect effects of PCV7, PCV10 and PCV13 used in a 3p+0 schedule with a vaccine cost of $10 for lower middle-income countries and $20 for upper middle-income countries. The overall ICER was US$ 1600/DALY averted for PCV7, $1000/DALY averted for PCV10, and $900/DALY averted for PCV13.

Limitations of the economic evaluation of PCV10 vs. PCV13 are important to consider. There have been no head-to-head clinical comparisons between PCV10 and PCV13 within a single trial, so vaccine effectiveness is often assumed based on their head-to-head comparison with PCV7 or their sequential implementation in observational studies, and sometimes adjusted for serotype distribution. The indirect effects of PCV use are an influential parameter in sensitivity analyses, but many studies do not account for herd effects or serotype replacement. In addition, most evaluations use static models, meaning they assume that the probability of disease exposure and other model parameters are constant over time. For a transmissible infectious disease this is not a realistic assumption. Finally, few health economic studies look at the potential broader value of vaccines. Failing to include all value that accrues from vaccination in estimates of cost effectiveness may result in ongoing undervaluation of vaccines' impact on economic and societal well-being and risk underinvestment on the part of countries and partners. While there is a theoretical framework linking vaccine use to broader economic and behavioral effects, empirical research is needed to test these linkages and provide quantitative field based measures of their magnitude.

Rationale of Economic Evaluation of Vaccines

Economic evaluation is the process by which the costs and benefits associated with health interventions are identified, measured or modeled, and valuated in order to compare their net impact and determine whether or not the benefits of a given intervention are worth the cost.

Economic evaluations provide important information for policy makers assessing the value of vaccines in the setting of finite resources that need to be allocated for maximum health impact in a target population.

The return on investment of meeting vaccine coverage targets in 94 LMICs in the Decade of Vaccines 2011-2020 would result in 16 times greater benefits than costs incurred, compared to no vaccination, for ten diseases.(317) The return on investment for pneumococcal disease and PCV use is 3.13.

Universal and high coverage (90%) with PCV in Gavi-eligible countries could avert US$24 billion in costs—mostly from productivity gains--prevent 21 million disease cases and save 1.5 million lives between 2011 and 2020.

Vaccination has had a major impact on children's lives and healthcare around the world. In many countries, the use of vaccination has been instrumental in bringing about major changes in healthcare delivery. In the developing world, where economic development frequently excludes the poorest and most vulnerable communities, it is difficult to sustain treatment and prevention programs against certain childhood infectious diseases. Although antibiotic therapy, nutrition, clean water, housing and indoor air quality have reduced the childhood incidence of infectious diseases in some countries, improvements are not always possible because of the slow economic progress that characterize developing countries and the lack of access to appropriate healthcare. Vaccination in this case offers the possibility of preventing childhood diseases immediately and more equitably than do some of the other interventions.

Despite their availability and demonstrated cost-effectiveness, vaccines continue to be under-used. Children still die each year from diseases for which vaccines are available at low cost. The reasons for this under-use are many and complex and are beyond the scope of this chapter. It was estimated that in 2008 1.5 million children U5 died of vaccine preventable diseases, representing 17% of total U5 deaths worldwide.(318)(Table K) There will be new estimates coming from the Maternal and Child Epidemiology Estimation (MCEE) project in 2016 and 2017 which will provide 2015 estimates and a time series back to year 2000. The December 2015 VIMS report from Johns Hopkins' IVAC states that "29% of the world's infants (39.8 million) are not likely to receive Hib vaccine this year because either their country has not yet introduced (this vaccine). . ., or they are not receiving routine immunizations (measured by DTP3 coverage)."(14) For similar reasons, 56% of the world's infants (76.3 million) are not likely to receive PCV this year, 74% of infants (99.5 million) are not likely to receive rotavirus vaccine, and 51% of infants (69.3 million) are not receiving inactivated polio vaccine.(14)

Table K: Estimates of deaths in children U5 years due to vaccine preventable diseases

Pathogen	**WHO estimates for 2008 U5 deaths(318)**
Hib	199,000
Measles	118,000
Tetanus	61,000[1]
Rotavirus	453,000
Pertussis	195,000
Pneumococcus	476,000
Total	**1,502,000**

Note:
[1]Includes neonatal and non-neonatal tetanus

Economic evaluation is the process by which the costs and benefits associated with health interventions or health care programs are identified, measured or modeled, and valuated in order to compare their net impact and determine whether or not the benefits of a given intervention or health care program justify the cost. Outputs from modeling can help policy makers understand the relative economic value of implementing different interventions to achieve a specified health outcome in a target population in order to allocate resources most efficiently. The perspectives adopted in these analyses can vary widely depending on the audience and proposed use of the economic analysis, taking a narrow agent-specific

payer perspective (concerned only with the cost/benefit implications for individual entities) to a broader societal perspective (concerned with incorporating the entirety of costs/benefits experienced by all actors in a society).

Economic evaluations provide valuable information to assess the value of vaccines, an important consideration for policy makers facing finite resources that need to be allocated for maximum health impact. Increased coverage of new and underused vaccines in Gavi-eligible countries could have significant health and economic benefits. A 2016 publication estimated the return on investment (ROI) associated with achieving projected coverage for ten vaccine preventable diseases in 94 LMICs from 2011-2010.(317) Compared to the scenario of no vaccination, the net economic benefits (based on averted treatment costs and productivity lost minus vaccine program costs) divided by vaccine program costs for ten diseases would results in an ROI of 16 (uncertainty range 10, 25). That means immunizations would return about 16 times greater cost savings than costs incurred over the decade.(317) The ROI for pneumococcal disease and PCV use alone was estimated to be just over 3: three times greater net cost savings than costs incurred in 94 LMICs compared to no use of PCV.(317)

Another study on the potential economic benefits of the "Decade of Vaccines" (2011-2020), with increases in the coverage of six vaccines to 90% in Gavi-eligible countries (including a new vaccine for malaria), estimated that 94% of the costs averted (US$145 billion) would be due to productivity gains from the prevention of premature death and long-term disability. 6% of averted costs (US$6.2 billion) would be due to reduced use of acute health care resources.(319) Increasing the coverage of three vaccines—Hib, PCV and rotavirus—to 90% in Gavi-eligible countries would potentially avert US$63 billion in costs between 2011 and 2020, according to an earlier 2011 study. (320)

Cost-effectiveness Analysis of PCV

There are several types of economic evaluations. Cost-effectiveness analysis (CEA) (also called cost-utility analysis (CUA)) is the most common type of economic evaluation, where the costs are expressed in monetary units and the health effects or outcomes are measured in natural units such as life years gained (LYG), disability-adjusted life years (DALYs) which measure a health loss, or quality-adjusted life years (QALYs) which measures a health gain. QALYs and DALYs are inverses of each other; QALYs are more commonly used in high-income countries, while DALYs are more commonly used in LMICs.

To calculate the cost-effectiveness of PCV, it is necessary to know the total cost of the vaccine and its administration, and the total health consequences and economic costs averted through vaccination.

According to the guidelines recommended for individual countries by the WHO Commission on Macroeconomics and Health, an intervention with an incremental cost effectiveness ratio (ICER) that is less than the per capita gross domestic product (GDP) is considered "highly cost-effective," and an intervention with an ICER that is less than three times the per capita GDP is considered "cost-effective."(6).

In recent years there has been a massive growth in availability of economic evaluations, particularly in high-income countries. This reflects: constrained resources, increasing demands; concern about the

escalating costs of health services; advances in the prevention, diagnosis and treatment of diseases; and development of the techniques of economic evaluation. Economic evaluation techniques are used in several decision-making contexts: the international level, where agencies or organizations make recommendations and/or funding decisions; the national level, where a single agency or organization makes decisions for the whole health care system; and the local level, where many different decisions are made by various actors within the health care system itself. In high-income countries the majority of studies consider tertiary care, while in LMICs the main focus has been on preventive programs.

There are a number of forms of economic evaluations including cost-minimization analysis (CMA), cost-effectiveness/cost-utility analysis (CEA/CUA), and cost-benefit analysis (CBA). Economic evaluations differ in their theoretical basis, methods for measuring and valuing outcomes, acceptability in health care, and implications for achieving efficiency

CMA is an economic evaluation where the health impact of two or more alternative interventions is equivalent, and the aim is to determine the least costly alternative. The aim of these analyses is to find the least costly health intervention or health care program among those shown or assumed to be of equal benefit.

CBA measures the net social benefits of a health intervention or program and weighs that against the cost of the program. The key feature of this type of evaluation is that everything (including the benefits) is measured in monetary terms. One of the disadvantages of this type of analysis is that it places too much emphasis on labor market activity and is therefore likely to underestimate the true production gain to society through effects on people who do not earn wages, but who nevertheless do a valuable job for society, for example, in looking after children.

CEA/CUA is the currently the preferred methodology for trying to move toward allocative efficiency within the health sector, where the costs are expressed in monetary units and the health effects are expressed in non-monetary units such as life years gained (LYG), disability-adjusted life years prevented (DALYs), or quality-adjusted life years gained (QALYs). In CEA/CUAs, the health consequences of alternative interventions usually differ in magnitude. Single or multiple outcome measures can be used, but these need to be common to both alternatives. The consequences are measured in natural units, which may be intermediate indicators such as number of children vaccinated, or final health outcome indicators such as LYG or DALYs averted. This type of analysis relies on estimates of the averted health care associated costs and health outcomes achieved.

The concept of CEA is based on a simple optimization problem where a decision maker faces a 'menu' of health care programs from which to choose. The decision maker's objective is to choose a combination of health care programs from the menu to maximize total benefits, or effectiveness, which is generally measured in terms of LYG, DALYs averted, or QALYs gained. Each health care program uses part of the budget and, in effect, has a cost budget. The program also contributes to total benefits and, in that sense, generates effectiveness. Any combination of health care programs on the menu is feasible, if it satisfies the budget constraint.

The outcomes commonly reported in CEA include incremental costs per: life saved, disease case averted, DALY averted or QALY gained. DALYs and QALYs combine both mortality and morbidity estimates. DALYs "quantify the number of years lost as the result of premature death and the number of years lived with disability."(321) CEAs/CUAs conducted in the developing world almost exclusively use DALYs

as a summary measure of population health. The DALY was specifically developed to measure burden of disease (represented by years of healthy life lost), whereas QALYs (or similar measures) typically look at years of healthy life gained due to an intervention. While QALYs are based on self-assessed measures of health states, which require the kind of primary data collection that is not feasible on a global scale, DALYs are estimated for specific diseases and do not incorporate self-assessment.

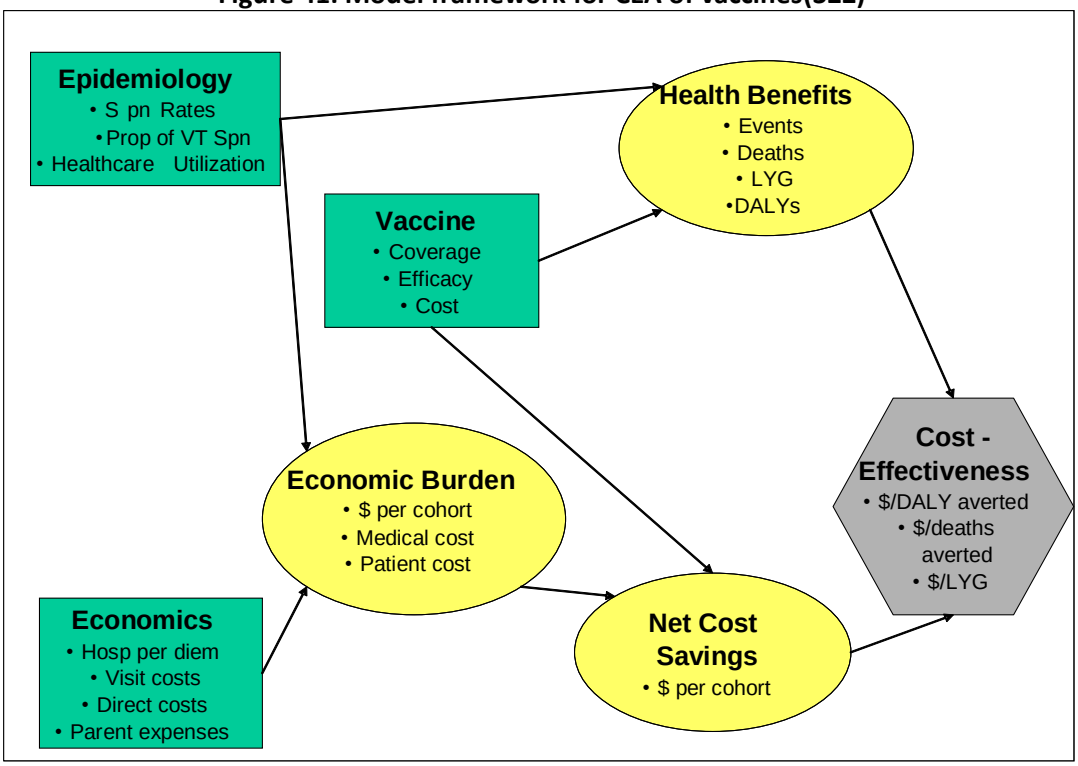
The incremental cost effectiveness ratio (ICER) is calculated as the ratio of the incremental cost to the incremental benefit of a health care program relative to the next most effective one that is also cheaper. The health care program is 'thrown out' if it is both less effective and more expensive than other health care programs. Such health care programs are 'dominated'. In this instance, the choice between strategies is straightforward. If neither of the health care programs shows dominance, which is often the case, the ICER is compared to an acceptable threshold criterion for the ICER. In calculating an ICER, the choice of comparator is crucial. The ICER of vaccination is generally defined as:

$$\text{ICER} = \frac{\text{Cost}_{vac} - \text{Cost}_{no\ vac}}{\text{Effect}_{vac} - \text{Effect}_{no\ vac}}$$

Where C_{vac} = cost of vaccine group
$C_{no\ vac}$ = cost of no vaccine group
E_{vac} = outcome of vaccine group
$E_{no\ vac}$ = outcome of no vaccine group

Figure 41 illustrates a diagram of the model framework that is generally used to estimate the economic burden and cost-effectiveness of vaccines using PCV as an example. The boxes (in green) identify the primary inputs needed for the model (epidemiological, economic and vaccine data). The (yellow) circles represent the intermediary outputs (health benefit, economic burden, net cost savings). The primary outputs of the model are displayed in (light grey) hexagons and are cost-effectiveness estimates – which in this diagram are expressed as cost per death averted, cost per DALY averted, or cost per LYG. This diagram provides only a very broad representation of the inputs and outputs of the model. The next section provides a more in-depth look at the structure of the model.

Figure 41: Model framework for CEA of vaccines(322)



Spn Prop refers to the proportion of pneumonia or meningitis attributable to *Streptococcus pneumoniae*. Adapted from Constenla D. Evaluating the cost-effectiveness of a pneumococcal conjugate vaccination programme in Latin America.

As shown in the above diagram, to calculate the cost-effectiveness of PCV, it is necessary to know the total cost of the vaccine and its administration, and the total health consequences and economic costs averted through vaccination. Calculating the total costs averted requires information on direct medical, direct non-medical and indirect costs of care. These costs depend on the proportion of children seeking each of various levels of care and the costs of each level of care. The estimate of total costs also requires knowledge of the cost and effectiveness of the vaccine and its administration. To estimate the health consequences averted requires estimates of the pneumococcal disease morbidity and mortality rate as well as the proportion of caused by the vaccine serotypes. All calculations depend on the size of the target population (those potentially affected by pneumococcal disease), which could be the birth cohort U5 years of age in a country.

Several standards can be used to determine whether an intervention is cost-effective in terms of cost per DALYs averted or cost per QALYs gained. The appropriateness of the different approaches depends on the perspective of the decision maker. According to the guidelines recommended for individual countries by the WHO Commission on Macroeconomics and Health, an intervention with an ICER that is less than the per capita gross domestic product (GDP) is considered “highly cost-effective,” and an intervention with an ICER that is less than three times the per capita GDP is considered “cost-effective.”(6).

Recent studies of actual country decision making have illustrated that just because an intervention is assessed to meet a cost-effectiveness threshold does not alone drive its implementation. Newall, et. al. report that a vaccine program being deemed highly cost-effective for a particular country “was not

sufficient to lead to funding" and that it is "likely that other factors beyond cost effectiveness, including the overall budgetary impact, are particularly important for decision making" in LMICs.(323) The authors also conclude, that for "local decision makers, the criterion for understanding cost effectiveness should have some relation to the budget available for allocation," thus thresholds need to be locally adopted based on budgetary realities. In practice, there is a distinction between "interventions that represent value for money," that is are cost-effective, "and those that are affordable in the context of the local budget and other competing healthcare priorities."(323) In summary, even if a program is assessed to be highly cost effective, if you don't have the money in the budget to pay for the program, it cannot be implemented.

Cost-Effectiveness Model Inputs

Major components of CEA of PCV include estimating the economic burden of disease—the cost of illness—vaccine introduction and program costs, and vaccine effectiveness in the target population.

As shown in Figure 41, there are numerous assumptions or decisions to make when setting up a CEA model. These decisions will affect the output of the model, so whenever possible, input decisions should be stated clearly--allowing for transparency in the evaluation process—and be based on primary, country-specific data. A discussion of various components of the CEA model follows, including some of the sources of information and approaches to gaps in available information, particularly in the context of LMICs.

Cost of Illness

Economic burden of disease can include direct medical and non-medical costs as well as indirect costs such as productivity losses.

The economic burden of disease is an important component of a CEA model and can be obtained from primary sources, such as studies that measure the "total costs attributable to a particular disease and can include both direct (medical and non-medical) and indirect costs (e.g., productivity losses.)"(324) Cost of illness is specific to a disease syndrome (e.g., pneumonia, meningitis, etc.) and the level of care obtained by the patient. For example, cost of pneumonia treatment will differ depending on whether a patient is cared for as an outpatient or inpatient, and if an inpatient, the level of hospital accessed for care. Examples of primary sources of cost of illness information can include government budgets, hospital databases, or physician or parent interviews.(324) Generally, primary sources that use "micro-costing methodology" collect patient-level data prospectively and consider the societal perspective.(324) Direct medical costs include medications, diagnostic tests, health professional fees and hospitalization or outpatient visit costs. Direct non-medical costs include costs of transportation to and from health care facilities. Indirect costs such as productivity losses can be calculated based on the lost days of paid work (i.e. days of hospitalization or half day for an outpatient visit) multiplied by a self-reported wage or country mean wage.(324)

The costs of illness will depend on the perspective of the CEA. The main perspectives used in vaccine CEA are: "(a) societal perspective, in which all medical and non-medical direct costs, as well as indirect costs incurred by health systems, patients, and their families (are) included in the analysis; (b) public health system perspective, in which only direct costs incurred by the public health system (are) included in the analysis; and (c) private health system perspective, in which only costs reimbursed by health insurance companies (usually direct medical costs) (are) included in the analysis."(324)

Table L provides some examples of cost of illness data available on pneumococcal disease syndromes by country/region and level of care based on a review of PubMed literature done in May 2014. [See Appendix B for literature search methodology.] A study by Stack, et al. reported that in Gavi-eligible countries, pneumonia treatment costs were on average US$99 (2009 US$) per case for inpatient and outpatient care. Inpatient pneumonia care averaged US$189, and inpatient meningitis care averaged US$409.(319) Corresponding costs of illness were higher in middle-income countries.(324) Another study on the costs of meningitis in 27 LMICs found wide variability in the costs of direct medical care per case from US$37 (2012 USD) in Malawi to US$25,000 in China.(325) Multiple linear regression analysis done to predict meningitis treatment costs in other LMICs included the variables: GDP per capita, population density, percentage of the population living in urban areas, the U5 mortality rate, and the health expenditure per capita. This model predicted that meningitis treatment costs range from US$42 to $9,300 per case. The median treatment costs were estimated to be $170 for low-income countries, $790 for lower-middle income countries, and $2,100 for upper-middle income countries.(325)

The WHO developed an important resource in the estimation of health care cost at the national level through their CHOICE "Choosing Interventions that are Cost Effective" project. This tool provides national decision-makers with the ability to estimate the per diem cost of public hospitals, outpatient visits, and health center visits. The WHO-CHOICE database contains unit cost estimates for service delivery in 193 countries expressed in the local currency and international dollars. Prices are given for a daily bed at primary, secondary and tertiary-level hospitals, and for an outpatient visit at a health center, primary and secondary-level hospital. WHO-CHOICE data likely underestimates the cost of illness as it only accounts for per diem rates; other direct medical costs such as drug therapy and diagnostic tests are not included in the CHOICE calculations. The WHO-CHOICE database can be accessed at: http://www.who.int/choice/country/country_specific/en/ and was last revised in July 2011. The WHO CHOICE database is being revised now. Look for an update in 2016 or 2017.

