# Pneumococcal disease and vaccination recommendations

## The state of play

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**Overall large reductions in cases of the severe form of pneumococcal disease have been achieved with the pneumococcal vaccination program targeting all infants and older adults and individuals with risk conditions. However, uptake of vaccination recommendations targeting groups with risk conditions and Indigenous adults is suboptimal, and currently a disproportionate burden of pneumococcal disease is borne by these people. Ensuring these individuals receive the full schedule of recommended vaccine doses on time is crucial.**

Pneumococcal disease is a collection of clinical manifestations caused by *Streptococcus pneumoniae* (also called pneumococcus). In studies of the global disease burden of pneumococcal disease in children published in both 2009 and 2018, about 11% of all deaths among children under 5 years of age were reported to be attributable to pneumococcal infection.[1,2] Invasive pneumococcal disease (IPD) is the severe end of the pneumococcal disease spectrum. In IPD, *S. pneumoniae* is detected in normally sterile sites such as blood and cerebrospinal, pleural, pericardial, peritoneal or joint fluid.[3] IPD causes significant mortality and morbidity in children, particularly among young infants. In developed countries, IPD commonly (about 70% of cases) presents in children as bacteraemia with no identifiable specific focus of infection.[4,5] Among adults, the most common presentation of IPD is bacteraemic pneumonia.[6,7] Noninvasive pneumococcal disease, which is localised mucosal infections of *S. pneumoniae*, is generally less serious and more common than IPD. Among pneumococcal disease manifestations that are noninvasive, acute otitis media is the most common in children.[8] Also, most cases of community-acquired pneumonia (CAP) caused by pneumococci among adults are noninvasive.[9]

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### Bacteriology of pneumococcal disease

*S. pneumoniae* is an encapsulated Gram-positive coccus. The polysaccharide capsule is the important virulence factor.[3,10,11] Currently, about 97 pneumococcal serotypes belonging to about 40 serogroups have been identified.[12,13] Serotypes differ in the chemical composition of their polysaccharide capsules and are therefore immunologically distinct.[14,15] In most cases, *S. pneumoniae* resides in the nasopharynx leading to stable asymptomatic colonisation (carriage), which is a precursor to disease and plays an important role in horizontal transmission between individuals.[16] High pneumococcal carriage seen in young children acts as the main reservoir for disease in older adults.[16,17] Pneumococcal serotypes vary in their tendency to cause asymptomatic carriage or disease, and a limited number of serotypes are responsible for pneumococcal disease.[14,16,18-20] Vaccines target the serotypes that commonly cause disease.

### Pneumococcal vaccines available in Australia

Two types of pneumococcal vaccines have been developed and used against pneumococcal disease: pneumococcal

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polysaccharide vaccines (PPVs) and pneumococcal conjugate vaccines (PCVs).[21-23] PCVs comprise a selected number of pneumococcal polysaccharides conjugated to a protein carrier.[24,25] PPVs generate protective antibodies against pneumococcal disease without involving T cells, which are required for long-term immune memory.[13] As a result, immunity triggered by PPVs is relatively short lived, and they are less immunogenic in children under 2 years of age. The covalent coupling to the protein carrier in PCVs converts the pneumococcus polysaccharide to a T cell-dependent antigen, thereby inducing immune memory and enhancing the antibody response.[21] PCVs are therefore able to elicit robust, high-quality immune responses sufficient to prevent pneumococcal disease even in very young infants.

There are two pneumococcal vaccines available in Australia through the National Immunisation Program (NIP):

- Prevenar 13 (Pfizer), 13-valent pneumococcal conjugate vaccine (13vPCV).
- Pneumovax 23 (Seqirus/Merck), 23-valent pneumococcal polysaccharide vaccine (23vPPV).

Recommendations of the Australian Technical Advisory Group on Immunisation (ATAGI) regarding the use of pneumococcal vaccines are published in the *Australian immunisation handbook* (https://immunisationhandbook.health.gov.au).[26] These recommendations regarding which vaccine to use and the required number of doses and timing are based on the different characteristics of the vaccines and a person's individual risk of IPD. An individual's risk of IPD varies by:

- age
- Indigenous status
- state/territory of residence
- the presence and nature of risk factors, including both immunocompromising and nonimmunocompromising underlying medical and selected behavioural conditions
- previous doses of pneumococcal vaccines received.

Table 1 summarises important details regarding pneumococcal vaccines currently available in Australia.

Most of the ATAGI-recommended pneumococcal vaccine doses are fully funded by the government under the NIP, and for some recommendations the vaccine cost is subsidised under the PBS. People occasionally have to pay the full cost of the vaccine.

