Pneumococcal polysaccharide vaccine

WHO position paper

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO is issuing a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers, which are concerned primarily with the use of vaccines in large-scale immunization programmes, summarize essential background information on the respective diseases and vaccines, and conclude with the current WHO position concerning their use in the global context. The papers have been reviewed by a number of experts within and outside WHO and since April 2006 they are reviewed and endorsed by WHO's Strategic Advisory Group of Experts (SAGE) on vaccines and immunization. The position papers are designed for use mainly by national public health officials and immunization programme managers. However, they may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community, scientific media, and the public.

Summary and conclusions

Infections caused by Streptococcus pneumoniae are a major public health problem of children and adults worldwide. Serious manifestations of pneumococcal infection include bacteremia, meningitis, non-bacteremic pneumonia and other lower respiratory infections. Acute otitis media and other upper respiratory infections such as sinusitis are less serious manifestations but cause considerable morbidity and health care costs. It is estimated that 1.6 million people die of pneumococcal disease, mostly pneumonia, every year, including 0.7 - 1 million children < 5 years of age, most of whom are in developing countries. In all age groups, individuals suffering from immunocompromising conditions are at particular risk of serious pneumococcal disease.

Given the high burden of pneumococcal disease in children and adults, WHO considers prevention of pneumococcal disease a high priority in both industrialized and non-industrialized countries. Reduced options for specific treatment due to increasing resistance of S. pneumoniae to commonly used antibiotics further underlines the urgent need to prevent pneumococcal infections through vaccination.

Antibodies to the capsular polysaccharide of S. pneumoniae may provide serotype-specific protection against pneumococcal infections, and pneumococcal vaccines are designed to include the serotypes most frequently associated with invasive pneumococcal disease. Two pneumococcal vaccines are currently available; a 23-valent pneumococcal polysaccharide vaccine (PPV23) for use in adults and older children and the more recently developed 7-valent polysaccharide-protein conjugate vaccine (PCV7) which is designed for infants and young
children and represents a new generation of pneumococcal vaccines. In 2003, WHO published recommendations concerning the use of these two vaccines. Revised recommendations on the use of PCV7 in infants and young children are presented in the WHO Weekly Epidemiological Record No 12, 2007, 82, 93-1004. The current position paper updates and replaces the 2003 position paper concerning the use of PPV23.

While randomized controlled trials and meta-analyses of such trials of PPV23 in developed countries have generally demonstrated no efficacy against invasive pneumococcal infection or all-cause pneumonia in older and high risk adults, most observational studies suggest an effectiveness of up to 50–80% against bacteremia or invasive infection in those populations.

Although the clinical effectiveness of PPV23 remains a topic of controversy, available data provide some support for use of the vaccine in countries where it is already recommended for the elderly and other high-risk groups. In those countries, public health emphasis should be placed on increasing vaccination coverage among these target populations.

Countries not currently using PPV23 and that may wish to consider the possible benefits of giving PPV23 to the elderly and others at high risk of pneumococcal infection should not allow the introduction of PPV23 to detract from achieving high levels of coverage with PCV7 among infants.

Primary immunization with PPV23 consists of a single subcutaneous or intramuscular dose of the vaccine. The optimal timing, frequency and clinical effectiveness of additional doses of PPV23 are unknown and national recommendations regarding revaccination vary. However, on the basis of currently available data on duration of vaccine-induced protection, most authorities recommend a single revaccination 5 years or more after a first vaccination for those at highest risk and most likely to have a rapid decline in antibody levels after vaccination (i.e. asplenic and immunocompromised persons).

In a number of wealthy and middle income countries routine use of PPV23 is recommended for HIV-infected adults and older children, based on the high risk of pneumococcal disease in these individuals and the potential benefits and safety of the vaccine. The role of PPV23 among corresponding groups in low income countries remains controversial, and most low income countries have relied on other measures that may help preventing pneumococcal disease in these individuals, such as antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP), which may also confer some protection against pneumococcal disease.

No adverse consequences have been reported among newborns whose mothers were vaccinated during pregnancy and hence, pregnant women with underlying medical conditions that are indications for PPV23 vaccination may be vaccinated. Ideally, however, women with risk factors for pneumococcal infection should be vaccinated before pregnancy.