Table L: Examples of cost of illness studies by syndrome and level of care

Country/region	Syndrome	Level of care	Average cost of illness (range)	Currency	Reference
Low-income countries	Meningitis	Inpatient	$170[1]	2012 US$	(325)
Lower-middle income countries	Meningitis	Inpatient	$790[1]	2012 US$	(325)
Upper-middle income countries	Meningitis	Inpatient	$2100[1]	2012 US$	(325)
72 Gavi-eligible countries	Pneumonia	Outpatient and inpatient	$99 (31-264)	2009 US$	(319)
	Pneumonia	Inpatient	$189 (58-514)		
	Meningitis	Inpatient	$409 (126-113)		
Latin America and Caribbean	All-cause pneumonia	Outpatient	$122 (55-252)	2010 US$	(324)
	All-cause pneumonia	Inpatient	$1057 (1054-1060)		
	Pneumococcal pneumonia	Outpatient	$164 (20-669)		
	Pneumococcal pneumonia	Inpatient	$2062 (412-6899)		
	Pneumococcal meningitis	Inpatient	$4692 (889-24026)		
	Bacteremia/sepsis	Outpatient	$140 (61-259)		
	Bacteremia/sepsis	Inpatient	$3578 (332-14946)		
Latin America and Caribbean	Chest X-ray confirmed pneumonia	Outpatient	$117 (80-236)	2005 US$	(326)
	Chest X-ray confirmed pneumonia	Inpatient	$1017 (571-2174)		
	Meningitis	Inpatient	$1843 (680-2802)		
	Bacteremia/sepsis	Inpatient	$1344 (914-1543)		
Kenya	Pneumonia or	Inpatient	$75	US$	(327)

	bacteremia/sepsis		(Standard deviation (SD) 37)		
	Meningitis	Inpatient	$358 (SD 335)		
The Gambia	Pneumonia	Outpatient and inpatient	$191	2005 US$	(328)
	Meningitis	Inpatient	$229		
The Gambia	Pneumonia	Outpatient provider costs	$8	2010 US$	(329)
	Pneumonia	Outpatient total costs (provider, family out of pocket and time lost from work)	$15		
	Pneumonia	Inpatient provider costs	$64		
	Pneumonia	Inpatient total costs (provider, family out of pocket and time lost from work)	$109		
	Bacteremia/Sepsis	Inpatient provider costs	$87		
	Bacteremia/Sepsis	Inpatient total costs (provider, family out of pocket and time lost from work)	$144		
	Meningitis	Inpatient provider costs	$124		
	Meningitis	Inpatient total costs (provider, family out of pocket and time lost from work)	$170		

[1]Results based on multiple linear regression model.

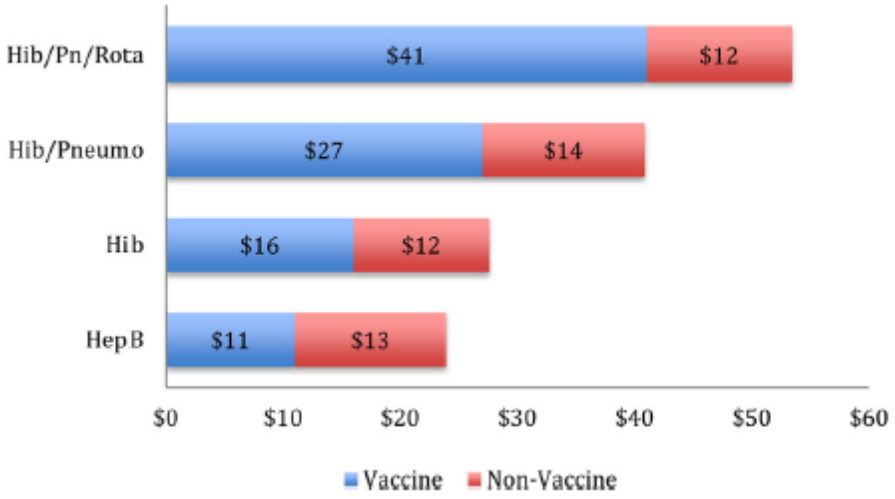
Vaccine Costs

Vaccine program costs are increasing as new and more expensive vaccines are added to EPI schedules and as coverage rates increase to include hard-to-reach populations.

Vaccine program costs are driven by vaccine price and service delivery costs, primarily labor costs.

Another important cost input into the CEA model is the cost of the vaccine and the vaccination program costs. This includes the purchase price of the vaccine (commodity price) and programmatic costs associated with vaccine delivery. Worldwide, the costs of routine immunization are on the rise as new and more expensive vaccines have been introduced into the EPI schedule and vaccine coverage increases.(330) In a report based on Gavi eligible countries' comprehensive multi-year plans, vaccines themselves are the major cost driver (51%)--and will become an increasing fraction of total costs (61%) in the next couple of years (projected up to 2016)--followed by immunization-specific personnel costs(22%).(330) Currently, in Gavi-eligible countries the total routine immunization costs are on average $26.72 (2010 USD) to fully immunize a child, with regional variation from $23.72 (SEARO/WPRO) to $65.43 (EUR). About half of this total cost is the cost of vaccines. Non-vaccine delivery costs represent 44% of total routine immunization costs, and this large proportion suggests that "health systems delivery costs are an equally important factor for understanding cost requirements for immunization programs."(330) The total routine immunization costs per fully immunized child is projected to increase to $45.16 by 2016.(330) As newer vaccines are added, increase in routine immunization costs are primarily due to the increase in vaccine costs, and the "share of delivery costs to total unit costs steadily declines with each new vaccine in the schedule from 54% (HepB alone) to 22% (Hib, PCV and rotavirus)."(330) (Figure 42) This reduction in the fraction of total costs that are attributable to delivery is intuitive when most new vaccines are added to the existing schedule and do not require a new visit. Nevertheless, added cold chain space, more time for administration and other added delivery costs are inherent with each new vaccine introduction.

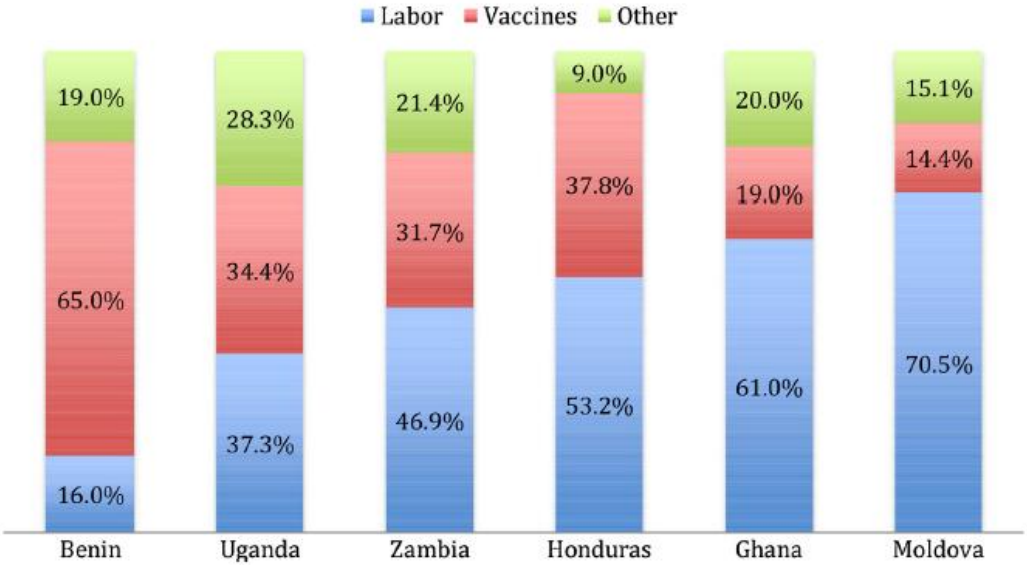
Figure 42: Effect of new vaccine introductions on cost per infant in Gavi-eligible countries (330)



Data from the EPI Costing and Financing (EPIC) studies reviewed the financing of routine and new vaccines from the government perspective in six countries (Benin, Ghana, Honduras, Moldova, Uganda

and Zambia.) Based on a sample of 319 primary health care facilities, the EPIC studies found wide variation in total and unit costs of vaccine within each country (60- to 200-fold) as well as between countries.(331) The proportion of labor costs increased with the level of economic development.(331)(Figure 43) The cost per fully immunized child ranged from $25 to $332 in the six countries studied.(331)

Figure 43: Cost drivers at facility level for the EPIC studies (331)



A costing analysis of 94 LMICs included in the GVAP also found that service delivery and vaccine price are the main drivers of cost.(332) The full vaccination program costs in the 94 countries are projected to be US$61.9 billion (95% CI $42.7 to 87.4 billion) for the Decade of Vaccines (2011-2020).(332) More than half (55%) of these projected costs are for service delivery, including costs for "program management, training, social mobilization, and surveillance." Thirty-eight percent of costs are due to vaccine and injection supplies, and 7% represent supply chain costs.(332)

In a detailed study of the cost of delivery of PCV in The Gambia, the authors looked at the following programmatic costs of PCV delivery: cold storage, vaccine monitoring, waste management, transport, staff training, social mobilization, personnel time, and stationery (e.g., printing of immunization cards).(333) In The Gambia, the purchase price of US$7 per PCV dose accounted for 91% of the total incremental cost of PCV introduction. The incremental transport cost of PCV was US$0.07 per dose. The total incremental cost of vaccinating a child with three doses of PCV was US$25. Changing the purchase price of PCV to US$3.50 per dose decreased the incremental cost to US$13 per fully immunized child.(333) In a study on PCV introduction in Latin America and the Caribbean, vaccine program costs derived from countries' financial sustainability plans ranged between US$0.27-0.97 per dose.(334) These costs included capital, transport, personnel, injection supplies, training and other expenses for vaccine delivery.

It is important to note that a relevant comparator is key for framing the costs in an economic evaluation. For some countries that have not yet introduced PCV, the comparison to no PCV use is a fair scenario. But for countries that have already introduced PCV7, the most relevant comparison to make for PCV is the incremental CEA of using PCV7 vs. PCV10 vs. PCV13. "Limiting the analysis to one PCV candidate, or using 'no vaccination' as a comparator, when the current situation or the next best alternative is different" can be fundamentally misleading for decision makers.(335)

Other CEA Inputs

The other main inputs to a CEA model are estimates of the burden of disease, vaccine effectiveness against disease, and indirect effects. Burden of disease and PCV effectiveness against different clinical syndromes have been discussed previously in Chapters 1 and 3, respectively. Another key variable in CEA is the inclusion or exclusion of the vaccine's estimated indirect effects (ie. herd effects against the strains protected by the vaccine) and serotype replacement. Costs associated with the reduction in vaccine preventable disease burden due to herd immunity or the increase in NVT disease as a result of serotype replacement are an important component that will affect the outcome of a cost-effectiveness model.

Dealing with Uncertainty in CEA Models

Since CEA is a modeling tool, it is only as good as the quality of data going into the model.

High-quality data on some of the model inputs may be lacking in low-income countries, and so a well-conducted CEA should include an analysis of the variability in outcome based on different input scenarios (sensitivity analysis).

Findings from CEAs/CUAs of PCV are highly dependent on the parameters of vaccine price, vaccine efficacy, disease incidence, and indirect effects used in the model.

There are gaps in knowledge with respect to the components that go into a CEA, and hence it is necessary to evaluate the extent to which these uncertainties affect the output of the model. Particularly for low-income countries, there may not be primary data on costs of illness and disease burden. So cost-effectiveness modeling may need to be done using clearly stated assumptions or secondary data from other countries and adapting the data, as best as possible, to the low-income setting. As stated by Tasslimi et al.: "there remains a paucity of country-specific data for several model inputs. In particular, information is lacking for pneumococcal disease burden in older children and adults, serotype coverage, PCV's potential indirect effects in Gavi-eligible settings, and family out-of-pocket costs."(336)

Sensitivity analyses are a way of quantifying the variation in outcome based on a range of values for any given input variable in the CEA model. Sensitivity analyses are an integral part of a well-conducted CEA. The CEA model should define a base case scenario, with defined values for the input variables. Then one

at a time or simultaneously, the input variables may be changed over a range of plausible values, and the corresponding range in outcomes given. A ranking of those variables found to be most influential through one-way sensitivity analyses is often provided in CEAs in the form of a tornado diagram. Sensitivity analyses in CEA studies have shown PCV's cost-effectiveness estimates to be highly dependent on a number of input variables depending on the particular model used: vaccine price per dose(327, 334, 335, 337), vaccine efficacy(334, 335), vaccine serotype coverage(337), pneumococcal disease incidence(335, 337), access to care(327), and the inclusion of indirect effects(327, 335).

Cost-Effectiveness of PCV—Findings from Selected Studies

PCV10 and PCV13 are expected to be cost effective in all 73Gavi eligible countries (based on ICER<3xGDP) and highly cost effective in all but one country (ICER<GDP). The lowest incremental costs are in Gavi-eligible countries with the highest burden of U5 deaths.(336)

A study of PCV cost-effectiveness in 77 middle-income countries found PCV10 and PCV13 to be cost-effective for all countries compared to no vaccine (ICER<3xGDP). In this study, PCV10 would be highly cost-effective for 68 middle-income countries and PCV13 for 71 countries (ICER<GDP).(337)

While PCV13 may prevent more cases of IPD—depending on local serotype prevalence--PCV10 may prevent more cases of AOM as it has the potential benefit of reducing AOM due to non-typeable *Haemophilus influenzae (*NTHi).(335)

There is a growing body of literature on the economic evaluation of PCV in a variety of settings. Studies differ on key input variables—such as cost of vaccine, estimated vaccine effectiveness, perspective and inclusion of indirect effects—thus making direct comparisons of their results difficult. Findings from selected CEAs in LMICs are presented here and summarized in Table M.

A recent review by Wu, et al. reviewed economic evaluations of PCV7, PCV10 and PCV13 published between 2006 and 2014.(335) Twenty-eight studies were included in the review based on their inclusion of PCV10 or PCV13 as one of the vaccines evaluated. The studies varied widely in vaccine cost per dose, and most studies did not perform sensitivity analyses on vaccine cost, which can be highly influential. Of the 28 studies, 17 studies were funded by industry: all the Pfizer-funded studies found PCV13 to be positive, and all the GSK-funded studies preferred PCV10. This difference mainly lies in the assumptions made in the models: GSK studies assumed PCV10 to confer cross-protection against 19A, an assumption for which data is still accruing, and to provide considerable additional effectiveness against AOM caused by non-typeable *Haemophilus influenzae* (NTHi). Of the 11 "independent" studies, four had no dominant message of preferentially choosing one PCV product but "show the impact of pivotal assumptions on the results."(335) The authors conclude that "both PCV13 and PCV10 were likely to be judged preferable to the current situation (i.e. often PCV7). Which of these two formulations to choose is less clear, due to fundamental uncertainties on serotype replacement and herd effects, serotype cross-protection, and NTHi AOM protection. Essentially it depends on the price difference between both vaccines, and the weight policy makers wish to attach to potentially preventing extra IPD cases through PCV13 use versus extra AOM cases through PCV10 use."(335)

Limitations of the economic evaluation of PCV10 vs. PCV13 are important to consider. There have been no head-to-head clinical comparisons between the PCV10 and PCV13 within a single trial, so vaccine effectiveness is often assumed based on their head-to-head comparison with PCV7 or their sequential implementation in observational studies, and sometimes adjusted for serotype distribution. The indirect effects of PCV use are an influential parameter in sensitivity analyses, but many studies do not account for herd effects or serotype replacement. Most evaluations use static models, meaning they assumed that the probability of disease exposure and other model parameters are constant over time. For a transmissible infectious disease this is not a realistic assumption. Transmission dynamic models, which better model interpersonal spread of disease, "have been rarely used for pneumococcal infections, because they require data on age-specific carriage of pneumococcal serotypes in healthy and diseased people alike" that is currently unavailable from most settings.(335)

Indeed, the inclusion of herd effects can have a large effect on the CEA findings. In a CUA study from Thailand done using a Markov model, a 2p+1 schedule, societal perspective, and PCV10 and PCV13 costs per dose of US$61.90 and $46.2, respectively, the ICER of PCV10 vs. no vaccination was US$45,183 per QALY gained without inclusion of herd effects.(338) Assuming a herd effect on IPD of 40% for 20-39 year olds, 14% for 40-64 year olds, and 29% for elderly over 65 years, the ICER of PCV10 decreased to US$17,173 per QALY gained. For PCV13 vs. no vaccination, the ICER without herd effects was US$49,220 per QALY gained, and with inclusion of herd effects in the model, the ICER decreased to US$17,437 per QALY gained.(338)(Table M)

Tasslimi, et al. provide a CEA of PCV7, PCV10 and PCV13 using a 3p+0 schedule compared to no vaccine in Gavi-eligible countries.(336) The authors conclude that PCV10 and PCV13 would be cost effective for all 72 Gavi-eligible countries (ICER<3xGDP) and highly cost-effective for all but one country (ICER<GDP). "This finding was robust when assumptions regarding disease epidemiology and vaccine-related effects were varied in sensitivity analyses."(336) This study accounts for indirect effects, herd immunity and serotype replacement, and takes a 10-year societal perspective. Outcomes included in the model are: pneumococcal pneumonia, pneumococcal meningitis and non-pneumonia, non-meningitis IPD in children U5 years; and pneumococcal meningitis, pneumococcal sepsis and all-cause pneumonia in older children and adults. The study finds that PCV could avert 294,000 to 603,000 deaths, depending on formulation, and 9.3 to 17.6 million DALYs annually. Ninety-one percent of the DALYS averted would result from PCV's direct effect on children U5 years. Taking into account both direct and indirect effects, the ICER of PCV7 is 2005 US$146/DALY averted, PCV10 is $88/DALY averted, and PCV13 is $77/DALY averted.(Table M) These ICERs vary greatly by countries' U5 mortality rate. Countries with a higher mortality rate would have lower ICER: PCV use is more cost-effective in these settings.(Table N) In addition, there is "notable improvement in pooled cost effectiveness, all other variables being equal, when moving from PCV7 to PCV10, but little additional improvement from PCV10 to PCV13."(336)

Table M: Summary of selected CEAs of PCV, updated through December 2014[2]

