

PNEUMOCOCCAL VACCINE FOR INFANTS AND TODDLERS

Mitchell, T BPharm, Correspondence to: Medifile@medikredit.co.za

SUMMARY

The South African launch of Prevenar®, a new polyvalent conjugate vaccine, has resulted in many questions being posed by health care providers and parents alike. Without a government policy on the role of this vaccine and considering its high cost, there is much debate on its place in therapy, cost benefit and long term epidemiological effect. This article provides an overview of the vaccine, its known advantages, potential disadvantages, place in therapy and administration.

BACKGROUND

Streptococcus pneumoniae, also known as pneumococcus, is a bacterium that causes meningitis, bacteraemia, pneumonia, paranasal sinusitis and otitis media.^{1,2} Pneumococcal meningitis and bacteraemia are frequently referred to as *invasive pneumococcal disease* (IPD).

S. pneumoniae is a major cause of serious infections in young children worldwide. The highest incidence of IPD occurs in children <5 years, especially children <2 years of age. Pneumococcus is also the most common cause of community-acquired pneumonia, acute otitis media and sinusitis in children.^{3,4}

A 23-valent pneumococcal vaccine (PPV23) was first introduced in 1983 and has been available in South Africa since 1992 as Pneumovax® (MSD) and since 1998 as Imovax Pneumo 23® (Aventis). However this 23-valent vaccine is ineffective in children under 2 years. Although the PPV23 serotypes do match the majority of pneumococcal infections in children, many of the polysaccharides in this vaccine are *not immunogenic* in children under 2 years and may not be immunogenic for most serotypes until children are >5 years old.^{3,4}

Pneumococcal Conjugate Vaccine

Prevenar® is the first pneumococcal vaccine licensed for use in infants and toddlers. It is a **heptavalent pneumococcal conjugate vaccine (PCV7)**. The vaccine contains purified capsular polysaccharide antigens of *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, those most often responsible for serious disease.^{5,6,7}

In PCV7, the problem of polysaccharides in PPV23 being non- or partially-immunogenic in children is overcome by converting the viral polysaccharide to a T cell-dependent antigen by covalent coupling to an immunogenic protein carrier. This improves the antibody response, and induces immune-memory and a strong anamnestic response if re-exposure occurs.^{3,4} CRM₁₉₇, a mutant non-toxic diphtheria toxin, is used as a carrier protein in PCV7. The seven serotypes in Prevenar® are individually conjugated to CRM₁₉₇.^{3,6}

Prevenar® was launched in South Africa in October 2005 and is indicated for immunization of infants and children from 6 weeks to 9 years of age for the prevention of invasive disease, pneumonia and otitis media.^{6,8} It is not registered for adults. This schedule 2 drug is manufactured by Wyeth Vaccines and Pediatrics, and is available as a suspension in a glass vial or pre-filled syringe. The administration route is intramuscular only.⁶

Efficacy of PCV7

Invasive Pneumococcal Disease (IPD)

In a large prospective double-blind US study by the Kaiser Permanente Vaccine Study Center Group (NCKP), 37,868 healthy

children were randomly assigned to receive either PCV7 or a meningococcus conjugate in a 1:1 ratio. PCV7 was given to infants at 2, 4, 6 and 12 to 15 months of age. The primary outcome of this study was invasive disease caused by the vaccine serotype. A secondary outcome included overall invasive disease, regardless of serotype.^{3,4,9,10}

The study showed that PCV7 had a 97.4% efficacy (95% CI=82.7%-99.9%) against serotype-specific IPD in children who were fully vaccinated, 93.9% efficacy (95% CI=79.5%-98.5%) in partially vaccinated children and 89.1% (95% CI=73.7%-95.8%) efficacy against IPD due to any serotype.^{4,8,9,10}

Another group-randomised study was conducted on 8,292 Navajo and White Mountain Apache children under 2 years of age. This population group is considered to be a high risk population as it is documented to have one of the highest rates of pneumococcal disease in the world. In children immunized according to the study protocol, the vaccine reduced vaccine serotype-specific IPD by 76.8% (95% CI=-9.4%-95.1%). However it reduced IPD against all serotypes by only 54.1%, far lower than the 89.1% reported in the NCKP study. This result may be of significance in similar developing world settings where there is a broad serotype distribution of disease.¹¹ Data from Klugman et al's trial of a 9-valent pneumococcal conjugate vaccine on HIV positive and negative children (n= 39,836) in Soweto show a similar trend to the Navajo study – vaccine efficacy in all children for first episodes of vaccine-type IPD was 72% (95%CI=23%-68%) and all serotype IPD was 50% (95% CI=23%-68%).¹²