## Key points

- **Pneumococcal disease is a collection of clinical manifestations that includes life-threatening meningitis, pneumonia and septicaemia caused by *Streptococcus pneumoniae*.**
- **13-valent pneumococcal conjugate vaccine (13vPCV; Prevenar 13) and 23-valent pneumococcal polysaccharide vaccine (23vPPV; Pneumovax 23) are offered under the National Immunisation Program (NIP) and recommendations for their use differ by target population.**
- **The recent change in the recommended schedule for 13vPCV for infants to include a 12-month age booster dose after primary doses at age 2 and 4 months is expected to prolong protection for vaccinated children as well as improve herd benefit for others.**
- **For individuals with underlying medical conditions that increase their risk of pneumococcal infection there are targeted vaccine recommendations and vaccine providers need to ensure that all such people are identified and given the full course of the recommended pneumococcal vaccines on time.**
- **A dose of 23vPPV is recommended and fully funded under the NIP for Indigenous adults at 50 years of age and non-Indigenous adults at 65 years of age.**

## Risk factors for pneumococcal disease

Certain medical and lifestyle conditions are associated with increased risk of pneumococcal infection as well as more severe disease outcomes across populations . After they were licensed, pneumococcal vaccines were offered to those population groups at high risk of IPD; the specific recommendations for additional vaccine doses for those groups are still

**Table 1. Pneumococcal vaccines currently available in Australia**

| Vaccine* | Shared serotypes | Additional serotypes | Age group registered for use | Recommended populations for use |
|---|---|---|---|---|
| Prevenar 13 (13vPCV; Pfizer) | 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F | 6A | ≥6 weeks | Infants<br>People with highest risk of IPD as described in the *Australian immunisation handbook* |
| Pneumovax 23 (23vPPV; Seqirus/ Merck) | | 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F | ≥2 years | Non-Indigenous adults aged ≥65 years<br>Aboriginal and Torres Strait Islander adults aged ≥50 years<br>People with increased risk of IPD as described in the *Australian immunisation handbook* |

Abbreviations: IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine; PPV = pneumococcal polysaccharide vaccine.
* Synflorix (GSK) 10-valent PCV is also registered for use in Australia it contains all 'shared serotypes' in the table except serotypes 3 and 19A and is licensed for use in children from 6 weeks to 5 years of age.

**Conditions associated with an increased risk of IPD in children and adults, by severity of risk**[*†]

**Category A: Conditions associated with the highest increased risk of IPD**

- Functional or anatomical asplenia, including:
  - sickle cell disease or other haemoglobinopathies
  - congenital or acquired asplenia (e.g. splenectomy), splenic dysfunction
- Immunocompromising conditions, including:
  - 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 corticosteroid therapy at a dose of 2 mg/kg daily or more of prednisolone or equivalent for more than one week) or radiation therapy, when there is sufficient immune reconstitution for vaccine response to be expected
  - haematological and other malignancies
  - solid organ transplant
  - haematopoietic stem cell transplant
  - HIV infection (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 IPD**

- Chronic cardiac disease
  - particularly cyanotic heart disease or cardiac failure in children
  - excluding hypertension only (in adults)
- Chronic lung disease, including:
  - chronic lung disease in preterm infants
  - cystic fibrosis
  - severe asthma in adults (requiring frequent hospital visits and use of multiple medications)
- Diabetes mellitus
- Down syndrome
- Alcoholism
- Chronic liver disease
- Preterm birth at less than 28 weeks' gestation
- Tobacco smoking
- History of previous pneumococcal disease (in children)

Abbreviation: IPD = invasive pneumococcal disease.
[*] Adapted from the *Australian Immunisation Handbook*.
[†] For those aged over 5 years (but not for those aged 5 years and under), recommendations for pneumococcal vaccination differ between the risk-factor categories in this table.

in place but compliance seems poor. Studies have shown that pneumococcal vaccines led to a decline in IPD caused by serotypes targeted by the vaccines in some of these groups, but the decline is less than that observed among people with no such risk conditions (risk factors).[27,28] As a result, in this post-PCV era a large proportion of pneumococcal disease in children and adults is in those with risk factors. Individuals with risk factors are susceptible to disease caused by a broader range of pneumococcal serotypes than those with no risk factors.[29,30] The use of 23vPPV is recommended for these people to account for this.

The magnitude of the increased risk of pneumococcal disease varies quite considerably by individual risk conditions. People who are unable to mount an adequate immune response to pneumococcal capsular antigens because of immunocompromised states caused by disease or therapy are at particularly high risk of IPD, some as much as up to 100 times greater than those with no risk conditions.[3,31,32] Several studies have reported HIV infection and immunosuppressive therapy (e.g. after solid organ transplantation) as major factors associated with increased susceptibility to IPD.[28,33-37] Other chronic diseases shown in these studies as strong risk factors for IPD include bronchial asthma, renal disease, chronic airway disease and diabetes mellitus.[28,38] In addition, the incidence of pneumococcal disease is substantially higher among those with inherited conditions such as sickle cell disease and primary immunodeficiencies.[27,39,40] There are also other chronic medical conditions that are important risk factors for IPD.[41] In the *Australian immunisation handbook* the conditions for which risk factor-based pneumococcal vaccination recommendations apply are grouped into categories A and B based on their associated level of risk, and for that reason the recommendations vary between the two categories (Box).[26]

The incidence of IPD among Indigenous Australians is currently higher than that among non-Indigenous Australians for all age groups. Since the introduction of funded pneumococcal vaccination in early 2000, the IPD burden for Indigenous Australians has only decreased among children directly

targeted for vaccination.[42] Among Indigenous adults, including young adults, the total IPD incidence has increased, in contrast to that in the non-Indigenous population, in which substantial reductions were seen across all ages due to direct as well as good indirect (herd) impact of the childhood vaccination program. As a result, in the last decade or so the disparity of IPD incidence between Indigenous Australians and non-Indigenous Australians has widened. Currently, the lowest incidence of IPD among Indigenous adult age groups is in the 15 to 24 years age group and is comparable with the incidence among non-Indigenous adults aged 65 years and over.