Vaccine	Country/region	Vaccine price per dose	Number of doses	Vaccine efficacy	Perspective	Type of model	ICER	Notes	Ref
PCV7	Gavi-eligible countries (n=72)	AMC price + $1 administration cost per dose	3	85%	Societal	Static	2005 US$146/DALY averted	Includes indirect effects and serotype replacement, discounting 3%	(336)
PCV10	Gavi-eligible countries (n=72)	AMC price + $1 administration cost per dose	3	85%	Societal	Static	2005 US$88/DALY averted	Includes indirect effects and serotype replacement	(336)
PCV13	Gavi-eligible countries (n=72)	AMC price + $1 administration cost per dose	3	85%	Societal	Static	2005 US$77/DALY averted	Includes indirect effects and serotype replacement	(336)
PCV7	Middle-income countries (n=77)	$10 or $20 +$5 administration cost per dose	3	85%	Societal	Static	2005 US$1,600/DALY averted	Includes indirect effects and serotype replacement, discounting 3%	(337)
PCV7	Lower middle-income countries (n=35)	$10+$5 administration cost per dose	3	85%	Societal	Static	2005 US$1,500/DALY averted	Includes indirect effects and serotype replacement	(337)
PCV7	Upper middle-income countries (n=42)	$20+$5 administration cost per dose	3	85%	Societal	Static	2005 US$1,900/DALY averted	Includes indirect effects and serotype replacement	(337)
PCV10	Middle-income	$10 or $20	3	85%	Societal	Static	2005	Includes indirect	(337)

[2] Based on findings from PubMed search done in May 2014 and updated through the end of December2014. Also included are studies from the Wu 2015 review that were not industry funded and were conducted in LMICs.

	countries (n=77)	+$5 administration cost per dose					US$1,000/DALY averted	effects and serotype replacement	
PCV10	Lower middle-income countries (n=35)	$10+$5 administration cost per dose	3	85%	Societal	Static	2005 US$920/DALY averted	Includes indirect effects and serotype replacement	(337)
PCV10	Upper middle-income countries (n=42)	$20+$5 administration cost per dose	3	85%	Societal	Static	2005 US$1,300/DALY averted	Includes indirect effects and serotype replacement	(337)
PCV13	Middle-income countries (n=77)	$10 or $20 +$5 administration cost per dose	3	85%	Societal	Static	2005 US$900/DALY averted	Includes indirect effects and serotype replacement	(337)
PCV13	Lower middle-income countries (n=35)	$10+$5 administration cost per dose	3	85%	Societal	Static	2005 US$800/DALY averted	Includes indirect effects and serotype replacement	(337)
PCV13	Upper middle-income countries (n=42)	$20+$5 administration cost per dose	3	85%	Societal	Static	2005 US$1,100/DALY averted	Includes indirect effects and serotype replacement	(337)
PCV7	Latin America and the Caribbean countries (n=45)	$20	3	97%	Societal	Static	2005 US$1,747/DALY averted	Does not include indirect effects	(326)
PCV7	Latin America and the Caribbean countries (n=45)	$20	3	97%	Societal	Static	2005 US$59,000/life saved	Does not include indirect effects	(326)
PCV7	The Gambia	$3.50	3	26% against all-	Societal	Static	2005	Direct effects	(339)

				cause pneumonia, 16% against pneumococcal meningitis/sepsis			US$910/DALY averted	only in base case scenario, adding indirect effects reduced ICER to $830/DALY averted	
PCV10	The Gambia	$3.50	3	35% against all-cause pneumonia, 22% against pneumococcal meningitis/sepsis	Societal	Static	2005 US$670/DALY averted	Direct effects only in base case scenario, adding indirect effects reduced ICER to $550/DALY averted	(339)
PCV13	The Gambia	$3.50	3	41% against all-cause pneumonia, 26% against pneumococcal meningitis/sepsis	Societal	Static	2005 US$570/DALY averted	Direct effects only in base case scenario, adding indirect effects reduced ICER to $480/DALY averted	(339)
PCV9	The Gambia	$5	3	35-37% against pneumonia, 77% against VT-IPD and 16% against all-cause mortality	Public healthcare	Static	$30/DALY averted	Direct effects only, costs of illness and VE from PCV9 clinical trial in The Gambia(124)	(328)
PCV10	Kenya	$3.50	3	77% against pneumonia, 92% against sepsis and meningitis	Societal	Static	2010 US$59/DALY averted	Inclusion of indirect effects reduced ICER to $32/DALY	(327)

								averted	
PCV10	Kenya	$3.50	3	77% against pneumonia, 92% against sepsis and meningitis	Societal	Static	2010 US$1,958/life saved	Inclusion of indirect effects reduced ICER to $1158/life saved	(327)
PCV13	Kenya	$3.50	3	77% against pneumonia, 92% against sepsis and meningitis	Societal	Static	2010 US$47/DALY averted	Inclusion of indirect effects reduced ICER to $25/DALY averted	(327)
PCV13	Kenya	$3.50	3	77% against pneumonia, 92% against sepsis and meningitis	Societal	Static	2010 US$1,558/life saved	Inclusion of indirect effects reduced ICER to $888/life saved	(327)
PCV10	Uganda	$3.50 program cost per dose	3	85% in HIV-negative children	Public healthcare	Static	US$38.50/DALY averted	Only direct effects and direct medical costs included. PCV10 would be cost-saving at co-financing cost of $0.15 per dose	(321)
PCV10	Thailand	$61.90	3	89% against IPD, 6% against pneumonia, 6% against AOM	Societal	Static	2013 US$45,183 per QALY gained	PCV10 vs. no vaccination without inclusion of herd effects	(338)
PCV10	Thailand	$61.90	3	89% against IPD, 6% against pneumonia, 6% against AOM	Societal	Static	2013 US$17,173 per QALY gained	PCV10 vs. no vaccination with herd effects: 40% against IPD in 20-39 year olds, 14%	(338)

								against IPD in 40-64 year olds, and 29% against IPD in >65 year olds	
PCV13	Thailand	$46.20	3	89% against IPD, 6% against pneumonia, 6% against AOM	Societal	Static	2013 US$49,220 per QALY gained	PCV13 vs. no vaccination without inclusion of herd effects	(338)
PCV13	Thailand	$46.20	3	89% against IPD, 6% against pneumonia, 6% against AOM	Societal	Static	2013 US$17,437 per QALY gained	PCV13 vs. no vaccination with herd effects: 40% against IPD in 20-39 year olds, 14% against IPD in 40-64 year olds, and 29% against IPD in >65 year olds	(338)
PCV10	Brazil	$19.60	4	94% against IPD in 0-5 year olds, 87.5% against VT pneumonia in 0-2 year olds, 57.5% against VT AOM in 0-2 year olds	Healthcare, societal	Static	2013 US$11,815 per DALY averted	Universal PCV10 vaccination vs. high-risk PCV10 vaccination	(340)
PCV10	Colombia	$16.20	3	74% against Spn meningitis, 21% against radiological pneumonia, 34%	Societal	Static	2013 US$1,892 per LYG gained	PCV10 vs. no vaccination	(341)

				against AOM					
PCV13	Colombia	$17.90	3	83% against Spn meningitis, 24% against radiological pneumonia, 9% against AOM	Societal	Static	2013 US$9,801 per LYG gained	PCV13 vs. no vaccination	(341)
PCV10	Peru	$14.24	3	13% against AOM, 81% against IPD multiplied by serotype coverage of 71%	Government	Static	2011 US$1,605 per DALY averted	PCV10 vs. no vaccination, highly cost-effective	(342)
PCV13	Peru	$16.34	3	8% against AOM, 81% against IPD multiplied by serotype coverage of 81%	Government	Static	2011 US$1,304 per DALY averted	PCV13 vs. no vaccination, highly cost-effective	(342)
PCV10	Paraguay	$14.85	3	34% against AOM, 6% against all-cause pneumonia, 80% against IPD multiplied by 80% VT coverage	Government, societal	Static	2009 US$3,851 per DALY averted (government perspective), US$1,920 per DALY averted (societal perspective)	PCV10 vs. no vaccination, cost-effective from government perspective and highly cost-effective from societal perspective	(343)
PCV13	Paraguay	$20	3	6% against AOM, 6% against all-cause pneumonia, 80% against IPD multiplied by	Government, societal	Static	2009 US$4,901 per DALY averted (government perspective), US$3,657 per	PCV13 vs. no vaccination, cost-effective from both government and societal	(343)

				85% VT coverage			DALY averted (societal perspective)	perspective	

Table N: ICER (US$/DALY averted) by U5 mortality strata in Gavi-eligible countries (336)

Under five mortality strata	<25 deaths/1000 live births	25-99 deaths/1000 live births	100-149 deaths/1000 live births	>=150 deaths/1000 live births
PCV7	$1078	$283	$103	$65
PCV10	$582	$152	$66	$41
PCV13	$471	$125	$60	$37

A study of PCV cost-effectiveness in 77 middle-income countries found PCV7 to be cost-effective for 72 countries, and PCV10 and PCV13 to be cost-effective for all countries compared to no vaccine.(337) PCV7 would be highly cost-effective for 53 middle-income countries, PCV10 for 68 countries and PCV13 for 71 countries. The study modeled direct and indirect effects of PCV7, PCV10 and PCV13 used in a 3p+0 schedule with a vaccine cost of $10 for lower middle-income countries and $20 for upper middle-income countries. The cost of vaccine administration was assumed to be $5 per dose. From a societal perspective over 10 years, PCV use would prevent at least 11 million disease cases and 314,000 deaths in children U5 years, "one-third of the pneumonia and invasive disease cases and deaths that would occur in this age group without vaccination."(337) Herd protection would result in an additional 3.1 million cases and 163,000 deaths averted in older children and adults. DALYs averted range from 11.1 million to 18.5 million, depending on PCV formulation. The overall ICER for PCV7 is 2005 US$ 1600/DALY averted, PCV10 is $1000/DALY averted, and PCV13 is $900/DALY averted.(Table K) For lower middle-income countries, the estimated ICER for PCV7 is $1500/DALY averted, PCV10 is $920/DALY averted, and PCV13 is $800/DALY averted. For upper middle-income countries, the corresponding ICER estimates are $1900/DALY averted for PCV7, $1300/DALY averted for PCV10, and $1100/DALY averted for PCV13.(337)

In a study modeling PCV7 cost-effectiveness in Latin America and the Caribbean, PCV7 was determined to be highly cost-effective up to a price of $40 per dose.(326) This study did not take into account indirect effects. PCV7 was projected to "prevent 857,000 cases of pneumococcal disease annually, including 9,500 deaths," and avert 321,000 DALYs annually in the region. PCV7 would save 0.9 lives per 1000 children vaccination and avert 60 cases per 1000 children vaccinated.(326) Regionally, from a societal perspective, the ICER of PCV7 compared to no vaccine ranged from $154/DALY averted, assuming a vaccine cost of $5 per dose, to $5252/DALY averted, with a vaccine cost of $53 per dose.(326)(Table L)

Two economic evaluations focus on The Gambia but yield quite different cost-effectiveness ratios. In the first, the direct effects of PCV7, PCV10 and PCV13 were compared to no vaccination. Based on a vaccine price of $3.50 per dose and a societal perspective, all PCV formulations would be cost-effective with an ICER of $910/DALY averted for PCV7, $670/DALY averted for PCV10, and $570/DALY averted for PCV13. Inclusion of indirect effects in the model reduced the ICER for PCV by 9% to 18%.(Table L) The study concluded that PCV would be highly cost-effective up to a unit vaccine price of $1.24 and cost-effective up to a price of $4.20 per dose.(339) Another study from The Gambia, conducted in conjunction with a clinical trial of PCV9 (124), found a lower cost per DALY averted. Based on direct effects only, the public healthcare perspective and a vaccine price of $5 per dose, this study estimated the ICER for PCV9 to be $30/DALY averted, $175/disease case averted, and $807/death averted.(328)(Table L)

PCV10 and PCV13 use was modeled in Kenya and found to be highly cost-effective from a societal perspective.(327) At a vaccine cost of $3.50 per dose and including only direct effects, PCV10 had an ICER of US$59/DALY averted (95% CI 26, 103). The ICER was US$300/disease case averted (95% CI $145, $488) and US$1958/death averted (95% CI $665, $2764). For PCV13, the ICER was US$47/DALY averted (95% CI $20, $83), US$238/case averted (95% CI $110, $390), and US$1558/death averted (95% CI $665, $2764).(327)(Table L) Inclusion of indirect effect estimates had a significant impact on the model results, reducing ICERs by 48% to 56%: for PCV10, the ICER was $32/DALY averted and $189/case averted when including indirect effects, and for PCV13 it was $25/DALY averted and $147/case averted.(327)

A study done from the public healthcare perspective in Uganda predicted PCV10 would be cost-saving at a cost of US$0.15 per dose, the Gavi co-financing cost to the government. At this cost, PCV10 would avert US$1.63 per child in medical costs. This study only included the direct effects of vaccine and direct medical costs. In secondary analysis, using the AMC cost of $3.50 per dose, PCV10 is still highly cost-effective in Uganda.(321)(Table L)

Broader Perspective on the Value of Vaccination

Few health economic studies look at the potential broader value of vaccines. Failing to include all value that accrues from vaccination in estimates of CE may result in ongoing undervaluation of their impact on economic and societal well-being and risk underinvestment on the part of countries and partners.

While there is a theoretical framework linking vaccine use to broader economic and behavioral effects, empirical research is needed to test these linkages and provide quantitative field based measures of their magnitude.

Some researchers advocate for a broader view when considering the potential value of vaccines, including benefits on economic and societal well-being. Indeed, "failing to account for the full spectrum of benefits . . . will result in an undervaluation of vaccination" which will bias economic evaluations.(344) A broader framework of vaccination benefits has been developed through WHO-convened expert consultations and is shown in Figure 44.

Figure 44: Proposed framework for a broader valuation of vaccination benefits (345-348)

	Category	Definition	Examples of outcomes	Strength of evidence(348)
Narrow benefits	Health-related benefits			
	Health gains	Reduction in morbidity and mortality	Cases averted Deaths averted DALYs saved	NA[1]
	Health care savings	Reduction in cost of health care borne by the public sector or private individuals	Costs saved	NA[1]
	Productivity-related benefits			
	Productivity gains related to care	Reduction in lost days of work due to sickness or caring for a sick patient	Value of productivity gained	NA[1]
	Productivity gains related to health effects	Reduction in lost days of work due to sickness or death of a sick patient	Value of productivity gained Lifetime earnings	NA[1]
Broad	Productivity gains related to non-utility capabilities	Increased lifetime productivity because better health improves	Education outcomes Cognitive outcomes	Moderate experimental/observational evidence that

		cognition, educational attainment and physical strength	Lifetime earnings	immunization improves non-utility capabilities. Modelling evidence that immunization produces productivity gains via improvements in non-utility capabilities.
	Community or health system externalities			
	Ecological effects	Health improvements in unvaccinated community members as a result of ecological effects such as herd immunity and reduced antibiotic usage	Indirect vaccine protection Prevalence of antibiotic resistance	
	Equity	More equal distribution of health outcomes	Distribution of health outcomes	Moderate experimental/observational and modelling evidence
	Financial and programmatic sustainability	Improved financial sustainability of health care programs as a result of synergies with vaccination programs and/or stimulation of private demand	Financial benefits Private demand estimates	Modelling evidence
	Household security	Improved financial security of households as a result of reduced risk of catastrophic expenditure	Actuarial value of security	Modelling evidence
	Broader economic indicators			
	Changes to household behavior	Economic improvements due to changes in household choices such as fertility and consumption/saving as a result of improved child health and survival	Productivity Female labor participation Household investment Child dependency ratio	Conjecture
	Public sector budget impact	Change to an individual's net transfers to the national budget over a lifetime	Return on investment Net present value of investment	Modelling evidence
	Short-term macroeconomic impact	Changes to national income or production as a result of short-term exogeneous shocks to the economy	Change in per capita GDP Change in sectoral output	Modelling evidence
	Long-term macroeconomic	Changes to national income or production as	Change in per capita GDP	No evidence from vaccine studies, but weak

	impact	a result of long-term changes to drivers such as labor supply and foreign direct investment		observational evidence from non-vaccine fields

[1]NA=not assessed as there are numerous studies providing evidence for the narrow benefits of vaccination.

Adapted from Jit M, et al. "The broader economic impact of vaccination: reviewing and appraising the strength of evidence," Barnighausen T, et al. "Valuing vaccination," and Deogaonkar R, et al. "Systematic review of studies evaluating the broader economic impact of vaccination in low and middle income countries."

As summarized previously in this chapter, most economic evaluations on vaccination take a narrow perspective—including only health gains and health care savings—on potential benefits. Yet, vaccines, in particular, may warrant studies that incorporate a broader valuation because:

> "First, vaccinations are commonly given in early life phases, and the returns on vaccination investments, such as improved school attainment, economic productivity, and social functioning, are reaped throughout the life course. Second, vaccinations often disrupt transmission chains of infectious diseases throughout the community, leading to multiplier effects for the broader economic and social benefits of vaccination. Third, the child survival benefits of vaccinations typically catalyze or accelerate fertility decline and create potentially sizable opportunities for economic growth."(344)

These types of broader social and economic benefits are congruous with what is known about PCV impact. PCV may yield outcome-related productivity gains—benefits that follow on from improved health due to receipt of the vaccine—as "episodes of pneumococcal pneumonia will keep children out of school, impeding cognitive development and learning; survivors of pneumococcal meningitis can suffer from severe cognitive and neurological sequelae; (and) pneumococcal otitis media can impair cognitive development and lead to hearing loss."(344) PCV can also result in community health externalities because PCV use "decrease(s) the use of antibiotics and thus the rate of occurrence of antibiotic-resistant pneumococcal infections" and has been shown to have herd effects due to reduced circulation and transmission of VT pneumococci to unvaccinated members of the community.(344) In an RCT based in Israeli daycare centers, PCV9 recipients had 17% fewer antibiotic days than controls ($p<0.005$).(137) There is also some ecological data from the US and France that overall antibiotic use may be decreased in children but the use of broad-spectrum antibiotics has increased in the post-PCV period.(349, 350)

However, the empirical studies supporting the broader benefit of vaccines are limited. A recent evidence review by Jit, et al. concludes that "evidence of moderate quality from experimental and observational studies (is) found for benefits due to immunization in improved childhood physical development, educational outcomes, and equity in distribution of health gains."(348, 351-358) Some of the categories of broader benefits are only supported by modelling studies or from data outside the vaccine field (i.e. studies relating child mortality or life expectancy to macroeconomic indicators).(348) The authors also state that "the absence of evidence from interventional studies to support many of the proposed (broader economic) pathways does not imply evidence for the absence of such relationships," it just means that these pathways have not yet been studied. The reasons for this are manifold. Some of the studies needed would be expensive or time-consuming, and conditions for a "natural" experiment—in which some group(s) is not given a proven vaccine--are rare.(348) Efforts to collect

information on household behavior and long-term outcomes are worthwhile incorporating, when possible, into studies because such information may be influential to decision makers in LMICs.(347, 359) In a stakeholder analysis, evidence on macroeconomic impact, along with other factors such as burden of disease and ecological effects, was perceived as being valuable in aiding decision making for vaccine introduction.(347) Thus the broader economic impact of vaccines is a field of study with many pending questions that is of interest to policy makers.