In September 2005 the Centers for Disease Control and Prevention (CDC) reported on the effects of routine PCV7 immunization of children on the incidence of IPD in the Morbidity and Mortality Weekly Report (MMWR). Following the licensing of PCV7 in 2000, surveillance data from 2001 to 2003 was compared against 1998 and 1999 (baseline).¹³ These data demonstrated the following:

- The incidence of vaccine serotype-specific IPD in children <5 years decreased by 94% (95% CI=92%-96%) from 80 cases per 100,000 population at baseline to 4.6 cases per 100,000 in 2003.
- The incidence of all IPD in children <5 years, regardless of serotype, decreased by 75% (95% CI=72%-78%) from 96.7 per 100,000 at baseline to 23.9 per 100,000 in 2003.¹³

In another population-based surveillance study, Hsu et al reported that in the state of Massachusetts there was a 69% decrease in all serotypes of IPD in children <5 years, from an annual incidence of 56.9 cases per 100,000 population in 1990-1991 to 17.4 cases per 100,000 in 2001-2003.¹⁴

Pneumonia

Black et al reported a 4.3% reduction in first episodes of *all* clinically diagnosed pneumonia (95% CI= -35%-11.5%), a 9.8% reduction in episodes with a radiograph (95% CI= 0.1%-18.5%), and a 20.5% reduction in episodes with a confirmed radiograph (95% CI= 4.4%-34%).¹⁵

The following studies on the **9-valent** pneumococcal conjugate vaccine included analysis of vaccine efficacy against pneumonia:

- Klugman et al reported that radiologically confirmed first-episode pneumonia was reduced by 20% in HIV negative children (95%CI=2%-35%), by 13% in HIV positive children (95%CI=-7%-29%), and by 17% (95%CI=4-28%) across all children.¹²



- The Gambian study showed vaccine efficacy to be 37% (95%CI=27%-45%) against first episode of radiological pneumonia. It reduced first episodes of clinical pneumonia by 7% (95%CI=1%-12%).¹⁶

Otitis Media

Other secondary endpoints of the NCKP study included the vaccine's:

- Effectiveness against clinical otitis media (OM) visits and episodes
- Impact against frequent (≥ 3 episodes within 6 months or ≥ 4 episodes in a year) and severe episodes of OM & requirement for ventilatory tube placement (grommets)^{4,10}

The study showed that PCV7 reduced the overall incidence of visits for all episodes of OM by 7% (95% CI=4.1-9.7), frequent OM by 9.3% (95% CI=3.0-15.1) and ventilatory tube placement by 20.1% (95% CI=1.5-35.2).^{4,10}

A Finnish study by Eskola *et al* (2001) of 1662 infants showed that PCV7 decreased the number of episodes of vaccine serotype-specific acute otitis media (AOM) by 57% (95% CI=44%-67%). Despite the fact that there was a 33% increase in the rate of AOM attributed to pneumococcal serotypes not included in PCV7, the occurrence of all serotype AOM decreased by 34% (95% CI=21%-45%). AOM due to any cause reduced by 6% (95% CI=-4%-16%).^{4,17,18}

PCV7 and HIV

Satisfactory immunogenicity and safety of PCV7 have been demonstrated in children with HIV. Some small studies showed that children with more advanced HIV disease were less likely to respond than children in early stage of the disease, but this was not observed after a 3rd vaccine dose. It is therefore recommended that children with HIV infection should be immunized as early in the course of disease as possible.³

Other Effects of PCV7

Herd Immunity

Herd immunity occurs when vaccinated persons in a population indirectly protect unvaccinated people by impeding the transmission of the infectious agent in the population.¹⁹ This is thought to be as a result of a decrease in nasopharyngeal carriage of vaccine serotype strains in immunized children and consequently reduced transmission to other individuals in the community.¹³

In a recently published study, Dr Katherine Poehling *et al* showed that even if not vaccinated themselves, newborns benefit from PCV7 vaccination. The prospective population-based study of infants 0-90 days old surveyed laboratory records for IPD infections from 1997 to 2004. It showed a 40% decrease in all serotype IPD in 0 to 90-day old infants from 11.8 (95% CI 9.6-14.5) to 7.2 (95%CI 5.6-9.4; $p=0.004$) per 100,000 following the introduction of PCV7. There was a 39% decrease in infants under 30 days, 45% in infants between 31-60 months and 32% in infants 61-90 days old. The authors wrote: "These data are the first to suggest that neonates and infants too young to receive PCV7 are benefiting from 'herd immunity'".^{19,20}

