Sero-epidemiology of *Streptococcal Pneumoniae* in developing countries and Issues Related to Vaccination

*Vipin M Vashishtha, Puneet Kumar, Amol Mittal*

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**Vipin M Vashishtha**¹, **Puneet Kumar**², **Amol Mittal**³

**Abstract:**
Pneumococcal infections and disease are responsible for significant morbidity and mortality in developing countries. However, unlike the developed industrialized countries, the epidemiology of pneumococcal infections and exact disease burden are poorly defined in these regions. With the availability of pneumococcal conjugate vaccines followed by aggressive attempts from international health agencies and organizations to get these vaccines introduced in national immunization programs of developing countries, many issues have arisen. They include reliability of disease estimates put forward by World Health Organization, knowledge of circulating serogroups/serotypes of pneumococci in developing countries, need of devising an optimum dosing schedule, lack of indigenous cost-effective analysis of mass vaccination program, lack of disease surveillance system to monitor community impact of mass vaccination and the shortcomings of currently available pneumococcal conjugate vaccines. All these issues along with various issues related to introduction of a new vaccine in to the national immunization programs of developing countries are discussed in details in this review article.

**Keywords:** Epidemiology, pneumococcal serotypes, pneumococcal conjugate vaccines

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**Introduction**

Diseases caused by *Streptococcus pneumoniae* (*S. pneumonia* or pneumococcus) are a major public health problem worldwide. Serious diseases that are often caused by pneumococci include pneumonia, meningitis and febrile bacteremia; otitis media, sinusitis and bronchitis are more common but less serious manifestations of infection. In 2005, WHO estimated that 1.6 million people die of pneumococcal disease every year; this estimate includes the deaths of 0.7–1 million children aged <5 years, most of whom live in developing countries (1,2). According to latest estimates, pneumococcal disease caused about 826 000 deaths (582 000–926 000) in children aged 1–59 months, of which 91 000 (63 000–102 000) were in HIV-positive and 735 000 (519 000–825 000) in HIV-negative children (2). Of the deaths in HIV-negative children, over 61% (449 000 [316 000–501 000]) occurred in ten African and Asian countries. Ten countries with the greatest number of pneumococcal deaths in children aged 1–59 months include India (142 000), Nigeria, (86 000), Ethiopia (57 000), Democratic Republic of the Congo (51 000), Afghanistan (31 000), China (30 000), Pakistan (27 000), Bangladesh (21 000), Angola (20 000), and Uganda (19 000) (2).
In populations with high child-mortality rates, pneumonia is the leading infectious cause of mortality and accounts for about 20–25% of all child deaths (3). In these populations, *Streptococcus pneumoniae* is identified consistently as the leading cause of bacterial pneumonia, and pneumococcal bacteraemia is an important cause of child mortality (4, 5). HIV infection increases risk for pneumococcal disease 20–40-fold, and antibiotic resistance makes treatment difficult and expensive (6). Thus pneumococcal disease is a major global-health issue.

The efficacy of pneumococcal conjugate vaccines (PCVs) and their remarkable success in operational use in North America challenge us to define the burden of pneumococcal disease and the likely benefits of PCV use in developing countries. PCVs will be effective where there is a demonstrable burden of invasive pneumococcal diseases (IPDs) attributable to vaccine serotypes but herd protection and serotype replacement effects are unpredictable given existing knowledge of pneumococcal epidemiology in developing countries. Operational use of PCV in well-monitored settings is required to estimate these effects (7).

However, there are certain issues that need clarifications before embarking upon the wide-scale use of PCVs in developing countries having the highest burden of both morbidity and mortality of pneumococcal diseases.

**Disease burden: Do we have reliable estimates?**

A review of both published and unpublished data reveals that the incidence of IPD in some countries is well documented by way of large, long-duration studies, while in other countries, much of the available data have been extrapolated from international studies or have come from small population studies of limited geographical coverage. However, the data regarding the incidence of IPD in Asia are grossly lacking and reinforces the need for urgent and more substantial studies (8).

The figures provided by WHO are debated intensely and doubts have been raised on the numbers provided and even the methodology used by the premier agency has been challenged (9). Even a large country like India does not have reliable estimates. There are only few sporadic reports available mainly from southern India and date back to last decade. There is no recent large-scale community based study; most estimates are based on data acquired through hospital-based studies. The one multi-centered study which is being most frequently cited by the experts is again a multi-centric hospital based study performed in mid 90s (10). According to this study, 5.41% of all enrolled individuals with an overall case-fatality rate was 21.1% had streptococcal pneumonia infection (10).

