Pneumococcal conjugate vaccine: an Australian perspective

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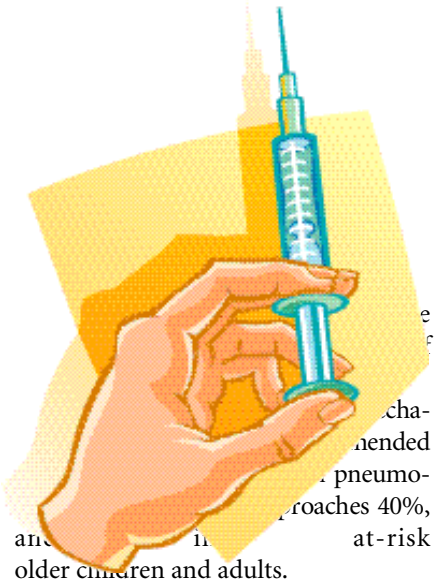
Streptococcus pneumoniae is the most important cause of bacterial meningitis, pneumonia and septicaemia in Australian infants. The conjugated vaccine allows immunisation of children under the age of 2 years.



Since 1 January 2005, all Australian infants have been able to receive federally funded vaccination against *Streptococcus pneumoniae* (pneumococcus). This organism is the most common cause of bacterial meningitis in Australian children, and it causes the most severe cases. Pneumococcus is also the most important cause of bacterial pneumonia and septicaemia. Universal vaccination with the pneumococcal conjugate vaccine (PCV) has been recommended for infants by the NHMRC Australian Technical Advisory Group on Immunisation (ATAGI) since 2003.

What is special about the conjugate vaccine?

Previously, the only available vaccine against pneumococcus was the pneumococcal polysaccharide vaccine (PPV), Pneumovax 23, which contains capsular polysaccharide antigens of 23 pneumococcal serotypes. Polysaccharide vaccines do not produce an immune response, because of immaturity of the immune system, in children aged under 2 years, who are the highest risk group for invasive pneumococcal disease. Conjugate vaccines overcome immunological immaturity by containing polysaccharide antigens conjugated to a protein carrier that is recognised by infant immune systems. Effective immune responses are created to both the protein carrier and the polysaccharide antigens. Other examples of conjugate vaccines include those against *Haemophilus influenzae* type B and group C meningococcus.

The only currently licensed pneumococcal conjugate vaccine, Prevenar, includes antigens to seven common serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), which are responsible for about 80% of invasive pneumococcal disease in urban Australian children.[1] This vaccine provides good initial immunity as well as immunological memory. It is immunogenic in children from 2 months of age. Conjugate vaccines are being developed that have greater coverage to combat serotypes causing invasive disease in

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Who should receive the conjugate vaccine?

The ATAGI recommends that all babies receive the pneumococcal conjugate vaccine at 2, 4 and 6 months of age. All children born after 1 January 2003 are eligible for free (federally funded) vaccine. The schedule for healthy infants presenting for their first vaccination after 2 months of age is shown in the Table. Children with predisposing conditions for invasive pneumococcal disease (see the box on page 70) and Aboriginal and Torres Strait Islander children living in Central Australia are eligible for funded pneumococcal conjugate vaccination up to the age of 5 years. They may require additional conjugate vaccine doses as well as the pneumococcal polysaccharide

Table. Primary pneumococcal conjugate vaccination schedules for healthy children*

Age at first dose (months)	Primary pneumococcal conjugate vaccine schedule
2 to 6 months	3 doses, 2 months apart
7 to 17 months	2 doses, 2 months apart
18 to 23 months	1 dose
24 to 59 months†	1 dose

*Adapted with permission from Table 3.18.3 of the NHMRC's *Australian Immunisation Handbook* – 8th edition, 2003.
†Catch up vaccination is not funded unless at increased risk (see the box on page 70).

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Invasive pneumococcal disease rates

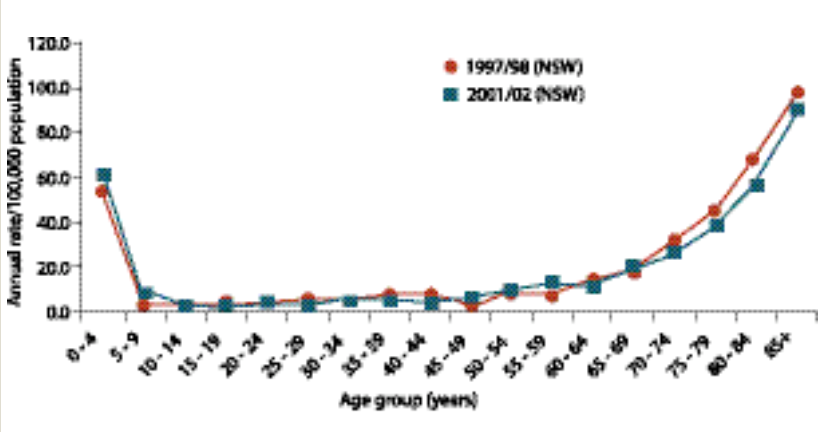

Figure. Invasive pneumococcal disease rates according to age in New South Wales, 1997-2002.

