Technical Information for National-level PCV Policy Recommendations

Summary of available evidence to guide decision-making

A high-level summary of evidence available for national-level technical policy-making around the use of pneumococcal conjugate vaccine (PCV), with a focus on low- and middle-income countries and adapted to a NITAG-focused decision-making framework. Made possible with support from Gavi, the Vaccine Alliance.

International Vaccine Access Center, Johns Hopkins University Bloomberg School of Public Health
Purpose and overview

This set of summaries related to pneumococcal conjugate vaccine (PCV) evidence was developed as a reference by Johns Hopkins’ International Vaccine Access Center (IVAC) to facilitate access to recent research around PCVs relevant to vaccine use in routine immunization programs worldwide. National Immunization Technical Advisory Group (NITAG) members, Expanded Program on Immunization (EPI) staff and other vaccine decision-makers are the primary audiences for these summaries.

The goal has been to put forth a series of high-level summaries of the best available data that may assist these groups in synthesizing and locating the available evidence needed to formulate decisions regarding introduction or optimal use of PCV in multiple settings. These briefings have been based upon a more in-depth analysis of the best available research and data. This in-depth information is contained in IVAC’s “PCV evidence base (PCV EB)” document, which was developed in 2015 and 2016 to serve as a comprehensive resource of the highest quality information about PCVs and pneumococcal disease as is currently available. These documents have been carefully vetted by a number of international pneumococcal and vaccine experts. Semi-annual updates to the PCV Evidence Base are planned beginning in mid-2017.

The format of this document follows the structure of the SIVAC Initiative’s document, *Elements to Consider in Developing a Framework for Issuing Immunization Related Policy Recommendations*. In this overview of evidence around PCV, we have been able to include statements summarizing research in the following areas:

- **Section 1: PCV Vaccine and Immunization Characteristics**
  p. 4-11
- **Section 2: Pneumococcal Disease**
  p. 12-19
- **Section 3: Economic Considerations**
  p. 20-25

The 4th section of the *Elements to Consider*... is dedicated to “Health Policy and Programmatic Issues”. Given the context-specific nature of the data needed for each country to evaluate issues in this area, we are not able to address and summarize these sections here. Some issues suggested in the SIVAC Framework in section 3, described as Operational Considerations, are also not addressed here because of the country-specific nature of these issues.

The final section of this document is:

- **Appendix: Elements to Consider in Developing a Framework for Issuing Immunization Related Policy Recommendations**
  p. 26-28

Important notes about this document

- The PCV Briefings (sections 1-3) were developed by synthesizing evidence reviewed in the “Evidence Base for Pneumococcal Conjugate Vaccines” (PCV Evidence Base) produced by IVAC at Johns Hopkins in 2016. Several comprehensive and systematic literature reviews contributed to the Evidence Base (and thus to the PCV Briefing documents), and were supplemented with additional targeted searches of peer-reviewed published literature undertaken to fill gaps in the evidence. Specific sources and methods are described in Appendix B of the PCV evidence base found on page 213 of that document.
❖ Please see Appendix A for a list of resources that may be especially useful to members of NITAGs and other technical bodies.

❖ Questions and comments may be directed to Julie Younkin – jbuss2@jhu.edu

Additional evidence expected to be available in 2017

A number of important new studies, estimates and resources are currently in process and expected to be available in 2017. These include:

a. **Disease burden**: New global, regional and national estimates of the causes of child mortality, L. Liu et al: expected to be published in early 2017

b. **Disease burden**: New global, regional and national estimates of pneumococcal disease mortality and morbidity in children under 5 years of age, a time-series analysis for each year 2000-2015: expected 2017

c. **Pneumonia etiology**: The Pneumonia Etiology Research for Child Health (PERCH) project is anticipated to publish a supplement of papers in 2017 detailing the methods, inputs and results of their multisite analysis of the causes of childhood pneumonia.


e. **PCV Impact study analysis**: The PCV Review of Impact Evidence (PRIME) is a project of the PCV Technical Coordination Group, co-chaired by WHO and IVAC at Johns Hopkins University. A systematic review of PCV evidence (i.e. immunogenicity studies and clinical outcome studies including invasive pneumococcal disease, pneumonia, and nasopharyngeal colonization) was performed in 2010 to support the SAGE recommendation on the use of either 3-dose (3p+0 or 2p+1) or 4-dose (3p+1) PCV Schedules. An update to this systematic review is underway and will include 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. Expected in late 2017.

f. **Online PCV impact study database**: In 2017, the VIEW-Hub tool ([www.view-hub.org](http://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.

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Section 1: PCV: VACCINE AND IMMUNIZATION CHARACTERISTICS

Pneumococcal Vaccines and Immunization Characteristics Summary
Two pneumococcal conjugate vaccines, the ten-valent Synflorix (PCV10) and the thirteen-valent Prevnar13 (PCV13), are marketed internationally and prequalified by the World Health Organization (WHO) for procurement. In clinical trials and in real world effectiveness studies, these vaccines have been shown to have a major impact on the morbidity and mortality of pneumococcal disease, with sustained effect beyond the year of vaccination. Pneumococcal vaccines have an excellent safety profile in infants, young children and those with HIV infection. PCV10 and PCV13 are safe, effective and cost-effective vaccines that are recommended for inclusion in all National Immunization Programs by the WHO.

