

Summary of key points



WHO Position Paper on Pneumococcal conjugate vaccines in infants and children under 5 years of age– February 2019

Published in the Weekly Epidemiological Record on 22 February 2019

Background

- Pneumococcal infections can lead to serious invasive diseases such as meningitis, septicaemia and pneumonia, as well as milder but more common illnesses such as sinusitis and otitis media.
- There are > 90 known serotypes of *S. pneumoniae*. The distribution of serotypes that cause disease varies over time and by age, disease syndrome, disease severity, geographical region and the presence of antimicrobial-resistant genes.
- Of the estimated 5.83 million deaths among children < 5 years of age globally in 2015, 294 000 (uncertainty range [UR], 192 000–366 000) were estimated to be caused by pneumococcal infections.
- Before the introduction of pneumococcal conjugate vaccines (PCVs) in the different WHO regions, 6–11 serotypes accounted for ≥ 70% of all invasive pneumococcal disease (IPD). The reported mean annual incidence of IPD in children aged < 2 years was 44.4/100 000 per year in Europe and 167/100 000 per year in the United States of America. In comparison, the annual incidence of IPD in children < 2 years in Africa ranged from 60/100 000 in South Africa to 797/100 000 in Mozambique.
- On average, about 75% of cases of IPD and 83% of cases of pneumococcal meningitis occur in children aged < 2 years, but the incidence and age distribution of cases may vary by country, study method and socio-economic status within countries.
- Case fatality rates from IPD in children can be high, ranging up to 20% for septicaemia and 50% for meningitis in low and middle income countries (LMICs).

Disease, diagnosis and treatment

- Pneumococcal infection and disease can affect various organ systems. Bloodstream invasion results in bacteraemia that occasionally causes infection at secondary sites, such as the meninges, joints and peritoneum. Contiguous spread from the nasopharynx can cause diseases such as otitis media or sinusitis.
- Pneumonia is often caused by aspiration of pneumococci from the nasopharynx and may also be caused by blood-borne spread.
- Long-term neurological sequelae such as hearing loss, mental retardation, motor abnormalities and seizures have been observed in 24.7% (interquartile range, 16.2–35.3%) of survivors of childhood pneumococcal meningitis; the risk of sequelae was 3 times higher among survivors in Africa and Asia than among those in Europe.
- Lack of exclusive breastfeeding, nutritional deficiency and indoor air pollution are risk factors for pneumonia, including pneumococcal pneumonia, in infants and young children.
- While clinical diagnosis of pneumonia or meningitis is based on symptoms, signs and radiological tests, diagnosis of pneumococcal disease requires laboratory confirmation. A definitive diagnosis of pneumococcal infection is made by isolating the bacterium from blood or other normally sterile body sites, such as cerebrospinal fluid.
- Pneumococcal disease can be treated with antimicrobials. The choice of antimicrobial and the duration of treatment depend on the site of infection and the pattern of susceptibility to antimicrobials; the outcome depends on age, disease syndrome, severity, duration of illness before initiation of treatment and susceptibility to the antimicrobials used.

Pneumococcal conjugate vaccines

- Two polysaccharide-protein conjugate vaccines have been on the market since 2009: the 10-valent (PCV10) and the 13-valent (PCV13) vaccines. Previously, a 7-valent pneumococcal conjugate vaccine (PCV7) was available.
- This position paper pertains to the currently licensed PCV10 and PCV13 used in children < 5 years of age.
- Both PCV10 and PCV13 have been shown to be safe and effective and to have both direct (in vaccinated individuals) and indirect (in unvaccinated individuals living in communities with vaccinated children) effects against pneumococcal disease caused by vaccine serotypes when used in a 3-dose schedule (either 2p+1 or 3p+0) or in a 4-dose schedule (3p+1).
- After the third dose of each schedule (post-booster for 2p+1 and post-primary for 3p+0), the 2p+1 schedule resulted in higher GMCs but a similar percentage of responders as compared with a 3p+0 schedule for most serotypes, except for serotype 6B, for which the percentage of responders was higher with the 2p+1 schedule.
- Both PCV10 and PCV13 induce antibodies against the serotypes common to both vaccines (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). Although the mean antibody response to the common serotypes differed with the 2 products, in general, they induced comparable immunogenicity.
- PCV13 has 3 additional serotypes, 3, 6A and 19A. PCV13 induces an immune response to serotype 3; PCV10 contains neither serotype 3 nor any cross-reactive serotype, and immunogenicity against serotype 3 is not measured in studies of this vaccine. Both PCV10 and PCV13 induce an antibody response to serotype 6A, which is included in PCV13 but not in PCV10. Both PCV10 and PCV13 induce an antibody response against serotype 19A.

WHO Position

- WHO recommends the inclusion of PCVs in childhood immunization programmes worldwide.
- Currently available PCVs are safe and effective, and the increase in the number of serotypes in these vaccines as compared with the first licensed PCV7 represents significant progress in the fight against pneumococcal disease-related morbidity and mortality, particularly for developing countries.
- Use of pneumococcal vaccine should be complementary to other disease prevention and control measures, such as appropriate case management, promotion of exclusive breastfeeding for the first 6 months of life and reducing known risk factors such as indoor air pollution and tobacco smoke.
- Despite the lack of comprehensive data on the immunogenicity, effectiveness and safety of all possible combinations of PCV and other routine vaccines, co-administration for programmatic reasons appears to be acceptable.