The September 2005 edition of MMWR also highlighted the herd immunity effect of the vaccine on non-vaccinated age groups: in people >5 years the incidence of vaccine serotype-specific IPD decreased by 62% (95% CI=59%-66%). The editor concluded that "indirect benefits of PCV7 (cases prevented in unvaccinated persons) exceeded direct protective benefits among immunized children, with more than twice as many cases of vaccine-type IPD prevented indirectly as directly in 2003."¹³

Flannery *et al* reported that a US active laboratory-based surveillance study of data between 1998 and 2003 showed that since

introduction of PCV7 for children, there was an overall 19% decrease ($p=0.002$) in invasive pneumococcal disease among HIV-infected adults, but a 44% increase in the ratio of disease caused by non-vaccine pneumococcal serotypes.¹⁸

The impact of herd immunity needs to be taken into account in assessing the cost effectiveness of PCV7.

Reduction in Antibiotic Resistance

Treatment of pneumococcal diseases is usually with B-lactam antibiotics. Since 1960 there has been a massive increase in pneumococcal strains resistant to penicillin and other antibiotics due to widespread use of antibiotics.^{2,4,22} In Southern Israel a study of pneumococcal isolates from children's middle ear fluid showed that 68% of children with pneumococcal acute otitis media (AOM) are resistant to one or more antibiotics, 61% to penicillin and 13% are resistant to three or more classes of antibiotics.^{22,23}

It had been postulated that as widespread use of PCV7 reduces the incidence of pneumococcal infections, this should result in decreased use of antibiotics. Indeed the NCKP study showed a 5.3% reduction in the use of antibiotics in children who used PCV7.^{4,22} This may in turn reduce antibiotic resistant pneumococcal disease.

A study by Garbutt *et al* of 327 children <7 years (*Pediatrics* June 2006) reported that the prevalence of *S. Pneumoniae* resistant to penicillin reduced from 25% to 12% from 2000 to 2004 in St Louis, Missouri, following the introduction of widespread PCV7 immunization. It specifically reduced in children who had 3 or more vaccine doses. However penicillin resistance did not vary in children <2 years of age. Resistance to amoxicillin remained <5%. Based on the study, the authors recommend that uncomplicated AOM should be treated with "standard-dose amoxicillin (40-45mg/kg/day) for children with ≥ 3 doses of heptavalent pneumococcal vaccine, regardless of age and child care status. High-dose amoxicillin should be used for children with <3 doses of heptavalent pneumococcal vaccine and those treated recently with an antibiotic."²⁴

Whitney *et al* reported a 35% decrease in the rate of pneumococcal disease caused by resistant strains (4.1 cases per 100,000 in 2001 versus 6.3 cases per 100,000 in 1999).²⁵

Replacement Disease

An ongoing concern related to the use of PCV7 is that of "replacement disease". This refers to an increase in disease caused by non-vaccine pneumococcal serotypes. The results of several studies have raised this concern:

- MMWR reported an 11% increase (95% CI=3%-21%) in IPD caused by the 16 serotypes included in the PPV23 not included in PCV7, however this did not contribute much to the burden of pneumococcal disease compared to that prevented by Prevnar®.¹³
- The Finnish Otitis Media Vaccine Trial showed a 33% (95% CI -1%-80%) increase in the rate of AOM attributed to pneumococcal serotypes not included in PCV7.¹⁸
- McEllistrem *et al* found an increased ratio of non-PCV7 *S. pneumoniae* serotypes in the middle ear fluid of children with AOM which increased over time and in children who had more than one dose of PCV7.^{17,26} The study did not indicate an increase of penicillin non-susceptible strains.²⁶
- A recently published data analysis of 4 AOM studies conducted by the University of Texas showed an increase in the proportion of *Haemophilus influenzae* and *Moraxella catarrhalis* in the middle ear fluid of children vaccinated with PCV7. They also found that there was no reduction in *S. pneumoniae* colonization of the nasopharynx in PCV7-immunized children.¹⁷



