Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination

Immunization, Vaccines and Biologicals

World Health Organization

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Acknowledgements

Abbreviations & acronyms

AIDS	acquired immunodeficiency syndrome
Anti-PRP	anti-polyribosyl ribitol phosphate
AVI	Accelerated Vaccine Introduction Initiative
BCG	bacille Calmette-Guérin (vaccine)
BP	blood pressure
CDC	Centers for Disease Control and Prevention
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
DTP	diphtheria-tetanus-pertussis vaccine
EPI	Expanded Programme on Immunization
GAVI	GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunizations)
GBD	Global Burden of Disease project (WHO)
GFIMS	Global Framework for Immunization Monitoring and Surveillance
GRL	Global Reference Laboratory
Hi	*Haemophilus influenzae*
Hib	*Haemophilus influenzae* type b
HibCV	*Haemophilus influenzae* type b conjugate vaccine
HIV	human immunodeficiency virus
IBD	invasive bacterial disease
IB VPD	invasive bacterial vaccine-preventable disease
ICD	International Classification of Diseases
IPD	invasive pneumococcal disease
IRB	institutional review board
IRR	incidence rate ratio
LP	lumbar puncture
OPV	oral polio vaccine
OR	odds ratio

PCR	polymerase chain reaction
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
PneumoADIP	Pneumococcal Conjugate Vaccine Accelerated Development and Introduction Plan
PRP	polyribosyl ribitol phosphate
RCT	randomized controlled trial
RR	relative risk
RRL	Regional Reference Laboratory
RSV	respiratory syncitial virus
TBD	to be decided
UNICEF	United Nations Children's Fund
VPD	vaccine-preventable disease
WHO	World Health Organization

Preface

Streptococcus pneumoniae and *Haemophilus influenzae* type b (Hib) are two of the leading causes worldwide of vaccine-preventable disease (VPD) in young children. In 2000, in children under five years of age, more than 820 000 deaths were estimated to have been caused by pneumococcus and more than 370 000 deaths by Hib. The World Health Organization (WHO) recommends the use of pneumococcal conjugate vaccine (PCV) and *Haemophilus influenzae* type b conjugate vaccine (HibCV) in routine childhood immunization programmes in all countries.

Recent years have seen an unprecedented worldwide increase in the introduction of new vaccines, such as PCV, and underutilized vaccines, such as HibCV, into routine childhood immunization programmes. WHO recommends that the impact of vaccination on disease occurrence is assessed in countries that introduce vaccines, such as PCV and HibCV, in line with the Global Framework for Immunization Monitoring and Surveillance (GFIMS) recommendations. Demonstrating vaccine impact on disease occurrence can provide evidence to: inform and sustain vaccine policy decisions; allow parents, health-care providers and decision-makers to appreciate the benefits of vaccination; assess the programmatic use of vaccine, and monitor progress towards national and international child health goals. Some new and underutilized vaccines can be significantly more expensive than existing vaccines used in national immunization programmes. There is, therefore, substantial interest among decision-makers regarding the value of PCV and HibCV and, importantly, their impact on health outcomes.

Bearing in mind the pressing need for vaccine impact assessments, public-health officials and researchers should be aware that it is essential to choose a method to generate national data that takes into account surveillance capacity in any given country. Should more specific information be required than surveillance alone can provide, a vaccine impact study could be conducted. The choice of design of such a study should be carefully considered. Furthermore, the interpretation of the possible outcomes of surveillance or a study should be considered in advance of data collection. Failure to do so is likely to result in inaccurate conclusions, or uninterpretable data, that could mislead or confuse rather than resolve or clarify the local situation.

The current manual describes approaches to measuring PCV and HibCV impact on disease occurrence and a framework for determining the best methodology for measuring that impact for different country or epidemiologic settings. The document is divided into five sections containing a brief description of pneumococcal and Hib disease and their associated conjugate vaccines, approaches to assessing their impact using surveillance data and observational studies and a framework for deciding the most appropriate method for the setting. The annexes provide protocols and data-collection instruments that would accompany the studies described in the main body of the document, and specifically a prototype protocol for a case-control study to assess PCV effectiveness against invasive pneumococcal disease. This prototype protocol can be adapted for HibCV, submitted to institutional review boards (IRBs) and implemented following site-specific modifications.

1. Introduction

Globally, *Streptococcus pneumoniae* (pneumococcus) is the most important cause worldwide of vaccine-preventable deaths in children <5 years, causing an estimated 820 000 deaths in 2000 (*1*). In 2000, *Haemophilus influenzae* type b (Hib) caused an estimated 370 000 deaths in the same age group, before widespread use of the vaccine (*2*). Pneumonia is one of the leading killers of children worldwide, and pneumococcus and Hib are two of the most important causes of severe pneumonia where pneumococcal conjugate vaccines (PCV) and Hib conjugate vaccines (HibCV) are not routinely used (*3*). Due to this high disease burden, the introduction of PCV and HibCV into routine childhood immunization programmes is a high priority for many national governments and international agencies, including the World Health Organization (WHO) and the GAVI Alliance.

PCV and HibCV have excellent safety profiles and have shown high effectiveness against pneumococcal and Hib disease, respectively. WHO recommends the use of PCV and HibCV in routine childhood immunization programmes in all countries and especially those with a high child mortality (*4,5*). Studies have estimated that specific PCV formulations and HibCV could reduce overall under-five mortality by 11% and 4%, respectively (*6,7*), suggesting that use of these vaccines is important for achieving Millennium Development Goal (MDG) 4, to reduce under-five mortality by two-thirds between 1990 and 2015 (*8*). Routine use of PCV and HibCV is increasing worldwide, although PCV is just beginning to be implemented in low-income countries, where it is needed most (*9*). The largest rise in the use of HibCV in recent years has occurred in developing countries (*10*).

WHO recommends an assessment of the impact of programme-based introduction of PCV or HibCV (*11*). A vaccine impact assessment is a study that measures changes in outcomes that are attributable to a public-health intervention or programme, in this case, changes in pneumococcal or Hib disease following PCV or HibCV introduction, respectively (*12*). Vaccine impact assessments can measure effects of the vaccine that are direct (occur among vaccinated community members) and indirect (occur among unvaccinated community members). Both PCV and HibCV can reduce nasopharyngeal carriage, and the subsequent reduction in circulation and transmission of the organism and disease in unvaccinated individuals is called the indirect effect, or herd protection.

This document outlines different methods to measure the impact of PCV and HibCV on disease occurrence. It is important to remember that data analysis and studies must be conducted using surveillance data of the highest possible quality and with the best possible epidemiological and statistical oversight. Ensuring high quality of data, analysis and interpretation can avoid the problem of misleading or uninterpretable studies. If policy decisions are based on poor-quality data or analyses, immunization programmes may suffer. Thus, it is essential to understand the quality of surveillance data available and to establish surveillance of the highest possible quality. If further studies are needed to provide additional information to surveillance, then the appropriate study design should be judiciously selected for each given setting and purpose. The primary objective of this guide is to provide a systematic and standardized framework for measuring impact of PCV and HibCV on disease burden, and relevant to settings with a range of surveillance, epidemiologic study capacities and financial resources. It is divided into five sections.

1) Section 1 is an introduction that contains a brief description of pneumococcal and Hib disease, PCV and HibCV, and approaches to assessing their impact, and also a framework for deciding the most appropriate methods for the setting.

2) Section 2 describes how to measure PCV and HibCV impact using surveillance data.

3) Section 3 discusses methods to measure PCV and HibCV efficacy and effectiveness (i.e. is the vaccine as effective in the field as would be expected from clinical trials).

4) Section 4 discusses identification of cases and health-outcome measures that can be considered when measuring the impact of PCV and HibCV.

5) Section 5 provides the conclusion and summary of the methods described.

1.1   Target audience and scope of the manual

This manual is targeted at public-health officials and scientists in countries where PCV or HibCV will be introduced in the near future, or where PCV or HibCV has recently been introduced within the last six months to a year. Within these countries, this document should be useful for programme managers and technical staff in ministries of health and other agencies working in national disease surveillance and immunization services. Its purpose is to help country health planners and public-health officials identify the most appropriate method to measure the impact of PCV or HibCV in their particular setting, and to understand the advantages and disadvantages of each method. The manual does not provide a comprehensive description of how to carry out each method. Country officials considering a vaccine impact assessment should discuss their plans with local and regional experts, including research partners, and WHO and UNICEF colleagues. For example, if a country has no existing meningitis surveillance, there are resources available through, WHO and other partners, that describe how to set up such a system (13,14,15). Laboratory methods to be used to diagnose meningitis resulting from these vaccine-preventable pathogens can be found at *http://whqlibdoc.who.int/hq/2011/WHO_IVB_11.09_eng.pdf*. If country public-health officials wish to conduct a surveillance analysis or an epidemiological study (such as a case-control study), they may need to consult with an epidemiologist, statistician or other appropriately experienced person, to develop a comprehensive protocol. Interpretation of surveillance findings is particularly challenging when surveillance begins around the time of vaccine introduction. Detailed description of the interpretation of surveillance findings, or an epidemiological study, is beyond the scope of this document, but should be recognized as essential for understanding and meaningfully interpreting the impact of PCV and HibCV.

The methods discussed in this document can be applied to a range of settings, but particular emphasis will be placed on the options for resource-limited countries whose technical capacity may be constrained by limited human and financial resources, limited routine disease surveillance infrastructure, or weak health systems.

This manual is a companion to other WHO documents on approaches to establish and strengthen hospital-based sentinel surveillance systems for invasive bacterial vaccine preventable diseases (IB VPD) (see *http://www.who.int/nuvi/surveillance/resources/en/index.html*). The manual does not discuss methods for evaluating the impact of PCV or HibCV introduction on the immunization programme itself. However, there is a Post Introduction Evaluation (PIE) Tool to determine the impact of introducing a new vaccine on the vaccine programme (available at *http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.03_eng.pdf*). Other tools are also available that describe how to evaluate specific aspects of the immunization programme, such as immunization coverage surveys (*http://www.who.int/vaccines-documents/DocsPDF05/www767.pdf*) and vaccine management assessments (*http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.02_eng.pdf*).

1.2   Why are vaccine impact assessments necessary?

Measuring the effects of newly introduced vaccines can, in principle, demonstrate vaccine impact on morbidity and sequelae, as well as on mortality in the field, and establish epidemiologic patterns of pneumococcal and Hib disease after vaccine implementation (Table 1). Pneumococcal conjugate vaccine is not yet widely used globally, but the vaccine has had dramatic effects on pneumococcal disease in the primarily high-income countries where PCV is currently used routinely (*16,17,18*). While randomized controlled clinical trials have demonstrated the efficacy of PCV against a range of pneumococcal disease outcomes in many countries, including two in Africa (*6,19,20*), currently, few low-income countries have introduced PCV into their national immunization programmes. This evidence base is further supported by observational studies following routine use of PCV in industrialized countries, but little information is available on the impact of routine PCV use in low-income settings where circulating pneumococcal serotypes may differ. This contrasts with HibCV, which has been implemented in a large number of developing countries where it has been shown to be highly effective (*21–25*). While there is little need to demonstrate repeatedly that HibCV works well, studies that demonstrate the impact of the vaccine are needed, to provide geographical representation and show effectiveness in special populations, such as children with human immunodeficiency virus (HIV) infection.

Second generation PCV, with increasing numbers of pneumococcal serotypes, are licensed on the basis of immunogenicity trials showing that they are non-inferior to the first generation 7-valent conjugate vaccine. As these trials depend on immunogenicity, not disease outcomes as their end-points, there will be little, if any, disease-specific impact or efficacy data for these products before their routine use. For this reason, post-licensure vaccine impact assessments of newer, higher-valency PCV will be important to evaluate the effectiveness of PCV against serotypes not included in the lower-valency products, and to ensure comparable effectiveness against common serotypes.

Although WHO recommends that all countries assess the impact of PCV and HibCV on disease, the depth of this assessment can vary considerably and depends on the local context and availability of human, financial and technical resources. Surveillance for vaccine-preventable diseases (VPD) should be linked to introduction of new vaccines, as part of strengthening health systems and also potential research capacity. Rigorous measurement of the degree to which pneumococcal and Hib disease is reduced due to PCV or HibCV introduction can provide reliable information to guide priorities and policy decisions. Impact assessments are most valuable when complementary programmatic information is gathered, in addition to data, on the reduction in disease occurrence. For example, information on challenges in vaccine delivery and cold-chain capacity provides reasons why the measured vaccine effectiveness in terms of disease reduction may be lower than anticipated (*26*). Furthermore, capturing timely and valid epidemiological information to control VPD is one of the aims of WHO and the GFIMS (*11*).

High-quality data, that is globally representative, will also continue to be required to monitor serotype shifts. Following PCV7 introduction, data from selected countries, or populations within countries, have shown decreases in invasive pneumococcal disease (IPD) due to PCV7 serotypes, while IPD due to serotypes not in PCV7 have increased, though the magnitude of increase varied across countries (*27,28*). Reduction in IPD overall was observed in all sites for children under five, despite increases in incidence of non-vaccine serotypes. In the older age group, the results were variable, with some sites showing overall increases in disease and others showing overall decreases. For meningitis, the most serious of the pneumococcal syndromes, reductions in PCV7-type and all-serotype meningitis for children under five were evident at 3–4 years post-introduction; by five or older, all-serotype meningitis had declined by approximately 75% (*29*).

There may be numerous drivers of these rate increases, including PCV introduction and other factors, such as improved identification of cases coinciding with vaccine introduction and natural disease trends or outbreaks (*29,30*). Serotype replacement continues to be a topic of scientific investigation. Efforts are underway to more clearly understand the drivers of pneumococcal disease epidemiology and the role that PCV may play in such serotype shifts. However, based on available data, concern over serotype replacement should not be an impediment to PCV introduction, and the observed increases in non-vaccine serotype IPD with the use of PCV 7 are likely to be mitigated by the use of PCVs with broader serotype coverage.

Table 1: Objectives and rationales for assessing pneumococcal and Hib conjugate vaccine impact

Objective	Rationale
Measure vaccine impact on pneumococcal/Hib morbidity and mortality in a routine use setting.	• The impact of PCV and HibCV on mortality and morbidity from randomized trials may not be applicable to the real-world setting where limited resources may lead to immunization programme problems, such as breaks in the cold chain, alternative immunization schedules and delayed or incomplete vaccination. Conversely, in some settings, indirect effects could result in benefits greater than those seen in clinical trials, as non-vaccinated populations may receive protection from populations vaccinated through the routine immunization programme. • Although clinical trials illustrate robust PCV and HibCV efficacy against many health outcomes, including X-ray confirmed pneumonia and all-cause mortality, post-introduction impact data for PCV are not yet available for all regions of the world. Post-introduction impact data are missing or limited in regions and settings where these vaccines have not been widely used. • Economic evaluations using health impact data provide the evidence base that allows for informed decision-making and priority setting. • Measured impact can form the basis for rational decisions on whether to sustain or enhance PCV and/or Hib vaccination coverage. Such studies can also contribute to decisions on whether to introduce PCV or HibCV in neighbouring countries. • The effectiveness of alternative immunization schedules, including delayed or incomplete vaccination due to programme limitations, is not well understood. • Evidence of ongoing disease after introduction of new vaccines can reveal new or pre-existing weaknesses in vaccine-delivery systems, such as compromises in the cold chain that could reduce vaccine potency (i.e. freezing vaccines), and logistical challenges that reduce coverage.
Establish epidemiologic patterns of pneumococcal and Hib disease after vaccine implementation.	• Following vaccine introduction, particularly of PCV, age, serotype distribution and antimicrobial resistance patterns of disease can change. • Herd protection (i.e. reduction in disease among non-vaccinated populations because of reduced transmission) can be assessed following vaccine introduction and may be an important component of a vaccine programme's overall benefit.
Measure the impact of routine use of the vaccines on nutritional status and all-cause, i.e. overall infant survival.	• Preventing Hib and pneumococcal disease episodes may have a greater effect than expected on child development, growth and overall survival, by making children generally less vulnerable to disease and malnutrition.

1.3 Epidemiology of pneumococcal and Hib disease

1.3.1 Pneumococcal disease

S. pneumoniae is a gram-positive, encapsulated bacterium with more than 90 identified serotypes. Serotypes are characterized by the different polysaccharide configurations that make up the capsule of the bacterium. Not all serotypes have the same potential to cause disease; the distribution of disease-causing serotypes varies to some degree by geography, age and disease syndrome. In spite of this variability, a limited set of serotypes are commonly found to cause disease among children under five around the world (*31*). Pneumococcus frequently colonizes the upper respiratory tract, and the human nasopharynx is the only natural reservoir for it. Pneumococcus is transmitted through contact with respiratory droplets, and nasopharyngeal carriage is the first step of pathogenesis. Nasopharyngeal carriage rates of pneumococcus in children <5 years of age vary from 40% to greater than 90% (*32,33*); there is a paucity of data on carriage rates in children above nine years of age and in adults, but limited data from high-income countries indicates that they are much lower (an estimated 10%) than seen in young children (*34*). Different serotypes vary in their tendency to cause asymptomatic nasopharyngeal colonization. For example, serotype 1 is a common cause of disease in much of the world but is rarely identified as being carried in the nasopharynx in asymptomatic individuals.

Pneumococcus can cause a wide range of disease syndromes of varying severity. Invasive pneumococcal disease (IPD) is caused when pneumococcus enters the bloodstream or cerebrospinal fluid (CSF) from the respiratory tract and presents as meningitis, bacteraemic pneumonia, or sepsis. Other diseases caused by pneumococcus include non-bacteraemic pneumonia, otitis media, sinusitis, bronchitis and conjunctivitis. The most common manifestation of severe pneumococcal infection is pneumonia, accounting for >95% of all pneumococcal disease globally (*1*). Pneumococcus is estimated to account for about one-third of all pneumonia with an alveolar consolidation confirmed by chest X-ray (*1*). Pneumococcal meningitis is very severe. Case-fatality rates for pneumococcal meningitis range from 27% to 80% globally, with higher rates observed where medical resources are limited (*1,35*); survivors often have long-term sequelae such as hearing loss and other neurological damage (*36*).

In 2000, globally, pneumococcal infections caused an estimated 14.5 million cases of severe disease and more than 820 000 deaths in children <5 years of age, with the majority of deaths occurring in developing countries (*1*). Pneumococcal disease is most common in the very young and very old but can cause disease throughout life. In the United States, before PCV introduction, the annual incidence of invasive pneumococcal disease was nearly 100 cases per 100 000 population in children <5 years of age and adults >80 years of age. Pneumococcal disease is significantly more common in individuals with HIV/AIDS (*37*), which shifts the burden of pneumococcal disease to young adults in countries with a large HIV burden such as in central and southern Africa. Pneumococcal disease is also more common in individuals with sickle-cell disease and other immunocompromising conditions (*38*). The risk of pneumococcal disease is increased following viral respiratory infections such as influenza and respiratory syncitial virus (RSV), and in smokers. In general, pneumococcus is not prone to epidemics, but there can be large seasonal and secular trends in serotype distribution, and epidemics of serotype 1 pneumococcal meningitis have been seen in Africa (*39*).

Following PCV introduction, the changes in pneumococcal epidemiology occur, not only in the age group targeted for vaccine use, but also in other age groups (*40*). Because of declines in disease incidence caused by serotypes included in the vaccine among vaccinated young children, there is consequential reduction in disease among unvaccinated individuals; these serotypes have been virtually eliminated in the United States seven years after vaccine introduction (*41*). In some populations, there has been an increase in the incidence of disease caused by non-vaccine serotypes. This has been termed "serotype replacement" and implies that such increases are caused by the introduction of PCV. However, care must be exercised in applying this term because increases in non-vaccine type disease rates are also observed as temporal trends unrelated to PCV introduction, or as changes in reporting of pneumococcal disease improves as vaccine is introduced. The magnitude of replacement disease has been variously reported. Among American and Australian children, invasive disease caused by non-vaccine serotypes has increased relatively little compared to reductions in vaccine-type disease (*41,42*). Among Alaska Native children living in a remote region, increases in nonvaccine serotype disease have been more substantial (*27*). In the USA, serotype 19A, which is not included in the previously used 7-valent formulation, has been reported to have increased the most following PCV introduction (*28*). PCV introduction has resulted in overall reductions in IPD incidence in children <5 years of age despite increases in incidence of IPD caused by nonvaccine serotypes; the magnitude of the reduction in all serotype-IPD depends in part on the magnitude of increase in pneumococcal disease rates from serotypes not included in the vaccine; serotype replacement should not be an impediment to PCV introduction, and the observed increases in nonvaccine serotype IPD with the use of PCV7 are likely to be mitigated by the use of PCVs with broader serotype coverage (*29*).