*Reproduced from: Andrews RM, Counahan ML, Hogg GG, McIntyre PB. Effectiveness of a publicly funded pneumococcal vaccination program against invasive pneumococcal disease among the elderly in Victoria, Australia. Vaccine 2004; 23: 135; with permission from Elsevier.

vaccine. (See the *Australian Immunisation Handbook*, 8th edition [www1.health.gov.au/immhandbook].)

When is the polysaccharide vaccine used?

The NHMRC recommends vaccination with the pneumococcal polysaccharide vaccine in:[2]

- all people aged 65 years and over
- Aboriginal and Torres Strait Islander people aged 50 years and over
- adults and children aged over 5 years with underlying chronic illnesses (including diabetes, renal, pulmonary or cardiac disease, and asplenia) or immunocompromise predisposing to developing invasive pneumococcal disease or its complications
- adults and children aged over 5 years with CSF leaks
- tobacco smokers.

The polysaccharide vaccine is recommended as a booster following a primary course of the conjugate vaccine in:

- Aboriginal and Torres Strait Islander children living in regions of high incidence at 18 to 24 months of age
- in children at increased risk of invasive disease, due to regional incidence or comorbidity, at 4 to 5 years of age.

Why is the pneumococcal conjugate vaccine important?

The conjugated vaccine allows immunisation of children aged under 2 years – an age group with a significant amount of morbidity related to pneumococcal infection.

Epidemiology

Invasive disease (bacteraemia and meningitis)

In Australia, pneumococcus is the leading cause of serious community acquired infection. In childhood the risk of invasive disease (i.e. bacteraemia and/or meningitis, not pneumonia or otitis media) is greatest under the age of 2 years; in adulthood the risk rises steeply after the age of 65 years (as shown in the Figure). The national annual incidence of invasive pneumococcal disease is 50 to 100 cases per 100,000 children aged under 2 years and 50 to 100 cases per 100,000 adults 65 years and over.[3,4] These high rates pale into insignificance compared with the toll of invasive pneumococcal disease in indigenous children; in the Northern Territory, annual incidence is more than 1500 cases per 100,000 children aged less than 2 years.[3,5]

The overall case fatality rate of invasive pneumococcal disease is 14%.[3] In children, fever and bacteraemia without an infective focus is the presentation in 60% cases.[6] Up to 15% of children with invasive disease develop meningitis – accounting for 200 cases a year in Australia – with long term neurological sequelae occurring in 25 to 56% of survivors.[2,7]

In Australia, invasive pneumococcal disease kills an estimated 175 people (adults and children) each year, while worldwide an estimated one million people die annually from this potentially preventable disease.[1,7]

High risk groups

At especially high risk of invasive disease are people with functional or anatomical asplenia, immunosuppressive conditions, cardiac, pulmonary, kidney or liver disease and sickle cell disease.[7] Community risk factors include lack of breastfeeding, exposure to tobacco smoke and day care attendance. Childhood morbidity increasing the risk is listed in the box on page 70.

Noninvasive disease

Pneumococcal pneumonia and acute otitis media usually occur without bacteraemia, so are not included in pneumococcal surveillance but are a major cause of morbidity and mortality.[3,6] Estimates suggest that annually in Australia, there are 1300 hospital admissions for pneumococcal pneumonia in children aged under 5 years and 40,000 episodes of pneumococcal otitis media in children aged under 2 years. As with invasive disease, the greatest burden of acute otitis media is borne by indigenous children, among whom two of

Conditions predisposing children aged under 5 years to invasive pneumococcal disease*

Conditions compromising immune response to pneumococcal infection

– Congenital immune deficiencies
– Immunosuppressive therapy or radiation therapy
– Compromised splenic function or asplenia
– HIV infection, before and after development of AIDS
– Renal failure, or relapsing or persistent nephrotic syndrome
– Down's syndrome

Conditions associated with higher rates or severity of invasive disease

– Cardiac disease associated with cyanosis or cardiac failure
– Prematurity associated with chronic lung disease
– Prematurity of less than 28 weeks' gestation
– Cystic fibrosis
– Insulin-dependent diabetes mellitus
– Proven or presumptive cerebrospinal fluid leak
– Intracranial shunts and cochlear implants

*Adapted with permission from Table 3.18.1 of the NHMRC's *Australian Immunisation Handbook* – 8th edition, 2003.

every three children starting school have hearing impairment and ear disease.[8]

What are the vaccine's benefits?

