4.13 PNEUMOCOCCAL DISEASE

4.13.1 Bacteriology

*Streptococcus pneumoniae* (pneumococcus) is a Gram-positive coccus. The polysaccharide capsule is the most important virulence factor of pneumococci. Over 90 capsular antigenic types (serotypes) have been recognised, each of which elicits type-specific immunity in the host. In a large majority of hosts, pneumococci are carried with no apparent symptoms. Different pneumococcal serotypes vary in their propensity to cause nasopharyngeal colonisation or disease. Worldwide, only a limited number of serotypes are responsible for most cases of invasive pneumococcal disease (IPD) but the predominant serotypes vary by age group and geographic area. Antibiotic resistance in pneumococci is an increasing challenge; in 2006, 11% of Australian IPD isolates were non-susceptible to penicillin and 3% were non-susceptible to ceftriaxone/cefotaxime.

4.13.2 Clinical features

Person-to-person transmission of *S. pneumoniae* occurs via contact with respiratory droplets of colonised persons. Almost all pneumococcal disease probably begins with the establishment of nasopharyngeal colonisation. From the nasopharynx, pneumococci may spread locally into adjacent sites to cause sinusitis, otitis media or pneumonia. Pneumococci may enter the bloodstream, and also localise in the meninges, causing meningitis, or at other sites including bones, joints and soft tissues. For disease surveillance purposes, detection of *S. pneumoniae* in a normally sterile site, such as blood, cerebrospinal fluid or pleural fluid, by culture or nucleic acid testing, is classified as IPD. The major clinical categories of IPD are meningitis, bacteraemic pneumonia, and bacteraemia without focus. In adults, pneumonia with bacteraemia is the most common manifestation of IPD. Although more difficult to measure for non-bacteraemic cases, it is estimated that pneumococci account for over one-third of all community-acquired pneumonia and up to half of hospitalised pneumonia in adults. In children, the most common manifestation is bacteraemia without focus, accounting for approximately 70% of IPD, followed by pneumonia with bacteraemia. Meningitis, although least common, is the most severe category of IPD and has an estimated case-fatality rate of about 30%. Acute otitis media (AOM) is the most common non-invasive manifestation of pneumococcal disease in children. *S. pneumoniae* is detected in 28 to 55% of middle ear aspirates from children with AOM.

Immunocompromised persons who are unable to mount an adequate immune response to pneumococcal capsular antigens, including those with asplenia, have the highest risk of IPD. Household crowding, exposure to cigarette smoke, childcare attendance, excessive alcohol consumption and certain non-immunocompromising chronic medical conditions are also associated with greater risk and/or severity of IPD. Indigenous populations in developed countries, including Aboriginal and Torres Strait Islander people in Australia, have a disproportionately high burden of IPD.

4.13.3 Epidemiology

The highest incidence of IPD is seen at the extremes of age, in young children and the elderly. In Australia, vaccination with 7-valent pneumococcal conjugate vaccine (7vPCV) was first funded under the NIP from mid-2001, to 5 years of age for Indigenous children living in Central Australia and children with specified predisposing medical conditions, and to 2 years of age for non-Indigenous children living in Central Australia and Indigenous children in the rest of the country. One dose of the 23-valent pneumococcal polysaccharide vaccine (23vPPV) at 18–24 months of age, as a booster following a primary 7vPCV schedule, was also funded for Indigenous children without predisposing medical conditions living in jurisdictions with the highest incidence of IPD (the Northern Territory, Queensland, South Australia and Western Australia). From January 2005, NIP-funded 7vPCV was extended to all infants nationally, together with catch-up vaccination for all...
children aged <2 years. High vaccination uptake of over 90% has been maintained since the inception of universal infant pneumococcal vaccination.

The introduction of 7vPCV led to a dramatic reduction in the overall incidence of IPD in Australia, which was greatest in the primary target group of children <2 years of age and for IPD caused by the seven vaccine serotypes. Among non-Indigenous children <2 years of age, the overall notification rate of IPD declined by 75%, from 78 per 100 000 in the pre-vaccination period (2002–2004) to 19.5 per 100 000 in the post-vaccination period (2007); IPD due to 7vPCV serotypes decreased by 97%, from 60.9 to 2.1 per 100 000, respectively. There was also a marked reduction in pneumonia hospitalisations, presumed to be attributable to 7vPCV vaccination, in children <2 and 2–4 years of age (of 38% and 28%, respectively). 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 >5 years of age. Although 7vPCV use resulted in a marked reduction in rates of IPD due to vaccine serotypes, IPD among Indigenous children remains disproportionately higher than in non-Indigenous children, due to significantly higher rates of IPD caused by non-7vPCV serotypes. Serotype distribution of pneumococcal disease is more diverse in adults than in children, and more diverse in Aboriginal and Torres Strait Islanders than in other Australians. Prior to universal infant vaccination, 85% of IPD in children aged <2 years was caused by the seven vaccine serotypes; however, the proportion differed substantially between Indigenous children (46%) and non-Indigenous children (88%). Since the implementation of the universal 7vPCV program, increased rates of IPD caused by certain serotypes not contained in 7vPCV (replacement disease) have been observed in Australia and several other countries. This is particularly so among non-Indigenous children aged <2 years, in whom 44% of IPD in 2007 was due to serotype 19A. In 2009 and 2010, two extended-valency pneumococcal conjugate vaccines (the 10-valent [10vPCV] and the 13-valent [13vPCV], respectively) became available in Australia. In the Northern Territory, 10vPCV replaced 7vPCV from October 2009. In other jurisdictions, 13vPCV (which includes serotype 19A) replaced 7vPCV under the NIP for infants in July 2011, and in the Northern Territory replaced 10vPCV from September 2011.