Note: For an in-depth discussion of these and other topics related to PCV and for additional references, please consult the “Evidence Base for Pneumococcal Conjugate Vaccines” IVAC at Johns Hopkins University, 2017

SAFETY

PCV safety has been well demonstrated in children in clinical trials and has been confirmed after the distribution of more than 198 million doses in over 60 countries worldwide¹. PCVs are safe and well tolerated in infants, young children and those with HIV infection.²⁻⁸ The vaccines can be administered concurrently with other Expanded Program on Immunization (EPI) vaccines.¹ ⁴

- 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.” ⁹,¹⁰
- Several studies from various countries demonstrate that PCV10 and PCV13 have a similar safety profile as PCV7,¹⁴,⁵
- 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.⁶⁻⁸,¹¹
- The WHO states that “PCVs are considered safe in all target groups for vaccination, (including) . . . immunocompromised individuals.”¹¹

VACCINE EFFICACY & EFFECTIVENESS

PCVs are safe and efficacious vaccines. Their use in children in a variety of settings directly reduced the risk of invasive pneumococcal disease (IPD) – including meningitis and septicemia – radiologically-confirmed pneumonia and clinical pneumonia, otitis media and nasopharyngeal carriage due to serotypes contained in the vaccine¹,⁹,¹²,¹³.

- Efficacy against IPD and pneumonia: In clinical trials, pneumococcal conjugate vaccine (PCV) was 80% efficacious against vaccine type IPD and prevented 36% of severe pneumonia in children⁹. In a high mortality African community, PCV reduced all-cause mortality by 16%¹⁴.
- Efficacy in HIV+ children: PCV is slightly less efficacious in HIV-infected children, but the absolute impact on disease reduction is greater in these children who are at higher risk for pneumococcal infection⁶,¹⁵. HIV infection was associated with a 9- to 43-fold increased relative risk of invasive pneumococcal disease (IPD)⁶.
**PCV Impact on Antibiotic Resistance**

- 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.\(^{16}\)
- 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.”\(^{17}\)

**Serotype distribution and replacement**

- The serotypes in PCV10 and PCV 13 account for an estimated 70-82% of IPD cases in children under five in Asia, Africa, Oceana and Latin America/Caribbean\(^{18}\).

### Serotypes included in PCV10 and PCV13 product formulations

<table>
<thead>
<tr>
<th>Serotype</th>
<th>1</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6A</th>
<th>6B</th>
<th>7F</th>
<th>9V</th>
<th>14</th>
<th>18C</th>
<th>19A</th>
<th>19F</th>
<th>23F</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV10</td>
<td></td>
<td></td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCV13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

= Serotype included in the vaccine

### Proportion of IPD-causing serotypes in region covered by specific vaccine formulations


- Although serotype replacement by non-vaccine serotypes in NP carriage has been nearly complete following PCV7 implementation, **minimal serotype replacement in pneumococcal disease has occurred** because of the lower invasiveness of replacing serotypes. In all settings, the increase in non-vaccine type invasive pneumococcal disease has been outweighed by a significant reduction in vaccine type disease\(^{12,19-21}\).
**Duration of protection**

There are limited data on the duration of protection following PCV administration, although there is some evidence of a more rapid decline in protection among HIV-infected children.

- The role of natural immune system boosting following exposure to circulating serotypes complicates the interpretation of long-term follow up studies comparing immunized and unimmunized children. The majority of follow up studies performed four to ten years post-immunization have found little difference in protective serum pneumococcal antibody levels between previously immunized and unimmunized children (for example, see Klein, 2013). This may be in part because of the natural history of pneumococcus in humans: a trend of decreasing colonization prevalence after the first few years of life.

- In a follow up study to the South African randomized controlled trial (RCT) using PCV9 in a 3p+0 schedule, vaccine efficacy remained significant against vaccine-type IPD after six years. 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.

**CORRELATES OF PROTECTION**

Serological correlates of protection for pneumococcal conjugate vaccines were determined after the licensing of PCV7, the first vaccine in this class, and were based on the protective pneumococcal antibody concentrations to the seven serotypes in this vaccine that were found in three large controlled trials.

- A vaccine efficacy of 93% correlated with an overall protective level of anti-capsular antibodies of 0.35 µg/ml. Although the aggregate correlate of protection is 0.35 µg/ml, subsequent studies have shown that serotype-specific correlates of protection vary widely and range between 0.14 (0.09 to 0.40) µg/ml for serotype 18C to 2.83 (1.16 to ∞) µg/ml for serotype 3.

**VACCINE INDIRECT EFFECTS**

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.

- In a systematic review of data on the indirect effect of PCV use in 14 countries, VT-IPD consistently decreased after PCV introduction, although the magnitude of the reduction varied in age groups spanning from U5 to >65 years. The magnitude of the decrease among unimmunized adults grew over the first seven years after PCV introduction, the duration for which data was available. The indirect effect was dependent on vaccine coverage rates; when coverage rates were high, the indirect impact was consistent. Lower coverage rates yielded mixed indirect impact, with some reductions in disease demonstrated starting at 40% coverage.

- In the US, it was estimated that over twice as many cases of VT-IPD were prevented in adults in 2003 compared to cases prevented in vaccinated children under 5.

- 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.

- 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.

**VACCINE CHARACTERISTICS**
The two pneumococcal conjugate vaccines, Synflorix® and Prevnar13, are licensed for global use and are prequalified for procurement by the World Health Organization. Both vaccines have been shown to be effective in large-scale clinical studies and in real-world use and can be co-administered with other vaccines.

Currently, PCV10 is available in one- and two-dose presentations and PCV13 is available in a one-dose presentation. In the next two years, both vaccines will be available in a 4-dose presentation that includes a preservative. By 2018, PCV10 4-dose vials will be the only presentation available to Gavi countries for this vaccine. When Gavi countries submit their request to renew support for PCV for 2018, they will no longer be able to choose PCV10 in a 2-dose presentation.

