*Editorial*

## Pneumococcal Vaccination for Indian Children

Six years have passed since the last editorial on pneumococcal vaccines, written by Prof. Kim Mulholland, appeared in this journal(1). At that time, Prof. Mulholland made a number of key points related to the burden of pneumonia and pneumococcal disease. He rightly highlighted pneumonia as the illness that kills more children than any other world wide. He also indicated that "many, perhaps most"pneumonia deaths are likely to be due to *Streptococcus pneumoniae*.

Perhaps most poignantly, he concluded that pneumococcal disease was "the most important target" for childhood vaccination globally. In relation to the pneumococcal conjugate vaccines, he highlighted the need for data from vaccine trials in developing countries as important for decision-making, and in particular, the need for data on the vaccine's efficacy for prevention of pneumonia and all cause mortality. Lastly, he stressed the importance of addressing the issues of financing and pricing as important for assuring developing country access to the vaccines.

With this editorial, we consider what has changed –and what has not–in the six years since the last Indian Pediatrics editorial, and how new information, policy guidance, and developments in financing might be used to formulate a national policy on routine pneumococcal vaccination for infants and children in India.

### Pneumonia and the Burden of Pneumococcal Disease

Regrettably, little has changed in terms of the burden of pneumonia and pneumococcal disease since 2001. In 2007, pneumonia remains the leading infectious killer of children worldwide. Perhaps more importantly, pneumonia remains the leading killer of children in India. A recent UNICEF publication estimated that 410,000 children under age 5 years die of pneumonia each year in India, and a recent editorial by Dr. Naveen Thacker, President, IAP, showed a striking graphic that an estimated 25% of all child deaths in India are due to pneumonia(2). That this high burden of pneumonia has remained undiminished in India in spite of economic growth and decline in child mortality due to other diseases is a reminder of the importance of tackling pneumonia head on with dedicated resources.

Quantifying the burden of pneumococcal disease through observational studies and surveillance remains a challenge. Culture of the bacterium from normally sterile fluids of patients with signs of pneumonia, meningitis, and sepsis remains the gold-standard, but also remains very insensitive (*i.e.*, it misses most "true" cases of pneumococcal disease). Invasive disease surveillance is useful for descriptive epidemiology, characterization of the distribution of pneumococcal serotypes occurring locally, and informing clinical management with antibiotic resistance. It however misses the vast majority of true pneumococcal disease. The yield from pneumonia patients may be increased by applying molecular techniques to sterile body fluids but more work is needed in this area before they are considered as routine diagnostic techniques for case management(3).

Experimental studies, especially randomized, clinical trials of highly efficacious pneumococcal vaccines, provide the most robust estimate of the burden of pneumococcal disease. This is especially true for pneumococcal pneumonia, where the insensitivity of blood cultures is most pronounced. Meta-analysis of four high quality, randomized, controlled trials of pneumococcal conjugate vaccines suggests that about 30-40% of all severe pneumonia in children is likely to be pneumococcal in origin. If this figure is applied to the UNICEF estimate of 410,000 childhood pneumonia deaths each year, then one can project that in India between 123,000 and 164,000 children aged less than 5 years die annually from pneumococcal pneumonia!

## Pneumococcal Conjugate Vaccines

Since 2000, prevention of pneumococcal disease in young children has been possible by vaccination using multivalent glycoconjugate vaccines. The currently licensed 7 valent pneumococcal conjugate vaccine (PCV 7) contains 2 $\mu$g of capsular polysaccharides of serotypes 4, 9V, 14, 19F and 23F; 2 $\mu$g of oligosaccharide from 18C; and 4 $\mu$g of polysaccharide of serotype 6B in a 0.5 mL dose; each serotype is conjugated to the non-toxic diphtheria CRM 197 protein and adsorbed onto aluminium salt to enhance the antibody response.