Vaccination using 23vPPV was introduced in 1999 for all Indigenous adults aged ≥50 years and younger Indigenous adults with risk factors. Since January 2005, 23vPPV has also been funded under the NIP for non-Indigenous adults aged ≥65 years. Persons aged ≤65 years with a condition(s) associated with an increased risk of IPD can access 23vPPV through the Pharmaceutical Benefits Scheme. Most IPD isolates in adults belong to serotypes contained in 23vPPV. In non-Indigenous adults, the prevalence of risk factors among those with IPD increases with age. In contrast, among Indigenous adults, there is a high prevalence of risk factors in IPD cases of all ages. Overall, among adults aged ≥65 years, the incidence of IPD was 29% lower in 2006–2007 than in 2002–2004. This was mostly due to a 53% decrease in the incidence of serotypes included in 7vPCV, despite increases in IPD caused by serotypes both included in (46%) and not included in (57%) 23vPPV.

The impact of 23vPPV on rates of IPD in Indigenous adults has varied in different geographical areas and, at a national level, disparities remain in disease rates between Indigenous and non-Indigenous adults. As is the case for influenza and pneumonia, rates of IPD are highest in older Indigenous adults (refer to 3.1 Vaccination for Aboriginal and Torres Strait Islander people).

4.13.4 Vaccines

There are two different types of pneumococcal vaccines – pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPV). Among the pneumococcal conjugate vaccines, formulations vary in the number of pneumococcal serotypes included and the conjugating proteins used. Pneumococcal conjugate vaccines are immunogenic in young infants and can induce an
immune memory response. In contrast, 23vPPV is poorly immunogenic for most serotypes in children aged <2 years and does not induce immune memory; however, 23vPPV contains more serotypes.

**Pneumococcal conjugate vaccines**

- **Synflorix** – GlaxoSmithKline Australia Pty Ltd (10-valent pneumococcal conjugate vaccine; 10vPCV). Each 0.5 mL monodose vial or pre-filled syringe contains 1 µg of pneumococcal capsular polysaccharide of serotypes 1, 5, 6B, 7F, 9V, 14, 23F and 3 µg of serotype 4, conjugated to a total of 9–16 µg of non-typeable *H. influenzae* protein D, 3 µg of serotype 18C conjugated to 5–10 µg of tetanus toxoid carrier protein, and 3 µg of serotype 19F conjugated to 3–6 µg of diphtheria toxoid carrier protein, adsorbed onto 0.5 mg aluminium as aluminium phosphate.

- **Prevenar 13** – Pfizer Australia Pty Ltd (13-valent pneumococcal conjugate vaccine; 13vPCV). Each 0.5 mL monodose pre-filled syringe contains 2.2 µg each of pneumococcal capsular polysaccharide of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F and 4.4 µg of serotype 6B, conjugated to non-toxic *Corynebacterium diphtheriae* CRM197 protein, adsorbed onto 0.565 mg aluminium phosphate; succinic acid; polysorbate 80.

### 7-valent pneumococcal conjugate vaccine (7vPCV)

A 7vPCV with the mutant non-toxic diphtheria CRM197 protein as the conjugating protein (Prevenar) became available in Australia in 2001. Efficacy data on the 7vPCV from a pivotal trial in the United States found greater than 95% protective efficacy against IPD caused by the serotypes contained in the vaccine.²² A Cochrane review of clinical trials estimated an efficacy of 80% against vaccine-type IPD for PCVs (most, but not all, of which used CRM197 as the conjugating protein) in children <2 years of age.²³ Based on the included studies, the effectiveness against IPD of any serotype among these children was 58%,²³ noting that the proportion of IPD due to vaccine serotypes varies among different populations. Effectiveness against X-ray confirmed pneumonia (using World Health Organization [WHO] criteria) was lower, at 27%.

A 3-dose primary vaccination schedule for 7vPCV consisting of doses at 2, 4 and 6 months of age without a booster in the 2nd year of life was recommended in Australia from 2001 (except for persons at increased risk of IPD). This recommendation was initially based on data suggesting similar efficacy against type-specific IPD with either 3 or 4 doses.²⁵ Subsequent Australian data have shown similar degrees of direct and indirect reduction in IPD and pneumonia hospitalisations as those seen in countries with alternate schedules.²⁴-²⁷

7vPCV is no longer available, having been replaced in 2011 by 13vPCV made by the same manufacturer.

### 10-valent pneumococcal conjugate vaccine (10vPCV)

10vPCV has been registered for use in Australia since 2009 and is included under the NIP. The protein D of non-typeable *H. influenzae* (NTHi) is one of the main conjugating proteins in this vaccine. This vaccine was used for all children aged <2 years in the Northern Territory from October 2009 to September 2011, after which 13vPCV has been used. (Refer also to 3.1 *Vaccination for Aboriginal and Torres Strait Islander people*.)

Clinical trials on 10vPCV with efficacy outcomes are not yet published; registration of 10vPCV in Australia was based on immunogenicity data.²⁸-³² A clinical study of a prototype 11-valent pneumococcal vaccine (containing the 10 serotypes in 10vPCV plus serotype 3), also conjugated to NTHi protein D, showed significant protective efficacy of approximately 58% against acute otitis media caused by vaccine serotypes (as well as protective efficacy of approximately 36% against AOM caused by *H. influenzae*).³³ 10vPCV has been shown to produce robust antibody responses to
all 10 serotypes contained in the vaccine after a 4th (booster) dose in the 2nd year of life, but lesser antibody responses after 3 primary doses given in infancy.\textsuperscript{31,32} Although 10vPCV does not contain specific antigens for serotypes 6A or 19A, there were also measurable levels of antibody against these cross-reacting serotypes in functional antibody assays.\textsuperscript{31,32}

13-valent pneumococcal conjugate vaccine (13vPCV)

13vPCV has been registered in Australia since 2010, and used in the NIP since July 2011. A single supplementary dose of 13vPCV for children aged 12–35 months who completed primary vaccination with 7vPCV was available under the NIP for 12 months from October 2011.