1.3.2 Haemophilus influenzae

Haemophilus influenzae (Hi) is a gram-negative bacterium that can be either encapsulated or non-encapsulated; either form can cause infection. There are six typeable encapsulated Hi serotypes (a–f). Type b Hi (Hib) causes over 90% of invasive disease in settings where HibCV is not routinely used (*43*). Both non-encapsulated Hi and Hib frequently colonize the upper respiratory tract and are transmitted through contact with respiratory droplets. Hib may colonize the nasopharynx for several months without causing disease. Carriage rates of Hib can vary from 1% to 10% in different populations (*44,45*).

In 2000, Hib caused an estimated eight million serious cases of illness globally and 371 000 deaths in children <5 years of age, the majority in developing countries (*2*). Invasive Hib disease is caused when Hib enters the bloodstream through the respiratory mucosa. Invasive Hib disease most frequently presents as meningitis (approximately 50% of invasive Hib infections), followed by septic arthritis, sepsis, bacteraemia and bacteraemic pneumonia, cellulitis and epiglottitis (*46*). In addition, epiglottitis has a higher incidence in North America and Europe and a lower incidence elsewhere.

The clinical syndromes seen in a given country vary depending on the frequency and likelihood of a sick child having blood cultures collected, and on the laboratory capacity for successfully isolating Hib. Disease syndromes that do not include bloodstream, CSF, or joint fluid infection are usually considered non-invasive and include non-bacteraemic pneumonia, otitis media, sinusitis and conjunctivitis. Similar to pneumococcus, the most common manifestation of Hib infection is pneumonia.

In settings without routine HibCV use, HibCV is expected to prevent about 20% of all pneumonia with an alveolar consolidation identified on chest X-ray, 5% of all hospitalized severe pneumonias (*47,48*) and 42% of all bacterial meningitis cases with known etiology in children <5 years of age (*43*). Based on vaccine probe studies, the incidence of severe pneumonia preventable by HibCV is approximately 200–300 per 100 000 children under age two per year (*49–51*) and for all pneumonias may be as high as 1500 per 100 000 per year (*50,51*). The case-fatality rate for Hib meningitis documented among patients that present for medical care and diagnostic evaluation ranges from 3% to 20% globally; in many resource-poor settings, patients with Hib meningitis are likely not to access medical facilities in time to receive appropriate antibiotic therapy and, in these circumstances, Hib meningitis case-fatality rates may approach 100% (*2,52*). Survivors have a high risk of long-term sequelae such as hearing loss and other neurological damage (*35,53*).

1.4   Pneumococcal and Hib conjugate vaccines

1.4.1 Pneumococcal conjugate vaccines

The first pneumococcal vaccines were inactivated whole-cell vaccines developed in the early 1900s. These were highly reactogenic but also effective. These first vaccines were supplanted by polysaccharide vaccines that included one or more pneumococcal capsular serotypes. However, penicillin became widely available to treat pneumococcal disease, so that further development and deployment of pneumococcal vaccines largely ceased. Continued morbidity and mortality from pneumococcus during the antibiotic era in the 1960s led to the development of the next generation of purified capsular polysaccharide vaccines. Unfortunately, these vaccines did not give strong or long-lasting immunity, especially in infants among whom disease rates were highest. The next step in development resulted in today's vaccines. The discovery that capsular polysaccharide could be linked—or covalently conjugated—to carrier proteins that stimulate a robust, lasting immune response in infants and young children revolutionized the field.

Pneumococcal conjugate vaccines (PVCs) have been commercially available since 2000. They have been shown in clinical trials to be highly effective for protecting infants and young children against IPD caused by vaccine serotypes, and to diminish acquisition of carriage by serotypes included in the vaccine. Pneumococcal conjugate vaccines currently licensed contain antigens for 7, 10 and 13 serotypes (Table 2). All three vaccines are now prequalified by WHO for use in developing countries. Researchers are currently working on additional conjugate vaccines, as well as vaccines made of protein antigens that are conserved across pneumococcal serotypes so that an immune response can be generated against all pneumococci regardless of their serotype.

Table 2: Current pneumococcal conjugate vaccines

Pneumococcal vaccine	Serotypes included	Conjugate protein	Trade name (manufacturer)
PCV7	4, 6B*, 9V, 14, 18C, 19F, 23F	Mutant diphtheria toxoid (CRM 197 protein)	Prev(e)nar® (Pfizer)
PCV10	4, 6B*, 9V, 14, 18C, 19F, 23F, 1, 5, 7F	Protein D from non-typeable *Haemophilus influenzae*, tetanus toxoid and diphtheria toxoid	Synflorix® (GlaxoSmithKline)
PCV13	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A	CRM 197 protein	Prev(e)nar-13® (Pfizer)

*Also favourable cross-protection against serotype 6A.

The WHO recommends the use of PCV in routine childhood immunization programmes in all countries and particularly in countries where all-cause mortality among children aged <5 years is >50 per 1000 live births or where >50 000 annually children die from any cause, and in countries with a high prevalence of HIV infection (*4*). By contrast to HibCV, PCV are not currently available in a combined form with other vaccines and, considering the antigenic load, are unlikely to be combined with other vaccines. Among countries using PCV, a variety of immunization schedules are used. The most common schedules are three PCV doses in the first six months with a booster near or after 12 months of age, two early PCV doses with a booster near or after 12 months and three early PCV doses without a booster (*http://apps.who.int/immunization monitoring/en/globalsummary/ScheduleSelect.cfm*). Accelerating the introduction of PCV is a global priority, particularly in low-income countries.

Data from PCV clinical trials have demonstrated efficacy against a number of outcomes: vaccine-type IPD (80%–89%), all serotype IPD (55%–58%), vaccine serotype otitis media (29%–55%), radiograph-confirmed and clinical pneumonia (27%–29% and 6%, respectively) and all-cause mortality (11%) (*6,54*). PCV have been found to be safe and have few side effects (*55*).

1.4.2 Hib conjugate vaccines

Hib conjugate vaccines are some of the safest vaccines available and, in clinical trials and post-licensure studies, have been shown to be over 90% efficacious against invasive Hib disease (*13*). Hib conjugate vaccines have been widely used in industrialized countries for nearly 20 years. Currently, HibCV is available in monovalent, tetravalent, pentavalent and hexavalent preparations, and there are more than 30 Hib-containing vaccine products available worldwide. Most low-income countries using HibCV use a pentavalent (diphtheria-tetanus-pertussis [DTP]-hepatitis B-Hib) formulation in a three-dose primary infant schedule without a booster dose. Among middle- and high-income countries, a variety of formulations are utilized, and the majority of schedules include a booster dose in the second year of life (*http://www.who.int/vaccines/ globalsummary/immunization/diseaseselect.cfm*).

Accelerating the global use of Hib conjugate vaccine, particularly in low-income countries, has been a high priority for several international agencies and global immunization partners. Studies have shown the effectiveness of Hib vaccine in a variety of settings, although data from some regions, such as northern and eastern Africa and eastern Europe, are still relatively limited (56).

1.5 How to approach pneumococcal and Hib conjugate vaccine assessment in the context of routine immunization

At its simplest, measuring vaccine impact compares the burden of disease caused by the pathogen included in the vaccine, in a population that has received the vaccine, to the burden of disease in a population that has not received the vaccine. On a practical country level, this can be accomplished by using two analytic strategies.

1) Surveillance or surveys to assess disease burden changes over time (e.g. if pneumococcal disease burden goes down after PCV introduction). This can be assessed in terms of direct effects and/or indirect effects, depending on the data available.

2) Special epidemiological studies to determine vaccine efficacy (the degree to which the vaccine, when given under optimal research conditions, lowers disease incidence) or vaccine effectiveness (the degree to which the vaccine reduces the occurrence of disease in routine settings).

Within these two analytical strategies, there are a number of common study designs that are used and these will be discussed in Sections 2 and 3 (Table 3). Surveillance is generally used to assess vaccine impact by evaluating trends in disease burden data. As a general rule, population-based or sentinel hospital surveillance is conducted based on laboratory-confirmation of the causative organism from clinical specimens. Using surveillance data to assess vaccine impact on disease outcomes requires consistent and reliable surveillance data, ideally for two years before and at least three years after vaccine introduction, for accurate measurement of disease burden changes. If serotype replacement issues are to be assessed, surveillance is recommended for at least five years after PCV introduction. Passive national surveillance systems that are laboratory-based can also be used; however, passive surveillance is likely to underestimate disease occurrence. Special epidemiological studies to assess vaccine efficacy and effectiveness can determine the proportion of a given outcome preventable by vaccine, either in a clinical trial or routine use setting, respectively. Surveillance and special studies are not meant to be exclusive, and countries may choose to do both, since these two strategies have different functions. Choosing the strategy most appropriate for a country depends on the chosen outcome and the data sources that are available. Choice of which health impact to be measured will be discussed in Section 4, and the sources of data that can be used will be discussed in the sections on each respective study design.

Table 3: Study designs and analytic methods used to monitor impact of vaccines

Assessing vaccine impact by evaluating trends in disease burden data	Assessing vaccine impact through vaccine efficacy or effectiveness
• Population-based, active surveillance • Sentinel site surveillance • Periodic surveys	• Randomized clinical trial or vaccine probe study randomizing individuals or communities • Stepped-wedge design • Cohort study • Indirect cohort study • Case-control study • Screening method

It should be noted from the outset that there are some settings where it may not be possible, under current circumstances, to accurately measure vaccine impact, such as in settings with small population size, limited laboratory capacity, certain clinical-care characteristics, high use of antimicrobial agents, high migration of the population of interest or too few resources to conduct an appropriately designed study. This manual will also assist countries in determining how to develop the capacity to measure vaccine impact themselves.

1.6   Summary and key points

1)   PCV and HibCV are recommended for use in routine childhood immunization programmes in all countries, and PCV is specifically recommended where childhood mortality is high or where there is a high prevalence of HIV infection.

2)   Where the appropriate capacity exists or can be built, public-health officials are encouraged to assess the health impact of PCV (following introduction of the vaccine into their routine childhood vaccination schedule) as an important component of the vaccine introduction activities. The effect of PCV and HibCV on decreasing adverse health outcomes can be measured through a number of methods.

3)   As HibCV has been well documented in many locations around the world to decrease disease, vaccine impact assessments of HibCV would be most useful in countries without good regional data on the magnitude of the disease reduction, or with specific understudied populations, such as HIV-infected individuals.

2. Assessing vaccine impact by monitoring trends in disease surveillance data

Surveillance is defined as the ongoing and systematic collection, consolidation, analysis and dissemination of data to monitor disease and to identify and describe patterns of infection. Pneumococcal and Hib disease surveillance in children has the following main objectives.

1) Demonstrate the burden of confirmed pneumococcal and Hib 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 and HibCV.

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 epidemiologic patterns of pneumococcal and Hib disease after vaccine introduction, including changes in serotype distribution.

Surveillance may be active or passive. Active case finding—where efforts are made to proactively capture all cases in a population—will provide a more complete count than passive reporting where public-health officials rely on clinicians or laboratories to report cases, without regular reminders. Regardless of whether surveillance is active or passive, changes in surveillance practices may occur around the time of vaccine introduction, as a clinician's awareness may be raised about the diseases prevented by the vaccine, and this factor should be considered when interpreting surveillance data. Additionally, vaccine impact on adverse health outcomes is affected by many factors, including vaccine efficacy, vaccine coverage, time elapsed since vaccine introduction, indirect effects and/ or the presence of a vaccination catch-up campaign for older children. A high level of immunization coverage may be needed to show an impact on more non-specific disease outcomes, and year-to-year variation of pneumococcal and Hib disease, and diseases with similar clinical manifestations (e.g. influenza and meningococcal disease) can make it difficult to tease out the actual effects of vaccine if clinical outcomes are used. Despite these known limitations of using trends to monitor vaccine impact, surveillance is an essential part of any immunization and public-health programme because data will be provided to meet the desired objectives described above.

In order to obtain globally representative data for Hib and pneumococcal disease, WHO recommends a layered approach to IB VPD surveillance that utilizes sentinel hospitals and a 3-tiered approach (*http://www.who.int/nuvi/surveillance/en/*) (*57*). WHO's vision is that the data from this global surveillance network would be combined with data from special studies to provide a complete and geographically representative global picture. Countries that participate in the first tier of surveillance, the core activity,

enroll children with suspected meningitis less than five years of age into surveillance that is usually conducted at a limited number of high functioning hospital sentinel sites. Here, cerebrospinal fluid (CSF) specimens are collected from suspected cases of meningitis and tested for *Haemophilus influenzae, Streptococcus pneumoniae* and *Neisseria meningitidis* via gram stain, culture and rapid tests. Polymerase chain reaction (PCR) methods have been shown to increase detection of these organisms and can be performed within the country or at a regional reference laboratory. Positive CSF specimens are stored at the hospital site, or national laboratories, and forwarded for serotyping at regional reference laboratories.

The second tier of IB VPD surveillance targets children less than five years of age with meningitis, pneumonia or sepsis, that are admitted to a participating sentinel hospital. Countries with more technically-equipped hospital sentinel sites and those wishing to invest more resources are able to perform this tier of surveillance. Here, in addition to CSF collected from suspected meningitis cases, blood cultures are also collected from cases of pneumonia and/or sepsis and tested for *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* via gram stain, culture, rapid tests or PCR methods.

At least one site per WHO region is also expected to conduct population-based surveillance, which reflects the third tier of IB VPD surveillance and involves enumeration of the catchment population in order to generate incidence rates of disease; these are particularly useful for evaluating vaccine impact and safety. This manual does not describe in detail how to conduct pneumococcal or Hib disease surveillance, as other documents exist that provide more in-depth guidance on Hib and bacterial meningitis (*13,14*) and also pneumonia surveillance (*58*).

A high-quality surveillance system for Hib and pneumococcal disease can be expensive, both in terms of establishing and maintaining the required epidemiological infrastructure and laboratory capacity. Ideally, laboratories in the limited number of selected hospital sentinel sites supporting surveillance activities should function 24 hours a day, seven days a week, 365 days a year, because the bacterial organisms are fragile and CSF specimens should be processed by the laboratory within one hour. This may not be feasible in many settings, so sentinel hospital surveillance should be limited to hospitals that can ensure appropriate laboratory capacity. CSF and blood specimens should be collected according to the standard criteria on all children with suspected bacterial meningitis, and transported to the laboratory within one hour. Clinical and laboratory standard operating procedures should remain stable during the surveillance period; if changes are made, the effect of these must be taken into account in interpreting trends.

The availability of high quality and reliable surveillance for pneumococcal and Hib diseases varies from country-to-country. Based on a critical analysis of Hib disease surveillance following HibCV introduction, the following guidance was proposed for improving quality of invasive bacterial vaccine-preventable disease surveillance studies (*59*).

1) Use standardized case definitions and collect information in a standardized manner. In many settings, this will involve the use of a standard case report/ investigation form.

2) Report laboratory and case-ascertainment methods.

3) Address limitations of laboratory methodology and case ascertainment.

4) Assess prior antibiotic use.

5) Acknowledge that surveillance for invasive bacterial disease (IBD) provides a gross underestimate of total disease burden as clinical syndromes, such as pneumonia, are much more common.

6) Present both unadjusted estimates, and estimates which attempt to incorporate cautiously the effects of cases missed, using the adopted surveillance strategy.

Additionally, the quality of the surveillance system should be monitored over time by standard surveillance performance indicators. The indicators used in the WHO IB VPD surveillance network are included in Annex 4.

2.1 Primary data sources

Primary data sources for Hib or pneumococcal disease involve prospectively-gathered data from population-based surveillance, sentinel site surveillance, periodic surveys, or nationally notifiable disease surveillance. Some examples of primary sources are listed below.

2.1.1 Active population-based surveillance

When available, population-based active surveillance for IBD is the most accurate method of monitoring trends in IBD. Active population-based surveillance ideally takes place in all hospitals and clinics within a geographically well-defined community with good access to health facilities, little inward or outward migration and few changes in health-seeking behaviour. It is essential to ensure that everyone from the at-risk population will be captured in the hospitals or health-care centres selected. If these criteria are not met, a survey of health-care utilization practices can help define the health-seeking behaviour of the population. The most accurate population-based surveillance is prospective and involves actively finding cases, either in the community or at a hospital. The catchment area of patients utilizing the hospitals and clinics should be known, and participating hospitals and clinics should be the sole source of treatment in the area for children with serious pneumococcal and Hib disease.

Because active, population-based surveillance results in a complete case count among a defined at-risk population, this method of surveillance can be truly representative and allows incidence rates (i.e. the number of cases divided by the population at risk) to be calculated. An accurate estimate of the size of the population under surveillance is needed for this calculation. As culture-proven pneumococcal and Hib disease are relatively difficult to identify, the population under surveillance must be large enough to generate a sufficient number of cases, particularly as the number of pneumococcal and Hib cases will decline following vaccine introduction. A significant disadvantage of active, population-based surveillance is that tracking the population at risk is highly resource intensive. Hospital-based surveillance may not provide an accurate measure of disease burden in a population when subjects do not seek care at participating facilities and appropriate testing is not reliably performed.

2.1.2 Hospital-based sentinel site surveillance

Hospital-based sentinel site surveillance is the most common method used for describing pneumococcal and Hib disease trends in resource-poor settings because it is less resource intensive than active, population-based surveillance, and can be restricted to a limited number of hospitals that have adequate laboratory capacity. In contrast to population-based surveillance, sentinel site surveillance typically takes place in one or more, but not all, hospitals or clinics in a country or region. The participating hospitals record all clinical and laboratory-confirmed cases of meningitis (Tier 1 sites) or IBD (Tier 2 sites, enrolling meningitis plus pneumonia and/or sepsis cases), regardless of whether the patients are from the catchment area or not. This type of surveillance system does not allow calculation of incidence rates, as the true catchment population is usually unknown, but it does allow measurement of disease trends over time if hospital admission rates, health-seeking behaviour and surveillance methods remain stable. The generalizability of surveillance data is limited if the sentinel site or population is not representative of the national population, particularly if vaccine coverage varies sub-nationally. In general, it is best to choose large hospitals as sentinel hospitals in order to identify the largest possible number of cases for surveillance analyses. However, the relatively small number of patients with IB VPD at a single sentinel hospital, even a large referral facility, may limit the ability to use sentinel hospital surveillance to demonstrate direct vaccine impact on disease occurrence. In addition, referral hospitals often take care of children who have been transferred from other facilities; many of these children have already received antibiotic treatment, and it can be more difficult to identify cases of pneumococcal or Hib disease in these patients.

2.1.3 Periodic surveys

In some cases, as ongoing surveillance is not feasible or too expensive to maintain, periodic surveys can provide a method of gathering data on a regular basis. This study design is often used with serosurveys, for immunogenicity studies, and carriage studies, where a defined number of children are tested for carriage of pneumococcus or Hib before and after vaccine introduction, one or more years apart, but often at the same time of year to account for seasonal variation.

2.1.4 Nationally-notifiable disease surveillance

Nationally-notifiable diseases are legally mandated to be reported to public-health officials to help monitor, prevent and control disease. Notifiable disease surveillance is a passive system where cases are reported by medical or laboratory professionals. The list of notifiable diseases in some countries may include pneumococcal or Hib disease. If reporting of notifiable diseases has been consistent, the surveillance system can be used to monitor trends in disease. However, it is important to recognize that, because this type of surveillance is passive, underreporting of disease will be common and so this method is likely to underestimate its true occurrence. There may also be other biases in reporting that are difficult to measure and account for.

2.2 Secondary data sources

In contrast to primary data sources that are collected on health outcomes, secondary data sources are existing data collected for another purpose, such as routine hospital clinical and administrative data and national mortality data. Such secondary data sources are a potential source of information to describe trends and can be analysed retrospectively. Secondary data have been successfully used to monitor the impact of vaccines, such as rotavirus vaccines, on diarrhoeal disease (*60*), and in places where active surveillance is not available. It is attractive to consider using existing data to monitor PCV or HibCV impact. The usefulness of secondary data for measuring PCV or HibCV impact is dependent, in part, on the choice of outcome. If laboratory and health-care utilization practices have been stable, meningitis cases at hospitals may be robust enough to retrospectively demonstrate an impact on disease; however, hospital-to-hospital variation may yield inconsistent results when measuring the impact of HibCV and PCV among individual medical facilities (*61*). For pneumonia outcomes, the impact of PCV introduction has only been shown in large, stable, secondary datasets that use specific case definitions or administrative codes, such as with national surveys, provincial health administrative records, or large health maintenance organization databases in the United States, Canada, and Australia (*62–66*). These analyses may require sophisticated statistical techniques, such as interrupted time series, and may not be specific enough to demonstrate the impact of vaccine. These data could be gathered retrospectively, or prospectively through medical record reviews or administrative data (e.g. with ICD-9 or ICD-10 codes). In general, secondary data sources are not recommended to be used as the main method of measuring PCV or HibCV impact. However, there may be settings, such as those with large enough populations under surveillance, and for a sufficient period, where it can be a useful and compelling adjunct to primary data collection or observational studies.