Chapter 6: Implementation of PCV

Chapter 6 Overview

Two formulations of PCV are currently WHO prequalified and available through UNICEF procurement: PCV10 and PCV13. Both preparations are administered intramuscularly by injection of 0.5 ml of liquid vaccine. Both vaccines come with a vaccine vial monitor (VVM) to provide a quality assurance of vaccine potency based on temperature stability. PCV10 (two-dose vial without preservative) and PCV13 (single dose vial) are procured by UNICEF and available to Gavi-eligible countries for a copayment as low as US$0.20 per dose (for low-income countries). In 2017 and 2018 4-dose presentations of PCV13 and PCV10, respectively, are expected to be available to Gavi-eligible countries. PCV13 contains antigens of three additional serotypes (3, 6A and 19A) that are not in PCV10. // The current formulation of PCV13 takes up 2.5 times the cold chain volume per dose as does PCV10. PCV10 is available in 100-vial cartons; each vial contains two-doses, corresponding to a volume of 4.8 cm^3 per dose. PCV13 is available in 50-vial cartons; each vial is a single-dose, corresponding 12 cm^3 per dose. The single-dose PCV13 vial reduces vaccine wastage (5% estimated) compared to a two-dose vial that, if opened and not used in the same day, must be discarded (10% estimated wastage). A preservative-free two dose vaccine has not previously been used in UN-supported programs, and so the WHO specified that post-introduction monitoring of PCV10 be conducted to assess safety and adverse events following immunization. A Kenyan study found that the risk of abscess following the second vs. first vial dose of PCV10 was not significantly increased compared to another EPI vaccine (pentavalent vaccine), lending support to the feasibility of safely using this formulation in Africa and low-income settings.

There are two options for PCV dosing of infants that have been approved by the WHO: 3p+0 or, alternatively, 2p+1. The dosing options were systematically reviewed and results published in 2014 on the evidence for vaccine effectiveness based on the number and timing of primary doses--including the interval between doses and the initial age to begin vaccination—and the presence or absence of a booster dose. In the 2014 review, there was little data from low-income country settings and almost no data on PCV10 or PCV13. With respect to immunogenicity, the number of primary doses (2 or 3) did not meaningfully affect geometric mean concentration (GMC) of IgG measured in the second year of life except for serotype 6B, and a booster dose significantly increases the GMCs for all serotypes regardless of the priming schedule. Older age at immunization and longer intervals between primary doses may optimize immune responses in the first year of life. One important caveat to bear in mind is that the immunological correlate of protection varies based on the outcome studied-- disease or NP carriage—and serotype. Immune response also varies significantly by geographical regions with higher IgG responses in children from Asia, Africa and Latin America compared to Europe and North America.

Differences between dosing schedules on VT-IPD are relatively small compared to the overall benefit of PCV use on this outcome with any of the commonly used schedules: 2p+1, 3p+0 and 3p+1. Similarly, differences between dosing schedules on the outcomes of clinical pneumonia and radiologically confirmed pneumonia are also hard to discern. The case definitions of clinical pneumonia, radiologically confirmed pneumonia, pneumococcal pneumonia, and empyema often vary between studies and preclude directly comparing study results.

There is evidence that three primary doses may be better than two doses for reducing VT carriage in the first year of life prior to a booster dose, but this difference is no longer discernible after the first year or following a booster dose. A 3 primary dose schedule (3p+0) is not as good as 2

primary doses and a booster (2p+1) in maintaining decreased VT NP carriage in the second year of life, indicating that the booster dose is important for continued suppression of VT carriage. The 2014 review of NP carriage was based primarily on studies of PCV7, it did not include studies using PCV10 or PCV13. Data on the 2p+1 schedule came from European studies, whereas data on the 3p+0 schedule came from clinical trials in LMICs. These countries have different epidemiological patterns of NP carriage, and these differences confound the impact of different schedules on carriage prevalence.

The WHO recommends PCV introduction in all countries, especially in countries with a high U5 mortality rate where PCV introduction is deemed a "high priority." In making dosing decisions, policy makers should consider three fundamental questions: who is most affected, that is, what is the epidemiology of pneumococcal disease in the country; what schedule will prevent the most disease or deaths; and what schedule best fits with the current EPI schedule? Lessons learned from recent new vaccine introductions demonstrate a potential for positive and negative effects on the immunization supply chain. Constraints of the supply chain are important to assess because overburdening the system can compromise the perceived availability of all EPI vaccines. Training of health staff on the side effects of PCV is also an important part of PCV introduction planning. Health staff should also be familiar with other important key messages for parents regarding the risk of pneumonia, even with vaccination, and appropriate care seeking for signs of pneumonia. New vaccine introductions can also be an opportunity to strengthen disease surveillance systems with enhanced surveillance for diseases prevented by the new vaccines and improve awareness and reporting of adverse events following immunization (AEFIs).

In 2009 the Advanced Market Commitment (AMC) for pneumococcal vaccine was established. The AMC provides an innovative finance mechanism to incentivize the scaling up of PCV production to meet developing country needs. Both GSK (the manufacturer of PCV10) and Pfizer (the manufacturer of PCV13) have been accepted as part of the AMC. Eighty percent of eligible countries have applied for Gavi support to obtain PCV10 or PCV13 at reduced cost. Eligibility for Gavi support and a country's vaccine co-financing contribution is based on per capita GNI. For low-income countries, those with a GNI less than US$1,045 per person, the country must co-finance US$0.20 per PCV dose. Intermediate Gavi-eligible countries, with GNI between US$1,045-US$1,580 per person, start co-financing at US$0.20 per dose with a 15% annual increase. Countries with a GNI above US$1,580 graduate from Gavi support. Graduating countries pay an additional 20% of the difference between their initial co-financing amount and the projected price of PCV in the year Gavi support ends, so that in five years they become responsible for the full cost of PCV.

Financing issues are most complicated and difficult for lower middle-income countries that are just above the Gavi-eligibility threshold. These countries are left out of the financing and AMC pricing agreements and yet are not well-resourced to finance PCV independently on the open market. This gap is evinced by the low proportion of lower middle -income countries that have introduced PCV without Gavi support.

The WHO has developed a post-introduction evaluation (PIE) tool to help conduct a systematic, qualitative assessment of vaccine introduction at multiple levels of the health system. New vaccine introduction can be a vehicle for both positive and negative impacts on the broader health system. There are principles to help guide vaccine introduction planning to maximize its beneficial impact. A immediate, quantifiable outcome measure in vaccine delivery is achieving high, equitable coverage rates all districts.

Ultimately, the measure of vaccine program performance is a reduction in the burden of preventable disease. High-quality surveillance provides valuable insight into program performance and disease epidemiology post-introduction, but the lack of a surveillance program should not be an impediment to PCV introduction. The 2012 WHO position paper on PCVs states: "high-quality

surveillance should be conducted in selected countries and defined populations that represent different epidemiological profiles worldwide. Surveillance of disease incidence should begin at least 2 years prior to PCV introduction and continue for at least 5 years post-introduction." There are three tiers of surveillance. The first tier is hospital-based sentinel surveillance for all children with suspected meningitis U5 years of age. The second tier is hospital-based sentinel surveillance for all children U5 with meningitis, pneumonia or sepsis. The limitation of hospital-based sentinel surveillance is that it is not easy to assess vaccine impact, there are small numbers of cases, and the denominator (the true catchment population) is unknown so incidence of disease cannot be determined. The third tier of surveillance is active population-based surveillance that provides the most accurate method of monitoring disease trends. This type of surveillance, where the denominator (population size) from which cases are detected is known, allows incidence rates to be calculated. Quality assurance (QA) and quality control (QC) measures should be used to assess the quality of the disease surveillance system in place and the interpretation of the results as they reflect on vaccine programming.

PCV Formulation and Product Details

PCV13 contains antigens of three serotypes (3, 6A and 19A) that are not in PCV10. The current formulation of PCV13 takes up 2.5 times the cold chain volume per dose as does PCV10.

Two formulations of PCV are currently WHO prequalified and available through UNICEF procurement: PCV10 and PCV13. Both preparations are administered intramuscularly by injection of 0.5 ml of liquid vaccine. Both vaccines come with a vaccine vial monitor (VVM) to provide a quality assurance of vaccine potency based on temperature stability. PCV10 (two-dose vial without preservative) and PCV13 (single dose vial) are procured by UNICEF and available to Gavi-eligible countries for a copayment as low as US$0.20 per dose (for low-income countries), with annual increases in copayment for countries in the intermediate and graduating categories.(360) PCV13 is also produced in a pre-filled syringe which is procured in non-Gavi markets, especially high-income markets. The vaccine manufacturer is reimbursed up to US$7.00 per dose if the manufacturer's product is part of the Advanced Market Commitment (AMC) agreement which stipulates that the product must meet certain criteria and stipulates the number of doses procured under the AMC.(361)

In 2017 and 2018, PCV13 and PCV10, respectively, will be made available in 4-dose vials. By 2018, PCV10 4-dose vials will be the *only presentation* available to Gavi countries for this vaccine. PCV13 will be available in a 4-dose vial beginning in early 2017 and continue to be available to Gavi countries in a single-dose vial for the foreseeable future. The slightly lower per-dose cost of the 4-dose PCV13 product may be offset by higher wastage compared to the slightly more expensive single-dose presentation and these trade-offs should be considered carefully.

Table O provides further product details. The main difference between the two PCV formulations—in addition to the inclusion of serotypes 3, 6A and 19A in PCV13—is the packaging. PCV10 is available in 100-vial cartons; each vial contains two-doses, corresponding to a volume of 4.8 cm^3 per dose.(Figures 45 and 46) PCV13 is available in 50-vial cartons; each vial is a single-dose, corresponding 12 cm^3 per dose, or 2.5 times the volume of PCV10.(Figures 47 and 48) The single-dose PCV13 vial requires more space for cold chain storage and distribution, but it reduces vaccine wastage (5% estimated) compared to a two-dose vial that if opened and not used in the same day must be discarded (10% estimated wastage).

PCV10, trade name Synflorix, is manufactured by GlaxoSmithKline. Protein D, an outer membrane protein of non-typeable *Haemophilus influenzae*, is used as the carrier protein for 8 of the 10 serotypes. Serotype 19F is conjugated to diphtheria toxoid, and serotype 18C is conjugated to tetanus toxoid. The final PCV10 formulation was the result of an iterative process. Originally, an 11-valent vaccine conjugated to protein D was studied. However, as there was no evidence for serotype 3 efficacy, this serotype was dropped from the vaccine. In the final PCV10 formulation, the amount of serotype 4 capsular polysaccharide was increased to boost its immunogenicity, and serotypes 18C and 19F were conjugated to different carrier proteins to boost their immunogenicity.(362) PCV10 is adjuvanted with aluminum phosphate and presented in a single-dose (non-Gavi countries) or two-dose vial (Gavi and non-Gavi countries). Each dose contains 1 mcg of polysaccharide for the serotypes 1, 5, 6B, 7F, 9V, 14 and 23F, and 3 mcg of serotypes 4, 18C and 19F.(10) Concern was raised that a two dose vial without preservative might pose safety issues, including severe disease from toxic shock, or local abscesses, should the vial become contaminated. A preservative-free two dose vaccine has not previously been used in UN-supported programs, and so the WHO specified that post-introduction monitoring of PCV10 be conducted to assess safety and adverse events following immunization.(363) The safety of the preservative-free, two-dose PCV10 formulation was specifically assessed in a Kenyan study prior to receiving full pre-qualification by the WHO. In this study, the risk ratio for abscess following injection with the second vs. first vial dose of PCV10 was not significantly increased compared to another EPI vaccine (pentavalent vaccine), lending support to the feasibility of safely using this formulation in Africa and low-income settings.(364)

PCV13, trade name Prevenar (or Prevnar) 13, is manufactured by Pfizer. The vaccine contains polysaccharide antigens of 13 serotypes conjugated to non-toxic diphtheria CRM (cross-reactive material) 197 carrier protein A. The 0.5 ml dose of PCV13 contains 2.2 mcg of polysaccharide antigen from each of 12 serotypes and 4.4 mcg from serotype 6B. PCV13 is available as a liquid vaccine in single-dose vials or prefilled syringes (non-Gavi countries) with 0.125 mg of aluminum phosphate per dose as adjuvant.(25) PCV13 is also preservative-free.(10)

Figure 45: 100-vial carton of PCV10

Figure 46: PCV10 two-dose vial

Figure 47: PCV13 single-dose vial

Figure 48: 50-vial carton of PCV13

Table O: PCV product formulation and details(112, 113)[3]

PCV	Serotypes included	Manufacturer	Trade name(s)	Carrier proteins	Year prequal by WHO	Avail from UNICEF	Wastage rate	Storage conditions	Packaging	Volume per dose	VVM
PCV10 1-dose vial, preserv-ative free	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F	GlaxoSmithKline (GSK)	Synflorix Synflorix	Protein D from non-typeable *Haemophilus influenzae*, tetanus toxoid and diphtheria toxoid	2009	No	5%	2-8 Celsius, do not freeze.	Cartons of 1, 10 and 100 vials	57.7, 11.5 and 9.7 cm^3 per dose	VVM30: quite stable under high temperatures
PCV10 2-dose vial, preserv-ative free					2009	Yes	10%	2-8 Celsius, do not freeze. An opened two-dose vial should not be returned to the refrigerator after a vaccination session or after 6 hours, whichever comes first.	Cartons of 100 vials	4.8 cm^3 per dose	
PCV104-dose vial, preserv-ative 2-PE[4]					2017 (expected)	Yes (expected)	10%	2-8 Celsius, do not freeze.		2.4 cm^3 per dose	
PCV13, single-dose vial	Addition of 3, 6A and 19A	Pfizer	Prevnar13, Prevenar 13	Mutant diphtheria toxoid (CRM 197 protein)	2010	Yes	5%	2-8 Celsius, do not freeze	Cartons of 50 vials	12 cm^3 per dose	VVM30: quite stable under high temperatures
PCV13 4-dose vial, Preserv-ative 2-PE4					2016		10%		Cartons of 25 and 50 vials	3 cm^3 per dose	

[3] Information on 4-dose formulations may be found at http://www.gavi.org/library/gavi-documents/guidelines-and-forms/pcv-4-dose-vials-faqs/

[4] 2-phenoxyethanol

Future PCV Formulations

Figure 49 lists the current and future formulations of pneumococcal vaccine in various stages of development. Four-dose vial presentations of the currently licensed products—both PCV10 and PCV13—with 2PE as the preservative, are in development by their respective manufacturers and are expected to receive WHO prequalification in the next few years. Protein pneumococcal vaccines and combination conjugate and protein vaccines are also in development but are not expected to reach the market before 2025.(365)

Figure 49: Current and future formulations of pneumococcal vaccine in development

Vaccine Type	Company	Country	Product	Serotypes	Carrier(s)	Status
PCV	Pfizer	US	PCV13 Prevenar	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	CRM197	Approved
	GSK	UK	PCV10 Synflorix	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Protein D, DT, TT	Approved
	FioCruz	Brazil	PCV10 Synflorix	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	Protein D, DT, TT	Tech transfer
	SK/Sanofi	Korea	PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F		Phase III
	SII	India	PCV10	1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F	CRM197	Phase II
	Finlay Institute	Cuba	PCV7	1, 5, 6B, 14, 18C, 19F, 23F	TT	Phase II
	Merck	US	PCV15	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F or 33F	CRM197	Phase II
	Panacea	India	PCV10	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F	CRM197	Phase I
	CNBG	China	PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	CRM197	Phase I
	BioE	India	PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	CRM197	Pre-Clin
	PnuVax	Canada	PCV13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	CRM197	Pre-Clin

	Walvax	**China**	**PCV13**	**1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F**		**Pre-Clin**
Common Protein	**Sanofi**	**US**	**Protein–3 valent**	**-**	**-**	**Phase II**
	Biofarma	**Indonesia**	**Whole cell**	**-**	**-**	**Phase I/II**
	Genocea	**US**	**Protein-3 valent**	**-**	**-**	**Phase I**
PCV + Protein	**GSK**	**UK**	**PCV10 + 2 pro**	**1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F + 2 proteins**		**Phase II**
	Affinivax	**US**	**MAPS13**	**1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F + 4 proteins**		**Pre-Clin**

PCV Dosing Schedules

There are a few options for PCV dosing of infants that have been approved by the WHO. The dosing options were systematically reviewed and results published in 2014 on the evidence for vaccine effectiveness based on the number and timing of primary doses-- including the interval between doses and the initial age to begin vaccination—and the presence or absence of a booster dose. The full review papers are available at: http://journals.lww.com/pidj/toc/2014/01002. The outcomes studied included immunogenicity, IPD, pneumonia, NP carriage and indirect effects. The "PCV Dosing Landscape" analysis findings are presented below and include articles published up through September 2010.

An update to the comprehensive "PCV Dosing Landscape" study previously published (7-9, 227, 367, 370, 374-5) **is expected in 2017 and will include an updated comprehensive analysis of PCV impact evidence. An overview of this forthcoming review, called PRIME (PCV Review of Impact Evidence), is available in Appendix A at the end of this document.**

In 2014 discussions in the technical community began about moving from a 3-dose to a 2-dose schedule for the maintenance phase of PCV once control of VT disease and colonization was well established. The concept is that if a 1+1 schedule can be successful in maintaining the suppression of VT colonization (through the booster dose) and provide some modest direct protection early in life (through the first priming dose), substantial cost savings could accrue by dropping the second priming dose. The clinical studies to establish this evidence are underway as of 2016 and this policy is under consideration, pending this evidence and programmatic evaluation.(366)

Immunogenicity

The number of primary doses (2 or 3) did not meaningfully affect geometric mean concentration (GMC) of IgG measured in the second year of life except for serotype 6B.

A booster dose significantly increases the GMCs for all serotypes regardless of the priming schedule.

