Pneumococcal conjugate vaccine – advancing child health in South Africa

Pneumococcal disease caused by *Streptococcus pneumoniae* is a major cause of death, hospitalisation and morbidity in children in South Africa and Africa.[1] Paediatric pneumococcal disease manifests most commonly as otitis media, pneumonia or meningitis. Otitis media is commonest, occurring approximately 10 times more frequently than pneumonia and 100 times more than meningitis. However, pneumonia or meningitis are severe forms of disease, responsible for a large proportion of childhood mortality and morbidity. *S. pneumoniae* is the most important bacterial cause of pneumonia in children,[1,2] responsible for 1 - 4 million episodes of pneumonia in Africa annually.[3]

Pneumococcal disease is the leading cause of vaccine-preventable death in children under 5 years of age.

The HIV epidemic has increased the burden and mortality from pneumoccocal disease in children. The incidence of pneumococcal bacteraemia or invasive disease is up to 40-fold greater in HIV-infected than in uninfected children.[2] **Importantly, 75% of severe invasive pneumococcal disease in South African children occurs in the 5 - 6% of the childhood population who are HIV infected.**

Pneumococcal conjugate vaccine (PCV) is a highly effective intervention to reduce invasive pneumococcal disease and pneumonia. The only commercially available PCV includes 7 serotypes that cause 70% of all invasive pneumococcal disease (IPD) in South African children.[4] Studies evaluating a 9-valent PCV in South Africa and the Gambia found a 72 - 77% reduction in vaccines-serotype (VT)-specific IPD among vaccinated children and a 13 - 37% reduction in radiological pneumonia (Table I).[5,6] As chest radiographs are insensitive for detecting the burden of pneumococcal pneumonia, the true burden of pneumococcal pneumonia prevented by vaccination is probably much greater than that detected by radiographs.[7] Moreover, as childhood pneumonia is frequently due to mixed infections such as bacterial-viral infections, use of PCV reduces severe viral-associated pneumonia, as indicated by a reduction by a third in admissions for viral pneumonia in immunised children.[8]

As most of the pneumococcal serotypes associated with antibiotic resistance are included in conjugate vaccine, vaccination has also been associated with a reduction in antimicrobial-resistant invasive disease. PCV may also reduce childhood mortality, especially in areas with limited access to health care, as shown in a Gambian study in which PCV reduced childhood mortality by 16%.[6] In addition to the direct effects of PCV, there is a substantial reduction in disease burden through indirect protection of non-vaccinated populations.

PCV is immunogenic in HIV-infected children and provides protection against invasive disease or pneumonia in a substantial proportion of children. Although the efficacy of PCV for prevention of invasive disease or pneumonia is lower in HIV-infected than in uninfected children, the overall burden of disease prevented is much greater in HIV-infected children because of the higher burden of pneumococcal disease in these children (Table I). The rate of vaccine-preventable invasive disease is almost 60 times higher in HIV-infected than in uninfected children, while the reduction in pneumonia in HIV-infected children is 15-fold greater.

Although there has been concern about the potential for replacement disease with non-vaccine strains, overall a substantial and sustained reduction in invasive disease has occurred in populations with widespread childhood immunisation. Routine childhood immunisation is now the standard of care in most developed countries. However, PCV is much less accessible to children in low-income countries due to cost and availability. Cost-efficacy analysis indicates that use of the vaccination is potentially highly cost-effective.

The recommended schedule for vaccination in infants is 3 doses of PCV given intramuscularly at least 4 weeks apart beginning at 6 weeks of age concurrently with the other routine childhood vaccines, followed by a booster dose of PCV at 15 - 18 months, which may be especially important in HIV-infected children (Table II). Children immunised between 12 and 24 months of age should receive at least two doses one month apart, and children aged 2 - 9 years of age require a single dose of PCV (Table II). Additional booster doses may be

TABLE I. EFFICACY (MIDPOINT EFFICACY ESTIMATE, 95% CONFIDENCE INTERVAL) OF PNEUMOCOCCAL CONJUGATE VACCINE FOR INVASIVE DISEASE IN CHILDREN

Study	Vaccine serotypes	All serotypes
USA (7-valent)	94% (80, 98)	89% (75, 95)
Native American (7-valent)	83% (23, 96)	46% (-6, 73)
South Africa (9-valent)*		
HIV infected	65% (24, 86)	53% (21, 73)
HIV uninfected	83% (39, 97)	42% (-28, 75)
South Africa (9-valent)†		
HIV infected	39% (-8, 65)	46% (19, 64)
HIV uninfected	78% (34, 93)	35% (-61, 68)
Gambia (9-valent)	92% (44, 99)	45% (19, 63)

*Surveillance until 2.5 years of age.
†Extended surveillance until 6 years of age in the absence of any booster dose of pneumococcal vaccine.