In countries using PPV23, high levels of coverage with the vaccine in at risk populations may help reduce the risk of pneumococcal bacteremia and associated complications and
mortality following seasonal or pandemic influenza. The ideal time to accelerate PPV23 vaccination as part of pandemic preparedness would be during the inter-pandemic and pandemic alert phases (phases 1 through 3), when the threat of an influenza pandemic is not imminent.

Background

Epidemiology of pneumococcal disease
The pneumococcus is a major cause of morbidity and mortality in children and adults worldwide. Despite its importance, there is a paucity of information on the burden of pneumococcal disease, especially among older children and adults, and existing estimates of the disease burden vary widely. These variations probably reflect not only the dynamic epidemiology of pneumococcal infections, but also study design, seasonal variation, and the inherent problem of obtaining an etiological diagnosis in cases of pneumonia. WHO data suggest that 1.6 million cases of pneumococcal disease occur worldwide annually (Bryce J et al, 2005). The highest burden of pneumococcal disease is at the extremes of life, with infants and the elderly bearing the brunt of infection, morbidity, and mortality. Immunocompromised individuals of all ages are at increased risk.

Invasive pneumococcal disease (IPD) is defined as any condition in which S. pneumoniae is present in blood, spinal fluid, or another normally sterile body site. Compared to pneumococcal pneumonia, IPD occurs less frequently, but its diagnosis is unambiguous and hence, IPD is frequently studied as an indicator of the burden and the distribution of serotypes causing pneumococcal disease.

In industrialized countries, the reported annual incidence of IPD ranges from 8 to 34 cases per 100,000 total population, with the highest incidence occurring in the first 2 years of life and in the elderly. In persons aged at least 65 years, the annual incidence ranges from 24 to 85 cases per 100,000 population. In Europe and the United States, S. pneumoniae is thought to be the cause of approximately 30-50% of community-acquired bacterial pneumonias requiring hospitalization in adults.

The incidence of IPD in the general adult population of developing countries is largely unknown. Community-based studies of so-called “native” populations in the USA and Australia have shown annual incidences of IPD in the range of 53-178 per 100,000 population in the age group 20-59 years and 121 – 172 per 100,000 in adults >60 years of age (Torzillo PJ et al, 1995). Studies from hospitals in East and Southern Africa during the period 1957-1990 showed that 10-13% of adult hospital admissions were attributed to pneumonia; in other hospital-based studies the proportion of all pneumonia episodes attributed to S. pneumoniae ranged from 38% - 58%. Among South-African gold miners the annual incidence of “putative” pneumococcal pneumonia was 90 per 1000. Taken in combination, the available studies suggest that pneumococcal disease is an important cause of morbidity and hospitalization among adults in developing countries.

The incidence of invasive S. pneumoniae infection is higher in those with abnormal splenic function (e.g. sickle cell disease) or immune deficiency. The latter group includes those with
inherited immune deficiency and acquired immune deficiency due to such conditions as cancer and HIV infection. Pneumococcal bacteremia has been noted to be >8 times higher in HIV-seropositive adults compared to the incidence in HIV-seronegative individuals.

Bacterial community-acquired pneumonia is a frequent complication of seasonal and pandemic influenza. During previous influenza pandemics, secondary bacterial pneumonias (occurring 8 – 21 days post influenza) were an important cause of morbidity and mortality, with an estimated 7-20 % of persons with influenza during 1918-1919 developing secondary bacterial pneumonia. Attack rates of secondary bacterial pneumonia during the less severe 20th century influenza pandemics are thought to have been lower (~5%). Among those who acquired secondary bacterial pneumonia during prior influenza pandemics, 20-36% died, although access to antibiotics and supportive care not available during prior pandemics, may reduce the case fatality ratio in future pandemics. The bacteria responsible for the secondary bacterial pneumonia that occur during influenza pandemics has not been well elucidated, but it is believed that the pneumococcus plays an important role.