As of early 2017, PCV13 is now available in a 4-dose vial, and continues 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 1: Currently available pneumococcal conjugate vaccines product formulation and details

<table>
<thead>
<tr>
<th>Vaccine/Manufacturer (presentation)</th>
<th>Synflorix® GlaxoSmithKline&lt;sup&gt;31&lt;/sup&gt; (single-dose vial&lt;sup&gt;*&lt;/sup&gt;)</th>
<th>Synflorix® GlaxoSmithKline&lt;sup&gt;31&lt;/sup&gt; (two-dose vial, preservative free&lt;sup&gt;*&lt;/sup&gt;)</th>
<th>Prevnar13 Pfizer&lt;sup&gt;32&lt;/sup&gt; (single dose vial&lt;sup&gt;*&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotypes included</td>
<td>1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23</td>
<td>1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23</td>
<td>Addition of 3, 6A, and 19A</td>
</tr>
<tr>
<td>Carrier proteins</td>
<td>Protein D from non-typeable <em>Haemophilus influenzae</em>, tetanus toxoid and diphtheria toxoid.</td>
<td>Protein D from non-typeable <em>Haemophilus influenzae</em>, tetanus toxoid and diphtheria toxoid.</td>
<td>Mutant diphtheria toxoid (CRM 197 protein)</td>
</tr>
<tr>
<td>Year prequalified by WHO</td>
<td>2009</td>
<td>2009</td>
<td>2010</td>
</tr>
<tr>
<td>Available through UNICEF</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wastage rate</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>2-8°C Celsius, do not freeze</td>
<td>2-8°C Celsius, do not freeze. An opened two-dose vial should not be returned to the refrigerator after a vaccination or after 6 hours, whichever comes first.</td>
<td>2-8°C Celsius, do not freeze</td>
</tr>
<tr>
<td>Packaging</td>
<td>Cartons of 1,10 and 100 vials</td>
<td>Cartons of 100 vials</td>
<td>Cartons of 50 vials</td>
</tr>
<tr>
<td>Administration</td>
<td>Injection of 0.5 ml vaccine intramuscularly</td>
<td>Injection of 0.5 ml vaccine intramuscularly</td>
<td>Injection of 0.5 ml vaccine intramuscularly</td>
</tr>
<tr>
<td>Vaccine Vial Monitor Label?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*See Table 2 for a description of the four-dose vial presentations for both PCV10 and PCV13 that are/will soon be available.

### Table 2: 4-dose presentations of PCVs available beginning in 2017-2018

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>PCV10</th>
<th>PCV13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>2-dose vial</td>
<td>4-dose vial</td>
</tr>
<tr>
<td>Pharmaceutical form</td>
<td>Liquid</td>
<td>Liquid</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Preservative</td>
<td>None</td>
<td>Yes*</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>GSK</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Serotypes covered</td>
<td>1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F**</td>
<td>1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F</td>
</tr>
<tr>
<td>WHO Prequalified</td>
<td>Yes</td>
<td>No, anticipated in late 2017</td>
</tr>
<tr>
<td>Schedule</td>
<td>3 doses</td>
<td>3 doses</td>
</tr>
<tr>
<td>Primary packaging</td>
<td>3 mL vial</td>
<td>3 mL vial</td>
</tr>
<tr>
<td>Shelf life at 2-8°C</td>
<td>36 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Cold chain volume per dose</td>
<td>4.8 cm³</td>
<td>2.4 cm³</td>
</tr>
<tr>
<td>Vaccine Vial Monitor</td>
<td>VVM 30</td>
<td>VVM 30</td>
</tr>
<tr>
<td>Handling of open vials†</td>
<td>Opened vials to be kept 6 hours</td>
<td>To be confirmed. Current assumption is opened vial to be kept for 28 days.</td>
</tr>
<tr>
<td>Wastage Rate†</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Freeze sensitivity</td>
<td>2º-8º C</td>
<td>2º-8º C</td>
</tr>
<tr>
<td>Indicative maximum price per dose (US$)</td>
<td>3.40-3.50; 3.05 from 2017</td>
<td>3.05</td>
</tr>
</tbody>
</table>

*2-PE: 2- phenoxyethanol

**VACCINE ADMINISTRATION SCHEDULE

For either vaccine (PCV10 or 13), WHO recommends a 3p+0 or, alternatively, a 2p+1 schedule for routine infant immunization.\(^1\)\(^,\)\(^3\)\(^,\)\(^4\) Dosing schedules should be selected based on locally relevant factors including the age distribution of pneumococcal disease, the likely vaccine coverage and a schedule that fits best with the current EPI schedule. An in-depth discussion of schedules can be found in a recent dosing schedule landscape analysis.\(^3\)\(^,\)\(^4\)

- A 3p+0 dosing schedule is used by the majority of Gavi countries that have introduced PCV (52 of 54 countries).\(^3\)\(^,\)\(^5\) Under a 3p+0 schedule, vaccination can be initiated as early as 6 weeks of age with an interval of 4-8 weeks between doses, and administered along with Pentavalent (DTP-HepB-Hib) and rotavirus vaccine.
- With a 2p+1 dosing schedule, the 2 primary doses should be completed by six months of age, with a minimal interval of 8 weeks between doses. The booster dose should be given between 9-15 months of age, alongside the measles vaccine and Vitamin A supplementation.
- Catch-up doses for unvaccinated older children ages 12-24 months, and for children aged 2-5 years at high risk of pneumococcal infection is two doses administered with an interval of at least 8 weeks.\(^1\)\(^,\)\(^1\)\(^1\)

Map of PCV dosing schedules by country
Note: See PCV NITAG Briefing Appendix for a list of African and Asian countries using PCV, by product and dosing schedule

