ARTICLE

Pneumococcal vaccines: past, present and future

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SUMMARY

Universal vaccination of Australian children with the 7-valent pneumococcal conjugate since 2005 has substantially reduced invasive pneumococcal disease. Herd immunity has also been observed in adults.

Conjugate vaccines of higher valency, which provide additional serotype coverage, became available in 2009. The 13-valent vaccine replaced the 7-valent vaccine in the National Immunisation Program in July 2011.

The 23-valent polysaccharide vaccine is recommended for all adults aged 65 years or over and for Aboriginal and Torres Strait Islander adults aged 50 years or over. It is also indicated in younger people with risk factors for invasive disease.

Additional pneumococcal vaccine doses are recommended for children and adults at increased risk of invasive disease.

The Australian Immunisation Handbook 10th edition contains detailed recommendations.

Introduction

Pneumococcal vaccines are designed to prevent diseases caused by *Streptococcus pneumoniae* (pneumococci), broadly referred to as pneumococcal disease. There are two different types – the conjugate vaccines and a polysaccharide vaccine (Table 1). The conjugate vaccines can induce an immune memory response, and are immunogenic in young infants. In contrast, the polysaccharide vaccine is poorly immunogenic in children under two years and those with impaired immunity. Although it contains more serotypes, it is not conjugated to a protein and does not induce a memory immune response.

Among the pneumococcal conjugate vaccines, formulations vary in the number of pneumococcal serotypes included (valency) and the conjugating proteins used. Table 1 shows the serotypes contained in the pneumococcal vaccines registered in Australia. The original 7-valent conjugate vaccine has now been superseded in the National Immunisation Program by the 13-valent conjugate vaccine.

Pneumococcal disease

S. pneumoniae is a Gram-positive bacterium with a polysaccharide capsule, which is a virulence factor. More than 90 polysaccharide serotypes have been identified, with each serotype eliciting serotype-specific immune responses. Different serotypes vary in their propensity for nasopharyngeal colonisation and for causing disease. In Australia in 2002–04, before the universal infant pneumococcal conjugate vaccination program, 85% of invasive pneumococcal disease in children under two years was caused by the serotypes contained in the 7-valent conjugate vaccine (Table 1).[1] Serotype distribution of pneumococcal disease is more diverse among Aboriginal and Torres Strait Islander people, including children, and among adults in general compared to children.

Transmission and carriage

Transmission of pneumococci occurs via respiratory droplets from individuals with nasopharyngeal colonisation.[2] Carriage of pneumococci in the nasopharynx varies with age and environmental factors. The duration of carriage is generally longer in children. All pneumococcal disease presumably begins with nasopharyngeal colonisation.

Invasive disease and its risk factors

For disease surveillance purposes, detection of *S. pneumoniae* in a normally sterile site, such as blood, cerebrospinal fluid or pleural fluid, by culture or polymerase chain reaction, is classified as invasive pneumococcal disease. The highest incidence of invasive pneumococcal disease is seen among young children, especially those under two years, and in the elderly.[3,4] The major categories of invasive pneumococcal disease are:

1. meningitis, which is associated with the highest case-fatality rate and possible neurological sequelae among survivors
2. bacteraemic pneumonia
3. bacteraemia without focus, the commonest clinical category in young children.

Various medical, environmental and lifestyle factors are associated with an increased risk of developing invasive disease (see Box).[5,6] Aboriginal and Torres Strait Islander children and adults have a higher rate of invasive pneumococcal disease compared with other Australians.[7,8]

Table 1 **Pneumococcal vaccines and their serotypes**

Vaccine type	Valency (brand name)	Conjugating protein	Shared serotypes	Additional serotypes
Conjugate vaccines	7-valent (Prevenar)	non-toxic *Corynebacterium diphtheriae* CRM_{197} protein	4, 6B, 9V, 14, 18C, 19F, 23F	–
	10-valent (Synflorix)	protein D from non-typeable *Haemophilus influenzae,* tetanus toxoid, and diphtheria toxoid	4, 6B, 9V, 14, 18C, 19F, 23F	1, 5, 7F
	13-valent (Prevenar 13)	non-toxic *Corynebacterium diphtheriae* CRM_{197} protein	4, 6B, 9V, 14, 18C, 19F, 23F	1, 5, 7F, 3, 19A, 6A
Polysaccharide vaccine	23-valent (Pneumovax 23)	none	4, 6B, 9V, 14, 18C, 19F, 23F	1, 5, 7F, 3, 19A, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F