Table 1: Children at risk for invasive pneumococcal infection ^{3,4,9,27}

High risk	<ul style="list-style-type: none"> • Sickle cell disease • HIV-infection • Congenital or acquired asplenia or splenic dysfunction
Presumed high risk	<p>Immunocompromising conditions, including:</p> <ul style="list-style-type: none"> • Congenital immune deficiency • Disease associated with immunosuppressive treatment eg solid organ transplantation • Chronic renal disease, renal failure • Children on high dose corticosteroids <p>Chronic illness, including:</p> <ul style="list-style-type: none"> • Chronic pulmonary disease (asthma excluded) • Chronic cardiac disease • Cerebrospinal uid leaks • Uncontrolled Diabetes Mellitus • Cochlear implants or intracranial shunts
Moderate risk	<ul style="list-style-type: none"> • All children between 2 and 5 years, especially: <ul style="list-style-type: none"> ➢ Children between 2 and 3 years ➢ Children attending group day-care centers ➢ Children from certain ethnic groups eg African Americans, Alaska Natives, certain American Indian populations in US, aboriginal populations in northern Canada

Candidates for PCV7

Invasive pneumococcal disease occurs more frequently in children with immunocompromising or certain chronic medical conditions.^{4,9,27} See **table 1** for children at risk.

The ACIP (USA) and National Advisory Committee on Immunization (NACI - Canada) recommend the following use of PCV7^{3,4}:

- Children ≤23 months: vaccinate all children
- Children 24-59 months: vaccinate all children at high and presumed high risk. Children at moderate risk may also benefit from PCV7- these children should be considered for vaccination. (See table 1)

As data of the efficacy of PCV7 in children >5 years is lacking, ACIP recommends that PPV23, and not PCV7, should be administered to children >5 years who are at risk for IPD.⁴ Although Canada's NACI also recommends PPV23 for at-risk children >5 years, under certain circumstances it allows PCV7 to be given as an initial dose followed by a booster dose of PPV23 after 8 weeks.³

Vaccination schedule

See **table 2** for the recommended dosing schedule of PCV7. The first dose for primary vaccination is usually at the age of 2 months, but it can be given as young as 6 weeks of age.⁶

PCV7 can be administered concurrently with other pediatric vaccines according to recommended immunization schedules, although different syringes and different injection sites must be used. It should be administered intramuscularly into the anterolateral aspect of the thigh in infants and into the deltoid in older children.⁶ It may however lower the immunogenicity of certain concurrently administered vaccines e.g. Hib, pertussis and polio vaccines^{4,6}, however the clinical significance of these decreased responses is uncertain.^{4,6}

As PCV7 is administered intramuscularly, it should not be given to children with thrombocytopenia or any coagulation disorder. Hypersensitivity to diphtheria toxoid is a contraindication to the use of the vaccine.⁶

Duration of Protection

The long-term efficacy of PCV7 is not known. However because the highest incidence of pneumococcal disease occurs early in

life and as the vaccine induces memory cells, it is likely that the majority of vaccine-serotype disease burden will be prevented using PCV7. In infants ≤20 months who received 2 or 3 doses of PCV7, immunologic memory was demonstrated at 18 months. In children ages 2 to 3 years who received 1 dose of a bivalent vaccine, a booster response was demonstrated up to 20 months.^{3,4}

Vaccine Safety

The ACIP conclude that the frequency and types of adverse events associated with PCV7 administration are "acceptable when compared with the demonstrated benefits of the vaccination".⁴ Reported side effects include⁶:

- Injection site erythema, induration, swelling and pain (≥10%)
- Fever (≥10%)
- Diarrhea, vomiting (≥10%)
- Decreased appetite (≥10%)
- Drowsiness, restless sleep (≥10%)
- Irritability (≥10%)
- Seizures, including febrile seizures (≥0.01% and <0.1%)
- Hypotonic-hyporesponsive-episodes (≥0.01% and <0.1%)
- Rash, urticaria (≥0.1% and <1%)
- Localised lymphadenopathy (<0.01%)
- Angio-oedema, erythema multiforme (<0.01%)

The NCKP trial showed that fever was more common in patients receiving PCV7 together with other recommended vaccines than among patients receiving control vaccine. Febrile seizures were slightly more common in the PCV7 group, but most cases occurred when PCV7 was administered concurrently with whole-cell pertussis vaccine.⁴

Cost- Benefit Analysis

In an early cost-effectiveness study based on NCKP data (JAMA 2000), Lieu et al, in the absence of considering the indirect effects of the vaccine, concluded that the PCV7 vaccine has the *potential* to be cost-effective. Based on the vaccine's list price of US\$58 per dose in the USA, they calculated that infant vaccination would cost society US\$80,000 per life year saved and that vaccination of healthy infants would only result in net savings to society if the cost of the vaccine was ≤US\$46 per dose and to *health-care payers* if the cost was ≤US\$18 per dose.²⁵ These figures were later revised to US\$110,000 per life year saved.²⁸; break-even figures were revised to US\$40 and US\$17 for society and health-care payers respectively.⁴