Cold chain and logistics: PCV is a liquid vaccine which should be stored and transported between 2-8° Celsius and must not be frozen. A Vaccine Vial Monitor (VVM) is placed on the cap of the vial, which tracks cumulative heat exposure over time and indicates the endpoint of potency of the vial contents. UNICEF's Cold Chain Weight and Volume Calculator is a useful tool for determining the cold chain requirements for various products and may be found at: http://www.unicef.org/supply/index_51098.html


Section 2: PNEUMOCOCCAL DISEASE

Pneumococcal Disease Summary

Pneumococcal disease is caused by the bacterium *Streptococcus pneumoniae*—also known as pneumococcus. The World Health Organization estimated that in 2008, nearly half a million HIV-negative children under the age of 5 worldwide died of pneumococcal disease, including pneumococcal pneumonia, meningitis, and other clinical manifestations of serious pneumococcal infections.\(^1\) Pneumonia, an acute respiratory infection that affects the lungs, is the single leading cause of death in children under 5 years of age. Although pneumonia can be caused by a number of infectious agents, pneumococcus is responsible for between 27-36% of all pneumonia deaths in children under 5, as determined by the vaccine probe approach.\(^2,3\) Researchers have estimated that there were 120 million episodes of pneumonia in 2010, 14 million of which progressed to severe pneumonia.\(^4\) Pneumococcal disease causes severe illness and death primarily in children <5 years of age, the elderly, and those who are immunocompromised (e.g., HIV positive).

Note: For an in-depth discussion of these and other topics related to PCV and for additional references, please consult the “Evidence Base for Pneumococcal Conjugate Vaccines” IVAC at Johns Hopkins University, 2017

DISEASE BURDEN

Pneumonia is one of the world’s leading killers of children and *Streptococcus pneumonia* or ‘pneumococcus’ is the most common cause of bacterial pneumonia. Pneumonia is the most common manifestation of serious pneumococcal disease. Pneumococcus also causes meningitis, sepsis, otitis media and other invasive and non-invasive pneumococcal diseases.

- **Mortality:** Pneumococcal disease remains a leading cause of vaccine-preventable child death and illness despite continuing reductions in both overall childhood mortality and pneumonia deaths.\(^5,6\) Globally, 81% of childhood pneumonia deaths occur in children younger than 2 years.\(^4\)
  - The highest burden of pneumonia deaths is in Africa and Southeast Asia, which together account for almost one million of the estimated 1.3 million pneumonia deaths worldwide in children under 5 years of age in 2011. Pneumococcal pneumonia alone killed 177,000 African and 146,000 Southeast Asian children under the age of 5 in 2011\(^4\), and a significant proportion of those deaths could have been prevented through vaccination.

- **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 hospitalization\(^4\).

- **Age distribution:** 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. 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.\(^7\) 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_schedule_s_session_nov11.pdf](http://www.who.int/immunization/sage/6_Russel_review_age_specific_epidemiology_PCV_schedule_s_session_nov11.pdf).

- **Pneumococcal Meningitis:** Pneumococcal meningitis has the highest risk of serious neurological sequelae among bacterial causes of meningitis in children, and for children who do not receive treatment or do not have access to care, the case fatality rate is over 90%.\(^3,8\) Among children who survive pneumococcal meningitis, about 25% suffer long-term disability, including hearing loss, vision loss, cognitive delay, motor delay/impairment, behavioral problems, and seizures.\(^8,9\)
Low-income countries: Most invasive pneumococcal disease overall, and meningitis specifically, in low- and middle-income countries occurs in age groups shifted towards younger children compared to the age groups bearing the greatest disease burden in high income countries.6

Risk Factors: Risk factors for pneumococcal disease include environmental factors such as indoor air pollution, parental smoking and living in crowded homes as well as infection with sickle cell disease10, other respiratory pathogens such as influenza, and especially, HIV infection. HIV infection was associated with a 9- to 43-fold increased relative risk of invasive pneumococcal disease (IPD).11 Routine use of highly active retroviral therapy (HAART) has been shown to reduce the incidence of IPD by 50% in HIV infected children, but risk of IPD continues to be much higher in this population compared to age-matched, HIV uninfected children.12

CLINICAL CHARACTERISTICS

Streptococcus pneumoniae classification: Streptococcus pneumoniae, or ‘pneumococcus’, is a Gram-positive, encapsulated diplococcus which is adapted to colonize the human nasopharynx (NP). The polysaccharide capsule of this bacterium defines over 90 distinct serotypes and functions as an essential virulence factor.

Pneumococcal serotypes: 93 pneumococcal serotypes exist, which are immunologically distinct and vary in their potential to cause disease. While there is some variation in serotypes by region, the same 10 serotypes account for at least 70% of invasive pneumococcal disease (IPD) in all regions.6,13

Serotypes causing IPD in children under 5 years, 1980-2007: data from 20 Gavi-eligible countries

Source: Johnson et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. 201013

Pathophysiology: Pneumococcus is a natural colonizer of the human nasopharynx (nose and throat), and is particularly prevalent in young children. Pneumococcal colonization is a required step in the pathophysiology of pneumococcus, as well as serving as a reservoir and source of pneumococcal transmission between individuals. Progression to serious disease and death can occur due to pneumonia (infection in the lungs; cause of approximately 90% of pneumococcal deaths), meningitis (inflammation of the protective covering of the brain and spinal cord; cause of approximately 7% of pneumococcal deaths), sepsis (infection of the blood), or other diseases.2

Diagnosis: Pneumococcus is difficult to detect in the laboratory, and newer diagnostic tests are adding to our understanding of the burden of disease.14 Because of the limitations of current diagnostic
techniques and pre-diagnostic antibiotic use, pneumonia etiology studies often underestimate the true burden of pneumococcal disease.

