

# Prevention of pneumococcal disease in children....

## Which pneumococcal vaccine to use

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### Abstract

Children under five years of age, but especially those under two years of age, are considered to be at increased risk of invasive pneumococcal disease (IPD). Vaccination plays an important role in preventing IPD. Conjugated vaccines have been found to be effective in reducing the disease among young children who have been vaccinated, as well as providing indirect protection ("herd protection") to unvaccinated older children and adults. Polysaccharide vaccines are not effective in children under two years of age and should only be used for children over two years of age who are at an increased risk of invasive disease and its complications.

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### Introduction

*Streptococcus pneumoniae* or pneumococcus is one of the most common causes of bacteraemia among children under two years of age and is also a leading cause of bacterial meningitis in children younger than five years of age.<sup>1,2,3</sup> The very young, the elderly, people who are immunocompromised and those with an absent or non-functioning spleen are at increased risk for invasive pneumococcal disease (IPD).<sup>2</sup>

Since the introduction of pneumococcal conjugated vaccines, there has been a substantial decrease in the incidence of IPD caused by the vaccine-serotypes among both children and adults.<sup>1,2,4</sup>

This article will focus on the differences between the available pneumococcal vaccines and will provide guidance on vaccinating children and adolescents.

### Pneumococcal disease

#### *S. pneumoniae* serotypes

*Streptococcus* is a Gram-positive bacterium, also known as pneumococcus.<sup>2,3,5</sup> The bacterial capsule (which consists of complex sugars), is the most important virulence factor of the bacterium and provides protection against the host's specific defences.<sup>6,7</sup>

There are more than 90 different pneumococcal serotypes. Different serotypes are distinguished by differences in the composition of the bacterial capsule.<sup>1,2,6-8</sup> It has been estimated that the 10 most common serotypes are responsible for most cases (62%) of IPD globally.<sup>1</sup>

According to the World Health Organization (WHO) serotypes 1, 5, 6A, 6B, 14, 19F, and 23F are common causes of IPD in children under five years of age worldwide.<sup>8</sup>

### Transmission

Bacteria are usually spread from person-to-person through droplets, direct contact with respiratory droplets or via autoinoculation in persons carrying the bacteria in their upper respiratory tract.<sup>1,2,3</sup> Many healthy people carry the bacteria in the nasopharynx without having any symptoms (asymptomatic carriers), with disease occurring only in a small percentage of infected individuals.<sup>2,7</sup>

Factors that may influence carriage rates include age, presence of upper respiratory infections and environment.<sup>1</sup> Infants and young children are believed to be the main reservoirs for *S. pneumoniae*.<sup>1,7,8</sup> The prevalence of nasopharyngeal carriage ranges from 85% in developing to 27% in developed countries.<sup>8</sup>

### Pneumococcal spectrum of disease

Peak levels of pneumococcal infections are usually seen during the winter and in early spring, which is also when respiratory diseases are more prevalent.<sup>1,2</sup>

*S. pneumoniae* is capable of causing a spectrum of disease ranging from mild (sinusitis, otitis media) to severe disease (bacteraemic pneumonia, meningitis, bacteraemia).<sup>1,2</sup> It is referred to as invasive (systemic) pneumococcal disease when *S. pneumoniae* is isolated from normally sterile body fluids such as blood, pleural fluid or cerebrospinal fluid.<sup>5,7</sup> IPD is a leading cause of morbidity and mortality worldwide.<sup>2,7</sup>

Children under five years of age, particularly those under two years of age, as well as adults over 65 years of age, are at increased risk for IPD.<sup>3,7</sup> In addition, risk for invasive disease is more than 50 times higher in children with certain medical conditions (such as functional or anatomic asplenia – particularly those with sickle cell disease) and immunocompromised children (including human immunodeficiency virus [HIV] infection), compared to children of the same age without these conditions.<sup>1</sup>