2.3 Data collection, analysis and reporting

Appropriate, timely, accurate and complete recording of surveillance data is essential to facilitate meaningful data analysis. Data should be compiled regularly in an electronic database or paper tracking logbook that allows for easy updating and checking of records, both at surveillance sites and at a central unit in the country. Missing information should be obtained and entered into the surveillance database. External supplemental data, such as that from a reference laboratory, should be entered upon receipt. In addition, simple data checks should be in place to help maintain quality of the data. For example, where surveillance is among children less than five years of age, only an age between 0 and 59 months should be allowed in the database. One adequately-resourced unit or institution per country should be responsible for overall data management, and one person in that unit should routinely perform quality-control assessments, such as measuring rates of lumbar punctures (LP) among suspected meningitis cases, and ensuring completion of missing data. The surveillance performance indicators which are recommended to be collected within the WHO coordinated IB VPD surveillance system can be found in Annex 4.

Preliminary analysis of surveillance data should be done periodically by persons experienced in interpretation of data, to look for trends, as well as for additional checks of data problems. Data analysis for a vaccine impact assessment should only occur after the data has been cleaned (i.e. when data are as accurate and complete as possible). When available, incidence rates are preferable to case counts as, over time, they will

account for population denominator variations. The incidence of all disease syndromes can be crudely adjusted for access to care, by dividing the measured incidence by the estimated proportion of children with those disease syndromes that go to a health-care facility, a figure typically obtained from health-care utilization surveys in the actual, or a comparable, setting. The simplest method to measure the impact of PCV or HibCV on disease when only sentinel site data are available, is to observe the change in the absolute number of cases of the outcome of interest using the pre-vaccine year(s) as the baseline. Alternatively, one can measure the change in the percentage of Hib or pneumococcus among all bacterial meningitis cases. Table 4 presents suggested analyses that can be used for population-based or sentinel surveillance systems. A statistician or epidemiologist familiar with measuring vaccine impact should be consulted or involved with vaccine impact calculations. Recommendations for analysis of surveillance data are contained in WHO's VPD surveillance manual (14) and IB VPD surveillance guidelines (*http://www.who.int/nuvi/surveillance/resources/en/index.html*)

Several important points should be considered when analysing surveillance data to measure vaccine impact.

1) Seasonal and natural year-to-year variation in meningitis, pneumonia, pneumococcal and Hib disease rates can occur independent of vaccination. This variation can cause large swings in disease rates, especially pronounced in surveillance conducted in a single community or small number of hospitals. To account for this variation, at least two years of data prior to vaccine introduction should be analysed to establish baseline rates (although one year of pre-vaccination data may be sufficient in some settings and in others two years may be inadequate). Three years of post-vaccine data are recommended to show impact and five years of post-vaccine data are recommended to assess serotype replacement issues following PCV introduction. Maximum impact may take longer to assess if vaccine uptake is slow and depending on whether or not a catch-up campaign of older children is included in vaccine introduction.

2) In countries with epidemic meningitis, evaluations using direct measures (such as laboratory confirmation) of pneumococcal or Hib meningitis can occur regardless of the presence of a meningitis epidemic. However, analysis of pre- and post-vaccine surveillance data for a particular geographic site, and use of less specific case definitions (such as purulent meningitis) should be performed only for years when no meningococcal meningitis epidemic was declared in the region under surveillance.

3) Over time, substantial changes in the surveillance system will make changes in disease burden difficult to interpret, so surveillance performance indicators are useful. For example, when surveillance moves from a passive to an active system, the number of cases identified will increase, even if there is not a true increase in incidence of disease. Artifactual changes in disease rates may also occur if case-identification methods are enhanced at the time of vaccine introduction, or if persons reporting cases through a passive system increase reporting, which can occur due to the attention on disease generated by vaccine introduction. A change in laboratory practices, such as introduction of latex agglutination testing or lack of laboratory materials, may also affect data, as the addition of testing could lead to more case finding and a lack of supplies could result in less case finding. Similarly, changes in the catchment area of sentinel hospitals or large inward or outward migration from the catchment area will also affect data.

4) The cause of a decline in disease and the quality of the surveillance system can be assessed by comparing trends in the incidence of disease from another pathogen. For example, when assessing the impact of HibCV on Hib meningitis when PCV is not part of the routine childhood immunization system, a stable rate of *S. pneumoniae* meningitis will provide some confidence that the decline is due to HibCV.

5) In settings with high HIV prevalence, analyses must factor in the impact of changes in the HIV epidemiology, including treatment with anti-retroviral therapy or implementation of programmes to prevent maternal-to-child transmission. As prevention and treatment of HIV improves, rates of Hib and pneumococcal disease, especially pneumonia, will decline, which might obscure or overestimate impact seen by vaccine introduction. The prevalence of other important diseases, such as malaria, may also impact the health outcome, and should be considered.

6) Before introduction of HibCV, investigations in some countries calculated the burden of Hib disease using WHO's Hib Rapid Assessment Tool (*67*), which estimates Hib disease burden based on an extrapolation of the number of confirmed Hib cases in a sentinel site. While these estimates are useful for planning purposes, this tool is not designed to measure vaccine impact, as uncertainty around the estimates it generates is too great.

2.4 Summary and key points

1) High-quality pneumococcal and Hib disease surveillance in a large population of children under five years of age can measure and monitor the impact of PCV and HibCV, and this data can contribute to evidence-based decisions regarding PCV and HibCV use.

2) Population-based active surveillance for laboratory-confirmed cases of IBD is the most accurate method of monitoring trends in disease incidence over time, and allows for calculation of the direct and indirect impact.

3) Every country may wish to conduct hospital-based sentinel site surveillance for meningitis (Tier 1 IB VPD surveillance), which can serve as one method for measuring Hib and pneumococcal vaccine impact on disease occurrence in settings where either population-based surveillance or surveillance for all invasive disease (including bacteraemic pneumonia) is not possible, or not desired due to the financial and human resource implications. However, while surveillance limited to meningitis can measure vaccine impact against a serious and easily identified disease, meningitis is only a small subset of Hib or pneumococcal cases that would be identified through surveillance for all invasive disease syndromes (including bacteraemic pneumonia). Thus, meningitis surveillance by itself will underestimate the true impact of the vaccine on the overall burden of disease caused by Hib or pneumococcus because the vaccine's impact on pneumonia and sepsis is not assessed.

Table 4: Suggested metrics to demonstrate vaccine impact on adverse health outcomes from surveillance data

Metric	Calculation/method	Comment
Percent reduction in incidence of pneumococcal or Hib disease (which includes clinical syndromes caused by Hib or pneumococcus).	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 two years pre-vaccine introduction and three years post-vaccine introduction data. If pneumococcal serotype distribution is assessed, data collection is recommended for five years post-vaccine introduction. • A decline in incidence or case counts may be observed in the first year following vaccine introduction.
Percent reduction in the number of cases of pneumococcal or Hib 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 or Hib 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 Hib or pneumococcus.	Percent reduction: compare the percentage of Hib or 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 or Hib 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 or Hib disease following introduction of PCV.	Review case notes/vaccination history for cases of pneumococcal and Hib 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 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.	• Data usually obtained by using surveillance to identify cases and then conducting subsequent in-depth investigation to describe the characteristics of the cases. To obtain high-quality data on the vaccination status of cases, public-health professionals should usually collect additional data (i.e. review of vaccination cards) to complement the information provided from the sentinel hospital. • Data on the vaccination status of cases are essential to interpret and respond to ongoing cases of pneumococcal and Hib disease (68).

3. Measuring pneumococcal and Hib conjugate vaccine efficacy and effectiveness by special studies

Vaccine *efficacy* is defined as the proportionate reduction in disease incidence attributable to a vaccine when given under ideal conditions (*12, 69,70*), such as those found in a controlled vaccine trial. By contrast, we define vaccine *effectiveness* as the proportionate reduction in disease incidence attributable to vaccination under real-world conditions, including the effect of programmatic factors, such as injection techniques, reduced vaccine potency following inappropriate storage, indirect (herd) protection against the target illness, pre-existing immunity to the target illness such as that conferred by indirect immunity (for live vaccines) or previous episode of the target illness, population characteristics such as malnutrition, and any other factors that distinguish a community immunization programme from the controlled setting of a vaccine trial (*12, 69,70*). This definition, which corresponds to what has also been called "field efficacy" (*71*), does not capture low population effect of an immunization programme caused by low vaccination coverage, which is an important cause of suboptimal impact of vaccination programmes in many low- and middle-income countries.

Indirect protection occurs when vaccination of a targeted population provides immunity against disease in a population not targeted for vaccine receipt by reducing transmission of the disease within the population. By the same mechanism, it also protects individuals who were meant to be vaccinated but who were not reached by the vaccination programme. Indirect immunity occurs when vaccination of a targeted population also provides protection against disease in those not vaccinated through transmission of a live vaccine strain from the vaccinated to the unvaccinated. Where there is no indirect protection, effectiveness is normally lower than efficacy because, at the population level, extrinsic factors, such as coverage, injection techniques, cold-chain integrity and vaccine stability, can affect outcomes. With indirect protection, effectiveness may be higher than efficacy, provided coverage is sufficiently high. Indirect immunity may cause the same biases to effectiveness estimates as indirect protection (*72,73*), but it is not discussed here because indirect immunity is not a concern with killed vaccines such as HibCV or PCV. Indirect protection can substantially increase the impact of vaccination beyond what vaccine efficacy and coverage would indicate, and has contributed significantly to eliminate poliomyelitis from large parts of the world and to reduce pneumococcal disease burden in the United States and elsewhere (*41*).

Both vaccine efficacy and vaccine effectiveness can be calculated using similar formulas:

Vaccine efficacy/effectiveness

= *Incidence in unvaccinated population – Incidence in vaccinated population*
  Incidence in unvaccinated population

= *1 –* *Incidence in vaccinated population*
        Incidence in unvaccinated population

= *1 – Relative risk*

A theoretically perfect vaccine would cause the incidence of disease in the vaccinated population to be zero and would yield a vaccine efficacy of 100%. Vaccine efficacy estimates cannot be greater than 100%; a vaccine that leads to more disease in vaccinated individuals than unvaccinated individuals will yield a negative vaccine efficacy.

Vaccine impact in the population as a whole as measured in cluster-randomized trials and stepped-wedge design studies can be calculated using a similar formula:

Vaccine efficacy/effectiveness

= *Incidence in population groups not targeted for vaccination –*
  Incidence in population groups targeted for vaccination
  Incidence in population groups not targeted for vaccination

= *Incidence in population groups targeted for vaccination*
  Incidence in population groups not targeted for vaccination

= *1 – Relative risk*

A number of epidemiologic study designs can be used to estimate vaccine efficacy and effectiveness (Table 5). Post-licensure vaccine-impact studies often measure vaccine effectiveness through observational study designs such as case-control studies. With some post-licensure observational study designs and, provided sufficient information about vaccine quality and administration in the field is available, adequately assessing vaccination status and adjusting for confounding can allow for the estimation of vaccine *efficacy.* For all such vaccine studies, it is strongly advised that literature and also experts be consulted to properly address study design, surveillance protocols (if surveillance is used), sample size and selection procedures, bias and appropriate adjustment for confounders, all of which may not be recognized in advance. The remainder of this section of the manual will address some of the methods commonly used for conducting vaccine efficacy or effectiveness studies.

Table 5: Study designs and analytic methods used to measure vaccine efficacy and effectiveness

Experimental studies	Observational studies
• Randomized controlled trial randomizing individuals or clusters • Randomized controlled trial, such as stepped-wedge design randomizing communities or clusters	• Stepped-wedge design, without randomization of groups under observation • Cohort study • Indirect cohort study • Case-control study • Screening method

3.1 Experimental studies

Randomized controlled trials (RCTs) are considered the "gold standard" for measuring efficacy of treatments, vaccines and other health-care interventions. The key elements for vaccine efficacy studies are: (1) a vaccinated (study) group receives the vaccine according to protocol; (2) a corresponding *control* group receives no vaccine (receives a placebo) or an alternate vaccine, and (3) individuals or groups are *randomly* allocated to receive the vaccine or no vaccine (e.g. a placebo). The study participants are recruited in such a way that the likelihood of exposure to infectious agents and other risk factors for the target disease is representative of an intended population, such as a specific age group, in a given country.

Demonstrating vaccine efficacy through prospective, placebo-controlled trials randomizing individuals is necessary prior to licensure of most new vaccines. This was the case with the first PCV and HibCV that were developed (*6*). Since further placebo-controlled clinical trials for newer vaccines would deny timely administration of the vaccine to children (the control group) who might otherwise receive it, placebo-controlled randomized clinical trials are not generally considered ethical and are not recommended for present-generation PCV and HibCV. The ethical challenges of conducting a vaccine trial may be overcome by conducting a non-inferiority trial comparing a new vaccine to the existing one. Using a stepped-wedge design, if a ministry of health plans to roll out vaccine in a geographically sequential manner (for logistic or financial reasons), it would capture vaccine impact directly. These designs do not delay vaccine roll-out or deny vaccine to a particular group. The stepped-wedge design involves the phased or staggered introduction of the vaccine in a population by group (e.g. health-facility catchment population or district) until the entire target population is covered, and should be considered in settings where the vaccine cannot be rolled out nationwide simultaneously due to programmatic reasons. The order in which the groups are given the intervention is randomized. A stepped-wedge study can be technically challenging to conduct and, to date, no Hib or pneumococcal vaccine studies have been conducted using this design. It has, however, been used to measure hepatitis B vaccine impact (*74*).

Since PCV and HibCV have been proven to be safe and effective in clinical trials in many settings, there are not likely to be any further PCV and HibCV trials which randomize individuals. Another type of individually randomized, controlled vaccine trial follows a bio-equivalence or non-inferiority design according to guidelines set out by the European Medicines Agency or United States Food and Drug Administration. These studies use immunogenicity measures as a proxy for efficacy of new vaccines relative to licensed vaccines.

In the past, countries have considered conducting vaccine probe studies to evaluate the impact of vaccination. Vaccine probe studies are similar in design to RCTs but use a vaccine of known efficacy (or where the efficacy will be known at the end of the study) to estimate the burden of syndromic disease that can be prevented by the vaccine (for example, meningitis or pneumonia). Such studies can determine the burden of pneumococcal disease when laboratory confirmation of clinical disease is difficult, but probe studies have the same ethical concerns as RCTs since some children are denied access to a vaccine.

3.2   Observational studies

After a vaccine is introduced into a population, post-licensure, observational studies are needed to evaluate the impact of the vaccine in the field outside of the ideal conditions specific to a randomized controlled trial. Observational studies reflect routine use, and the effectiveness estimate is influenced by the practical issues, such as vaccine cold chain, delivery, indirect protection and potential effects that vary between population groups. Post-licensure impact studies are especially important for newer PCV where licensure will be granted solely on the basis of immunogenicity bio-equivalence studies and not RCTs. When vaccine impact is less than expected, vaccine effectiveness studies can help to explain this finding. Vaccine effectiveness studies can also answer specific questions related to the immunization programme, such as coverage, timeliness and an estimation of the relative effectiveness of different dosing schedules.

The analytical options for estimation of vaccine effectiveness are surveillance-based approaches (see Chapter 2) and targeted epidemiological studies. It is not always possible for countries to have surveillance in place before vaccine introduction to monitor impact of PCV and HibCV on disease. Surveillance may not have been in place long enough to have an adequate baseline, or the vaccine coverage may be too low to show an impact of the vaccine with a reasonable sample size. In these cases, countries may consider using a specialized epidemiologic method, such as a case-control study, to calculate vaccine effectiveness. These studies can be less resource-intensive and can often be completed over a shorter time period than establishing surveillance programmes and analysing their data.

3.2.1 Cohort studies

When feasible, the cohort design is an excellent and rigorous method for measuring vaccine efficacy or effectiveness. The premise is to follow a population, with known vaccination status, over a period of time. Members of the cohort are classified by their vaccination status—vaccinated or unvaccinated. Pneumococcal or Hib disease incidence is calculated in each group. If the vaccine were given randomly to individuals in the group, in effect the cohort study would constitute an RCT. If the vaccine is given as part of a routine infant immunization schedule, other factors such as vaccine integrity or potency (whether it is still potent or exposed to unacceptable temperatures) and administration (deep intramuscular rather than subcutaneous) and herd protection, could influence the measured vaccine effectiveness. The cohort method can be used either prospectively or using historical data (retrospectively). The cohort design allows direct calculation of the relative risk (RR) of disease and, therefore, a direct calculation of vaccine effectiveness using the relevant algebraic definition. Vaccination of children in a country is not a random event, so special care must be taken to register possible confounding variables, such as urban or rural location, socio-economic status, or access to health services, thus enabling adjustment during analysis. A cohort study which

considers vaccinated children as being exposed, and unvaccinated children as unexposed, will not capture the effect that suboptimal coverage has on vaccine impact.

Cohort studies require a cohort with a large number of children since laboratory-proven IBD is a relatively rare event. Accurate vaccine registries and disease surveillance systems are required to adequately identify cases and their vaccination status, but these systems do not exist in many settings and, if they do, are frequently incomplete. The cohort study design is commonly used to measure vaccine effectiveness in outbreak situations, such as with varicella and pertussis, and may also be used for pneumococcal and Hib disease outbreaks. Because pneumococcal and Hib disease do not often cause outbreaks, this method is not commonly used for measuring PCV or HibCV effectiveness.

3.2.2 Indirect cohort study

One cohort study method that can estimate PCV effectiveness is the indirect cohort, or case-only method, which can successfully be used to calculate PCV effectiveness in the first few years after introduction (75,76). Using this design, the vaccination status of cases with pneumococcal disease caused by vaccine-specific serotypes is compared with the vaccination status of cases of pneumococcal disease caused by serotypes not included in the vaccine. This method requires serotyping of all cases of pneumococcus. It was originally designed for measuring effectiveness of the 23-valent pneumococcal polysaccharide vaccine (77,78) but can also successfully be used to calculate PCV effectiveness in the first few years after introduction (75,76). The method requires high-quality serotype and pneumococcal surveillance data, but there are concerns that using the indirect cohort study design to measure PCV effectiveness violates the assumption that the vaccine not affect the occurrence of non-vaccine serotype disease differently among vaccinated and unvaccinated children.

3.2.3 Case-control studies

Case-control studies have become a widely used approach to document HibCV effectiveness and they are also appropriate for PCV. In a case-control study, children with Hib or pneumococcal disease (cases) are ascertained through active or passive surveillance, and one or more appropriate controls (children without the disease) are selected for each case. Vaccination status is determined for the cases and controls. Vaccine effectiveness is calculated using the appropriate formula and applying the rare-disease assumption to substitute odds ratio (OR) for RR, since the OR is an estimate of the RR. The use of regression-based statistical models to account for factors such as differences in demographic characteristics, economic level or access to health care that may exist between cases and controls may control for confounding and produce *adjusted* effectiveness estimates that better approximate "field efficacy" than unadjusted estimates. If controls are identified concomitantly with the cases (which they should be), temporal variation in Hib or pneumococcal disease is adequately accounted for. Cases and controls may later serve as another case or control (79). Such an OR, with its confidence interval, is very similar to the corresponding RR with its confidence interval, which cannot be directly calculated in case-control studies.

In contrast to cohort studies, case-control studies represent a more feasible methodology for rare events, such as culture-proven IBD, because details like vaccination history are needed only for the case children and a relatively small number of control children from the population under surveillance. (Please refer to Annex 2 for a more complete discussion of choosing controls.) Compared to other study designs, case-control studies can be cost-effective and time efficient. Because case-control studies are ideal for measuring effects on rare outcomes, this method can sometimes be used to compare effectiveness of a full series versus an incomplete series, effectiveness of multiple outcomes (e.g. all serotype-specific disease or vaccine-serotype disease for pneumococcal disease), and the impact on effectiveness of co-administration of other vaccines.

Notwithstanding the advantages cited above, case-control studies are susceptible to confounding and bias. Just like cohort studies, case-control studies will not capture reduced vaccine impact due to suboptimal coverage, and cannot provide a picture of overall vaccine programme performance; cluster-randomized trials and stepped-wedge studies and, to some extent, surveillance programmes that track disease rates over time, can provide that information. In addition, because a number of factors can be related to both receipt of vaccine and disease risk—such as age, access to care and socioeconomic factors—care must be taken to reduce the influence of these potential confounders on vaccine effectiveness estimates by appropriate statistical adjustment. As for all case-control studies, a clear case definition is critically important, and only incident (new) cases should be included. For example, a child who recently recovered from the disease in the case definition, or who develops the disease shortly after being identified, should be allowed to be included as a control. Cases should be allowed to be included again as cases, or later as controls and, vice versa, controls should be allowed to again be included as controls or later as cases. Not allowing such children to be included as controls may bias the measured effect of the vaccine. Defining the population from which controls are drawn as a representative sample of the source population that gave rise to the cases is critically important. A more detailed description of how to conduct case-control studies to assess pneumococcal vaccine effectiveness against invasive pneumococcal disease is included in Annex 2.