The pathogen

*S. pneumoniae* is a Gram-positive, encapsulated diplococcus. The polysaccharide capsule is an essential virulence factor. Based on differences in the composition of this capsule, > 90 distinct pneumococcal serotypes have been identified. The spectrum of prevailing capsular types varies with age, time and geographical region, although common serotypes are consistently identified throughout the world. Worldwide, approximately 20 serotypes are responsible for over 70% of invasive pneumococcal disease in all age groups. Inability to establish unambiguously the etiologic agent in cases of non-bacteremic pneumonia prevents an assessment of the serotype distribution of this important manifestation of pneumococcal disease, though the spectrum of involved serotypes is presumed to be similar to that for invasive pneumococcal disease. In recent years, many developed countries have introduced the 7-valent pneumococcal conjugate vaccine (PCV7) in their routine infant immunization program, potentially influencing the epidemiology of pneumococcal infections in the entire population through direct effects in the vaccinated and indirect (“herd”) vaccine effects in the unvaccinated.

Pneumococci are transmitted by direct contact with respiratory secretions from patients and healthy carriers. Although transient nasopharyngeal colonization rather than disease is the normal outcome of exposure to pneumococci, contiguous spread to the sinuses or the middle ear, or invasion of the blood stream, may lead to disease in persons susceptible to the involved serotype.

Pneumococcal resistance to commonly used antimicrobials, such as the penicillins, cephalosporins, trimethoprim/sulfamethoxazole, macrolides and fluoroquinolones, is a serious and increasing problem worldwide, complicating specific treatment and underlining the need for effective immunization against pneumococcal diseases.

Laboratory diagnosis of *S. pneumoniae* based on growth in culture media is possible in most clinical microbiology laboratories, though prior antibiotic treatment; improper handling and transport of specimens; and use of inappropriate culture media often result in failure to isolate the organism. Newer rapid diagnostic tests may help overcome some of these obstacles and
improve the detection of S. pneumoniae in the future. Serotyping and molecular typing is performed only in reference laboratories.

Pneumococcal disease
Pneumonia with empyema and/or bacteraemia, febrile bacteraemia, and meningitis constitute the commonest manifestations of invasive pneumococcal infection. Pneumococci are also believed to be a frequent cause of non-bacteremic pneumonia, a common and serious non-invasive disease syndrome. In many developing countries, non-bacteremic pneumonia could account for the majority of pneumococcal deaths in infants and young children. Middle-ear infection, sinusitis and recurrent bronchitis represent less severe, but considerably more common non-invasive manifestations of pneumococcal infection. In industrialized countries, pneumococcal bacteraemia is associated with a case-fatality ratio (CFR) of up to 10 - 20%.

The high-risk groups for pneumococcal disease include persons with splenic dysfunction or asplenia; chronic diseases of the heart, lung, liver, or kidney; diabetes mellitus; alcoholism; cerebrospinal fluid leakage; congenital or acquired immunodeficiency; haematological or generalized malignancies; those receiving immuno-suppressive therapy, including systemic corticosteroids; and recipients of organ or hematopoietic cell transplantation. In groups with such predisposing conditions, the CFR may exceed 50%.

Pneumococcal vaccines

Two different pneumococcal vaccines are currently commercially available, namely the conjugated PCV7 and the polysaccharide (unconjugated) PPV23. The emphasis of this position paper is on PPV23 and its uses.

PPV23
The PPV23 was developed for the prevention of pneumococcal disease and pneumonia in adults. Currently, this vaccine is widely licensed for this use in adults as well as in children aged > 2 years.

A 0.5 ml dose of PPV23 contains 25 micrograms of purified capsular polysaccharide from each of the 23 capsular types (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) that collectively accounted for most (85–90%) cases of invasive pneumococcal disease among adults in the U.S and other industrialized countries before the introduction of routine childhood immunization with PCV7. The PPV23 also includes capsular polysaccharides of the most common drug resistant serotypes. PPV23 contains no adjuvant. The vaccine should be stored at 2–8°C.

For primary immunization, PPV23 is administered as a single 0.5 mL subcutaneous or intramuscular dose. It should not be mixed in the same syringe with other vaccines, but may be administered at the same time as influenza vaccine (by separate injection in the other arm) without an increase in adverse effects or decreased antibody response to either vaccine. Protective capsular type-specific antibody levels generally develop by the third week following vaccination.
Safety
The PPV23 is considered very safe. Adverse reactions, such as transient redness and pain at the injection site, occur in 30–50% of vaccinees, more commonly following subcutaneous than intramuscular administration; low-grade fever occurs rarely. Local reactions may be more frequent in recipients of subsequent doses of the vaccine (Jackson LA et al, 1999). The only absolute contraindications to vaccination with PPV23 is an anaphylactic reaction to a previous dose.