Overall, 85 to 90% of pneumococcal isolates from Australian children with invasive disease are covered by the pneumococcal conjugate vaccine,[3] and US data suggest that the vaccine covers about 60% of middle ear isolates.[9] In indigenous Australian children with invasive disease, about 65% of isolated strains are covered.[8]

Invasive disease

In Australia, the pneumococcal conjugate vaccine may prevent around 80% of all invasive infections.[6] Post-licensing surveillance in the USA showed a 69% reduction in total invasive pneumococcal disease in children under 2 years. Surprisingly, a reduced incidence of invasive disease was seen also in almost one-third of unvaccinated adults aged 20 to 39 years and one-fifth of unvaccinated adults aged 65 years or more, presumably representing 'herd immunity' due to reduced transmission.[1,7,10] Recently presented US data have suggested that this herd protection may require the use of a fourth dose for each infant, which is not part of the Australian schedule.[11]

Pneumonia

The use of the pneumococcal conjugate vaccine in Australia is predicted to prevent annually about 750 admissions for pneumonia in children aged under 5 years.[6] In the USA, a 20% reduction in radiologically proven pneumonia was shown in children under 2 years of age following introduction of the vaccine.[1,7] It is likely that pneumococcus is responsible for some of the remaining 80% cases not prevented by the vaccine.

Acute otitis media

In the USA, episodes of acute otitis media were reduced by only 7% after introduction of the conjugate vaccine, with a reduction in doctor visits and antibiotic use of similar magnitude. The benefit was modest because the reduction in cases of otitis media caused by serotypes covered by the vaccine was counterbalanced by an increase in cases caused by other pneumococcal serotypes.[12] Studies, however, have shown a 44% reduction in the need for tympanostomy tubes.[1,6]

What are the adverse effects?

Transient and mild local reactions to the vaccine occur. There is an increased risk of fever, fussiness, rashes and urticaria.[13] As with many other inactivated childhood vaccines occasionally an injection site nodule may develop that last weeks, but no treatment is needed.[14] Serious adverse events reportedly occur in 1.9 per 100,000 vaccinations, and the proportion of serious to mild adverse events is similar to that occuring with other vaccines. In US post-licensing surveillance, no deaths have been attributed to the vaccine.[13]

How much does it cost?

Pneumococcal conjugate vaccination on the Australian Immunisation Schedule is now funded by the Federal Government, so is free for eligible children. The pneumococcal conjugate vaccine is the most expensive vaccine on the Schedule, costing around $300 for three doses.[6] For nonfunded indications the vaccine costs between $110 and $160. It is hoped that in the future, licensing of competing vaccines may help decrease the cost.

What are the long term issues?

In the long term, immunising infants against seven common serotypes of pneumococcus may have several effects.

Serotype replacement. Studies have shown use of the vaccine to be associated with a change in nasal carriage in children, whereby pneumococcal serotypes not covered by the vaccine replace vaccine-covered serotypes .[15] This changing ecology has not yet resulted in increased invasive disease or pneumonia. An increase in nonvaccine-serotype pathogens has been observed in vaccinated children with otitis media but not in those with invasive disease.[1,7,16]

Antibiotic resistance. Vaccination reduces the risk of resistant pneumococcal

infections by 35%. This is largely due to the vaccine-covered serotypes also being the most drug resistant serotypes, while the 'replacement', or nonvaccine serotypes, have a much lower rate of antibiotic resistance.[10] Pneumococcal resistance to penicillin has been rapidly rising in Australia but may now stabilise because penicillin resistant strains occur more often in children. (Penicillin resistance, including intermediate levels of resistance, has risen to around 25%, with higher rates among indigenous Australians.[17])

Management of the febrile infant with no obvious focus. Most children will soon be vaccinated against the triad of pneumococcus, meningococcus and *Haemophilus influenzae* type B. Therefore, rates of occult bacteraemia in children are likely to be greatly reduced. Ongoing study will be needed to confirm whether this predicted decrease in bacterial sepsis will translate into practical changes in the investigation and empirical management of this frequent and troubling clinical scenario.[17]

Duration of immunity. How long the protection of this vaccine lasts remains unknown. Protection for at least two years has been demonstrated in the original study groups.[1]

Conclusion

The pneumococcal conjugate vaccine is an extremely welcome addition to the funded Australian Standard Immunisation Schedule. It is safe and effective. MT

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DECLARATIONS OF INTEREST: Dr Buttery is an investigator for trials conducted on behalf of the Murdoch Children's Research Institute, sponsored by vaccine manufacturers, and in the past has been an investigator for trials conducted on behalf of Oxford University and sponsored by vaccine manufacturers. He has received assistance to attend scientific meetings. He has received industry-sponsored honoraria for consultancies, lecturing and writing, which have been paid directly to an educational fund held by the Murdoch Children's Institute. Dr Bar-Zeev: None.