The PCV dosing landscape analysis provides a systematic review and meta-analysis of immunological response to PCV formulations.(367) IgG GMC was higher following a three-dose primary series, compared to a two-dose series, for all serotypes except serotype 1.(Figure 50a) This measured difference waned by about 12 months of age, when there was no difference between primary dose schedules pre-booster.(Figure 50b) GMCs were significantly higher for all serotypes when a third dose was administered in the second year of life (a 2p+1 schedule) compared to a third dose in infancy (3p+0), as expected since the dose in the second year of life acts as a booster dose. The 2p+1 schedule, in theory, may therefore confer increased protection against serotype 1, longer duration of protection, and more rapid impact of herd immunity because NP carriage among toddlers and older children will perpetuate transmission of pneumococcus in the community. Serotype 6B was different from other vaccine serotypes in that there was improved IgG response post-booster in a 3p+1 schedule compared to a 2p+1 schedule, this difference was not observed for other vaccine serotypes.(Figure 50c) Delaying the initiation of the first primary dose by one month did not significantly impact IgG response post-primary series.(Figure 50d) However, increasing the time between primary doses from 4- to 8-weeks improved IgG response for some serotypes: 6B, 14 and 23F.(Figure 50e)

A 2013 RCT of four different primary immunization schedules in infants in the Netherlands compared the immunogenicity of PCV13 given as 2- or 3- primary doses with varying intervals (four or eight weeks) and age at first immunization.(368) The schedules included in the study were: 2, 4 and 6 months; 3 and 5 months; 2, 3 and 4 months; and 2 and 4 months. At one month post-primary testing, the 2, 4 and 6 month schedule resulted in higher IgG GMCs for serotypes 6A, 6B and 23F compared to the 3 and 5 month schedule. The 2, 3 and 4 and 2 and 4 month schedules had lower GMCs for nine and 11 vaccine serotypes, respectively, compared to the 2, 4 and 6 month schedule. The authors concluded that "older age at vaccinations combined with longer intervals between vaccinations, is important to maintain optimal antibody levels during the period between the primary series and the booster dose."(368) After the booster dose, there were no statistically significant differences in antibody levels for all vaccine serotypes except ST1, which had higher GMCs with the 3 and 5 month primary schedule one month post-booster.(368)

There are some points to keep in mind when interpreting these immunological outcomes. The immunological correlate of protection is agreed to be 0.35 mcg/ml (when measured using the WHO ELISA method), but this does not imply that this should be used on an individual clinical basis. A higher immunological correlate (such as 4-5 mcg/ml) has been shown to correlate with protection against NP carriage.(369) However, it is not believed that the circulating serotype specific IgG is the effector for protection on the mucosal level; instead in immunized individuals these concentrations of IgG likely correlate with other immunologic effector molecules, like B-cells on the mucosa. The true individual threshold of protection will vary by disease syndrome and serotype. In a post-licensure, indirect cohort study of PCV13 in the UK, the threshold for protection was estimated to be higher than 0.35 mcg/ml for serotypes 1 (0.78 mcg/ml), 3 (2.83 mcg/ml), 7F (0.87 mcg/ml), 9V (0.62 mcg/ml), 19A (1.00 mcg/ml), 14

(0.46 mcg/ml) and 19F (1.17 mcg/ml), and lower than 0.35 mcg/ml for serotypes 6A (0.16 mcg/ml), 6B (0.16 mcg/ml), 18C (0.14 mcg/ml) and 23F (0.20 mcg/ml).(179) The aggregate correlate of protection for PCV13 serotypes plus serotype 6C was 0.98 mcg/ml.(179) Immune response also varies significantly by geographical regions with higher IgG responses in children from Asia, Africa and Latin America compared to Europe and North America.(Figure 51) The PCV dosing landscape review adjusted for region in the analyses, but it is difficult to control for all inter-study confounding as many factors are interrelated and so cannot be separated out. For example, it is hard to disentangle the effect of number of doses from the effect of age at immunization and interval between primary doses as these factors are region specific and thus linked. There is thus likely residual confounding, and the findings from North America and Europe cannot be fully extrapolated to other regions due to regional differences.(367, 370)

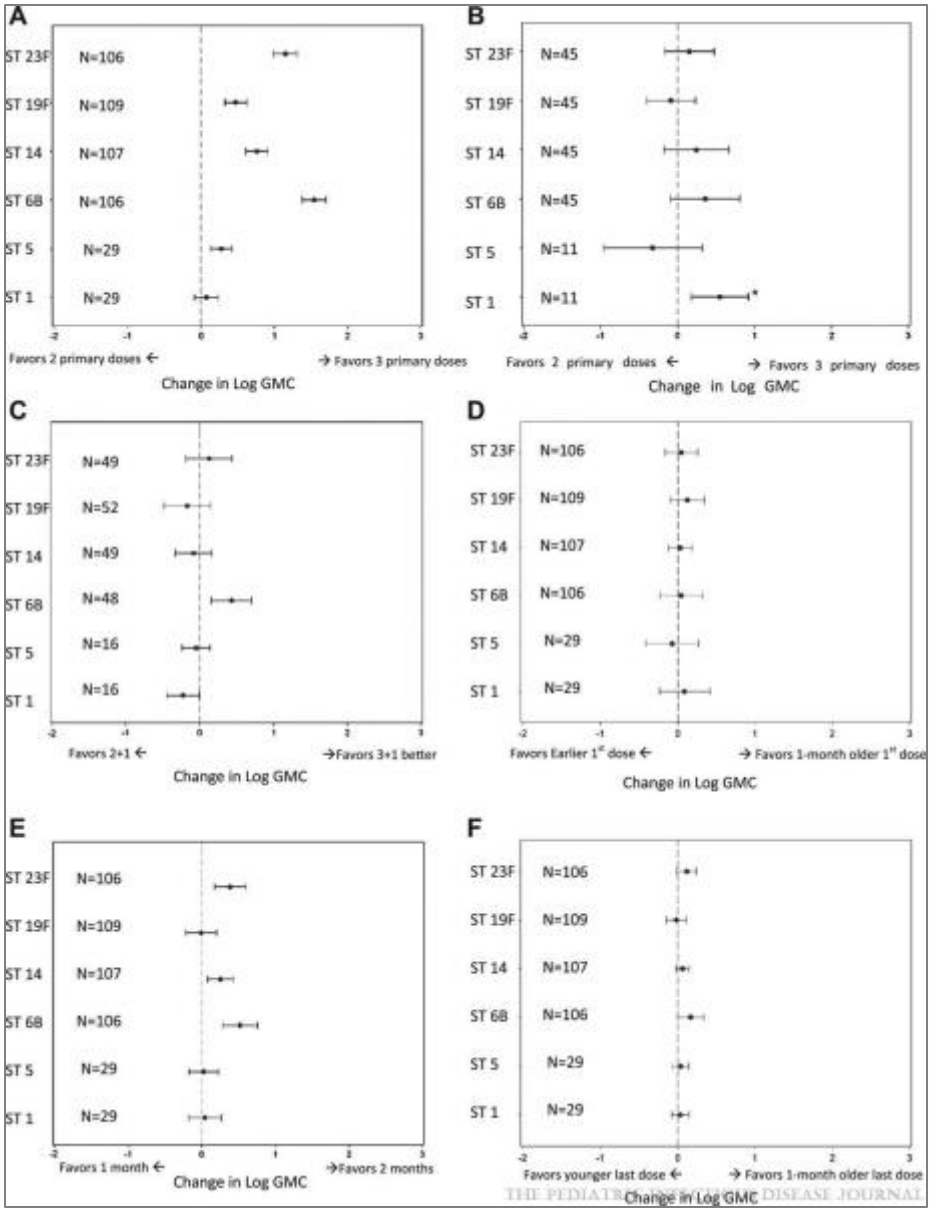
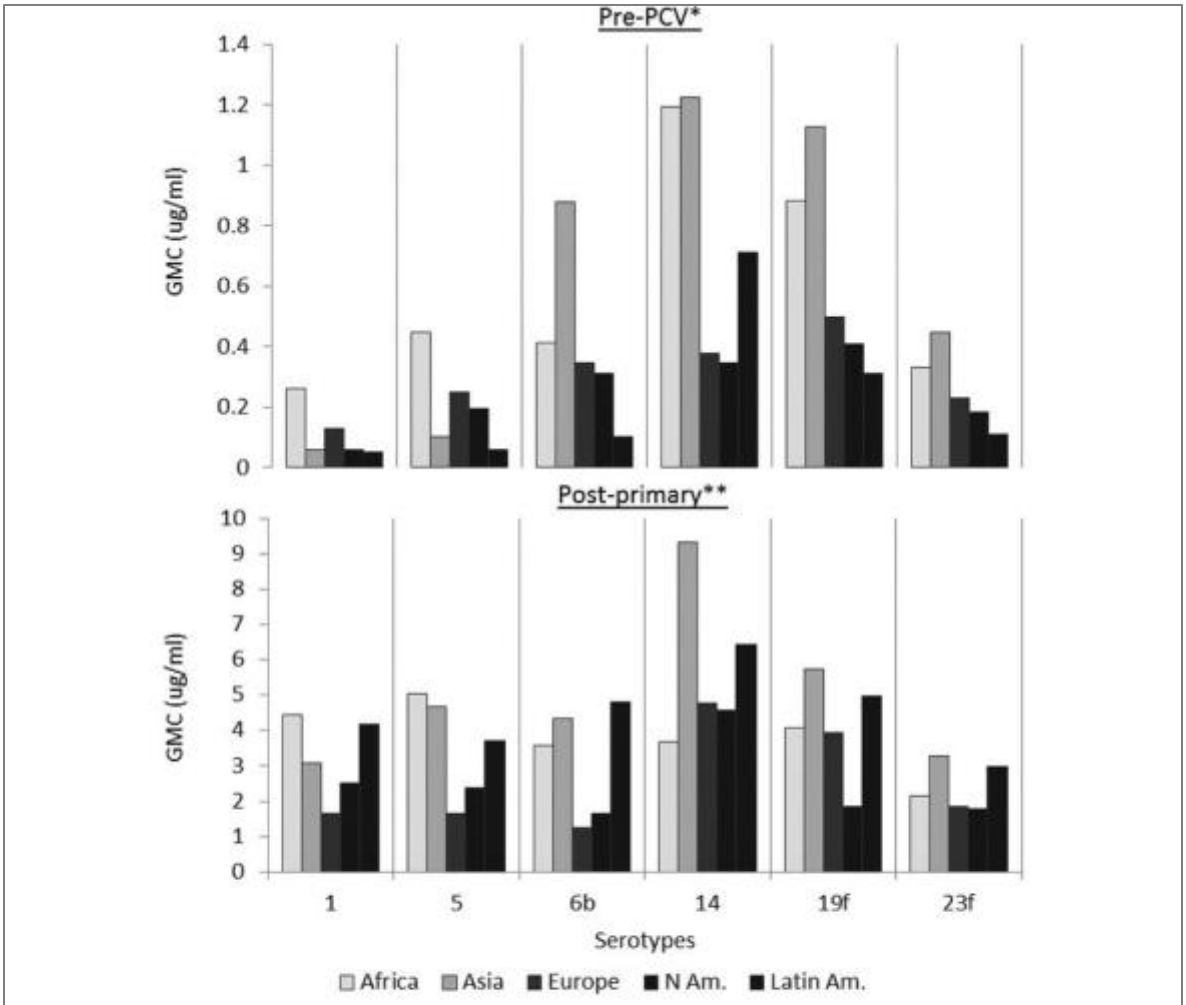


FIGURE 51:. Effect of primary PCV dosing schedule on GMC by serotype. A) 2-dose versus 3-dose primary schedule on postprimary (~7 months) GMC; B) 2-dose versus 3-dose primary schedule on preboost (~12 months) GMC; C) effect of 2-dose versus 3-dose primary schedule on postboost (~13 months) GMC; D) effect of delaying age at first dose by 1 month on postprimary (~7 months) GMC; E) effect of increasing the interval between doses from 1 to 2 months on postprimary (~7 months) GMC and F) effect of delaying age at last dose by 1 month on postprimary (~7 months) GMC. Adjusted for age at first dose, geographic region, PCV product, coadministration of DTaP versus DTwP and laboratory method (GSK vs. Wyeth/other). N is the number of study arms. Asterick indicates that the significant ST1 finding in Figure51B is due to 1 study where the two 2-dose arms had lower GMCs than the two 3-dose arms.33 Otherwise, when looking at other studies, there is no difference.

(367)



*Pre-PCV GMC calculated using the average GMC in children <3m prior to PCV vaccination. N=3, 1, 2, 2, and 1 for STs 1 and 5 in Africa, Asia, Europe, North America, and Latin America, respectively. N= 5, 7, 8-10, 9, and 1 for all other serotypes in the same regions.
** Post-PCV GMC calculated using the average GMC following 3-dose schedules in each region. N=5, 2, 11, 1, and 6 for STs 1 and 5 in Africa, Asia, Europe, North America, and Latin America, respectively. N= 8, 13, 30-32, 10, and 7 for all other serotypes in the same regions. PEDIATRIC INFECTIOUS DISEASE JOURNAL

FIGURE 51: Average pre- and post-PCV pneumococcal IgG GMC in children by serotype and region.(370)

VT-IPD

"Differences between schedules on impact on VT-IPD are difficult to discern based on available data."(7)

The PCV dosing landscape analysis summarized evidence on the outcome of VT-IPD from five RCTs and 31 observational studies. Most studies (75%) provided information on a 3p+1 schedule. All studies used PCV7, PCV9 or PCV11, except one study providing evidence on PCV10; no studies provided evidence on PCV13. In clinical trials, the efficacy of PCV against VT-IPD ranged from 71-83% for a 3p+0 schedule

(based on PCV9 use in two African studies) and 83-94% for a 3p+1 schedule (PCV7 use in the US). A meta-analysis of four 2p+1 schedules (primary doses given at 2 and 4 months or 3 and 5 months) found that the incidence rate ratio of VT-IPD decreased 90% (95% CI 70%, 96%) in children under 2. The meta-analysis included post-introduction surveillance from three different European countries, one to four years post-PCV introduction, and with over 80% vaccine coverage.(371) A recent head-to-head comparison of schedules using PCV10 in Finland found the efficacy of a 3p+1 schedule to be 100% and a 2p+1 schedule to be 92%.(131) In case-control studies and indirect cohort studies, the effectiveness of vaccine ranged from 70-99% for the 2p+0 schedule (ie. partially immunized children), 98-100% for 2p+1, 77-98% for 3p+0, and 81-100% for 3p+1. There is some evidence that a 3p+0 schedule does not protect children with HIV infection as well as HIV-uninfected children, and so a booster dose may be more important in this high-risk group. Ultimately, the authors concluded, delivering all the doses in any given schedule is likely more important than the relative differences between schedules.(7)

Pneumonia

There is "strong evidence of PCV benefit against clinical and radiologically confirmed pneumonia in the age group targeted for vaccination" using 2p+1, 3p+0 and 3p+1 schedules.

There is no discernible difference in the magnitude of impact for different schedules against clinical and radiologically confirmed pneumonia based on reviewed data.(8)

There are numerous outcomes for pneumonia which include pneumococcal pneumonia, or more commonly syndromic outcomes including clinical pneumonia or radiographic pneumonia, both of which might be defined by ICD codes or through a protocol specific case definition. Regardless, except for pneumococcal pneumonia, all pneumonia outcomes are nonspecific for pneumococcus. The 2014 systematic review of pneumonia outcomes included 42 citations: 20 reported on clinical pneumonia, 13 on radiologically confirmed pneumonia, 16 on pneumococcal pneumonia, and 9 on empyema.(8) Most of the studies (88%) were done using PCV7, and 1 study evaluated PCV10. All schedules (2p+1, 3p+0 and 3p+1) reduced clinical and radiologically confirmed pneumonia, and the magnitude of disease impact did not differ among schedules. Sixty percent of studies found a statistically significant reduction in clinical pneumonia and 55% in radiologically confirmed pneumonia. Only two studies provided direct comparisons between two schedules: one study from the US and the other from Australia.

Evidence for the impact of different schedules on the outcomes of pneumococcal pneumonia and empyema varied. All-cause empyema increased in five out of seven observational studies, which the authors attributed to NVT pneumococcus and other bacteria. For pneumococcal pneumonia, 44% of studies found a statistically significant reduction following PCV use. In the PCV dosing landscape review, there was little data from low-income country settings and almost no data on PCV10 or PCV13. The case definitions of clinical pneumonia, radiologically confirmed pneumonia, pneumococcal pneumonia and empyema also varied between the studies and precluded the performance of a meta-analysis.(8) A re-analysis of data from The Gambia PCV9 RCT considered vaccine efficacy against first episode of radiologic pneumonia and found no difference in efficacy when doses were given at one or two month intervals or when the first dose was given at 6 or 10 weeks of age.(372)

Nasopharyngeal carriage

PCV schedules of 2p+0, 2p+1, 3p+0 and 3p+1 all reduce carriage of VT pneumococcus compared to no administration of PCV.

Most studies show no effect of PCV on overall prevalence of pneumococcal NP carriage as there is an increase in the NP carriage of NVT strains following PCV administration.(9)

There is evidence that three primary doses may be better than two doses for reducing VT carriage in the first year of life prior to a booster dose, but this difference is no longer discernible after the first year or following a booster dose. A 3 primary dose schedule (3p+0) is not as good as 2 primary doses and a booster (2p+1) in maintaining decreased VT NP carriage in the second year of life, indicating that the booster dose is important for continued suppression of VT carriage. Receipt of a PPV booster does not appear to further reduce VT carriage beyond the effect of primary vaccination with PCV. The review of NP carriage was based primarily on studies of PCV7, it did not include studies using PCV10 or PCV13. Data on the 2p+1 schedule came from European studies, whereas data on the 3p+0 schedule came from clinical trials in LMICs. These countries have different epidemiological patterns of NP carriage, and these differences confound the impact of different schedules on carriage prevalence. Hence the results from different countries are not directly comparable. There are few studies from Oceania, Latin America and Asia included in the PCV dosing landscape analysis.(9)

Indirect effects

There is a significant indirect effect on reduction of VT-IPD demonstrated with all currently used PCV schedules.

The PCV dosing landscape analysis reviewed data on indirect effects in groups not targeted for PCV administration and the outcomes of VT-IPD, syndromic pneumonia and VT NP carriage. Nearly all studies (95%)—representing all dosing schedules of 2p+1, 3p+0, 3p+1 and 3p+PPV23—demonstrated a decrease in the incidence of VT-IPD in at least one adult age group. The degree of vaccine impact varied by age group and the number of years since PCV introduction. Decreases in VT-IPD were generally greater after three years post-introduction. (Figure 52) Only a 3p+1 schedule was shown to have a significant indirect impact on pneumonia among older children and adults. For VT NP carriage, only the 3p+1 and 3p+PPV23 schedules, studied in the US Native American/Alaskan Native populations and the Australian Aboriginal population, respectively, have shown significant indirect effect.(227) Please note that the summary of evidence is through 2010 and substantial amounts of additional data have been published since then and will be incorporated into an updated section.

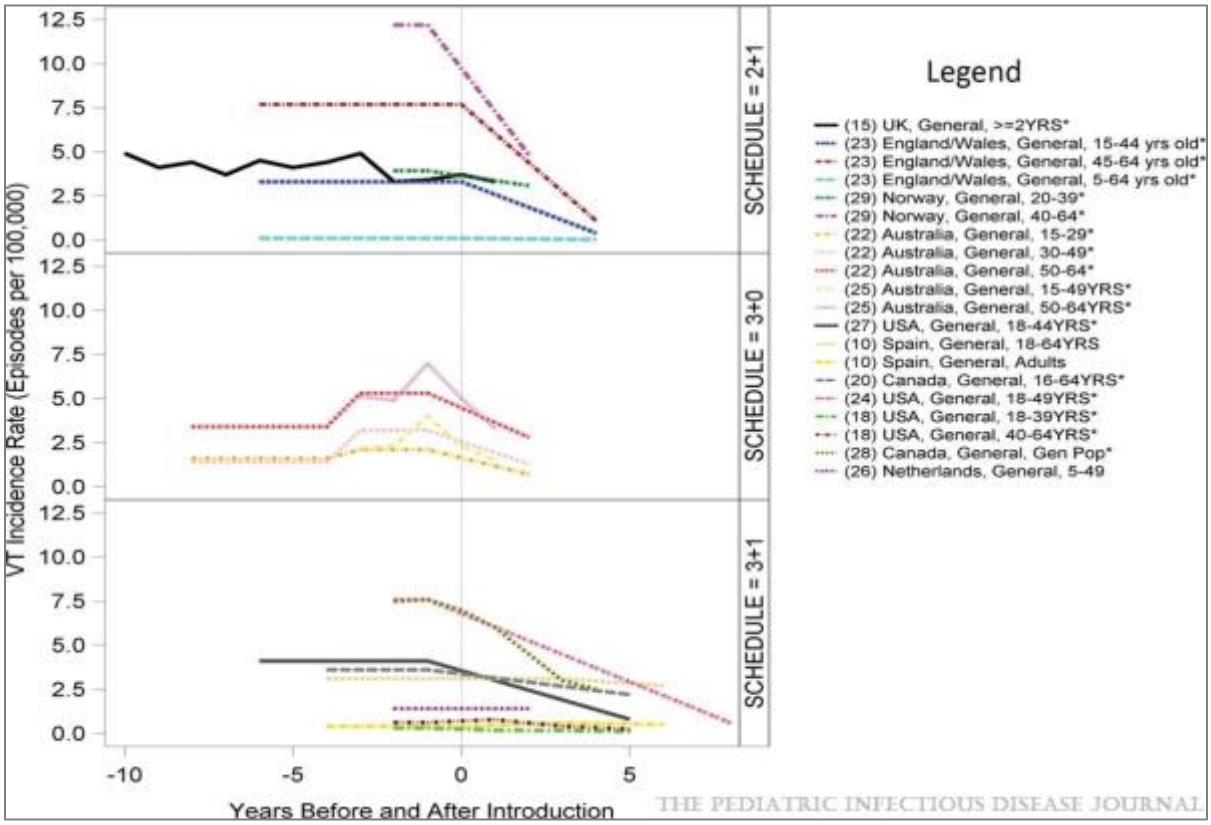


Figure 52: Incidence of VT-IPD among adults before and after PCV introduction, by dosing schedule.(227)

It is important to consider the setting in which a schedule is introduced and additional factors that may contribute to the indirect impact of PCV such as: the vaccine coverage rate, population density, the presence or absence of a catch up campaign, the proportion of the population U5 years of age (i.e. the target population), and the prevalence of HIV. The studies described in the PCV dosing landscape analysis are not directly comparable because these factors vary between countries and study populations. **The dosing review also did not include any studies using PCV10 or PCV13.** Herd effects may take years to fully realize in a population, and many of the studies took place over relatively short periods and thus may underestimate the indirect impact of PCV. Longer follow up studies are now available and in progress, including more studies from low-income countries where the transmission dynamics of pneumococcus differ.(227)

WHO Recommendations on Dosing of PCV

PCV introduction is recommended in all countries and is a high priority in countries with a high U5 mortality rate.