Immune response
Pneumococcal polysaccharides are T-cell independent antigens and thus are (a) poorly immunogenic in those under 2 years of age (although some serotypes such as type 3 do induce antibodies) and (b) fail to induce immune memory. The latter characteristic results in the poor persistence of vaccine induced antibody and the requirement for re-vaccination. Following a single dose of PPV23 serotype specific IgG, IgA and IgM are produced with the IgG2 subclass dominating the IgG response. Responses are serotype dependent and the highest titres are elicited in those 18 - 55 years of age to serotypes such as 14 and 19F. In elderly individuals, if functional antibodies rather than antibody binding titres are measured, responses are significantly worse than those seen in younger adults. Functional titres may be more biologically relevant than binding titres measured by ELISA. Additional data are needed on the possible induction of hyporesponsiveness following multiple doses of pneumococcal polysaccharides (O'Brien KL et al, 2007). Also, the potential use of pneumococcal conjugate vaccines for priming the immune response to PPV23 requires further study.

Efficacy and effectiveness
Despite the existence of multiple studies conducted over more than 30 years, the efficacy and effectiveness of PPV23 in children and adults remain poorly defined and the subject of controversy (Mangtani P et al, 2003). Numerous problems contribute to the difficulty of measuring the efficacy and effectiveness of this vaccine, including the rarity of the most specific outcome (i.e., invasive *S. pneumoniae* infection); the non-specificity of the diagnostic criteria for more common outcomes (e.g. pneumococcal pneumonia); and the likelihood/biological plausibility that efficacy and effectiveness vary with the presence and severity of various underlying conditions associated with an increased risk of pneumococcal infection. Further complicating the interpretation of the results of prior studies are methodologic imperfections in many of the randomized controlled trials of vaccine efficacy and the observational studies of vaccine effectiveness, as well as the possibility of selection bias and confounding that almost always exists in observational studies. Furthermore, there have been very few studies of the efficacy or effectiveness of PPV23 in children.

Comprehensive meta-analyses of the studies assessing PPV23 vaccine efficacy and effectiveness have been conducted, including a recent, as yet unpublished meta-analysis and review of the randomized, controlled trials (Moberley S et al 2008; Scott P et al, 2008). On balance, as shown in the meta-analyses, the results of the randomized controlled trials of PPV23 are consistent with a protective effect against invasive pneumococcal infection and all cause pneumonia among young, generally healthy adults. Such trials have not demonstrated that PPV23 is efficacious.
against either invasive pneumococcal infection or all cause pneumonia in higher risk populations, such as elderly adults, children with various underlying conditions putting them at increased risk of pneumococcal infection, or highly immunosuppressed individuals of any age. The single randomized controlled trial of PPV23 in HIV-infected adults in Africa found a surprising excess of all cause pneumonia among PPV23 recipients, although vaccine recipients experienced an overall survival advantage (French N et al, 2000). These results remain poorly explained. Overall, the available evidence from randomized controlled trials suggest that in those adults at highest risk of pneumococcal infection, the effect of PPV23 is, at best, modest.

At the same time, observational studies of the effectiveness of PPV23 generally show that the vaccine is at least partially effective at preventing invasive pneumococcal infection among immunocompetent elderly individuals and among individuals with various underlying illnesses who are not severely immunosuppressed; individuals who are severely immunosuppressed (e.g. those with late stage HIV infection) do not appear to benefit from PPV23. Other studies suggest that among recipients of PPV23 who nevertheless develop pneumonia, the severity of their illness and their risk of dying may be reduced. Based on the above information and cost-benefit calculations, some wealthy and middle income countries have promulgated guidelines that recommend that PPV23 be given to various target populations demonstrated to be at increased risk of morbidity and mortality from pneumococcal infection, including adults over 60 or 65 years of age; individuals with sickle cell disease or lacking a functional spleen; individuals with various underlying disease affecting the cardiopulmonary system; and individuals with immunosuppressive conditions, including HIV infection, among others (ACIP, MMWR, 1997; ECDC, 2007). To date, developing countries have not made the use of PPV23 a priority, and in HIV-infected individuals have relied on chemoprophylaxis with co-trimoxazole for prevention of PJP and/or anti-retroviral treatment, both of which may lower the risk or pneumococcal infection.