However, as data on herd immunity effect was not available at the time, Lieu *et al's* cost estimates did *not* take into account the indirect effects of the vaccine.¹³ Ray *et al* reviewed the initial model and in June 2006 published a cost-effectiveness analysis which takes into account the effect of the vaccine on non-vaccinated people. Based on a mean vaccine price of US\$52, they concluded that in the first 5 years of PCV7's use:

- 38,000 cases of IPD were averted at a cost of US\$33,000 per averted IPD case and US\$112,000 per life year saved before incorporating herd effects on the model
- 109,300 cases of IPD were averted at a cost of US\$5,500 per averted IPD case and US\$7,500 per life year saved after including reductions in IPD for non-vaccinated individuals.²⁹

The authors emphasize that these figures are in fact conservative, as they do not take into account morbidity associated with the prevention of OM, pneumonia and IPD that do not result in death.²⁹

Prevenar® has been launched in 60 countries and has been included in the universal vaccination programme of several industrialized countries, including the USA, Australia, Canada and Luxembourg.⁶

Conclusion

The advantages of PCV7 are clear. It is highly effective in re-



Table 2: Recommended Vaccination Schedule for PCV7⁶

	Age at Examination			
	Infants (primary vaccination)	7-11 months (previously unvaccinated)	12-23 months (previously unvaccinated)	Older than 24 months
Number of Doses	4	3	2	1 (single dose)
1st vaccine	Usually 2 months of age	At examination	At examination	At examination
2nd vaccine	4-8 weeks after 1 st dose	1 month after 1 st dose	2 months after 1 st dose	
3rd vaccine	4-8 weeks after 2 nd dose	After 1 st birthday At least 2 months after 2 nd dose		
4th vaccine	In 2 nd year of life			

ducing vaccine serotype-specific IPD in immunized children - various studies report vaccine efficacy to be between 76.8%-97.4%.^{4,8,9,10} Large, rapid declines in overall and vaccine-type IPD are specifically seen in children under 2 years of age.³⁰ It is also effective at reducing pneumonia and AOM, but efficacy is less than that of IPD, partly due to the poor specificity of outcomes used to measure vaccine effect against these outcomes.^{3,4,8-10,17,18} In addition routine vaccination of young children has resulted in a reduction of IPD in infants, older children and adults who have not been immunized: the so-called indirect effect or herd immunity.^{13,19-21,30} In US studies this herd immunity has been shown to prevent twice as many cases as the direct effects of vaccination alone.^{13,25,30} Studies have shown that widespread use of PCV7 reduces the use of antibiotics in immunized children and significantly reduces the frequency of antibiotic resistant pneumococcal disease.^{4,22} In addition the vaccine has eliminated racial disparities in disease incidence.^{11,30}

Concerns on the use of PCV7 include the possible increase in infections related to non-vaccine serotypes, so-called "replacement disease".^{3,13,18,21,26} However, these increases appear to be small in comparison to the overall reduction in vaccine-type infection. Nonetheless continued surveillance and vigilance is required to determine whether the impact of PCV7 in reducing pneumococcal disease is sustained, and whether "replacement" disease will erode the substantial benefits of routine vaccination. Trends in antimicrobial resistance and antibiotic use as well as vaccine related health events need to be followed.^{3,4,17}

In South Africa Prevenar® is not mandated in our immunization schedule. Although negotiations with the Department of Health have commenced, it is likely that the current cost of Prevenar® will be prohibitive. However, there are international initiatives underway to negotiate sustainable affordable pricing of the vaccine for developing countries: The Global Alliance for Vaccines and Immunization (GAVI Alliance) fund, which aims to increase immunization in developing countries, is working through PneumoADIP (Pneumococcal Vaccine's Accelerated Development and Introduction Plan) to add pneumococcal vaccines to existing immunization programmes.^{30,31} James Connolly, Wyeth's Executive Vice President and General Manager of the vaccine business unit, has concurred with this initiative and stated: "We are actively working with international agencies to help provide access to Prevenar® for children in the developing world"³¹ What remains to be seen is whether South Africa is included in this initiative.

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Contributor: Thealdi Mitchell
 Sub Editor: Elsabé van der Merwe
 Editorial Advisor: Dr J Noble

MediKredit Integrated Healthcare Solutions (Pty) Ltd ("MediKredit") 132 Jan Smuts Ave, Parkwood, PO Box 692, Parklands 2121, South Africa

Tel: (011) 770-6000 Fax: (011) 770-8325
 E-mail: Medifile@medikredit.co.za

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