## Pneumococcal disease epidemiology in Australia

IPD has been a nationally notifiable disease in Australia since 2001. The National Notifiable Disease Surveillance System (NNDSS) captures all notifications of IPD in the country. In 2018 there were 2032 cases of IPD notified to NNDSS with, as in other years, episodes peaking in the winter months.[43] There were 131 deaths in that year reported as being due to IPD, most among elderly adults. The incidence of IPD is highest in extremes of age, with about 18 per 100,000 population in children under 2 years of age and 25 per 100,000 population in adults aged over 85 years.[44]

In the 10 years after the rollout through the NIP of funded pneumococcal vaccination in 2005 for all children and older adults, the IPD incidence among all Australians halved.[45] The decline of more than 80% in young children was particularly remarkable. The pneumococcal disease incidence among Indigenous Australians is several-fold higher than for non-Indigenous Australians. Of all IPD cases in 2018, 11% were in Indigenous people, who make up about 3% of the Australian population.[43]

Unlike for IPD, there are limited data available on the epidemiology of noninvasive pneumococcal disease. Among Australian adults aged 65 years and over, about 45,000 are hospitalised because of pneumonia annually. Of these, about 6300 (14%) have pneumococcal CAP. A further 1400 patients with pneumococcal CAP are managed by GPs.[46,47]