**Durability of the Immune Response and Duration of Protection**

PPV23 induces an initial rise in ELISA antibody titers, which then decline over time. In older adults, antibody titers measured 4 to 7 years post-vaccination tend to approximate pre-vaccination baseline levels. The clinical significance of this decline is not well defined, as immune correlates of protection for pneumococcal vaccine in adults have not been established and there are relatively limited clinical data regarding the duration of protection against invasive infection induced by pneumococcal polysaccharide vaccine. Of the two observational studies that have evaluated the duration of clinical protection induced by PPV23, one found that effectiveness declined with increasing time since vaccination, and the other found that vaccine effectiveness was stable over time, although the confidence limits around the point estimates of the vaccine effectiveness at different time points were wide.

Because purified polysaccharide vaccines are not generally believed to confer long-lasting protection, and because the incidence of pneumococcal infection in adults increases dramatically with age, revaccination may provide a benefit in reducing the risk of invasive pneumococcal infection in older adults. However, consideration of possible revaccination strategies requires an evaluation of the evidence related to the safety of revaccination; the immunologic response to a second dose of pneumococcal polysaccharide vaccine; and the potential clinical benefits of revaccination. Although local reactions may be more frequent in recipients of a second or third dose of PPV23, reactions are generally self-limited and not severe. The magnitude of the antibody response to revaccination may be lower than that following a first dose of the vaccine.
The clinical significance of the lower antibody response is not known, but concern regarding possible immune tolerance has been one factor that has limited recommendations for revaccination in some countries. There is limited evidence concerning the clinical effectiveness of revaccination, particularly in the general population of older adults. Current practice with regard to revaccination varies substantially by country.

Cost-effectiveness of PPV23
Available studies of the cost-effectiveness of providing PPV23 to various risk groups are almost exclusively from industrialized countries. The outcomes of these studies vary, depending on the characteristics of the study population, the choice of endpoints, and other factors. Existing evidence suggests that PPV23 is relatively cost effective and potentially cost saving when given to selected high risk groups (e.g. adults 65-75 years of age). Of note, however, such studies were conducted before the introduction of PCV7 into infant immunization schedules. The cost-effectiveness of PPV23 warrants reconsideration in those countries in which high rates of coverage with PCV7 have been achieved.

The widespread use of PCV7 in infants has led to substantial reductions in the rate of invasive pneumococcal infections and all-cause pneumonia hospitalizations among adults of all ages. This indirect (“herd immunity”) effect of conjugate pneumococcal vaccine is attributable to the documented reduction in nasopharyngeal colonization by PCV7 serotypes and resultant decrease in transmission of these serotypes to age groups not receiving the vaccine. In some populations, the rate of infection with one or more pneumococcal serotypes not included in the PCV7 vaccine (e.g. serotype 19A) has increased following introduction of the vaccine into infant immunization programmes: it is not known whether such increases are due to "serotype replacement" or to unrelated changes in the rate. However, the observed increases in the rate of disease caused by these serotypes have thus far been modest and have not substantially reduced the overall positive effect of vaccination of infants with PCV7.

Maternal immunization with pneumococcal vaccines
No adverse consequences have been reported among newborns whose mothers were vaccinated during pregnancy. The possibility of immunizing pregnant women with pneumococcal vaccines to protect the newborn in the first few months of life before routine infant immunization with pneumococcal conjugate vaccine remains an area where further research is needed. Currently available data from developing countries are extremely limited concerning the burden of pneumococcal disease in the newborn and mother and concerning the potential public health benefits and risks of a maternal immunization strategy. A recent Cochrane Collaboration review concluded that there is currently insufficient evidence to support the notion that pneumococcal vaccination during pregnancy could reduce infant infections (Chaithongwongwatthana S, et al 2006).