WHO recommends a 3p+0 or, alternatively, a 2p+1 schedule for routine infant immunization.

In 2012 the WHO updated recommendations for the use of PCV10 and PCV13. The WHO "recommends the inclusion of PCVs in childhood immunization programmes worldwide. In particular, countries with high childhood mortality (i.e. under 5 mortality rate of >50 deaths/1000 births) should make the introduction of these multicomponent PCVs a high priority."(10) Both PCV10 and PCV13 are licensed for "active immunization for the prevention of invasive disease, pneumonia and acute otitis media caused by the respective vaccine serotypes . . . in infants and children from 6 weeks to 5 years of age. In addition, PCV13 is licensed for the prevention of pneumococcal disease in adults >50 years of age."(10) For administration of PCV, the WHO recommends either a 3p+0 or, alternatively, a 2p+1 schedule.(10)(Table P) When a two-dose primary is used, there is evidence that an interval between doses of at least 8 weeks is superior to a 4-week interval. (373) Thus the recommended spacing of doses differs in the two- and three-dose primary series.

Table P: WHO recommended dosing options for PCV(10)

Recommended schedules	**3p+0**	**2p+1 (alternative)**
Timing	May begin at 6 weeks of age	May begin at 6 weeks of age, booster between 9-15 months
Minimum interval between primary doses	4 weeks	8 weeks
Considerations	May be preferred if disease incidence peaks <32 weeks of age; preferred if coverage is poor for vaccines given near 1 year of age	Differences might be negligible with herd protection; high antibody level from booster dose may be important for certain serotypes (for example, serotype 1) or duration of protection
High-risk groups	HIV-infected and preterm infants may benefit from a booster dose in second year of life	

Factors to Consider in Dosing Decisions

In choosing between schedules, countries should consider "locally relevant factors including the epidemiology of pneumococcal disease, the likely coverage, and the timeliness of the vaccine doses."(10)

In making dosing decisions, policy makers should consider three fundamental questions:

1. Who is most affected: what is the epidemiology of pneumococcal disease in the country?
2. What schedule will prevent the most disease or deaths: how do the timing of doses overlay with disease epidemiology and mortality risk?
3. What schedule best fits with the current EPI schedule?(374)

The local epidemiology of pneumococcal disease transmission is an important consideration: what are the existing carriage and transmission rates in the community, the age of peak carriage and transmission, and the duration of disease risk?(374, 375) A three-dose primary series may be preferable to optimize protection of infants in the first year of life if that coincides with peak disease risk. It may also be preferable in countries where coverage rates for routine immunizations given late in the first

year or in the second year of life are challenging or uncertain.(7, 374) Booster doses may address disease that peaks in the second year of life.(374) In low-income countries, most pediatric pneumococcal disease and deaths occur in the first half of infancy, with a peak in disease incidence before 6 months of age. In high-income countries, disease peaks closer to 12 months of age. For example, in South Africa the disease peak is 3-6 months of age, and in the US, pneumococcal disease peaks between 12-18 months of age.(374)(Figure 53) However, apart from peak age of disease is the consideration of impact on NP carriage. Evidence favors schedules with a booster dose since there appears to be increased impact on carriage following schedules with a booster compared with those without a booster. So the population wide impact may be greater for 2+1 schedules if the booster dose is administered at high coverage levels.

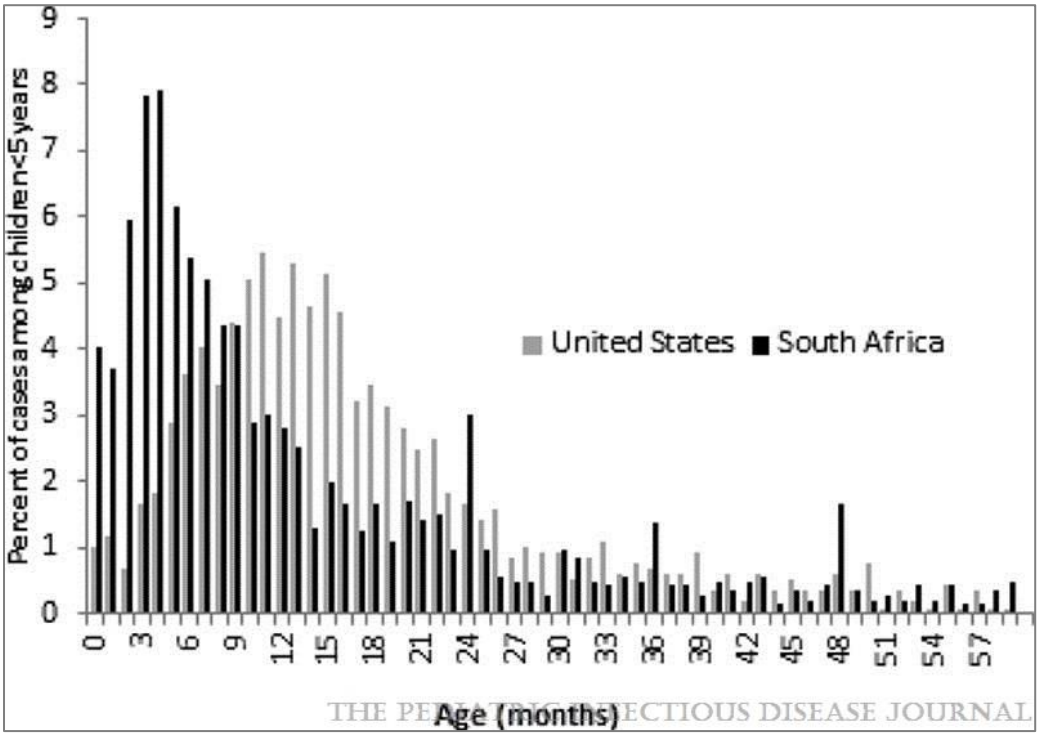


Figure 53: Distribution of cases of IPD for children U5 years, by month of age for children in a developing country (South Africa) and in an industrialized country (United States) [Data are unpublished and from the Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa (GERM-SA), courtesy of Anne Von Gottberg and the US Active Bacterial Core surveillance/Emerging Infections Program Network, courtesy of Matthew Moore.].(374)

There is some variation in schedule effectiveness by serotypes, particularly for serotypes 1 and 5. Serotypes 1 and 5 behave differently: these serotypes can occur in epidemics and are more likely associated with pneumonia. The age distribution of these serotypes is also shifted to older ages. These epidemiological factors suggest that a schedule that includes a booster dose may be more effective against serotype 1 and 5 disease.(374)

Catch up campaigns targeting toddlers can help quickly reduce transmission of VT pneumococci in the community as well as provide protection in an age group still at relatively increased risk for disease.

Findings from a systematic review of studies conducted in LMICs show that PCV administration in older pediatric age groups is immunogenic and significantly reduces VT NPC and VT IPD in immunized children.(376) However, the added benefit of a catch up campaign has not been directly measured.(374) There is one modeling study, based on NP colonization and IPD disease data from Kilifi, Kenya, which provides estimates of the quantitative impact of U1, U2 and U5 catch up schedules. In addition, high-risk subgroups in the population may warrant a different PCV dosing schedule (i.e. a four-dose schedule), while the general pediatric population has a reduced schedule.(366, 374)

The differences between PCV dosing schedules are likely "only relevant early in the course" of a PCV program, "once coverage is sufficient to induce herd effects such differences would likely be minimized and difficult to measure."(374) In mature PCV programs--a few years post-introduction, with good coverage rates and where VT carriages rates have been reduced to low levels--the risk of disease in the period before a booster dose may be sufficiently low (the force of infection, that is the rate at which susceptible persons acquire infection, becomes very low) such that a third priming dose is not important to maintain protection against disease.(375)

From a programmatic standpoint, countries need to consider how best to integrate PCV into existing vaccine schedules and the performance of the vaccine program to deliver high coverage at various ages in order to maximize impact on disease burden.(374, 375) In general, PCV is safe and effective to coadminister with other routine EPI vaccines. There is some evidence of an interaction between PCV and infant coadministration of DTwP and antenatal (maternal) administration of a low-dose diphtheria-containing vaccine. With respect to infant vaccine coadministration, the immune response for serotype 14 was higher when PCV was coadministered with DTaP than when it was given with DTwP.(370) In the UK, efforts to control pertussis led to antenatal administration of a combined vaccine (Repevax, Sanofi Pasteur) containing acellular pertussis, low-dose diphtheria, tetanus and IPV. Maternal receipt of this vaccine was associated with diminished infant response to pertussis, and CRM-containing vaccines.(377) CRM is a naturally occurring diphtheria toxin, and in the presence of higher levels of maternally derived anti-diptheria antibodies, it is postulated that infants may respond less to CRM-conjugated vaccines such as PCV13. This in fact was the case in the UK study for 7 of the 13 PCV serotypes which found diminished GMC titer increases in infants whose mothers received the combined vaccine compared to historical controls. For 10 serotypes similarly high proportions of infants still reached the threshold for the correlate of protection $\geq$0.35 mcg/ml in the maternal vaccine group, however, this was not the case for serotypes 3, 5 and 9V.(377)

The number of injections at a single visit is becoming an issue as the EPI schedule expands and new vaccines are introduced. With the addition of inactivated polio vaccine at 14 weeks of age to the EPI schedule, a number of countries have become concerned about giving three injections at the 14 week visit. Some have done this successfully, such as Albania and South Africa, while others have chosen to move the third PCV dose to a different time, such as Nepal (PCV-2nd dose at 10 weeks in a 2+1 schedule and Bangladesh (PCV-3rd dose at 18 weeks in a 3+0 schedule). As of December 2015, PCVs are administered routinely to infants through national immunization programs in 125 countries. As of January 2016, 30 countries were using a 3p+1 schedule, 60 countries—including 51 Gavi-eligible countries—were using a 3p+0 schedule, and 42 countries—including 2 Gavi-eligible countries (Moldova and Nepal)—were using a 2p+1 schedule. (See figure 54 for map as of July 2015.)

Figure 54: PCV dosing schedules, by country

Source: www.view-hub.org, IVAC, February 2017

Supply Chain and Cold Chain Requirements

Lessons learned from recent new vaccine introductions demonstrate a potential for positive and negative effects on the immunization supply chain.

Constraints of the supply chain are important to assess because overburdening the system can compromise the perceived availability of all EPI vaccines.

Supply chain assessments are an integral part of planning for the introduction of any new vaccine including PCV. The Gavi application requires a cold chain assessment. Depending on the choice of PCV10 or PCV13, the latter being nearly three times the volume per dose, the requirements of cold chain storage and transport will differ. There are computational models available, such as HERMES (Highly Extensible Resource for Modeling Event-Driven Supply Chains) which can help assess capacity at different levels of the vaccine supply chain (http://hermes.psc.edu/home.html). These models have been applied in Niger and Thailand to demonstrate the effect of PCV and rotavirus vaccine introduction, evaluating storage and transport capacity as a factor of delivery frequency.(378, 379) Constraints of the supply chain are important to assess because overburdening the system can compromise the availability of all EPI vaccines, not just the new vaccine introduced.(379)

Lessons learned from new vaccine introductions indicate some potential positive and negative impacts on the immunization supply chain. Introduction of new vaccines can catalyze expansion of the cold chain infrastructure, more often at the national or central level, and increase the use of safe injection equipment.(380) Sometimes these positive effects benefit the broader health system. For example, the use of auto-disable syringes or safety boxes with new vaccines may increase their use during the provision of other health services. Also the expansion of cold chain for other medical products may be considered in conjunction with a new vaccine assessment.(380) However, "existing weaknesses in vaccine forecasting and stock management were sometimes amplified with" new vaccine introductions.(380) In another paper, case studies from six LMICs revealed that new vaccine introduction had no impact on forecasting and procurement of vaccines and injection supplies, stock management, wastage rates or cold chain management. New vaccine introduction was accompanied by stock outs of the new vaccine in all routine introduction cases either because "demand exceeded expectations or a catch-up strategy had not been incorporated into forecasting predictions." These stock outs resulted in public perception that all EPI vaccines were not available, and so families may have stayed away and missed other routine immunizations that were in stock.(381)

Training of Staff

Trained staff should communicate to caregivers that vaccinated children may still get pneumonia due to other pathogens, and if so, children need to be evaluated by an appropriate health care provider to avoid complications or death.

Side effects following PCV administration are mild, such as soreness at the site of injection and transient fever, and serious adverse events extremely rare.

The WHO helps provide guidance on content for training of staff in conjunction with a new vaccine introduction. There are two handbooks available online specific for the training of district and health facility staff for the introduction of PCV10 http://apps.who.int/iris/bitstream/10665/90378/1/WHO_IVB_13.09_eng.pdf and PCV13 http://apps.who.int/iris/bitstream/10665/90380/1/WHO_IVB_13.10_eng.pdf. In general, training of health staff should include:

- "Basic knowledge of the disease targeted by the new vaccine, and the potential impact of routine childhood immunization on disease burden (e.g. meningitis, pneumonia . . .)
- Knowledge of clear take-home messages for parents and guardians, e.g. when to return for the next dose, normal side-effects and management, severe adverse events in the event of which the child should be taken to the health facility or nearby hospital.
- Vaccine safety and the public's perception of safety which could influence vaccine demand.
- Transport, storage, preparation and administration of vaccine, including an understanding of the impact of inappropriate storage and handling; familiarity with vaccine reconstitution (if applicable), and use and disposal of auto-disable . . . syringes."(382)

Handling of PCV should reinforce the temperature range for maintaining vaccine potency (2 -8 degrees Celsius). The "shake test" can be performed to check if the vaccine has been frozen. Besides freezing, heat exposure reduces the vaccine potency and so the Vaccine Vial Monitor(VVM) should be checked.(112) Figure 55 is an example of a refrigerator sticker for PCV10 from the WHO handbook.(112)

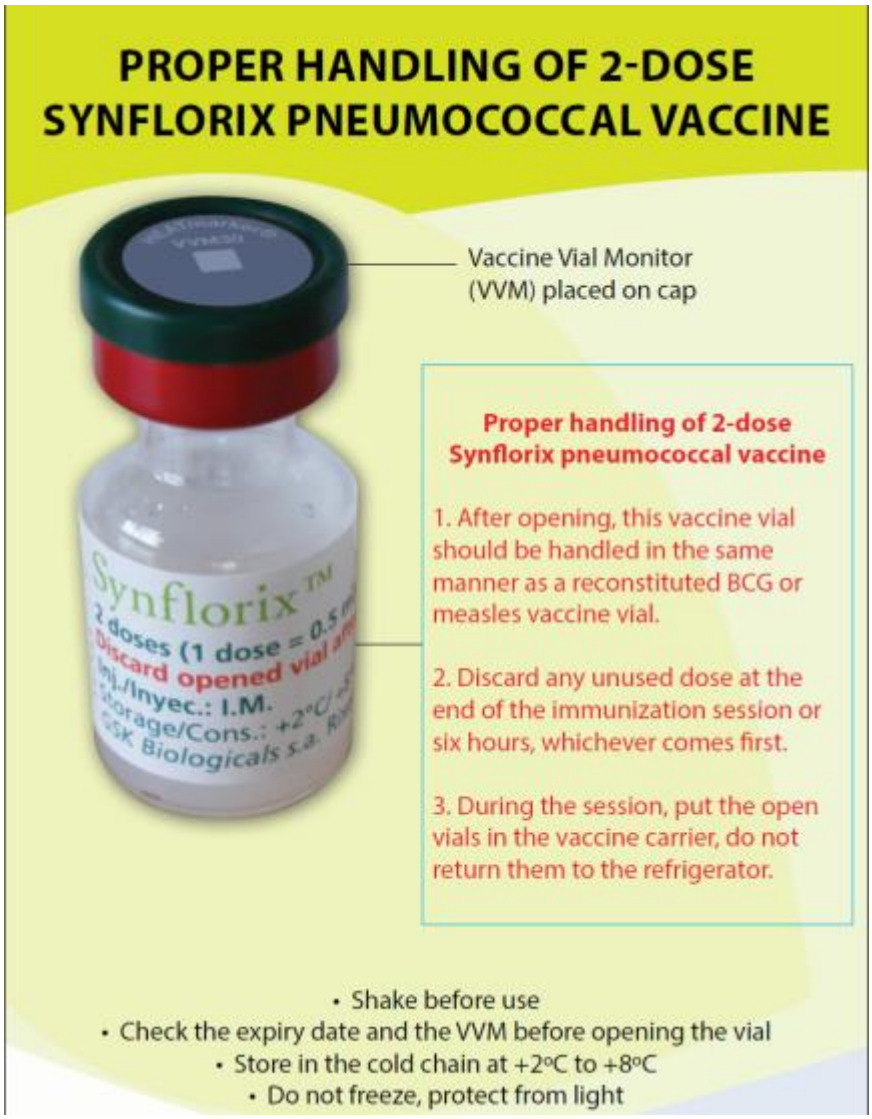


Figure 55: Example of a refrigerator sticker for PCV10(112)

The side effects of PCV are mild and include soreness at the injection site and transient fever in less than 5% of vaccinees. Other side effects include local reactions that have been reported in 10-20% of vaccinees, only about 3%, however, were considered severe, such as "tenderness that interferes with arm or leg movement."(112, 113) Health staff should also be familiar with other important key messages for parents regarding the risk of pneumonia, even with vaccination, and appropriate care seeking for signs of pneumonia:

- "Children who have received pneumococcal vaccine may still get pneumonia or meningitis from other pathogens however both these diseases will occur less frequently in immunized children.
- If your child has severe cough or difficulty breathing or any other severe illness, always take your child immediately for assessment by a qualified health professional. Early treatment of pneumonia can prevent complications and death. This is also true for children who have received all their vaccines." (112, 113)

Accurate parental education can help "avoid misunderstandings and frustrations later on when people continue to present with diseases not covered by the vaccine."(11) In a summary of 11 post-introduction evaluations of PCV introduction in African countries, two findings pertain to staff training:

- "Health worker knowledge that PCV provides protection against only one cause of pneumonia was crucial to ensure that they educated caretakers on other options for prevention and treatment of pneumonia.
- Weaknesses in the underlying capacity of the immunization systems included needs for innovative training approaches to address the complexity of messages relating to use of new vaccines. . . ."(13)

Staff training should also cover the reporting of adverse events following immunization (AEFI). AEFI is a "medical incident, usually severe, that occurs after an immunization and is believed to be caused by the immunization."(382) AEFI following PCV administration is "extremely rare," but "sensational media coverage may seriously undermine immunization activities."(112) Program managers must therefore have a plan for a special communication strategy regarding AEFI and staff should be trained on correct reporting and investigation of an AEFI. The rates of AEFI with PCV use and the PCV safety information sheet can be accessed at http://www.who.int/vaccine_safety/initiative/tools/Pneumococcal_Vaccine_rates_information_sheet.pdf?ua=1.