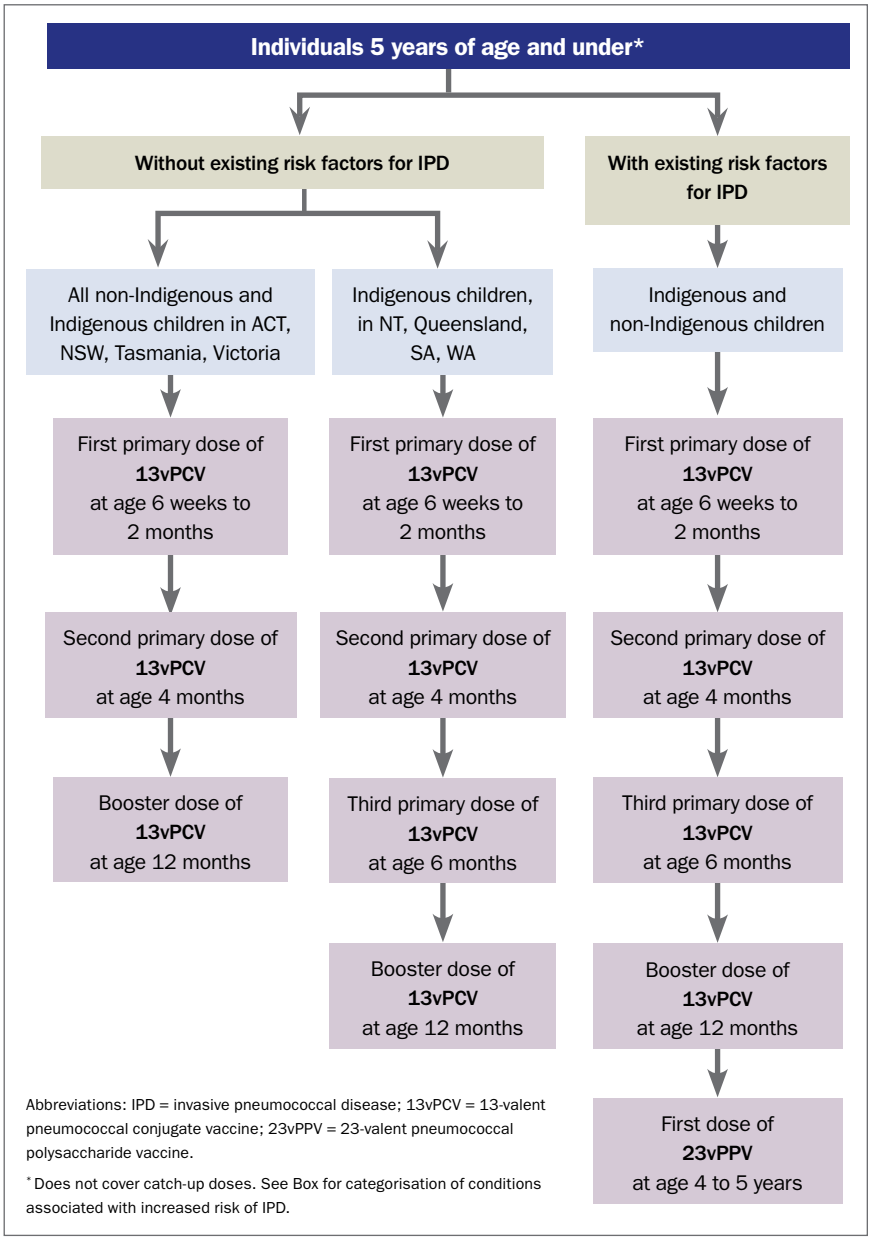


**Figure 1. Current schedule for pneumococcal vaccination of infants and young children.**

Among Australian children, the two PCVs that have been used in the universal infant pneumococcal vaccination program, 7vPCV and 13vPCV, are highly efficacious. The three-dose schedule of both vaccines had more than 90% effectiveness in children against IPD caused by serotypes they contained.[48,49] These vaccine effectiveness assessments showed that without a booster dose vaccine-induced immunity waned when children reach their second year of life.[49,50] This led to ATAGI revising the schedule for 13vPCV by moving the third dose given at 6 months of age to be a booster dose at 12 months of age to prolong immunity. The PCV programs also led to large declines in IPD caused by vaccine serotypes in unvaccinated older children and adults, mediated through reduction in asymptomatic carriage of pneumococcus in vaccinated children. The 23vPPV vaccine offered to older adults had 61% effectiveness against IPD caused by serotypes covered in

**Table 2. Recommendations for pneumococcal vaccination of children aged between 5 and 18 years with conditions associated with an increased risk of IPD if newly diagnosed, based on the *Australian immunisation handbook***

| IPD risk category (see Box) | Previous 13vPCV received | Previous 23vPPV received | Recommended dose(s) of pneumococcal vaccine(s)* |
|---|---|---|---|
| Newly diagnosed Category A conditions – highest increased risk | Yes | No | First dose of 23vPPV at diagnosis<br>Next dose of 23vPPV five years after the first 23vPPV dose<br>Subsequent dose of 23vPPV 10 years later |
| | No | No | One dose of 13vPCV at diagnosis<br>First dose of 23vPPV two months later<br>Next dose of 23vPPV five years after the first 23vPPV<br>Subsequent dose of 23vPPV 10 years later |
| Newly diagnosed Category B conditions – increased risk | Yes or no (regardless) | Yes | One dose of 23vPPV five years after the first 23vPPV<br>Next dose of 23vPPV five to 10 years later (counted as first adult 23vPPV dose) |
| | | No | First dose of 23vPPV at diagnosis<br>Next dose of 23vPPV five to 10 years later (counted as first adult 23vPPV dose) |

Abbreviations: IPD = invasive pneumococcal disease; 13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine.
* Haematopoietic stem cell transplant recipients require three doses of 13vPCV post transplantation, followed by 23vPPV, irrespective of previous vaccine doses received.

that vaccine in Australian adults aged 65 years and over.[51] In recent IPD notifications data, about 40% of cases in children under 5 years of age were caused by 13vPCV serotypes.[43]

## Current pneumococcal vaccination strategy in Australia

The *Australian immunisation handbook* digital version contains the current ATAGI recommendations for pneumococcal vaccination.[26] They are summarised below according to age and risk-factor status. The ATAGI recommendations differ in some ways from the manufacturers' product information. Previous anaphylaxis with vaccine or components is an absolute contraindication to vaccination.

### For children without risk factors

For all non-Indigenous children and Indigenous children in the ACT, NSW, Tasmania or Victoria without any of the risk factors listed in the *Australian immunisation handbook* (Box), three doses of 13vPCV at ages 2 months, 4 months and 12 months (2+1 schedule) are recommended and funded (Figure 1). It is also recommended that the first dose can be given at 6 weeks of age, at the same time as the first dose of pertussis-containing vaccine. Those infants should still receive their next scheduled dose at age 4 months. Before 1 July 2018, the schedule recommended for these children was three primary doses at ages 2, 4 and 6 months. The third primary dose was then moved to become a booster dose in order to make vaccine-induced protection last longer. During the transition period, it was recommended that children who had already received three doses of 13vPCV who reached the age of 12 months after 1 July 2018 also receive the booster dose at 12 months of age. Having this booster dose in the 13vPCV schedule is expected to also substantially improve herd protection.

For Indigenous children living in the NT, Queensland, SA and WA, a booster dose of 13vPCV after three primary doses at 2 months, 4 months and 6 months of age is recommended and funded (3+1 schedule). This booster dose was previously given at age 12 months in SA and 18 months in NT, Queensland and WA. The recommended schedule point for the 13vPCV booster for all eligible children from 1 July 2018 onwards is 12 months of age.

For children who have a delayed start to their vaccination and for those missing doses, the schedule to follow depends on their age at presentation; the *Australian immunisation handbook* stipulates the number and timing of 13vPCV doses in these scenarios. No pneumococcal vaccine doses are recommended for children after 5 years of age unless they have underlying risk conditions, owing to the otherwise relatively low risk of pneumococcal disease.