**Table 1.** Conditions associated with an increased risk of IPD in children and adolescents<sup>1,2,5</sup>

<b>Immunocompetent persons</b>	With chronic conditions	<ul style="list-style-type: none"> <li>• Chronic heart disease (particularly cyanotic congenital heart disease, cardiac failure, and cardiomyopathy)</li> <li>• Chronic lung disease</li> <li>• Diabetes mellitus</li> <li>• Chronic liver disease</li> <li>• Alcoholism</li> </ul>
	With anatomic barrier defects	<ul style="list-style-type: none"> <li>• Cerebrospinal fluid leak</li> <li>• Cochlear implant (or candidate for cochlear implant)</li> </ul>
<b>Persons with functional or anatomic asplenia</b>	<ul style="list-style-type: none"> <li>• Sickle cell disease and other haemoglobinopathies</li> <li>• Congenital or acquired asplenia or splenic dysfunction</li> </ul>	
<b>Immunocompromised persons</b>	<ul style="list-style-type: none"> <li>• HIV infection</li> <li>• Chronic renal failure</li> <li>• Nephrotic syndrome</li> <li>• Congenital or acquired immunodeficiencies – includes B- or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3 and C4 deficiencies), and phagocytic disorders (except chronic granulomatous disease)</li> <li>• Generalised malignancies (e.g. metastatic disease treated with chemotherapy)</li> <li>• Haematologic malignancy (e.g. leukaemia, lymphoma or Hodgkin disease, multiple myeloma)</li> <li>• Iatrogenic immunosuppression (e.g. solid organ transplantation or conditions associated with immunosuppressive or radiation therapy)</li> </ul>	

Children with cochlear implants are at increased risk for pneumococcal meningitis and it has been shown that children younger than 59 months of age and attending childcare centres, have a two to three-fold higher risk of contracting IPD and acute otitis media.<sup>1</sup>

Table 1 contains a list of conditions associated with an increased risk of IPD in children and adolescents.

### Pneumococcal disease in South Africa and the impact of vaccination

The first pneumococcal conjugate vaccine (PCV) was introduced into the Expanded Programme on Immunisation (EPI) in South Africa in 2009 and contained seven serotypes (PCV7). In 2011, PCV7 was replaced with PCV13, targeting additional serotypes.<sup>9</sup>

Results from a study by von Gottberg *A et al.*, 2014, showed that the rates of IPD among children in South Africa fell significantly by 2012.<sup>4</sup> Figure 1 depicts the changes in the incidence of IPD among children younger than two years of age (all serotypes combined declined by 69%) from 2005 to 2012.<sup>4</sup> Indirect benefits of vaccination have also been seen among older children and adults ('herd immunity').<sup>4</sup>

Data from 2005 to 2017 showed that, since the introduction of pneumococcal vaccination into the EPI, IPD reduced by 79% in children under five years of age and by 46% in children five years of age and older.<sup>9</sup>

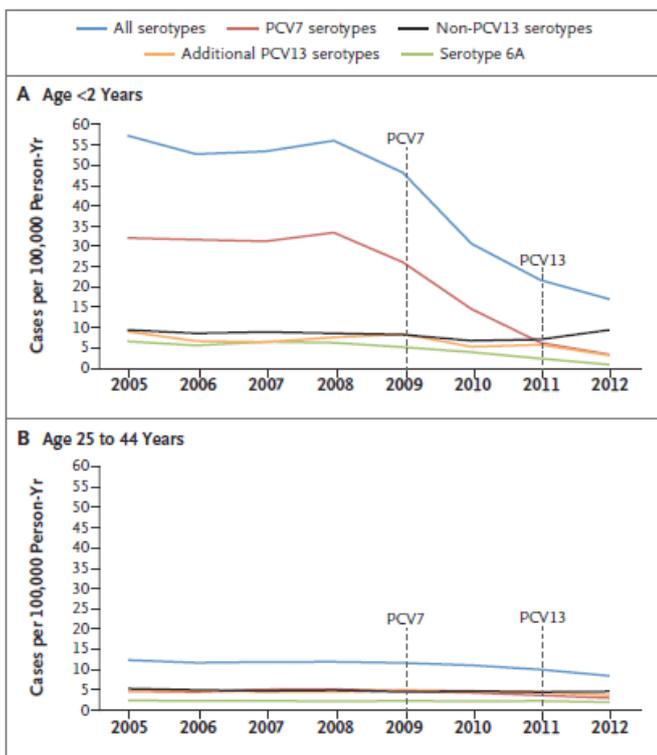
Data from the National Institute for Communicable Diseases (NICD) showed that, in South Africa:

- The highest burden of IPD in 2017 was in infants (children under one year of age) (Figure 2) and
- Among children under five years of age, the most predominant serotypes causing IPD, were 8 followed by 15A and 19A.<sup>9</sup>

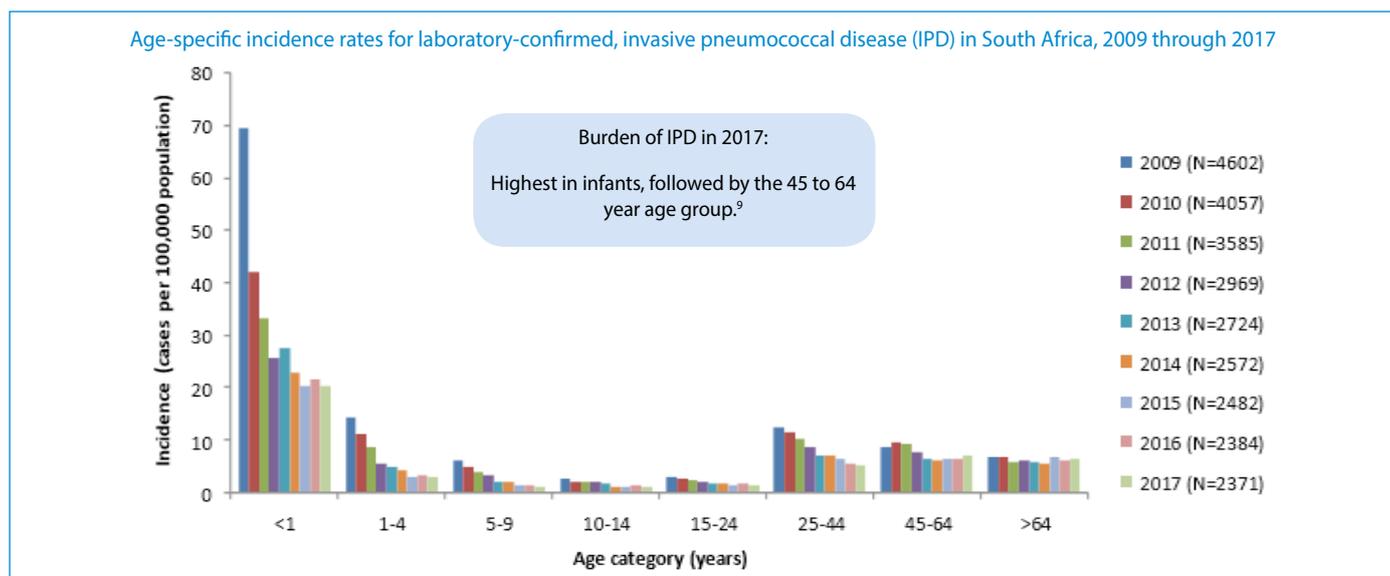
According to the NICD, "the majority of vaccine-type disease in children under five years of age occurred in children who have not received adequate doses of PCV13. In addition, HIV infection and infant HIV exposure continued to be risk factors for pneumococcal disease."<sup>9</sup>

### Pneumococcal vaccines

Pneumococcal vaccines are inactivated vaccines and do not contain live organisms. These vaccines can therefore not cause the diseases against which they protect.<sup>2,9</sup>



**Figure 1.** Changes in the incidence of invasive pneumococcal disease, according to age and serotype. PCV7 was introduced in 2009, and PCV13 in 2011. Additional PCV13 serotypes are PCV13 serotypes not included in PCV7. (Adapted from von Gottberg *A et al.*, 2014).<sup>4</sup>



**Figure 2.** Age-specific incidence rates\* for laboratory-confirmed, invasive pneumococcal disease reported to GERM-South Africa, 2009 through 2017. \*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100 000 population.<sup>9,10</sup> (Adapted from NICD’s Public Health Surveillance Bulletin, Sept. 2018.<sup>10</sup> Available from: <http://www.nicd.ac.za/wp-content/uploads/2018/09/Volume-16-Issue-2-September-2018.pdf>)

