Streptococcus pneumoniae is a leading vaccine-preventable cause of childhood death with an estimated 716,000 deaths occurring annually. Recent advances have seen the development of vaccines targeted against Streptococcus pneumoniae that are immunogenic and efficacious in very young children. These pneumococcal conjugate vaccines have now been evaluated in developed and industrialising countries with consistent efficacy against invasive pneumococcal disease at least due to the serotypes included in the vaccine. The vaccine has also been efficacious in preventing radiographically confirmed pneumonia, but has had less effect on pneumococcal acute otitis media. The introduction of the vaccine into the USA has been greatly successful and exceeds its expectations based upon the vaccine efficacy trials. In addition to preventing a greater than expected burden of invasive disease and pneumonia than anticipated in vaccinated children, the vaccine has also been associated with marked reduction in pneumococcal disease among unvaccinated members of the population, referred to as ‘indirect protection’. The introduction of the vaccine into the immunisation programme of industrialising countries, such as in South Africa, require robust surveillance to evaluate the effectiveness of the vaccine in such settings where the epidemiology of pneumococcal diseases differs to that in developed countries.

**Introduction**

Pneumonia is the leading global cause of childhood death, outside of the neonatal period, and contributes to 19% of the 10 million childhood deaths occurring annually, the majority of which occurs in industrialising countries.1 Despite the successes in improving primary healthcare in South Africa since 1994, pneumonia nevertheless remains a leading cause of childhood death in South Africa, aggravated by the HIV/AIDS epidemic.

That pneumonia remains an important cause of childhood death in South Africa and other industrialising countries, is very much reflective of difficulties with implementing strategies aimed at treating rather than preventing the causes of this illness. Examples thereof include the World Health Organization’s acute respiratory tract infection case management strategy, which is focused on early detection and antimicrobial therapy of suspected pneumonia cases. Although a meta-analysis thereof supports its efficacy in reducing pneumonia mortality by 36% (95% CI: 20-49%)2 in high-mortality countries, only 48% of children with pneumonia are taken to healthcare facilities and only a third of children with pneumonia receive antibiotics.3 The key challenges to managing this simple-to-treat, yet important causes of childhood mortality relate to access to appropriate quality healthcare. In general, resources required to develop and sustain curative services are much more intense and challenging than that required to prevent disease through vaccination.

In South Africa, despite being an emerging economy country, access to basic healthcare remains limited, especially in rural areas. The last available South African data from 1998 indicated that only 37% of children with diarrhoea and 75% of children with pneumonia received treatment in South Africa.3 Additionally, South Africa was identified as one of a few countries in which the under-5 mortality rates have increased since 1990, largely attributable to the HIV/AIDS epidemic. Consequently whilst countries with much lower gross domestic products such as Bangladesh have shown decreases in the under-5 mortality rate from 149 to 69 per 1,000 live births between 1990 and 2006, the mortality rate in South Africa has increased by 19% from 60 to 69 per 1,000 live births during the same period. Although, the ongoing HIV epidemic is clearly a major driving force for this reversal in child health gains, pneumonia and diarrhoeal deaths contribute to this unacceptably high under-5 mortality rate in HIV-infected and HIV-uninfected children.

Against this background, it is encouraging that the Department of Health in South Africa has announced the introduction of two new vaccines, namely pneumococcal conjugate vaccine and rotavirus vaccine, into the national immunisation programme, starting from September 2008, and which should be available throughout the country by April 2009. The decision to undertake this measure is especially laudable considering the high costs of these vaccines, particularly for countries such as South Africa which is not eligible for donor support to purchase these vaccines, as well as that South Africa is among the first of any industrialising country and the first in

**Review: Introduction of the pneumococcal conjugate vaccine into the South African public immunisation programme: dawn of a new era?**

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Africa to introduce both these vaccines into the public immunisation programme. The introduction of both of these vaccines is also supported by pivotal studies conducted in South Africa which informs the likely benefit of these vaccines in South Africa and elsewhere in Africa. The clinical efficacy trials of both these vaccines in South Africa as well as experience from elsewhere are summarised below.

