

Vaccination Against Invasive Pneumococcal Disease in Saudi Arabia: Where Do We Stand?

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S*treptococcus pneumoniae* (pneumococcus) is a bacterial pathogen that causes invasive infections, including septicemia and meningitis, as well as non-invasive infections such as community-acquired pneumonia, sinusitis and acute otitis media. Invasive pneumococcal disease is a leading cause of morbidity and mortality worldwide, particularly in young children, elderly subjects and those with underlying diseases.¹⁻⁵ There are no community-based epidemiological studies of *S. pneumoniae*-invasive disease in Saudi Arabia. However, hospital-based studies from different parts of the Kingdom show that *S. pneumoniae* is an important cause of meningitis and bacteremia, particularly in children.⁶⁻¹³ A recent population-based, prospective study by the Saudi Ministry of Health of bacterial meningitis in five different regions across the country⁶ showed that *S. pneumoniae* is one of the leading bacterial causes of meningitis (the others being *H. influenzae* and *N. meningitidis*) in children younger than 5 years, with an estimated overall incidence of 7 per 100 000 children. The majority of the cases occurred between the ages of 2 to 12 months. With the introduction of *H. influenzae* b conjugate vaccine into the routine immunization schedule of infants in the Kingdom, the role of *S. pneumoniae* as a cause of meningitis in children will become even more prominent as infections caused by *H. influenzae* decline. As is the case in most other countries, antibiotic resistance among *S. pneumoniae* isolates in the Kingdom has been increasing.¹²⁻¹⁸ Resistance has ranged between 6.2% to 51% to penicillin, and 4.5% to 76% to co-trimoxazole. Increased antibiotic resistance adds to the disease burden and the cost of invasive pneumococcal disease.

Invasive pneumococcal disease can be prevented through the use of pneumococcal vaccine and, in some situations chemoprophylaxis. There are 90 serotypes of *S. pneumoniae*. In the USA and other western countries, 23 of these 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) account for the majority of invasive disease in children and adults.²⁻⁴ Two types of pneumococcus vaccine are currently licensed: the 23-valent pneumococcal polysaccharide vaccine (*Pneumo 23*, *Pnu-Immune 23*), and the

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Ann Saudi Med 2005;25(2):90-93

heptavalent diphtheria CRM197 protein conjugate vaccine (*Prevnar*). The serotypes contained in these vaccines and recommendations for their use are based mainly on epidemiologic studies done in the USA and other western countries. Both vaccines are safe and could be given concurrently with other vaccines. The 23-valent pneumococcal polysaccharide vaccine (23-PPV) contains the aforementioned 23 serotypes and induces antibody response to these serotypes in children 2 years of age or older. The limitation of this vaccine, however, is that it has poor immunogenicity in children under the age of 2 years, a group at high risk of invasive pneumococcal disease. The effectiveness of this vaccine against invasive disease caused by vaccine serotypes has ranged from 57% to 84% depending on the age, underlying disease, degree of immunocompetence, and the serotype.²⁻¹⁹ The vaccine was found to be cost-effective when given to elderly subjects.² Immunization with 23-PPV vaccine is currently recommended in numerous countries for subjects 2 years of age and older who are at high risk of invasive pneumococcal disease, as well as routine vaccination of all subjects 65 years of age or older (Table 1). The pneumococcal vaccine that is registered in the Kingdom is *Pneumo 23*, and the cost is SR39/dose (personal communication, Regional Office, Aventis Pasteur).