Furthermore, the burden of different syndromes caused by *Streptococcus pneumoniae* in developing countries is not quite clearly specified. Only very rough estimates based on extrapolation of data from neighboring countries or from developing countries or in some instances data from probe studies of PCVs are available (2). Unlike the African countries, the major burden of disease syndrome caused by Strep. pneumoniae is pneumonia not meningitis. Hence, until the vaccines have good effectiveness at mass level against prevention of pneumonia; the desired impact of introduction of PCVs cannot be obtained. Here again, considering the very low prevalence of routine culture practices in febrile patients and virtual absence of registry of pneumonia and meningitis cases, exact impact on epidemiology of pneumococcal incidence and burden of pneumonia and meningitis cases in developing countries cannot be obtained. Any pneumococcal vaccine that has good efficacy and effectiveness at community level especially against pneumonia is urgently needed in most developing countries.

There is an urgent need to undertake multi-centric population-based surveillance studies to extend evidence to the far believed notion that IPDs constitute serious public health problem in majority of developing countries. Though lack of evidence does not mean lack of disease, the need is to undertake large community-based multi-centric surveys to gather evidence on exact burden of pneumococcal diseases.

Few countries such as Nigeria and China have already undertaking such surveys.

**Sero-epidemiology of *Streptococcal pneumoniae* in Asia and other developing countries:**

The capsule of pneumococcus bacteria is comprised of polysaccharides. However, there is great diversity in the structure of these polysaccharides from one pneumococcus to another. Although there are more
than 90 serotypes, not all of these are equally likely to cause serious, invasive pneumococcal disease. This combined with the fact that current vaccine prevention strategies are directed against the polysaccharide capsule of the pneumococcus together highlight the importance of understanding the distribution of capsular types in disease causing organisms. The serotype distribution of these disease causing pneumococci vary to greater or lesser degrees according to the site of infection, invasive potential, geographic region, antibiotic sensitivity pattern, and age of the host (11). Serogroup prevalence varies quite significantly from region to region. For example, outside the US, Canada and Europe, serogroups 1 and/or 5 are among the 3 most frequently isolated serogroups in blood, CSF and middle ear fluid (MEF). In Europe these two serogroups comprise about 10% of blood isolates. However, in the US and Canada, serogroups 1 and 5 comprise a very small percentage of cases of bacteremia in young children (11). However, in Asia and other developing countries, serotypes 1 and 5 are encountered much more frequently than in the developed world (12), although they also cause disease at relatively high rates in minority populations in the developed world. Many factors such as environmental, socioeconomic milieu and blood culture practices affect serotypes distribution across the globe. Serotype diversity of pneumococci make them different and difficult organism to target for control and elimination by vaccination in comparison to Hib which is characterized by single pathogenic subtype. Each serotype of pneumococcal bacteria behaves as an entirely different organism in epidemiological sense. Hence, an exact and most recent knowledge of serotypes circulating in a particular geographic region and in different parts of a country are of paramount importance when any policy decision on vaccination strategy against pneumococcal infections is contemplated.

Coverage of different serogroups and serotypes: A review

The data on exact epidemiology of pneumococci in developing countries is sparse and limited to few hospital based studies. A review of epidemiology of streptococcal pneumonia in many developing countries particularly the Asian countries has further strengthened this assumption. In Egypt, 205 isolates of Streptococcus pneumoniae, collected from the CSF of meningitis patients identified between 1998–2003, during sentinel meningitis surveillance. Five serotypes (6B, 1, 19A, 23F and 6A) accounted for 37% of the total isolates. Overall, 29 and 42% of serotypes were represented in the 7- and 11-valent conjugate vaccines, respectively. However, vaccine coverage for children <2 years was 38 and 56% for the 7- and 11-valent, respectively (13). In S. Arabia, a hospital based study of eight hospitals during 2000-01 found that 88% of serotypes belonged to ten serotypes: 6, 19, 1, 15, 14, 23, 7, 18, and 22. The potential coverage of different vaccine formulations of PCV was 54%, 65%, and 73% for 7-valent, 9-valent, and 11-valent, respectively (14). In Taiwan, a total of 522 Streptococcus pneumoniae invasive isolates from diverse sources were collected from January 2002 to December 2003. The most frequently isolated serotypes of S. pneumoniae were types 14 (18.4%), 23F (15.1%), 3 (13.8%), 19F (13.4%), 6B (8.2%), 9V (3.6%) and 4 (2.5%). The majority of cases were either under 5 years of age (24.1%) or older than 65 years (36.6%). The coverage of 7- and 11-valent protein conjugate vaccines of the serotypes in children under 2 years of age would be 78.8 and 86.5%, respectively (15).