- **Treatment:** Treatment is accomplished through appropriate care seeking, where caregivers recognize serious symptoms, seek care and have appropriate care available. Specific strategies include appropriate care seeking and referral, case management at community and health facility levels, continued feeding of children, appropriate antibiotic selection, and oxygen therapy, if indicated. 
  
  ➢ Access to treatment is variable among countries and regions, but poorer children and those in rural areas have especially low rates of access to appropriate treatment for pneumonia.

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**Proportion of children under 5 with symptoms of pneumonia taken to a healthcare provider, by wealth quintile 2009-2013**

![Graph showing proportion of children under 5 with symptoms of pneumonia taken to a healthcare provider, by wealth quintile 2009-2013](image)

*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.

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- **Protective Immunity:** The natural history of pneumococcus includes a decline in NP colonization after the first few years of life, which coincides with natural immune system boosting following exposure to circulating serotypes.

- **Long-term Sequelae:** Pneumococcal meningitis has a high rate of death and serious neurological sequelae among bacterial causes of meningitis in children. Serious neurological sequelae following pediatric meningitis include hearing loss, vision loss, cognitive delay, speech/language disorder, motor delay/impairment, behavioral problems and seizures.
  
  ➢ Pneumococcal infection has the highest risk of neurological sequelae among the bacterial causes of meningitis. In a global review, about 25% (IQR 16%, 35%) of pneumococcal meningitis cases resulted in major neurological sequelae.
  
  ➢ 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.

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**USE AND COSTS OF HEALTHCARE**

In addition to the morbidity and mortality caused by the clinical spectrum of pneumococcal disease, treating pneumococcal disease carries a significant cost burden for families and countries.
Global Health Utilization:

- 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. Corresponding costs of illness were higher in middle-income countries.

- 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$20,000 in China.

- 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.

Select Country-Specific Cost Burdens:

- The Gambia: the economic burden of childhood pneumococcal diseases for outpatient pneumonia, inpatient pneumonia, pneumococcal sepsis and meningitis was US$ 15, US$ 109, US$ 144 and US$ 170 when family members’ time loss from work was taken into account. The health system meets 50-80% of these costs, nevertheless, out-of-pocket costs were one to ten times household expenditures.

- Taiwan: families spent an average of US$ 653 or US$ 218 when their child was diagnosed with invasive pneumococcal disease or pneumonia, respectively, representing 27-81% of the monthly salary of an unskilled worker.

- Kenya: treatment costs for pneumonia in regional and district hospitals vary from US$ 54-99, and up to US$ 177 in the national hospital. Depending on the type of facility used, 40 to 100% of treatment costs were charged to the use.

- Zambia: outpatient and inpatient treatment costs were estimated to be US$ 48 and US$ 215, respectively.

PREVENTATIVE/CONTROL MEASURES

Strategies to prevent children from contracting pneumonia include universal coverage of immunization with measles vaccine, pertussis vaccine, Hib conjugate vaccine and PCV, HIV prevention, breastfeeding for the first six months and healthy environments.


  - PROTECT: with exclusive breastfeeding for 6 months, adequate complementary feeding, and Vitamin A supplementation
  - PREVENT: with vaccines for PCV, Hib, pertussis and measles; reduction of indoor air pollution; HIV prevention and cotrimoxazole prophylaxis for HIV-infected and exposed children
  - TREAT: with improved care seeking and referral, appropriate treatment with antibiotics and oxygen, and continued feeding (including breastfeeding)

REGIONAL/INTERNATIONAL CONSIDERATIONS

Based on efficacy, effectiveness and vaccines impact data, WHO recommends all National Immunization Programs (NIP) adopt pneumococcal vaccines into their routine immunization schedules.

- WHO Recommendations: WHO has recommended PCV for inclusion in all immunization programs. Those countries with high mortality in children under 5 (i.e., over 50 deaths/1000 births) are especially
encouraged to make the introduction of pneumococcal conjugate vaccines a high priority. The increased number of serotypes in PCV10 and PCV13, compared to the first licensed PCV7, represent significant progress in disease control, especially from a developing country perspective. 

- In 2012, WHO recommended catch-up vaccination to accelerate herd protection in children under 5; PCVs can be administered with any other vaccines in infant immunization programs.
- About 80% of countries in sub-Saharan Africa have introduced pneumococcal conjugate vaccines, while less than 50% of the 38 countries in Southeast Asia and the Western Pacific region have introduced PCV.

**WHO/UNICEF Goals:** The Global Action Plan for Pneumonia and Diarrhea (GAPPD) outlines the following WHO/UNICEF goals of reducing the health impact of pneumonia by 2015:

- Reduce mortality from pneumonia in children less than 5 years of age to fewer than 3 per 1000 live births.
- Reduce the incidence of severe pneumonia by 75% in children less than 5 years of age compared to 2010 levels.
- Reduce by 40% the global number of children less than 5 years of age who are stunted compared to 2010 levels.

**Global Vaccine Introduction Status:** Nearly 140 countries have introduced pneumococcal conjugate vaccines into their National Immunization Program, including 130 universal introductions, 4 subnational and 5 at-risk programs (see map below). An additional 18 countries are planning PCV introduction.

