MedicineToday PEER REVIEWED

Pneumococcal disease

The latest on immunisation

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Pneumococcal vaccination has been funded for almost a decade for all Australian children and adults aged 65 years and over, as well as people at increased risk of invasive pneumococcal disease. In that time, new conjugate vaccines have been introduced and the epidemiology of pneumococcal disease has changed. What is the latest on pneumococcus and pneumococcal vaccination?

MedicineToday 2014; 15(6): 58-61

In 2005, the WHO estimated that 1.6 million people die of pneumococcal disease every year, including 0.7 to one million children under 5 years of age.[1] Pneumococcal vaccination has been shown to reduce infections with vaccine serotypes by 97%. However, vaccine development is a particular challenge because of the organism's polysaccharide capsule, which protects it from the primary immune response and is responsible for the large number (90-plus) of serotypes. Further, since the introduction of widespread vaccination, there is evidence that vaccine serotypes are being replaced among carriers by nonvaccine serotypes. This article describes pneumococcal disease, the pneumococcal vaccines used in Australia, the rationale for their use and future challenges in this ongoing battle.

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SIGNIFICANCE OF PNEUMOCOCCAL BACTERIA

Up to 36% of adult cases of community-acquired pneumonia and 50% of cases of hospital-acquired pneumonia are caused by pneumococcus (*Streptococcus pneumoniae*). In children, the most common manifestation of the organism is bacteraemia without focus; meningitis is less common but is the most severe manifestation with a case fatality rate of 30%. Pneumococcus is also responsible for a significant proportion of cases of acute otitis media.

The organism was first isolated by Pasteur in 1881 from the saliva of a patient with rabies. The association between pneumococcus and lobar pneumonia was first described in 1883, but pneumococcal pneumonia was confused with other types of pneumonia until the development of the Gram stain in 1884 which revealed *S. pneumoniae* as a Gram-positive coccus. Pneumococcal disease is still a common bacterial complication of influenza and measles, with a case fatality rate of 5 to 7% in the general population and up to 60% in older people.

Pneumococci are transmitted directly between people in close contact via respiratory droplets. There is no animal reservoir or insect vector. Transmission and transient nasopharyngeal colonisation are thought to be common, but clinical illness occurs infrequently. Invasive pneumococcal disease (IPD) occurs when *S. pneumoniae* is found in a normally sterile site, such as blood, cerebrospinal fluid or pleural fluid. Direct spread to the sinuses

or middle ear or invasion of the bloodstream may lead to disease in susceptible humans.[2]

Capsular polysaccharides are the primary basis for the pathogenicity of pneumococcus. These polysaccharides are antigenic and are used to classify pneumococci by serotype. The polysaccharide capsule may also explain why it is more difficult to develop a primary immune response to pneumococci than to bacteria with surface proteins and also to make a vaccine that provides longstanding protection.[3]

Predominant pneumococcal serotypes vary by age group and geographic area. There are more than 90 identified serotypes, but only a limited number cause significant disease, with the 10 most common estimated to account for about 62% of IPD worldwide.[4]

PNEUMOCOCCAL VACCINES

Interest in developing a pneumococcal vaccine waned with the advent of penicillin in the 1940s but revived as resistance to penicillin increased in the 1960s. Since the first vaccines were licensed in the late 1970s, they have gained importance in management of pneumococcal disease.

There are two types of pneumococcal vaccine – polysaccharide vaccines and conjugate vaccines. Vaccine formulations vary in the number of pneumococcal serotypes included (seven, 10, 13 or 23) and, additionally for the conjugate vaccines, in the conjugating proteins used (protein D of nontypable *Haemophilus influenzae* or mutant nontoxic diphtheria CRM197 protein).

Polysaccharide vaccines

Pneumococcal polysaccharide vaccines (PPVs) have been effective in helping protect many adults against invasive and potentially life-threatening pneumococcal illness. However, their limitations include:

- little or only short-lived impact on the carriage of pneumococcus
- an apparent decreased immune response after repeated doses
- limited ability to protect children under 2 years of age.[5]

The 23-valent polysaccharide vaccine (23vPPV) contains polysaccharides derived from the 23 most frequent or most virulent capsular types isolated from normally sterile body sites in the 1970s and early 1980s in the USA; worldwide serotype distribution and potential cross-reactive serotypes were also taken into consideration. These 23 serotypes are responsible for most cases of IPD in adults in Australia.[6]

Conjugate vaccines

Pneumococcal conjugate polysaccharide vaccines (PCVs) are developed by attaching the polysaccharide antigen to a carrier protein. This helps the body to recognise the antigen as a foreign substance that must be destroyed.