A recent study from central Thailand conducted during 2006-2009 reported 6B, 23F, 14, 19F, and 19A the most common serotypes in children below 5 yrs of age while 6B, 19A, 23F, 4, 9V in patients >65-year old (16). Potential coverage of different vaccine formulations (PCV) were: 70.3% for PCV 7 and 81.2% for PCV 13 (<5yrs old). PCV-9, PCV-10, PCV-11 had very similar coverage as PCV-7 (16). Similarly, 19F, 14, 23F, and 6B were found to be most common serotypes from a recent surveillance project from Colombo, Sri Lanka (17). Of the serotypes found, 60% are covered by the currently available 7-valent protein conjugate pneumococcal vaccine. In Nepal, as part of the pneumococcal surveillance project of the South Asian Pneumococcal Alliance Network a total of 2528 children with suspected invasive bacterial disease were recruited in Kanti Children’s Hospital and 50 were found to be having strep. pneumoniae as the etiological agent of invasive disease. The most common serotypes found were 1, 5, 2, and 7F, followed by 12A, 19B, and 23F (18). From a population-based surveillance project from rural Bangladesh conducted from 2004 to 2007, the overall IPD incidence was found to be 86 cases per
100,000 child-years. The most prevalent pneumococcal serotypes were serotypes 1, 5, 14, 18C, 19A, and 38 (19).

In a recently concluded surveillance project of GAVI and WHO undertaken in 14 resource-constrained developing countries, where 191,000 blood specimens and 34,000 CSF specimens collected and processed during the course of 4 years, a marked variability in the results was observed (20). Most notably, the data show that the severity of pneumonia among patients, with use of the same standard definition, varied considerably across sites, sometimes even within the same country or city. These countries include Bangladesh, Nepal, Sri Lanka, Pakistan, Taiwan, Thailand, Burkina Faso, Nigeria, Mozambique, Ethiopia, Kenya, Tanzania, Togo, and Uganda. The *S. pneumoniae* was isolated from 0.8–19.4% of under-5 yrs children from the CSF and 0.1–2.3% from blood. Types 1, 2, 6A, 6B, and 14 were the most common serotypes, whereas penicillin non-susceptible serotypes ranges from 0-90% from different countries. The incidence of pneumococcal pneumonia ranges from 10.6 to 43 cases per 100,000 person-years whereas pneumococcal meningitis incidence also showed marked variability and ranges from 3–48.7 cases per 100,000 person-years. Based on serotypes distribution in different countries and regions, the coverage of 7-, 10-, and 13-valent PCV also had a marked variability and ranges from 6-79%, 35-100%, and 41-100%, respectively (20).

As far as prevalence of pneumococcal infections in India is concerned, the scene is not much different. There are only handful of small hospital-based studies mostly from south India are available, and the only comparatively large multi-centric study is almost a decade back and again a hospital based study. From one study from CMC, Vellore, South India, over one-third of pneumococci in children and nearly half in adults were serotype 1 followed by serogroups/types 5, 6 and 7. These 4 serogroups/types accounted for 79% strains in children and 71% of all strains in adults (21). The remaining 11 strains belonged to 8 serogroups/types, namely 3, 4, 10, 11, 12, 13, 19 and 20. Another study done on nasopharyngeal carriage of 100 healthy subjects attending well baby clinic of the same institution found colonization with pneumococci on at least one occasion in 81 infants (22). The common SGTs identified were 6, 19, 14 and 15. However, the serotype 1, which was a common invasive isolate in children in the same hospital during this period, was not isolated from these children (22).

In yet another study from south India, majority (59.3%) of the isolates belonged to one or other of the serotypes 1, 6, 19, 5, 23 and 7 and serotype 1 was the commonest isolate (23). From our own hospital’s data, pediatric meningitis (3mo to 18 yrs) cases constituted around 2.04% of total indoor admissions in year 2009, and pneumococcal meningitis constituted more than half (56.25%) of these cases (unpublished data).

However, it is the Invasive Bacterial Infection Surveillance (IBIS ) multi-centric study from six centers across India in 1994-1997 that is most frequently quoted. In this study, the characteristics of invasive pneumococcal infections in six hospitals in India were studied over 4 years, in patients with suspected pneumonia (3686), pyogenic meningitis (1107), septicaemia (257), or localised pus-forming lesions (688). Overall, 215 (70%) of the isolates were of serotypes 1, 6, 19, 7, 5, 15, 4, 16, and 18 (order of frequency). The most common serotypes in children under 5 years were 6, 1, 19, 14, 5, 4, 5, 45, 12, and 7. Serotypes 1 and 5 accounted for 29% (92 of 314) of disease (92 of 314) of disease. Serotypes 1 and 5 accounted for 29% (92 of 314) of disease (10). Intermediate resistance to penicillin was noted in only four (1.3%) isolates; however, resistance to cotrimoxazole (trimethoprim-sulphamethoxazole) and chloramphenicol was seen in 173 (56%) and 51 (17%) isolates, respectively (10).