Lessons learned from other new vaccine introductions shed light on some of the effects on staff training. Positive effects of new vaccine introduction, as found in six case studies from LMICs, included skills strengthening through training and boosting of staff morale. One negative effect was a temporary increase in staff workload around the time of introduction. (381) New vaccine introductions also strengthened disease surveillance systems with enhanced surveillance for diseases prevented by the new vaccines in some countries and improved awareness and reporting of AEFIs.(380)

Financing Options

The Pneumococcal Advanced Market Commitment (AMC) created in 2009 provides an innovative finance mechanism to incentivize the scaling up of PCV production to meet developing country needs.

Both manufacturers of pre-qualified PCV products (Pfizer and GSK) have applied and had their products accepted as part of the AMC.

Eighty percent of Gavi-eligible countries have applied for support to obtain PCV10 or PCV13 at reduced cost.

Financing issues are most complicated and difficult for lower middle-income countries that are just above the Gavi-eligibility threshold. These countries are left out of the financing and AMC pricing agreements and yet are not well-resourced to finance PCV independently on the open market.(11)

In 2009 the Advanced Market Commitment (AMC) for pneumococcal vaccine was established. This was a pilot AMC. Donors pledged a total of US$1.5 billion to fund the AMC to accelerate the development and availability of pneumococcal vaccines that meet developing country needs and accelerate vaccine uptake.(383) The AMC provides an innovative finance mechanism to incentivize the scaling up of PCV production to meet developing country needs by guaranteeing the initial purchase price for a specified quantity of PCV. Both PCV10 and PCV13 have been approved as eligible AMC vaccines that meet the Target Product Profile for developing country needs. Gavi forecasts set a goal of procuring 200 million doses annually by 2015 with AMC funds.(384) Six vaccine supply agreements made with GlaxoSmithKline and Pfizer have spent 73% of the AMC funds, US$1.14 billion, on a contracted supply of 1,460 million doses of PCV to be provided through 2024.(383) In 2014, AMC funds were used to procure 100 million doses of PCV, up from 58 million doses procured in 2013.(385)

According to the terms of the AMC, the price of PCV10 and PCV13 paid to manufacturers is US$3.50 per dose, the "tail price," which is meant to cover the incremental production cost of vaccine.(384) For a specified number of doses, the price to the supplier will be topped up by another $3.50/dose to US$7.00 by AMC donor funds. The number of doses procured at this premium price is capped by the proportion of the total forecasted doses (200 million doses annually) that the vaccine manufacturer is supplying.(361) So, for example, if a supplier has committed to provide 30 million doses annually (15% of the 200 million doses), the supplier will receive 15% of the AMC funds paid as the additional US$3.50 per dose topped up price for a set number of doses.(384) Recent supplier agreements have reduced the tail price of PCV10 and PCV13 to US$3.40 and US$3.30, respectively.(383) The AMC also stipulates that PCV must be procured through the UNICEF Supply Division to obtain the agreed price. As of March 2015, 59 out of 73 Gavi-eligible countries have applied for Gavi support to introduce PCV: 58 countries have been approved, and 50 countries have introduced PCV, with ten countries introducing the vaccine between April 2014 and March 2015.(385)

Eligibility for Gavi support and a country's co-financing contribution is based on per capita GNI. For low-income countries, those with a GNI less than US$1,045 per person, the country must co-finance US$0.20 per PCV dose. Intermediate Gavi-eligible countries, with GNI between US$1,045-US$1,580 per person, start co-financing at US$0.20 per dose with a 15% annual increase. Countries with a GNI above US$1,580 graduate from Gavi support. Graduating countries pay an additional 20% of the difference between their initial co-financing amount and the projected price of PCV in the year Gavi support ends, so that in five years they become responsible for the full tail price cost of PCV. Gavi honors all existing approved multi-year commitments to graduating countries for the duration of the multi-year plans. So for example, a graduating country would still be able to pay the AMC negotiated tail price of PCV for the duration of its original Gavi-approved plan.(386, 387) In July 2015, Gavi adopted a new approach to graduation to strengthen support for countries to achieve financial and programmatic sustainability. Gavi will continue to provide support for already introduced vaccines, with the application of the co-financing policy applicable to graduation. Countries entering graduation also have an additional year to apply for Gavi new vaccine support. Gavi will honor all existing multi-year commitments for health systems strengthening support to countries in the graduation phase. New or renewed health system strengthening support may be available to graduating countries with pentavalent vaccine dose 3 coverage below 90%.(388)

Gavi policy also provides access to AMC-priced PCV to countries that are no longer eligible for full support. Countries that were Gavi-eligible in 2003 will have access to PCV through Gavi under the terms

and conditions of the AMC. These countries, however, will have to pay the tail price for PCV from the outset. As of March 2014, only one country, Mongolia, has been approved for this type of access to reduced cost PCV.(383)

In addition to the AMC, the international finance facility for immunization (IFFIm) is another innovative financing mechanism to increase funds available to Gavi in support of new and underused vaccine uptake in developing countries. The IFFIm "is a funding mechanism through which long-term, legally binding commitments are made by donors to support the sale of long-term bonds in international capital markets."(11) The IFFIm has raised about US$2 billion for Gavi expenditures.(11)

Other options for reducing vaccine cost include pooled procurement and supply-side approaches. Procurement of vaccine at reduced cost is made possible through the Pan American Health Organization (PAHO) revolving fund and through the UNICEF Supply Division.(11) UNICEF procurement services has a multi-year middle income country (MIC) new vaccine tender that has been of limited success in securing affordable vaccine supply for MICs.(389) Five non-Gavi eligible and 28 Gavi-eligible MICs have participated in the UNICEF procurement services. Feedback from manufacturers on UNICEF pooled procurement has indicated that there is a need for greater certainty in demand forecasts and a desire for manufacturers to establish relationships with governments directly for a more long-term transition to self-procurement.(389) There is also an example of a technology transfer agreement between a middle-income country and a manufacturer. Brazil has agreed to purchase US$2.2 billion of PCV10 from GlaxoSmithKline over an 8-year period in exchange for technology transfer that will eventually allow Brazil to manufacture the vaccine for itself.(11)

Financing issues are most complicated and difficult for countries that are just above the Gavi-eligibility threshold, lower middle-income countries. These countries are left out of the financing and pricing AMC agreements and yet are not well-resourced to finance PCV independently on the open market.(11) This gap is evinced by the low proportion of lower middle -income countries that have introduced PCV without Gavi support.(13) These countries will need to be a "major focus of efforts (to) assure access to vaccines "in the upcoming years.(11)

In addition to the two PCV formulations that are WHO pre-qualified and eligible based on the AMC Target Product Profile, two other manufacturers have registered for inclusion in the pneumococcal AMC. These two manufacturers are Panacea Biotec Limited (India) and Serum Institute of India. Several PCV products from both multinational and developing country manufacturers are in development, and their entrance into the market could take pressure off the current pricing and somewhat reduce cost. However, as these are complicated products to manufacture, the likely prices will still be above what might be perceived as an ideal target price for vaccine of US$1 per dose.

Recent articles published on lessons learned from new vaccine introductions reveal some insights into financing options. In case studies of six LMICs, "the impact of . . . new vaccines on domestic and external financing was viewed positively."(381) While domestic funding met co-financing requirements, operational budgets, however, often did not change and there were some concerns regarding the financial sustainability of the new vaccine commitment.(381) A literature review on new vaccine introductions also found concern about long-term financial sustainability and over-reliance on donor

funding. "Collateral expenses" related to new vaccine introductions were often "not adequately anticipated or budgeted."(380) On the positive side, countries were often able to meet short-term changes to provide co-financing and funding for safe injection equipment. "There was (also) some evidence of reduced expenditures for the health system since (new vaccines) contributed to a reduced need for" health care visits and reduced costs of treating disease and responding to disease outbreaks.(380)

Vaccine Program Evaluation

A post-introduction evaluation (PIE) is a systematic, qualitative assessment of vaccine introduction on multiple levels of a country's immunization program and can reveal important areas for improvement.

Equitable coverage, as well as high coverage, in all districts and communities is a key intermediate goal of the vaccine program.

New vaccine introduction can be a vehicle for both positive and negative impacts on the broader health system. There are principles to help guide vaccine introduction planning to maximize its beneficial impact.

Measuring the performance and impact of the PCV immunization program is an important part of planning for vaccine introduction. Program process indicators can include criteria such as: the presence of a legal framework or legislation that guarantees immunization financing, the presence of an independent technical advisory group on immunization policy, the efficacy of vaccine delivery and equity of coverage such that 80% of children in every district are immunized, and the vaccine drop-out rate.(100) The WHO has developed a post-introduction evaluation (PIE) tool to help conduct a systematic, qualitative assessment of vaccine introduction at multiple levels of the health system. The PIE tool is available online at: http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.03_eng.pdf. The PIE is an "evaluation of the overall impact of the introduction of a new vaccine(s) on a country's national immunization programme. It focuses on a range of programmatic aspects, such as pre-introduction planning, vaccine storage and wastage, logistics of administering the vaccine, and community receptiveness to the vaccine."(382)

Post-introduction evaluation (PIE) of PCV in Rwanda: Lessons Learned

Rwanda was the first country in sub-Saharan Africa to introduce PCV with support from Gavi in April 2009. It conducted a PIE one year later, and some of the lessons learned were:

- "New vaccine introduction requires a lead time of at least 12 months, a decentralized system of primary health care, and staff trained and responsible at the operational level.
- New vaccine introduction can require an increase in vaccine storage capacity. To do this, it is indispensable to organize an evaluation of the cold chain storage capacity, to identify the real needs and to determine the gaps which must be closed to accommodate the new vaccine.
- New vaccine introduction requires prior training of all personnel participating in vaccination activities, not only for the vaccine in question but also for all technical areas of vaccination to insure quality services.
- To assure parental acceptance, new vaccine introduction requires the development of key message(s) which take into account parental concerns.
- Taking account of the high costs of new vaccines, advocacy with the political authorities is indispensable to securing new vaccines (co financing)."(1)

The immediate, quantifiable outcome measure in vaccine delivery is achieving high, equitable coverage rates. PCV vaccine coverage is calculated as:

$$\frac{\text{Number of children receiving PCV1 (or 2 or 3)} \times 100}{\text{Number of surviving infants}}$$

(382)

The PCV coverage rate can be compared with the DTP coverage rate to help assess if any differences are a function unique to PCV delivery or a larger, systematic issue. Drop-out rates are defined as the "difference in the percentage of children who start, and those who complete the schedule of a particular vaccine," and are important in "measuring vaccine uptake and programme inefficiencies."(382)

$$\text{Pneumococcal drop-out rate} = \frac{(\text{PCV1} - \text{PCV3 vaccinees}) \times 100}{\text{PCV1 vaccinees}}$$

PIE of Pneumococcal and Rotarix vaccines in Botswana 2013: Recommendations and Lessons Learned

Botswana introduced both PCV and Rotarix in July 2012 and conducted a PIE in 2013. Some recommendations and lessons learned from this evaluation are as follows:

Recommendations

- "Pre-implementation planning and vaccine introduction: provide adequate reference materials to districts for guidance; update recording and reporting tools; develop introduction plan based on the national plan to guide district implementation.
- Training: provide regular refresher training and increase duration of training at sub-national levels; provide practical demonstrations during training.
- Vaccine coverage: provide updated target population figures for the sub-national levels; retrain districts on RED (Reaching Every District) and DQS (Data Quality Self-assessment) and support implementation.
- Cold chain management: monitor vaccine fridge temperatures in districts and health facilities twice daily including weekends; use freeze watch/freeze tags during vaccine transportation.
- Vaccine management, transport and logistics: conduct refresher training on vaccine management at sub-national levels; ensure that all expired vaccines are handed over to the relevant authorities for destruction.
- Advocacy and communication: conduct national and district launches for new vaccines and supply adequate IEC (information, education and communication) materials to sub-national levels; train health workers on interpersonal communication
- Surveillance: find long term solutions to revamp Pneumonia and Bacterial Meningitis sentinel surveillance"

Lessons Learned

1. "Availability of local evidence of disease burden, strong political will and effective stakeholder engagement are necessary requisites for introduction of new vaccines.
2. Adequate planning, mobilization of sufficient resources and close monitoring are critical for smooth implementation of new vaccines particularly multiple vaccines.
3. Communication and social mobilization are essential so that health workers and communities are well informed and . . . mobilized for immunization services and new vaccines in particular.
4. Use of Balanced Score Card in MOH (Ministry of Health) at national level to monitor immunization performance at sub-national levels on a quarterly basis is a good practice."

Source: Botswana Ministry of Health, UNICEF, Organization WH. 2013 Botswana: post-introduction evaluation of pneumococcal and Rotarix vaccines in Botswana UNICEF2013 [cited 2015 January 12]. Available from: http://www.unicef.org/evaldatabase/index_72935.html

As reported in 2013, in countries that had introduced PCV at least two years prior, the median coverage for three doses of PCV (PCV3) was 90% (range 1-99%). The median coverage was 92% among high-income countries, 76% among upper middle-income countries, 44% among lower-middle income countries, and 95% among two low-income countries.(13) Taking into account countries that have introduced PCV as well as those which have not, in 2013, it was estimated that 25% of infants worldwide received PCV3. This vaccine coverage rate varied by region from 0% in South-East Asia to 77% in the Americas.(390) Updated WHO/UNICEF data from 24 Gavi-eligible and graduating countries in January 2015 indicate that two years after PCV introduction, the coverage of PCV3 ranged from 23% to 98%, with a median value of 88%.(391) Coverage of other routine vaccines do not appear to change after introduction of PCV in four countries reported as case studies in a 2014 descriptive article, though health staff perceived a positive impact on vaccine coverage.(381) In 11 post-introduction evaluations from African countries, a key finding documented was the need for "accurate data to define target populations, accompanied by clear messages to health workers and the community to prioritize those target populations."(13) Indeed, it is becoming increasingly evident that equitable coverage is a key component of program success, and immunization can be a "front runner" to lower equity gaps in other maternal and child health interventions.(392) According to the WHO, "almost 70% of incompletely vaccinated children worldwide live in only 10 countries (50% live in only 3 countries), highlighting inequity among countries."(390) The three countries contributing the most to the number of children incompletely vaccinated are India, Nigeria and Pakistan. IVAC conducted a landscape analysis of routine immunization in Nigeria and findings are presented below in the box. Two-thirds of countries achieved the GVAP target of 90% DTP3 coverage nationally, but fewer than one-third achieved over 80% DTP3 coverage in every district, an indication of in-country disparities.(390) The Reaching Every District (RED) Strategy, launched by the WHO and UNICEF in 2002, aimed to scale up coverage above 80%. Now ,the Reaching Every Community (REC) strategy is aiming to bring the focus to the sub-district level to really examine which groups are being left behind in planning for and actualizing high coverage rates.(15)

While vaccine introduction has positive and negative impacts on the national EPI program, there is a "possibility for immunization programmes to demonstrate impacts on wider health system strengthening, by acting where possible as a platform for delivery of a wider range of health delivery service packages."(15) While "the effect of immunization programmes will be enhanced by their integration as a core component of primary health care," there is a tension between the pressures to meet "short-term goals" and making long-term efforts to "establish and sustain strong systems for vaccine delivery, surveillance and monitoring."(11) Lessons from PIE and new vaccine introductions has revealed that "opportunities for strengthening the broader health system were consistently missed" during new vaccine introductions; and future vaccine introductions should "explicitly consider and plan to optimize and document the impact . . . on broader health systems."(393) An ad-hoc working group reporting to the WHO's Strategic Advisory Group of Experts on immunization (SAGE) in April 2012 articulated the following principles that should ideally guide new vaccine introductions to ensure a broader impact on the health system:

1. "A strong, country-led, evidence-based decision-making, planning and prioritization process that is accountable and coordinated with other components of the health system.
2. A well-performing or improving and responsive immunization programme.
3. Seizing the opportunity to achieve:
    a. A well-trained and motivated workforce
    b. Quality education and communication about the new vaccine for the health workforce and community
    c. Functional cold storage, logistics and vaccine management systems

d. Safe immunization practices and monitoring of adverse events
e. High-quality monitoring and evaluation, including disease surveillance and immunization coverage monitoring
f. Resource, performance, and management accountability.

4. Maximizing opportunities to deliver vaccines as integral components of comprehensive health promotion and disease prevention and control efforts so that vaccines are delivered as part of a package of effective, feasible, and affordable interventions based on national contexts.
5. Sufficient allocation of human and financial resources to introduce the new vaccine and sustain its use without adversely affecting other programmes and services.
6. A safe and efficacious vaccine that is appropriate for local use and is available with an uninterrupted, sufficient supply."(380)

Landscape analysis of routine immunization in Nigeria: findings from the IVAC study

In 2011 IVAC conducted a landscape analysis to identify key barriers to routine immunization coverage in Nigeria and a range of potential high-impact solutions. DTP3 coverage was estimated at 69% nationally in 2010—below the average for African countries—and there is significant coverage heterogeneity among states. Thirty key barriers in six domains were identified, and proposed interventions address these barriers.

Intervention Package Components & Targeted Barriers

Intervention Package	Potential Components	Barriers Targeted
Financing and Vaccine Security	• Financial guarantees • Re-designating vaccine budget line from capital to recurrent • Creation of a basket fund • Flexible funding for vaccine logistics	• Vaccine stock-outs • Delay in release of budgeted funds • Inadequate funding, esp. at LGA level • Low access to hard-to-reach communities
Transport	• Transportation contracts • Vehicle procurement and distribution	• Vaccine stock-outs • Transportation challenges at peripheral points • Low access to hard-to-reach communities
Cold Chain	• Provision of solar fridges • Maintenance contracts • Satellite cold storage centers	• Vaccine stock-outs • Inadequate cold chain capacity • Poorly maintained equipment • Overly long links in supply chain
Performance Management	• Results-based financing • Data checks • Mid-level management training • SMS reminders to staff	• Poor accountability • Administrative data are not reliable or valid • Data are not used for decision-making • Poor performance management • Low morale • Staff shortages • Inefficient distribution of staff
Advocacy and Leadership	• State Primary Health Care Development Agencies (SPHCDAs) • Transition period from donor to gov't funding • Targeted state-level advocacy • Collaboration with traditional leaders	• Poor accountability • Disconnect of responsibility, authority, and capacity • Poor performance management in settings where vaccine supply is adequate, • Non-sustainable financing of donor projects • Inadequate funding at all levels • Lack of community engagement • Demand-side barriers
Demand Creation	• SMS reminders to parents • Vouchers to pay for future health services • Conditional cash transfers	• Demand-side barriers

Source: Wonodi C, Stokes-Prindle C, Aina M, Oni G, Olukowi T, Pate MA, Privor-Dumm L, Levine O. "Landscape analysis of routine immunization in Nigeria". IVAC 2012. Available at: http://www.jhsph.edu/research/centers-and-institutes/ivac/projects/nigeria/IVAC-Landscape-Analysis-Routine-Immunization-Nigeria-Brief.pdf. Accessed July 1, 2015.

