Part II: Target Product Profile (TPP)

for the Advance Market Commitment (AMC) for Pneumococcal Conjugate Vaccines

Supplementary Information

World Health Organization

Contents

Abbreviations

ABCs	Active Bacterial Core Surveillance
AIDS	Acquired Immunodeficiency Syndrome
AMC	Advance Market Commitment
ARIVAC trial	Acute Respiratory Infection Vaccine trial
BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CRM197	Cross Reactive Material of Diphtheria Toxin
DALY	Disability Adjusted Life Years
DTwP	Diphtheria-Tetanus-whole Cell Pertussis Combination vaccine
DTaP	Diphtheria-Tetanus acellular Pertussis Combination vaccine
ELISA	Enzyme-Linked Immunosorbent Assay
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration
FT	Full Term
GAVI Alliance	The Global Alliance for Vaccines and Immunization
GSP	Global Serotype Project
GSKBio	GlaxoSmithKline Biologicals
GMC	Geometric Mean Concentration
GACVS	Global Advisory Committee on Vaccine Safety
Hib	Haemophilus Influenzae type b
HIV	Human Immunodeficiency Virus
IPV	Inactivated Polio Vaccine
IM	Intramuscular
LBW	Low Birth Weight
MDVP	Multi-Dose Vial Policy
NRA	National Regulatory Authority
NCKP	Northern California Kaiser Permanente
OPV	Oral Polio Vaccine
OPA	Opsonophagocytic Assay
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal Conjugate Vaccine
PHiD-CV	Pneumococcal Haemophilus influenzae Protein D Conjugate Vaccine

PPV23	23-valent Pneumococcal Polysaccharide Vaccine
Pneumo ADIP	Pneumococcal Vaccines Accelerated Development and Introduction Plan
PT	Preterm
PspA	Pneumococcal surface protein A
PsaA	Pneumococcal surface adhesin A
SAGE	Strategic Advisory Group of Experts
S. pneumoniae	*Streptococcus pneumoniae*
SC	Subcutaneous
TPP	Target Product Profile
TRS	Technical Report Series
UNICEF	United Nations Children's Fund
VPPAG	Vaccine Presentation and Packaging Advisory Group
VVM	Vaccine Vial Monitor
WER	Weekly Epidemiological Record
WHO	World Health Organization

I. Statement of purpose

This document has been prepared for the Advance Market Commitment (AMC) for pneumococcal vaccines. The AMC is a financial commitment to subsidize the future purchase, up to a pre-agreed price for a vaccine not yet available, if it is requested by a GAVI-eligible country. The pneumococcal vaccine has been selected to pilot this new financing instrument. As part of the AMC process, specifications for eligible products need to be defined in advance. These product specifications are called the target product profile (TPP). In accordance with the relevant AMC legal documents, the characteristics are set at the beginning of the AMC process and can subsequently only be modified by the independent assessment committee (IAC) to render the product requirements less stringent. The TPP defines essential criteria that relate to the public health impact and suitability of the product, covering measures of vaccine efficacy, safety, dose-scheduling, presentation and packaging. The suitability for use in GAVI-eligible countries is the overall guiding principle. At the same time the criteria should help to stimulate a competitive vaccine supply environment, by providing incentives to a large number of vaccine developers. Therefore, essential vaccine attributes need to be demanding, yet realistic, in relation to the innovation that can be achieved over the duration of the pneumococcal AMC. All attributes must be unequivocal and measurable by vaccine developers.

The target product profile should be read together with WHO requirements for product prequalification, and all the related WHO technical documents and guidelines applied in this process. Wherever applicable, the TPP refers to these documents, but sets additional criteria in accordance with the expected use of the pneumococcal vaccines in GAVI-eligible countries. In relation to some TPP attributes, scientific advances may lead to refined criteria over the coming years. In these cases, and as indicated in the TPP, the relevant future WHO guidelines should apply.

While the most advanced pneumococcal candidates vaccines are conjugate vaccines containing capsular polysaccharides, other vaccines based on common proteins may reach the market during the AMC period. Most attributes set in the TPP are not linked to a specific vaccine technology, but for a protein based vaccine some attributes will require adaptation. The public health benefit (i.e. prevention of pneumococcal disease) of these novel vaccines should be equivalent or better than that defined for conjugated vaccines.

The *essential* (Minimally Acceptable Profile) product criteria are included in the TPP Master Table and both *essential* and *desirable* attributes for new pneumococcal vaccines are described in this document. While the table sets the minimum requirements for eligibility for AMC

support, the desirable target profile is intended to foster competition among vaccine manufacturers to develop pneumococcal vaccines with improved performance in GAVI-eligible countries.

II. General introduction

A. *S. pneumoniae* and pneumococcal disease

S. pneumoniae is a major cause of both mild and severe infections worldwide. The primary clinical syndromes associated with pneumococcal infections are pneumonia, meningitis, bloodstream infections and acute otitis media, with pneumonia being the most important of these in terms of total morbidity and mortality. Of the estimated 10 million deaths worldwide amongst children less than 5 years of age each year, WHO estimates that more than 700,000 are caused by pneumococcal infections. Disease rates are highest in children <5 years of age, are low in older children and healthy young adults, and increase again in the elderly (1;2). Pneumococcal disease is endemic worldwide, but the observed incidence of infection varies geographically, not only because of true differences in disease risk but also because of variation in the use of diagnostic tests. Rates of disease, deaths, and complications are higher in developing countries than in industrialized settings, with the majority of deaths occurring in Africa and Asia. In the US, which has among the highest reported invasive disease rates for industrialized countries, annual invasive disease incidence was 96/100,000 children <5 years before the pneumococcal conjugate vaccine was introduced (3). A recent study in Kenya estimated an incidence of presentation to hospital with pneumococcal bacteraemia of 597/100,000 children <5 years of age per year (4). Case fatality can be high for invasive pneumococcal infections, ranging up to 20% for sepsis and 50% for meningitis in developing countries. Among meningitis survivors, long-term neurologic sequelae such as hearing loss, mental retardation, motor abnormalities and seizures can occur in up to 58% of cases, as seen in The Gambia (5).

Major risk factors for disease include young age (particularly age <2), underlying immunodeficiency (such as HIV infection or AIDS), certain other chronic illnesses, day care attendance and exposure to household and tobacco smoke; breastfeeding has been shown to be protective. Invasive disease rates vary, and are higher among indigenous populations of Australia and New Zealand and among the Black, Alaska Native and some American Indian populations in the US relative to the general population (6-8).