**Pneumococcal conjugate vaccine**

*Streptococcus pneumoniae* is recognised as the leading bacterial cause of pneumonia in children as well as having been identified as a common cause of super-imposed bacterial infection in individuals with respiratory virus-associated pneumonia.** Additionally, the pathogen is identified as the most important cause of meningitis in South African children since the introduction of *Haemophilus influenzae* type b conjugate vaccine, as well as a leading cause of acute otitis media, especially complicated cases that are associated with antimicrobial resistance. The burden of pneumococcal disease in South Africa is further aggravated by the HIV epidemic, with 70% of invasive pneumococcal disease occurring in HIV-infected children, despite them constituting <5% of the childhood population. This is further illustrated by the doubling in incidence of invasive pneumococcal disease documented in South African children one decade after the onset of the HIV epidemic.** It is estimated that *S. pneumoniae* causes 716,000 deaths annually in children.

**Pneumococcal conjugate vaccine and invasive pneumococcal disease**

A 9-valent pneumococcal conjugate vaccine (PCV) evaluated in South Africa showed that the vaccine was able to reduce vaccine serotype-specific invasive pneumococcal disease by 83% in HIV-noninfected children as well as 65% in HIV-infected children. Importantly, despite the lower efficacy in HIV-infected children, the benefit of vaccinating this group was evident by the greater burden of disease (830 vs. 19 per 100,000 in HIV-uninfected children) prevented through vaccination mainly because of the 40-fold greater incidence of invasive pneumococcal disease in HIV-infected children.** Similarly, whilst the 9-valent PCV was less efficacious in reducing radiographically confirmed pneumonia in HIV-infected (13%) compared with HIV-uninfected children (20%), a greater burden of disease requiring hospitalisation was prevented in HIV-infected children (910 vs. 100 per 100,000 child years) compared with HIV-noninfected children.**

The same 9-valent PCV was also found to reduce radiographically confirmed pneumonia by 37% in a rural setting in The Gambia as well as reducing all-cause childhood mortality by 16%**. The vaccine to be introduced into South Africa, however, only includes seven of the nine serotypes that were evaluated in the African vaccine efficacy trials and importantly do not include serotypes 1 and 5 which make up 15–20% of all serotypes causing invasive pneumococcal disease in African countries.** Nevertheless, despite a sub-optimal formulation of the vaccine being introduced into South Africa, the great burden of pneumococcal disease in such settings still justify the introduction of the 7-valent vaccine as a significant burden of these will still be prevented by the 7-valent formulation of the vaccine.

It is, however, important to recognise that vaccinating against a bacteria as complex as *S. pneumoniae* is not without other potential challenges. Some of these challenges which have already been identified include that the T-cell-dependent nature of the immune response to the vaccine which results in induction of memory responses, to help protect against pneumococcal disease later in childhood, among HIV-noninfected children may not be effective in HIV-infected children. Consequently, whilst efficacy against vaccine serotype invasive pneumococcal disease persists into later childhood in HIV-uninfected children, the efficacy of the vaccine was diminished from 65% at 2.3 years after vaccination to 38% in HIV-infected children five years following vaccination in the absence of booster doses of vaccine.** Furthermore, as protection induced by PCV is largely specific to the serotypes included in the vaccine, since there are 91 different serotypes, ongoing pneumococcal disease due to non-vaccine serotypes is an ongoing risk. Changes in the burden of non-vaccine serotypes may result due to immunological pressures resulting from vaccinating against selected serotypes as well as from secular changes that may be independent of pneumococcal conjugate vaccine use.