Box **Risk factors for invasive pneumococcal disease** [6]

Category A: Conditions associated with the highest increased risk of invasive disease

Functional or anatomical asplenia:

- sickle cell disease or other haemoglobinopathies
- congenital or acquired asplenia (e.g. splenectomy), splenic dysfunction

Immunocompromising conditions:

- congenital or acquired immune deficiency, including symptomatic IgG subclass or isolated IgA deficiency (Note: children who require monthly immunoglobulin infusion are unlikely to benefit from vaccination)
- immunosuppressive therapy (including high-dose corticosteroids for more than one week) or radiation therapy, where there is sufficient immune reconstitution for vaccine response to be expected
- haematological and other malignancies
- solid organ transplant
- haematopoietic stem cell transplant*
- HIV (including AIDS)
- chronic renal failure, or relapsing or persistent nephrotic syndrome

Proven or presumptive cerebrospinal fluid leak

Cochlear implants

Intracranial shunts

Category B: Conditions associated with an increased risk of invasive disease

Chronic cardiac disease:

- particularly cyanotic heart disease or cardiac failure in children
- excluding hypertension only (in adults)

Chronic lung disease:

- chronic lung disease in preterm infants
- cystic fibrosis
- severe asthma in adults (requiring frequent hospital visits and use of multiple medications)

Diabetes

Down syndrome

Alcoholism

Chronic liver disease

Preterm birth at <28 weeks gestation†

Tobacco smoking

* Recommendations vary for haematopoietic stem cell transplant recipients[6]

† All infants born at <28 weeks gestation should receive the recommended vaccine doses as for those with an increased risk of invasive disease, up to age 5 years. After that, they only require further vaccine doses if they have chronic lung disease or another chronic medical condition that increases their risk.

Non-invasive disease

Otitis media and pneumonia (without bacteraemia) are classified as non-invasive disease for surveillance purposes. Pneumococcus is estimated to account for over a third of all community-acquired pneumonia in adults.[2]

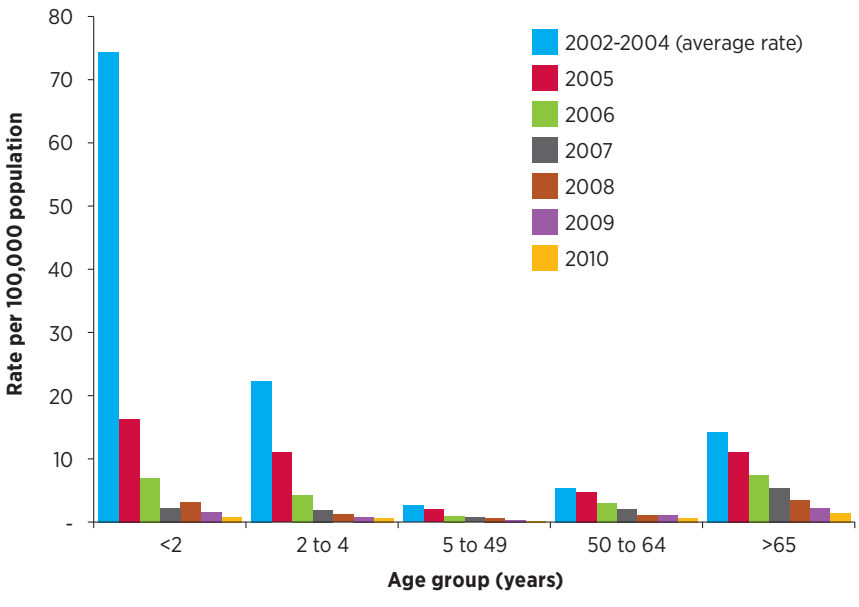
The impact of pneumococcal vaccination in Australia

In January 2005, Australia implemented universal vaccination of all young children with the 7-valent conjugate vaccine, and of adults aged 65 years and over with the 23-valent polysaccharide vaccine. Before then, there were publicly-funded pneumococcal vaccination programs for Australians with increased risks of pneumococcal disease[3] (www.ncirs.edu.au/immunisation/history/Pneumococcal-history-June-2012.pdf).