Ninety distinct serotypes of *S. pneumoniae* have been identified based on structural differences in the polysaccharide capsule, but according to previous analyses approximately 10 or 11 serotypes account for over 70% of invasive paediatric infections in all regions of the world (9). The distribution of serotypes causing disease varies by age, disease syndrome, disease severity,

geographic region, and over time. Large outbreaks of meningitis caused by serotype 1 have been reported from the African meningitis belt (10;11). Pneumococci that are resistant to penicillin, erythromycin, co-trimoxazole or multiple drugs are common in many regions (12).

B. Pneumococcal carriage

Pneumococcal carriage isolates are the source of invasive strains in an individual. The epidemiology and characteristics of carried isolates are thus directly relevant to disease epidemiology. In a study of the natural history of pneumococcal infection in US children followed from birth, nearly all (79 of 82) were found to carry one or more pneumococcal serotype by their second birthday (13). Children acquired their first type by a mean age of 6 months, and duration of carriage was found to decrease with successive strains carried. For 24 infants who developed pneumococcal disease (28 episodes of otitis media, two of bacteraemia, and one of meningitis), the illness usually occurred within 1 month of acquiring a new serotype, and the carriage serotype usually matched the serotype causing disease.

Pneumococcal carriage is more common and prolonged among children than among adults (14;15). Carriage has also been noted to be significantly more common and occurs earlier among children in developing countries than in industrialized settings. While most information on carriage is from developed countries, some studies have been conducted describing the epidemiology of NP carriage in developing world settings. As an example, in South Africa, the prevalence of pneumococcal carriage was 30% among children sampled at age 6 weeks, 44% at 10 weeks, 51% at 14 weeks and 61% at age 9 months (16). There are other countries or subpopulations within countries where the prevalence of pneumococcal carriage in the nasopharynx occurs even earlier than this and where the rates of colonization are even higher.

C. Current conjugate vaccines

Conjugate vaccines represent a technical advance over pure polysaccharide vaccines as they induce antibodies in young children under the age of 2 years. The inability of pure pneumococcal polysaccharide vaccines to induce a protective immune response for important serotypes in young children precludes their consideration for infant immunization. A 7-valent pneumococcal conjugate vaccine (PCV7) is the only conjugate formulation that is currently licensed and it has been recommended for use in developing countries with high disease burden by WHO's Strategic Advisory Group of Experts (SAGE)(17). A 10-valent (PCV10) and a 13-

valent (PCV13) vaccine are in phase III clinical trials (table 1) and expected to be licensed in the next few years. Additional phase III trials have been performed using 9-valent (PCV9) and 11-valent (PCV11) vaccines that are not expected to reach market. Twenty other pneumococcal conjugate vaccines are in early stages of development (18).

Table 1: Pneumococcal conjugate vaccines: licensed or in late stage of development

Manufacturer	***Serotype composition***	***Carrier***	***Current status***	***Use Worldwide***
Wyeth (Prevnar/ Prevenar)	7 serotypes 4, 6B, 9V, 14, 18C, 19F, 23F	CRM197	licensed	In use. USA since 2000, widespread European introduction from 2006
GSKBio	10 serotypes 7-valent + 1, 5, 7F	Protein D	phase III	
Wyeth	13 serotypes 7-valent + 1, 3, 5, 6A, 7F, 19A	CRM197	phase III	

(i) Pneumococcal conjugate vaccine efficacy trials

The Northern California Kaiser Permanente (NCKP) trial assessed PCV7 impact on pneumonia and invasive disease. Vaccination reduced episodes of pneumonia confirmed by radiograph by 20% (19). Vaccine effect on radiologically confirmed pneumonia was greater in children <2 years (23% reduction) than among children ≥2 years (9% reduction). A later analysis of these data using WHO radiograph protocols reported that the efficacy against pneumonia was 25.5% in an intention to treat analysis, and 30% per protocol (20). Efficacy against invasive disease caused by vaccine serotypes was 97% (21). In a community randomized trial in the US, PCV7 was found to be effective against invasive disease among Navajo and Apache children <2 years of age, reducing episodes caused by vaccine serotypes by 83% (15).

Two trials of PCV9 have been completed in developing countries; the first found that vaccination prevented invasive disease in both HIV-positive and HIV-negative infants in South Africa, although point estimates of efficacy were higher in HIV-negative children, 85% vs. 65% (22). Vaccination significantly reduced radiologically-confirmed pneumonia in children who

were HIV-negative but not in those who were HIV-positive. In a trial in The Gambia, PCV9 reduced radiologically-confirmed pneumonia by 37% and invasive disease caused by vaccine serotypes by 77% (23). The most striking findings in this second trial were that vaccination reduced hospital admissions and deaths from any cause by 15% and 16%, respectively. A third study conducted in Bohol in the Philippines has been completed but results have only been presented orally in abstract form [12th International Congress on Infectious Diseases, Lisbon 2006]. Infants received 3 doses of an experimental 11-valent bi-carrier vaccine (sanofipasteur) before the age of 6 months: the primary endpoint in the study was the first episode of radiologically-confirmed pneumonia. The vaccine prevented approximately one quarter of all pneumonia in children under the age of 2 years.

Efficacy studies in the US, Israel and Europe have evaluated the effects of conjugate vaccines on otitis media. In a large randomized, double-blinded clinical trial among NCKP members, infants receiving PCV7 (at 2, 4, 6 and 12-15 months) had 7% fewer episodes of otitis media, 9% fewer infants with frequent otitis media, and 20% fewer children requiring ventilatory tube placement compared to controls (21). In a trial in Finland, infants receiving PCV7 had 6% fewer episodes of otitis media (24), with 57% fewer episodes of otitis media caused by vaccine serotypes. Notably, children in the PCV7 vaccine group had 33% more episodes of otitis media caused by non-vaccine serotypes. In Israel, PCV9 vaccination reduced episodes of otitis media in day-care attendees aged 12-35 months, but the change was not statistically significant (17% fewer episodes, 95% CI –2 to 22%) (25). Significant reductions were seen for upper and lower respiratory tract infections and days of antibiotic use. However, a study in the Netherlands, where PCV7 was given in combination with 23-valent pneumococcal polysaccharide vaccine (PPV23) to children aged 1 to 7 years with a history of recurrent otitis media, reported no significant benefit for reducing ear infections (26). Another study conducted in the Czech Republic and Slovakia used an 11-valent vaccine containing the 9-valent serotypes + serotypes 3 and 7F, each conjugated to protein D of *H. influenzae* (27). The vaccine was shown to provide an efficacy of 52.6% against vaccine serotypes when assessed against the endpoint of acute otitis media diagnosed on referral to an ENT specialist. Overall effect against any acute otitis media was 33.6%, including protection afforded by protein D against *H. influenzae* infection.