Disease Surveillance and Measuring Impact Post-Introduction

High-quality surveillance provides valuable insight into program performance and disease epidemiology post-introduction, but the lack of a surveillance program should not be an impediment to PCV introduction.

There are different types (or tiers) of surveillance, and the method employed will determine the metrics that can be obtained. Limitations of the data and methodology should be considered to carefully interpret and draw conclusions on program performance and impact.

Ultimately, the measure of vaccine program performance is a reduction in the burden of preventable disease. Vaccine impact assessment "measures changes in outcomes that are attributable to a public-health intervention or programme, in this case, changes in pneumococcal . . . disease following" PCV introduction. Impact assessment includes both the vaccine's direct effect and indirect effect.(394) The WHO has a manual to help countries plan to measure PCV impact using a variety of possible methods: http://apps.who.int/iris/bitstream/10665/75835/1/WHO_IVB_12.08_eng.pdf. The WHO position paper on PCVs states: "high-quality surveillance should be conducted in selected countries and defined populations that represent different epidemiological profiles worldwide. Surveillance of disease incidence should begin at least 2 years prior to PCV introduction and continue for at least 5 years post-introduction. However, lack of population-based surveillance should not be an impediment to PCV introduction."(10) The objectives of high-quality surveillance are:

1. "Demonstrate the burden of confirmed pneumococcal . . . disease and also clinical syndromes caused by the bacteria.
2. Provide data for evidence-based decision-making regarding the introduction and sustained use of PCV. . . .
3. Monitor for problems within vaccination programmes (e.g. an increase in disease incidence could be due to a breakdown in the cold chain, suboptimal coverage or lack of vaccines).
4. Establish epidemiological patterns of pneumococcal . . . disease after vaccine introduction, including changes in serotype distribution."(394)

Informing trends in serotype replacement, surveillance is particularly important for diseases caused by organisms with "antigenic diversity, such as pneumococcus."(11)

Key decisions regarding case definition, the age of persons to be surveyed, and the type of surveillance determine the kind of information provided by surveillance and its interpretation. Case definitions can be based on microbiological confirmation of *Streptococcus pneumoniae* from a normally sterile site, or syndromic disease based on a constellation of symptoms. A proposed hierarchy of syndromes for surveillance is as follows: meningitis (suspected, probable bacterial and definite bacterial), pneumonia (probable, radiologically confirmed, probable severe, radiologically confirmed severe, probable very severe, and radiologically confirmed very severe), very severe disease (sepsis and other life-threatening syndromes), bacteremia, and other.(51) A suggested target age group for surveillance is children from 2 months to <60 months of age. The WHO provides guidance on estimating the potentially preventable disease burden in country by employing the formulas:

> Estimated number of severe IPD cases that can be prevented= expected vaccine effectiveness x national PCV3 coverage x national estimate of VT-IPD cases (obtained from GDB estimates or local data)

Estimated number of IPD deaths that can be prevented = expected vaccine effectiveness x national PCV3 coverage x national estimate of VT-IPD deaths (obtained from GDB estimates or local data)(394)

WHO recommends a tiered approach to surveillance of invasive bacterial vaccine preventable disease such as caused by pneumococcus. The invasive bacterial vaccine preventable disease (IB-VPD) surveillance network was established in 2008 with 90 sentinel hospital sites in 36 countries. The IB-VPD network has expanded to include 150 sites in 58 countries in 2012.(395) There are three tiers of surveillance. The first tier is hospital-based sentinel surveillance for all children with suspected meningitis U5 years of age. This is based on the collection of CSF for microbiological testing. The second tier is hospital-based sentinel surveillance for all children U5 with meningitis, pneumonia or sepsis. This is based on the collection of CSF and blood. The limitation of hospital-based sentinel surveillance is that it is not easy to assess vaccine impact, there are small numbers of cases, and the denominator (the true catchment population) is unknown so incidence of disease cannot be determined.(394) In addition, "care-seeking behavior in the population, referral practices to the (sentinel sites), and case-ascertainment practices within each hospital" influence surveillance findings.(51) The third tier of surveillance is active population-based surveillance that provides the most accurate method of monitoring disease trends. This type of surveillance, where the denominator (population size) from which cases are detected is known, allows incidence rates to be calculated.(394) Table Q describes suggested metrics for quantifying vaccine impact based on surveillance data.

Table Q: Suggested metrics to demonstrate vaccine impact from surveillance data(394)

Metric	Calculation/method	Comment
Percent reduction in incidence of pneumococcal disease: all serotypes and vaccine serotypes	Incidence rates: incidence of bacterial disease is calculated by dividing the number of children <5 years with the disease from the hospital catchment area by the total number of children <5 years from the hospital catchment area. Percent reduction: compare each post-introduction year incidence rate to the baseline pre-vaccination rates.	Data obtained by conducting active population-based surveillance; passive population-based surveillance may be used but the data must be cautiously interpreted as cases of the disease are likely to be missed. Recommend data collection for at least 2 years pre-vaccine introduction and 3 years post-vaccine introduction. If pneumococcal serotype distribution is assessed, data collection is recommended for 5 years post-vaccine.
Percent reduction in the number of cases of pneumococcal disease	Percent reduction: compare each post-introduction year case count to the baseline pre-vaccination rate.	Data obtained by conducting sentinel surveillance or active population-based surveillance. It is important to note that an absolute decrease in pneumococcus resulting from vaccine use will necessarily cause an increase in the proportion of other bacterial etiologies of probable bacterial disease.
Percent reduction in the proportion of meningitis cases that are pneumococcus	Percent reduction: compare the percentage of pneumococcus cases among all laboratory-confirmed cases in the pre- and post-vaccine years.	Data obtained by conducting sentinel surveillance or active population-based surveillance. It is important to note that an absolute decrease in pneumococcus resulting from vaccine use will necessarily cause an increase in the proportion of other bacterial etiologies of probable bacterial disease.
Review ongoing cases of pneumococcal disease following PCV introduction	Review case notes/vaccination history for cases of pneumococcal disease. The following are possible reasons for cases continuing to occur: 1. Child not eligible for vaccination (due to age) 2. Child eligible but not vaccinated or incompletely vaccinated 3. Child fully vaccinated but has waning immunity 4. Child fully vaccinated but has an	Data usually obtained by using surveillance to identify cases and then conducting subsequent in-depth investigation to describe the characteristics of the cases. Data on the vaccination status of cases are essential to interpret and respond to ongoing cases of pneumococcal disease.

	underlying condition (e.g. HIV/AIDS) which may reduce vaccine effectiveness 5. Child fully vaccinated but is diagnosed with non-vaccine serotype 6. Child fully vaccinated but vaccine failed	

Finally, quality assurance (QA) and quality control (QC) measures should be used to assess the quality of the disease surveillance system in place. Suggested QA/QC measures include:

- Average time from specimen collection on the wards to storage or processing in the laboratory
- Laboratory days of operation and daily hours of operation
- Percentage of media batches tested for sterility and ability to support growth
- Use of human blood
- Source of blood agar
- Availability of ATCC strains
- Frequency of staff QA/QC training
- Proficiency testing for identification of pneumococcus and other organisms
- Storage temperature of isolates
- Storage medium for isolates
- Percentage of isolates sent to reference laboratory for confirmatory testing
- Transport medium for isolates
- Percentage of *S. pneumoniae* isolates confirmed by reference lab (of those tested)(51)

In 2013 WHO, an informal Technical Advisory Group, and partners undertook a strategic review to assess IB-VPD surveillance performance. Fifty-six higher performing sentinel sites in Gavi-eligible countries were selected for targeted technical and financial support.(395) Areas needing improvement within the surveillance network include: "uniformly instituting zero case reporting (meaning reporting on a monthly basis even when zero cases were found); moving all sites from aggregate to case-based reporting; focusing on improved quality assurance in laboratory testing and reporting; piloting a web-based data management system; improving laboratory methods; and collecting serotype/serogroup data to determine what proportion of the three pathogens detected by the surveillance network (pneumococcus, meningococcus and Hib) are vaccine preventable."(395) Investments to improve the IB-VPD network will pay off in providing better data to inform country decision-making on vaccine usage, post-licensure impact, and vaccine program performance.

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Appendix A: Useful Resources and Websites

General Resources

- ✓ **Vaccine Information and Epidemiology Window (VIEW-Hub):** Developed by Johns Hopkins, IVAC with inputs from WHO, Gavi, UNICEF and others, VIEW-Hub is a web-based tool designed to provide fast, accurate and secure data on the state of access to Hib, pneumococcal and rotavirus vaccines in 194 countries. VIEW-Hub allows users to view and export data and to create custom maps and graphics. The platform is open access and available on www.view-hub.org For questions or comments, please contact **Kirthini Muralidharan** at **IVAC** at **kmurali2@jhu.edu**
  The latest VIEW-Hub quarterly Vaccine Introduction Status report may be downloaded here: **http://www.jhsph.edu/research/centers-and-institutes/ivac/view-hub/**

  In 2017, VIEW-Hub will launch the PCV Impact Study module which will allow users to search, filter and link to completed and ongoing PCV impact studies worldwide through the website.

- ✓ **NITAG Resource Center**: a web-based interactive database to provide information, tools and training materials to NITAGs and to the international immunization community in order to support evidence-informed decision making for immunization programs and policies. The NITAG Resource Center is managed by the SIVAC initiative, whose aim it is to support the development and strengthening of NITAGs in LMIC (www.sivacinitiative.org).
  The NITAG Resource Center is available at: http://www.nitag-resource.org/

Chapter 1: Burden of Pneumococcal Disease

- ✓ The Pneumococcal Global Serotype Project 2010 manuscript, "Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the Pneumococcal Global Serotype Project" is available at: http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000348.

  For age distribution curves of IPD, refer to the report by Russell FM, et al.: http://www.who.int/immunization/sage/6_Russel_review_age_specific_epidemiology_PCV_schedules_session_nov11.pdf

Chapter 2: Interventions to Prevent and Control Pneumococcal Disease

- ✓ WHO and UNICEF's Global Action Plan for Pneumonia and Diarrhea (GAPPD) is available at: http://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/.

- ✓ **Lives Saved Tool (LiST)–** a Microsoft Windows-based software tool used to model the impact of scaling-up health interventions aimed to reduce mortality and morbidity in mothers, newborns, and children under five years of age. LiST allows users to set up and run multiple scenarios in order to estimate the impact of different health intervention packages based upon coverage at the national or subnational level. More information is available at: http://livessavedtool.org/

- ✓ **WHO PCV Position Paper**: The 2012 WHO position paper on pneumococcal vaccines is available at: http://www.who.int/wer/2012/wer8714.pdf?ua=1.

Chapter 4: PCV Impact Studies

- ✓ **PCV Review of Impact Studies (PRIME):** an update to the systematic review of PCV dosing schedules published in 2014 (see the first bullet under Chapter 6 resources below), the PRIME project consists of a systematic review on PCV immune response and both direct and indirect effects of PCV on nasopharyngeal carriage, otitis media, pneumonia, invasive disease, and mortality by dosing schedule and PCV product globally. This analysis is planned to be completed in late 2017. For more information, please see the PRIME overview page at the end of Appendix A.

Chapter 5: Economic Evaluation of PCV

- ✓ **The "WHO guide for standardization of economic evaluations of immunization programmes"** (December 2008) is available at: http://whqlibdoc.who.int/hq/2008/WHO_IVB_08.14_eng.pdf.

- ✓ **The WHO CHOICE** "Choosing Interventions that are Cost Effective" database contains unit cost estimates for service delivery in 193 countries expressed in the local currency and international dollars. Prices are given for a daily bed at primary, secondary and tertiary-level hospitals, and for an outpatient visit at a health center, primary and secondary-level hospital. The WHO-CHOICE unit database can be accessed at: http://www.who.int/choice/country/country_specific/en/ and was last revised in July 2011.

- ✓ **OLIVES**: a repository of country-specific data on demography, disease burden, health service costs, health service utilization, and vaccine-related costs. Data can be searched and exported for country planning purposes. More information is available at: http://provac-olives.com/.

Chapter 6: Implementation of PCV

- ✓ **PCV dosing landscape analysis review papers:** PCV dosing options were systematically reviewed and results published (some of which are referenced here: references 7-9, 227, 367, 370, 374-5) in 2014 on the evidence for vaccine effectiveness based on the number and timing of primary doses-- including the interval between doses and the initial age to begin vaccination—and the presence or absence of a booster dose. The outcomes studied included immunogenicity, IPD, pneumonia, NP carriage and indirect effects. The full set of review papers from the PIDJ Supplement (January 2014) are available at: http://journals.lww.com/pidj/toc/2014/01002.

- ✓ **Measuring PCV Impact Manual**: WHO's "Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination" (September 2012) provides methodological details and guidance on designing impact studies and surveillance systems. The document is available at: http://apps.who.int/iris/bitstream/10665/75835/1/WHO_IVB_12.08_eng.pdf.

- ✓ **WHO PCV10 Introduction Handbook:** WHO's "Introduction of pneumococcal vaccine PCV10, two dose presentation, a handbook for district and health facility staff" (2013) provides programmatic guidance on planning the introduction of PCV10 and is available at: http://apps.who.int/iris/bitstream/10665/90378/1/WHO_IVB_13.09_eng.pdf.

- ✓ **WHO PCV13 Introduction Handbook:** WHO's "Introduction of pneumococcal vaccine PCV13, a handbook for district and health facility staff" (2013) is available at: http://apps.who.int/iris/bitstream/10665/90380/1/WHO_IVB_13.10_eng.pdf.

- ✓ **Immunization Financing Resource Guide:** In February, 2017, Results for Development released a new set of tools entitled "Immunization Financing: A Resource Guide for Advocates, Policymakers and Program Managers". The guide "…collects 26 brief documents on topics related to the cost and financing of national immunization programs in low- and middle-income countries" and may be accessed here: http://www.immunizationfinancing.org/

- ✓ **SIVAC**: Supporting National Independent Immunization and Vaccine Advisory Committees. The SIVAC Initiative aims to support the development of sustainable NITAGs in low- and middle-income countries. Available at http://www.sivacinitiative.org/ is a list of publications, technical documents and a resource center with information helpful for NITAGs.

Appendix B: Literature Search Methodology

Evidence review: Articles were identified in a variety of ways to try to provide an overview of the evidence informing PCV introduction.

1. Bibliographies and reports were identified from the IVAC, CDC, GAVI, NITAG Resource Center and WHO websites (January 2014).
2. References were added by cross-checking the bibliographies of an internal IVAC reference list, the Africa Compendium (IVAC), the Asia Compendium (IVAC) and the 2012 WHO PCV Position Paper (January 2014).
3. References were added by reviewing the search results from the IVAC recurring literature search from 2013 through January 16, 2016. Search terms may be found below.
4. The PubMed database was searched using the search terms ((streptococcus pneumoniae[MeSH Terms]) AND Pneumococc*) OR pneumococcal vaccines[MeSH Terms].
   Time range: Articles published between October 1, 2010 and May 16, 2015.
   Rationale: These dates were selected based on the dates of the recently published and systematic review "Optimum dosing of pneumococcal conjugate vaccine for infants: a landscape analysis of evidence supporting different schedules."[5] The PCV dosing landscape analysis was based on articles published between January 1994 and September 2010 and summarizes the information available on immunogenicity, IPD, pneumonia, NP carriage and indirect effects by dosing schedule.
5. Whenever possible, systematic literature reviews (such as the Global Disease Burden project, Global Serotypes Project, and PCV dosing landscape analysis) are used to summarize information relating to the content of the EB. The primary sources included in literature reviews were not re-reviewed unless there was a particular question or clarification needed.
6. Poster abstracts from the 9th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD) conference held in Hyderabad, India in March, 2014 were reviewed for their relevance to the Evidence Base sections.

Search terms used in the IVAC recurring PCV literature search referenced in #3 above:

Disease Burden and Impact

(pneumococcus OR pneumococcal OR "streptococcus pneumoniae"[MeSH] OR "streptococcus pneumoniae" OR "Pneumococcal Infections"[Mesh]) AND ("Health Impact Assessment"[Mesh] OR "serotype replacement" OR "strain changes" OR "strain distribution" OR serotype OR safety OR "vaccine impact" OR "vaccine effectiveness" OR "disease burden" OR catch-up OR etiology) AND ("2015/XX/XX"[Date - Publication] : "2015/XX/XX"[Date - Publication])

Economics

[5] O'Brien KL, Goldblatt D, Whitney CG, eds. Optimum dosing of pneumococcal conjugate vaccine for infants: a landscape analysis of evidence supporting different schedules. PIDJ 2014; 33(1, Suppl 2).

(pneumococcus OR pneumococcal OR “streptococcus pneumoniae”[MeSH] OR “streptococcus pneumoniae” OR "Pneumococcal Infections"[Mesh] OR "Pneumococcal Vaccines"[Mesh] OR “pneumococcal vaccine”) AND (“cost of illness”[MeSH] OR cost-effective OR cost-effectiveness OR "cost effective" OR "cost effectiveness" OR economics OR “economic burden of disease”) AND ("2015/XX/XX"[Date - Publication] : "2015/XX/XX"[Date - Publication])

Vaccine Dosage and Wastage

("Pneumococcal Vaccines"[Mesh] OR "pneumococcal vaccine" OR “vaccines, pneumococcal” OR “Pneumovax” OR “Pnu Imune Vaccine” OR “Prevnar” OR “Synflorix” OR “Pneumococcal Conjugate Vaccine” OR “pneumococcal conjugate” OR “PCV” OR “10 valent pneumococcal vaccine” OR “10-valent pneumococcal vaccine” OR “PCV10” OR “PCV-10” OR “13 valent pneumococcal vaccine” OR “13-valent pneumococcal vaccine” OR “PCV13” OR “PCV-13” OR OR “Pnuemococcal Polysaccharide Vaccine” OR "new vaccine") AND (vaccine OR immunization) AND (dosing OR ”schedules, immunization” OR “immunization schedule” OR “vaccine potency” OR vial OR "vial size" OR strategy OR schedule OR optimizing OR optimization) AND ("2015/XX/XX"[Date - Publication] : "2015/XX/XX"[Date - Publication])

New Vaccine Introductions

("Pneumococcal Vaccines"[Mesh] OR "pneumococcal vaccine" OR “vaccines, pneumococcal” OR “Pneumovax” OR “Pnu Imune Vaccine” OR “Prevnar” OR “Synflorix” OR “Pneumococcal Conjugate Vaccine” OR “pneumococcal conjugate” OR “PCV” OR “10 valent pneumococcal vaccine” OR “10-valent pneumococcal vaccine” OR “PCV10” OR “PCV-10” OR “13 valent pneumococcal vaccine” OR “13-valent pneumococcal vaccine” OR “PCV13” OR “PCV-13” OR OR “Pneumococcal Polysaccharide Vaccine” OR "new vaccine") AND (impact OR "best practices" OR strategies OR delivery OR “immunization program” OR “immunization schedule”) AND ("vaccine introduction" OR "vaccine adoption" OR "immunization introduction" OR "immunization adoption") AND ("2015/XX/XX"[Date - Publication] : "2015/XX/XX"[Date - Publication])

Clinical Trials

("Pneumococcal Vaccines"[Mesh] OR “pneumococcal vaccine”) AND (trial OR “vaccine trial”) AND ("2015/XX/XX"[Date - Publication] : "2015/XX/XX"[Date - Publication])