Pneumococcal disease in sub-Saharan African children: what is the effectiveness of the pneumococcal conjugate vaccine?

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Streptococcus pneumoniae is still a leading cause of morbidity and mortality among children in developing countries. Young children represent a high-risk group for severe pneumococcal disease, not only because of their physio-logical susceptibility but also because polysaccharide vaccines are not effective for them. Pneumococcal conjugate vaccines have shown a high protection against pneumococcal diseases all over the world. Therefore, the expanded use of this vaccine must be considered as a major world health priority.

The impact of pneumococcal disease in Africa

S pneumoniae (pneumococcus) is still a leading cause of morbidity and mortality among children in both developed and undeveloped countries. The lack of diagnostic facilities in most developing settings and a 'disease surveillance system virtually non-existent' are, according to S Obaro, the reasons why accurate pneumococcal disease estimations for developing countries are not available. Nevertheless, all the reports highlight that the burden of pneumococcal disease in the developing world is higher than in industrialised countries.[1,2]

As the World Health Organization (WHO) proclaim, at least 4 million children worldwide do not reach their fifth birthday due to pneumonia and other related conditions. Pneumococcus is the one to blame for at least 1 million of these deaths.[3] Recently a slightly lower prevalence has been reported by Scott; approximately 815 000 deaths in children aged <5 years in low-income countries and 1–4 million episodes of pneumococcal pneumonia in Africa.[2] Even these conservative estimations indicate that urgent action is required against pneumococcal disease so as to improve child survival – a major world health problem.[4,5]

The promising results that pneumococcal vaccines have achieved in United States and Europe have raised new hopes for decreasing child mortality in developing countries. Assessing the real impact that pneumococcus has among sub-Saharan Africa, as well as the epidemiological distribution of different serotypes, would be the first step to optimise and evaluate every vaccine programme.[2]

As previously stated, there are few studies about the real impact of pneumococcal disease in sub-Saharan Africa; Holliman et al. found 140 cases of laboratory-confirmed invasive pneumococcal disease (IPD) in a prospective study conducted from January 2002 to April 2005 in Kumasi, Ghana.[6] Though lack of epidemiological data meant the authors were unable to estimate the prevalence of IPD in Ghana, this study demonstrated the high mortality rate (47%), and what is worse, no evidence was found of improved prognosis compared with other previous studies conducted in the region. The disease was more prevalent among children under 5 years and a seasonal cluster of cases was observed with a high peak in February after the dry *harmattan* wind which, according to the authors, might alter nasopharyngeal defences. Serotype 1 was the most prevalent in this series, being isolated in 36% of the cases.[6] Gordon et al. reported 628 cases of IPD among patients admitted to emergency in Blantyre, Malawi from 1996 to 1998. Once again children were more susceptible to the infection. Serotypes 1 and 5 were the most prevalent isolates; 27% and 23% from paediatric blood and cerebrospinal fluid (CSF), respectively.[7]

Campbell et al. found 106 cases (5%) of IPD among 2049 febrile children in Bamako, Mali. The fatality rate was lower than other studies (24%), and the most prevalent serotypes were 5 and 2, isolated in 54% and 14% of cases, respectively.[8] Berkley et al. showed that pneumococcus was the leading cause of bacteraemia among children > 2 months in Kenya.[10] O'Dempsey and colleagues showed that the incidence of PID in Gambia was at least 554 per 100 000 per year in children <1 year and 240 per 100 000 in children <5 years with a high fatality rate (55%), especially among children with meningitis. Boys around 15 months of age were the highest risk group and serotypes 6, 14, 19, 1, and 5 were the most prevalent.[10]

The common risk factors for IPD, summarised in Table 1, have been identified in studies carried out in industrialised countries. O'Dempsey et al.,[10] in the study previously mentioned, highlighted the relevance of other factors such as poor weight gain, serious illness in the previous 6 months, or exposure to smoke (cigarettes or

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being carried on mother's back while cooking). Obaro has emphasised the relevance of other factors such as: younger age, HIV, malaria, malnutrition, genetic factors (e.g. homozygosity for the sickle cell gene or black race), and poor socioeconomic conditions together with the high prevalence of pneumococcal disease in sub-Saharan Africa.[11]

All these studies underline the devastating effect that pneumococcal infection has in low-income countries. IPD is a major cause of admission and mortality in Africa with rates up to ten-fold higher than in industrialised countries.[2] Thus, every effort to fight against IPD in developing countries will decrease the unacceptable current rates of childhood mortality.

