

The burden of pneumococcal disease in children – advances in the fight of this epidemic

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Abstract

Streptococcus pneumoniae, the most important cause of acute otitis media, pneumonia, septicaemia and meningitis worldwide, comes in 90 different serotypes. Only a few serotypes cause most of the serious disease. Different serotypes are distinguished by differences in the complex sugars that made up the bacteria's capsule that provide protection against the host's specific defenses. The burden of invasive pneumococcal disease in South Africa subjects is estimated to be 100 - 200 per 100 000. The conjugate pneumococcal vaccine has been shown to be effective in reducing invasive pneumococcal disease due to vaccine serotypes in all countries where it has been introduced. This benefit has extended to unvaccinated subjects. Reduction in penicillin resistant pneumococcus related to vaccine serotypes has been recorded. Replacement disease by non vaccine serotype has eroded the benefit of the vaccine. Industry, donors and governments need to interact to ensure accelerated implementation of this vaccine in developing countries.

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Introduction

Streptococcus pneumoniae is a bacterium that causes serious illness, including, pneumonia, meningitis, sepsis and otitis media. It is the most common cause of bacterial pneumonia. Acute respiratory infections (ARI) account for 62% (3.9 million) of the total deaths in children and adults globally each year. Of these, almost half (1.9 million) occurred in children under 5 years of age; a further 30% occurred in people over the age of 74 years. Seventy percent of these deaths occurred in sub-Saharan Africa and south-east Asia. Infections with pneumococcus account for an estimated 1.6 million deaths each year, 1 million of these in children under the age of 5 years. It is also the most severe cause of bacterial meningitis worldwide. In high mortality areas, pneumococcus kills 1% of all children born and leaves 50% of surviving children with serious sequelae. Children with HIV/AIDS are 20-40-times more likely to acquire pneumococcal disease than HIV uninfected children. Penicillin resistant pneumococcal infection is common in areas where antimicrobial use is high. With the increasing incidence of HIV disease and antimicrobial resistance there is an urgent need for life saving measures such as vaccines. An estimated 3.6 million lives could be saved by 2025 if serious efforts are made to introduce the conjugated and other novel protein based pneumococcal vaccines. Industry, donors and governments need to interact to ensure accelerated implementation of these vaccines. In

addition special attention should be placed on basic provisions for poor including adequate housing, food and safe fuels for combustion.

Epidemiology:

The relative incidences of the different organ systems involvement with pneumococcus varies from country to country. It usually occurs in the winter months each year. There are over 7 million cases of pneumococcal otitis media in the USA each year. In Europe and the USA the incidence of pneumococcal pneumonia, bacteraemia and meningitis is 100, 15-19 and 1-2 per 100 000 respectively while the associated mortality rate is between 10 and 20%. In South Africa laboratory surveillance of pneumococcus conducted at the respiratory and meningeal pathogen research unit, showed a low incidence of 5.4 per 100 000 for pneumococcal pneumonia between 1999 and 2003. This figure is grossly underestimated given that many areas rarely performed appropriate samples to determine the aetiology of pneumonia. When samples are mandatory, such as in cases of meningitis, the incidence of pneumococcal meningitis was significantly higher than that reported from industrialised countries. Chris Hani Baragwanath Hospital reported rates of 45 per 100 000 for pneumococcal meningitis with mortality rates of over 50% in high risk cases. The incidence rate for invasive pneumococcus disease in South Africa is unknown but estimated to be between 100 - 200 per 100 000.

Risk factors associated with higher disease burden

There is a much higher burden of disease in developing than developed countries due to overcrowded living conditions, child care centers, associated malnutrition and chronic illness, HIV disease and immunosuppression. The other major difference is the geographic variation of serotypes especially type 1, 3, 5 and 6A are common among subjects in Africa. Type 1 and 5 serotypes are responsible for pneumococcus outbreaks; type 3 is associated with pneumococcal emphysema. Antibiotic use and seasonal variation also influences serotype distribution. Pneumococcus disease mainly occurs in the extremes of age and in certain ethnic population e.g. Navajo Native Americans, White Mountain Apaches and the Aborigines. There is early onset (before 3 months of age) dense colonisation of the upper respiratory tract.

Pathogenesis

Pneumococcus is a gram positive encapsulated coccus. The polysaccharide capsule gives the pathogen its virulent characteristics. There are greater than 90 serotypes based on differences in the polysaccharide capsule which accounts for the differential disease burdens and diversity of the 20 commonly caused diseases. The capsule protects the pneumococci. Recently, sequencing of the cluster of genes responsible for synthesis of the capsular polysaccharide (cps gene loci) has been completed. Genetic finger printing of pneumococcal isolates from patients with invasive