(ii) Vaccine effectiveness following introduction into national immunization campaigns (direct and indirect effects)

The US was the first country to introduce pneumococcal conjugate vaccine, adding it to the routine infant schedule (at 2, 4, 6 and 12-15 months) in 2000. Intermittent supply problems from 2001 through 2004 may have slowed introduction elsewhere and reduced vaccine coverage among infants in the US. As of early 2007, 16 countries are routinely using PCV7 for all

children (Australia, Belgium, Canada, France, Germany, Greece, Italy, Kuwait, Luxembourg, Mexico, Norway, Qatar, Switzerland, The Netherlands, UK, US). Most countries have implemented a 2-dose or 3-dose schedule in early infancy with an additional dose between the ages of 11 and 18 months. In addition, 30 GAVI-eligible countries have expressed interest in introducing PCV7.

Routine use of PCV7 in the US has rapidly reduced rates of invasive pneumococcal disease in children. The impact of the vaccine was noted within 1 year of introduction. According to CDC's Active Bacterial Core Surveillance (ABCs) the incidence of invasive pneumococcal disease among children <5 years dropped 75% from 97 cases per 100,000 population during 1998 and 1999 to 24 cases per 100,000 population in 2005; disease caused by vaccine-type strains fell 94% from 80 cases per 100,000 population to 4.6 (2;3). A multi-centre study of hospitalized patients found that 77% fewer cases in children <2 years were caused by vaccine serotypes in 2002 compared to the average number of cases during 1994 to 2000 (28). Surveillance programmes evaluating PCV7 in single geographic areas in the United States have generally reported findings similar to the multi-site studies (29-32), with the exception of Utah (33), where an increase in disease caused by non-vaccine serotypes reduced the overall effect on disease burden. PCV7 use also appears to be reducing non-invasive pneumococcal infections, including otitis media and pneumonia (34-37). In a recent study using the Nationwide Inpatient Sample, the largest available inpatient database in the U.S., an interrupted time-series analysis found reductions in hospitalizations coded as all-cause and pneumococcal pneumonia comparing 1997-1999 (pre-PCV7 years) to 2001-2004 (post-PCV7 years) (35). In addition, PCV7 reduced differences in the risk of invasive vaccine-type pneumococcal disease between racial and ethnic groups (7;38). Published surveillance data on vaccine impact from outside the US are currently limited. Data from the Calgary area in Canada showed a 93% reduction in vaccine-type invasive disease in children <2 years of age (39). In Australia, early data suggested a reduction in cases of PCV7-serotype disease in indigenous children <2 years of age (8).

The **direct effectiveness** of PCV7 against invasive disease has been formally evaluated. Two surveillance programmes—the U.S. Pediatric Multicenter Pneumococcal Surveillance Group and the Massachusetts Department of Public Health— combined their data and used a case-only method to estimate the effectiveness of abbreviated or delayed dosing regimens against invasive pneumococcal disease (40). In children not at high risk for invasive disease, the effectiveness of the full 4-dose schedule vaccine against vaccine serotypes was estimated to be 91%. Effectiveness was somewhat higher when measured in a large case-control study that used cases of invasive disease identified through US CDC's ABC multi-site surveillance programme and age-matched controls. This study found that 1 or more doses of PCV7 was 96% effective

against invasive disease in healthy children, 81% effective in children with co-morbid medical conditions and 76% effective overall against disease caused by strains resistant to penicillin (41). Vaccination was shown to be significantly protective against all 7 individual vaccine serotypes and vaccine-related serotype 6A, but not against vaccine-related serotype 19A. A case-control study from Spain also reported high effectiveness (88%) against invasive disease caused by vaccine serotypes. The study found a higher likelihood of nonvaccine type disease among vaccinated children (matched odds ratio 6.2, 95% CI 1.6- 23.3), however, than among controls. Methods for case identification and verification of vaccination histories differed from those used in other studies and the study occurred in a setting of low vaccine coverage (27% among controls), which may in part explain the findings (42).

In the US, invasive disease in adults 65 years and older has dropped by about one-third since introduction of pneumococcal conjugate vaccine for children, due to an approximately 80% reduction in disease caused by PCV7 serotypes between 1999 and 2005 (CDC unpublished data) demonstrating the powerful indirect effect of the vaccines. A drop of similar magnitude was seen in hospitalizations for pneumococcal bacteraemia in older adults (43). In Calgary, Canada, however, early surveillance data did not find an overall decrease in adult disease (39). Following PCV7 introduction, invasive disease caused by PCV7 serotypes fell by about half among newborns and infants too young to have been vaccinated (44). Among adults, indirect benefits were as strong among African-American, who are at higher risk for invasive disease, as were seen among persons of white race (38). Between pre-vaccine years (1998 and 1999) and 2003, an overall reduction of 19% in invasive disease rates was noted among adults 18-64 years of age with HIV or AIDS, a group with disease rates up to 100 times that of healthy adults the same age (45). In contrast to the findings for invasive disease, rates of pneumonia hospitalizations among older adults have not dropped significantly following PCV7 introduction (35).

(iii) Serotype replacement: In most but not all pneumococcal carriage studies, carriage of non-vaccine type strains increased among children receiving conjugate vaccine. Despite the reduction in carriage of vaccine serotypes the overall prevalence of pneumococcal carriage was not different in vaccinated and unvaccinated children (15). The implications of this replacement colonization in terms of disease are not yet clearly understood, although replacement disease is not anticipated to result in increases in the overall burden of pneumococcal disease (18). Replacement disease was not observed in the invasive disease efficacy trials, but in the Finnish Otitis Media trial, children in the pneumococcal vaccine group had 33% more episodes of otitis media caused by serotypes not in the vaccine or related to vaccine types (24). Measurement of serotype replacement after vaccine introduction is complicated by the natural variation in serotype distribution over time. In the US, a relatively small but statistically significant increase

was seen in invasive disease caused by non-vaccine-type strains, in particular serotype 19A after PCV7 introduction (46). Surveillance in Utah, where the overall reduction in disease was only 27%, showed that a decrease in vaccine-type disease was accompanied by an increase in non-vaccine type disease (33). Recent data also indicate that an increase in invasive disease caused by non-vaccine-type pneumococci has eroded some benefits of PCV7 among Alaska Natives (47). Overall, serotype replacement has so far had only minimal impact on vaccine effectiveness, and the measured replacements may in part be due to secular trends or antibiotic use patterns. Vaccine introduction should be accompanied with disease surveillance to monitor the occurrence of replacement disease.