Host defence against pneumococcus and development of vaccines

Pneumococcus is a Gram-positive diplococci whose outer surface consists of a cell wall surrounded by a polysaccharide capsule. The composition and quantity of capsular polysaccharide is the most important virulence factor because it protects the bacteria from host phagocytosis.[12] Capsular polysaccharides are highly heterogeneous and over 100 serotypes have been described so far. Most IPDs are caused by relatively few serotypes but the distribution of serotypes changes with time and age, and differs within geographical locations.[13,14]

The infection leads to homologous serotype immunity because, as Bogaert et al.[15] mentioned, the antigenicity of the capsule is type-specific. However, cross-reactions occur due to shared polysaccharides. At the same time, the cell wall is responsible for the intense inflammatory reaction that occurs in pneumococcal infections. Nasopharyngeal colonisation is common among healthy children but might lead to IPD if, for instance, pneumococcal clearance from the lung is not achieved. Adequate host immunity to pneumococcus requires phagocytosis and intracellular killing of the bacteria by neutrophils and intracellular macrophages in the presence of type-specific immunoglobulins and active complement. This antibody-initiated complement-dependent opsonisation is, according to Bogaert et al., the major immune protective mechanism.[15] If pneumococcus avoids these immune responses, it might penetrate the blood stream causing bacteraemia and other focal infections such as meningitis. Notwithstanding, not all pneumococcal serotypes are equally invasive.

Once in the blood, clearance of pneumococcus requires type-specific antibodies, complement, and phagocytosis in the liver and spleen. Several cell wall components can be recognised by the immune system and immunoglobulins against some of them like pneumococcal surface protein A (PspA) or pneumococcal surface adhesion A (PsaA) are under evaluation as possible components of future vaccines.[12]

The profound differences in the immunological properties of carbohydrates as compared to proteins are, as Obaro noted, the main reason for the limitations of carbohydrate vaccines (see Table 2).[4] T-cells help B-cells to produce antibodies to protein antigens. Such collaboration does not occur with carbohydrate antigens and a T cell-independent response occurs. This implicates the absence of memory B-cells and limits the length of protection. These properties of carbohydrate antigens have hindered the use of pure carbohydrate vaccine in high-risk groups such as infants or immunocompromised patients noted by Whitney.[16] The T-cell-dependent immune response against pneumococcus is present from birth but induces mainly IgG1 subclass in the first years of life and type-specific immunoglobulins are more effective if they belong to IgG2 subclass. In adults, the antibody response against capsule polysaccharides mainly generates these IgG2 subclass antibodies, whereas young children mostly generate IgG1 antibodies, which as Bogaert et al. observed, could enhanced susceptibility to pneumococcal infection.[15]

The development of pneumococcal vaccines throughout last century has tried to provide protection among younger children. Conjugating pneumococcal polysaccharide to a carrier protein such as diphtheria toxin mutant (CRM197), can lead to a T-cell-dependent response even in the first year of life as Whitney and colleagues have repeatedly demonstrate among children in the US.[3,16] Therefore, two types

Table 1 Risk factors associated with pneumococcal infection (adapted from references 4 and 11)