### For older adults without risk factors

A dose of 23vPPV is recommended and fully funded under the NIP for Indigenous adults at 50 years of age and non-Indigenous adults at 65 years of age (Figure 2). These people are still eligible to receive the funded 23vPPV at any age if they have not been vaccinated when reaching these scheduled ages. For older Indigenous adults only, a second dose of 23vPPV is recommended and funded five years after the previous dose. Before 2011 a second 23vPPV dose was recommended for non-Indigenous older adults also, but due to the high rates of local reaction – including some severe injection-site adverse events – ATAGI decided to discontinue the recommendations for a repeat 23vPPV dose except for those with increased risk of pneumococcal disease.

### For people with risk factors listed in the Box

For children with underlying medical risk factors (both category A and B), three primary doses of 13vPCV at age 2, 4 and 6 months followed by a booster dose at 12 months of age (i.e. 3+1 schedule) are recommended and funded (Figure 1). After the course of 13vPCV, children with medical risk factors are also funded to receive a dose of 23vPPV at 4 to 5 years of age.

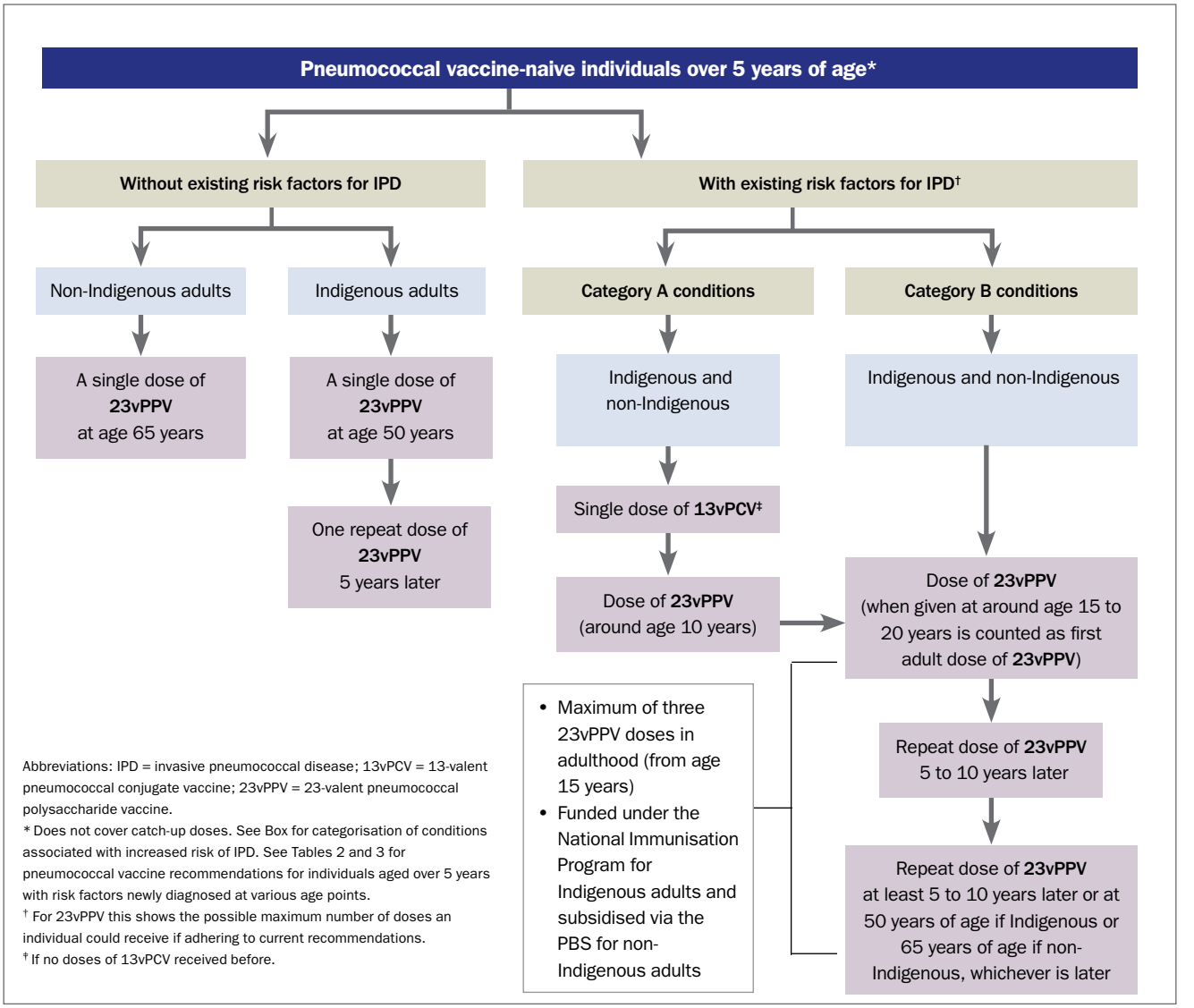


**Figure 2. Current schedule for pneumococcal vaccination of older children and adults.**

It is recommended that children with a category A risk factor receive a second dose of 23vPPV about five years after the previous 23vPPV dose (i.e. at about 10 years of age) followed by another 23vPPV about 10 years after the previous dose or at about 18 to 20 years of age, whichever is later.

