

## UNIT NO. 3

# PNEUMOCOCCAL, AND H1N1 AND SEASONAL INFLUENZA VACCINES FOR CHILDREN – HOW TO ADVISE

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**ABSTRACT**

**This review provides information on the two vaccines that have become more widely used in Singapore children in the recent year (2009/2010). These are the pneumococcal conjugate vaccines, which have been included into the Singapore Childhood Immunization Program since October 2009, and the introduction of the novel H1N1 Influenza A vaccine, also known as the pandemic influenza vaccine, in December 2009.**

**KEYWORDS: Vaccines, vaccine-preventable disease, pneumococcal conjugate vaccine, H1N1 influenza A vaccine, pandemic influenza vaccine, Childhood Immunization Programme.**

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**INTRODUCTION**

This review intends to provide the family physician with update information on two vaccines that have become more widely used in Singapore children in the recent year (2009/2010). Pneumococcal vaccination in children was recently introduced into the Singapore Immunization Program in October 2009. Two (Prevenar®, Synflorix®) of three versions of pneumococcal conjugate vaccines are currently registered for use in Singapore, and a third (Prevenar 13®) is likely to become within the next year. Confusion may arise from the choice of vaccine, their interchangeability and their recommended schedules and these will be discussed in this review.

Although seasonal influenza vaccination has not been introduced for universal vaccination into the Singapore childhood immunization program, the recent influenza A H1N1 pandemic in 2009 has provided impetus for the use of influenza vaccination, in particular the pandemic vaccine in children. We should also always bear in mind the clinical situations in which annual seasonal influenza vaccination is recommended in children.

**PNEUMOCOCCAL DISEASE IN SINGAPORE**

*Streptococcus pneumoniae* is a common cause of invasive pneumococcal disease (IPD) such as bacteraemia, sepsis, bacteraemic pneumonia and meningitis, and non-invasive disease

such as pneumonia and otitis media in children worldwide. Epidemiology studies also show that it is a significant burden in Singapore. An earlier study from 1977 to 1986 of 43 paediatric and 143 adult isolates found an overall mortality rate of 25%, and penicillin resistance of isolates was 0.5%<sup>1</sup>. A more recent study in children<sup>2</sup>, showed that the estimated overall average incidence of IPD was 13.6 per 105 children under 5 years of age, and possibly as high as 70 per 105 children under 5 years old for non-invasive disease. The overall antibiotic resistance was higher than in the earlier study: penicillin 44.4% (15% intermediate, 31% resistant) ceftriaxone 15% (14.3% intermediate, 0.75% resistant), erythromycin 62%, trimethoprim-sulfamethoxazole 67%. The peak age incidence for invasive disease was in the 2-5 year age group (46.9% of cases) with a mean age of infection at 3.75 years. This age distribution is higher compared to western populations where the peak age of incidence is 1.5 years of age, and the authors have postulated that the later age of childcare attendance in Singapore during the period of study may be one of the reasons.

**CONJUGATED PNEUMOCOCCAL VACCINES**

The development of protein conjugated pneumococcal vaccines paved the way for effective prevention of invasive pneumococcal disease in infants and young children. Protein conjugation confers immunogenicity to the pneumococcus carbohydrate antigen, which is normally poorly immunogenic to the immature infant immune system. Their introduction into routine childhood immunization programs have markedly reduced the incidence of invasive pneumococcal disease and pneumonia, not only in children, but also in the elderly through herd protection<sup>3</sup>. These vaccines have also been shown to be well tolerated. The details of commercially available conjugate pneumococcal vaccines, Prevenar®, Synflorix®, Prevenar 13® are summarized in table 1.

**Table 1: Commercially available conjugated pneumococcal vaccines**

Vaccine Valency and conjugate carrier protein	Brand Name Manufacturer	Vaccine Serotypes	Registered in Singapore (as at April 2010)
7 Diphtheria CRM 197 protein	Prevenar Pfizer	4, 6B, 9V, 14, 18C, 19F, 23F	Yes
10 Protein D (derived from non-typeable <i>Haemophilus influenzae</i> )	Synflorix GlaxoSmithKline	Above plus 1, 5, 7F	Yes
13 Diphtheria CRM 197 protein	Prevenar 13 Pfizer	Above plus 3, 6A, 19A	No

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## WHICH PNEUMOCOCCAL CONJUGATE VACCINE TO SELECT

The first pneumococcal conjugate (7-valent) (7vPnC) vaccine was developed based on epidemiology of the distribution of invasive pneumococcal infections in North America<sup>4</sup>. This seven-valent vaccine therefore confers protection against the 7 most common serotypes causing invasive pneumococcal disease in the North American population. Fortunately, based on local data<sup>1</sup>, this seven-valent vaccine also provides good coverage of invasive pneumococcal infections in Singapore, with 89% of infections involving vaccine-related serotypes for children under 5 years of age<sup>2</sup>.