C. Cost-effectiveness

Most published studies of the cost-effectiveness of pneumococcal vaccine have been done in the US or in Western European countries. Recently, however, Sinha et al (2007) carried out an analysis of the available 7-valent pneumococcal conjugate vaccine for the 72 countries that in 2005 were eligible for financial support from GAVI (48). The analysis found that at a cost of $5 per dose, the programme would cost around $100 per DALY, ranging from $56 in Azerbaijan up to $14800 in Cuba. If each country's per capita gross domestic product were used as the benchmark for a 'highly cost-effective and affordable' intervention, the vaccine would qualify in 68 of the 72 countries. Assuming a 3 x GDP as benchmark it would be cost-effective in a further 3 countries.

The most important determinants of cost-effectiveness were vaccine cost and the vaccine's impact on mortality. Costs of $1 to $10 per dose were used in different scenarios. At $10 per dose the cost per DALY increased to around $200 on average. If one assumes a high price ($7 per dose) and a lower impact on all-cause mortality (3%, rather than the 7% central estimate), the overall cost/DALY rises to $500.

The analysis was intended to be conservative, meaning that the analysis excluded factors that would have improved the cost-effectiveness of the vaccine. The only benefits of vaccination accounted for were prevention of deaths among children aged 3 to 29 months. Benefits from prevention of deaths after 29 months of age and of non-fatal morbidity, including avoidance of the associated health care costs of treatment, were excluded. A secondary analysis incorporating non-fatal disease reduced the cost to $80 per DALY averted. Although benefits of this kind were disproportionately found in countries with well-developed health care infrastructures, the potential to prevent large numbers of hospitalizations could prove important in countries with low mortality rates. Benefits to unvaccinated children and adults through herd immunity were also excluded. In US-based analyzes, 'external' benefits through herd immunity

were substantial, but there are no herd immunity data from developing countries and the authors chose not to extrapolate the US results to the GAVI-eligible countries. On the other hand two factors were excluded that could have an adverse effect on cost-effectiveness: the occurrence of serotype replacement and delays in children receiving vaccine doses.

In summary, the limited evidence available suggests that pneumococcal conjugate vaccines that reduce mortality by 7% would be highly cost effective in the great majority of GAVI-eligible countries if the price is around $5 per dose or less. Vaccine formulations that contain serotypes that prevent a lower proportion of disease than was assumed in the study by Sinha et al may require additional cost-effectiveness analyses.

E. Protein based vaccines

The pneumococcal AMC does not stipulate the type of pneumococcal vaccine eligible, therefore protein-based pneumococcal vaccines should they become available during the course of the AMC, are potentially eligible for AMC funds. Many of the requirements outlined in this TPP are theoretically applicable to protein vaccines. However, protein vaccines are still in pre-clinical or early clinical development and their pathways to licensure are not yet defined. The most important open question includes the demonstration of vaccine efficacy in direct comparison to licensed conjugated vaccines. To date, only one protein vaccine, which contained PspA and PsaA has been assessed in phase 1 studies in adults. As stated in the scope of the document, eligibility criteria for these vaccines will need to be developed as vaccine candidates' progress.

III. Vaccine characteristics relevant to the Target Product Profile

A. Vaccine serotypes

The vaccine's public health impact in different geographic settings will depend upon the match between vaccine serotypes and the pneumococcal serotypes that account for paediatric pneumococcal disease locally. Hence, AMC eligible vaccines must include at least a minimum set of strains to assure that an adequate public health impact is achieved in regions where the vaccines will be used. The 2008 Pneumococcal Global Serotype Project (GSP) undertook a systematic literature review and meta-analysis of published and unpublished studies of invasive pneumococcal disease isolates from around the world (http://www.preventpneumo.org/pdf/GSP Version 2 Summary for IAC 2008Dec.pdf). The aim of the GSP was to establish the serotype distribution of disease causing strains among children < 5 years of age globally and regionally. The GSP analysis includes 169 studies from 70 countries and data on >60,000 isolates. The analysis is reasonably robust at a global and regional level but data paucity makes sub-regional analyses less reliable.

The GSP analysis has several key findings. Serotype 14 is the most common serotype in all regions of the world among children< 5 years. Serotypes 1 and 5 are among the top 6 ranked serotypes occurring among children < 5 years in regions with the highest pneumococcal disease burden (Africa, Asia, and Latin America, and the Caribbean) and among the top 3 ranked serotypes occurring in GAVI-eligible countries as a whole. A limited set of seven serotypes (1, 5, 6A, 6B, 14, 19F, 23F) are common and important in all regions with a substantial number of GAVI eligible countries. Together, these 7 serotypes account for ~58%-66% of all invasive pneumococcal disease in each region. Vaccines with fewer than 10 serotypes can provide broad protection. With as few as 6-7 serotypes (including serotypes 1, 5, and 14, and assuming 6A/B cross-protection), it should be possible to develop pneumococcal conjugate vaccines that include serotypes causing at least 60% of all invasive pneumococcal disease in each region.. Although a 60% coverage level may be considered moderate, vaccines that include serotypes with this level of coverage would be expected to have a considerable public health impact and be favourably assessed by cost effectiveness analysis.

Based on these findings, vaccines will be assessed for AMC eligibility based on two requirements: (1) they must include serotypes 1, 5 and 14, and (2) the serotypes included in the

vaccine must account for at least 60% of disease causing isolates, as calculated at the regional level. In calculating the cumulative proportion of disease covered by a putative product, manufacturers may wish to include serotypes that are related to those in the vaccine, the so-called cross-reactive types. In order to include the proportion of disease accounted for by cross-reaction from a type included in the vaccine, manufacturers must provide evidence that the product is highly likely to provide protection against disease from the cross-reactive type of interest.