Physiological
Very young (<2 years of age) or elderly (>65 years of age)
Certain ethnic groups such as African or Indian Americans or Alaska native
Non-immunological defects
Disruption of bronchial epithelium (exposure to smoke, dust, viral infections, etc.)
Obstruction of eustachian tube (previous otitis etc.)
Decreased vascular perfusion (sickle cell disease, cardiac failure, nephritic syndrome)
Skull fracture or cerebrospinal fluid shunt
Immunological defects
Primary antibody deficiencies
Hypogammaglobulinaemia, IgG subclass deficiencies, B-cell malignancies
Phagocyte abnormalities (neutropenia, hyposplenia, liver cirrhosis, etc.)
Complement deficiencies (C2, C3, sickle cell)
Secondary antibody defects
Human immunodeficiency virus (HIV) infection
Lymphorecticular malignancies, post-cancer chemotherapy

Table 2 Major characteristics of T-cell-dependent antigens, T-cell-independent antigens, and polysaccharide (PS) conjugate antigens[4]

	T-cell-dependent antigens	T-cell-independent antigens	PS–protein conjugate antigens
T-cells required	Yes	No	Yes
Memory induction	Yes	No	Yes
Response in infants	Yes	No	Yes
Affinity maturation	Yes	No	Yes
Maturation of response	Early	Late	Early
IgG isotype	No	Yes	No

of vaccines are available nowadays:pneumococcal polysaccharide vaccine (PPV) and pneumococcal conjugated vaccine (PCV).

One polysaccharide vaccine (Pneumovax 23®) is licensed and contains 23 purified capsular polysaccharide antigens of 23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F) which covers 85-90% of pneumococcal diseases and, as Bogaert et al.[15] have shown, is effective in 61–75% of children above 2 years of age and adults. Several studies like that conducted by Huebner et al.[17] have revealed an additional benefit of the PPV vaccine used as a booster in patients who have previously received the conjugate vaccine. Besides, the past receipt of PPV has shown no effect in vaccine response to PCV in HIV-infected Ugandan adults, according to Miiro et al.[18] The shorter duration of antibody response in HIV-infected patients who, at the same time, have a pneumococcal attack rate up to 40 times higher, accounts for the recommendation of revaccination with PPV every 3 years (instead of every 5 years) in HIV-infected children.[19]

In February 2000, a multivalent protein–polysaccharide conjugate vaccine (PCV7; Prevnar® in USA and Prevenar® in EU) was licensed for use in infants and young children. The PCV7 includes polysaccharide antigens for 7 serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F.[16] The PCV7 has a potential coverage of over 85% of pneumococcal isolates in USA, 60-70% in EU and 55% in Asia according to Pelton and colleagues.[20] The recommended dosage is summarised in Table 3. PCV7 contains CRM197 as the protein carrier component, other licensed PCV products include different proteins such as tetanus toxoid or meningococcus group B outer membrane protein.[16] The limitation in the number of serotypes included is a major limitation of the PCV; too many serotypes may impair the antibody response to the polysaccharides by mechanisms such as antigens competition and a low number of serotypes will prevent its use in regions with different serotype distributions.[21]

Efficacy of conjugate pneumococcal vaccine in sub-Saharan Africa

The efficacy of the PCV7 was first assessed in Northern California in a prospective, double-blind, randomised trial in nearly 38 000 children. Efficacy in preventing vaccine-type IPD was 97.4% in children fully vaccinated. Since then, many other efficacy trials have been conducted in industrialised countries with different PCV products.[23] Protection against IPD, nasopharyngeal colonisation, otitis media, pneumonia, and antimicrobial resistance has been reported.[24-26] A summary of the most relevant studies carried out in developed countries is shown in Table 4.

Since 1996, when the first evidence of a decrease in pneumococcus carriage after PCV was published by Obaro et al. in Gambia, more data of improved child survival in sub-Saharan Africa with the use of PCV have encouraged the expanded use of this PCV in low-income countries.[27] The relevance that serotypes 1 and 5 have in developing countries is the reason why a nine-valent PCV – including serotypes 4, 6B, 9V, 18C, 19F, 23F, 1, and 5 has been advocated for those settings. The leading studies of efficacy of 9PCV in Africa were carried out in Gambia and South Africa (see Table 4). Due to their crucial contribution to encouraging the use of this vaccine in Africa, a more detailed description will be given here.