For all individuals who undergo allogeneic or autologous haematopoietic stem cell transplant, three doses of 13vPCV followed by a dose of 23vPPV are recommended regardless of previous pneumococcal vaccines received. The three doses of 13vPCV are to be given six, eight and 12 months after transplant and the 23vPPV dose 12 months after the last 13vPCV dose.

The recommendation for children with category B risk factors is to give the second dose of 23vPPV about 10 years after the first dose that was given at 4 to 5 years of age (i.e. at age 15 to 18 years).

People may be diagnosed with these risk factors at different ages. The schedule to follow varies according to the age, whether the person is Indigenous or non-Indigenous, their risk factor category (A or B) and what pneumococcal vaccines, if any, they have received already. Table 2 summarises the recommendations for those who have risk factors diagnosed between the ages of 5 and 18 years. Of note, if the person has a category A risk factor then a dose of 13vPCV is to be offered if it has not been given previously. Thereafter, 23vPPV is to be given at the specified intervals.

It is recommended that all adults (Indigenous and non-Indigenous) aged 18 years or over who have risk conditions (either category A or B) receive up to three lifetime doses of 23vPPV (Figure 2 and Table 3). For adults with Category A risk factors a single dose of 13vPCV is recommended if they have not previously received any dose of 13vPCV, although this is not currently subsidised. If the person has received a dose of 23vPPV previously, the recommended interval before the 13vPCV dose is 12 months. Thereafter, a dose of 23vPPV is recommended after an

**Table 3. Recommendations for pneumococcal vaccination of adults with conditions associated with an increased risk of IPD if newly diagnosed (based on the *Australian immunisation handbook*)**

| IPD risk category | Indigenous status | Age at diagnosis | Recommended dose(s) of 13vPCV | Recommended dose(s) of 23vPPV*† |
|---|---|---|---|---|
| Category A conditions† | Non-Indigenous | 18 to 64 years | Single dose† | Initial dose<br>Second dose five to 10 years later<br>Third dose at age 65 years§ |
| | | 65 years and over | Single dose† | Initial dose<br>Second dose five years later<br>Third dose five years after the second dose |
| | Indigenous | 18 to 49 years | Single dose† | Initial dose<br>Second dose five to 10 years later<br>Third dose at age 50 years§ |
| | | 50 years and over | Single dose† | Initial dose<br>Second dose five years later<br>Third dose at age 65 years§ |
| Category B conditions | Non-Indigenous | 18 to 64 years | – | Initial dose<br>Second dose five to 10 years later<br>Third dose at age 65 years§ |
| | | 65 years and over | – | Initial dose<br>Second dose five years later¶ |
| | Indigenous | 18 to 49 years | – | Initial dose<br>Second dose five to 10 years later<br>Third dose at age 50 years§ |
| | | 50 years and over | – | Initial dose<br>Second dose five years later¤ |

Abbreviations: IPD = invasive pneumococcal disease; NIP = National Immunisation Program; 13vPCV = 13-valent pneumococcal conjugate vaccine; 23vPPV = 23-valent pneumococcal polysaccharide vaccine.

* The minimum interval between any two doses of 23vPPV should be five years, and no more than three lifetime adult doses of 23vPPV are recommended (from age 15 years). For adults, prior childhood doses of 23vPPV that may have been given at either 18 to 24 months and/or 4 to 5 years of age should not be counted.

† Haematopoietic stem cell transplant recipients require three doses of 13vPCV post transplantation, followed by 23vPPV, irrespective of previous vaccine doses received.

‡ For patients with a Category A condition, a single dose of 13vPCV is recommended if they have not previously received any 13vPCV dose. This dose should precede the first dose of the recommended 23vPPV vaccine by two months. For those who have previously had a 23vPPV dose, this 13vPCV dose should be given at least 12 months after the most recent dose of 23vPPV.

§ This third dose should be given at the specified age or five years after the second dose, whichever is later.

¶ People whose Category B condition is diagnosed after receiving their NIP recommended dose of 23vPPV at 65 years of age should receive one single revaccination (second) dose at diagnosis or five years after the previous dose, whichever is later.

¤ People whose Category B condition is diagnosed after receiving their NIP recommended dose of 23vPPV at 50 years of age should receive one single revaccination (second) dose at diagnosis or five years after the previous dose, whichever is later.

interval of at least two months and at least five years since the last dose of 23vPPV. The next 23vPPV dose is recommended at about five to 10 years (minimum five years) after the previous 23vPPV dose. For Indigenous adults the third and final dose of 23vPPV is recommended at age 50 years or at least five years after the second dose (whichever is later). For non-Indigenous adults, the third and final dose of 23vPPV is recommended at 65 years of age or at least five years after the second dose (whichever is later).

If adults with category A risk conditions present for their first pneumococcal vaccination at or after 50 years of age, if Indigenous, and 65 years of age, if non-Indigenous, a dose of 13vPCV followed by up to three doses of 23vPPV vaccine are to be given conforming to the intervals described above. For Indigenous adults the third dose is to be given at a minimum of 65 years of age. If the adult has a category B risk factor then two doses of 23vPPV are recommended.