Serotypes 1, 5 were selected as essential serotypes because these are among the most common types in regions particularly relevant to GAVI and are of epidemic and endemic disease importance especially in Asia and Africa, the two regions with the greatest pneumococcal disease burden among children. Serotype 14 was also included as an essential serotype because it is the most common isolate among children below 5 years of age in all regions. The stipulation of these three serotypes is not intended to diminish the importance of other serotypes. **Manufacturers are strongly encouraged to develop formulations which take into consideration the major disease causing serotypes in regions and globally. They are also encouraged to select formulations which address the importance of antimicrobial resistance and the potential for serotype replacement disease** [For estimations on serotype specific prevalence in different geographic regions of the world refer to the 2008 GSP report, available at: http://www.preventpneumo.org/pdf/GSP Version 2 Summary for IAC 2008Dec.pdf].

The choice of 60% coverage was selected on the basis of several principles, balancing the imperative for a significant public health benefit with the likelihood that manufacturers will be motivated and successful in developing pneumococcal vaccines for the GAVI market.

First, the 60% coverage accounts for the smallest number of serotypes responsible for the greatest amount of invasive disease. In regions with GAVI-eligible countries (i.e. all regions except North America), the incremental coverage by serotypes beyond 60% becomes smaller and smaller. For example, 60% coverage requires 4-7 serotypes for each region (assuming 6A/6B cross-protection), while 80% coverage (i.e. an additional 20% coverage) requires 2-8 additional serotypes in each region except Asia which requires an additional 14 serotypes.

Second, a single formulation covering at least 60% of disease in every region is possible with only 6-7 serotypes, again assuming 6A/6B cross-protection. Limiting the number of serotypes decreases the complexity of the vaccine and thus increases the number of manufacturers likely to successfully make pneumococcal vaccines.

Third, when applied to the absolute burden of pneumococcal disease in children, 60% coverage still represents a major public health impact thereby assuring that all AMC eligible vaccines

deliver a significant public health benefit. Levels higher than this would require additional complexity in the production for relatively smaller increases in health impact.

Furthermore, the proposed 60% level is consistent with the level of protection on which a cost-effectiveness analysis of pneumococcal conjugate vaccine in GAVI-eligible countries was based (48). This cost-effectiveness analysis, which contributed to decision-making for introduction of these vaccines, was based on the mortality impact from The Gambia pneumococcal vaccine trial (23). In that trial, the vaccine prevented 50% of invasive pneumococcal disease (IPD) - that is, IPD due to all serotypes. With this 50% reduction in pneumococcal disease, there was also a 16% reduction in all-cause child mortality among vaccine recipients – a prevention of 7.4 deaths for every 1000 vaccinated children.

The model estimated the impact on mortality in other countries by indexing The Gambia trial mortality reduction on the relative under 5 mortality rate in The Gambia compared with that of other countries. For example, the impact of PCV on mortality in a country with an under 5 mortality rate half of that seen in The Gambia was assumed to be 8%, or half of 16%.

How does the 60% serotype requirement link with The Gambia trial results and the cost-effectiveness analysis? The 50% impact on all-serotype invasive pneumococcal disease is, by definition, the product of the proportion of the serotypes covered by the vaccine and the vaccine's efficacy against serotypes in the vaccine. A recent Cochrane meta-analysis of all PCV efficacy trials around the world estimated efficacy against vaccine-serotype invasive disease to be 88% (49). Assuming 88% efficacy against vaccine serotype IPD, a 50% reduction in all invasive pneumococcal disease requires a vaccine with 57% serotype coverage. Therefore, 60% coverage should assure that vaccines provide a health impact similar to or higher than that used in the cost-effectiveness analyses for GAVI-eligible countries reported by Sinha et al.

AMC eligibility should be based on regional data as defined in the GSP 2008 report, even if subregional and country level data are available. If a country is in a region where a vaccine formulation was found to meet the two required AMC eligibility criteria based on the GSP 2008 report, then the country may request that vaccine formulation under the AMC, notwithstanding reliable sub-regional or country level data to the contrary. However, in choosing between different AMC-eligible vaccines it is likely that countries will be influenced by their expected impacts on disease. Updates to the Pneumococcal GSP will be carried out periodically in the future. The purpose and use of the updated analyses are for country decision-making and demand assessments and are not to be used for vaccine eligibility assessments, which will be based on the 2008 Pneumococcal GSP.

Attribute	Minimally acceptable profile
A. Vaccine serotypes	The serotypes in the vaccine formulation must cover at least 60% of the invasive disease isolates in the target region, and must include serotypes 1, 5 and 14 which are the most frequent isolates in GAVI eligible countries.

B. Immunogenicity

For pneumococcal conjugate vaccines, the main method of evaluation of immunogenicity is quantification of serum IgG using ELISA, although many studies have also used opsonophagocytic assays to evaluate functional antibody activity. Analysis of data from the NCKP clinical trial suggested that a titre ≥0.20 μg/ml 1 month following receipt of the third dose of the primary series predicted protection against invasive disease (50). A re-analysis using additional data from other clinical trials indicated that ≥0.35 μg/ml was a more appropriate cut off (51); this cut-off also corresponded to a threshold of opsonic antibody titre of 1:8, and no significant differences were seen among the different vaccine serotypes.

Defining correlates of protection for otitis media has been more difficult. An analysis of the Finnish Otitis Media study identified an association between antibody concentration and risk of otitis media, but large differences were seen between serotypes; the predicted efficacy for type 19F was negligible up to the highest geometric mean concentration tested, but 6B was found to be highly efficacious (>65%) at a geometric mean concentration of 0.5 μg/mL (24).

Immunogenicity in high risk populations also needs to be considered where the vaccine is likely to be used in such children. Children with HIV are at a substantially increased risk of invasive pneumococcal disease. PCV7 is immunogenic in children with HIV and has demonstrable efficacy against invasive disease in these children (52;53). **Manufacturers of pneumococcal vaccines eligible for AMC support should provide evidence of the immunogenicity of the vaccine in HIV positive children where relevant.**

Persons with sickle cell disease and other hemoglobinopathies resulting in functional asplenia are also at high risk for serious infections with *S. pneumoniae* (54-57). PCV7 induces significant increases in serum antibody concentration among infants with sickle cell disease that appear to be as high as those induced in healthy infants (58). In older children, 2 doses of PCV7 followed by a booster with 23-valent pneumococcal polysaccharide vaccine resulted in higher GMCs and OPA titers than 23-valent polysaccharide vaccine alone (54). The reactogenicity of

PCV7 is not different between children with and without sickle cell disease; however, children with sickle cell disease who had a 3-dose primary series of PCV7 had somewhat stronger reactions to a booster with 23-valent polysaccharide vaccine than those who had a single dose at 12 months (58). Preliminary analysis of invasive disease trends among children <5 years of age with sickle cell disease in Atlanta found that rates declined 66% in the 2 years following PCV7 licensure, suggesting that routine use of PCV7 provides protection among children with sickle cell disease (59).