From the above description, one can appreciate the paucity of adequate data on incidence/ prevalence of pneumococcal infections and disease in many developing countries. There are many potential reasons why surveillance systems for invasive bacterial disease are uncommon in developing countries, but certainly the costs and complexity associated with them have been common barriers. The above review also reflects a wide variation in both in terms of overall disease burden and serotypes distribution. Considering the peculiar epidemiology of individual serotype, this wide variation would ultimately limit the effectiveness of current PCV7 formulation and call for the need of incorporation of wide range of common serotypes or novel vaccine production technique like protein based vaccines. On
the other hand, there are few community based studies pointing toward a shift in the spectrum of bacteria causing pneumonia, and gram negative organisms like *Klebsiella pneumonia* are increasingly reported from nasopharyngeal aspirates of children having acute lower respiratory tract infections (24). This further strengthens the need for keeping a strict vigil on changing epidemiology of childhood pneumonia in developing countries. Countries should now invest in erecting robust disease surveillance systems across the countries.

**Multi drug-resistance Streptococcus pneumoniae:**

Streptococcus pneumoniae resistant to penicillin, non-lactam agents, or both have been reported with increasing frequency worldwide, with some countries in the Asian continent reporting up to 70% resistance to penicillin (25). There are, however, very few reports of penicillin-resistant pneumococci from India, and those that do report, present no details on the susceptibility profile to other classes of antibiotics (26, 27). The growing incidence of multi-drug resistant pneumococci calls for monitoring of resistance and mapping of serotype distribution from developing countries. Fortunately, penicillin-resistance is still not widely prevalent in India but resistance to other antibiotics like cotrimoxazole and chloramphenicol is rising and few sporadic reports of multi-drug resistance including penicillin and cephalosporins should send warning signals to health authorities in India.

**Sero-epidemiology of Streptococcal pneumoniae in industrialized countries:**

Quite unlike the scenario in developing countries of Asia, the sero-epidemiology of *Streptococcal pneumoniae* in industrialized countries is very well defined. However, even in developed countries, there is vast difference in epidemiology, for example, the annual incidence of IPDs in USA and Canada varies from 161.2 to 235 per 100,000 (between 6-11mo and 6-17 mo, respectively) whereas in UK and Finland it varies from 35.8 to 45.3 per 100,000 (between 6-11 mo and below 2 years, respectively) (28). This difference could be due to different blood culture practices in these regions. Even in these countries, there is a marked geographic variation in different communities-being highest in Native Americans and Alaskan Natives than in other ethnic groups and whites. Similar variation is noted in other developed countries like Australia and Israel (28).

Hence, just to conclude, the adequate data on disease burden caused by pneumococci is available from the developed countries only, whereas the data from the developing countries is only sparse and inadequate. Even some large countries like India the exact data on disease burden of pneumococcal infections and the syndromes caused by the bacteria are sparse and not up-to-date. There is marked diversity in distribution of different serotypes in developing countries and the serotype distribution is different from industrialized countries. This diversity in distribution of various serotypes ultimately affect the coverage of different PCVs available in the market and will ultimately decide the exact impact on diseases caused by pneumococci.

**Use of existing PCVs in developing countries: Formulation, schedule and booster?**

According to World Health Organization, PCV introduction is a priority for countries with high child mortality. Countries with mortality among children under the age of 5 years of >50 deaths/1000 births, or with >50,000 annual deaths among children, should make the introduction of PCV-7 a high priority for their immunization programmes” (29). These WHO guidelines were criticized by many and viewed as an attempt to benefit vaccine manufacturers rather than the developing countries (9). Notwithstanding these criticisms, the fact is introduction of a new vaccine in any of the developing countries call broad based discussion and many issues need to be considered before a decision is reached.

**Issues related to introduction of a new vaccine in NIP:**

The issues and concerns related to the public use of a newly introduced vaccine are different and rather complex particularly if enough data on disease burden and epidemiology is lacking than individual use of a vaccine. There are various queries that need to be answered before any move to introduction of a vaccine is even contemplated. Such queries include: Is the disease serious enough to merit mass prevention? What is the disease burden? What are the different modalities to prevent/treat the disease? Is the vaccination only effective measure? Is the available vaccine/s effective? Are the vaccination only effective measure? Is the available vaccine/s cost-effective? Are the available vaccine/s cost-effective? What are the funding alternatives? Will the funding be sustainable in long term? Will the
introduction affect coverage of other vaccines? Does the health system flexible enough to accommodate new vaccine? Do we have the disease surveillance system in place to measure/monitor impact (both positive & negative) of vaccine use?