## Conclusion

The pneumococcal vaccination program targeting all infants and older adults and individuals with risk conditions led to large reductions in the severe form of pneumococcal disease overall. However, currently a disproportionate burden of pneumococcal disease is borne by Indigenous adults and people with risk conditions. Although there are vaccination recommendations specifically targeting groups at high risk, it is likely that uptake is suboptimal. The susceptibility of these high risk groups to disease caused by a broader range of pneumococcal serotypes compounds the problem. Recent changes to the infant 13vPCV schedule will lead to longer-lasting protection in vaccinated children and better herd effect, benefitting all. Vaccine providers need to particularly focus on ensuring that all people with risk conditions are identified and given the full course of recommended pneumococcal vaccine doses. **RMT**

## References

A list of references is included in the online version of this article (www.respiratorymedicinetoday.com.au).

COMPETING INTERESTS: None.

# Pneumococcal disease and vaccination recommendations

## The state of play

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### References


1. O'Brien K, Wolfson L, Watt J, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009; 374: 893-902.
2. Wahl B, O'Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health 2018; 6: e744-e757.
3. Black S, Eskola J, Whitney C, Shinefield H. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 5th ed. Philadelphia, PA: Saunders Elsevier; 2008: 531-568.
4. Bjornson GL, Scheifele DW, Halperin SA. Population-based epidemiology of invasive pneumococcal infection in children in nine urban centers in Canada, 1994 through 1998. Pediatr Infect Dis J 2002; 21: 947-950.
5. Jefferson T, Ferroni E, Curtale F, Giorgi Rossi P, Borgia P. Streptococcus pneumoniae in western Europe: serotype distribution and incidence in children less than 2 years old. Lancet Infect Dis 2006; 6: 405-410.
6. McIntyre PB, Gilmour RE, Gilbert GL, Kakakios AM, Mellis CM. Epidemiology of invasive pneumococcal disease in urban New South Wales, 1997-1999. Med J Aust 2000; 173(Suppl): S22-S26.
7. Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: opportunities for prevention in the conjugate vaccine era. JAMA 2001; 285: 1729-1735.
8. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001; 344: 403-409.
9. Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS One 2013; 8: e60273.
10. AlonsoDeVelasco E, Verheul AF, Verhoef J, Snippe H. Streptococcus pneumoniae: virulence factors, pathogenesis, and vaccines. Microbiol Rev 1995; 59: 591-603.
11. Kaplan SI, Barson WJ, Lin PI, et al. Serotype 19A is the most common serotype causing invasive pneumococcal infections in children. Pediatrics 2010; 125: 429-436.
12. Richter SS, Heilmann KP, Dohrn CL, Riahi F, Diekema DJ, Doern GV. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States, 1999-2011. Emerg Infect Dis 2013; 19: 1074-1083.
13. Geno KA, Gilbert GL, Song JY, et al. Pneumococcal capsules and their types: past, present, and future. Clin Microbiol Rev 2015; 28: 871-899.
14. Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. Lancet Infect Dis 2005; 5: 83-93.
15. Kadioglu A, Weiser J, Paton J, Andrew P. The role of Streptococcus pneumoniae virulence factors in host respiratory colonization and disease. Nat Rev Microbiol 2008; 6: 288-301.
16. Simell B, Auranen K, Kayhty H, Goldblatt D, Dagan R, O'Brien KL. The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines 2012; 11: 841-855.
17. Jochems SP, Weiser JN, Malley R, Ferreira DM. The immunological mechanisms that control pneumococcal carriage. PLoS pathogens 2017; 13: e1006665.
18. Rodrigues F, Danon L, Morales-Aza B, et al. Pneumococcal serotypes colonise the nasopharynx in children at different densities. PLoS One 2016; 11: e0163435.
19. Rodríguez MAG, González AV, Gavín MAO, et al. Invasive pneumococcal disease: association between serotype, clinical presentation and lethality. Vaccine 2011; 29: 5740-5746.
20. Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med 2010; 7: e1000348.
21. Klein DL. Pneumococcal conjugate vaccines: review and update. Microb Drug Resist 1995; 1: 49-58.
22. Feldman C, Anderson R. Review: current and new generation pneumococcal vaccines. J Infect 2014; 69: 309-325.
23. Pletz MW, Maus U, Krug N, Welte T, Lode H. Pneumococcal vaccines: mechanism of action, impact on epidemiology and adaption of the species. Int J Antimicrob Agents 2008; 32: 199-206.
24. Hausdorff W, Bryant J, Paradiso P, Siber G. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. Clin Infect Dis 2000; 30: 100-121.
25. Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. Clin Infect Dis 2000; 30: 122-140.
26. Australian Technical Advisory Group on Immunisation. Australian immunisation handbook. Canberra: Australian Government Department of Health; 2018.