The clinical efficacy of this vaccine was first demonstrated in a large-scale field study in the United States, where efficacy against IPD caused by vaccine serotypes of 97.4% (95% CI 82.7-99.9) among children who received at least three doses (per-protocol analysis) was observed(4). In the same study, 30.3% reduction in radiologically confirmed pneumonia was observed in the per protocol analysis(5).

A similar vaccine but containing two additional serotypes, namely types 1 and 5, was evaluated in large scale field trials in South Africa and The Gambia. In both trials high efficacy against IPD caused by vaccine serotypes was observed(6,7). Importantly, 25% and 37% reduction in radiologically confirmed pneumonia was observed in South Africa and The Gambia, respectively(6,7). In the trial in the Gambia a 16% reduction in all-cause mortality was observed among vaccinated children - in other words, about one child death was prevented for every 150 vaccinated children in this high mortality, rural area(7). Though there are no efficacy data from India, pneumococcal conjugate vaccines have been shown to be immunogenic and efficacious in all populations in which they have been tested, including indigenous populations in the United States(8).

## Routine Use Experience

The impact of the vaccine following routine introduction into childhood immunization programs has been even more impressive than the efficacy trials. In the United States and Canada, where the vaccine has been in use for over 5 years, impressive decline was seen in rates of invasive pneumococcal disease (IPD) in immunized children, but also in unimmunized older age groups, including the elderly, through herd effect(9-11). The vaccine has also reduced racial and socio-economic disparities in disease incidence in the United States(12,13). Recent data from the United States also showed a 39% reduction in all-cause pneumonia admissions following the introduction of pneumococcal conjugate vaccines(14). Additional gains were also observed in terms of reduction in outpatient visits for otitis media, and for tympanostomy placement(15,16) as well as reduction in disease caused by antibiotic resistant strains of pneumococcus(17).

## Potential for Pneumococcal Vaccination in India

The serotypes included in PCV-7 account for close to 80% of those causing severe pneumococcal disease in the United States. Data on the serotypes or serogroups causing severe pneumococcal disease in India is limited, but available data suggest that the serotypes in the 7-valent vaccine account for approximately 52% of severe disease in children under the age of 5 years(18). While the burden of pneumonia in India is widely recognized, careful population-based studies to estimate the incidence of invasive pneumococcal disease (IPD) from India are lacking. Fortunately, data from neighboring countries with similar epidemiologic patterns, such as Bangladesh, show incidence rates several fold higher than in the United States. If the same incidence rates were applicable to India, the incident cases of invasive disease prevented by the 7-valent vaccine would be higher than in the United States. The burden of preventable pneumonia would be even higher.

If India chooses, vaccination can begin now with the 7-valent vaccine and continue with extended protection vaccines in the future. By 2010, vaccines with 10 and 13 serotypes and including serotypes 1 and 5 are expected to become available. These vaccines would increase the health impact of pneumococcal vaccination.

## Indirect Effects and Replacement

Pneumococcal conjugate vaccines are shown to reduce nasopharyngeal carriage of serotypes included in the vaccine. Reduction in carriage among children, the age group most likely to carry pneumococci in their nasopharynx, would result in

reduced transmission of these serotypes and indirect protection of others in the community. Indeed, introduction of PCV-7 in routine immunization in the United States and Canada have shown impressive reductions in disease in older children and adults who were unimmunized(9,11).

Clinical trials have also shown that reduction of carriage of vaccine serotypes of pneumococci are associated with a comparable increase in carriage with non-vaccine serotypes, raising concerns about the potential for increased disease by these serotypes, a phenomenon termed as *replacement disease*. Replacement disease was observed in clinical trials of otitis media, where the decline in disease by vaccine serotypes was almost completely offset by the increase in disease by other serotypes of pneumococci and by *Hemophilus influenzae* (19,20). Replacement invasive disease was not observed in the clinical trials but was observed following widespread use of the vaccine in the United States. However, the magnitude of increase in disease due to non-vaccine types was small as compared to substantial decline seen in invasive disease caused by vaccine types(9).