Klugman et al. evaluated the efficacy of 9PCV (see Table 4) in a prospective, randomised, double-blind study in 19 922 children from Soweto, South Africa, where HIV

Table 3 Recommendations for use of PCV (adapted from AAP and CDC)[22]

Age at first vaccination (months)	Vaccine administration
<6	2, 4, 6, and 12-15 months
7–11	2 doses 2 months apart; 3rd dose 12–15 months
12–23	2 doses 2 months apart
24–59	2 doses 2 months apart for children with high risk factors; consider one dose for healthy children
Note Vaccination is recommended for all children ≤23 months old or children 24–59 months old who are at risk of IPD AAP = American Academy of Paediatrics CDC = Centres for Disease Control and Prevention, USA	

Table 4 Clinical trials assessing the efficacy of PCV in children (adapted from Whitney)

Author	**Location**	**Vaccine**	**Schedule**	**Outcome**	**Per protocol analysis efficacy**
In industrialised countries					
Black et al.[29]	California 2000	PCV7	2, 4, 6, and 12 months	PID, vaccine serotypes Pneumonia Otitis media Ventilatory tube replacement	97.4% (82.7, 99.9) 20.5 % (4.4, 34.0) 7.0 % (4.1, 9.7) 20.1 % (1.5, 35.2)
Eskola et al.[30]	Finland 2001	PCV7	2, 4, 6, and 12 months	Any otitis media Otitis media, vaccine serotypes Otitis media, cross-reactive serotypes Otitis media, non-vaccine serotypes	6 % (–4, 16) 57% (44, 67) 51% (27, 67) 33 % (–80,1)
Dagan et al.[31]	Israel 2001	PCV9	1 or 2 doses	Upper respiratory infections Lower respiratory infections Otitis media Antibiotic use	15% (4, 24) 16 % (2, 28) 17% (–2, 22) 15% (13, 21)
O'Brien and Levine.[21]	American Indians 2003	PCV7	2, 4, 6, and 12 months	IPD, vaccine types	82.6% (21.4, 96.1)
In developing countries					
Klugman et al.[28]	South Africa 2003	PCV9	2, 4, and 6 months	Pneumonia with alveolar consolidation, HIV-negative IPD, vaccine types, HIV-negative IPD, non-vaccine types, HIV-negative IPD, vaccine types, HIV-positive IPD, non-vaccine types, HIV-positive IPD, penicillin-resistant	20% (2, 35) 83% (39, 97) –300% (–19 599 to 60) 65% (24, 86) –13% (-235 to 62) 67% (19, 88)
Cutts et al.[32]	Gambia 2005	PCV9	2, 3, and 4 months	Pneumonia, X-ray confirmed IPD, vaccine types All-cause admissions Mortality	37% (27, 45) 77% (51, 90) 15% (7, 21) 16% (3, 28)

infection was highly prevalent and pneumococcus antibiotic-resistance common. Among HIV-negative children, an 83% reduction in the incidence of a first episode of IPD caused by vaccine serotypes was observed, whereas a 65% reduction was reported among HIV-positive children. Overall a 50% protective efficacy of the vaccine against all serotypes was reported with an evidence of protection to some vaccine-related serotypes such as 6A but not to others like 19A.[28]

In HIV-uninfected children the incidence of first episode of radiologically confirmed pneumonia was reduced by 20%, whereas in HIV-infected children it was reduced by 13%. The incidence of IPD due to penicillin-resistant strains was also diminished by 67% in all the children studied. Mortality was reduced by 5% in the entire population and by 6% in HIV-infected children without any major adverse effects after vaccination (only a slightly increase in incidence of asthma and a transient increase in respiratory syncitial virus pneumonia). Therefore, this trial showed that this 9PCV was highly effective with similar efficacy rates to those observed in industrialised countries. Kulgman et al. also demonstrated the high efficacy of 9PCV in HIV-infected children.[28] The devastating consequences that the HIV pandemic has had among African children, as well as the increased risk that HIV infection confers to IPD, urges the extended use of 9PCV in developing countries.[33,34]

The increase in colonisation with non-vaccine serotypes has been noted since the PCV was licensed. This 'replacement' is one of the main concerns of the extended use of the vaccine. In the USA, where the coverage of 7PCV is high, the frequency of non-vaccine serotypes has risen, and has been shown as a cause of PID.[22] Nevertheless, this increase is considered smaller with the overall decline in vaccine-included serotypes.[35,36] In the study carried out by Klugman and colleagues,[28] there was also a non-significant increase in the incidence of non-vaccine serotypes, but as the authors argued, 'that only reinforces the importance of implementing strong sustained surveillance to monitor the effect of vaccination' rather than discouraging the use of 9PCV.