Use of PPV23 for Influenza Pandemic Preparedness
*S. pneumoniae* is believed to be a common etiology of secondary bacterial pneumonia in individuals with influenza. As PPV23 has not been demonstrated to prevent non-bacteremic community-acquired pneumonia, however, the effect of PPV23 in preventing secondary pneumococcal pneumonia associated with influenza is uncertain, and might be limited to reducing the risk of pneumococcal bacteremia and related complications. There is some...
evidence, from observational studies, that PPV23 might lead to improved clinical outcomes in those who develop pneumococcal pneumonia in this setting.

**WHO position on the use of PPV23**

In recent years further results of studies and meta-analyses on the efficacy and effectiveness of 23 valent pneumococcal polysaccharide vaccine (PPV23) have become available. In addition, the heightened concern about an influenza pandemic has raised questions about the potential role of pneumococcal vaccines in the prevention of secondary bacterial pneumonias in individuals with influenza. Furthermore, many developed countries have introduced the 7-valent pneumococcal conjugate vaccine (PCV7) in their routine infant immunization program, potentially influencing the epidemiology of pneumococcal infections in the population through direct and indirect ("herd") vaccine effects. To address these developments, the text concerning PPV23 published in the position paper of 2003 has been revised.

Given the high burden of pneumococcal disease in children and adults, WHO considers prevention of pneumococcal disease a high priority in both industrialized and non-industrialized countries.

Although the clinical effectiveness of PPV23 remains a topic of controversy, available data provide some support for its use in countries where the vaccine is already recommended for the elderly and high-risk groups.

Countries not currently using PPV23 and that may wish to consider the possible benefits of giving PPV23 to the elderly and others at high risk of pneumococcal infection should not allow the introduction of PPV23 to detract from achieving high levels of coverage with PCV7 among infants.

In a number of high- and middle income countries, routine use of PPV23 is recommended for HIV-infected adults and older children based on the high risk of pneumococcal disease in these individuals and the potential benefits and safety of the vaccine. The role of PPV23 among corresponding groups in low-income countries remains controversial and most of those countries have relied on other approaches such as antimicrobial prophylaxis with co-trimoxazole for PJP and treatment with anti-retroviral drugs, which may reduce the risk of pneumococcal disease.

Pneumococcal conjugate vaccine formulations might hold promise for maternal immunization aiming at protection of the newborn. However, the narrower serotype coverage of the current conjugate vaccine could limit its utility in preventing illness in infants in the first months of life; currently no data are available. On the other hand, herd protection in children aged 0-3 months has been demonstrated in the USA from routine immunization of older infants with PCV7. A research strategy should be considered for the evaluation of pneumococcal maternal immunization. Areas where more data are needed include: optimal serotypes, vaccine type (polysaccharide or conjugate); ability to transfer antibodies from mother to fetus; protective antibody concentrations in neonates; duration of vaccine-induced protection in the newborn; and possible need and safety of repeated polysaccharide vaccine doses during subsequent pregnancies.
In general, pneumococcal vaccines should be deferred during pregnancy because their effect on the fetus have not been fully evaluated, particularly during the first trimester, although no adverse consequences have been reported. Although ideally, women with identifiable risk factors for pneumococcal infection should be vaccinated before pregnancy, women with underlying medical conditions that are considered indications for PPV23 vaccination may be vaccinated even when pregnant.

In countries using PPV23, high levels of coverage with the vaccine in at risk populations may help reduce the risk of pneumococcal bacteremia and associated complications and mortality following seasonal or pandemic influenza. However, administering pneumococcal vaccines during a pandemic may be complicated by personnel shortages due to illness and vaccine shortages due to excessive demand. Also, competing demand for personnel and other resources may be anticipated. Therefore, ensuring that all persons with indications for PPV23 have been vaccinated before a pandemic occurs may be the best way to prevent pneumococcal disease during an influenza pandemic. The ideal time to accelerate vaccination efforts would be during the inter-pandemic and pandemic alert phases (phases 1 through 3), when the threat of a pandemic is not imminent.

Suggested references to be inserted in the text (max 12 allowed)


Scott P, Egger M, Huss A. Effectiveness of pneumococcal polysaccharide vaccine: systematic review and meta-analysis of randomised controlled trials. Submitted for publication