The 7vPnC vaccine, however, does not protect against a significant proportion of certain non-vaccine serotypes that cause invasive pneumococcal disease in some other parts of the world. Of these, serotypes 1 and/or 5 may be relatively more common which were 2 of three the serotypes (1, 5, and 14) should be included in the new generation pneumococcal conjugated vaccine recommended by WHO. Hence the newer generation 10vPnC, which has been registered in many countries globally, including Singapore, addresses this issue by the inclusion of 3 additional serotypes, serotype 1, 5 and 7F. These serotypes, particularly serotype 1 and 5 are important in some countries in Asia and Europe, hence making it a more globally relevant vaccine<sup>5</sup>. These 3 serotypes do not seem to be common in Singapore from the data during 1997-2004<sup>2</sup>.

Besides the additional 3 pneumococcal serotypes, the 10vPnC-10-valent pneumococcal non-typable Hemophilus influenza protein D conjugated vaccine (PHiD, Synflorix) may also confer an additional advantage. The conjugate carrier protein of this vaccine, Protein D of non-typeable Hemophilus influenza (NTHi), also confers immunity to this protein and therefore to NTHi. It has been shown that vaccination with 10vPnC results in a reduction in nasal carriage of NTHi6, and that it could in turn reduce the prevalence of acute otitis media due to NTHi. The reduction in otitis media infections reported in this study, however, did not reach statistical significance<sup>6</sup>.

There is yet a third pneumococcal vaccine (13 - valent) that there has recently been approved by the Food and Drug Authorities and European Medicines Agency, but not registered in Singapore yet. This vaccine has a further additional 3 serotypes (3, 6A and 19A) compared to the 10-valent vaccine. These include emerging serotypes, also known as replacement serotypes, which have been found to cause a proportion of invasive disease since the introduction of universal 7vPnC vaccination in the US and other countries<sup>7</sup>.

The selection of PnC vaccines used in population would therefore depend greatly on the epidemiology of invasive pneumococcal infections and the pneumococcal serotypes involved, as well as possibly that of NTHi infections, which are usually otitis media and pneumonia. For example, the USA has adopted the 13vPnC, while Canada has adopted 10vPnC with NTHi carrier protein.

It should also be noted that with increasing valency of the pneumococcal vaccines, there has been compromise to immunogenicity of all the serotypes especially the less immunogenic ones which are serotypes 6B, 23F, 9V and 3. Despite this, however, it is likely that based on derived antibody levels of protection, these lowered antibody responses would still be protective. Post marketing surveillance on the epidemiology of invasive pneumococcal infections would be crucial to confirm the efficacy of these vaccines as clinical trials are very costly, and most countries have already introduced pneumococcal vaccination into their program.

## WHICH VACCINE SCHEDULE TO ADOPT

With the implementation of universal pneumococcal vaccine globally, alternative schedules have been adopted by various countries outside the USA (Table 2). The conventional USA immunization schedule uses the schedule that is recommended by the manufacturers. This is a 4 dose schedule, with 3 primary doses and 1 booster (3+1). Other countries like the United Kingdom and some countries in Europe have adopted an alternative 3 dose schedule, with 2 primary doses and 1 booster (2+1). Singapore has also elected to follow this 3 dose schedule. Immunogenicity studies have been performed to compare the 4 dose and 3 dose schedules. These studies have shown reduced immunogenicity of serotypes 6B and 23F after the 2 primary doses. This reduced immunogenicity is however improved after the booster dose, where titres become comparable to the 3+1 schedule<sup>8</sup>. A similar study comparing schedules for the 10vPnC vaccine show similar findings<sup>9</sup>. Some states in Canada have adopted the 3 dose (2+1) schedule with this vaccine.

**Table 2: Vaccination Schedules for Prevenar and Synflorix**

Age Group	Recommended* Schedule (Primary**+booster)	Examples of Countries adopted
6w-6m	3+1	USA (Prevenar )
>6m-<11m#	2+1	Canada (some states)
12m-23m#	1+1	(Synflorix <sup>^</sup> )
24m-9yrs#	1	
<b>Alternative schedules</b>		
6w-6m	2+1	UK and Singapore
>6m-<11m#	1+1	(Prevenar)
12m-59m#	1	Canada (some states)
		(Synflorix) <sup>^</sup>
6w to 6m	3+0	Australia

\* Recommended schedule according to product insert

\*\* Primary doses should be at least 1 month apart

Booster dose should be at least 2 months apart from the primary dose

# Catch up vaccination

<sup>^</sup> Current prescribing information indicates that Synflorix is not to be used above the age of 2 years.