3.2.4 Screening method (case-population method)

More experience with the "screening method" is required to assess its suitability for measuring PCV effectiveness (80,81,82). Such a study is a variant of the case-control method where, instead of one or more individual controls per case, the whole population is used as a control group (80,81). This method has been used to estimate the vaccine effectiveness of Hib, pertussis, mumps and measles vaccines (83–86). It is an attractive method in settings where disease surveillance data is available, but where few other resources are available. Only three data points are needed to calculate vaccine effectiveness; the total number of disease cases and the number of cases occurring in vaccinated children, both of which may be identified from surveillance, and the percentage of the population vaccinated, which may be estimated from vaccine coverage surveys or available from a national registry.

Because of the arithmetic simplicity of this analysis, that is, because there are only three inputs, estimates of effectiveness from the screening method are very sensitive to otherwise minor errors in the three inputs estimates. Furthermore, there is no way to adjust explicitly for confounders. A number of strong assumptions must be in place for the computation to produce reliable estimates of effectiveness. It is critical that the vaccination coverage estimates correspond precisely to the population from which the cases originate. Administrative data, or vaccine registry data, may or may not be complete and precise enough. Effectiveness will be overestimated if the coverage is also overestimated. Stability in population vaccine coverage is required for the screening computation to produce accurate estimates, and rates of pneumococcal and Hib disease typically decline rapidly after vaccine introduction. Obtaining accurate administrative data on vaccination coverage can also be difficult for the required age group, geographic region and time period. To summarize, more experience is required with this method to assess its suitability for measuring PCV effectiveness (*82*).

3.3 Minimizing bias and limitations

Consistent case definitions and accurate verification of vaccination history can minimize bias in observational studies. In addition and, if possible, blinding the data gatherers to the case or control status of study subjects minimizes information bias. Potential bias related to control selection in case-control studies is discussed more thoroughly in Annex 2.

3.4 Data collection and management

After consent, when required, has been obtained from parents or guardians, data should be collected by interviewing study participants using a study questionnaire, medical record review and vaccine history review. An accurate, detailed vaccination history including dates of vaccination is critical, and should ideally be obtained from written records. Data-collection forms should not include any identifiable information (e.g. name) but instead use unique identifiers. A separate form should be maintained that links the identifiers with participant names. Once data collection and analysis have been completed, the linking form should be destroyed.

Once completed, copies of the data-collection forms should be sent to a main study office with the originals remaining at the surveillance site where the data was collected. To maintain confidentiality, all data-collection forms should be kept in secure, locked cabinets, accessed only by the necessary study personnel. A central electronic database should be developed for all surveillance sites, and should be maintained at the main study office. Data from each surveillance site should be entered into the database and reviewed for completeness, and any data entry errors. Means of capturing data directly on hand-held computers or mobile phones may, over the next few years, become the preferred choice for data capture.

3.5 Data analysis

Vaccine efficacy and effectiveness can be calculated using the formulas cited at the beginning of this section. RCTs and cohort studies yield relative risks (RRs) or incidence rate ratios (IRRs); case-control studies yield odds ratios (ORs). Multivariable regression analysis allows adjustment for confounding variables, such as gender and age. Regression modelling can also quantify and measure the precision of any effect modification. Subgroup-specific effect measures, with their confidence intervals, as well as statistical significance levels of such interactions, can thereby be identified and reported.

For the primary vaccine effectiveness analysis, fully vaccinated study subjects should be compared with unvaccinated subjects. For a secondary analysis, fully and/or partially vaccinated subjects should be compared with unvaccinated subjects to determine if partial vaccination is effective. Lastly, a sensitivity analysis should be conducted where subjects for whom vaccination status could not be obtained are considered fully, partially or unvaccinated.

Secondary analyses may be performed depending on the study method employed and the power and richness of data in the study. These may include serotype-specific vaccine effectiveness and vaccine effectiveness in high-risk populations, such as HIV-infected children. Conversely, children with underlying medical conditions (such as HIV infection or sickle-cell disease) may be excluded from the primary analysis if the desired outcome is effectiveness among healthy children. Case and control selection can be designed to measure vaccine effectiveness specifically in these populations.

3.6 Interpretation and extrapolation of results from vaccine studies

The efficacy of PCV and HibCV has been established from a number of pre-licensure trials, so the findings of any new vaccine efficacy or effectiveness study should therefore be interpreted in the light of earlier results. If vaccine effectiveness is found to be different than expected, it is particularly important that further investigation should be conducted, including an examination of the vaccine management and vaccine administration techniques. The results can then be used to take corrective action, if necessary (*80*). The study methods should also be examined to ensure that case definitions were applied consistently, that case ascertainment was appropriate, vaccination status was appropriately determined, that confounding was controlled for and that biases do not adversely affect results. As has been shown with many other vaccines, the effectiveness of a vaccine in the field can be less than the efficacy in clinical trials, for example, if the vaccine had low potency or was administered at suboptimal ages, in too few doses or was injected inappropriately. Vaccine impact can, for the same reasons, be lower than efficacy, but when coverage of an appropriately administered and highly potent vaccine is high, and indirect protection is prominent, impact can even be higher than efficacy. Vaccine impact can be measured directly in cluster-randomized trials, including those using a stepped-wedged design, or extrapolated from the results of less complex vaccine studies. For example, when population-based surveillance data, including pre-vaccination incidence of pneumococcal disease, are available, the amount of disease prevented by pneumococcal vaccine can be estimated by calculating the product of: (a) the incidence of a particular disease outcome (e.g. IPD) from pre-vaccine surveillance; (b) the population under surveillance; (c) vaccine coverage, and (d) the vaccine efficacy or estimated in a randomized trial, or effectiveness estimated in a case-control study or some other study design.

In some cases, meningitis cases caused by pneumococcus or Hib may not be identified through microbiological testing. Therefore, pre-vaccination pneumococcal or Hib meningitis incidence can be estimated by taking the incidence of confirmed pneumococcal or Hib meningitis for at least one year pre-vaccination and adding the incidence of additional pneumococcal or Hib meningitis cases that are identified as purulent with no etiology. This can be calculated by multiplying the incidence of purulent meningitis with no identified cause pre-vaccination, by the proportion of purulent meningitis cases estimated to be caused by pneumococcus or Hib (using vaccine coverage and vaccine effectiveness against purulent meningitis, calculated through a case-control study or some other study design).

In 2009, WHO published global, regional and country-specific estimates of the burden of pneumococcal and Hib disease as part of a Global Burden of Disease (GDB) project (*http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf*). This project provided the number of cases and deaths of pneumococcal and Hib meningitis, pneumococcal and Hib pneumonia, and non-pneumonia, non-meningitis invasive pneumococcal and Hib disease. These numbers were calculated by modelling available country-level data from well-conducted invasive pneumococcal and Hib disease burden studies, aggregating these data to derive regional and global estimates, and applying estimates of the proportion of pneumonia caused by Hib or pneumococcus to the estimated number of overall cases of pneumonia. The estimates give the burden of disease in 2000 before widespread global use of PCV and HibCV. These estimates can be useful in estimating the number of cases and deaths potentially averted by a vaccination programme in a particular country, especially where local data are not available. This method is illustrated in Table 6 below. The impact of PCV and HibCV on pneumonia can be extrapolated by applying the ratio of pneumococcal pneumonia to meningitis cases to the measured impact on purulent or laboratory-confirmed pneumococcal meningitis. The ratio of pneumococcal pneumonia to meningitis cases can be estimated based on a review of pneumococcal clinical trials, surveillance data from other countries and the WHO GDB project.

Table 6: Using pneumococcal global disease burden estimates to calculate the number of pneumococcal or Hib cases and deaths potentially preventable in a country

Expected vaccine effectiveness or efficacy	National pneumococcal conjugate vaccine or Hib conjugate vaccine (3rd dose) coverage	National estimate of severe invasive bacterial disease cases caused by vaccine serotypes	National estimate of invasive bacterial disease deaths	Estimated no. of severe invasive bacterial disease cases averted	Estimated no. of invasive bacterial disease deaths averted
A 90%–95% for serotype-specific invasive pneumococcal or Hib disease*	B Obtain from local records**	C Obtain from Global Disease Burden estimates or local data***	D Obtain from Global Disease Burden estimates or local data***	=A*B*C	=A*B*D

* Source: published literature or local vaccine efficacy or effectiveness studies.
** Source: WHO/UNICEF joint reporting form or country immunization records.
*** WHO Global Disease Burden project. For PCV, will need to account for the estimated amount of pneumococcal disease caused by serotypes included in the PCV used.

3.7   Summary and key points

1) Many methods can be used to measure vaccine effectiveness and efficacy of PCV and HibCV in the field.

2) Although demonstrating vaccine efficacy through double-blind randomized, placebo-controlled trials is necessary prior to licensure of most new vaccines for use in the general population, randomized trials may not be ethical or necessary for current and future PCV or HibCV, and therefore there is a role for observational methods of post-licensure field impact studies.

3) A case-control study with IBD as the outcome is probably the most feasible method to accurately measure PCV or HibCV effectiveness in most settings. If, in addition, it is intended to directly capture the part of vaccination impact that is driven by suboptimal coverage and indirect protection, more extensive, and expensive designs may be required, such as cluster randomized trials including stepped-wedge studies.

4. Designing surveillance and special studies to measure the impact of pneumococcal and Hib vaccines

4.1 Case finding and identification

Choosing the appropriate outcome to monitor impact of PCV or HibCV depends on the objective of the study, the laboratory and clinical capacity and the current surveillance systems that are in place. Firstly, patients are identified with clinical syndromes that could be caused by *S. pneumoniae* or Hib. Then, when possible, etiology is determined among suspected cases by performing appropriate diagnostic tests. Other aspects, such as the age and location of cases, should be accurately recorded.

4.2 Choosing the outcome

Several outcomes can be used to measure the disease impact of PCV or HibCV. First and foremost, a consistent and accurate case definition must be developed that can operationally identify cases and distinguish persons with the disease from those individuals without the disease. When choosing a case definition, there is an art to balancing sensitivity and specificity. Outcomes will vary in their sensitivity and specificity depending on whether they are microbiologically confirmed (such as confirmed pneumococcal meningitis, which has a high specificity but low sensitivity) or clinical (such as clinical pneumonia, which has a high sensitivity but low specificity). Using case definitions and outcomes that are very specific, such as measuring the impact of PCV on laboratory-confirmed IPD, is the most direct way to assess impact of vaccine. However, more specific outcomes will limit the number of illnesses that are identified and caused by pneumococcus or Hib, and larger surveillance populations may be needed. By contrast, case definitions with high sensitivity will capture the largest proportion of Hib or pneumococcal illnesses that occur, and promote representativeness, but highly sensitive definitions may be less specific. Less specific outcomes, such as clinical meningitis and pneumonia may be considered, because these are relevant for overall disease burden and because of the difficulty of isolating pneumococcus and Hib, but vaccine efficacy and effectiveness assessments using these definitions carry an inherent bias towards lower effect sizes.

Demonstrating an impact on pneumonia can be compelling to decision-makers since it is such a common disease with a large burden. The most common fatal manifestation of pneumococcal and Hib disease is non-bacteraemic pneumonia, but diagnosing and identifying cases of this syndrome is difficult. Furthermore, it can be difficult to demonstrate the impact of vaccine on non-specific outcomes, such as pneumonia, and a small vaccine impact may be misinterpreted as lack of overall vaccine impact.

It is recommended to use the case definitions for pneumococcal and Hib syndromes and other severe bacterial infections that were developed by WHO and are listed in Annex 1 and at *http://www.who.int/nuvi/surveillance/en/* (*14,87*). Although there may be local reasons for using other case definitions, using common case definitions allows comparison across surveillance sites. It is recommended to avoid a case definition for the final outcome of interest that is based solely on clinical diagnoses. Instead, the case definition for the final outcome of interest should be based on laboratory confirmation and measurable signs and symptoms. Clinical case definitions can identify patients who should receive appropriate clinical care and who should be enrolled into surveillance. However, clinical case definitions are generally too non-specific to distinguish episodes of pneumococcal or Hib disease from those caused by other agents. Table 7 summarizes characteristics of the various outcomes discussed in this section.

4.2.1 Laboratory-confirmed invasive bacterial (pneumococcal and Hib) disease

Measuring the impact of PCV or HibCV on laboratory-confirmed Hib disease or invasive pneumococcal disease caused by serotypes included in the vaccine under evaluation is the most specific, direct measurement of the vaccine effect. Invasive bacterial vaccine-preventable disease (IB VPD) is defined as illness in a person from whom pneumococcus or Hib is cultured, or pneumococcal or Hib antigen or deoxyribonucleic acid (DNA) is detected in a normally sterile body fluid such as CSF, blood or pleural fluid. Laboratory testing can be performed, depending on the capacity and needs of the setting, using basic clinical microbiology or molecular techniques such as polymerase chain reaction (PCR) assays.

Both laboratory-confirmed cases for meningitis (Tier 1 IB VD surveillance) and IBD (Tier 2 IBD surveillance for meningitis, pneumonia and sepsis) have each been used to successfully demonstrate an impact of HibCV introduction in low-income countries (*24,61*) and an impact of PCV in high-income countries (*16,88*). However, few health-care providers in low-income countries perform routine blood cultures on those patients with syndromes characteristic of pneumococcal or Hib infection (e.g. pneumonia, fever without a source) as blood culturing can be expensive and of low clinical value, even under ideal conditions. Adequate laboratory capacity is necessary for blood culturing to capture IBD. Isolation of pneumococcus and Hib can be difficult, particularly in areas where a high proportion of children are treated with antibiotics prior to hospitalization. Hence, surveillance and vaccine impact assessments that rely on routinely-available microbiological data most often focus on pneumococcal and Hib meningitis, and do not include blood culture surveillance for other clinical syndromes possibly caused by these bacteria. Note, however, that surveillance restricted to meningitis substantially underestimates the morbidity of pneumococcal and Hib disease as it does not include the other more common clinical presentations of these bacteria, especially pneumonia. Because of the difficulty of adequately identifying the complete burden of pneumococcal and Hib disease (namely difficulties in case finding, obtaining cultures and laboratory identification of bacteria) even surveillance for all invasive disease syndromes will not adequately measure the true pneumococcal or Hib severe disease burden.

Whenever possible, pneumococcal and Hib isolates should be stored and sent to a reference laboratory for confirmatory testing and serotyping so that vaccine type disease can be distinguished from disease caused by serotypes not included in the vaccines. Because many laboratories in low- and middle-income countries do not have the capacity to serotype *Haemophilus influenzae* (Hi), untyped Hi can be used as an outcome to measure impact of HibCV. Where HibCV is not used, approximately 95% of Hi disease is caused by type b (*14*). However, this will only be appropriate in the first year or so after vaccine introduction since the serotype distribution of Hi changes as the amount of Hib disease falls. It is also possible that non-typeable Hi causes a large amount of pneumonia, but this is not well-characterized. WHO also currently coordinates a network of global and regional reference laboratories that may be able to perform serotyping for interested countries.

In contrast to HibCV, it is important to measure the impact of PCV on IPD that is classified as disease caused by serotypes included in the vaccine (vaccine-type disease) and disease caused by serotypes not included in the vaccine (non-vaccine-type disease). This is because of the specificity of the vaccine against certain serotypes and the dynamic nature of serotype epidemiology before and following vaccine introduction. This will be especially important for when countries change from one PCV formulation to another with different serotypes included.

Urine antigen testing is not specific for pneumococcal disease since it can be positive among children who are nasopharyngeal carriers of pneumococcus. Pneumococcal urine antigen testing cannot be used as a diagnostic test for pneumococcal disease in children because over 50% of children are pneumococcal carriers in many settings.

4.2.2 Probable bacterial meningitis (purulent meningitis)

In settings where pneumococcus or Hib is infrequently isolated from clinical specimens, probable bacterial meningitis can be an appropriate outcome to measure for vaccine impact assessments. Probable bacterial meningitis is a less specific case definition than IBD or culture-confirmed meningitis and is defined as an episode of clinical meningitis with CSF findings consistent with a bacterial etiology (e.g. leukocytosis) without isolation of pneumococcus or Hib by bacterial culture or other testing. WHO recommends the definition for paediatric bacterial meningitis be based on CSF examination showing at least one of the following: (1) turbid appearance; (2) leukocytosis (>100 cells/mm3), or (3) leukocytosis (10–100 cells/mm3) and either an elevated protein (>100 mg/dl) or decreased glucose (<40 mg/dl). A cutoff of ≥10 white blood cells/mL is often used to define leukocytosis; the sensitivity of this case definition can be increased by lowering the white blood cell count (e.g. >5 cells/mL) required to be included as a case; however, this increases the false-positive rate and may lead to more testing and a strain on resources.

Probable bacterial meningitis is most commonly caused by pneumococcus, Hib or *Neisseria meningitides* (the meningococcus). In general, before vaccine introduction, Hib is the most common cause of bacterial meningitis among young children; however, in areas with high HIV prevalence, *S. pneumoniae* may exceed Hib as the most important cause of paediatric bacterial meningitis, even in the absence of HibCV (*89*). In most countries considering PCV introduction, HibCV is already in widespread use and most probable bacterial meningitis will be caused by pneumococcus. Since *N. meningitidis* is epidemic prone, it can be the most common cause of probable bacterial meningitis during epidemics. In some regions, depending on the year, it may be

difficult to evaluate the impact of PCV or HibCV on probable bacterial meningitis due to meningococcal epidemics. If pneumococcus or Hib causes a relatively small proportion of bacterial meningitis, determining the impact of PCV or HibCV on probable bacterial meningitis may be difficult. In spite of these challenges, probable bacterial meningitis has been used successfully in some settings to demonstrate impact of HibCV introductions, and the same may be true for PCV introduction, as more studies evaluate impact using this outcome. For example, a study in Rwanda demonstrated impact of HibCV using probable bacterial meningitis as an outcome since there were too few Hib isolates to use Hib as an outcome, and most probable bacterial meningitis episodes were likely caused by Hib (90). As with measurement of laboratory-confirmed meningitis, accurate measurement of this outcome requires suspected cases to be identified and evaluated at a health facility, lumbar punctures to be performed routinely, and CSF to be tested appropriately to quantify leukocytosis, protein and glucose.

4.2.3 Suspected meningitis (meningitis clinical syndrome)

Clinically diagnosed meningitis, often called suspected meningitis, as it has not been laboratory confirmed, is not recommended for use as an outcome. Suspected meningitis may be caused by viruses or bacteria, and it is difficult to distinguish between these etiologies solely on clinical grounds. Despite the classic purpuric rash that can be seen in some cases of meningococcemia, it is difficult to determine the etiology clinically even among cases of bacterial meningitis. The advantage of using suspected meningitis as an outcome is that these data are often reported routinely in many countries. However, the case definition is highly non-specific and includes epidemic-prone diseases such as viral encephalitis, meningococcal meningitis and Japanese encephalitis. The specificity of this outcome may be improved by using only hospitalized meningitis cases; a large HibCV trial in Indonesia found that hospitalized meningitis cases are usually more severe and therefore more likely to be bacterial in origin than non-hospitalized cases (50).

4.2.4 WHO-defined end-point pneumonia

When measuring pneumonia, it is recommended to use the WHO standardized definition of radiologically-confirmed pneumonia in children, which can be used to identify a relatively specific subset of pneumonia that is likely to be bacterial; the definition's criteria require a chest radiograph showing a consolidated lobar infiltrate (91). Pneumonia is the most common clinical manifestation of pneumococcal and Hib disease, but the vast majority of pneumonia caused by these bacteria is not bacteraemic and is therefore difficult to identify with routine diagnostic cultures. Measuring the effect of PCV or HibCV on WHO end-point pneumonia in a routine clinical setting poses challenges related to the difficulties of obtaining X-rays on each case of clinical pneumonia, and in standardized interpretation of X-rays. The specificity may be improved by including biomarkers, such as C-reactive protein and procalcitonin, in the case definition; however, these are not yet accepted markers for pneumococcal or Hib pneumonia (92). In adults, pneumococcal pneumonia may be identified by pairing a clinical pneumonia case definition with a positive urine antigen test. Notably, a HibCV trial in Lombok, Indonesia, did not find an impact on WHO end-point pneumonia, in spite of an effect on Hib meningitis, for reasons that remain unclear (50).

4.2.5 Pneumonia (pneumonia clinical syndrome)

Clinical pneumonia is an even less specific case definition than WHO end-point pneumonia and can be challenging to use as an outcome. Clinical pneumonia encompasses a wide range of viral, bacterial and fungal respiratory infections; moreover, tachypnea and difficulty breathing can be the presenting signs and symptoms of other common diseases, such as malaria and asthma. A diagnosis of pneumonia can be based on a clinical assessment by a medical provider, but this may not be a sufficiently standardized case definition for surveillance or a special study. In clinical trials where this case definition has been used, suspected pneumonia is most commonly defined using WHO Integrated Management of Childhood Illnesses criteria (*93*). This standardized case definition has been developed for clinical use and is therefore highly sensitive but not specific. As such, seasonal variations in etiology, such as during seasonal activity of respiratory syncitial virus (RSV) and influenza season, may obscure any impact of PCV or HibCV on suspected pneumonia. In most settings where it has been studied, PCV and HibCV prevents a sizeable proportion of WHO-defined end-point pneumonia, but their impact on all hospitalized or severe pneumonias, or other clinically defined pneumonias, is much smaller and thus harder to measure.