27. Pilishvili T, Zell ER, Farley MM, et al. Risk factors for invasive pneumococcal disease in children in the era of conjugate vaccine use. Pediatrics 2010; 126: e9-e17.
28. van Hoek AJ, Andrews N, Waight P, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect 2012; 65: 17-24.
29. Hsu KK, Shea KM, Stevenson AE, Pelton SI. Underlying conditions in children with invasive pneumococcal disease in the conjugate vaccine era. Pediatr Infect Dis J 2011; 30: 251-253.
30. Yildirim I, Shea K, Little B, Silverio A, Pelton S. Vaccination, underlying comorbidities, and risk of invasive pneumococcal disease. Pediatrics 2015; 135: 495-503.
31. Centers for Disease Control and Prevention (CDC). Pneumococcal disease. In: Atkinson W, Wolfe S, Hamborsky J, eds. Epidemiology and prevention of vaccine-preventable diseases. 12th ed. Washington, DC: Public Health Foundation; 2011: p. 233-247.
32. Weinberger D, Harboe Z, Sanders E, et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. Clin Infect Dis 2010; 51: 692-699.
33. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357: 2601-2614.
34. Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection: epidemiologic, clinical, and immunologic perspectives. Ann Intern Med 1992; 117: 314-324.
35. Kumar D, Humar A, Plevneshi A, et al. Invasive pneumococcal disease in solid organ transplant recipients – 10-year prospective population surveillance. Am J Transplant 2007; 7: 1209-1214.
36. Steenhoff AP, Wood SM, Rutstein RM, Wahl A, McGowan KL, Shah SS. Invasive pneumococcal disease among human immunodeficiency virus-infected children, 1989-2006. Pediatr Infect Dis J 2008; 27: 886-891.
37. Tran L, Hebert D, Dipchand A, Fecteau A, Richardson S, Allen U. Invasive pneumococcal disease in pediatric organ transplant recipients: a high-risk population. Pediatr Transplant 2005; 9: 183-186.
38. Pelton SI, Weycker D, Farkouh RA, Strutton DR, Shea KM, Edelsberg J. Risk of pneumococcal disease in children with chronic medical conditions in the era of pneumococcal conjugate vaccine. Clin Infect Dis 2014; 59: 615-623.
39. Picard C, Puel A, Bustamante J, Ku C, Casanova J. Primary immunodeficiencies associated with pneumococcal disease. Curr Opin Allergy Clin Immunol 2003; 3: 451-459.
40. Poehling KA, Light LS, Rhodes M, et al. Sickle cell trait, hemoglobin C trait, and invasive pneumococcal disease. Epidemiology 2010; 21: 340-346.
41. Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis 2014; 1(1): ofu024.
42. Jayasinghe S, Chiu C, Pennington K, Krause V, Hood J, Blyth C. Rising disparity: an increasing burden of invasive pneumococcal disease in Australian Aboriginals (2002-2014). 11th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-11). Melbourne, Australia; 2018.
43. Corvisy R; Enhanced IPD Surveillance Working Group, for the Communicable Diseases Network Australia. Invasive pneumococcal disease surveillance. Invasive pneumococcal disease quarterly report, 1 October to 31 December 2018. Australian Government Department of Health, 2019. Available online at: https://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-ipd-reports.htm (accessed May 2019).
44. NNDSS Annual Report Working Group. Australia's notifiable disease status, 2015: annual report of the National Notifiable Diseases Surveillance System. Communicable Dis Intell (2018) 2019; 43.
45. Jayasinghe S, Menzies R, Chiu C, et al. Long-term impact of a '3 + 0' schedule for 7- and 13-valent pneumococcal conjugate vaccines on invasive pneumococcal disease in Australia, 2002-2014. Clin Infect Dis 2017; 64: 175-183.
46. Earle K, Williams S. Burden of pneumococcal disease in adults aged 65 years and older: an Australian perspective. Pneumonia (Nathan) 2016; 8: 9.
47. Yin JK, Jayasinghe SH, Charles PG, et al. Determining the contribution of Streptococcus pneumoniae to community-acquired pneumonia in Australia. Med J Aust 2017; 207: 396-400.
48. Gidding HF, McCallum L, Fathima P, et al. Effectiveness of a 3 + 0 pneumococcal conjugate vaccine schedule against invasive pneumococcal disease among a birth cohort of 1.4 million children in Australia. Vaccine 2018; 36: 2650-2656.
49. Jayasinghe S, Chiu C, Quinn H, Menzies R, Gilmour R, McIntyre P. Effectiveness of 7- and 13-valent pneumococcal conjugate vaccines in a schedule without a booster dose: a 10-year observational study. Clin Infect Dis 2018; 67: 367-374.
50. Zimmermann P, Perrett KP, Berbers G, Curtis N. Persistence of pneumococcal antibodies after primary immunisation with a polysaccharide-protein conjugate vaccine. Arch Dis Child 2019 Feb 22. pii: archdischild-2018-316254. Epub ahead of print.
51. Menzies RI, Jayasinghe SH, Krause VL, Chiu CK, McIntyre PB. Impact of pneumococcal polysaccharide vaccine in people aged 65 years or older. Med J Aust 2014; 200: 112-115.