Furthermore, the experience of the importance of non-vaccine serotypes following the introduction of PCV may vary between settings, possibly related to differences in the epidemiology and serotype distribution of pneumococcal disease prior to introduction of PCV. Illustrative of this is the marked differences observed on the impact of PCV introduction on the overall burden of invasive pneumococcal disease between different communities. Whilst introduction of the 7-valent PCV was associated with a 90% reduction in the overall burden of invasive pneumococcal disease in the general USA childhood population post vaccination introduction,** the introduction of PCV into the native Alaskan community whilst associated with a reduction in vaccine serotype invasive disease was associated with almost reciprocal increases in non-vaccines serotype disease.** Consequently, the benefit of vaccinating against selected pneumococcal serotypes was mitigated by replacement disease due to non-vaccine serotypes. The overwhelming majority of the ‘replacement’ disease due to non-vaccine serotypes resulted from a few selected serotypes, which were associated with disease even prior to introduction of PCV in this community. Additionally, whilst replacement disease due to non-vaccine serotypes may result from strains of pneumococcus switching their capsule to a non-vaccine serotype, ongoing pressure such as antibiotic use may also facilitate the heightened presence of specific serotypes. Unfortunately, it remains difficult to predict what the extent of replacement disease may be in different settings, hence making it essential that surveillance for pneumococcal disease be maintained following the introduction of PCV. This is perhaps even more pertinent in South Africa where serotypes which may not be virulent in HIV-uninfected children may in fact be virulent in HIV-infected children and become more dominant with the introduction of the 7-valent PCV.

**Pneumococcal conjugate vaccine and indirect protection**

Surveillance post introduction of PCV, however, also needs to be focused upon measuring the effectiveness of the introduction of PCV on the overall burden of pneumococcal disease, including the more
The introduction of PCV has, however, been associated with serotypes that are included in the 7-valent formulation of antibiotic-resistant strains which frequently are mainly associated from indirect protection resulting from reduced circulation of the vaccine among unvaccinated members in the community. This indirect effect of the vaccine is attributed to the ability of the vaccine to reduce nasopharyngeal colonisation among vaccinated individuals. Since young children are the main sources of transmission of pneumococcus within a community, reducing colonisation of vaccine serotypes among the young children through vaccination, resulted in a reduction in the non-vaccinated population especially very young infants (<3 months) and adults commonly in contact with children (18-39 and >65 years of age) which was greater than 2.2-fold compared with that prevented directly in vaccinated children.

**Pneumococcal conjugate vaccine and antibiotic resistance**

The PCV was also shown to reduce invasive pneumococcal disease associated with antibiotic-resistant strains in the South African vaccine efficacy trial. The impact of introduction of PCV into the USA has similarly shown a dramatic decline in the burden of invasive pneumococcal disease associated with antibiotic-resistant pneumococcal strains, and has also shown such reductions occurring in the rest of the unvaccinated population. This too has resulted from indirect protection resulting from reduced circulation of the antibiotic-resistant strains which frequently are mainly associated with serotypes that are included in the 7-valent formulation of PCV. The introduction of PCV has, however, been associated with some antibiotic-resistant strains now being encapsulated by non-vaccine serotypes, especially serotype 19A. The emergence of these non-vaccine serotypes as more important causes of invasive pneumococcal disease and antibiotic-resistant related strains cannot, however, be solely attributed to the introduction of PCV.