Following universal vaccination, the overall incidence rate of invasive pneumococcal disease decreased by 75% among non-indigenous children under two – from 78 per 100 000 in 2002–04 to 19.5 per 100 000 in 2007. Invasive disease caused by the seven vaccine serotypes declined by 97%, from 60.9 per 100 000 to 2.1 per 100 000.[3,9] Rates of hospitalisation due to pneumonia have decreased by 38% in children under two years.[10] Substantial reductions in invasive disease were also observed in older children and adults, the age groups who did not receive the vaccine. The decline was mostly due to a decrease in invasive disease caused by the seven vaccine serotypes (see Fig. 1).[3,4] This suggests a strong benefit of herd immunity, additional to any direct effect arising from the adult 23-valent vaccine program.

Increasing rates of invasive pneumococcal disease caused by serotypes not contained in the 7-valent vaccine ('serotype replacement') have been observed since 2005. Serotype 19A has emerged to become the dominant serotype causing invasive pneumococcal disease,[8] constituting 44% of all invasive disease among non-indigenous children under two years of age in 2007.[9] The number of cases due to serotype 19A among non-indigenous Australians increased by more than four-fold between 2002 and 2008 in most age groups.[8] However, this was not seen among indigenous Australians.[9,11]

Fig. 1 **Notification rate for invasive pneumococcal disease caused by serotypes contained in the 7-valent pneumococcal conjugate vaccine, Australia, 2002 to 2010, by age group** *



* Figure modified with permission from reference 4

Current vaccination schedules and recommendations

In Australia, recommendations on the specific pneumococcal vaccines vary according to age, indigenous status, jurisdiction and risk of invasive disease. For more detail about the risk categories and vaccine recommendations, consult the Australian Immunisation Handbook 10th edition.[6]

Children

Table 2 summarises the current recommended childhood pneumococcal vaccinations. For the 13-valent conjugate vaccine, a three-dose primary vaccination schedule, at two, four and six months of age without a booster dose, is recommended. Based on efficacy data from the pivotal randomised controlled trial of the 7-valent conjugate vaccine,[12] the potential additional benefits are not considered sufficient to justify a routine booster (fourth) dose for healthy non-indigenous children. For those with a higher risk of invasive disease or indigenous children living in states and territories where there is a high incidence of invasive disease (WA, NT, SA and Qld), a fourth dose of the 13-valent conjugate vaccine is now recommended (see immunise.health.gov.au).

Guidance on catch-up vaccination schedules for children who are delayed in presenting for pneumococcal vaccination or who have an increased risk of invasive disease, including those diagnosed after completion of the age-based recommended course, can be found in the Australian Immunisation Handbook 10th edition.[6]

Adults

Table 3 summarises the current recommended adult pneumococcal vaccinations in Australia. A single dose of the 23-valent polysaccharide vaccine is recommended for healthy non-indigenous adults

Table 2 **Australian recommendations for pneumococcal vaccinations in children under 5 years**

Conjugate vaccine	Indigenous status, risk and jurisdiction	Age of child			
		2, 4 and 6 months*	12 months	12–18 months	4–5 years
13-valent	All healthy children in ACT, NSW, Tas or Vic Non-indigenous healthy children in NT, Qld, SA or WA	13-valent vaccine	–	–	–
	Indigenous healthy children in NT, Qld, SA or WA	13-valent vaccine	–	13-valent vaccine	–
	All children with increased risk of invasive disease	13-valent vaccine	13-valent vaccine	–	23-valent polysaccharide vaccine
If 10-valent is used	All healthy children	10-valent vaccine	–	10-valent vaccine	–

Table modified from the Australian Immunisation Handbook 10th edition [6]
* The first dose can be given as early as six weeks of age. The next scheduled doses should still be given at 4 and 6 months of age.