**Global PCV Introduction Status, December 2016**


- **Gavi Country Status:** Of the 73 Gavi-eligible countries, and as of December 2016, 57 countries have introduced PCV into their National Immunization Program. Two countries have been approved, with or without clarification, for Gavi support to introduce. Six countries have announced plans to introduce PCV into their national immunization program. Eight countries have yet to make a decision regarding PCV.
PCV Introduction Status in Gavi Countries, December 2016

SECTION 2: REFERENCES


Section 3: PCV ECONOMIC CONSIDERATIONS

PCV Economic Considerations Summary
Pneumonia and pneumococcal disease impose a heavy financial burden on health systems as well as affected families. Beyond inpatient and outpatient treatment costs (direct medical costs), the economic costs of morbidity and mortality due to pneumonia can include lost productivity and capability (DALYs), lost caregiver wages (indirect costs), transportation for care (direct non-medical costs), and impact of long-term sequelae of pneumococcal meningitis.

Note: For an in-depth discussion of these and other topics related to PCV and for additional references, please consult the “Evidence Base for Pneumococcal Conjugate Vaccines” IVAC at Johns Hopkins University, 2017

ECONOMIC IMPACT OF INTERVENTION ON IMMUNIZATION PROGRAM/HEALTH SECTOR

Economic evaluations of pneumococcal conjugate vaccines have found them to be cost-effective across low-, middle- and high-income countries and across a range of vaccine prices.

There are several types of economic evaluations. Cost-effectiveness analysis (CEA) is the most common type of economic evaluation. The results of cost-effectiveness analyses are expressed as incremental cost-effectiveness ratios (ICERs), where the costs are represented in monetary units and the health effects or outcomes are measured as follows:¹

- Life Years Gained (LYG) measures health effects in “natural units”
- Disability-adjusted Life Years (DALYs) measure a health loss; more commonly used in Low- to Middle-Income Countries
- Quality-adjusted Life Years (QALYs) measure a health gain; are more commonly used in high-income countries

With the objective of providing policy-makers with evidence for deciding on interventions and programs that maximize health for the available resources in their country, the WHO-CHOICE (Choosing Interventions that are Cost-Effective) initiative was developed. This provides country-level information for analyses on health interventions. WHO-CHOICE uses a multiple of country per capita gross domestic product (GDP) as an indicator of cost-effectiveness. Using GDP, the range of incremental cost effectiveness ratio (ICER) calculation will lead to one of the following categories of cost-effectiveness:² ³

- ICER less than the per capita GDP is considered “highly cost-effective”
- ICER less than three times the per capita GDP is considered “cost-effective”
- ICER equal to or greater than 3 times per capita GDP is “not cost-effective”

Many studies on the cost-effectiveness of pneumococcal conjugate vaccines have been published ⁶⁻²⁵. These studies vary widely in both methodologies employed and key input variables such as price of vaccine, associated delivery costs, vaccine effectiveness, and other factors such as herd effect. Despite the heterogeneity of approaches to estimate cost-effectiveness, the vast majority of
countries modeled demonstrate a positive economic value for the introduction of pneumococcal conjugate vaccines into their respective NIPs.

- One such study estimated that 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 2020.4
- The return on investment of meeting vaccine coverage targets for ten diseases in 94 Lower- and Lower-middle-income countries during the Decade of Vaccines 2011-2020 would result in 16 times greater benefits than costs incurred, compared to no vaccination.5 The estimated return on investment for pneumococcal disease and PCV use is more than 3 times cost of vaccination programs.5

The table below provides data from select cost-effectiveness studies for PCV13. All costs are in U.S. dollars.

### Results of selected cost-effectiveness studies for PCV13

<table>
<thead>
<tr>
<th>Country</th>
<th>Price per dose</th>
<th>Effectiveness against vaccine serotypes</th>
<th>Coverage—3 doses</th>
<th>Healthcare system savings</th>
<th>Deaths averted</th>
<th>Hospitalization averted</th>
<th>ICER: per DALY averted</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>$3.50</td>
<td>83%</td>
<td>---</td>
<td>$1.97 million</td>
<td>6358</td>
<td>50,326</td>
<td>$47</td>
<td>11</td>
</tr>
<tr>
<td>Uganda (PCV10)</td>
<td>$0.15</td>
<td>85%</td>
<td>79%</td>
<td>$0.4 million</td>
<td>10,796</td>
<td>94,071</td>
<td>---</td>
<td>10</td>
</tr>
<tr>
<td>Gambia</td>
<td>$3.50</td>
<td>73%</td>
<td>90%</td>
<td>---</td>
<td>40</td>
<td>630</td>
<td>---</td>
<td>14</td>
</tr>
<tr>
<td>Egypt</td>
<td>$14.24</td>
<td>81%</td>
<td>96.5%</td>
<td>$20.6 million</td>
<td>8583</td>
<td>106,401</td>
<td>$3916</td>
<td>15</td>
</tr>
<tr>
<td>Turkey</td>
<td>$30.00</td>
<td>83%</td>
<td>86%</td>
<td>---</td>
<td>303</td>
<td>23,000</td>
<td>$6696*</td>
<td>20</td>
</tr>
<tr>
<td>Taiwan</td>
<td>$91.75</td>
<td>94%</td>
<td>90%</td>
<td>$252.6 million</td>
<td>420</td>
<td>540,719</td>
<td>$11,299**</td>
<td>17</td>
</tr>
<tr>
<td>Philippines</td>
<td>$15.84</td>
<td>92%</td>
<td>86%</td>
<td>---</td>
<td>2399</td>
<td>34,140</td>
<td>$1233</td>
<td>19</td>
</tr>
<tr>
<td>Peru</td>
<td>$16.34</td>
<td>81%</td>
<td>92.5%</td>
<td>$47.2 million</td>
<td>10,386</td>
<td>112,331</td>
<td>$1,304</td>
<td>25</td>
</tr>
</tbody>
</table>