4.2.6 Overall mortality

Stringent criteria are needed if the impact of PCV and HibCV on mortality is to be measured. Based on data from clinical trials, PCV is estimated to reduce overall mortality among children <5 years of age by an estimated 11% and HibCV by 4% in settings with high childhood mortality (*6,7*), although the true percentages may be much higher. Despite the disproportionate number of child deaths in low- and middle-income countries compared to high-income countries, vital registration in these countries may be fragmented, incomplete and sometimes non-existent. Therefore, detecting even a 10% reduction in overall childhood mortality requires a very large sample size and, in most cases, would not be possible to do from routine data sources. Verbal autopsies are non-specific for pneumococcal and Hib disease and also highly labour intensive; hence they may not be useful for measuring vaccine impact on a large scale. In addition, as multiple child survival interventions tend to occur simultaneously, determining what proportion of each intervention was attributable to the reduction in mortality (should one be observed) would be difficult. Many children who die from pneumococcus or Hib have underlying conditions, such as HIV infection or malnutrition, which can, in turn, lead to death from other causes. Even if mortality data are restricted to cases of pneumonia or meningitis, demonstrating an impact on mortality is very difficult due to large year-to-year variability in the incidence of pneumonia or meningitis caused by different etiologic agents, and difficulties in standardization of case definitions. For all of these reasons, failure to observe a reduction in mortality rates (overall or specific to pneumonia) among children <5 years of age following PCV or HibCV introduction should not lead to the conclusion that the vaccine is ineffective. Because of the preceding issues mentioned, under-five mortality would not generally be appropriate to use as an outcome for a PCV or HibCV impact assessment. Yet, if sufficiently similar protocols are used, pooling data from several countries with high child mortality may enable measurement of impact on overall childhood mortality. Even if the impact of PCV or HibCV on mortality is not commonly measured, calculating the case-fatality rates of cases can help describe the severity of pneumococcal and Hib disease.

4.2.7 Pneumococcal and Hib nasopharyngeal carriage

Using nasopharyngeal carriage as an outcome may be useful in some circumstances, such as in small populations, in settings with limited clinical laboratory facilities, in settings where antibiotic resistance is a major public-health concern or in the context of measuring the impact of different vaccination schedules. Disease from pneumococcus and Hib is preceded by nasopharyngeal carriage, although as many as 90% of children carry pneumococcus and 10% carry Hib in their nasopharynx without causing disease. Since pneumococcal and Hib carriage is much more common than disease outcomes, and is causally linked to disease, measuring carriage of these bacteria can be used as an outcome for PCV or HibCV impact assessment. Declines in nasopharyngeal carriage of vaccine-type pneumococcus have been observed in response to PCV7 use but, in general, non-vaccine type pneumococcal carriage increases such that overall pneumococcal carriage remains about the same before and after PCV7 introduction. Declines in oropharyngeal carriage of Hib have been observed in response to Hib vaccination. However, pneumococcal and Hib carriage rates and rates of invasive bacterial vaccine-preventable disease are poorly correlated; for example, why some children who carry pneumococcus in their nasopharynx develop invasive disease and some do not is unclear, and the proportion of children who carry the organisms and who develop invasive disease is low. Some pneumococcal serotypes are more likely to be carried in the nasopharynx than others, and serotypes differ in their ability to cause invasive disease (*94*). Therefore, while measuring carriage before and after PCV introduction can demonstrate the impact of PCV on pneumococcal carriage if absent, or significantly lowered, it may be difficult to extrapolate and conclude that a reduction in carriage of vaccine-type pneumococci has led to a reduction in pneumococcal disease.

Demonstrating the impact of PCV or HibCV on carriage can be useful as it is a biological measure of the vaccine effect, and it is possible to see a reduction in carriage within a year of vaccine introduction, making this method relatively timely. This method can also indicate indirect effects of the vaccine by showing a change in unvaccinated age groups. However, carriage studies can be expensive and time-consuming. Since carriage rates vary substantially in different settings, carriage rates pre- and post-vaccination are needed to interpret the data.

4.2.8 Pneumococcal and HibCV immunogenicity and serology

Measurement of pneumococcal or Hib antibody levels is typically recommended only as part of advanced special studies or as an adjunct to other impact evaluations (*95*). Vaccines produce an antibody response in individuals, and these antibodies protect against disease by destroying invading bacteria. An amount of antibodies above which a group of vaccinated individuals is not likely to get disease is referred to as a "correlate of protection." By measuring the proportion of individuals vaccinated who reach such a pre-defined antibody level, vaccine efficacy can be estimated without having to measure clinical outcomes. For example, because a correlate of protection was determined for the 7-valent PCV, this method has been used to obtain data for licensure of new preparations of PCV without the need for a randomized controlled trial to evaluate impact on disease (*96,97*). A serosurvey of a population of vaccinated children could be used to measure the impact of PCV or HibCV on antibody levels (*95*); however, one problem in using this method for HibCV evaluation is that antibodies to *Escherichia coli* cross-react with antipolyribosyl ribitol phosphate (anti-PRP) antibodies, posing difficulties for the interpretation of findings (*98*). Immunological studies may be useful in answering certain questions, such as optimal dosing schedules, the need for

a booster dose (*99*) or measuring susceptibility in a vaccinated community. Tests for antibodies or other immunological studies require sophisticated laboratory techniques, and samples must be gathered prospectively since they are not part of routine medical data collection or public-health surveillance. Thus, measurement of pneumococcal or Hib antibody levels is typically recommended only as part of advanced special studies or as an adjunct to other impact evaluations (*95*) and is beyond the scope of this manual. For those considering such a study, WHO has criteria for measurement of immunogenicity of PCV (*100*).

4.2.9 Other outcomes

In the past, the surveillance systems supported by WHO and the Pneumococcal Conjugate Vaccine Accelerated Development and Introduction Plan (PneumoADIP) defined a case definition for a syndrome termed "very severe disease." Patients met this definition if they had at least two danger signs (such as convulsions or lethargy), a lumbar puncture, and did not meet one of the other case definitions. This case definition attempted to clinically identify serious non-meningitis, non-pneumonia pneumococcal disease; however, it is poorly sensitive and not useful for measuring the impact of PCV or HibCV. Thus, this case definition is not used in the WHO IB VPD surveillance network.

The impact of PCV against otitis media have been demonstrated in high-income countries, but otitis media is a highly non-specific clinical syndrome of low severity that is not recommended as an outcome in most settings for vaccine-impact studies.

4.3   Choosing the age of cases to measure direct and indirect effects

When conducting hospital-based sentinel surveillance, WHO recommends that all children under the age of five years who are admitted with the disease of interest (e.g. meningitis, pneumonia or sepsis) should be included in the surveillance. The case report form should capture the specific age of the child.

Declines in disease incidence outside the targeted vaccination age groups, including in adults, reflect the indirect effects of the vaccine due to decreased transmission in a community. As time passes, the indirect effects of vaccination can decrease the amount of disease in the population targeted for vaccination. Depending on the vaccination schedule, children younger than 6–8 weeks of age are too young to have been vaccinated and any changes in incidence in this age group would be due to the indirect effects of the vaccine; in addition, children should be allowed two weeks after vaccination to develop antibodies. Children over two years of age, and adults, are generally too old to have been vaccinated (at the start of a programme, particularly if there is no catch-up vaccination campaign for children >2 years) and any changes in these groups within the first two years after introduction would also be due to the indirect effects of the vaccine. The upper age limit for inclusion of children in any assessment will depend on whether there was a catch-up campaign or not. If there was no catch-up campaign, the upper age of the children included in the assessment will be the age of first vaccination plus the time that has elapsed between vaccine introduction and the start of the assessment. If there was a catch-up campaign, the upper age limit will be the upper age of children vaccinated plus the number of months that elapsed between vaccine introduction and the start of the study.

When conducting special studies, subjects should be included in an assessment of the direct effect of the vaccine, only once they have had a chance to be vaccinated. For example, PCV and HibCV are given in infancy as part of the routine immunization schedule. The impact of the vaccines is likely to be highest in children from the age of two weeks after the third dose to two years of age, when both disease incidence and prevalence and vaccination coverage rates are highest.

4.4   Choosing the location of cases

Cases identified in a surveillance system should ideally be representative of the cases in the population. In most resource-poor countries, identifying cases in hospital settings is often the most feasible, since clinical evaluation and diagnostic testing is more readily available there than in other settings. However, identifying cases at a referral facility will select for more severe and complicated cases in patients that may have already received antimicrobial treatment. Limiting case identifications to hospitalized cases will probably not however identify non-severe pneumonia, which comprises a large portion of the pneumococcal and Hib burden. When choosing the site for case identification, one should balance selecting referral and primary-care facilities and rural and urban settings—the representativeness—with the practical aspects of identifying cases and performing appropriate diagnostic and laboratory tests.

4.5   Vaccination status ascertainment

Ascertaining whether a child has been vaccinated can be extremely difficult. In study designs with cases and controls, vaccine status must be gathered from cases and controls in a non-differential way. To reduce recall bias in the study, it is necessary to obtain accurate vaccination records for all study participants. Notably, as vaccine coverage increases, a larger proportion of cases will occur among vaccinated individuals. Therefore, all cases should be retained, and replacement cases and controls can be obtained for those who say they have been vaccinated but do not have documentation.

- vaccination cards (e.g. EPI cards);
- provider records (hospitals, health clinics), although it can be more difficult to obtain vaccination records from private medical facilities.

Vaccination histories that are given verbally should ideally be confirmed with written records (vaccination-card or medical record). If a history of receiving vaccine cannot be confirmed and the caregiver cannot confirm that the child was never vaccinated, the participant should typically be excluded from the study. However, unvaccinated children are more likely to give only verbal history of no vaccination; if these children are excluded this can bias the vaccine effectiveness estimates. All cases should be retained, but replacement cases and controls should be obtained for those who say they have been vaccinated but do not have documentation. This allows calculating effectiveness with both the original set of cases, as well as the replaced cases, to determine if there is a bias in excluding cases.

"Vaccinated" is typically defined as two weeks following receipt of ≥1 dose of PCV or HibCV. "Fully vaccinated" is defined as two weeks following receipt of ≥2 or ≥3 doses of PCV or HibCV depending on the schedule and "partially vaccinated" is defined as two weeks following one or two doses of PCV or HibCV. Other definitions can be used, such as defining "unvaccinated" as children who received 0 doses of PCV or HibCV, or "fully vaccinated" as receiving two or more doses.

4.6 Measuring pneumococcal conjugate vaccine or Hib conjugate vaccine impact with co-introduction of other vaccines

Globally, there are many traditional and other new and underutilized vaccines—rotavirus, influenza, meningococcal and Japanese encephalitis vaccines, to name but a few. Countries may choose to introduce more than one vaccine into the routine childhood immunization system at the same time as, or in quick succession with, PCV or HibCV. Two points should be considered when measuring impact of PCV or HibCV with co-introduction of other vaccines. Firstly, it may be possible to use resources effectively by conducting vaccine-impact studies for all new vaccines at the same time. For example, the same control group could be used to measure the vaccine effectiveness of vaccines that prevent similar clinical syndromes, such as PCV and influenza vaccines. In fact, cases identified as part of one vaccine effectiveness study (such as with rotavirus vaccine) could be used as controls for another vaccine effectiveness study (such as with PCV), and vice versa. Secondly, the introduction of two vaccines may have synergistic or additive effects on some outcomes. For example, since pneumonia and diarrhoea are the leading killers of children worldwide, introduction of PCV and rotavirus vaccines may have a more measurable impact on mortality in children less than five years of age than each vaccine separately.

4.7 Summary and key points

1) Consistent and appropriate case definitions are critical.

2) In general, showing vaccine impact is easier with a more specific case definition that is based on laboratory-confirmed IBD. Additionally, it is important to ensure proper specimen collection, rapid transport to, and processing by, the laboratory, as well as use of appropriate laboratory methods *http://whqlibdoc. who.int/hq/2011/WHO_IVB_11.09_eng.pdf*.

3) Despite pneumonia being the most common clinical manifestation of pneumococcal and Hib infection, measuring the impact of PCV and HibCV on pneumonia can be difficult because the case definition of pneumonia does not specifically identify whether these two bacteria are the causative organisms. Using chest radiographs interpreted using WHO criteria to determine lobar pneumonia can improve specificity. Studies that aim to measure the effect on clinically-defined pneumonia will almost certainly fail to see an effect because of the non-specific outcome measure. This may lead to inaccurate conclusions that the vaccine is not effective against pneumonia when, in fact, it is working against Hib and/or pneumococcal pneumonia, but these are only a fraction of the cases identified as clinical pneumonia.

Table 7: Suitability of pneumococcal disease outcomes for surveillance and special studies that evaluate vaccine efficacy, effectiveness and impact

Outcome	Suitable outcome for surveillance to assess PCV and HibCV impact	Suitable outcome for special studies to evaluate PCV and HibCV efficacy or effectiveness	Laboratory requirements	Sensitivity	Specificity	Comment
Laboratory-confirmed invasive bacterial vaccine-preventable disease	Yes	Yes	Ability to culture CSF and blood and to perform rapid testing; serotyping desirable	Low	High	Many low-income countries have at least one hospital sentinel site that conducts surveillance for paediatric bacterial meningitis. Blood cultures or other laboratory tests are not performed to an adequate quality in many resource-constrained settings.
Probable bacterial meningitis (purulent meningitis)	Yes	Yes	Ability to accurately measure white cell count, as well as glucose and protein concentrations	Medium	Medium	Suitable for sites where culturing is not performed, inadequately performed, or yield is very low. However, requires reliable quantification of leukocytosis, protein and glucose. Results may be influenced by outbreaks or seasonality.
Suspected bacterial meningitis (clinical meningitis)	No	No	None required	High	Low	Many countries have existing clinical meningitis surveillance, but it is difficult to interpret data due to variations in data quality, lack of case confirmation and seasonality of diseases and outbreaks.
WHO-defined end-point pneumonia	Yes	Yes	None required, but X-ray capacity needed	Medium-high	Medium	Requires high quality X-rays and staff trained in WHO's standardized X-ray interpretation guidelines. Can be resource intensive. Usually only done as part of a special study.
Suspected pneumonia (pneumonia clinical syndrome)	No	No	None required	High	Low	Difficult to interpret these data due to variations in case definition, data quality, lack of case confirmation, seasonality and outbreaks.

Outcome	Suitable outcome for surveillance to assess PCV and HibCV impact	Suitable outcome for special studies to evaluate PCV and HibCV efficacy or effectiveness	Laboratory requirements	Sensitivity	Specificity	Comment
Overall mortality	No	No	None required	High	Low	Many countries do not have a reliable death registry system and any reduction in mortality is likely to be too small to detect through routine death statistics. Pneumonia-specific mortality is subject to fluctuations due to seasonality and outbreaks. May be possible to measure an effect with large populations.
Nasopharyngeal carriage	Possibly	No	Ability to identify bacterial carriage from nasopharyngeal swabs; serotyping highly recommended	High	Low	Measures impact on bacterial carriage rather than on bacterial disease; carriage of vaccine-type pneumococcal organisms is anticipated to decrease after vaccine introduction but an increase in non-vaccine serotypes may not be correlated with disease occurrence, so added information is limited; may be useful in exploring herd protection.
Immunogenicity and serology serosurveys	No	No	Ability to identify antibodies to Hib or pneumococcus	Low	High	May be useful as an adjunct to other impact evaluations.

5. Conclusion

This manual discusses methods for measuring the impact of PCV and HibCV and describes both surveillance and special studies. Choosing a method to monitor the impact of PCV or HibCV will depend on whether an existing surveillance system is in place, how long it has been in place and the quality of the surveillance data. Surveillance can allow evaluation of vaccine impact, but if surveillance is not adequate because baseline data are lacking, an observational study may be preferable.

Table 8 summarizes the characteristics of the impact assessment approaches discussed in this manual. In general, choice of study should balance scientific rigour with the technical capacity required and resources available. Some methods, such as cohort studies, are scientifically rigorous but may not be the most practical method for a resource-limited setting that does not have adequate vaccine and disease registries in place. Measuring impact using sentinel site surveillance data may be less rigorous than using population-based surveillance data, but sentinel surveillance is a practical and frequently used method for settings without population-based surveillance systems. Depending on the needs in a particular setting and the availability of adequate resources, public health leaders may choose to both establish surveillance in order to assess the impact of vaccine on adverse health events and to conduct vaccine effectiveness studies if an appropriate surveillance system is in place from which to identify. The resulting high-quality data from either option will provide important information for decision-makers at national, regional and global levels.

Table 8: Characteristics of recommended Hib and pneumococcal conjugate vaccine impact
and vaccine effectiveness assessment approaches to impact assessment methods by monitoring trends

Method	Technical capacity required	Time required	Relative cost	Scientific rigour (internal validity)	Outcome(s) measured	Comments
Population-based active surveillance	High	Recommend data collection for at least two years pre-vaccine introduction and three years post- vaccine introduction	High	High	Trends in incidence of IBD, pneumococcal and Hib meningitis, purulent meningitis	Allows burden of disease and overall impact of the vaccine to be measured. Cost is dependent on whether only meningitis surveillance or invasive bacterial disease surveillance (i.e. meningitis, pneumonia and sepsis) is carried out.
Sentinel surveillance	Medium	data; countries wishing to monitor S. pneumoniae serotype changes should conduct surveillance for five years following vaccine introduction	Medium, but low incremental cost if routine/ongoing sentinel system	Medium	Trends in case-counts due to probable bacterial meningitis or laboratory-confirmed meningitis cases due to the VPDs; trends in the proportion of meningitis cases due to S. pneumoniae or Hib among all laboratory-confirmed meningitis cases. In some selected and higher performing sites that conduct surveillance for Tier 2 surveillance of meningitis, pneumonia and sepsis; trends in S. pneumoniae or Hib caused invasive bacterial disease as identified via blood culturing or other testing	Most common type of surveillance used for pneumococcal and Hib disease and is frequently restricted only to meningitis surveillance (Tier 1B VPD surveillance). Vaccine impact can be measured to varying degrees. Less expensive than population- based surveillance, but good quality hospital-based sentinel surveillance can be expensive and may not represent trends in the wider population.

Method	Technical capacity required	Time required	Relative cost	Scientific rigour (internal validity)	Outcome(s) measured	Comments
Carriage studies	Medium	First survey done before vaccine introduction, and second survey done after at least one year of vaccine use	Medium	High	Trends in carriage	Can be relatively easy and timely to conduct given adequate microbiological capacity. An assumption is required that an effect on pneumococcal or Hib carriage will translate into an impact on pneumococcal or Hib disease.
Experimental and observational study methods						
Cluster-randomized trial, including randomized stepped-wedge introduction of vaccination	High	1–3 years post-introduction	High	Very high	Vaccine impact	Best measure of vaccine impact. Captures directly both herd protection, which may be substantial for both Hib and PCV, as well as vaccine coverage. Important to adjust for confounders. Very costly and resource intensive. The stepped-wedge study design is possible to undertake during roll out of vaccine.
Cohort	High	2–3 years post-introduction	High	High	Vaccine efficacy or effectiveness against IBD, Hib and pneumococcal meningitis, purulent meningitis or radiologically confirmed pneumonia	Measures vaccine efficacy (if known that vaccine of optimal potency is administered optimally) or effectiveness. Requires accurate vaccine disease registration.
Case-control study	High	1–3 years post-introduction	Medium	Medium		Most commonly used method for measuring vaccine effectiveness. Useful when baseline surveillance data are missing. Surveillance is required to identify cases. Subject to many biases if not properly conducted.