Table 3 **Australian recommendations for pneumococcal vaccinations in adults**

Risk of invasive disease (see Box)	Indigenous status	Age (years)	13-valent conjugate vaccine*	23-valent polysaccharide vaccine†
Normal (healthy)	non-indigenous	≥65	–	single dose
	indigenous	≥50	–	two doses‡
Increased risk (category B)	non-indigenous	18–64 ≥65	– –	three doses# two doses‡§
	indigenous	18–49 ≥50	– –	three doses# two doses‡
Highest risk (category A)	non-indigenous	18–64 ≥65	single dose single dose	three doses# three doses‡
	indigenous	18–49 ≥50	single dose single dose	three doses# three doses‡∞

Table modified from the Pneumococcal vaccines for Australians factsheet of the National Centre for Immunisation Research and Surveillance, based on the 10th edition of the Australian Immunisation Handbook [6]
* Recommended for those with risk factors for invasive disease who have never received the 13-valent conjugate vaccine. This dose should precede the first dose of the recommended 23-valent polysaccharide vaccine by 2 months. For those who have had the polysaccharide vaccine, the 13-valent vaccine dose should be given at least 12 months later.
† The minimum interval between any 2 doses of 23-valent polysaccharide vaccine should be 5 years, with a maximum of 3 lifetime adult doses
‡ The second dose should be given 5 years after the first dose
# The second dose should be given 5–10 years after the first dose. The third dose should be given at 65 years for non-indigenous people and 50 years for indigenous people or 5 years after the second dose, whichever is later.
§ Those diagnosed as being at increased risk after receiving the 23-valent vaccine at age 65 should receive a second dose at time of diagnosis or 5 years after the previous dose, whichever is later
∞ The third dose should be given at 65 years or 5 years after the second dose, whichever is later

at age 65. A routine second dose is no longer recommended, based on a harm–benefit re-evaluation in 2011.[13]

Younger adults with an increased risk of invasive disease, including smoking (see Box), should also be vaccinated. More doses of the 23-valent vaccine are recommended for Aboriginal and Torres Strait Islander people or those with risk factors for invasive disease. The minimum interval for a repeat dose of the 23-valent polysaccharide vaccine is five years. The maximum number of lifetime doses in adulthood is three, based on concerns regarding adverse events and limited effectiveness, and uncertainty about immune hyporesponsiveness following multiple revaccinations.

Adults with a medical condition associated with the **highest** increased risk of invasive disease (category A conditions in the Box) are also recommended to have a single dose of 13-valent conjugate vaccine.

7-valent conjugate vaccine

A pivotal US trial in a setting similar to the Australian general population found that the vaccine reduced the risk of invasive pneumococcal disease due to the seven vaccine serotypes by about 95% among infants and toddlers.[12] Some cross-protection against serotype 6A invasive pneumococcal disease was also shown.[14]

A Cochrane review of conjugate pneumococcal vaccines reported that the pooled vaccine efficacy was 80% (95% CI 58–90%) against vaccine-type disease and 58% (95% CI 29–75%) against all-serotype invasive disease in children under two years. Effectiveness against X-ray defined pneumonia was lower at 27% (95% CI 15–36%).[15]

Another Cochrane review on young children concluded that while the efficacy against clinically defined otitis media due to serotypes in the vaccine was about 60%, the overall preventive benefit against acute otitis media due to any cause was only 6–7%.[16] This is due to the cancelling out of the preventive benefits of 7-valent vaccine against disease due to vaccine serotypes by non-vaccine serotypes and other organisms. However, studies from several countries, including Australia, have shown a decrease in the likelihood of tympanostomy tube insertion among vaccinated children.

The 7-valent vaccine is safe. However, it is more commonly associated with local adverse events and fever than comparator vaccines such as hepatitis B or meningococcal C conjugate.[17] There is no pattern of increasing local reactogenicity with subsequent doses.[12]

Higher valency conjugate vaccines

The 10-valent and 13-valent conjugate vaccines were registered for young children based on non-inferiority of immunogenicity compared with the 7-valent vaccine. There are no definitive serological correlates of clinical protection against the whole spectrum of pneumococcal disease, especially where specific serotypes are concerned. Currently, clinical efficacy data are not available for either of these two vaccines.

10-valent vaccine (Synflorix)

This vaccine was approved in 2009 for children. While its clinical efficacy is yet to be published, a study of a prototype vaccine containing 11 pneumococcal serotypes (the 10 serotypes in the 10-valent plus serotype 3), also conjugated to *H. influenzae* protein D, showed significant protective efficacy against acute otitis media caused by vaccine serotypes (57.6%; 95% CI 41.4–69.3%) as well as by *H. influenzae* (35.6%; 95% CI 3.8–57.0%).[18]

The safety profile of the 10-valent vaccine is similar to that of the 7-valent vaccine, with no clinically relevant difference when co-administered with routine childhood vaccines.[19]

There are no specific data available that address the immunogenicity and safety around the interchangeability of the 10-valent vaccine and other CRM_{197}-conjugated vaccines (see Table 1). However, a mixed schedule consisting of different conjugate vaccines necessitated by changes in vaccination programs is considered acceptable.