For the majority of pneumococcal serotypes, nasopharyngeal carriage precedes invasive disease. Thus, reduction of carriage is likely to be associated with a reduced incidence of disease. Clinical trials of pneumococcal conjugate vaccines demonstrated a reduction in nasopharyngeal carriage of vaccine serotypes (15;16;60-62). As expected on the basis of these results, routine use of pneumococcal conjugate vaccine in the US has reduced carriage of vaccine serotypes among children, although the overall prevalence of pneumococcal carriage has remained unchanged (7;63-67). There was some evidence that the timing of immunization is important. In Texas, investigators found that while the overall prevalence of pneumococcal carriage remained between 24-30% for the visits from 6 to 18 months, the proportion of vaccine-type pneumococci dropped between the 12- and 18-month visits, corresponding to the timing of the 4th dose; at the same time, carriage of non-vaccine type pneumococci increased (63). In Kentucky, researchers evaluating carriage during a time of vaccine shortage noted that carriage of vaccine serotypes decreased following the third and fourth doses and that children with prolonged intervals between the second and third doses (>3 months) and the third and fourth doses (>8 months) were more likely to carry vaccine-type strains than children with shorter intervals between doses (65). Studies also indicate that carriage of vaccine-type pneumococci fell among adults following vaccination of children (67). Attempts have also been made to define correlates of protection against pneumococcal carriage. Dagan (68) and Millar (69) found that higher IgG concentrations led to a decreasing probability of having a newly-acquired strain. This was statistically significant for serotypes 14, 19F, and 23F, but like with otitis media, differences were seen by serotype. The ongoing PneumoCarr "Grand Challenges" Project will investigate these issues further, although currently no firm guidelines are available .

While reduction of carriage is likely to be a desirable outcome following pneumococcal vaccination no firm guidelines exist yet for this endpoint as part of the licensing pathway. However, **demonstration of reduced vaccine type carriage following vaccination would be highly desirable.**

Attribute	Minimally acceptable profile
B. Immunogenicity	Immunogenicity should be demonstrated in accordance with WHO criteria, which are based on non-inferiority to a licensed pneumococcal vaccine as outlined in WHO *Recommendations for the production and control of pneumococcal conjugate vaccines.* (WHO Technical Report Series, No 927, 2005 and any subsequent published guidance).

C. Target population/ Target age groups

Pneumococcal disease rates are highest in children <5 years of age, are low in older children and healthy young adults, and increase again in the elderly (1;2). Rates of disease and deaths are higher in developing countries than in industrialized settings. In the US, which has among the highest reported invasive disease rates for industrialized countries, annual invasive disease incidence was 96/100,000 children <5 years before the pneumococcal conjugate vaccine was introduced (3). In contrast, a recent study in Kenya estimated an incidence of presentation to hospital with pneumococcal bacteraemia of 597/100,000 children <5 years of age per year (4). Pneumococcal vaccines designed to have maximal public health impact must be optimised for disease prevention in children <5 years of age and in particularly be effective in those < 2 years of age.

Attribute	Minimally acceptable profile
C. Target population/ target age groups	The vaccine must be designed to prevent disease among children <5 years of age and in particularly be effective in those < 2 years of age.

D. Safety, reactogenicity and contra-indications

Clinical trials found PCV7 and PCV9 to be well-tolerated, and passive post-licensure surveillance for adverse events following receipt of PCV7 has indicated that the safety profile is comparable to other routinely used vaccines (70). Fever rates in the NCKP trial were higher

among children receiving PCV7 than among controls (21), and reported fever, but not measured fever, was higher among PCV9 recipients in The Gambia trial (23). In The Gambia, significantly more outpatient visits were made within a week after dose 1 among those receiving PCV9, but this difference was not seen with later doses. An increased risk for reactive airways disease or asthma may be a concern in children receiving PCV7. Preliminary observations among infants at the NCKP found reactive airway disease to be approximately 20% more common among PCV7 recipients than among historical controls (71). In the South African PCV9 efficacy trial, rates of viral pneumonias requiring hospitalization within the first week after vaccination and asthma-related diagnoses at any time following vaccination were somewhat higher among vaccine recipients (22). The WHO Global Advisory Committee on Vaccine Safety (GACVS) recently reviewed the current evidence on the safety of PCV7 and other pneumococcal conjugate vaccines and found it reassuring (19). Nevertheless, as with any new vaccine, it will be important to conduct surveillance for possible, rare unexpected effects after it is introduced in the target population.

Among low birth weight infants (LBW) and premature newborns (PT), rates of fever and local events after PCV vaccination were found to be similar in frequency to normal weight and age newborns when adjusted for clustering among multiple doses per child. When stratified for individual doses there was more redness and swelling among LBW infants and more swelling among PT infants after dose 3 (72). **Since developing countries have a high prevalence of malnutrition and LBW infants, studies in those populations will be desirable to ensure the safety profile of the candidate vaccines.**

Attribute	Minimally acceptable profile
D. Safety, reactogenicity and contra-indications	The safety and reactogenicity profile should be comparable to, or better than that of the currently licensed pneumococcal conjugate vaccine. Contra-indications should be restricted to known hypersensitivity to any of the vaccine components.

E. Vaccine dosage schedules

Clinical trials of PCV7 conducted in the US used a schedule of 2, 4, 6, and 12 months of age (15;21) and a 4-dose series was subsequently licensed and recommended. However, a growing body of evidence suggests that fewer than 4 doses may be effective. Phase III trials of the 9-valent vaccine in South Africa and The Gambia showed that a 3-dose primary series given in the

first year of life conferred substantial protection (22;23). In the NCKP study, efficacy for partially vaccinated children was 85.7% (95% CI 0, 100) (21). In Italy, a single-blind cohort study of vaccination at 3, 5, and 12 months showed less radiologically confirmed pneumonia, acute otitis media, and antibiotic use in children who had received PCV7 compared to those who had not, but the effects were not statistically significant after 12 months of age (34).