As far as pneumococcal disease and vaccines in developing countries are concerned, there is scarcity of data on exact community distribution of various serogroups and serotypes, and incidence of diseases caused by them. As a result, the coverage of different PCVs is not properly known. There are not many large scale efficacy trials, no cost-effective analysis models, and above all, there is absence of any effective disease surveillance system like Active Bacterial Core Surveillance (ABCs) of CDC. All these factors have negative impact on large scale use of any new antigen in the national immunization programs (NIPs) of developing countries.

**Pneumococcal Conjugate vaccines: Which one to choose?**

There are three different pneumococcal vaccines available for infants, each oriented to a specific set of serotypes. PCV-7, the oldest and most widely used product has established its efficacy and utility in many developed countries since its first introduction in USA in 2000 (28). In a recently published meta-analysis, the efficacy of pneumococcal conjugate vaccine in the reduction of invasive pneumococcal disease was 89% involving vaccine serotypes in both the intention-to-treat and per-protocol analyses and ranged from 63% to 74% for all serotypes. The efficacy to prevent acute otitis media sustained by vaccine serotypes was 55% in the intention-to-treat and 57% in the per-protocol analyses, whereas it was 29% to prevent otitis involving all serotypes in the per-protocol analysis. Finally, in the intention-to-treat and per-protocol analyses, the efficacy to prevent clinical pneumonia was 6% and 7%, respectively, whereas for the prevention of radiograph-confirmed pneumonia it was 29% and 32%, respectively (30). Hence, the pneumococcal conjugate vaccine produces a significant effect regarding prevention of invasive pneumococcal disease. Results on prevention of otitis or pneumonia have been less striking. The serotypes in 7-valent PCV represent over 80% of invasive pneumococcal disease (IPD) in North America and Europe, however, going by the latest report on PCV7 coverage in Asia, only 38% of all pediatric pneumococcal disease is prevented by this formulation (PneumoAdip report). Hence, this formulation is not suitable for most developing Asian countries despite wide variation which is prevalent as far as serotype distribution is concerned. One 11-valent conjugate vaccine (PCV-11) developed by Aventis Pasteur elicited diminished antibody responses to the serotypes conjugated to tetanus protein when coadministered with a vaccine containing acellular pertussis, and hence this formulation is not moving forward (28).

This left us with two new formulations which are recently been approved for mass use in Europe and USA, namely PCV-10, and PCV-13 (31, 32). The 10-valent and 13-valent conjugate vaccines include the serotypes 1 and 5, which together account for about 10-20% of invasive pneumococcal disease in Asia and Africa. This is to be stressed here that the number of serotypes that can be included in a single formulation of PCV is not as great as can be included in the polysaccharide vaccine, which has 23 serotypes.

The 10-valent pneumococcal vaccine (PCV-10, PHID-CV) contains all serotypes in 7-valent pneumococcal conjugate vaccine (PCV-7) plus serotypes 1, 5 and 7F. Protein D from nontypeable Haemophilus influenzae is the carrier protein for eight serotypes, while tetanus and diphtheria toxins are in the carrier proteins for the remaining two serotypes. Non-inferiority criteria of PCV-10 compared with PCV-7 were established in shared serotypes, except for serotypes 6B and 23F, and PCV-10 is immunogenic for additional serotypes as assessed by the percentage of subjects with antibody concentrations. PCV-10 is also immunogenic for ten serotypes as assessed by post-primary and post-booster dose opsonophagocytic activity (OPA) responses (31). However, further studies are needed to assess the potential advantages of protein D as a carrier and the potential efficacy of this new vaccine against H. influenzae.

The other new PCV, the 13-valent PCV PCV (PCV13) contains saccharides from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F conjugated to CRM197. This vaccine has been licensed by the US Food and Drug Administration, which, in addition to the 7 serotypes included in the original PCV7, contains the 6 pneumococcal serotypes responsible for 63% of IPD cases now
occurring in children younger than 5 years. Because of the expanded coverage provided by PCV13, it will replace PCV7 (32). All PCV13 serotypes were immunogenic, with 88% to 98% of infants achieving antibody concentrations of 0.35 µg/mL to shared PCV7 serotypes. For the 6 additional serotypes, 97% to 100% of PCV13-vaccinated infants achieved antibody concentrations of 0.35 µg/mL. Geometric mean antibody concentration for PCV13 recipients ranged from 1.32 µg/mL (serotype 23F) to 4.26 µg/mL (serotype 14). The ratio of OPA geometric mean titers for the 7 shared serotypes (PCV13:PCV7) ranged from 0.6 to 1.4, suggesting no clinically meaningful differences. For PCV13-only serotypes, OPA geometric mean titers were significantly higher in the PCV13 group than in the PCV7 group (33).