disease helps to identify clones with genetic mutation and switch mechanisms that confer resistance and help avoid vaccines. Only 11 serotypes viz 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F are responsible for more than 75% of the invasive diseases in children and adults. Transmission occurs through direct contact with respiratory secretions from carriers or patients. Pathogenesis of pneumococcal disease is a complex multi-step process which commences with colonization of the nasopharynx. Humans are the only known host and a long term commensal relationship rather than invasive pneumococcal disease (IPD) is preferred by the pathogen. In the majority of infected persons there is transient nasopharyngeal carriage. Virulence factors such pneumolysin and the capsule determines duration and density of carriage. Cell mediated immunity responses are more important than antibodies for clearance of pneumococcus which on average takes 6 to 9 months. Competition with other micro-organism in nasopharynx also determines carriage. Adhesive pili-like appendages enhance nasopharyngeal colonization while surface protein FBA contribute to adherence to receptor on lung epithelial cells called Flamingo. Acquiring new pneumococcal organism in nasopharynx predicts 78% of first AOM episodes. Repeated acquisition of same pathogen results in naturally acquired immunity to subsequent carriage. A few susceptible individuals develop mucosal penetration by the bacteria. Common sites involved include middle ear (otitis media), sinuses (sinusitis) and respiratory epithelium (ARI). If there is inadequate clearance of the microbe by the body defenses and antibiotics, the disease becomes invasive with spread to adjacent lungs (pneumonia), dissemination to the blood (bacteraemia) and meninges (meningitis).

Laboratory Evaluation

Appropriate samples for identifying pneumococci include blood, lung aspirates, bronchial alveolar aspirates following lavage and cerebrospinal fluid. Sputum and nasopharyngeal swabs are useful to identify carriage. Microbiological testing includes gram staining, culture, common polysaccharide antigen, simple and complexed DNA polymerase chain reaction and paired serology and antigen detection. Sero-typing is performed after confirmation of the pathogen. Automated multilocus

sequencing typing (MLST) has recently emerged as the most objective and reproducible genotyping method for large scale genotyping. Mono-plex opsonophagocytosis assay and killing delineates relevant difference in serotypes

Immune status and susceptibility

Both antibody dependent and independent B and T-cell mediated mechanism are important in prevention and pathogenesis of pneumococcal disease. Natural (innate and adaptive) and vaccine acquired immunity have been described in HIV infected and uninfected children. In HIV infected children without HAART there is waning off of immunity after 9v PCV vaccination while there is persistence of immunity in older HIV infected children that receive HAART and who maintain a cd4 count of >25% and viral load <100 000. In measuring cytokines and chemokines gene expression in children with IPD, HIV appears to significantly influence expression. The rate of development of antibodies to pneumococcal polysaccharide has been shown in some children to be delayed making them more susceptible to infection. Boosting with an additional dose of vaccine after 12 months has been shown to be beneficial.

Drug resistance

Penicillin has been the drug of choice for children with pneumococcal disease. Since the first report of pneumococci resistance to penicillin in the 1960's in South Africa, there has been a steady and gradual increase the proportion of penicillin resistant pneumococci seen. Fortunately most of the pneumococcal isolates have intermediate susceptibility so that high dose penicillin is adequate to induce clinical and bacteriological remission. For cases of pneumococcal meningitis with intermediate resistance to penicillin, third generation cephalosporins or a high dose penicillin should be advocated. In 2003 77% of isolates at the RMPRU were fully sensitive, 22% were intermediately susceptible and 0.5% resistant. Pneumococci resistant to macrolides have also increased in prevalence substantially over the last decade with resistance rates of 50% seen in some regions of South Africa. Pneumococci resistant to cephalosporins has been seen infrequently globally. Childhood vaccination with the 7v PCV has resulted in the reduction in the prevalence of

penicillin resistant pneumococci especially amongst the 7 vaccine serotypes. However, replacement non vaccine serotypes are showing increased resistance to macrolides and penicillins. Resistance to quinolones of pneumococcus has stabilized at 5% and linezolid resistance by pneumococcus has been documented.

Vaccination:

Polyvalent purified capsular polysaccharide vaccine

Anti-capsular antibodies are a poor correlate to immunity. Antibodies to 23 valent polysaccharide capsular protein vaccines do not regularly elicit antibodies or immunological memory in children under 2 years of age or in the immunodeficient. In the elderly the 23 polyvalent purified capsular polysaccharide vaccine (23v PPV) protects against 90% of serious pneumococcal disease in the western world. It produces a 60-70% antibody response after 2-3 weeks. The antibodies can cross the placenta and into breast milk but their benefit in pregnancy is not established. In HIV infected adults with viral loads of less than 100 000 23v PPV has been shown to be effective.

Conjugated polysaccharide vaccines

There are several conjugated polysaccharide pneumococcal vaccines that have and are undergoing clinical evaluation in children. These include the 7 valent, 9 valent, 10 valent, 11 valent and 13 valent pneumococcal vaccines. Only the 7v conjugate pneumococcal vaccine (Prevenar) has been licensed for use in South Africa. Nasopharyngeal carriage for vaccine serotypes and non typeable *Haemophilus influenzae* (NTHi) were 41% and 43% respectively.