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Annexes

Annex 1:
Case definitions

      Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination

Case type	Definition	Reference
Suspected meningitis (meningitis clinical syndrome)	Any child aged 0–59 months admitted to a hospital conducting surveillance with sudden onset of fever (> 38.5 °C rectal or 38.0 °C axillary) and one of the following signs: neck stiffness; altered consciousness with no other alternative diagnosis, or other meningeal sign. OR Every patient aged under five years of age hospitalized with a clinical diagnosis of meningitis.	*WHO-recommended standards for surveillance of selected vaccine-preventable diseases, 2003.*
Probable bacterial meningitis	A suspected meningitis case (as defined above) with CSF examination showing at least one of the following: • turbid appearance; • leukocytosis (> 100 cells/mm3); • leukocytosis (10–100 cells/ mm3) AND either an elevated protein (>100 mg/dl) or decreased glucose (< 40 mg/dl). Note: if protein and glucose results are not available, diagnose using the first two conditions (i.e. turbid appearance or leukocytosis > 100 cells/mm3).	*WHO-recommended standards for surveillance of selected vaccine-preventable diseases, 2003.*
Laboratory-confirmed meningitis	A suspected meningitis case that is laboratory-confirmed by growing (i.e. culturing) or identifying (i.e. by Gram stain or antigen detection methods) a bacterial pathogen (Hib, pneumococcus or meningococcus) in the CSF or from the blood, in a child with a clinical syndrome consistent with bacterial meningitis.	*WHO-recommended standards for surveillance of selected vaccine-preventable diseases, 2003.*
Laboratory-confirmed invasive bacterial (pneumococcal and Hib) disease	A person from whom pneumococcus or Hib is cultured or pneumococcal or Hib antigens or DNA are detected in a normally sterile body fluid, such as CSF, blood or pleural fluid.	Case definitions for pneumococcal syndromes and other severe bacterial infections. *Clinical Infectious Diseases, 2009, 48(Suppl. 2):S197–S202.*
Pneumonia (pneumonia clinical syndrome)	Any child aged 0–59 months admitted to a sentinel hospital conducting surveillance, demonstrating a cough or difficulty breathing and displaying fast breathing when calm (as defined by age): • age 0 to <2 months: 60 breaths/minute or more; • age 2 to < 12 months: 50 breaths/minute or more; • age 12 to <59 months: 40 breaths/minute or more.	WHO/UNICEF *Integrated Management of Childhood Illness Chart Booklet — Standard, 2008.*

Case type	Definition	Reference
Severe pneumonia	Any child aged 0–59 months admitted to a sentinel hospital conducting surveillance, demonstrating a cough or difficulty breathing and displaying one or more of the following: • inability to drink or breastfeed; • vomiting everything; • convulsions; • prostration/lethargy; • chest indrawing; • stridor when calm.	WHO/UNICEF *Integrated Management of Childhood Illness Chart Booklet — Standard, 2008.*
WHO-defined end-point pneumonia	Pneumonia in a patient with a chest radiograph showing an infiltrate consistent with pneumonia i.e. dense, fluffy alveolar consolidation and/or pleural effusion (79).	Cherian T et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. *Bulletin of the World Health Organization*, 2005, 83(5):353–359.

Annex 2:
Example of a complete case-control protocol for assessing pneumococcal vaccine effectiveness against invasive pneumococcal disease

Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination

Contents

The following protocol is meant to provide an example of a complete case-control study protocol for a pneumococcal conjugate vaccine effectiveness study against invasive pneumococcal disease. This protocol is designed for easy adaption and implementation. With site-specific and methodologic modifications, it can be adapted for any country or outcome (such as pneumonia) and is intended for use with assessing pneumococcal conjugate vaccine, as well as Hib vaccine. The text in brackets and italics seen throughout this Annex contains supplemental information that provides further explanation and guidance for planning and implementing a vaccine effectiveness study. The text represents a discussion of issues to be considered and finalized by anyone who may wish to use the protocol.

Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination

1. Project overview

1.1 Title

Case-control study to estimate the effectiveness of a pneumococcal conjugate vaccine against invasive pneumococcal disease.

1.2 Protocol summary

The primary aim of this study is to determine the effectiveness of a pneumococcal conjugate vaccine (PCV) against invasive pneumococcal disease (IPD) in children in [COUNTRY], following its introduction into the national routine immunization programme. IPD is an important cause of illness and death in children. Clinical trials, in both developed and developing countries, have shown the pneumococcal conjugate vaccine to be efficacious against invasive pneumococcal disease as well as other disease entities caused by *Streptococcus pneumoniae*. However, evaluating the performance of this vaccine in a real-world setting is also necessary, to allow parents, health-care providers and decision-makers to appreciate the benefits of vaccination in reducing the burden of severe pneumococcal disease.

This study will employ a matched case-control study design. The study will be conducted at [NUMBER] enhanced surveillance sites located in [CITY/COUNTRY]. Children will be eligible for the study if they are aged ≥8 weeks and part of the birth cohort eligible to receive PCV. Cases will be defined as illnesses with *Streptococcus pneumoniae* identified from normally sterile-site specimens (e.g. cerebrospinal fluid [CSF], blood, joint fluid, pleural fluid) diagnosed at designated, sentinel surveillance sites. [NUMBER] matched hospital controls will be selected for each case enrolled. Children admitted to the same hospital as the case, or attending the hospital outpatient department for a diagnosis which is not IPD or pneumonia or another vaccine-preventable disease (VPD), will be eligible for enrolment as a control. Controls will be matched to cases on date of birth, hospital and date of admission.

PCV effectiveness against IPD in children will be calculated by comparing the odds of having been vaccinated among cases and controls and adjusting for potential confounders.

2.Introduction

2.1 Literature review/background knowledge about pneumococcal disease

Of the 8.8 million deaths in children under five years of age annually, approximately 18% are due to pneumonia (*1*). *Streptococcus pneumoniae* contributes to 60%–75% of bacterial pneumonia in children (*2,3,4*). *S. pneumoniae* can cause pneumonia, otitis media and sinusitis, as well as invasive diseases, such as bacteraemia and meningitis. A systematic review of literature on pneumococcal disease burden suggests that there were approximately 826 000 pneumococcal deaths in children aged <5 years in 2000 (*5*).

The pneumococcal polysaccharide-protein conjugate vaccine (PCV) has been identified by the World Health Organization as an important public-health intervention to prevent deaths due to pneumococcal disease in developing countries (*6*). In 2000, PCV7 (Prevnar®, Pfizer) was licensed by the United States Food and Drug Administration targeting the seven serotypes causing over 80% of invasive disease in young children in the United States (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) (*7*). Since 2000, PCV7 has been licensed in more than 70 countries, and is routinely given to more than 30 million children annually. The efficacy of PCV, variably composed of 7, 9 and 11 serotypes, against pneumonia, has been demonstrated in four randomized control trials, including two in Africa (PCV9) (*8,9*), one in North America (PCV7) (*10*) and one in the Philippines (PCV11) (*11*).

When PCV7 was introduced in the United States in 2000, substantial reductions of all IPD were documented within a year of introduction among children targeted for vaccination (69% reduction from 188 cases per 100 000 children <2 years in 1998–1999 to 59 cases per 100 000 population in 2001) (*12*). Reductions in disease have also been documented among unvaccinated populations, demonstrating the potential for this vaccine to prevent disease by a herd or indirect effect (*13*). Conjugate vaccines induce mucosal immunity, preventing the new acquisition of vaccine-serotype pneumococci in the nasopharynx (*14–17*). This effect on carriage reduces the number of children who are carriers of pneumococci and decreases the chance of transmission to other at-risk individuals (*18,19*). PCV7 has also demonstrated effectiveness in preventing hospitalizations due to pneumonia in children (*20,21*), and the reduction of antimicrobial-resistant IPD (*22,23*).

2.2 Justification for the study

A pneumococcal conjugate vaccine [VACCINE NAME] was introduced in [COUNTRY] on [DATE]. Demonstrating the impact of the vaccine, through its routine use in the national immunization programme, will help to inform national vaccine policy by assessing the benefits of the vaccine, and will also aid decisions about PCV introduction in other countries in the region.

2.3 Intended use of study findings

These findings may be used to help: (1) make evidence-based decisions about implementing PCV into national immunization programmes; (2) advocate for further resources to introduce PCV in countries with high disease burden, and (3) identify barriers that might affect the performance of PCV in real-world settings. The results will be communicated through presentations to various groups and may be submitted for publication to a peer-reviewed journal.

2.4 Audience and stakeholder participation

The primary target audience for this study is public-health officials and policy-makers in [COUNTRY] who are responsible for making decisions about continued implementation of PCV into the national immunization programme. International policy-makers, public-health organizations and funders may also be interested in the study findings. This study will be a collaborative effort between [COLLABORATORS].

2.5 Objectives

Primary

To determine the effectiveness of a complete series of pneumococcal conjugate vaccine (PCV) against invasive pneumococcal disease (IPD) among children eligible to receive a complete vaccination series through the routine vaccination programme in [COUNTRY], compared to no vaccination.

Secondary

To determine the effectiveness of a partial PCV series against IPD (1 dose or 2 doses), compared to no vaccination, among children eligible to have received at least this number of doses.

Other objectives for consideration:

- *estimation of PCV effectiveness against vaccine-type serotype or other serotype specific disease;*

- *evaluation of dosing schedules (i.e, effectiveness of two infant doses compared to three infant doses);*

- *evaluation of effectiveness of a booster dose after 9–12 months of age;*

- *evaluation of PCV effectiveness in healthy children compared to children at higher risk for pneumococcal disease (i.e. HIV-infected, sickle-cell disease, indigenous populations);*

- *estimation of risk factors for disease (i.e. IPD, pneumonia, etc.) in [COUNTRY].*

3. Methods

3.1 Study design

The study will employ a matched case-control study design to evaluate PCV effectiveness against IPD. This study approach has been used to study bacterial conjugate vaccine effectiveness in a number of settings, including PCV in the United States (24) and *Haemophilus influenzae* type B (Hib) conjugate vaccines in a number of other countries (*25–28*). Case patients will be children, diagnosed at surveillance sites, with *S. pneumoniae* identified from normally sterile-site specimens (e.g. CSF, blood, joint fluid, pleural fluid). Controls will be enrolled from children admitted to the same hospital as the case or attending the hospital outpatient department for a diagnosis which is not IPD or pneumonia, or another VPD. For each case, three controls, matched on age, hospital and date of admission, will be included. *[This protocol provides text for choosing hospital controls but, in many cases, community controls are preferred and the researchers will need to change the language in the protocol. A more in-depth discussion of control selection appears later in the protocol.]*

[The case for case-control studies

Case-control studies have the advantage, in field studies, of allowing vaccine effectiveness to be calculated without needing baseline data. Additionally, applying vaccine effectiveness and coverage rates can provide a good idea of vaccine impact on disease burden. Compared to other study designs, case-control studies may be more cost effective and time efficient, and can also assess multiple objectives (i.e. full dosing series versus partial dosing series, serotype-specific disease and co-administration of vaccines). Please refer to Section 3.2.3 (case-control studies) of the manual for further explanation of case-control studies.]

3.2 Study setting/location

The study will be conducted at [NUMBER] enhanced surveillance sites located in [CITY/COUNTRY].

[SITE A] description

[SITE B] description

[SITE C] description

Sites included in the study should have:

- *populations that are representative of the target population and large enough to achieve case numbers;*

- *good surveillance for case finding;*

- *laboratory capacity with the ability to identify cases.]*

3.3 Study population

The study will include children aged ≥ 8 weeks up to 59 months of age in [COUNTRY] who are part of the birth cohort eligible to receive PCV through the national immunization programme. All age-eligible children admitted to one of the surveillance hospitals during the study period will be eligible for study inclusion. Both cases and controls will be identified at the surveillance sites.

3.3.1 Case definition, inclusion/exclusion criteria, identification and enrolment

Cases will be defined as illnesses in patients who are part of the birth cohort eligible to receive PCV with *S. pneumoniae* identified from normally sterile-site specimens (e.g. CSF, blood, joint fluid, pleural fluid) and diagnosed at any of the study surveillance sites.

Cases will be eligible for inclusion into the study if they meet **all** of the following criteria.

- A child admitted to (or evaluated at, if outpatients included) a study hospital with laboratory-confirmed IPD, after the study start date; *[in most cases, using vaccine-type IPD as the outcome is recommended because it is the most specific case definition and requires a smaller sample size. Case definitions should be standardized to provide consistency throughout the study and to reduce any selection bias. Standardized case definitions also allow for comparisons of disease, over time, and between studies. Using consistent case definitions also allows for findings to be generalizable to similar populations. Please refer to Section 4.2 ("Choosing the outcome") in the manual for further explanation of* Streptococcus pneumoniae *outcomes.]*

- Eligible to have received at least one dose of PCV at least two weeks prior to admission (to allow for adequate immune response to vaccination), but less than five years of age; *[cases that are enrolled should be old enough to have received at least one dose of the vaccine. Two weeks is typically allowed following vaccine administration before recruiting a case or a control, to allow build-up of antibody levels. However, in some settings, more weeks may be advisable to account for variations in the given vaccine schedule and when children actually receive vaccine. The maximum age of children enrolled in the study should not exceed five years of age, as incidence for pneumococcal and Hib disease decreases significantly after this age. Additionally, most catch-up immunization programmes limit vaccination to children under five years. However, most studies last 2–3 years and consideration of maximum age is not likely to be relevant.]*

- Available immunization records; *[excluding patients with no immunization records can introduce bias as those with no records are often not vaccinated. Confirming the history for children who the parent says has never received any vaccines can be complicated, but should be pursued through clinic records or other means.]*

- Consent to be included in the case-control study.

Cases will be excluded from the study if **any** of the following criteria apply:

- hospital admission is not due to pneumococcal disease;

- absence of verifiable immunization records *[see above comment];*

- child's parent/guardian is unwilling and/or unable to provide informed consent;

- previous episode of IPD during the study period (to ensure that a case will only be enrolled one time into the study). *[If able to account for clustering in the analysis, all cases of IPD can be included in the study to reduce bias when not enrolling IPD cases in the same patient. However, recurrent cases of disease are uncommon and it may be simpler to exclude cases with previous IPD.]*

Cases will be identified by on-site surveillance officers who will review surveillance logbooks, or microbiology laboratory records, for eligible patients. This will be conducted on a daily basis until the desired sample size is met. Once potential cases have been identified, their parents or other guardians will be approached for enrolment into the case-control study.

Parents or guardians will be asked to participate in an interview consisting of a list of standardized questions. Additional information on the illness and medical history will be obtained from hospital records. Written evidence of the immunization history will be actively sought, including examination of immunization records plus contacting clinic or health facilities providing immunization, as relevant.

Medical treatment will still be the standard treatment provided by the participating hospital for all patients, whether or not they agree to participate in the case-control study. A registry of all patients approached for enrolment but declining study inclusion, and reasons for non-enrolment, will be compiled.

3.3.2 Control inclusion/exclusion criteria, identification and enrolment

[Considerations for control selection

Choosing the appropriate comparison group, or controls, is one of the most important factors in minimizing bias in a case-control study design. The assumptions underlying the choice of appropriate controls are twofold. Firstly, controls should be representative of the population from which the cases come, in the sense that they should have been identified as a case if they met the case definition. This is an important criterion in case-control studies and therefore contributes to ensuring that the controls are equally as likely to be exposed to pneumococci as the cases (29). Secondly, controls must be defined well enough so as not to be misclassified as cases. Although this seems simple, it can be challenging to find suitable controls and most choices will have both strengths and limitations.

A common question when selecting controls is whether to recruit hospital or community controls. Hospital controls are drawn from the same hospital as cases, and community controls from the same community as cases. Table 1 outlines some of the advantages and disadvantages of each. As most children with confirmed invasive pneumococcal disease are hospitalized, selecting hospital controls for these cases is convenient. However, while this, to some extent, may match for access to health care, referral patterns and health-seeking behaviour may vary between different types of illnesses. Also this approach does not match for socio-economic status, for which community is often used as a proxy measure nor, for underlying medical conditions, since hospitalized controls are more likely to be more ill. Community controls are generally preferred because they are likely to be more representative of the community giving rise to the cases; however, knowledge of care-seeking behaviour and referral patterns, such as those generated by a health-care utilization survey, may be a prerequisite to properly define the source population from which controls should be drawn. Which type of controls should be chosen depends on the local circumstances, such as resources, number of cases, the outcome measure under investigation and knowledge about referral patterns and health-seeking behaviour. Some studies of Hib vaccine effectiveness have used both community and hospital controls, but this design poses a risk of difficulty in interpreting findings if vaccine effectiveness (VE) results from the two control sets differ. We therefore recommend that countries consider undertaking a health utilization survey which maps health-care

seeking and referral patterns; this can also provide an opportunity to select controls from the population from which the cases in the hospital arise. Community controls can be found through a variety of ways, including census/demographic surveys, birth registries or a random selection of households. Factors to consider when selecting community controls include the following: (1) they should live within the same community as the case; (2) they should be included within 72 hours of identifying the corresponding case. The time and date of inclusion should be recorded, even if such a narrow time window cannot be met. (3) If an eligible control cannot be included, for example because his or her family living in the randomly selected household is travelling, or because parents refuse consent, it is important to record that such a control was missed and attempt to collect some information about the family. (4) A child identified as eligible should be included irrespective of whether he or she has been included as a case or as a control previously in the study (in which case this can be accounted for in the analyses). These criteria will adjust for temporal variations in the occurrence of infections with the causative agents, and will ensure that the OR derived from the analyses are a direct measure of the IRR, which again is a very close estimate of the RR. The current protocol primarily describes the use of hospital controls because this may be the most feasible approach. For case-control studies of Hib vaccine effectiveness, hospital controls with pneumococcal disease were often a convenient control group, since both could often be identified through the same surveillance system, were in the same population and, before vaccination was available, were not vaccine preventable. However, most countries that introduce PCV have already introduced Hib vaccine, and Hib controls are not likely to be available. There are still a number of hospital-based controls that can be considered, such as patients with the following.

1) *Rotavirus-negative diarrhoea if rotavirus vaccination is implemented; any hospitalized diarrhoea if rotavirus vaccination not yet introduced.*

2) *Meningococcal disease, if meningococcal vaccine is not used.*

3) *Salmonellosis.*

4) *Bronchiolitis or asthma, if it can be distinguished from pneumococcal pneumonia, for example, by response to a bronchodilator and a normal chest radiograph.*

5) *Non-purulent suspected acute bacterial meningitis, although this control group might be misclassified if these controls are early or partially treated cases of bacterial meningitis.]*

Table 1: Advantages and disadvantages of using community versus hospital controls in PCV effectiveness case-control studies

Community controls	Hospital controls
More expensive (e.g. transport, time in the field, etc.)	Less expensive
Usually more plentiful and easier to find	May be limited by hospital census
May take longer, particularly when recruiting controls from rural areas	Usually more convenient if cases are recruited from the hospital
Overmatching on access to vaccination is possible	Controls, to some extent, for access to health services, although this may differ from illness-to-illness
Can, to some extent, control for socio-economic status and area of residence	May not control adequately for socio-economic status and rarely controls for area of residence
Needs accurate address information to locate case house	Address information not required, although area of house should be recorded (where available) and adjusted for if it acts as a confounder
Controls are generally healthy and therefore rarely excluded due to having a pneumococcal-like illness	Potential difficulty in getting age- matched controls without pneumococcal-like syndromes (e.g. pneumonia and meningitis), particularly in smaller sites. Controls may be ill or malnourished, or have other underlying medical conditions and are often not representative of the population
Easier to get vaccination status if a vaccination card is kept at home	Can be easier to get medical history from hospital medical records; obtaining vaccination history can be problematic

Children admitted to the same hospital as the case, or attending the hospital outpatient department for a diagnosis which is not IPD, pneumonia or another clinical syndrome caused by pneumococcus, will be eligible for enrolment as a control.

Children will be eligible for inclusion into the study as controls if they are:

- admitted acutely (within 72 hours) to the same hospital as the case for a diagnosis which is not IPD, pneumonia or another clinical syndrome caused by pneumococcus; eligible to have received at least one dose of PCV at least two weeks prior to admission (to allow for adequate immune response to vaccination). *[Controls that are enrolled should be old enough to have received at least one dose of the vaccine. Two weeks is typically allowed following vaccine administration before recruiting a case or a control to allow build-up of appropriate antibody levels.]*

- Available immunization records. *[However, controls should be selected independently of their vaccination status and you need to be aware that excluding children who don't have a vaccination card can lead to a biased OR estimate because these children tend to be unimmunized. Note that confirming the history for children who the parent says has never received any vaccines can be complicated, but should be pursued through clinic records or other means.]*

- Would have sought treatment at the hospital where the case is admitted, if IPD had developed. *[As controls should be representative of the population from which cases originate, controls should also have the same health-care utilization patterns as cases. This can be accomplished by choosing hospitalized controls from the same hospital as cases. A health utilization survey may be required to determine the degree to which this is actually true. If not, there may be a need to increase the number of hospitals which take part in the case-control study.]*

- Consent from caregiver to be included in the case-control study.