The seven-valent conjugate vaccine (7vPCV) became available in Australia in 2001. The 10-valent conjugate vaccine (10vPCV) has been registered for use in Australia since 2009 and is included in the National Immunisation Program. This vaccine was used for all children aged under 2 years in the Northern Territory between October 2009 and September 2011, after which time the 13-valent conjugate vaccine (13vPCV) has been used. The 13vPCV has been registered in Australia since 2010 and used in the National Immunisation Program since July 2011.

VACCINE CHALLENGES

Despite the advantages of conjugate vaccines, the complex process involved in conjugation of polysaccharides has limited the number of conjugate vaccines that are commercially available. In addition, the benefit of these vaccines in older people is not clear as studies of available vaccine have not shown that they improve immunity in groups at increased risk of IPD (Box 1).[6]

Given the limitations of 23vPPV in preventing pneumococcal disease in older people and those who are immunosuppressed, there is a clear need for the development of protein-based pneumococcal vaccines that contain more serotypes.[2]

Which pneumococcal serotypes need to be covered is another challenge as currently available conjugate vaccines provide suboptimal coverage of IPD-causing serotypes and there is evidence that vaccine serotypes are being replaced by nonvaccine serotypes, reducing the benefit of immunisation.[7]

Proof of clinical efficacy of the new conjugate vaccines will be needed, not only in healthy individuals but also in the predefined, immunocompromised risk groups who are most in need of pneumococcal vaccination.[8]

CHANGING PNEUMOCOCCAL DISEASE

A reduction in all-cause pneumonia admissions was seen in children younger

1. CONDITIONS ASSOCIATED WITH AN INCREASED RISK OF INVASIVE PNEUMOCOCCAL DISEASE IN CHILDREN AND ADULTS*

Highest increased risk of IPD

- Functional or anatomical asplenia (e.g. sickle cell disease, splenectomy)
- Immunocompromise (e.g. congenital or acquired immune deficiency, immunosuppressive therapy, malignancy, transplant, HIV infection, chronic renal failure)
- Cerebrospinal fluid leak (proven or presumptive)
- Cochlear implant, intracranial shunt

Increased risk of IPD

- Chronic cardiac or lung disease (e.g. cyanotic heart disease, cystic fibrosis, severe asthma in adults)
- Diabetes mellitus
- Down syndrome
- Alcoholism or chronic liver disease
- Preterm birth <28 weeks' gestation
- Tobacco smoking

*Based on: Australian Technical Advisory Group on Immunisation. The Australian immunisation handbook. 10th ed.[5]

2. RECOMMENDED PNEUMOCOCCAL IMMUNISATION SCHEDULES*

Children

- All children are recommended to receive a complete course of PCV, beginning at age 2 months but the first dose can be given as early as 6 weeks of age
- Use 13vPCV (as it includes the highest number of serotypes)
- Some at-risk children may need later doses of 23vPPV
- Total number of doses depends on:
  - the vaccine type used
  - whether the child has a medical condition associated with an increased risk of IPD (see Box 1)
  - the child's Indigenous status
  - whether the child is living in a jurisdiction with a high incidence of IPD (i.e. the Northern Territory, Queensland, South Australia or Western Australia)

Adults

- Use 23vPPV
- Give any subsequent doses at least five years apart
- Schedule depends on risk and Indigenous status as follows:
  - Normal risk: one dose only from 65 years of age
  - Normal-risk Indigenous: first dose from 50 years of age, followed by one more dose
  - High risk (see Box 1): first dose from 18 years of age, followed by two more doses
- In addition, use one dose of 13vPCV for adults at highest increased risk of IPD (or three doses for haematopoietic stem cell transplant recipients)
- Special clinical situations may have complex recommendations (e.g. after stem cell transplantation); consult the latest update of *The Australian Immunisation Handbook* if uncertain

ABBREVIATIONS: 13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine; IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine.
*Based on: Australian Technical Advisory Group on Immunisation. The Australian immunisation handbook. 10th ed.[5]

than 2 years in the USA after introduction of 7vPCV infant immunisation.[9] This provides an estimate of the proportion of childhood pneumonias attributable to vaccine-preventable pneumococci and supports the beneficial effects of PCVs in children. There was also a reduction in IPD in adults following widespread 7vPCV infant immunisation in the USA, presumably because of herd immunity.

Similarly in Australia, the incidence of IPD caused by 7vPCV serotypes decreased overall by 97%, accounting for 9% of IPD cases in 2007 versus 71% in 2002.[10] There was also a marked reduction in pneumonia hospitalisations, presumed to be attributable to 7vPCV vaccination, in children under 2 years of age and 2 to 4 years of age (of 38% and 28%, respectively).[11] Reductions in IPD were also observed in age groups not targeted for vaccination (herd immunity effect); the incidence of IPD due to 7vPCV serotypes declined by between 50 and 60% in various age groups over 5 years of age.[5]

It is unclear whether the use of 13vPCV in children will lead to a reduction in adult IPD cases caused by the additional serotypes in 13vPCV compared with 7vPCV that is similar to the reduction seen in cases caused by 7vPCV serotypes after widespread use of that vaccine in children.[5] In addition, in the absence of evidence that 13vPCV is more effective than 23vPPV against IPD or non-IPD pneumonia, the relative benefit of 13vPCV for adults is uncertain, as its serotype coverage is more limited than 23vPPV.