Registration of 13vPCV was based on immunogenicity studies showing non-inferiority for the 7vPCV serotypes and comparable antibody response to the additional serotypes.\textsuperscript{34-39} This includes serotype 19A, for which high levels of functional antibody have been demonstrated. Early data from 13vPCV use in England and Wales in 2011 have shown an impact against IPD caused by the additional serotypes contained in the vaccine.\textsuperscript{40}

Based on the substantial impact of the 7vPCV program on serotype-specific IPD, the similar composition of 13vPCV and 7vPCV, and immunogenicity data, a 2, 4, 6 month schedule without a booster is also recommended for 13vPCV (except for those with a medical condition(s) associated with an increased risk of IPD or Indigenous children living in high-incidence regions). The comparative effectiveness of this schedule will continue to be monitored.

13vPCV has also been registered since October 2011 for use in adults aged \(\geq 50\) years, based on immunogenicity data showing equivalent or better antibody responses than those provided by 23vPPV for the shared vaccine serotypes. Since May 2014, the registered age of use for 13vPCV has been extended to include any person from 6 weeks of age. There are currently no data on clinical outcomes for 13vPCV, but a study examining its efficacy against pneumonia in adults is underway.\textsuperscript{41} In the absence of evidence of superior effectiveness against IPD or non-IPD pneumonia, the relative benefit of 13vPCV over 23vPPV for adults is uncertain, since the serotype coverage of 13vPCV is more limited. It is also uncertain whether the level of reduction in IPD due to the additional serotypes contained in 13vPCV among adults (herd immunity effect) will be similar to that seen following widespread use of 7vPCV in children.

Pneumococcal polysaccharide vaccine

- \textit{Pneumovax 23} – bioCSL Pty Ltd/Merck Sharp & Dohme (Australia) Pty Ltd (23-valent pneumococcal polysaccharide vaccine; 23vPPV). Each 0.5 mL monodose vial contains 25 \(\mu\)g each of pneumococcal capsular polysaccharide of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F; 0.25% phenol.

23vPPV contains polysaccharides derived from the 23 most frequent or most virulent capsular types of \textit{S. pneumoniae} isolated from sterile fluids in the United States in the 1970s/early 1980s, with worldwide serotype distribution and potential cross-reactive serotypes also taken into consideration.\textsuperscript{42} These serotypes are responsible for most IPD cases in adults in Australia. 23vPPV induces significant immune responses in immunocompetent adults, including the elderly, with no substantial differences in immune response between older and younger subjects, but poor responses in the immunocompromised.\textsuperscript{43} In children <2 years of age, the antibody response is limited to a small number of serotypes without previous 7vPCV vaccination.\textsuperscript{44}

A Cochrane review published in 2008 found an estimated overall protective efficacy of 74\% for pneumococcal polysaccharide vaccines against IPD, based on randomised controlled trials (RCTs). The review also found a vaccine effectiveness of 52\% against IPD in older adults or adults with conditions associated with an increased risk of IPD, based on observational studies, but lower efficacy against all-cause pneumonia, based on RCTs (29\%).\textsuperscript{45} Evidence from more recent
controlled trials and observational studies using 23vPPV in the elderly population is similar. Data from England and Wales reported 23vPPV vaccine effectiveness of 48% against IPD within 2 years of vaccination for adults aged ≥65 years, but effectiveness waned and became insignificant beyond 5 years. In the subset of adults aged 65–74 years with no risk factors, 23vPPV effectiveness was higher (65% within 2 years) and was maintained for longer. In Victoria, 23vPPV vaccine effectiveness was estimated to be 71% for adults aged >65 years.

There are no studies on the effectiveness of revaccination with 23vPPV for disease endpoints, although significant and sustained antibody responses after revaccination are seen in adults, including the elderly. Evidence of lesser antibody responses to 2nd or subsequent doses of 23vPPV in adults is variable, and, even if present, its correlation with clinical effectiveness is unknown.

4.13.5 Transport, storage and handling

Transport according to National vaccine storage guidelines: Strive for 5. Store at +2°C to +8°C. Do not freeze.

10vPCV should be protected from light.

4.13.6 Dosage and administration

The dose of pneumococcal conjugate vaccines (10vPCV, 13vPCV) is 0.5 mL, to be given by IM injection, in the opposite limb to other injectable vaccines if possible.

The dose of pneumococcal polysaccharide vaccine (23vPPV) is 0.5 mL, to be given by either IM or SC injection, in the opposite limb to other injectable vaccines, if possible. The IM route is preferred, as a 3-fold greater rate of injection site reactions is found following administration of 23vPPV by the SC route. However, a vaccine dose administered subcutaneously does not need to be repeated.

10vPCV (Synflorix) is registered for use in infants and children aged 6 weeks up to 5 years.
13vPCV (Prevenar 13) is registered for use in children aged ≥6 weeks and in adults.
23vPPV (Pneumovax 23) is registered for use in children aged ≥2 years and in adults.

Co-administration with other vaccines

10vPCV may be concurrently administered with other vaccines routinely used in the infant schedule.

13vPCV may be concurrently administered with other vaccines in the infant schedule, including inactivated trivalent influenza vaccine. However, parents/carers of infants or children who are recommended to receive both influenza vaccine and 13vPCV should be advised of a possible small increased risk of fever following concomitant administration of these vaccines (refer to 4.13.10 Precautions below).

Pneumococcal polysaccharide vaccine can be concurrently administered with Zostavax using separate syringes and injection sites. (Refer also to 4.24 Zoster.)

Interchangeability of 10vPCV and 13vPCV

There are no available specific data on the interchangeability of 10vPCV and 13vPCV. Although completion of a primary course of pneumococcal conjugate vaccine with the same formulation is generally preferred, if vaccination with 10vPCV is commenced (e.g. in children born overseas), completion of the course with 13vPCV is acceptable.