**Pneumococcal conjugate vaccine and pneumonia**

Additional findings realised through surveillance with the introduction of PCV in the USA included its greater than anticipated impact upon non-bacteraemic pneumococcal pneumonia. The absence of a sensitive tool with which to make an aetiologically specific diagnosis of pneumococcal pneumonia has been a major challenge in evaluating the impact of vaccination upon pneumococcal pneumonia. Nevertheless, despite the PCV only showing a 6-9% reduction in all clinically diagnosed pneumonia and a 20-37% reduction in radiographically confirmed pneumonia in the vaccine efficacy trials in the USA and Africa, the introduction of PCV into the USA has been associated with a 39% decline in hospitalisation for clinically diagnosed all-cause pneumonia. In another analysis, Zhou et al also showed a 52% (11.5 vs. 5.5 per 1,000 child years) reduction in hospitalisation for all-cause pneumonia and 41% (99.3 vs. 58.5 per 1,000 child years) reduction in pneumonia requiring an ambulatory visit. The importance of the changes in the burden of pneumonia temporarily associated with the introduction of PCV in the USA is manifest in that the annual reduction in hospitalisation for pneumonia in the USA (40,000 cases) was almost 13-fold greater than the burden of invasive pneumococcal disease (approximately 3,000 cases) prevented through vaccination. This affirmed that similar to industrialising countries, the greatest burden of serious pneumococcal disease even in the USA relates to non-bacteraemic pneumococcal pneumonia rather than invasive pneumococcal disease. The greater than anticipated reduction in all-cause clinical pneumonia in the USA may also suggest that PCV has reduced the burden of hospitalisation for respiratory viral-associated pneumonia, as respiratory viruses may be identified in as many as 70% of children with pneumonia. The observation from the South African vaccine efficacy trial in which children receiving PCV were 32% less likely to be hospitalised for pneumonia in which respiratory viruses were identified provides more direct evidence thereof and underscores the important role of pneumococcal co-infection contributing to the severity of respiratory viral infections. Despite these inroads being made in preventing pneumococcal pneumonia through vaccination, it is nevertheless important to appreciate that the current formulation of PCV, including a 9-valent formulation may be preventing only 36-45% of all pneumococcal pneumonia, and there remains a significant residual burden of pneumococcal pneumonia even post introduction of PCV.

**Pneumococcal conjugate vaccine and acute otitis media**

Although acute otitis media (AOM) is accorded lower public health priority in industrialising countries, it nevertheless remains an important cause of morbidity in industrialising and developed countries. *S. pneumoniae* is the most common pathogen identified in children and an important cause of complications and treatment failure associated with AOM, largely related to antibiotic-resistant strains. Additionally, the high incidence of AOM and management thereof with antibiotics is an important contributor to the increasing prevalence of antibiotic-resistant strains of pneumococci that emerge due to antibiotic pressure selection. The efficacy of PCV against AOM was somewhat dampened by the significant increase of non-vaccine serotype-associated PCV observed in children vaccinated with PCV. Consequently, despite the fact that vaccination with the 7-valent formulation of PCV was associated with a 52% reduction in AOM due to vaccine serotypes, there was a 33% increase in AOM due to non-vaccine serotypes, resulting in no overall reduction in culture-confirmed pneumococcal AOM. Additionally, the vaccine efficacy trials indicated that there was a slight increase in AOM due to non-typable *H. influenzae*. A newer formulation of PCV which, however, uses *H. influenzae* protein D as a conjugate and included 11 serotypes, showed higher efficacy of the vaccine against pneumococcal AOM as well as against AOM due to *H. influenzae*. The latter vaccine was reformulated to include 10 serotypes and is currently undergoing evaluation for efficacy against pneumococcal pneumonia and should be licensed shortly. More broadly, despite PCV only reducing all clinically diagnosed AOM by 5-7%, the vaccination was found to reduce tympanic tube insertion by as much as one-third. Vaccination of children with recurrent AOM has, however, not been found to be useful. Post-introduction of PCV in the USA
has, however, been associated with more dramatic declines in the diagnosis and treatment of AOM. Zhou et al showed that introduction of PCV was temporally associated with a 43% reduction in ambulatory visits for AOM and also associated with similar declines in antibiotic prescriptions for the treatment of AOM.31

Conclusion
There is still much to be learnt of the effectiveness of PCV in industrialising countries. Whilst the experience from the USA provides valuable information of the value of PCV in such settings, differences in the epidemiology of pneumococcal disease in industrialising countries caution against extrapolating the USA experience to industrialising countries and demand equally intense surveillance to determine the effect of introducing PCV on childhood morbidity and mortality in industrialising countries such as South Africa. Additionally, there are a number of unresolved issues which still need investigation in countries such as South Africa. These include addressing the issue of the need and response to booster doses of PCV, especially in HIV-infected children. Additionally, the effectiveness of introducing PCV as a two-dose schedule during infancy (at 6 and 14 weeks of age) and a booster dose at 9 months of age requires evaluation regarding the immunogenicity and direct and indirect effectiveness of this schedule.

References