a. Impact of conjugate pneumococcal vaccine on serious illness

In a study of 8091 Navajo Indians subjects, the 7v PCV CRM197 was shown to have a 77% and 83% efficacy on per person and intent to treat analysis respectively. The major effects of 7v PCV was the significant reduction in the incidence of IPD and pneumococcal related deaths. This led to the introduction of the 7 valent conjugate vaccine routinely to children in the USA. During surveillance, the US centers for disease control and prevention (CDC) has reported a 94% decrease in vaccine type invasive pneumococcal disease

in children with a coverage rate of just 68%. A significant decrease was also seen in the unvaccinated groups as a result of herd immunity due to decreased transmission from vaccinated children to unvaccinated contacts. This benefit was also seen in HIV infected individuals. In Alaska native children the reported rates for vaccine serotypes pneumococcus was reduced to 5/100 000 per year post introduction vaccine from 175/100000 per year revaccination. The Calagery streptococcus pneumonia epidemiology research team also demonstrated significant reductions in the rates of IPD in children fewer than 2 years of age. In addition an associated fall in the incidence of PCV 7 serotypes invasive disease amongst adults > 65 years was seen as a result of herd immunity. In a randomized, placebo controlled, double blind multicenter study of 40 000 subjects from Soweto, 9V pneumococcal vaccine was shown to have 83% vaccine efficacy against HIV uninfected children and 65% efficacy in HIV infected children on an intention to treat analysis. Efficacy against bacteraemia was 30 to 45% and against vaccine serotypes were 59 to 67%. In another randomized, placebo-controlled, double blind multicenter study of 9v pneumococcal vaccine in children from the Gambia, an overall 16% reduction in childhood mortality in vaccinated group (mainly in subjects from rural areas) as compared to unvaccinated was seen. Vaccine efficacy against related serotypes was 73%. Protection against bacteraemia was 77% and there was a 37% reduction against radiological pneumonia.

b. Impact of conjugate pneumococcal vaccine on mucosal disease

The 7v PCV impact on acute otitis media in the Fin OM and Northern California Kaiser-Permanente study is less clear due to replacement disease with non vaccine serotypes and the increased proportion of non typeable *Haemophilus influenzae* in AOM isolates, many of which were B lactamase producing strains. Long term follow up of these children suggest that the vaccine had significant impact on the incidence of chronic OM.

The 11v PCV conjugated to NHTi has shown a 34% overall reduction in AOM with 66% reduction in vaccine related serotypes disease and a 35% reduction in NTHi disease. The impact of 7v vaccine against community acquired pneumonia has not been proven.

c. Herd effect of conjugate pneumococcal vaccine

The conjugate pneumococcal vaccine has a significant protective effect that extends beyond those vaccinated to other children, teenager, young adults and the elderly. The incidence of pneumococcal disease has fallen by between half and two-thirds via the indirect effect of preventing colonization and invasiveness. This effect is related to a number of dose administrations being 37% for first dose, 60% for the second dose and 75% for the third dose of vaccine. It also reduces the effect on vaccine serotype related pneumococcal antimicrobial resistance.

d. Replacement non vaccine serotype disease

Surveillance across several countries where the 7V PCV vaccine has been introduced reveals replacement disease by non vaccine serotypes especially 19A and 16F. This has marginally reduced the benefits realized from the vaccine and that obtained from herd immunity. This will help guide the development of reformulated vaccines to new serotype that could exhibit virulence. There is also concern that previous exposure to the PPV vaccine in the previous 5 years may result in hyporesponsiveness with subsequent vaccination with PCV.

Vaccine dosing regimen

Standard recommendation is to use 3 doses of the vaccine separated at monthly intervals commencing at 6 to 8 weeks and a booster between the 1st and 2nd year. Boosting has been shown to be beneficial for all children especially in HIV infected children. In Africa given the high burden of pneumococcal disease in the first month of age, administration of the vaccine at birth may be required. Administration of the vaccine at birth has been studied and although the safety has been established, the response to the vaccine is poor and an additional dose may be required. In the United Kingdom, 2 doses of PCV at 2 and 6 months followed by a booster at 12-18 months were shown to be equally effective as the standard therapy. Passively acquired maternal pneumococcal antibody has an attenuating influence on the IgG response to primary doses of PCV for some serotypes. The effect is lost by 1 year of age. In setting with high pneumococcal antibody concentrations, dosing regimen policy decisions should consider this effect.

Cost of vaccination

South Africa, a middle income country with a birth cohort of 1 million children each year will require an estimated 2 - 3 million doses of pneumococcal vaccine per year. Given the other pressing health needs of the country, the vaccine could only become affordable if the cost for the vaccine could be substantially reduced to make the intervention cost effective. Globally, currently the total number of doses required is an estimated 352 million doses are required. Forty three million doses are required for high income countries, 131million in middle income and 178million in low income countries at a cost of 2.3 billion, 3.4 billion and 1.3 billion respectively. Global immunization and vaccine strategies by WHO and UNICEF for equal access for all are essential to aid this process. The 23 v PPV has been shown to cost effective in older subjects

New vaccines and alternative prevention and intervention strategies

Current strategies are limited by number of serotypes contained in the vaccines and the cost of the vaccine themselves. Pneumococcal proteins such as pneumolysin, bacterial toxins and cell surface proteins, neurominidase elicits protection against invasive disease in animal models. Whole cell killed vaccine used intranasally has been shown to protect against colonization. 🙋

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