TABLE II. RECOMMENDED IMMUNISATION SCHEDULE FOR PNEUMOCOCCAL CONJUGATE VACCINE (PCV) IN HIV-INFECTED AND UNINFECTED CHILDREN

Age of initial immunisation	Initial doses	Booster dose
< 1 year	6 weeks 10 weeks 14 weeks	15 - 18 months
1 - 2 years	2 doses 1 month apart	Nil*
2 - 9 years	1 dose	Nil*

* The need for intermittent booster doses of PCV and timing thereof should be evaluated further in HIV-infected children, especially in the absence of antiretroviral therapy.

All doses are given as 0.5 ml intramuscularly.

PCV should be given concurrently with other childhood immunisations.

Pneumococcal polysaccharide vaccine may benefit children older than 2 years at high risk of invasive disease, e.g. post splenectomy, sickle cell disease, etc., and should be given at least one month after completion of the primary series of PCV.

necessary in HIV-infected children, in whom immunity wanes and there is loss of protection against invasive disease in the absence of a booster dose of PCV.[9]

The use of PCV should be complementary to other pneumonia-control measures, including case management and the reduction of exposure to known risk factors such as malnutrition, biomass fuel exposure, tobacco smoke and HIV infection. The World Health Organization has recommended that inclusion of PCV7 vaccine should be a priority in national immunisation programmes, particularly in countries where mortality among children under 5 years is more than 50 per 1 000 live births or where more than 50 000 children die annually.[10] Furthermore, the WHO recommends that countries with a high prevalence of HIV prioritise the introduction of PCV7.

The launch of PCV7 for South African children in the public health sector as part of the primary immunisation programme is therefore a very welcome development. However, the operational and educational challenges in instituting wide coverage should not be under-estimated. In addition, ongoing surveillance for measuring the impact of the vaccine on the burden of pneumococcal infections and serotype changes that may occur is essential. Widespread use of the vaccine will contribute to reducing the burden of childhood illness and assist in achieving the Millennium Development Goal aimed at reducing under-5 mortality by two-thirds by 2015 compared with 1990 rates. The launch of PCV for all children is a great step forward for child health in South Africa.

Conflict of interest: SAM has received research support and serves on the speakers bureau for Wyeth Vaccines and Pediatrics.

Heather J Zar
School of Child and Adolescent Health
Red Cross War Memorial Children's Hospital and
University of Cape Town

Shabir A Madhi
Medical Research Council: Respiratory and Meningeal Pathogens
Research Unit and Department of Science and Technology/
National Research Foundation: Vaccine Preventable Diseases
University of the Witwatersrand
Johannesburg

The launch of PCV7 for South Africa children in the public health sector is a very welcome development.

References

1. Zar HJ, Hanslo D, Tannenbaum E, *et al.* Aetiology and outcome of pneumonia in human immunodeficiency virus-infected children hospitalized in South Africa. *Acta Paediatr* 2001; 90(2): 119-125.
2. Madhi SA, Petersen K, Madhi A, Khoosal M, Klugman KP. Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children. *Clin Infect Dis* 2000; 31(1): 170-176.
3. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis* 2002; 2(1): 25-32.
4. von Gottberg. A, de Gouveia. L, Quan. V, *et al.* Vaccine-preventable invasive pneumococcal disease, South Africa, 2006. *S Afr J Epidemiol Infect* 2007; 22: 95 (Abstract 101).
5. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003; 349(14): 1341-1348.
6. Cutts FT, Zaman SM, Enwere G, *et al.* Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005; 365(9465): 1139-1146.
7. Madhi SA, Klugman KP. World Health Organisation definition of 'radiologically-confirmed pneumonia' may under-estimate the true public health value of conjugate pneumococcal vaccines. *Vaccine* 2007; 25(13): 2413-2419.
8. Madhi SA, Klugman KP. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. *Nat Med* 2004; 10(8): 811-813.
9. Madhi SA, Adrian P, Kuwanda L, *et al.* Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. *Vaccine* 2007; 25(13): 2451-2457.
10. Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. *Wkly Epidemiol Rec* 2007; 82(12): 93-104.