The efficacy of PCV in reducing drug-resistant pneumo-coccus has been shown repeatedly, with favourable consequences not only for vaccinated children but also for the entire population due to a herd immunity effect.[37-39] As Whitney and Klugman mentioned,[40,41] the lack of further antibiotic options in most developing settings, makes the contribution of PCV particularly relevant. In addition, this specific advantage of PCV would be extremely useful in Africa where a growing number of HIV-infected patients live with an increased risk of IPD due to resistant strains. Nevertheless, selective pressure due to antibiotic use will still occur, and an adequate rationale for the use of antibiotics should be encouraged all over the world to minimise the impact of pneumococcus resistance.[41]

Cutts et al.[32] also evaluated the efficacy of 9PCV against pneumonia and IPD in a prospective, randomised, double-blind trial in 8718 children from Gambia (see Table 4). They showed an efficacy of 37% against first episode of radiological pneumonia, 77% against vaccine-related IPD, 50% against all-serotypes IPD (with a significant protection against the three commonest serotypes: 14, 5, and 23F), and 16% against mortality, with fewer adverse event rates in the control group than in the placebo one and a non-significant increase of non-vaccine serotypes. This group of investigators developed a more precise method of calculating vaccine efficacy and conclude that 'the preventable burden of pneumococcal related pneumonia is at least seven times greater than of IPD'. The high contribution of pneumonia to childhood mortality encourages the expanded use of PCV in Africa. The efficacy of 9PCV, according to Cutts and colleagues, was greater for radiological pneumonia than for clinical pneumonia (only 7%).[32] The disparate sensitivity of the diagnostic criteria for pneumococcal pneumonia used in different studies might explain the variation observed in public health effectiveness. Madhi et al.[42] have recently proposed the use of markers such as C-reactive protein to measure the effectiveness of PCV programmes in low-resource settings.

The studies conducted by both Klugman et al[28] and Cutts et al[32] provide evidence that 9PCV can improve childhood survival in sub-Saharan Africa. Some other reports have also encourage the use of this vaccine in Africa. For instance, Huebner and colleagues[43] have shown that even one dose of 9CPV protects children <6 months against IPD and Enwere et al. have assessed the reduction in pneumonia among Gambian children after the introduction of the 9PCV. As many researchers have claimed, making PCV available as soon as possible to children who need itthe most is a world health priority.

Future challenges

Current evidence promotes the use of PCV to reduce pneumococcal mortality in developing countries. Lack of supply and economic constraints have been major limitations for its expanded use in developing countries.[45] Nevertheless, the creation of bodies such as the Global Alliance for Vaccines and Immunization (GAVI) in 1999 might accelerate the introduction of vaccines where most needed. Despite evidence of the cost-effectiveness of PCV in developing countries,[46] curative interventions have received most of the international contributions in the past.[3,47] As this review highlights, an immediate and effective introduction of PCV in developing countries is critical to improve childhood survival.

Due to the lack of adequate surveillance systems in most of sub-Saharan Africa, the expanded use of this vaccine will require the implementation of surveillance programmes as well.[4] Replacement of non-vaccine serotypes should be closely monitored to preserve the efficacy of PCVs all over the world. Besides, the development of new vaccines with protection against more serotypes or new pneumococcus targets, such as PspA or PsaA, is needed.[15] The experience gained in industrialised countries after the routine use of PCV will optimise its use in developing countries where the highest burden of neumococcal disease still exists.[3]

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