However, to introduce these new pneumococcal conjugate vaccines in the developing countries they need to be tried and tested in developing countries setup. Though multi-centric bridging immunogenicity studies have been conducted in few of these countries that include India also, but trial results are yet to be made public. According to recent estimates, PCV-10 coverage rates for Asia is around 66% while PCV-13 covers 73% of prevailing serotypes according to PneumoAdip estimates. Hence, PCV-13 will score over PCV-10 as far as serotype coverage is concerned; however, true worth of these vaccines can only be ascertained once these formulations are used at mass level in the developing countries. The other interesting aspect will be to know what percentages of the serotypes contained in the vaccines are indeed responsible for the actual pneumococcal diseases in the community.

**Which is the most optimum dosing schedule?**

PCV-7 was tested for different schedules, both in clinical trials and in national immunization schedules after licensure. The most extensively studied schedules are 2, 4, 6 mo and 2, 3, 4 mo followed by a booster during 2nd year of life (28). In few trials performed in few African countries like South Africa and Gambia, the EPI schedule 6, 10, 14 week was also adopted (34, 35). Even an aggressive schedule of 0, 10, 14 week was also used in early clinical trial. Recently, studies have also examined vaccination at 2, 4, and 12 months or at 3, 5, and 11–12 months of age. Some countries like UK, Norway, Belgium, Mexico etc have plan to introduce these shorter schedules (28).

Although three doses were originally considered necessary for optimal immune response to conjugate vaccines (36, 37), some studies have indicated that even one dose of conjugate may be sufficient at least in circumstances where carrier priming and early stimulation with high carriage of pneumococci is common (38, 39).

Vaccine schedules adopted by the various countries differ considerably. For example, In the United States and most Canadian provinces, the vaccine is given to infants on a four-dose schedule with doses at 2, 4, 6, and 12–15 months (40, 41) identical to the schedule used in the United States vaccine trials (42, 43). In other settings, three doses are used, either given during the first 6 months of life (e.g., Australia) or as two doses during that period followed by a booster after 1 year of age (e.g., Quebec Province in Canada and the United Kingdom) (44, 45).

The fewest number of doses required for optimal prevention of disease is unclear. Three doses given during the first few months of life were efficacious in clinical trials in Africa (34, 35). Immunogenicity data indicate that the immune response following two doses during the first 4 months of life is similar to that following three doses for vaccine antigens other than serotype 6B (46). Data from a large case-control study in the U.S. indicate that a variety of schedules are effective against invasive disease, but use of a booster dose after 12 months may improve protection(47).

As far as immunological memory after two primary doses followed by a booster dose of PCV during 2nd year is concerned, there are now enough data to indicate effectiveness of shorter schedule. Two doses of PncCRM197 given at 3 and 5 months as a primary series, together with a booster at 11–12 months, seem to induce an immune response and induction of immunologic memory comparable to those noted with the standard four-dose schedule in both normal and preterm infants (48-51).

Direct comparisons between different schedules are still few and further evaluation of the quality of antibodies and induction of memory as well as of the determination of the optimal age of vaccination would be interesting (48, 52). A computer model of vaccination, by contrast, suggests that a single dose
of PncCRM197 could be effective if the timing of administration is chosen carefully (52). Although a single dose was not predicted to be as effective as a three- or four-dose regimen, the model suggested that a single dose given between 5 and 7 months of age could prevent up to one third of invasive pneumococcal disease. This might have the most impact in developing countries, where the cost of a full regimen of conjugate vaccine can be prohibitive. The shorter schedule of PCVs may be quite appealing and beneficial and for most poor developing countries considering the high cost of conjugate vaccines and limited production capability of vaccine manufacturers.

**Booster dose: PCV or PPV?**

Generally, GMCs of anticapsular antibodies rise 5–10-fold after the initial series relative to the pre-immunization concentrations. The antibody concentrations achieved are usually only sustained for a few months and decline thereafter to about the pre-immunization levels. However, a dose of the pneumococcal vaccine, either polysaccharide or conjugate, administered during the second year of life to children primed with any of the conjugates generally induces an approximately 10-fold increase in antibody concentrations (28).

Here comes an interesting option: can pneumococcal polysaccharide vaccine (PPV) substitute PCV as booster dose during 2nd year of life in individuals already primed with 2 or 3 doses of PCV? Again, this practice can have important implications in resource-limited developing country scenario as using a PPV booster instead of PCV will reduce the cost of immunization against pneumococci. A prospect of using 2 primary doses of PCV followed by a PPV booster during 2nd year will greatly cut down the cost of mass pneumococcal vaccination program. Although, the antibody response is generally higher after the PPV booster than after the PCV booster, a PCV booster will stimulate the generation and expansion of high-affinity B memory cells, whereas use of a PPV booster may even result in depletion of the memory pool (53). Therefore, boosting with a conjugate may prove important for the long-term persistence of immunity. Furthermore, the avidity of antibodies is increased in children given a PCV booster but not a PPV booster. But, more studies are needed to explore feasibility of this option in developing countries.