4.13.7 Recommendations

Children aged <2 years

All children are recommended to receive a complete course of pneumococcal conjugate vaccination. The total number of doses recommended depends on the vaccine type used, on whether
the child has a medical condition(s) associated with an increased risk of IPD (refer to List 4.13.1), on the child’s Indigenous status and on whether the child is living in a jurisdiction with a high incidence of IPD (the Northern Territory, Queensland, South Australia or Western Australia).

If 10vPCV is used for primary vaccination in infants, a total of 4 doses are recommended, regardless of the child’s Indigenous status or place of residence, or whether the child has any underlying medical condition(s) associated with an increased risk of IPD. The recommended schedule is 3 primary doses, at 2, 4 and 6 months of age, followed by 1 booster dose at between 12 and 18 months of age (at least 6 months after the 3rd primary dose) (a ‘3+1’ schedule).

If 13vPCV is used for primary vaccination in infants, the total recommended schedule for most children is 3 primary doses, at 2, 4 and 6 months of age (a ‘3+0’ schedule); however, additional doses are required for some children, as summarised in Table 4.13.1. A booster dose of 13vPCV is recommended for young Indigenous children living in the four jurisdictions specified above. In these children, the risk of IPD is comparable to the risk of IPD in children with certain medical conditions (refer to List 4.13.1).

The 1st dose of pneumococcal conjugate vaccine can be given as early as 6 weeks of age. If the 1st dose is given at 6 weeks of age, the next scheduled doses should still be given at 4 months and 6 months of age.

**Table 4.13.1: Recommendations for pneumococcal vaccination for children aged <5 years**

<table>
<thead>
<tr>
<th>Recommended age for pneumococcal vaccine doses</th>
<th>2 months*</th>
<th>4 months</th>
<th>6 months</th>
<th>12 months</th>
<th>12–18 months</th>
<th>4–5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children without any medical conditions associated with an increased risk of invasive pneumococcal disease (IPD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>10vPCV</td>
<td>10vPCV</td>
<td>10vPCV</td>
<td>–</td>
<td>10vPCV</td>
<td>–</td>
</tr>
<tr>
<td><strong>If 10vPCV is used for the primary course:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>10vPCV</td>
<td>10vPCV</td>
<td>10vPCV</td>
<td>–</td>
<td>10vPCV</td>
<td>–</td>
</tr>
<tr>
<td><strong>If 13vPCV is used for the primary course:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Indigenous children and Indigenous children in ACT, NSW, Tas or Vic</td>
<td>13vPCV</td>
<td>13vPCV</td>
<td>13vPCV</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Indigenous children in NT, Qld, SA or WA</td>
<td>13vPCV</td>
<td>13vPCV</td>
<td>13vPCV</td>
<td>–</td>
<td>13vPCV†</td>
<td>–</td>
</tr>
<tr>
<td><strong>Children with a medical condition(s) associated with an increased risk of IPD‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>13vPCV</td>
<td>13vPCV</td>
<td>13vPCV</td>
<td>13vPCV‡§</td>
<td>–</td>
<td>23vPPV</td>
</tr>
</tbody>
</table>

* The 1st dose can be given as early as 6 weeks of age; the next scheduled doses should still be given at 4 months and 6 months of age.
† Only one booster dose of 13vPCV is required in the 2nd year of life, even if a child is both Indigenous, living in the Northern Territory, Queensland, South Australia or Western Australia, and also has one or more medical conditions associated with an increased risk of IPD.
‡ Refer to List 4.13.1, Categories A and B, for medical conditions associated with an increased risk of IPD in children.
§ The booster dose is due at 12 months of age, or later, depending on when the medical condition is diagnosed; refer also to 2.1.5 Catch-up, Table 2.1.11 Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years.
For children aged 7–23 months who have not completed a full course of pneumococcal conjugate vaccines, the timing and number of further doses for ‘catch-up’ vaccination depends on age and previous doses administered. For recommendations, refer to the following three tables in 2.1.5 Catch-up:

- Table 2.1.9 Catch-up schedule for 13vPCV (Prevenar 13) for non-Indigenous children, and Indigenous children residing in the Australian Capital Territory, New South Wales, Tasmania and Victoria, who do not have any medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD), aged <5 years

- Table 2.1.10 Catch-up schedule for 13vPCV (Prevenar 13) for Indigenous children residing in the Northern Territory, Queensland, South Australia or Western Australia ONLY, who do not have any medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD), aged <5 years

- Table 2.1.11 Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years (for children aged 7–23 months with a medical condition(s) associated with an increased risk of IPD who have not completed a full course of pneumococcal conjugate vaccines).

If catch-up is required in a child who has commenced vaccination with 10vPCV, subsequent doses should be with 13vPCV. If 13vPCV is not available, 10vPCV may be used, and catch-up vaccination should be provided according to the rules in Table 2.1.10.

List 4.13.1: Conditions associated with an increased risk of invasive pneumococcal disease (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 ≥2 mg/kg per day of prednisolone or equivalent for more than 1 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 (HSCT)‡
  - HIV infection (including AIDS)
  - chronic renal failure, or relapsing or persistent nephrotic syndrome
- proven or presumptive cerebrospinal fluid (CSF) 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 <28 weeks gestation§
- tobacco smoking¶

* Refer also to 3.3.3 Vaccination of immunocompromised persons for more recommendations for immunocompromised persons, including more specific revaccination recommendations for haematopoietic stem cell transplant recipients.
† Recommendations for pneumococcal vaccination differ for those aged >5 years (but not for those aged <5 years) between categories in this table, i.e. depending on whether the person is in ‘Category A: Conditions associated with the highest increased risk of IPD’ or ‘Category B: Conditions associated with an increased risk of IPD’. Refer also to relevant sections below.
‡ HSCT recipients require 3 doses of 13vPCV post transplantation, followed by 23vPPV, irrespective of previous vaccine doses received (refer to Table 3.3.3 Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history).
§ All infants born at <28 weeks gestation should receive vaccines recommended for those up to age 5 years with a medical condition(s) associated with an increased risk of IPD, according to Table 4.13.1. Thereafter, they only require further pneumococcal vaccine doses if they have chronic lung disease, and/or other chronic medical conditions as specified above.
¶ Tobacco smoking is not a medical condition, but is associated with an increased risk of IPD.