Currently, interchanging 7vPnC with 10vPnV in the midst of the primary course of vaccination is not recommended, as the carrier conjugate proteins are not the same. There have been no studies to show their interchangeability, except for one study to show that after 3 doses of primary course of 7vPnC, a booster dose with 10vPnC could illicit booster antibody responses of the 7 common serotypes, albeit slightly lower than a booster with 7vPnC<sup>10</sup>. Antibody responses to the additional 3 serotypes were also documented. Switching from 7vPnC to 13vPnC at any stage of the vaccine schedule is possible, as these 2 vaccines from the same manufacturer, have the same carrier conjugate protein.

## POLYSACCHARIDE PNEUMOCOCCAL VACCINES

The 23-valent polysaccharide (not conjugated to protein) is the first pneumococcal vaccine available. Without the protein conjugation, it is not immunogenic in young infants and is therefore not recommended for use in children less than 2 years of age. The Ministry of Health Singapore recommends the use of this vaccine in high risk children above the age of 2 years. These include competent immune children with chronic lung and heart disease, diabetes mellitus, and cochlear implants; and immunocompromised children such as those with functional or anatomic asplenia. It is appropriate to immunize with a conjugate pneumococcal vaccine using the appropriate schedule for age, followed at least 2 months later by a dose of a 23-valent polysaccharide vaccine<sup>11</sup>. Booster doses are not routinely recommended, except for those with asplenia and chronic renal disease where boosters may be given every 5 years.

## SEASONAL AND H1N1 INFLUENZA IN SINGAPORE

In Singapore, like other tropical countries, influenza occurs year round with peaks usually in June and December<sup>12</sup>. The annual all-cause death rate from seasonal influenza in Singapore has been estimated at 14.8/100,000 person years with a significant proportion occurring in the elderly persons<sup>13</sup>. In April 2009, a novel influenza A virus (H1N1) of swine origin emerged in the United States and triggered alarm about its pandemic potential. The enhanced influenza surveillance in Singapore then implemented and the first case of pandemic (H1N1) 2009 was detected on May 26, 2009<sup>14</sup>. This was followed by a transition from influenza cases caused predominantly by seasonal influenza to one that was exclusively pandemic (H1N1) 2009 virus. It is fortunate that the disease caused by novel H1N1 Influenza A was not as severe as anticipated by the World Health Organization.

## H1N1 AND SEASONAL INFLUENZA VACCINATION IN CHILDREN

Influenza vaccination remains the most effective means of preventing influenza in the community. The 2009/2010

recommendations for the prevention of the American Academy of Pediatrics has a policy statement on to be the most extensive in terms of coverage in the population<sup>15</sup>. The policy statement recommends annual influenza immunization for:

- All children, healthy and at risk of complications from influenza, aged 6 months to 18 years;
- Household contacts and out-of-home care providers of children placed at high risk, and healthy children less than 5 years;
- Health care professionals;
- Pregnant women in mid trimester of pregnancy onwards.

In December 2009, the non-adjuvanted pandemic H1N1 influenza A strain of vaccine became available for immunization of children in Singapore. Following this, it is likely that this novel strain will be one of the dominant strains of circulating seasonal influenza viruses. The 2010 southern hemisphere seasonal influenza trivalent vaccine contains the novel H1N1 strain.

The schedule of vaccination of inactivated H1N1 and trivalent seasonal influenza is described in Table 3. These vaccines are considered immunogenic (30-90%) and efficacious, but is directly proportional to age<sup>16</sup>. They are generally well tolerated with the most common adverse effects being soreness of the injection site and fever. Fever usually occurs with 24 hours after immunization and affects approximately 10 to 33% of children younger than 2 years; and is lower in older children and adults. Until recently, these vaccines are contraindicated in severe egg allergy as the vaccine contains traces of egg protein. It may, however, be administered in divided doses in a specialized allergy clinic if vaccination is deemed necessary. Egg-free influenza vaccines are also recently available outside Singapore. Live attenuated influenza vaccine that is administered intranasally is also available outside Singapore.

**Table 3: Schedule of Annual Seasonal Influenza Vaccination in Children**

Age group	Dose	Booster
6m-36m	0.25ml	1 dose at week 4
>36m	0.5ml	1 dose at week 4
>9 yrs	0.5 ml	Nil

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## LEARNING POINTS

- **Protein conjugation confers immunogenicity to the pneumococcus carbohydrate antigen, which is normally poorly immunogenic to the immature infant immune system.**
- **Countries like the United Kingdom and some countries in Europe have adopted an alternative 3 dose schedule of pneumococcal vaccine, 2 primary dose and 1 booster (2+1). Singapore has also elected to follow this 3 dose schedule.**
- **The 23-valent polysaccharide (not conjugated to protein) is not immunogenic in young infants and is therefore not recommended for use in children less than 2 years of age.**
- **The policy statement recommends annual influenza immunization for (1) all children, healthy and at risk of complications from influenza, aged 6 months to 18 years; (2) household contacts and out-of-home care providers of children placed at high risk, and healthy children less than 5 years; (3) health care professionals; and (4) pregnant women in mid trimester of pregnancy onwards.**