*In CLYG, Cost per Life Year Gained
**ICER from societal perspective

### VACCINE RELATED COSTS AND RESOURCE USE

- **PCV10 and PCV13 are expected to be cost effective in all 72 Gavi eligible countries and highly cost effective in all but three countries.1 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. In this study, PCV10 would be highly cost-effective in 68 middle-income countries, and PCV13 for 71 countries.2**
- **In a study of 94 low- and middle-income countries, the return on investment for pneumococcal disease and PCV use is estimated as 3.13, that is, over three times greater net cost savings compared to no use of PCV.3 Universal and high coverage with PCV in Gavi-eligible countries could avert USD 24 billion in costs (mostly due to productivity gains; only 6% is due to reduced use of acute health care resources), prevent 21 million disease cases and save 1.5 million lives between 2011-2020.4**

### VACCINE AVAILABILITY
The secondary objective of Gavi’s Pneumococcal Advanced Market Commitment (AMC) is to balance the supply and demand of pneumococcal vaccines. The AMC incentivizes manufacturers to scale-up production capacity to meet the demand for PCV from developing countries by guaranteeing manufacturers a long-term market.\(^5\)

**VACCINE PRICE/AFFORDABILITY**

For all low-income Gavi-eligible countries, a $0.20/dose co-financing payment will be required. For countries preparing for or entering the transition phase, the price per dose will depend on the country’s gross national income (GNI) per capita on average over the previous three years.\(^a\) A diagram of Gavi’s current transition policy illustrates the relationship between financing and country eligibility over time: \(^{26}\)

- **The Pneumococcal Advanced Market Commitment (AMC) was created by Gavi and the World Bank in 2009 to ensure Gavi eligible countries could have access to the appropriate pneumococcal conjugate product at a predictable, long-term price. The AMC provides an innovative finance mechanism to incentivize the scaling up of PCV production to meet developing country needs.\(^6\)** Both manufacturers of pre-qualified PCV products, Pfizer and GSK, have applied and had their products accepted as part of the AMC.

- **Countries eligible for Gavi support can apply to receive assistance from Gavi to introduce PCV10 or PCV13 through the Advanced Market Commitment (AMC).** \(^{27,28}\) Eighty percent of Gavi eligible countries have applied for support to obtain PCV10 or PCV13 at reduced cost.

- **The “tail price”, which is the most a Gavi country would be asked to pay per dose once they have fully graduated from Gavi support, was initially set at USD 3.50, but in 2013 was reduced to USD 3.40 for PCV10 and USD 3.30 for PVC 13 (from 2014 onwards).** \(^{27,28}\)

  - The cost of PCV to low-income Gavi-eligible countries, with a GNI less than USD 1,045 per person, is USD 0.20 per dose. Intermediate Gavi-eligible countries, with a GNI between USD 1,045 and 1,550, pay USD 0.20 initially, with a 15% annual increase.

\(^a\) Gavi’s full co-financing policy may be found at: [http://www.gavi.org/about/governance/programme-policies/co-financing/](http://www.gavi.org/about/governance/programme-policies/co-financing/)
Graduating countries gradually become responsible for the full tail price cost of PCV over the course of five years. In addition, the seven graduating and graduated countries are eligible to apply to receive the PCV at the full tail price.

- As more competition emerges, PCV prices are expected to drop. The anticipated 4-dose vial of PCV will have implications in reducing price in the 2019-2020 time-frame.

- Lower-middle- and middle-income countries:
  - For countries in the PAHO region, the PAHO Revolving Fund exists to help with vaccine purchase. Information can be found at: http://www.paho.org/immunization/toolkit/vaccine-procurement-fund.html
  - Some manufacturers offer tiered pricing agreements with individual countries to provide vaccine at affordable prices.29

| Tiered pricing of pneumococcal conjugate vaccines--2011 29 |
|---------------------------------|-----------------|-----------------|
| **Country/Region**              | **Vaccine (manufacturer)** | **Price per dose in US$** |
| Gavi                            | PCV10, PCV 13    | US$ 3.50-3.30   |
| Brazil                         | PCV10 (GSK)      | US$16, drops to 7 |
| PAHO Revolving Fund            | PCV7 (Wyeth/ Pfizer) | US$21.75       |
|                                | PCV10 (GSK)      | US$14.85        |
| Europe                         | PCV10 (GSK)      | US$49-56        |
| United States                  | PCV7 (Wyeth/ Pfizer) | US$71.04       |
|                                | PCV13(Pfizer)    | US$91.75        |

SOCIO-ECONOMIC AND SOCIAL IMPACT OF DISEASE

Few studies look at the potential broader value of vaccines beyond direct health and economic benefits. Failing to include all value that accrues from vaccination in estimates of cost effectiveness may result in ongoing undervaluation of their impact on economic and societal well-being and risk underinvestment on the part of countries and partners. However, some evidence demonstrates that pneumococcal infection can have important negative consequences for cognition and social integration.

- In Gambia, 58% of children who survived a bout of pneumococcal meningitis “had clinical sequelae; half of them had major disability preventing normal adaptation to social life” (mental retardation, hearing loss, motor abnormalities, seizures)30
- A 2009 systematic literature review of studies in Africa found that one quarter of children who survived pneumococcal or Hib meningitis had neuropsychological deficits, which would be expected to interfere with education, cognition and long-term societal integration and productivity31
- A ten-year study in the US found that time spent with middle ear effusion during the first 3 years of life was significantly associated with lower scores on cognitive ability, speech, language and lower school performance.32
SECTION 3: REFERENCES


National Immunization Technical Advisory Groups (NITAGs) provide evidence based recommendations for the development of immunisation policies. These recommendations are generated from a systematic, credible and transparent process of selecting, reviewing and synthesising evidence.