The heptavalent diphtheria conjugate pneumococcal vaccine (7-PCV) is composed of serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to

Table 1. Persons at high risk of invasive pneumococcal disease^{2,3,5}

- All children younger than 2 years of age*
- All adults 65 years of age or older†
- Children ≥2 years with the following medical conditions:‡
 - Sickle cell disease
 - Congenital or acquired asplenia, or splenic dysfunction
 - Cochlear implants
 - Cerebrospinal fluid leaks
 - HIV infection
 - Congenital immune deficiency.
 - Chronic cardiac disease, particularly cyanotic congenital heart disease, cardiomyopathy, and cardiac failure.
 - Chronic pulmonary disease, including asthma treated with high-dose oral corticosteroid therapy.
 - Nephrotic syndrome and other conditions causing chronic renal insufficiency.
 - Diseases requiring immunosuppressive or radiation therapy.
 - Solid organ transplantation.
 - Diabetes mellitus
 - Metabolic disorders

*Routine vaccination of all healthy infants and children in this group is currently not recommended in Saudi Arabia. 7-PCV is recommended for subjects younger than the age of 2 years who have medical conditions that predispose them to pneumococcal disease. †23-PPV is recommended for these groups.

CRM197. These serotypes are responsible for more than 85% of invasive disease in young children in the USA, Canada and some other western countries.^{1-4,20-22} Unlike the 23-PPV, the heptavalent vaccine is highly immunogenic in infants and young children, including those with high-risk medical conditions.^{3,22} Studies in children younger than 6 years in the USA showed that the vaccine prevents >94% of invasive disease,³ >85% of bacteremic pneumonia, and 57% of otitis media caused by serotypes contained in the vaccine. In the USA and other western countries, the vaccine is currently recommended for routine immunization of all infants as a primary series of three doses given at 2, 4 and 6 months of age, and a booster dose at 15 to 18 months of age.^{3,21} In contrast to the 23-PPV, the heptavalent vaccine also decreases nasopharyngeal carriage, a substantial source of transmission of pneumococci. This vaccine is not registered in Saudi Arabia as yet, but is available at some hospitals and private clinics.

The efficacy and cost-effectiveness of the currently available pneumococcal vaccines in a particular population largely depends, among other factors, on the serotypes causing invasive disease in that population. Thus, knowledge of the serotype distribution is key to the development of guidelines or vaccination strategies against pneumococcus disease. Until recently, no information was available on the serotypes causing pneumococcal invasive disease in the Kingdom. In 2003, Memish et al¹² analyzed the

serotypes of 154 *S. pneumoniae* clinical isolates from different body sites collected from patients of all age groups at three major hospitals in different provinces in the country. The majority of isolates were from patients between 10 to 50 years of age. Six isolates were from children younger than 10 years, and fifteen isolates were from subjects older than 60 years of age. Of the 48 isolates from sterile sites (blood and cerebrospinal fluid) that belonged to known serotypes, 40 (83%) were represented in the 23-PPV vaccine. In this issue of the Journal, Al Mazrou et al¹³ report on the serotypes of 78 *S. pneumoniae* isolates from sterile body sites of patients in eight major hospitals in Riyadh. Forty-four of the isolates were from children 2 years of age or older. Of the 44 isolates from patients in this age group, 38 (86%) are represented in the 23-PPV. While both studies are limited due to their small sample size, the results are encouraging in that they give credence to practices that utilize the 23-PPV vaccine in high-risk groups older than the age of 2 years in this country.

In the study by Mazrou et al,¹³ 17 of the 27 (63%) *S. pneumoniae* isolates from subjects younger than 2 years of age are represented in the heptavalent conjugate vaccine (7-PCV). A cost-benefit evaluation of routine vaccination of all healthy infants in the USA with 7-PCV, using estimates of meningitis, bacteremia, pneumonia and acute otitis media, showed that vaccination would result in net savings to society if vaccine costs were less than USD \$46 (SAR173) per dose. As the vaccine is not registered in the Kingdom, the market cost is not known. It is expected, however, to be much more expensive than 23-PPV. In the USA, the average wholesale price for each dose of *Prevnar* is USD \$76 (Redbook 2004). The paucity of large-scale epidemiologic data on pneumococcal disease burden and serotypes in Saudi Arabia, and the high cost of the vaccine preclude a recommendation for mass immunization of all healthy infants with heptavalent vaccine in this country at this time. However, it would be prudent to provide 7-PCV for infants and children 2 years of age and younger who have medical conditions that predispose them to high risk of invasive pneumococcus disease for the following reasons: a) there is no alternative vaccine for prevention of pneumococcal infections in this age group; b) invasive pneumococcal disease is associated with high morbidity and mortality; c) the vaccine has a favorable safety profile, and d) the vaccine does not compromise the immunogenicity of other routine vaccines given for infants. It is important to note that the number of