Children aged 2–5 years

Children aged 2–5 years who do not have a medical condition associated with an increased risk of IPD are not routinely recommended to receive further pneumococcal vaccine doses. If they have not previously received any PCV doses, or had only 1 dose of a pneumococcal conjugate vaccine before 12 months of age, a single dose of 13vPCV is recommended (refer to 2.1.5 Catch-up, Table 2.1.9 Catch-up schedule for 13vPCV (Prevenar 13) for non-Indigenous children, and Indigenous children residing in the Australian Capital Territory, New South Wales, Tasmania and Victoria, who do not have any medical condition(s) associated with an increased risk of IPD, aged <5 years and Table 2.1.10 Catch-up schedule for 13vPCV (Prevenar 13) for Indigenous children residing in the Northern Territory, Queensland, South Australia or Western Australia ONLY, who do not have any medical condition(s) associated with an increased risk of IPD, aged <5 years).

Children who have a medical condition(s) associated with an increased risk of IPD, as described in List 4.13.1 (Categories A and B), should receive a dose of 23vPPV at 4–5 years of age. Table 4.13.2 indicates which vaccines are recommended, depending on prior vaccination history. The need for additional doses of pneumococcal vaccine is based on the continuing higher susceptibility of these children to IPD at older ages, and extrapolation from data showing that boosting of immune responses to certain 7vPCV serotypes occurs when a dose of 23vPPV follows a prior 7vPCV dose(s). Recommendations for children with a medical condition(s) associated with an increased risk of IPD (Categories A and B) are the same regardless of Indigenous status or jurisdiction of residence.
A minimum interval of 2 months between the last dose of 13vPCV and 23PPV is recommended, based on a small number of studies among children of different ages with underlying conditions, which have shown that 23vPPV is immunogenic if given approximately 2 months after a 7vPCV dose.\textsuperscript{70-73}

Table 4.13.2: Recommendations for pneumococcal vaccination for children aged 2–5 years with a medical condition(s) associated with an increased risk of invasive pneumococcal disease (IPD) (\textit{refer to List 4.13.1, Categories A and B})\textsuperscript{*}

<table>
<thead>
<tr>
<th>Vaccination history†</th>
<th>Recommendations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary course of any pneumococcal conjugate vaccine</strong></td>
<td><strong>Supplementary/booster dose of 13vPCV (at age ≥12 months)</strong></td>
<td><strong>Number of further 13vPCV dose(s) required for children aged 2–5 years</strong></td>
</tr>
<tr>
<td>Completed</td>
<td>Received</td>
<td>0</td>
</tr>
<tr>
<td>Completed</td>
<td>Not received</td>
<td>1</td>
</tr>
<tr>
<td>Not completed</td>
<td>Not received</td>
<td>2$</td>
</tr>
</tbody>
</table>

* HSCT recipients require 3 doses of 13vPCV post transplantation, followed by 23vPPV, irrespective of previous vaccine doses received (\textit{refer to Table 3.3.3 Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history}).

† \textit{Refer also to 2.1.5 Catch-up, Table 2.1.11 Catch-up schedule for 13vPCV (Prevenar 13) and 23vPPV (Pneumovax 23) in children with a medical condition(s) associated with an increased risk of IPD, presenting at age <2 years. Note: this table primarily refers to 13vPCV, but could apply to use of 10vPCV if the former was not available.}

‡ At least 2 months after the last dose of PCV, whichever is later.

§ Minimum interval between the 2 doses should be 2 months.

**Children aged >5 years to <18 years**

Pneumococcal vaccine is not recommended for children in this age group who do not have a medical condition(s) associated with an increased risk of IPD (\textit{refer to List 4.13.1}). The exception is in older Indigenous children (aged >15 years) who have an increased risk of IPD, especially in the Northern Territory, where a dose of 23vPPV is provided to all Indigenous adolescents at approximately 15 years of age, based on the very high prevalence of conditions associated with an increased risk of IPD and incidence of IPD in this sub-population (\textit{refer to ‘Adults aged ≥18 years’ below and 3.1 Vaccination for Aboriginal and Torres Strait Islander people}).

For children with a medical condition(s) associated with an increased risk of IPD, further pneumococcal vaccine doses are recommended, as discussed below, depending on the child’s level of risk.

**Those with the highest increased risk of IPD (List 4.13.1, Category A)**

Children aged >5 to <18 years with a \textit{pre-existing} chronic medical condition(s) associated with the highest increased risk of IPD (List 4.13.1, Category A), who were previously vaccinated according to the recommendations in Table 4.13.2, should receive another 23vPPV dose 5 years after their 1st 23vPPV dose, at approximately 10 years of age. Their next 23vPPV dose should be approximately 10 years later, at age 18–20 years. (\textit{Refer also to ‘Adults with a condition(s) associated with an increased risk of IPD’ below.}) If a child in this category has never received a dose of 13vPCV previously, 1 dose of 13vPCV should be administered, with the exception of HSCT recipients who should receive 3 doses of 13vPCV (\textit{refer to Table 3.3.3 Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history}). This should then be followed by 23vPPV approximately 2 months later (if no prior 23vPPV dose has been received), or a minimum of 5 years after a prior 23vPPV dose (\textit{refer above}). The minimum interval between a previous 23vPPV dose and the single 13vPCV dose, if required, is 12 months.
Children in this age group with a newly identified medical condition(s) associated with the highest increased risk of IPD (List 4.13.1, Category A) are recommended to receive a dose of 23vPPV at diagnosis. If they have not previously received a dose of 13vPCV, they should receive one 13vPCV dose at diagnosis, followed by their 1st 23vPPV dose a minimum of 2 months later. A further dose of 23vPPV is recommended 5 years after the 1st 23vPPV dose (minimum 2 months after 13vPCV). Their next 23vPPV dose should be approximately 10 years later, or at age 18–20 years, whichever is later (refer to ‘Adults with a condition(s) associated with an increased risk of IPD’ below).