Shortages of PCV7 that occurred in the US between 2001 and 2004 provided an opportunity to evaluate the effectiveness of incomplete vaccination with pneumococcal conjugate vaccine. Combined data from two surveillance programs -the U.S. Pediatric Multicenter Pneumococcal Surveillance Group and the Massachusetts Department of Public Health – estimated that in children not at high risk for invasive disease, the effectiveness against vaccine serotypes was 91% for the full 4-dose schedule, 77% for 3 doses given before 7 months of age, and 71% for 2 doses given before 5 months of age (40). A single dose given before 3 months of age did not provide statistically significant protection against vaccine serotypes, and none of the vaccine regimens provided significant protection against non-vaccine serotypes (41;41). Examination of different schedules found that nearly all provided some protection compared to no vaccine, although a single dose at <7 months was less protective than 2 or 3 doses received at <7 months of age**.** A direct comparison of 3 doses before 7 months of age plus a booster at 12-15 months with 3 doses before 7 months without a booster suggested that the booster added additional protection (p=0.03). Immunogenicity evidence from several studies in industrialised countries shows that schedules with two doses <6 months of age followed by a booster dose around 12 months, as expected, increases antibody levels above those elicited with a primary series. (73-76). Some serotypes like 6B and 23F may show lower antibody responses with less doses of vaccine, but this can be overcome by a booster. More immunogenicity data will be forthcoming on reduced dose schedules.

There are differences in responses to conjugate vaccines between developed and developing country settings. For example, an evaluation of PCV9 immunogenicity in the UK found that antibody levels increased following either 2 or 3 infant doses but declined to near pre-vaccine levels before the booster dose was given at 12 months (75). In contrast, in South Africa among HIV-uninfected children, antibody levels remained higher than among controls for up to 5 years (53). While direct comparisons between exact IgG GMC values from studies done at different times or in different laboratories should be undertaken with caution, antibody levels 4 weeks after the 3rd infant dose in African studies (16;77) were generally higher than that seen after the 3rd infant dose in the UK PCV9 study (75) or in PCV7 studies in the US (21;78). The reasons for these differences are poorly understood but may relate to the degree of natural exposure to vaccine-type and cross-reactive organisms and/or the maturation of immune responses. Further information will be available when data from reduced infant dose studies in Kenya

(Goldblatt/Scott), Fiji (Lehman) and Israel (Dagan) are presented. An analytic model of vaccination using surveillance and immunogenicity data suggested that a single dose of conjugate vaccine could be effective if the timing of administration is chosen carefully (79). Although a single dose was not predicted to be as effective as a 3- or 4-dose regimen, the model suggested that a single dose given between 5 and 7 months of age could prevent up to one-third of invasive pneumococcal disease.

Given these considerations, the target pneumococcal conjugate vaccine candidates for developing countries should be designed to elicit appropriate antibody responses using a maximum of 3 doses in infancy. The current developing country dose schedules vary among the regions, Latin America uses a 2, 4 and 6 month schedule, while Africa and Asia use the WHO recommended schedule of 6, 10 and 14 weeks. At a minimum, the vaccine should perform well when administered according to both of these schedules and the first dose should ideally be given at 6 weeks of age or earlier. The possibility of alternative schedules (e.g. two or less infant doses and a later dose at 9-12 months) should also be explored. WHO is currently undergoing a careful review of the EPI recommended schedule to adjust it to the newly available and future public health vaccines.

Data on duration of protection for pneumococcal vaccines are somewhat limited. WHO has proposed a concentration of IgG anticapsular polysaccharide antibodies by ELISA of $\geq$ 0.35μg/ml as protective, derived from the pooled estimate of data from 3 studies conducted in North America and Africa. However, as compared to Hib protective levels, no specific threshold has been defined for long term protection against pneumococcal disease. Priming for subsequent memory responses in the absence of persisting anti-capsular antibody may not be enough, as the incubation of *S. pneumoniae* infections is short and antibody levels are paramount for the protection of disease as demonstrated recently in the UK with Hib infections. However, in South Africa, HIV-uninfected children who received 3 infant doses of PCV9 showed no reduction in efficacy for up to 6 years, and antibody levels remained higher than among controls for up to 5 years (53); protection and antibody levels waned in HIV-infected children. Provided that 3 doses of vaccine in the first year of life will be efficacious in developing countries, **information on the need for booster doses may be desirable in the future to answer questions on herd immunity effects and persistence of protection.**

Attribute	Minimally acceptable profile
E. Dosage schedule	Vaccine scheduling must be compatible with national infant immunization programmes and consist of not more than 3 doses in the first year of life. The first dose must be shown to be administrable at 6 weeks of life or earlier.

F. Interference and co-administration with other vaccines

Co-administration of PCV7 with DTwP or DTaP, Hib, hepatitis B, and OPV or IPV is not associated with a clinically significant reduction in the response to any of the vaccines. Variable responses, especially lower GMC to pertussis antigens, have been demonstrated in a few studies when DTaP is co-administered with PCV-7 (80-82). However, these studies varied in schedule intervals and antigens delivered. In a study of PCV7 plus DTP-IPV/Hib, 96-100% of children achieved a post-dose three with IgG concentration of >0.15 μg/ml (the threshold chosen for this study) against each of the seven pneumococcal serotypes, showing no interference. Local reactions were significantly less frequent at the PCV7 injection site than at the DTP-IPV/Hib injection site; with the exception of fever >38 °C, systemic reactions were comparable (81).

The target candidate pneumococcal vaccines should provide evidence of no clinically significant immunological interference and safety interaction with vaccines administered concurrently in infancy as part of the national immunization programs in developing countries.

Attribute	Minimally acceptable profile
F. Interference and co-administration with other vaccines	There should be no clinically significant interaction or interference in relation to safety and immunogenicity with concurrently administered vaccines.

G. Route of administration

The intramuscular (IM) route is the only route of administration currently recommended for administration of pneumococcal conjugate vaccines in children. However, some data on subcutaneous (SC) administration are available for the 23-valent polysaccharide vaccine in adults. In a randomised, observer blind study of 254 elderly subjects, the immunogenicity of a 23-valent pneumococcal vaccine was not influenced by its route of administration (83). A low rate of systemic adverse reactions was observed with the vaccine (SC and IM both 6.3%). Local adverse reaction rates were: IM 7.1% and SC 18.9%, suggesting IM is a safer route, but in adults this response is influenced by previous levels of anti-pneumococcal antibodies (83). Theoretically, intra/trans-dermal, intranasal, aerosol vaccine administration or other routes may have advantages, both in terms of dose, immunogenicity and ease of administration for large-scale use. **Vaccine developers are encouraged to explore these routes of administration.**

Attribute	Minimally acceptable profile
G. Route of administration	Intramuscular or subcutaneous.