**Economic aspect of mass vaccination program: Will it be a viable option for developing countries?**

The many issues related to introduction of a new vaccine in NIP of any country are already enumerated above. Admittedly, these are complex and their complexity gets worse if one is to deal with an expensive vaccine in a resource-poor developing country setup with a backdrop of negligible knowledge regarding exact disease burden and the ‘face’ of the disease intended to be prevented through vaccination program. An indigenously developed economic model based on cost-effective analysis is needed for individual developing country interested in introducing mass pneumococcal vaccination program in their country since the current prices of available PCVs are exorbitant and beyond reach of many countries. The cost of PCV remains relatively high compared to other routine infant vaccines, in part because of its recent development and because at present only a handful, in fact, only two manufacturers have licensed products.

According to a cost-effective analysis of pneumococcal conjugate vaccine among the world's 72 poorest countries, a pneumococcal vaccination program was projected to prevent 262,000 deaths per year among children 3–29 months of age; with universal vaccination coverage 470,000 deaths could be prevented. At a cost of International 5 dollars per dose, vaccination on a 3-dose schedule was thought to be cost-effective in 68 or 72 countries evaluated at about 100 dollars per disability-adjusted life year averted, using each country's per head gross domestic product as a measure (54). However, in this evaluation the conflict of interest cannot be avoided altogether as few of the evaluators are active promoter of pneumococcal vaccine in developing world. What is needed a country-specific economic evaluation performed by indigenous workers without any conflict of interest. Further, any prospective economic modeling should also take in to account the recently available 10- and 13-valent PCVs as they may have great impact at ultimate evaluation. Increased serotype coverage of these new formulations is expected to have a substantial public health and economic impact on infectious disease, when considering direct and indirect effects (55).

Vaccine cost-effectiveness is dependent on many factors, such as, disease incidence, vaccine efficacy, herd effects, disease sequelae, number of doses and
cost per dose of the vaccine. A recent cost-effective analysis conducted amongst Dutch infants reveals that the current Dutch infant vaccination programme of four doses of PCV-7 is not cost effective because of increases in invasive disease caused by non-vaccine serotypes, which reduces the overall direct effects of vaccination and offsets potential positive herd protection benefits in unvaccinated individuals. The 10-valent and 13-valent PCVs could have better net health benefits than PCV-7 through less replacement disease and increased herd protection.

Both these effects could substantially reduce the incremental cost effectiveness ratio to possibly acceptable levels, if total programme costs can be lowered by reduced schedules, reductions in vaccine prices, or both (56). Similarly, another cost-effectiveness analysis in Korea concluded that though universal PCV-7 vaccination of infants could substantially reduce pneumococcal disease morbidity, mortality, and related costs by preventing pneumococcal infections, but at current market prices for the vaccine, a universal vaccination strategy was not cost-effective (57).

Funding of large-scale pneumococcal vaccination program is another issue that needs to be taken care of prospective developing country that wishes to introduce it in their NIP. Although, GAVI through its innovative financing mechanism, Advance Market Commitment (AMC) is willing to support introduction of PCVs in 75 countries eligible poor developing countries for next five years. According to the most recent estimates, the funding needs for childhood immunization in developing countries over the 2004–2014 would be approx. US $14–17 billion the total costs of providing immunization for the poorest countries, accounting for phasing in of new vaccines. Vaccine-related costs represented the largest share of this amount (US $7.1–9.3 billion), with US $4.3–6.5 billion for a set of new vaccines including pneumococcal conjugate vaccine (58). These estimates were for all 75 countries eligible for support from GAVI and covered existing vaccines (diphtheria/tetanus/pertussis, hepatitis B, Hib, and yellow fever) as well as future vaccines. But, the greater issue is for how long GAVI will be able to fund these programs? What will happen once GAVI commitment expires or certain unforeseen events force the alliance to prematurely interrupt its funding assistance? Will these poor countries be able to sustain nation-wide mass pneumococcal vaccination programs for time immemorial? Already, there are doubts raised on the financial well being of GAVI alliance which is in doldrums now (59).

**How to measure effectiveness of PCVs in developing countries?**

Measuring vaccine impact provides important information to policymakers and stakeholders to show the vaccine is effective. These data can also provide support for the sustainability of the vaccine program and important resources for personnel infrastructure and answer questions about implementation. Valuating vaccine efficacy requires consistent surveillance data collected through standardized methods on long-term outcomes. USA first introduced PCV-7 in 2000 in its NIP based on reasonable disease burden of pneumococcal diseases. It later could demonstrate its efficacy and effectiveness at public health. Later, even the impressive herd effect as well as serotype replacement and surge in replacement disease caused by non-vaccine serotypes like 19A were also documented (60-64). The latter ultimately pave the way for developing new better wide-spectrum PCVs and ‘next generation’ of protein vaccines (31-33).