WHO Position- Schedule

- For administration of PCV to infants, WHO recommends a 3-dose schedule administered either as 2p+1 or as 3p+0, starting as early as 6 weeks of age.
- In choosing between the 2p+1 and 3p+0 schedules, countries should consider programmatic factors, including timeliness of vaccination and expected coverage. The 2p+1 schedule has potential benefits over the 3p+0 schedule, when programmatically feasible, as higher antibody levels are induced in the second year of life, which may be important in maintaining herd immunity, although no high-quality evidence is available.
- If the 3p+0 schedule is used, a minimum interval of 4 weeks should be maintained between doses.
- If the 2p+1 schedule is selected, an interval of ≥ 8 weeks is recommended between the 2 primary doses, but the interval may be shortened if there is a compelling reason to do so, such as timeliness of receipt of the second dose and/or achieving higher coverage when a 4-week interval is used. The booster dose should be given at 9–18 months of age, according to programmatic considerations; there is no defined minimum or maximum interval between the primary series and the booster dose.
- Previously unvaccinated or incompletely vaccinated children who recover from IPD should be vaccinated according to the recommended age-appropriate regimens. Interrupted schedules should be resumed without repeating the previous dose.

WHO Position- Product Choice

- Both PCV10 and PCV13 have substantial impacts against pneumonia, vaccine-type IPD and nasopharyngeal (NP) carriage.
- There is at present insufficient evidence of a difference in the net impact of the 2 products on overall disease burden. PCV13 may have an additional benefit in settings where disease attributable to serotype 19A or serotype 6C is significant.
- The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes and antimicrobial resistance patterns.

WHO Position- Interchangeability of Vaccines

- Once a PCV vaccination programme has been initiated, product switching is not recommended unless there are substantial changes in the epidemiological or programmatic factors that determined the original choice of product, e.g. an increasing burden of serotype 19A.
- If a series cannot be completed with the same type of vaccine, the available PCV product should be used.
- Restarting a series is not recommended, even for the primary series.

WHO Position- Catch-up Vaccination

- Wherever possible, catch-up vaccination at the time of introduction of PCV should be used to accelerate its impact on disease in children aged 1–5 years, particularly in settings with a high disease burden and mortality.
- If there is limited availability of vaccine or of financial resources for catch-up vaccination, the youngest children (e.g. < 2 years of age) should be prioritized to receive catch-up doses of PCV because of their higher risk for pneumococcal disease.
- Catch-up vaccination can be done with a single dose of vaccine for children ≥ 24 months.
- Current data are insufficient for a firm recommendation on the optimal number of doses (1 or 2) required in 12–23-month-olds as part of catch-up vaccination, so countries choosing to use 1 dose might wish to monitor for impact and vaccine failures.
- Unvaccinated children aged 1–5 years who are at high risk for pneumococcal infection because of underlying medical conditions, such as HIV infection or sickle-cell disease, should receive at least 2 doses separated by at least 8 weeks.
- In humanitarian or other emergency situations, age-appropriate schedules of PCV vaccination should be used for children < 1 year of age and considered for children ≤ 5 years of age, as indicated by the situation.
- Catch-up vaccination may also be an important means to prevent outbreaks. Vaccine campaigns in response to outbreaks of confirmed vaccine-type pneumococcal disease are under consideration, but experience is currently lacking.

WHO Position- Vaccination of Special Populations

- PCVs should not be given to individuals with a history of anaphylactic reactions or severe allergic reactions to any component of the vaccine.
- HIV-positive infants and pre-term neonates who have received their 3 primary vaccine doses before 12 months of age may benefit from a booster dose in the second year of life.
- Travelling children are generally not at special risk of pneumococcal disease, unless they travel to an outbreak setting. They should follow the vaccine recommendations for the general population and ensure they are up to date with their vaccinations before travelling.

WHO Position- Surveillance

- While a comprehensive surveillance system for pneumococcal disease is recommended, countries without such a system in place should not wait to introduce PCV vaccines.
- WHO recommends that the epidemiological impact of PCV be carefully monitored in sustained, high-quality sentinel and population-based surveillance for pneumococcal disease and in periodic NP carriage surveys.
- Such surveillance and surveys should be conducted to monitor changes in disease and the circulation of pneumococcal serotypes in the community after use of different PCV products at different dosing schedules and in different geographical and epidemiological settings with different pneumococcal disease burdens and transmission.
- Ideally, surveillance should be started at least 1–2 years before introduction of PCV and be continued indefinitely but at least for 5 years after introduction.

WHO Position- Research Priorities

- Additional research should be conducted on:
 - further assessment of vaccine impact, duration of protection and indirect effects of different dosing schedules;
 - serotype replacement;
 - further establishment of serotype-specific immune correlates of protection against IPD in different transmission settings;
 - the epidemiology of pneumococcal outbreaks, particularly epidemics of serotype 1 disease, including use of PCV to prevent or respond to outbreaks;
 - the impact of PCV on antimicrobial use and resistance;
 - comparison of a 1-dose versus a 2-dose catch-up schedule for children > 12 months of age.