13-valent vaccine (Prevenar 13)

Children

This vaccine was approved in 2010 for children. Because of the extensive postmarketing data on the 7-valent vaccine, and established immunologic correlates of protection against invasive pneumococcal disease in children, efficacy trials have not been conducted.[20] Licensing in Australia has been based on non-inferiority of immunogenicity for the 7-valent conjugate vaccine serotypes and comparable antibody responses to the additional serotypes. This includes serotype 19A, which has emerged as the dominant serotype in Australia. Field effectiveness against invasive pneumococcal disease caused by the additional serotypes contained in 13-valent vaccine has been shown.[21]

The safety profile of the 13-valent vaccine is similar to that of the 7-valent vaccine.[22] However, post-licensure surveillance in the USA has suggested that there is a slightly higher risk of febrile seizures in young children within a day of concurrent administration with inactivated trivalent influenza vaccine compared with the vaccines given alone on separate days (especially in children aged 12–23 months).[23] Concurrent administration of these two vaccines is considered acceptable. However, if relevant, parents should be given the option of having the vaccines separately at least three days apart.[6]

Adults

In 2011, the 13-valent vaccine was registered in Australia for adults aged 50 years and over, based on immunogenicity data showing comparable or better antibody responses compared to the 23-valent polysaccharide vaccine for the shared vaccine serotypes.

There is only limited safety information on the 13-valent conjugate vaccine in adults. Pain, redness

and swelling at the injection site is observed in about half of vaccine recipients. Concurrent administration of trivalent inactivated seasonal influenza vaccine with the 13-valent vaccine may increase the frequency of systemic but not local reactions.[24]

23-valent polysaccharide vaccine (Pneumovax 23)

This vaccine is available for adults and children two years and over. The majority of serotypes found in invasive pneumococcal disease isolates of Australian adults are contained in this vaccine.[25,26]

A Cochrane review in 2013 estimated that pneumococcal polysaccharide vaccines have an overall protective efficacy of 74% (95% CI 55–86%) against invasive disease in adults.[27] Recent observational data from England and Wales have shown moderate effectiveness (48%) of the 23-valent vaccine against invasive disease within two years of vaccination in adults aged 65 years or over. However, effectiveness waned after two years and became insignificant after five years. In the subgroup of adults aged 65–74 years who had no clinical risk factors for pneumococcal disease, effectiveness was higher (65%) and was maintained for longer.[28] There are no specific studies on the clinical effectiveness of a second dose of the polysaccharide vaccine.

Boosting of antibody responses to the 7-valent vaccine serotypes after vaccination with the polysaccharide vaccine has been shown in small studies of children and adults with underlying medical conditions. Some antibody response to a few additional polysaccharide vaccine serotypes was also observed.

The frequency of adverse reactions varies among study populations (and possibly with age), and is higher with repeat doses. At least half of the recipients will experience some soreness at the injection site after the first dose. Swelling and redness are also very common (approximately 20%). More severe injection site reactions occur in up to 5% of first dose recipients and may occur in up to 20% of people after a second dose.[29-31] In these studies, repeat doses were given at least five years after the previous dose. Cellulitis-like reactions can also occur. Local adverse events occurred more often after subcutaneous administration than after intramuscular administration.[32] Systemic reactions like myalgia, fatigue and chills are also very common.

Conclusion

The universal childhood pneumococcal conjugate vaccination program has substantially reduced pneumococcal disease, especially invasive disease in the target age group. Herd immunity has been observed in other age groups. Introduction of the 13-valent vaccine is likely to lead to further reduction in invasive pneumococcal disease caused by emergent serotypes, particularly 19A.

The 23-valent polysaccharide vaccine is modestly effective against invasive pneumococcal disease in adults, including older adults, especially those without underlying chronic medical conditions. However, due to an increase in local reactions after repeat doses, revaccination should be limited to those with higher risks of invasive pneumococcal disease. ◁

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

5. A fourth booster dose of the 13-valent conjugate pneumococcal vaccine is not recommended for non-indigenous healthy children.

6. The 23-valent polysaccharide vaccine is recommended for all Aboriginal and Torres Strait Islander people aged 50 or older.

Answers on page 107

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