	Pneumococcal polysaccharide vaccine	Pneumococcal conjugated vaccine
<b>Composition</b>	Composed of the polysaccharide capsule (the cell wall of the bacteria which consists of long chain sugar molecules) of 23 serotypes. <sup>11</sup>	The polysaccharide is chemically linked to an immunogenic protein molecule. <sup>11,7</sup> Contains either 10 or 13 serotypes. <sup>12,13</sup>
<b>Type of immune response</b>	Elicits a T-cell-independent response. <sup>11</sup>	Elicits a T-cell dependent response <sup>11</sup> – induces immune memory. <sup>8</sup>
<b>Immunogenicity in children under two years of age</b>	Produces a poor or negligible immune response in children under two years of age; <sup>2,7</sup> possibly due to the immaturity of their immune systems. <sup>11</sup>	Conjugation enhances antibody response. <sup>8</sup> These vaccines are highly immunogenic in children from two months of age. <sup>2,11</sup>
<b>Booster (progressively higher) response with repeated doses</b>	Does not produce a booster response with repeated doses. <sup>11</sup> Revaccination does not substantially increase antibody levels. <sup>1</sup>	Produces an antibody booster response with multiple doses. <sup>11</sup>
<b>Effect on nasopharyngeal carriage</b>	Does not decrease carriage rates among vaccinees. <sup>1</sup>	Reduces the carriage rate among vaccinated children; thereby reducing the incidence of disease caused by the vaccine-type serotypes in vaccinated children as well as in groups that were not vaccinated (‘herd immunity’). <sup>5,7</sup>

There are two types, namely pneumococcal polysaccharide vaccines and pneumococcal conjugate vaccines. The main differences are highlighted in Table II.

**Pneumococcal vaccines currently available in South Africa**

There are currently three pneumococcal vaccines registered in South Africa.<sup>12,13,14</sup> The composition of the vaccines differ, they contain different numbers of serotypes (Table III), are indicated for different age groups and are used in different settings.<sup>1,2,5,12-14</sup>

- *Pneumococcal conjugated vaccines:*
  - Prevenar® (PCV13) is conjugated to a non-toxic diphtheria CRM197 protein and is indicated from six weeks of age.<sup>13</sup>
  - Synflorix® (PCV10) is conjugated to tetanus/diphtheria toxoid carrier protein and/or non-typeable *Haemophilus influenzae* (NTHi) protein D and is indicated from six weeks of age up to five years of age. PCV10 is also indicated for the prevention of acute otitis media caused by Non-Typeable *H. influenzae*.<sup>12</sup>
- *Pneumococcal polysaccharide vaccines*
  - Pneumovax 23® (PPSV23) is indicated from two years of age.<sup>14</sup>

Serotypes in Pneumococcal Vaccines																								
Vaccine	1	2	3	4	5	6A	6B	7F	8	9N	9V	10A	11A	12F	14	15B	17F	18C	19A	19F	20	22F	23F	33F
PCV 10	✓			✓	✓		✓	✓			✓				✓			✓		✓				✓
PCV 13	✓		✓	✓	✓	✓	✓	✓			✓				✓			✓	✓	✓				✓
PCV 23	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

**Table IV.** Primary immunisation in children: PCV10<sup>12</sup> and PCV13<sup>13</sup>

3p + 1			2p + 1		
					
3 Primary (p) doses			2 Primary doses		
Booster dose			Booster dose		
<i>First dose:</i> Usually given from two months of age but may be given from six weeks of age. <sup>12,13</sup>			<i>First dose:</i> From the age of two months.* <sup>12,13</sup>		
Vaccine	Primary series	Booster dose	Vaccine	Primary series	Booster dose
PCV10	Three doses with an interval of at least one month between doses	At least six months after the last primary dose	PCV10	Two doses two months apart	At least six months after the last primary dose
PCV13	Three doses four to eight weeks apart	At 12–15 months of age and at least 2 months after the third dose	PCV13	Two doses two months apart	At 11–15 months of age

Immunity resulting from disease or vaccination is generally serotype-specific.<sup>7, 8</sup> However, cross-protection between related serotypes can occur.<sup>1,8,9,12</sup>