Concerns have been raised about the emergence of nonvaccine serotypes. A 2011 review of international data concluded that since widespread vaccination with 7vPCV, the prevalence of nonvaccine serotypes has increased among asymptomatic carriers, suggesting there has been little or no net change in overall prevalence of pneumococcal carriage.[7] In many populations, pneumococcal disease caused by nonvaccine serotypes has also increased, but in most cases this increase has been less than the increase in their carriage. This discrepancy can be attributed, in part, to a lower invasiveness of the replacing serotypes.[7]

WHAT VACCINE, WHEN AND WHY?

Recommended immunisation schedules for children and adults are outlined in Box 2. Despite the smaller numbers of serotypes in the conjugate vaccines, current evidence suggests that they are superior in childhood because they target the serotypes that are responsible for a large proportion of disease and provoke a better (and longer lasting) immune response.

All children are recommended to receive a complete course of pneumococcal conjugate vaccine, preferably 13vPCV. The recommended number of doses depends on the vaccine type and the child's risk of IPD. At-risk groups are also recommended to have later doses of 23vPPV; this includes children who are medically at risk and Indigenous children (Box 1).[5]

Although 13vPCV is registered for use in adults aged 50 years or older, there is currently insufficient evidence to recommend its use in preference to 23vPPV at the individual or population level for persons aged 18 years or older who do not have a condition associated with an increased risk of IPD. Consequently, older people are recommended to have 23vPPV until evidence emerges that the conjugate vaccines are superior or technology allows the inclusion of more serotypes in conjugate vaccines. All adults with a condition associated with an increased risk of IPD (Boxes 1 and 2) and Indigenous adults are recommended to receive additional doses of 23vPPV. For adults with a condition associated with the highest risk of IPD, one or more doses of 13vPCV is also recommended.

Immunisation recommendations may change as evidence emerges and conjugate vaccines containing higher numbers of serotypes are introduced. The online version of *The Australian Immunisation Handbook* should be consulted for updates (www.immunise.health.gov.au/internet/immunise/publishing.nsf).[5]

ONGOING NEED FOR PREVENTION

In Australia, pneumococcal vaccination is listed on the National Immunisation Program and funded under Immunise Australia for infants, Aboriginal and Torres Strait Islander people and older Australians (65 years and older).[12-14]

Among older people, the population health impact of pneumococcal vaccination is likely to be high given the increased risk of disease in this age group.[15] However, whereas the message about influenza vaccination is clearly resonating, the message about pneumococcal vaccination is not.[16] Recent results from the BEACH study of general practice activity in Australia revealed that among patients aged 66 years, one in three had not yet been vaccinated against pneumococcal pneumonia despite being at risk and eligible for more than a year (since their 65th birthday) for government-subsidised pneumococcal vaccine.[5,17] Pneumococcal vaccination is also recommended for people with an underlying chronic illness.[5]

The 23vPPV vaccination program in Australia was suspended for a short time in 2011 because of side effects after second and subsequent vaccinations. However, it remains of clear benefit for high-risk groups to have two vaccine doses, and for those aged 65 years and over to have at least one. The interruption to the program undeservedly reduced confidence in 23vPPV, and GPs need to offer this vaccination.

In addition to pneumococcal vaccine, good hygiene can help prevent the spread of pneumococcal infection, including regular hand washing and keeping household surfaces clean. It is also important for GPs and the public to recognise the symptoms of pneumococcal pneumonia, including rapid or difficult breathing, cough, fever, chills and loss of appetite.[18,19]

CONCLUSION

The new conjugate pneumococcal vaccines (seven-, 10- and 13-valent) are proving effective in reducing IPD in children. They have the added benefit of reducing pneumococcal disease in the unvaccinated population because of herd immunity. We still need to use the polysaccharide vaccine (23vPPV) in people aged 65 years and over and in high-risk groups. 13vPCV is also recommended in adults at highest risk of IPD. Pneumococcal infections continue to cause significant morbidity and mortality in children younger than 2 years and people aged 65 years and over, so maintaining high vaccination rates remains an important challenge. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: Dr Pearce is a Director of the Influenza Specialist Group and was an unfunded spokesperson for the 2004 Lung Foundation Australia campaign promoting pneumococcal vaccination. His practice uses National Immmunisation Program vaccines.

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