Those with an increased risk of IPD (List 4.13.1, Category B)

Children aged >5 to <18 years with a pre-existing medical condition(s) associated with an increased risk of IPD (List 4.13.1, Category B) who received a dose of 23vPPV at 4–5 years of age should receive a 2nd dose of 23vPPV approximately 10 years later, at 15–18 years of age. That dose should be counted as their 1st adult 23vPPV dose.

For children in this age group with a newly identified medical condition(s) associated with an increased risk of IPD (List 4.13.1, Category B), a single dose of 23vPPV is recommended at the time of diagnosis. In the rare situation where a previous dose of 23vPPV has been given (e.g. in Indigenous children in some jurisdictions), this dose should be given at least 5 years after the previous 23vPPV dose. The next 23vPPV dose should be given approximately 5–10 years after the 1st 23vPPV dose and counted as their 1st adult 23vPPV dose (refer to ‘Adults with a condition(s) associated with an increased risk of IPD’ below).

Adults aged ≥18 years

The recommendations for use of 23vPPV in adults who do not have a condition(s) associated with an increased risk of IPD are summarised in Table 4.13.3. Recommendations for the use of 13vPCV and/or 23vPPV in adults with a condition(s) associated with an increased risk of IPD (List 4.13.1, Category A or B) are described in the text below.

The number of doses recommended depends on age, Indigenous status and the presence of a condition(s) associated with an increased risk of IPD. Up to 3 doses (i.e. 2 revaccinations) of 23vPPV in adulthood are recommended, depending on these factors. This is based on limited data on adverse events and effectiveness, as well as uncertainty regarding the clinical significance of blunting of antibody response (immune hyporesponsiveness) following revaccination with 23vPPV, especially with multiple revaccinations.

For adults, prior childhood doses of 23vPPV that may have been given at either 18–24 months and/or 4–5 years of age should not be counted; that is, they are not relevant to the recommendations given in Table 4.13.3. In the Northern Territory, a dose of 23vPPV is provided to all Indigenous adolescents at approximately 15 years of age, based on the very high prevalence of conditions associated with an increased risk of IPD and incidence of IPD in this population; this dose should be considered as a dose received in adulthood for the purpose of limiting the total lifetime number of 23vPPV doses to 3.

Although 13vPCV is registered for use in adults, there is currently insufficient evidence to routinely recommend its use in preference to 23vPPV at the individual or population level for persons aged ≥18 years who do not have a condition(s) associated with an increased risk of IPD (refer to 4.13.4 Vaccines above). Updated recommendations on the use of 13vPCV in adults will be made when more data are available (refer to Immunise Australia website www.immunise.health.gov.au).

Non-Indigenous adults

A single dose of 23vPPV is recommended for adults at 65 years of age. For those aged >65 years who did not receive a dose at 65 years of age, a single catch-up dose of 23vPPV should be offered as soon as possible. Routine revaccination with 23vPPV for non-Indigenous adults without a condition(s) associated with an increased risk of IPD is not recommended (refer to Table 4.13.3).
Aboriginal and Torres Strait Islander (Indigenous) adults

A 1st dose of 23vPPV is recommended for all Indigenous adults reaching the age of 50 years (Table 4.13.3). This is based on the increased risk of IPD in Indigenous adults compared with non-Indigenous adults, and the high prevalence of conditions associated with an increased risk of IPD (including tobacco smoking) in Indigenous adults after 50 years of age, compared with younger ages. A 2nd dose of 23vPPV is recommended 5 years after the 1st dose. For those aged ≥50 years who have never received a dose of 23vPPV, a 1st dose should be offered as soon as possible, with a 2nd dose recommended 5 years after the 1st dose.

Indigenous adults aged <50 years with a condition(s) associated with an increased risk of IPD (List 4.13.1), should be vaccinated according to the recommendation for ‘Adults with a condition(s) associated with an increased risk of IPD’ below.

Table 4.13.3: Recommendations for pneumococcal vaccination using 23vPPV for adults who do not have a condition(s) associated with an increased risk of invasive pneumococcal disease (IPD)*

<table>
<thead>
<tr>
<th>Non-Indigenous adults</th>
<th>1st dose of 23vPPV</th>
<th>2nd dose of 23vPPV (1st revaccination)</th>
<th>3rd dose of 23vPPV (2nd revaccination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to &lt;65 years</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>≥65 years</td>
<td>Give now</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indigenous adults</th>
<th>1st dose of 23vPPV</th>
<th>2nd dose of 23vPPV (1st revaccination)</th>
<th>3rd dose of 23vPPV (2nd revaccination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 to &lt;50 years</td>
<td>Not recommended†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 years</td>
<td>Give now‡</td>
<td>5 years after 1st dose‡</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

* Refer to List 4.13.1 for conditions associated with an increased risk of IPD. Recommendations for those who have a condition(s) that places them at an increased risk of IPD are listed in the text below.
† In the Northern Territory, a dose of 23vPPV is provided to all Indigenous adolescents at approximately 15 years of age, based on the very high prevalence of conditions associated with an increased risk of IPD and incidence of IPD in this sub-population. This dose should be considered a dose received in adulthood for the purpose of limiting the total lifetime number of 23vPPV doses to 3.
‡ The minimum interval between any 2 doses of 23vPPV should be 5 years, and no more than 3 lifetime adult doses of 23vPPV are recommended.