H. Product presentation

Vaccine packaging and presentation needs to be adapted to the programmatic requirements in developing countries. Inappropriate packaging and vial sizes can add substantially to the cost of immunization through excessive storage requirements, product wastage and others. The consideration of wastage is particularly important for vaccines that cost more than traditional EPI vaccines. A group of experts, the Vaccine Packaging and Presentation Advisory Group (VPPAG, see acknowledgements), has investigated several options of product presentation for pneumococcal vaccine, based on the likely price range for this vaccine and applying real wastage rates.

Based on this analysis the best presentation options are mono-dose and low multi-dose vials. Mono-dose presentations, in particular if available as auto-disable compact prefilled devices, help to assure safety of injection, reduce work load to health care workers, and reduce wastage of vaccines. Low multi-dose vials have reduced storage requirements and acceptable wastage rates. Preliminary analysis suggests that vials containing between 2-5 doses are appropriate. However, the selection of the number of doses per vial should be defined by the manufacturer.

To allow for use through subsequent immunization sessions, the vaccine needs to contain preservative at appropriate concentration as outlined in the Global Advisory Committee of Vaccine Safety statement (http://www.who.int/vaccine_safety/topics/thiomersal/en/index.html; accessed 18.10.2007). If a low multi-dose vaccine contains no preservative, it needs to be discarded at the end of the immunization session, and at latest 6 hours after the vial has been opened. To distinguish such products from those containing preservative, a specific labeling of the vial will be required. WHO is currently revising its policy on the use of opened multi-dose vials (*The use of opened multi-dose vials of vaccine in subsequent immunization sessions,* WHO/V&B/00.09), and information on the labeling should be obtained from WHO.

In conclusion, for the TPP, mono-dose or low multi-dose vial presentations are considered essential.. For mono-dose presentations, either single dose vials or auto-disable compact pre-filled devices must be used. All presentations should be optimized for space-efficiency in accordance with the WHO Guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23).

Attribute	Minimally acceptable profile
H. Product presentation	The vaccine must be available in mono-dose or low multi-dose presentations. Mono-doses must be either a single dose vial or a auto-disable compact pre-filled device. Low multi-dose presentations must be formulated and labelled in compliance with WHO policy or guidance.

I. Product formulation

Lyophilized vaccine formulations may have advantages in relation to storage temperature but the disadvantages for field use are several, including the need for reconstitution, additional storage capacity for the diluent, greater workload, especially when vials contain small number of doses, which will be the case for pneumococcal vaccines. It is therefore recommended that only liquid formulations will be used. The target volume should be 0.5ml/dose. This volume represents a balance between ease of administration and minimal pain on injection, and is the most frequently used in immunization.

Attribute	Minimally acceptable profile
I. Product formulation	Liquid formulation with a standard volume of 0.5 ml/dose

J. Storage and cold chain requirements

Available pneumococcal vaccines and those in advanced development are all liquid formulations requiring storage at 2 to 8 °C. Liquid vaccines containing aluminium adjuvants should not be frozen. If freeze-sensitive, pneumococcal vaccine manufactures should allow the use of the 'shake test' or other means (such as a vial-based freeze indicator) to assess whether freeze damage has occurred. Vaccine shelf life should be in accordance with WHO requirements (24 months), but **a prolonged shelf life would be desirable**. Vaccine vial monitors (VVM) to measure exposure to high temperature should be attached in accordance with existing WHO policy as outlined in *Making use of vaccine vial monitors. Flexible vaccine management for polio* (WHO/V&B/00.14). **Vaccines with increased thermostability are desirable because they permit more flexible use of the vaccine and ideally, new vaccines would not need a cold chain.**

Attribute	Minimally acceptable profile
J. Storage and cold chain requirements	The product must be stable at 2-8 °C with a shelf-life of at least 24 months and a vaccine vial monitor should be attached as outlined in *Making use of vaccine vial monitors. Flexible vaccine management for polio* (WHO/V&B/00.14).

K. Vaccine packaging and labelling

The vaccine should be packaged and boxed in a format designed to fit the widest range of currently deployed cold chain equipment. Extensive guidance is available from WHO *Guidelines on the international packaging and shipping of vaccines* (WHO/IVB/05.23). Equally, product name and labelling should follow internationally accepted standards set out in *Recommendations for the production and control of pneumococcal conjugate vaccines.* (WHO Technical Report Series, No 927, 2005).

Attribute	Minimally acceptable profile
K. Packaging and labelling	Name and labelling must be in accordance with WHO *Recommendations for the production and control of pneumococcal conjugate vaccines.* (WHO Technical Report Series, No 927, 2005). Packaging must ensure minimal storage space requirements as set out in *Guidelines on the international packaging and shipping of vaccines* (WHO/IVB/05.23).

L. Product registration and prequalification

Each vaccine procured via the AMC will require WHO prequalification as outlined in the *Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (WHO/IVB/05.19). In addition, WHO has developed guidelines on how to expedite country-level registration of a pre-qualified vaccine (see *Procedure for expedited review of imported prequalified vaccines for use in national immunization programmes (*WHO/IVB/07.08)).

Attribute	Minimally acceptable profile
L. Product registration and prequalification	The product must be WHO pre-qualified in accordance with *Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (WHO/IVB/05.19).

M. Post marketing surveillance

All newly introduced vaccines should be monitored through post marketing surveillance. Of particular interest are the monitoring of safety, protection of the target population, indirect effects (herd immunity) and potential serotype replacement following widespread use of the vaccine.

Attribute	Minimally acceptable profile
M. Post Marketing Surveillance	Post-marketing surveillance should be conducted in accordance with national regulatory authorities and WHO prequalification requirements as set out in *Guideline for preparation of the product summary file for vaccine prequalification* (WHO/IVB/06.16) , *Guidelines on clinical evaluation of vaccines: regulatory expectations* (WHO Technical Report Series, No 924, 2004) and any relevant published guidance.

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8. Guideline for preparation of the product summary file for vaccine prequalification (WHO/IVB/06.16)

9. Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO/IVB/05.19)

10. Procedure for expedited review of imported pre-qualified vaccines for use in national immunization programmes (WHO/IVB/07.08).

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