Table 2. Recommended schedule for heptavalent pneumococcus conjugate vaccine for children <24 months of age who have medical conditions that predispose them to invasive pneumococcal disease.

Age at First Dose	Primary Series	Booster Dose
2-6 months	3 doses, 6-8 weeks apart	1 dose at 15-18 months of age
7-11 months	2 doses, 6-8 weeks apart	1 dose at 15-18 months of age
12-23 months	2 doses, 6-8 weeks apart	–

doses of 7-PCV needed depends on the age of the child when the first dose is given (Table 2). A single dose of 23-PCV is also given to high-risk children starting at the age of 2 years (Table 3).

Based on experience and anecdotal reports, the use of 23-PPV in the Kingdom has been largely limited to patients with sickle cell disease and those with congenital or acquired asplenia. But even in such patients who are known to be at very high risk of invasive pneumococcus disease, vaccination rates are very low. In the year 2004, a total of 11 000 doses of *Pneumo 23* were purchased by the Ministry of Health, and 5000 doses by other hospitals and clinics in the Kingdom (personal communication, Aventis Pasteur Regional Office). Given the number of patients who are potentially at risk of invasive pneumococcal disease, the vaccine is definitely underutilized. This could be due to a number of reasons, but is primarily due to lack of awareness among healthcare providers and patients of the seriousness of pneumococcal disease and the benefits of vaccination, and the unavailability of a continuous supply of vaccine at clinics and hospitals.

An optimal strategy for use of pneumococcus vaccines in the Kingdom can only be determined on the basis of large-scale epidemiologic studies of disease burden across all age groups, serotype distribution, and other financial and logistical considerations. The Ministry of Health, in collaboration with the Medical College at King Saudi University, is embarking on a multi-center national epidemiologic study in children under the age of 5 years to determine the circulating serotypes and disease burden in this age group. Studies across all age groups, including the elderly are also needed. In the meantime, vaccination of high-risk groups of all ages with age-appropriate vaccines should be promoted to decrease morbidity and mortality from invasive pneumococcal disease. Immunization should be given at least 2 weeks before splenectomy. If this is not possible, it should be given two weeks after the operation. Whenever possible, immunization should be given to patients undergoing chemotherapy or radiation therapy at least 4 weeks before commencing treatment.

Additionally, children with sickle cell disease and other conditions associated with functional or anatomic asplenia should receive antibiotic prophylaxis regardless of their immunization status.

Table 3. Recommended schedule for pneumococcus vaccination for children 24-59 months of age who have medical conditions that predispose them to invasive pneumococcal disease.

Vaccine/ doses received before age of 24 months	Schedule
4 doses of 7-PCV	A first dose of 23-PPV at 24 months, at least 6 weeks after last dose of 7-PCV A second dose of 23-PPV, 3-5 years after the first dose of 23-PPV vaccine
1-3 doses of 7-PCV	A dose of 7-PCV A first dose of 23-PPV, at least 6 weeks after the last dose of 7-PCV A second dose of 23-PPV, 3-5 years after the first dose of 23-PPV vaccine
None	2 doses of 7-PCV, 6-8 weeks apart A first dose of 23-PPV, at least 6 weeks after the last dose of 7-PCV A second dose of 23-PPV vaccine, 3-5 years after the first dose of 23-PPV vaccine

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