Controls will be excluded from the study if **any** of the following criteria apply:

- Child admitted to the hospital for IPD or pneumonia. *[If known, it is important to exclude those controls with pneumococcal disease, or who have had pneumococcal disease before. Immunity to pneumococcus is serotype specific, so previous infection with pneumococcus protects you from subsequent infection from the same bacteria but does not protect you from future infection with pneumococcus. For this reason, controls that may have had pneumococcal infection should be excluded in studies where the pneumococcal serotype of previous infection is not known. However, in studies using a serotype specific outcome (i.e, vaccine-type IPD), controls that have been admitted to the hospital with IPD where serotype is known may be enrolled as a control if serotype is not vaccine type.]*

- Absence of verifiable immunization records. *[In some settings, clinic records can be used to supplement missing or incomplete vaccination cards. As for community controls, one needs to be aware that children without such records tend to have lower vaccination coverage than those who have such records; such exclusions may thus induce a selection bias.]*

- Child's parent/guardian is unwilling and/or unable to provide informed consent. *[If using community controls, children living in the same household as a case should be excluded from eligibility as a control.]*

Potential controls will be identified by daily review of hospital or casualty logs and selection of these patients from such logs. If necessary, bed-by-bed review of hospitalized patients will also be performed. A list of all eligible patients (meeting inclusion criteria and matched to the case) will be compiled. If fewer than the required number of controls are identified, all eligible controls will be approached for enrolment. If more than the required number of controls are identified, those closest to the age of the case will be approached first for enrolment. The process will be repeated daily until the required number of controls is enrolled. The study will aim to enrol a sufficient number of controls within 72 hours of the admission date of the case. If eligible controls are not able to be enrolled within a narrow time window in relation to cases, this window may be extended, but it is important to note the time lag between case and control enrolment. It is also important to note down the characteristics (e.g. age, illness, nutritional status) of eligible controls that could not be included, and record the reason for non-inclusion.

Once controls are identified, parents or guardians will be asked to participate in an interview consisting of a list of standardized questions. Additional information will be obtained from hospital records. Written evidence of the immunization history will be actively sought, including examination of immunization records, plus contacting clinic or health facilities providing immunization, as relevant.

Medical treatment will still be the standard treatment provided by the participating hospital, whether or not a patient's parent consents to participation in the study.

[Considerations for matching

Studies must account for major underlying differences between children who have the target disease and those who do not, especially if those factors may also be linked to receipt of vaccination; factors independently associated with both the outcome variable (disease) and exposure variable of interest (vaccine) are known as confounders. For example, controls may be from different socio-economic groups, be of different ages and have different access to vaccination than cases, and these factors may therefore be confounders. In order to avoid selection bias, or introduction of confounding based on how controls or cases are selected, controls should ideally be randomly chosen from among the population from which the cases were derived. Confounding variables, such as age, can be controlled for by design, i.e. by matching cases to controls with respect to the factor in question, or by adjusting for the variables in multivariable analysis. Matching controls to cases on specific characteristics can diminish confounding by helping to balance these characteristics between cases and controls. Matching can also adjust for factors that are unknown factors, or hard to adjust for. However, matching on multiple factors can make enrolment challenging and there is a risk of overmatching, which will increase the number of concordant (i.e. non-informative) case-control sets, i.e. that both the case and all of his or her matched controls are either vaccinated or not vaccinated. Overmatching is more likely to occur when matching is done on a factor closely associated with vaccination but not with the disease. If extensive, one may be forced to unmatch the case from its corresponding controls and undertake an unconditional analysis, which tends to bias the estimates towards lower effectiveness. Multiple controls per case reduce the risk of this being a major problem. The following are some matching factors.

1) *Age: as risk of pneumococcal disease and opportunity for vaccination vary by age, controls should be matched to cases by age.*

2) *Date: selecting controls to cases based on date helps control for factors that could lead to confounding. Often, the next available controls after a case has been enrolled can be chosen, or a control can be randomly chosen from a subset of eligible controls that were admitted on the same day or within the same week as cases. This concurrent control selection is particularly important in diseases such as pneumococcal and Hib disease, not only because it is a prerequisite for the matched OR being an unbiased estimate of the incidence rate ratio, but also because these infectious agents can spread rapidly in child populations; it thereby contributes to ensuring that the controls are representative of the population from which the cases are derived.*

3) *Location (hospital/community): controls should be chosen from the same community or hospital as cases. This tends to balance access to care and other environmental factors that might affect the association.]*

Controls will be matched to the cases on age, hospital and date of admission using a 3:1 ratio.

- Date of birth: within +/- 1 calendar month from age of case for children ≤12 months and +/- 2 months for children > 12 months of age. For children ≤12 months, age should not be below that required for last vaccine dose for which case was eligible. For example, if a 16 week-old case is enrolled in the study and the last eligible dose the case could have received was at 14 weeks, then eligible age-matched controls would be 14–20 weeks of age. Children that are 12–14 weeks of age would not be eligible as matched controls, despite being less than one calendar month of age of the case, because they are below the age at which they would be eligible to receive the same dose as the case.

- Same hospital case is admitted to.

- Date of admission (within one month after case admission date). *[Note: this is an example and may not be an appropriate design for all settings. Depending on the vaccine schedule used, for example, age matching within two weeks of date of birth may be more appropriate. For community controls, matching on hospital and admission date would not be appropriate, but matching on neighbourhood of residence may be optimal.]*

3.3.3 Sample-size calculation

[Considerations for sample size calculations

Sample size calculations are critical before beginning a case-control study to assess the feasibility of measuring an adequately precise effect. The number of cases needed is dependent on: (1) vaccine coverage; (2) outcome chosen and the presumed effectiveness of vaccine against that outcome, and (3) number of controls chosen per case. The most specific outcome, invasive laboratory-confirmed, serotype-specific pneumococcal disease, usually requires the smallest sample size. In general, a case-control study has the most power if the vaccine coverage is between 20% and 80%. Therefore, investigators will want to start a case-control study at least 2–3 months after vaccine introduction; evaluating how rapidly coverage increased after introduction of other new vaccines may help determine the best timing for the study. Furthermore, they will want to choose a catchment area large enough to identify sufficient cases within as short a time period as possible. Typically, at least three controls should be gathered per case. When vaccine coverage is high, more controls may be needed to find discordant pairs. In these instances, as many as 10 controls could be considered per case.

If a nonspecific (e.g, syndromic) outcome such as radiographically-confirmed pneumonia is chosen, the proportion of the outcome caused by vaccine-type pneumococcus will drop after vaccine is introduced, which will decrease the measured vaccine effectiveness. Therefore, sample size calculations should take into consideration that the true vaccine effectiveness may be lower than an initial estimate once the vaccine has been used for 1–2 years. Also, the number of cases of more specific outcomes, such as serotype-specific IPD, will also drop if the vaccine is working, so this must be taken into account when calculating how long the study will last.

Our experience suggests that studies often take longer than expected. If a study lasts too long and the vaccine is effective, fewer and fewer cases will be identified and the study may be difficult to complete.]

The sample size for this study was calculated at a significance level (α) of 0.05 and a power (1-β) of 0.90, using these parameters and assumptions:

- vaccine effectiveness of 40% against all-serotype IPD

- control to case ratio of 3:1

- vaccine coverage for a full PCV series among controls of 50%.

Based on these parameters and assumptions this study would need [NUMBER] case patients and [NUMBER] hospital controls to demonstrate a vaccine effectiveness of at least 40%.

3.4 Laboratory methods

Specimens will be collected from patients for diagnosis. This will be performed as part of the routine medical care provided and will follow standard operating procedures. *Streptococcus pneumoniae* will be identified from normally sterile-site specimens (e.g. CSF, blood, joint fluid, pleural fluid*). [Note: this is for studies with an invasive disease outcome. In some settings, specimen collection will be according to routine medical care; in others, specimen collection and processing will be enhanced to increase specificity and, when possible, sensitivity.]*

3.5 Variables

All variables will be collected using a standardized questionnaire, which is further described in the Section on data collection. The main exposure variable of interest will be vaccination status. The main study outcome will be whether the patient is a case of IPD or a control. Potential confounders are listed below.

Confounders that will be matched for the following:

a) **Age**: age is a potential confounder because the risk of IPD and the likelihood of vaccination changes with age. This will, to some extent, be controlled for by matching on age between cases and controls as described earlier, but because matching can only be done in age categories, residual confounding must be adjusted for.

b) **Hospital:** cases and controls will be matched on hospital of admission. This will serve as a proxy for geographic area. *[Note: this could be community rather than hospital.]*

c) **Date of admission**.

Potential confounders that will be evaluated and, if necessary, adjusted for in the multivariable conditional logistic regression analysis.

a) **Age**: due to the range of dates of birth and admission in which controls can be identified, ages of cases and controls are likely to differ, and this needs to be adjusted for.

b) **Sex**.

c) **Race group**: participants will be asked to classify which category would best describe their race.

d) **Ethnicity**: participants will be asked to classify which category would best describe their ethnicity.

e) **Education of caregiver**: the highest level of education for each participant's primary caregiver will be determined.

f) **Socio-economic status**: various tools will be used and adapted to determine the socio-economic status of participants.

g) **Locality type**: participants will be asked which category best describes the area in which they live. Options will include: urban formal; urban informal; rural formal or rural informal.

h) **Type of residential dwelling**: participants will be asked what best describes their place of residence.

i) **Crowding in residences**: this will be assessed by determining the number of people residing in the household, as well as the number of rooms in the household (excluding bathrooms and kitchen). An index of the number of people per room will be used to assess impact of crowding in the household.

j) **Cigarette smoke exposure**: passive smoking will be defined as a participant who resides in a household where there is active smoking indoors for more than three hours every week.

k) **Exposure to smoke in the household from indoor fires**.

l) **Medical history**: premature birth, birth weight, chronic underlying illness, recent infections, recent antimicrobial use, height/weight and receipt of other vaccines (influenza, rotavirus, diphtheria/tetanus/pertussis/Hib).

m) **Breastfeeding**: whether the child is currently being breastfed, exclusively, predominantly or partially.

n) **Attendance at day care**: attendance at a day-care facility with more than five other children for at least three days a week for three hours each day.

For all variables that change with time, the questions will focus on the month (30–31 days) before illness for cases and for controls. Dates will refer to a calendar month that most closely overlaps with the 30 days before the case's onset of illness.

[Special consideration for HIV infection in the study population

As HIV is an immunocompromising infection that significantly affects the body's ability to fight Hib and pneumococcal infection, HIV status is an important factor to consider in study settings where HIV prevalence is high. Determining HIV status for enrolment; before a child is enrolled into the study, either as a case or control, HIV status for that child should be determined. HIV testing results from a child's medical record or vaccination history can be considered appropriate documentation of a child's HIV status. Additionally, information should be collected on whether the mother was tested for HIV during pregnancy, and any results from HIV testing. If the mother tested negative during pregnancy and the child shows no signs or symptoms suggesting HIV infection, the child can be considered HIV uninfected.

For children with no information on previous HIV testing history or mother's HIV status, HIV testing should be administered and laboratory results received by study staff before enrolment in the study.

HIV as a confounder: in a case-control study evaluating vaccine effectiveness in a population with high prevalence of HIV infection, HIV status is a potential confounder and cases and controls should ideally be matched on this factor; however, this may not be practical and in that case HIV status may need to be controlled-for in the analysis. Furthermore, stage of HIV infection is a potential confounder and should also be considered during analysis. Study personnel should be trained in identification of HIV staging using the WHO staging system.

Data collection: the sample questionnaire and laboratory form located in the appendices of this generic protocol do not contain questions relating to HIV infection. However, if HIV infection is a factor for evaluation in a study, these questions should be addressed on the data collection forms.

- *Did the mother of the child have HIV testing done during pregnancy? If yes, what were the results? Source of results should also be documented.*

- *Has the child been tested for HIV infection previously? If yes, what were the results? (Source of results should also be documented.)*

- *If the child is HIV infected, is she or he on anti-retroviral therapy? Which medications?*

- *WHO clinical staging category if child is HIV infected.*

- *Laboratory results of HIV tests for child.]*

4. Data handling and analysis

4.1 Data collection

Prior to enrolment, consent to participate in the study will be sought from the parent or guardian of all potential case and control subjects. Study investigators will inform participants and caregivers about the data that will be collected and how it will be stored.

Data will be collected from study participants by interviews using the study questionnaire, which also includes a medical record review and vaccine history review (Appendix A). Data-collection forms will not include any identifiable information (i.e. name) but will instead use unique numerical identifiers. A separate form that links the numerical identifiers with participant names will be maintained. Once data-collection and analysis have been completed, the linking form will be destroyed.

Study coordinators will make every effort to obtain vaccination history. This information will first be sought by examination of vaccination cards or medical records. If not available, study personnel will then contact clinic or health facilities that provide immunization. Patients without verifiable vaccination histories will be excluded from the study. Because such exclusion may bias the effectiveness estimates, it is important that the number of such exclusions, and the characteristics of these children and these families, are recorded.

4.2 Data entry and management/quality assurance

Once completed, copies of the data-collection forms will be sent to the main study office, with the originals remaining at the surveillance site where the data were collected. All data-collection forms will be kept in secure, locked cabinets and only necessary study personnel will have access. A central electronic database for all surveillance sites will be developed and maintained using [SOFTWARE NAME] and will be kept at the main study office. Data from each surveillance site will be entered into the database and reviewed for any data entry errors.

The study coordinator will visit each surveillance site at least once a month to review data-collection forms and procedures.

4.3   Data-analysis plan

Data will be analysed using [SOFTWARE NAME]. Vaccine effectiveness will be calculated using the formula, vaccine effectiveness = (1 – OR) x 100%, where the OR is the adjusted matched odds ratio for PCV vaccination among cases compared to controls. Primary analysis will include all study participants who have received a complete PCV series compared to children who have received no doses of vaccine. A secondary analysis will include all study participants who have received a full or partial PCV series compared to children who have received no doses of vaccine. Analyses will be undertaken using conditional logistic regression to account for the matching. The study will assess risk factors, confounders, possible interaction and co-linearity, as part of the multivariable conditional logistic regression modelling process. Where interaction analysis indicates that PCV has a substantially different effect in different subgroups for a given factor, the vaccine effectiveness will be presented separately for these subgroups. Associations with p-values <0.05 will be considered statistically significant in the final models.

5. Reporting of results

Results will be summarized and reported to provincial and national Ministries of Health and participating surveillance sites, as well as funding bodies, if applicable. Findings will also be disseminated through relevant scientific meetings, presentations and publications in both local and international peer-reviewed journals.

6. Protection of human subjects

Study investigators will apply for ethics approval for the study from the Human Research Ethics Committee at [IRB ORGANIZATION]. Informed consent will be obtained by investigators from cases and controls prior to participation in the study. Parents/legal guardians of study participants will be asked to sign the informed consent on behalf of the minors. As most of the case and control children will be less than three years of age, it will not be possible to obtain assent. All forms containing personal identifiers will be kept in locked cabinets, and names and other identifiers will not be included in the study database.

6.1 Risks

There are no physical risks to the participants involved beyond normal clinical care. Parents/caregivers may feel embarrassed or uncomfortable when discussing sensitive topics that involve their children's past medical or vaccination history.

6.2 Benefits

Study participants may benefit if they are identified as needing vaccination. If an interviewer identifies a child who is due for vaccination, the interviewer will notify the parent of the vaccination(s) needed and provide information on where vaccines can be obtained. If PCV is found sufficiently effective within the study population, these findings could benefit children in the country and region by providing justification for continued use in the national immunization programme and subsequently leading to reduced morbidity and mortality from invasive pneumococcal disease.

6.3 Vulnerable populations and justification

Morbidity and mortality due to IPD is greatest during early childhood. PCV is only recommended for children <5 years. Therefore, a study measuring the effectiveness of PCV can be done only among young children.

6.4 Informed consent

At the time of enrolment, the surveillance officer will provide the parents or guardians of cases and controls with basic information about the study and review with them an informed consent document (Appendix B). The informed consent document will be read by the parent or guardian or read aloud to them if they are unable to read. Questionnaires will be translated and back-translated for the major languages within [COUNTRY]. For less commonly-used languages, the questionnaire will be verbally translated to the parent or guardian.

7. Study timeline

[Many studies often take 2–3 years to enrol cases because the number of cases decreases with time if the vaccine is working; however, the age of enrolment increases as more children are vaccinated and eligible for inclusion. Additionally, studies may take more time to complete if vaccine introduction is delayed, which often delays the start of the study. The timeline below is meant to serve as a guide and provides examples of major milestones often found in studies. Investigators will need several months to prepare before beginning enrolment. Studies in a single site may require less start-up time; multi-site studies may be able to reach a needed sample size more quickly.]

Dates	Activity
Month 1–month 8	Development of study protocol
Month 4–month 7	Implementation of routine PCV vaccination in [COUNTRY]
Month 9	Protocol submission to Institutional Review Board(s)
Month 11–month 12	Recruitment and training for study personnel
Month 13	Begin enrolment of cases and controls
Month 25	Mid-study interim analysis
Month 36	End enrolment of cases and controls, assuming sample size is met
Month 42	Complete analysis
Month 48	Dissemination of results

8. Personnel training

Prior to enrolment, all study personnel will be trained in case definition and identification for IPD as well as inclusion/exclusion criteria for enrolment of case children. Surveillance officers at each surveillance site will also be trained on: 1) procedures for screening and enrolment of control children; 2) obtaining consent from parents/caregivers, and 3) methods on data collection and completing case and control questionnaires. A full-time study coordinator will oversee the training of all study personnel.

9. Study limitations

The study will minimize biases by: 1) using accurate case definitions to identify case patients; 2) adhering to clear inclusion/exclusion criteria for cases and controls; 3) including only verifiable vaccination histories, and 4) matching cases to controls on potential confounders (age, hospital, date of admission).

However, there are a few limitations to this study that might present other biases, such as: 1) the use of only hospital-based controls might not adequately represent the population from which cases emerge; 2) as cases for this study will only be identified at certain surveillance hospitals, other cases of IPD may be missed if children receive care at other hospitals, or do not seek care at all, which may be due to lack of access to care and thus a greater chance of being unvaccinated.

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Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination

Appendix A:
Case and control questionnaire

Study ID: _____

[SENTINEL SITE] name: _____

Surveillance officer name: _____

This questionnaire is for a ☐ CASE ☐ CONTROL (check appropriate box)

Date of interview: (dd/mm/yyyy) ____ / ____ / ____

Place of interview: ☐ Hospital ☐ Telephone ☐ Other, please specify:

PART 1: CAREGIVER INTERVIEW

This information will be obtained by interview of parent/guardian.

Thank you for taking the time to be interviewed. I will be asking a few general questions about [CHILD'S NAME] and his or her health. The questions will take approximately 15–20 minutes to complete and most of the questions relate to events over the last month.

1) What is your (the interviewee's) relationship to [CHILD'S NAME]?

   ☐ Parent

   ☐ Other relative/caregiver

   ☐ Other, please specify _____

2) Are you the main person who looks after [CHILD'S NAME] at home?

   ☐ Yes

   ☐ No

   2a. If no, who is the main person: (choose one option)

   ☐ Mother/Stepmother   ☐ Grandparent

   ☐ Father/Stepfather   ☐ Other, please specify_____

3) What date was [CHILD'S NAME] born?   (dd/mm/yyyy) ____ / ____ / ____

4) How old is [CHILD'S NAME]?   _____ months

5) Is [CHILD'S NAME] a boy or a girl?

   ☐ Boy

   ☐ Girl

6) What is the race of [CHILD'S NAME]?

   ☐ White   ☐ Black   ☐ Mixed   ☐ Unknown

7) What is the ethnicity of [CHILD'S NAME]?

☐ _____ ☐ _____ ☐ _____ ☐ Unknown

8) If child is <2 years of age, during the last month, how was [CHILD'S NAME] fed? (choose one option)

☐ Breast exclusively   ☐ Mixed feeding (breast plus other)

☐ No breast milk   ☐ Unknown

9) During the last month did [CHILD'S NAME] attend a day-care centre outside the home?
(Attendance at a day care centre is defined as a facility with more than five other children for at least three days a week for three hours each day.)

☐ Yes

☐ No

☐ Unknown

DEMOGRAPHIC INFORMATION

I am now going to ask you some questions about where [CHILD'S NAME] lives and what facilities there are at home. These questions are important because where you live can have an impact on [CHILD'S NAME] health.

10) Which of the following best describes the area where [CHILD'S NAME] lives?

☐ Urban formal   ☐ Other, please specify _____

☐ Urban informal   ☐ Unknown/Refused to answer

☐ Rural formal

☐ Rural informal

11) Which of the following best describes [CHILD'S NAME] home or place of residence for the last month? (choose one option)

☐ House   ☐ Other, please specify _____

☐ Flat/apartment block   ☐ Unknown/Refused to answer

☐ Shack/informal dwelling

12) What type of building materials were used for the walls of [CHILD'S NAME] main dwelling? (choose one option)

☐ Brick   ☐ Mud bricks, wood, or traditional

☐ Tin   ☐ Unknown/Refused to answer

13) How many rooms are in [CHILD'S NAME] residence?

_____ rooms   ☐ Unknown

14) How many people are living in [CHILD'S NAME] residence (including the child)?

_____ people   ☐ Unknown

15) How many children (<5 years) live in [CHILD'S NAME] residence (including the child)?