All these actions were accomplished only because the USA has an excellent real-time disease surveillance system, the ABCs which provided crucial data on disease epidemiology as well as on vaccine performance. Would the same be achievable in a developing country-setting where even background rates of pneumococcal diseases are not available? Who knows a new serotype will unleash and create havoc after PCV introduction in a developing country that has recently decided to introduce PCV in its vaccination program. This is to be stressed here that certain populations are more prone to get “Replacement disease” than others and environmental, socioeconomic, or genetic factors may have some role. It has also been suggested that pneumococci may be adapting to vaccine use by acquiring genetic material that allows a switch in expressed capsular type (28).

Hence, the only option available to these countries would be to rely on vaccine as a probe to measure its impact on pneumococcal disease epidemiology which again has certain limitations. Although WHO says that absence of surveillance should not be a barrier to PCV introduction (28), nevertheless, surveillance is
strongly encouraged and should support disease control efforts and program management. Hence, the need is to establish an effective disease surveillance system in place to measure/monitor impact (both positive & negative) of PCV use.

Future pneumococcal vaccines: What role they can play?
Though availability of new PCVs, 10- and 13-valent will broaden the coverage of PCVs especially in developing countries of Asia, the problem of serotype replacement will still remain unresolved. There are several shortcomings of current conjugate vaccines such as they are only capable of protecting against infection with bacteria that express polysaccharide capsule types that are included in the vaccine, the potential for replacement disease with non-vaccine serotypes, and lastly, the complexity of conjugate vaccines production (28).

To circumvent these problems, efforts are already on to develop new advanced more refined pneumococcal agents. The options include new components in the conjugate, novel adjuvants, and new administration routes (28). Intranasal immunization with various adjuvants induces strong antibody responses both in serum and on mucous membranes in mice and can protect them against lethal infections (65). Even though these strategies may circumvent some of the problems of conjugates, they do not address the issues of coverage, replacement, or complexity of vaccine production. Therefore other types of immunogens, including whole-cell pneumococcal bacteria, DNA vaccines and protein antigens, are being evaluated as candidates for novel pneumococcal vaccines. However, attempts to develop pneumococcal DNA vaccines are still limited by the generic problems of immunogenicity associated with naked DNA in humans (28).

Currently, the most promising option that seems quite feasible also is development of protein-based pneumococcal vaccines. Protein-based vaccines are attractive for several reasons. They are expected to be immunogenic in early infancy and in the elderly due to their T-cell-dependent nature and their coverage should be at least in theory broader than that of conjugate vaccines. It is also claimed that they would offer stronger protection against colonization and by containing more than one species-specific antigen; they may be able to avoid the replacement phenomenon. In addition, they would be relatively simple to produce because they would have fewer components than multivalent conjugate vaccines; thus protein-based vaccines are expected to be less expensive, allowing wide use in all areas of the world (28). Already, few companies have initiated development of these novel vaccines and they are in different stages of development. Many philanthropic organizations like Bill and Melinda Gates foundations are actively involved with generous funding of these projects.

Several pneumococcal proteins such as Pneumococcal surface protein A (PspA), Pneumococcal surface protein C (PspC), Pneumococcal surface adhesin A (PsaA), Pneumolysin (Ply), Neuraminidase enzymes (NanA and NanB), pneumococcal histidine-triad proteins, etc are found to possess immunogenic properties and they have been considered essential for bacterial virulence. Many trials are underway to explore their potential as pneumococcal vaccines—either as such or as carrier proteins for pneumococcal conjugates. However, the best future option would be to develop a protein vaccine that have a combination of more than one such protein antigens (66), or even better would be to have a combination of a conjugate and a protein vaccine in order to get the best protection and the widest coverage. This type of futuristic pneumococcal vaccine will be most suited for developing countries obviating the need of ‘redesigning’ vaccine every alternate year to reduce the risk of replacement with strains not included in the vaccine.

Need of the hour:
Hence, the issues related to use of pneumococcal conjugate vaccine, especially their mass use in developing countries scenario are many. There is an urgent need to carry out community based surveys to establish exact disease burden of various syndromes caused by pneumococci and to establish an effective surveillance system to monitor prevalence of different serotypes. A watch on prevalence of multi-drug resistance will also prove fruitful to design future strategies to tackle pneumococcal diseases. Studies are urgently needed to document efficacy of newer broader PCVs and shortened schedule. The decision to introduce currently available conjugate vaccines should be based on exact disease burden, sero-epidemiology of the prevailing strains and the indigenous capability of the developing country to
monitor impact of the mass vaccination program i.e., an effective disease surveillance system. Indigenous production of new pneumococcal vaccines like protein based vaccines should be explored and pursued aggressively.

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