**The use of pneumococcal conjugated vaccines in children**

**Primary immunisation**

Children under five years of age and especially those under two years of age are considered to be at increased risk of IPD.<sup>3,5</sup> Conjugated vaccines are highly immunogenic in children<sup>2</sup> and it is recommended that all children two through 59 months of age should routinely be vaccinated using a pneumococcal conjugate vaccine.<sup>1</sup>

Either PCV10 or PCV13 may be used for primary immunisation.<sup>12,13</sup> Table IV contains information regarding the different primary immunisation schedules.<sup>12,13</sup>

\*PCV13 has been included in the EPI in South Africa and is routinely given to children from six weeks of age.<sup>3</sup> The South African EPI follows a slightly different schedule to that outlined above for PCV13:

- The first dose is given at six weeks of age,
- The second dose at 14 weeks of age followed by
- A booster dose at nine months of age.<sup>3</sup>
- An EPI-SA catch-up schedule is available for children below six years of age as well as for children with underlying medical conditions (see PCV13 catch-up).<sup>3</sup>

The 2p plus booster at ≥ nine months schedule as per the South African EPI has been found to be immunogenic and highly effective in preventing IPD caused by vaccine serotypes.<sup>5,15</sup>

**PCV13 Catch-up**

**Healthy children under 5 years of age**

It is recommended that healthy children under five years of age, who are unvaccinated or incompletely immunised with PCV should receive PCV13 catch-up vaccines.<sup>5</sup> Note: PCV13 is not routinely recommended for healthy children over 59 months of age.<sup>1</sup>

Catch-up schedules should be individualised. The number of PCV doses and intervals between doses would depend on:

- The age of the patient
- Vaccination history and
- Underlying medical conditions (if any)<sup>1,3,5,16,17</sup>

Catch-up schedules are available in the package inserts.<sup>12,13</sup> For further information on catch-up schedules for individual PCV13 catch-ups, nurses and pharmacists are encouraged to contact the Vaccine Helpline at 0860 160 160.

**PCV doses for children who are at increased risk of IPD**

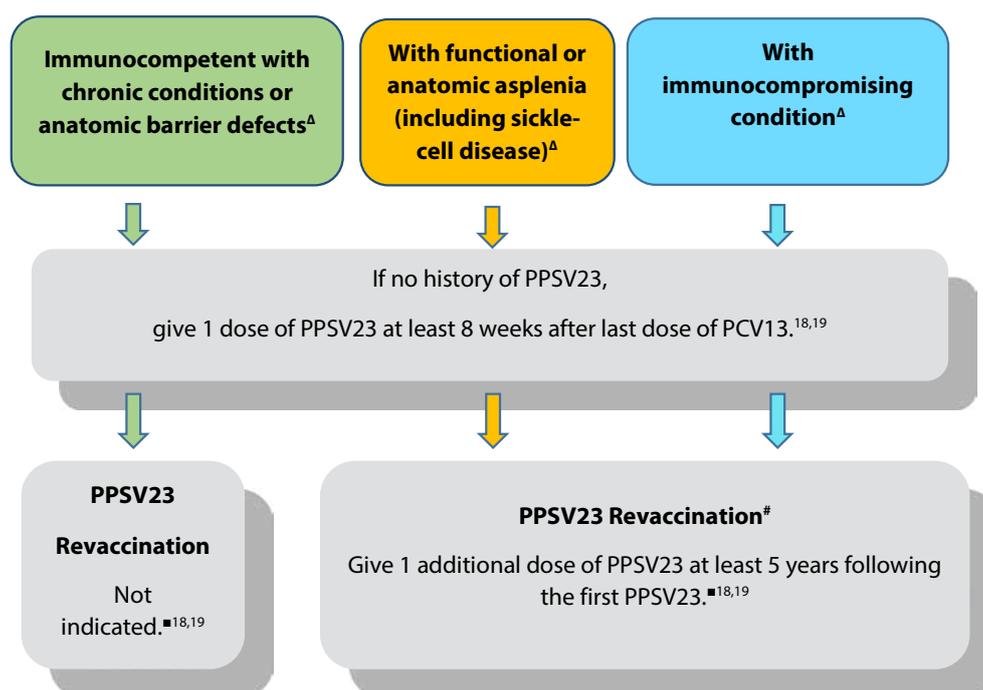
CDC recommends that unvaccinated children:

- Two through five years of age, with conditions associated with an increased risk of IPD (Table I), should receive two doses of PCV13, separated by at least eight weeks.<sup>5,18,19</sup>
- Six through 18 years of age with immunocompromising conditions (e.g. HIV infection), functional or anatomic asplenia (including sickle-cell disease) or anatomic barrier defects (cerebrospinal fluid leak or cochlear implant) should receive one dose of PCV13.<sup>5,18,19</sup>

**The use of pneumococcal polysaccharide vaccines in children**

PPSV23 should not be used in children under two years of age, since it is poorly immunogenic in this age group.<sup>8,5,14</sup> PPSV23 is also not routinely recommended for healthy children over two years of age.

However, PPSV23 is recommended for children, two years of age and older, who are at increased risk of IPD (Table I). Those at risk should receive PPSV23 after they have completed immunisation with PCV13 (Diagram 1).<sup>5</sup> The conjugated vaccine should preferably be administered before the polysaccharide vaccine (if possible) as this enhances the immune response of the polysaccharide vaccine.<sup>5,7</sup> PPSV23 provides protection against additional serotypes that are not included in PCV13.<sup>5</sup>

**Diagram 1.** Recommendations for the use of PPSV23 in children two years of age and older<sup>5,18,19</sup>

<sup>A</sup> Refer to Table I (Conditions associated with an increased risk of IPD in children and adolescents).

• The next recommended PPSV23 dose would be at 65 years of age.<sup>18,19</sup>

<sup>#</sup>PPSV23 Revaccination

Revaccination may be recommended for persons from two years of age, who are at highest risk of serious pneumococcal infection.<sup>1,5</sup> The CDC and the United States Advisory Committee on Immunization Practices (ACIP)<sup>20</sup> recommend that a second PPSV23 be given five years after the first dose with a total of two doses before 65 years of age.<sup>1,5,19,20</sup>

However, there is currently no consensus regarding PPSV23 revaccination – recommendations differ with regards to the interval between PPSV23 doses in children with sickle cell disease, functional or anatomic asplenia and those with conditions associated with a rapid antibody decline after initial vaccination.<sup>2,5,14</sup> There are also discrepancies regarding the number of PPSV23 doses before the age of 65, particularly in children with asplenia.<sup>1,5,18,19</sup>

## Vaccine safety

Persons with minor illnesses may be vaccinated. However, it is best to postpone vaccination in persons suffering from an acute febrile illness.<sup>2,13</sup> This will allow for differential diagnosis and prevent incorrectly attributing signs and symptoms from an acute illness to vaccination.<sup>2</sup>

Pneumococcal vaccines are contraindicated in persons with a history of a severe, life-threatening (anaphylactic) allergy to the vaccine or any ingredient in the vaccine.<sup>12-14</sup>

### Side-effects following vaccination

Very common side-effects of PCV10 and PCV13 include injection-site erythema or induration/swelling or pain/tenderness, fever, decreased appetite, irritability, drowsiness/increased sleep; restless sleep/decreased sleep.<sup>1,12,13</sup>

The most common adverse experiences reported with PPSV23 include fever and injection site reactions such as soreness, erythema, warmth, swelling and local induration.<sup>14</sup>

Please refer to the individual package inserts for a detailed list of ingredients, contraindications, precautions and side-effects.

## Conclusion

Vaccination plays an important role in preventing IPD. Conjugated vaccines do not only provide direct protection for the vaccinated person but may also provide indirect protection ("herd protection") for unvaccinated older children and adults.<sup>4,8</sup> Polysaccharide vaccines are not effective in children under two years of age.<sup>11</sup> However, children over two years of age with certain underlying medical conditions and/or risk factors may benefit from the additional serotypes contained in PPSV23.<sup>1,2,5,18-20</sup>

In addition, PCV vaccination has reduced the need for antibiotic consumption, which has led to a significant reduction in antibiotic-resistant pneumococcal infections.<sup>21</sup>

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