In generating evidence-based recommendations, NITAG begins with defining a recommendation framework. This recommendation framework outlines the elements on which evidence should be gathered. For each element, specific data required is identified. NITAG will then rank this data as critical (high priority), important (intermediate priority) or non-critical (low priority). Structured and comprehensive reviews of evidence are conducted for all critical and important data requirements.

The table provided lists key elements to be considered when developing an immunization recommendation. These elements may be related to the vaccine characteristics, disease, economic or operational considerations, or health policy and programmatic issues.
<table>
<thead>
<tr>
<th>ISSUE</th>
<th>ELEMENT</th>
<th>SPECIFIC DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VACCINE AND IMMUNIZATION CHARACTERISTICS</td>
<td>Safety</td>
<td>Type, consequences and frequency of short and long-term adverse events following vaccination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk groups or risk factors for adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindications</td>
</tr>
<tr>
<td></td>
<td>Efficacy and Effectiveness</td>
<td>Type specific protection afforded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Critical determinants of the immune response associated with protection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration of protection and waning of immunity if any</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interference regarding protection or immunity with other vaccines</td>
</tr>
<tr>
<td></td>
<td>Vaccine indirect effects</td>
<td>Impact on resistance to antibiotics and antivirals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Herd immunity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential negative population impact through change in age of infection for unprotected individuals e.g. rubella or varicella vaccine or emergence of non-vaccine serotypes</td>
</tr>
<tr>
<td></td>
<td>Vaccine characteristics</td>
<td>Vaccine presentation and formulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosage and route of administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administration schedule and possibility of co-administration with other vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flexibility of vaccination schedules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cold chain and logistic requirements</td>
</tr>
<tr>
<td>2. DISEASE</td>
<td>Burden of disease</td>
<td>Incidence of morbidity and mortality, age specific morbidity and mortality, risk groups, serotype/serogroup distribution, epidemic potential, disease occurrence over time, changes in epidemiology over time</td>
</tr>
<tr>
<td></td>
<td>Clinical characteristics disease</td>
<td>Signs and symptoms of disease, severe forms of disease, long term complications of disease, medical management of disease</td>
</tr>
<tr>
<td></td>
<td>Use and costs of health care</td>
<td>Primary/secondary/tertiary care implications, short and long term use of health care (e.g. treatments, hospitalization)</td>
</tr>
<tr>
<td></td>
<td>Alternative preventive and control measures</td>
<td>Alternative preventive and control measures (e.g. health education, hygiene, vector control) and their effectiveness, costs and practicality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other existing vaccines against the same disease and their effectiveness, costs and practicality</td>
</tr>
<tr>
<td></td>
<td>Regional and international considerations</td>
<td>Existence of regional and global recommendations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disease potential for international spread and pandemic potential</td>
</tr>
</tbody>
</table>
### 3. Economic and Operational Considerations

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>ELEMENT</th>
<th>SPECIFIC DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine related costs and resource use</td>
<td>Direct and indirect costs to administer the vaccine as they compare to those of other existing vaccines or other prevention or control measures</td>
</tr>
<tr>
<td></td>
<td>Vaccine availability</td>
<td>Availability of vaccine and long term supply</td>
</tr>
<tr>
<td></td>
<td>Vaccine affordability</td>
<td>Availability of fiscal space to effectively implement and sustain the recommendation in the programme</td>
</tr>
<tr>
<td></td>
<td>Socio-economic and social impact of disease</td>
<td>School and work absenteeism, Indirect costs to patients and families, Productivity losses, Stigma around a disease</td>
</tr>
<tr>
<td></td>
<td>Economic impact of intervention on immunization program as well as health sector</td>
<td>Reduction in health care costs, Health gain (years of life saved, QALY gained, etc), Cost effectiveness ratio of vaccination program</td>
</tr>
</tbody>
</table>

### 4. Health Policy and Programmatic Issues

<table>
<thead>
<tr>
<th>ISSUE</th>
<th>ELEMENT</th>
<th>SPECIFIC DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interaction with other existing intervention and control strategies</td>
<td>Impacts of program (catch up) on safety and efficacy of other vaccines and other health care sectors</td>
</tr>
<tr>
<td></td>
<td>Feasibility</td>
<td>Accessibility of target population</td>
</tr>
<tr>
<td></td>
<td>Vaccine registration and regulations</td>
<td>Availability of the vaccine and long term supply in public and private sector including collaborations with insurance sector, National regulatory authorities requirements for licensing the vaccine and/or its use in a different schedule as originally recommended</td>
</tr>
<tr>
<td></td>
<td>Impact on resources</td>
<td>Availability of human, technical and financial resources for distribution (including cold chain sustainability); consider additional training needs of health workers</td>
</tr>
<tr>
<td></td>
<td>Ability to evaluate</td>
<td>Availability of information systems to manage the vaccine supply chain and measure related performance metrics i.e. coverage and vaccine utilisation, Existence and reliability of surveillance system</td>
</tr>
<tr>
<td></td>
<td>Acceptability</td>
<td>Perception of the public and medical community about the disease and the vaccine</td>
</tr>
<tr>
<td></td>
<td>Equity</td>
<td>Universality, accessibility and gratuity of services for all the inhabitants in the country including vulnerable, hard to reach and immigrant populations</td>
</tr>
<tr>
<td></td>
<td>Social considerations</td>
<td>Non health related effects of vaccination, ethical considerations, legal implications etc.</td>
</tr>
</tbody>
</table>

**NB:** Vaccine safety data should always be selected as a component of a recommendation framework.