_____ children < 5 years   ☐ Unknown

16) Which of the following are available in [CHILD'S NAME] household? (check all that apply)

☐ Electricity supply   ☐ Television set

☐ Computer   ☐ Domestic worker

☐ Radio   ☐ Land (ownership)

☐ Cellular telephone   ☐ Bicycle

☐ Refrigerator   ☐ Car

☐ Unknown/Refused to answer   ☐ None of the above

17) What type of toilet facilities are available to [CHILD'S NAME] household? (choose one option)

☐ Flush toilet (private for household)

☐ Ventilated improved pit (VIP) latrine/pit latrine/bucket system (private for household)

☐ Flush toilet (communal)

☐ Ventilated improved pit (VIP) latrine/pit latrine/bucket toilet (communal)

☐ None

☐ Unknown/Refused to answer

18) What is the highest level of education that the primary caregiver (the interviewee) has completed? (choose one option)

☐ No school   ☐ College degree

☐ Some primary school   ☐ Postgraduate/professional

☐ Primary school   ☐ Other, please specify _____

☐ Secondary school   ☐ Unknown/Refused to answer

☐ Some college

SMOKE EXPOSURES

19) In the last month, did any of the people living in [CHILD'S NAME] house smoke indoors for more than three hours every week?

☐ Yes

☐ No

☐ Unknown

20) In [CHILD'S NAME] home which of the following are used? (check all that apply)

☐ Electric/gas stove   ☐ Other, please specify _____

☐ Paraffin stove   ☐ Unknown

☐ Open woodfire or coal fire

PART 2: MEDICAL HISTORY

This information may be obtained by interview of parent/guardian AND medical chart review.

	Yes	No	Unk	If yes, please specify condition
Any problem with the immune system (including HIV) (e.g. primary **immunodeficiency** conditions like immunoglobulin deficiency)?				
Chronic **kidney** disease (e.g. nephrotic syndrome, chronic renal failure)?				
Cardiac disease (including congenital and acquired cardiac conditions, valvular heart disease, heart failure)?				
Sickle-cell disease or other functional or anatomic asplenia (e.g. splenectomy)?				
Chronic **liver** disease (e.g. portal hypertension, cirrhosis)?				
Asthma, reactive airways disease, or more than one episode of wheezing?				
Protein-energy **malnutrition**?				
Any other chronic illness?				
Generally healthy (i.e. none of the above conditions)?				

21) In the past 12 months, how many ear infections has [CHILD's NAME] had?

☐ 0   ☐ 4 or more

☐ 1 to 3   ☐ Unknown

22) During the last month, did [CHILD'S NAME] have a cold or cough?

☐ Yes

☐ No

☐ Unknown

23) During the last month, did anyone in the household other than [CHILD'S NAME] have a cold or cough?

☐ Yes

☐ No

☐ Unknown

24) If [CHILD'S NAME] was taking antibiotics, were antibiotics taken in the 24 hours before admission?
(if no, skip to 25)

☐ Yes

☐ No

☐ Unknown

24a. When were the antibiotics initiated?   (dd/mm/yyyy) ____ / ____ / ____   ☐ Unknown

24b. Specify name of antibiotic(s).

1. _____   2. _____   3. _____   4. _____   5. _____   6. _____   ☐ Unknown

25) Has [CHILD'S NAME] been admitted to hospital in the last year (or since birth, if child <12 months of age) before this admission?

☐ Yes

☐ No

☐ Unknown

26) What was the date that he/she was discharged from his/her last hospital admission?

(dd/mm/yyyy) ____ / ____ / ____   ☐ Unknown

27) How many times was [CHILD'S NAME] admitted in the last year (or since birth if child <12 months of age)?

☐ Once

☐ Twice

☐ More than two admissions

☐ Unknown

PART 3: VACCINATION HISTORY AND GROWTH MEASURES

This information should be obtained from a vaccination history card if available, but may also be completed by the interviewee.

28) Birth weight: _____ grams   ☐ Not recorded   ☐ Unknown

29) Gestational age:_____weeks (_____mo)

☐ Term   ☐ Pre-term   ☐ Post-term   ☐ Not recorded   ☐ Unknown

30) Has [CHILD'S NAME] received any vaccines since birth?

☐ Yes

☐ No

☐ Unknown

30a. If no, reason why child has not received any vaccinations? _____

_____

31) What is the source of vaccination history? (mark all that apply)

☐ Direct observation from vaccination history card

☐ Parent report

☐ Other documented source, please describe _____

☐ Unable to obtain vaccination history

Please complete the details on the following vaccines:

Vaccine	Dose	Dose given	Batch Number of dose given (as recorded on the vaccination history card)	If yes, date given (dd/mm/yyyy)
PCV	1st dose	☐Yes ☐No ☐N/A	☐Unknown	___ / ___ / ___ ☐Unknown
	2nd dose	☐Yes ☐No ☐N/A	☐Unknown	___ / ___ / ___ ☐Unknown
	3rd dose	☐Yes ☐No ☐N/A	☐Unknown	___ / ___ / ___ ☐Unknown
	Catch-up dose	☐Yes ☐No ☐N/A	☐Unknown	___ / ___ / ___ ☐Unknown
Rotavirus	1st dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	2nd dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
Measles	1st dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	2nd dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	Catch-up dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
DTP/HepB/Hib (Pentavalent)	1st dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	2nd dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	3rd dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	4th dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
OPV/IPV	1st dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	2nd dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	3rd dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
	4th dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
BCG	1st dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown
Influenza (seasonal)	1st dose	☐Yes ☐No ☐N/A		___ / ___ / ___ ☐Unknown

PART 4: MEDICAL RECORD REVIEW

This information will be obtained from the child's medical record.

CURRENT ADMISSION

32) Date of admission   (dd/mm/yyyy) ____ / ____ / ____

33) Patient length   _____cm Percentile _____

34) Patient weight   _____kg Percentile _____

35) Has the child ever had IPD previously?

    ☐   Yes

    ☐   No

    ☐   Unknown

    35a. If yes, when did the child have IPD?   (dd/mm/yyyy) ____ / ____ / ____   ☐Unknown

36) FOR CASES ONLY: Diagnosis of pneumococcal infection (check all that apply)

    ☐   Pneumonia/ Lower respiratory tract infection

    ☐   Meningitis

    ☐   Diarrhoea

    ☐   Bacteraemia

    ☐   Other, please specify _____

37) FOR CONTROLS ONLY: Diagnosis (check all that apply)

    ☐   Gastroenteritis/diarrhoea

    ☐   Trauma

    ☐   Surgery

    ☐   Malnutrition

    ☐   Other, please specify _____

FOR CASES ONLY:

38) Final outcome of patient

    ☐   Discharged

    ☐   Died

    ☐   Refused hospital treatment (RHT)/Absconded

    ☐   Unknown

39) Date of final outcome of patient   (dd/mm/yyyy) ____ / ____ / ____   ☐Unknown

This now completes the interview. Thank you for taking the time to provide this information.

Appendix B:
Case laboratory form

Study ID: _____

PART I. SAMPLE COLLECTION

1) Was a lumbar puncture done on this child?

    ☐ Yes

    ☐ No

    ☐ Unknown

    1a. If yes, date of lumbar puncture (dd/mm/yyyy) ____ / ____ / ____

Results:

- Lymphocyte count: _____cells/   ☐ Unknown

- Neutrophil (polymorphonuclear leukocytes) count: _____cells/   ☐ Unknown

- Protein: _____g/dL   ☐ Unknown

- Glucose: _____mmol/L   ☐ Unknown

2) Was a blood sample taken on this child?

    ☐ Yes

    ☐ No

    ☐ Unknown

    2a. If yes, date of blood collection (dd/mm/yyyy) ____ / ____ / ____

PART II. LABORATORY TESTING

	Isolate #1	Isolate #2	Isolate #3	Isolate #4
Laboratory ID number:				
Site isolate obtained:				
Culture done?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Culture date (dd/mm/yyyy)	___ / ___ / ___	___ / ___ / ___	___ / ___ / ___	___ / ___ / ___
Culture result:				

PART III. ANTIBIOTIC SUSCEPTIBILITY TESTING

This section needs to be completed only if isolate was positive result for Streptococcus pneumoniae.

ANTIBIOTIC												
Oxacillin	S	I	R	S	I	R	S	I	R	S	I	R
Pen/Ampicillin	S	I	R	S	I	R	S	I	R	S	I	R
Erythromycin	S	I	R	S	I	R	S	I	R	S	I	R
Clindamycin	S	I	R	S	I	R	S	I	R	S	I	R
Cotrimoxazole	S	I	R	S	I	R	S	I	R	S	I	R
Linezolid	S	I	R	S	I	R	S	I	R	S	I	R
Vancomycin	S	I	R	S	I	R	S	I	R	S	I	R
Chloramphenicol	S	I	R	S	I	R	S	I	R	S	I	R
Ciprofloxacin	S	I	R	S	I	R	S	I	R	S	I	R
Rifampicin	S	I	R	S	I	R	S	I	R	S	I	R
Gentamicin	S	I	R	S	I	R	S	I	R	S	I	R

Resistance codes: S = Sensitive; I = Intermediate; R = Resistant.

Appendix C:
Case and control consent form

Purpose and procedures

We would like to invite your child to take part in a research study. The purpose of the study is to find out how well a vaccine works for preventing infections in young children. Starting in [DATE OF VACCINATION PROGRAMME START] this vaccine is now given routinely to all children in [COUNTRY]. The vaccine is called pneumococcal conjugate vaccine. The vaccine is made to prevent infections caused by a germ called *Streptococcus pneumoniae*, or pneumococcus. This germ commonly causes chest or ear infections in children, but can cause other infections as well. The vaccine has worked well in earlier studies. However, these studies included only a few groups of children. We want to make sure that the vaccine is working well among all children. The study is being conducted by [YOUR INSTITUTION], together with [COLLABORATORS] throughout [COUNTRY].

We will be contacting the parents or guardians of children who have had this infection, and a sample of parents of other children the same age. We will ask both groups about factors that might lead to these infections, and about vaccine use. We will also review medical records and vaccination histories. We will then compare the answers from healthy children, and children who have had the infections, to see how well the vaccine is working.

The interview will take approximately 15–20 minutes to complete. You may choose to have your child be a part, or not be a part, of the project. If your child does not join, s/he will continue to receive the treatment needed for this infection and s/he will not lose any health-care services. If you choose to have your child join the project, we will ask you a number of questions as part of the interview. During this interview, we will ask you questions about your child's present and past health, including questions about the vaccines s/he has received. We will also ask questions about your home and the other children living with you.

Risks

There are no physical risks involved to you if you participate in the study. However, you may feel embarrassed or uncomfortable when discussing sensitive topics that involve your children's past medical or vaccination history. You may choose not to answer any question. You may withdraw your participation from the study at any time. If you do not wish to participate in the study, your child's treatment will not change in any way.

Benefits

The information you provide will help us learn more about this germ and how this vaccine can help to keep children healthy.

Confidentiality

We will keep your entire information private, unless we are required by law to reveal any information. All private details that identify you or your child will be kept in sealed files, and locked in cabinets or offices. All study information will be identified by a study number and not by your name.

Costs

There is no cost and no payment to you for participating in this study.

Conditions

It is your choice whether you choose to participate in this study. If you choose not to participate, or if you wish to stop participating at any time during the study, your child's treatment will not change in any way.

Study contact information

If you have any questions about this study, you may contact any of the people below:
[CONTACT INFORMATION FOR THE PRINCIPLE INVESTIGATOR OR STUDY COORDINATOR]

Informed consent for study participation

I, _____ (*name of parent/legal guardian*), parent/legal guardian

of _____ (*name of participant*), acknowledge that the study questionnaire has been explained to me and that I agree to be interviewed and answer the questions from the study questionnaire on behalf of my relative and for the medical records of my relative to be reviewed.

Name of parent/guardian: _____

Signature of parent/guardian: _____

Date: _____

Annex 3:
Glossary of terms

Case-control study: Observational study design that compares vaccination status of cases of people with a disease of interest to vaccination status of a control group of people without a disease, in order to evaluate the impact of vaccination.

Cohort study: Observational study design that subsets a defined population into those that are vaccinated and those that are not vaccinated and compares rates of disease to evaluate the impact of vaccination.

Clinical trial: Study design that involves administering vaccine to evaluate efficacy. Subjects may be randomized either on an individual or at a community level.

Direct effects: Impact of vaccine among vaccinated community members.

Impact: The overall programme effect on morbidity and/or mortality from disease, brought about by an intervention under study.

Incidence: The number of new cases in a given population at risk over a specific period of time.

Incidence rate: The rate at which new cases occur in a population calculated by dividing the number of cases in specified time period by the number of persons exposed to the risk.

Incidence rate ratio: Incidence rate in the exposed group divided by the incidence rate in the unexposed group.

Indirect cohort study: Observational study that is a variant of the cohort study design where the vaccination status of cases with pneumococcal disease caused by vaccine-specific serotypes is compared with the vaccination status of cases of pneumococcal disease caused by serotypes not included in the vaccine. For example, in a PCV vaccine-effectiveness study, an indirect cohort study would compare the vaccination status of cases with vaccine-serotype disease against the vaccination status of cases with non-vaccine serotype disease. This is also known as the case-only method.

Indirect effects: Impact of vaccine among unvaccinated community members; includes indirect (herd) protection and indirect (herd) immunity.

Indirect (herd) immunity: Vaccination of a targeted population provides protection against disease in a population not targeted for vaccine receipt, by transmission of the vaccine from the vaccinated to the unvaccinated, such as with a live vaccine.

Indirect (herd) protection: Vaccination of a targeted population provides immunity against disease in a population not targeted for vaccine receipt, by reducing transmission of the disease within the population, such as with a killed vaccine such as HibCV or PCV.

Odds ratio: Ratio of the odds of getting disease if vaccinated compared with the odds of getting disease if not vaccinated; generated by case-control study designs.

Relative risk: Ratio of the risk (probability) of getting disease if vaccinated compared with the risk of getting disease if not vaccinated; generated by cohort study designs. This is also known as risk ratio.

Screening method: Observational study that is a variant of the case-control method where instead of one or more individual controls per case, the whole population is used as a control group. This is also known as the case-population method.

Vaccine effectiveness: The proportionate reduction in disease incidence attributable to vaccination under real-world conditions, including the effect of programmatic factors such as: injection techniques; reduced vaccine potency following inappropriate storage; indirect (herd) protection against the target illness; pre-existing immunity to the target illness, such as that conferred by indirect (herd) immunity (for live vaccines) or previous episode of the target illness; population characteristics such as malnutrition, and any other factors that distinguish a community immunization programme from the controlled setting of a vaccine trial. A measure usually found in observational studies.

Vaccine efficacy and effectiveness can be measured by:

=   (Incidence in unvaccinated population – Incidence in vaccinated population) / Incidence in unvaccinated population x 100%

=   (1– Incidence in vaccinated population / Incidence in unvaccinated population) x 100%

=   (1– Relative risk) x 100%

Vaccine efficacy: Proportionate reduction in disease incidence attributable to a vaccine when given under ideal conditions; a measure usually found in a clinical trial.

Annex 4:
Surveillance performance indicators for the WHO-coordinated Invasive Bacterial Vaccine Preventable Diseases Network

Tier 1: Meningitis surveillance

Indicators	Numerator	Denominator	Target
Percentage of sites that report data according to an agreed timeline for that site (at least quarterly)	No. of sites that report data according to an agreed timeline	Total no. of sites reporting	80%
Percentage of suspected meningitis cases that have a lumbar puncture (LP) performed	No. of suspected meningitis cases that had an LP performed	No. of suspected meningitis cases	90%
Percentage of lumbar punctures performed that have a culture result recorded	No. of LPs performed that have a culture result recorded	No. of suspected meningitis cases that had an LP performed	90%
Percentage of suspected meningitis cases with probable bacterial meningitis	No. of suspected meningitis cases with probable bacterial meningitis	No. of suspected meningitis cases	At least 20%[1]
Percentage of probable bacterial meningitis cases with a known outcome (e.g. died, improved) recorded	No. of probable bacterial meningitis cases with an outcome recorded	No. of suspected meningitis cases with probable bacterial meningitis	90%
Percentage of probable bacterial meningitis cases with Hi identified by culture, rapid tests (latex or immunochromatography) and/or PCR	No. of probable bacterial meningitis cases with Hi identified by culture, latex or PCR	No. of suspected meningitis cases with probable bacterial meningitis	Regional targets TBD by WHO, GRLs, and RRLs and based on vaccine use
Percentage of probable bacterial meningitis cases with pneumococcus identified by culture rapid tests (latex or immunochromatography) and/or PCR	No. of probable bacterial meningitis cases with pneumococcus identified by culture, rapid tests (latex or immunochromatography) and/or PCR	No. of suspected meningitis cases with probable bacterial meningitis	Regional targets TBD by WHO, GRLs, and RRLs and based on vaccine use
Percentage of probable bacterial meningitis cases with meningococcus identified by culture, rapid tests (latex or immunochromatography) and/or PCR	No. of probable bacterial meningitis cases with meningococcus identified by culture, latex or PCR	No. of suspected meningitis cases with probable bacterial meningitis	Regional targets TBD by WHO, GRLs, and RRLs and based on vaccine use
Percentage of CSF samples logged into the laboratory within one hour of the lumbar puncture	No. of CSF samples logged into the lab within one hour of the LP	No. of suspected meningitis cases that had an LP performed	75%
Percentage of CSF contamination	No. of CSF samples contaminated	No. of suspected meningitis cases that had an LP performed	$\leq 5\%$
Percentage of CSF specimens forwarded to the reference laboratory for PCR and genotyping	No. of CSF specimens	No. of suspected meningitis cases that had an LP performed	80%

[1] 2009 global VP IBD median: 32%

Tier 2: Pneumonia and sepsis surveillance

Indicators	Numerator	Denominator	Target
Percentage of sites that report according to the agreed timeline for that site (at least quarterly)	No. of sites that report data according to agreed timeline	Total no. of sites reporting	80%
Percentage of pneumonia cases with a known outcome (e.g. died, improved) recorded	No. of pneumonia cases with an outcome (i.e. vital status) recorded	No. of children who met the pneumonia case definition	90%
Percentage of sepsis cases with an outcome (e.g. died, improved) recorded	No. of sepsis cases with an outcome (i.e. vital status) recorded	No. of sepsis cases	90%
Percentage of pneumonia cases that have a blood culture performed	No. of pneumonia cases that have a blood culture performed	No. of children who met the pneumonia case definition	75%
Percentage of sepsis cases that have a blood culture performed	No. of sepsis cases that have a blood culture performed	No. of sepsis cases	75%
Percentage of pneumonia cases with a blood culture performed that have a culture result recorded	No. of pneumonia cases with a blood culture performed that have a culture result recorded	No. of pneumonia cases that have a blood culture performed	90%
Percentage of sepsis cases with a blood culture performed that have a culture result recorded	No. of sepsis cases with a blood culture performed that have a culture result recorded	No. of sepsis cases that have a blood cultured performed	90%
Percentage of pneumonia cases with a blood culture performed with Hi identified by culture, rapid tests and/or PCR	No. of pneumonia cases with a blood culture performed with Hi identified by culture, latex or PCR	No. of pneumonia cases that have a blood culture performed	TBD by WHO, GRLs, RRLs
Percentage of pneumonia cases with a blood culture performed with pneumococcus identified by culture, rapid tests and/or PCR	No. of pneumonia cases with a blood culture performed with pneumococcus identified by culture, latex or PCR	No. of pneumonia cases that have a blood culture performed	TBD by WHO, GRLs, RRLs
Percentage of sepsis cases with a blood culture performed with pneumococcus identified by culture, rapid tests and/or PCR	No. of sepsis cases with a blood culture performed with Hi identified by culture, latex or PCR	No. of sepsis cases that have a blood culture performed	TBD by WHO, GRLs, RRLs

Indicators	Numerator	Denominator	Target
Percentage of sepsis cases with a blood culture performed with Hi identified by culture, rapid tests and/or PCR	No. of sepsis cases with a blood culture performed with pneumococcus identified by culture, latex or PCR	No. of sepsis cases that have a blood culture performed	TBD by WHO, GRLs, RRLs
Percentage of blood cultures contaminated	Total no. blood cultures contaminated	No. of sepsis cases that have a blood culture performed + no. of pneumonia cases that have a blood culture performed	<5%
Percentage of blood culture bottles placed in incubator within two hours as evaluated during site visits	No. of blood culture bottles placed in incubator within two hours	Total no. of blood culture bottles placed in incubator	100%
Percentage of blood agar plates made (commercially or locally) with sheep or horse blood as evaluated during site visits	No. of blood agar plates made (commercially or locally) with sheep or horse blood	Total no. of blood agar plates made (commercially or locally)	100%
Percentage of blood cultures collected and processed with results of non-IB VPD pathogens documented and tabulated as evaluated during site visits	No. of blood cultures collected and processed with results of non-IB-VPD pathogens documented and tabulated	Total no. of blood cultures collected and processed	80%
Percentage of blood specimens forwarded to the reference laboratory for PCR and genotyping	No. of blood specimens	No. of suspected cases that had a blood culture performed	80%

The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization,Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases.
The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current inter-national norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

Department of Immunization, Vaccines and Biologicals
Family, Women's and Children's Health (FWC)