Adults with a condition(s) associated with an increased risk of IPD (List 4.13.1)

Use of 13vPCV

Adults with a medical condition(s) associated with the highest increased risk of IPD in List 4.13.1, Category A (immunocompromising conditions, functional or anatomical asplenia, CSF leak, cochlear implant), are recommended to receive a single dose of 13vPCV, with the exception of HSCT recipients who should receive 3 doses of 13vPCV (refer to Table 3.3.3 Recommendations for revaccination following HSCT in children and adults, irrespective of previous immunisation history). For those with a newly diagnosed (or newly recognised for the purposes of requiring vaccination) condition, the dose of 13vPCV should be given at the time of diagnosis and followed by 23vPPV doses. The 1st 23vPPV dose should be given a minimum of 2 months after 13vPCV (refer to ‘Use of 23vPPV’ below). For adults with a pre-existing condition listed in Category A, and who have received 1 or more prior doses of 23vPPV, the dose of 13vPCV should be given at least 12 months after the most recent dose of 23vPPV. (Refer also to ‘Persons with functional or anatomical asplenia’ in 3.3.3 Vaccination of immunocompromised persons.)
Although data on clinical benefit from 13vPCV in persons at increased risk of IPD are not yet available, providing a dose of 13vPCV to adults at the highest increased risk of IPD (Category A) is likely to be beneficial based on extrapolations from data on 7vPCV. Adults who have a condition listed in Category B in List 4.13.1 are not recommended to receive 13vPCV.

**Use of 23vPPV**

All adults with a condition(s) associated with an increased risk of IPD (List 4.13.1, Categories A and B) are recommended to receive additional doses of 23vPPV (compared with those who do not have an increased risk).

In adults with a pre-existing condition (List 4.13.1, Categories A and B) the 1st adult dose of 23vPPV is recommended at approximately 18 years of age (refer to ‘Children aged >5 years to <18 years’ above), or a minimum of 5 years after the most recent dose of 23vPPV, and is to be followed by up to 2 additional doses. For those newly diagnosed, or who have never received pneumococcal vaccination, a 1st dose of 23vPPV is recommended at identification of the risk condition if they are in Category B. If the adult has a condition(s) associated with the highest increased risk of IPD (listed in Category A), they should receive a single dose of 13vPCV at time of diagnosis (refer above), followed by a 1st dose of 23vPPV a minimum of 2 months later.

A 2nd dose of 23vPPV is recommended for all at-risk adults in Categories A and B at approximately 5–10 years (minimum of 5 years) after the 1st dose of 23vPPV. A 3rd dose of 23vPPV is recommended at the age of 50 years for Indigenous adults and 65 years for non-Indigenous adults, or a minimum of 5 years after the 2nd dose, whichever is later.

For older adults with a newly diagnosed condition who have already received an age-based 1st dose of 23vPPV at age 65 years (non-Indigenous) or 50 years (Indigenous), a single revaccination dose of 23vPPV is recommended a minimum of 5 years after the previous dose of 23vPPV. For persons with a medical condition(s) associated with the highest increased risk of IPD (Category A), a 3rd dose of 23vPPV is recommended, a minimum of 5 years after the 2nd dose or at age 65 years, whichever is later.

If a younger adult (e.g. an Indigenous adult living in the Northern Territory) has received a dose of 23vPPV before identification of a risk condition in Category B, a 2nd dose of 23vPPV is recommended at diagnosis of the condition, or a minimum of 5 years after the 1st dose, whichever is later. A 3rd dose of 23vPPV is recommended at the age of 50 years for Indigenous adults and 65 years for non-Indigenous adults, or a minimum of 5 years after the 2nd dose, whichever is later.

In general, no more than three 23vPPV doses are recommended during a person’s adult life.

**4.13.8 Pregnancy and breastfeeding**

Pneumococcal vaccines are not routinely recommended for pregnant women.

Women of child-bearing age who have a condition(s) associated with an increased risk of IPD should be vaccinated before a planned pregnancy or as soon as practicable after delivery (refer to 4.13.7 Recommendations above). Although data on the use of 13vPCV and 23vPPV in pregnant or breastfeeding women are limited, administration of these vaccines in pregnancy is unlikely to result in serious adverse effects and may be considered in individuals at the highest increased risk of IPD who were not vaccinated prior to pregnancy but require vaccination prior to delivery.

13vPCV and 23vPPV may be given to breastfeeding women.

Refer to 3.3 Groups with special vaccination requirements, Table 3.3.1 Recommendations for vaccination in pregnancy for more information.
4.13.9 Contraindications
The only absolute contraindications to pneumococcal vaccines are:
- anaphylaxis following a previous dose of any pneumococcal vaccine
- anaphylaxis following any vaccine component.

4.13.10 Precautions

13-valent pneumococcal conjugate vaccine and inactivated influenza vaccines

One study has demonstrated a slightly higher risk of fever and febrile convulsions in children aged 6 months to <5 years (especially those aged 12–24 months) with the concurrent administration of 13vPCV and inactivated trivalent influenza vaccine (compared with giving the vaccines separately).\(^77\) The risk was estimated to be about 18 excess cases per 100,000 doses in children aged 6–59 months, with a peak of 45 per 100,000 doses in those aged 16 months. Given that the reported increase in risk was relatively small, and a more recent study did not demonstrate the same association between febrile seizures and the concurrent administration of these two vaccines,\(^78\) administration of 13vPCV and inactivated influenza vaccine at the same visit is acceptable when both vaccines are indicated. (Refer also to 4.7 Influenza.) However, immunisation service providers should advise parents of the possible risk and provide the option of administering these two vaccines on separate days (with an interval of not less than 3 days).

4.13.11 Adverse events

10-valent pneumococcal conjugate vaccine

The safety profile of 10vPCV is similar to that of 7vPCV,\(^79\) with no clinically relevant difference when co-administered with routine childhood vaccines.\(^80\) In clinical trials, erythema, pain, or swelling of any degree at the injection site each occurred in approximately 30 to 50% of 10vPCV recipients. Erythema of >30 mm occurred in up to about 5% of 10vPCV recipients in the primary course. The frequency of local adverse events was higher after the booster dose. Irritability and drowsiness were reported in about 50% of 10vPCV recipients when co-administered with a DTPa-combination vaccine, but severe reactions occurred in fewer than 5%. When co-administered with DTPa-based combination vaccines, fever with temperature ≥38°C was reported in about 33% of 10vPCV recipients after primary or booster doses. Approximately 2 to 6% of 10vPCV recipients reported rectal temperature >39°C after primary vaccination and 1.5 to 3% after booster vaccination.\(^79\)

13-valent pneumococcal conjugate vaccine

Pooled safety analysis from 13 clinical trials showed that the safety profile of 13vPCV in young children is similar to that of 7vPCV.\(^81,82\) Pain/tenderness and erythema at the injection site occurred in about 50% of all 13vPCV recipients, and induration or swelling in about 33%. Pain interfering with movement occurred in about 8%. Moderate erythema and induration occurred more commonly after the toddler dose than after an infant dose, in about 13% of recipients. About 37% of 13vPCV childhood recipients reported fever, with about 5% reporting fever >39°C.\(^82\) Fever occurred more frequently after the toddler dose than after the primary doses.\(^83\) Other common systemic reactions included irritability, drowsiness/increased sleep and decreased appetite, reported in 70%, 60% and 39% of 13vPCV recipients, respectively.\(^82\) Frequencies of each of these adverse events were comparable to those in 7vPCV recipients.\(^82\)

There are fewer clinical studies of 13vPCV in adults.\(^84-88\) In two clinical studies of 13vPCV in persons aged 60–64 years, local reactions were commonly reported (71% and 82% of participants), with pain the most frequently reported local reaction.\(^84,85\) In both studies, the proportion of participants reporting local reactions following 13vPCV was greater than following 23vPPV which was also assessed (62% and 76%, respectively). The frequency of fever of any grade was low (<2%) after either 13vPCV or 23vPPV. Local reactions were more common following a 2nd dose
of 23vPPV given 1 or 3.5–4 years after a dose of 13vPCV than after a single dose of either 13vPCV or 23vPPV or following a 2nd dose of 13vPCV (independent of which vaccine was used as the initial dose).

Post-marketing surveillance in the United States has suggested the possibility of a higher risk of febrile seizure in children aged 6 months to <5 years, especially those aged 12–23 months, within a day of vaccination among those who received concurrent administration of 13vPCV and inactivated trivalent influenza vaccine (TIV) in 2010–2011, compared with those who received either vaccine alone (refer to 4.13.10 Precautions above).77 In a clinical study assessing co-administration of 13vPCV and TIV in adults 50–59 years of age, local adverse events were more common when TIV was co-administered with 13vPCV compared with when it was administered with placebo (89% and 76%, respectively).87 In a separate study in adults ≥65 years of age, the proportion of participants that reported local reactions following 13vPCV administered with TIV was similar to that when 13vPCV was administered with placebo 1 month following TIV.88 However, systemic reactions (chills, rash and new muscle pain) were reported among a significantly greater number of participants who received 13vPCV and TIV than 13vPCV and placebo. The frequency of fever was low in both study arms (<5%) and there was no significant difference in the prevalence of fever of any grade.

23-valent pneumococcal polysaccharide vaccine

The proportion of vaccine recipients reporting local and systemic reactions after a primary or a repeat dose of pneumococcal polysaccharide vaccines varies among different study populations, and possibly with age.55,57,89 About 50% or more of 23vPPV recipients will experience some soreness after the 1st dose, and swelling and redness are also very common, occurring in approximately 20% of recipients. Moderate or severe local adverse events that limit arm movement are also quite common, occurring in up to 5% of 1st dose recipients. Systemic reactions like myalgia, fatigue and chills are also very common. Fever ≥37.5°C occurs in up to 10% of 23vPPV recipients, but high fever is uncommon.55,57,89

Larger and more recent studies indicate that both local and systemic adverse events occur more commonly after a repeat dose of 23vPPV than after the 1st dose in adults, particularly more severe local adverse events, which may occur in up to approximately 20% of revaccinated subjects.55,57,89 These findings effectively supersede the inconsistent findings from some smaller studies, which were limited by subject numbers and methodology.90–94 Nevertheless, the local adverse events were mostly non-serious and self-limiting. In these studies, the repeat doses were given at least 5 years after the previous dose. Another study, which used hospitalisations coded as cellulitis or abscess of the upper limb within 3 days of pneumococcal vaccination as a proxy measure for very severe local adverse events, showed that these adverse events were significantly more likely when a repeat dose was given within 5 years of the 1st dose.95 As severe local reactions are also associated with higher antibody levels,57,62,89,96 this is the likely driver of the relationship with shorter intervals between the repeat and the primary dose and suggests that such local reactions are associated with more robust immunity.

4.13.12 Variations from product information

The product information for Prevenar 13 recommends 4 doses of 13vPCV for vaccination commencing at 6 weeks of age, with further doses at 4, 6 and 12–15 months of age; 3 doses for vaccination commencing between 7 and 11 months of age; and 2 doses for vaccination commencing between 12 and 23 months of age. The ATAGI recommends instead that 1 dose less than that stated in the product information be given to healthy children who are not at increased risk of IPD. The ATAGI recommends that the 1st dose be given at 2 months of age, and that this dose can be given as early as 6 weeks of age. The next scheduled doses should be given at 4 months and 6 months of age.
The product information for Pneumovax 23 states that Pneumovax 23 and Zostavax should not be given concurrently. The ATAGI instead recommends that Pneumovax 23 can be concurrently administered with Zostavax.

References
A full reference list is available on the electronic Handbook or website www.immunise.health.gov.au.


60. de Roux A, Schmöle-Thoma B, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits


74. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with