Replacement invasive disease appears more commonly in immunosuppressed populations, including those with HIV/AIDS(21). Increase in non-vaccine type invasive disease in the United States is mainly related to an increase in antibiotic resistant strains of serotype 19A(22). More recently higher rates of replacement invasive disease were reported in Alaska natives and were mainly related to an increase in disease due to serotype 19A(23). Fortunately, serotype 19A is contained in the 13 valent vaccine that is expected to be available around 2010, and preliminary immunologic data suggest that the 19F conjugate in the 10-valent vaccine candidate may also provide partial protection against 19A disease. The experiences in the USA with the emergence of 19A disease illustrate the importance of establishing and maintaining high-quality surveillance to monitor changes in invasive disease following vaccine introduction.

**WHO Recommends Pneumococcal Vaccine**

Based on a careful review of the available data on the burden of disease and the safety, efficacy and effectiveness of the vaccine, and on the recommendation of its Strategic Advisory Group of Experts (SAGE), WHO issued an updated position paper on pneumococcal conjugate vaccines in March 2007(24). Since the burden of pneumonia is highest in countries with high under 5 mortality rates, WHO considers the inclusion of this vaccine in national immunization programmes as particularly high priority in countries with under 5-mortality >50 per 1000 live births, or greater than 50,000 child deaths annually. With an infant mortality rate of >60 per 1000 live births and over 400,000 child deaths per year, India meets the WHO's criteria for countries where pneumococcal vaccination should be a priority for introduction. WHO's policy guidance is also supported by a "call to action" that appeared in the Lancet authored by many of the world's leading experts in pneumococcal disease and vaccination(25).

**Supply, Financing and Pricing Considerations**

India's birth cohort is the largest in the world. Consequently, a decision to introduce the vaccine into the national program can have a major impact on global supply and demand, and financing schemes. Currently, there is insufficient supply to meet all the needs of India's birth cohort. However, it is unlikely that India will be either willing or able to introduce the vaccine and reach all children in the next 12 months. A more realistic question then is to consider the timeline for achieving universal childhood immunization with pneumococcal vaccines and how India can work with suppliers and financers to achieve this goal without undue supply concerns or financing challenges.

Ultimately, vaccine suppliers from India and other emerging market countries are likely to play an important role in providing vaccines for India. Several emerging market manufacturers, including Indian manufacturers, are actively working to develop pneumococcal vaccines. However, these suppliers are likely to require at least 7 years to license a vaccine. Thus, the decision to introduce a vaccine into India's program will have to consider the health consequences of delaying introduction until a national supplier has a licensed vaccine.

One option that is currently available is to obtain

**Key Message**

- A timeline for introduction of Hib and pneumococcal vaccine is urgently needed bacause pneumonia remains the leading infectious killer of children in India.

pneumococcal conjugate vaccine with financial support from the GAVI Alliance. The GAVI Alliance makes new life-saving vaccines like Hib and pneumococcal conjugates available by buying the vaccines from suppliers at a cost of dollars per dose and then providing them to India and other low-income countries at a heavily subsidized price. If it chooses, the Government of India could obtain pneumococcal vaccine for between US$ 0.15 and 0.30 per dose. Although countries like India may be expected to gradually increase their contributions to procure the vaccine, GAVI's funding is expected to continue at this or similar levels through at least 2015.

In mid-April, the Government of India received a letter from the GAVI Alliance asking for non-binding expressions of interest in introducing pneumococcal vaccines. India's response could be an important first step to assuring a secure supply of pneumococcal vaccine and the needed financing. Failure to reply would be a major missed opportunity.

**Next Steps for India**

Much has changed in the six years since the last Indian Pediatrics editorial on pneumococcal vaccines. Many of the questions about the vaccine's performance in developing countries have been addressed. Clinical trials in Africa and Asia demonstrate the ability of pneumococcal conjugate vaccines to prevent pneumonia and even to significantly improve child survival. Furthermore, the vaccine's performance in routine use in industrialized countries has exceeded expectations. The experience with herd immunity in the United States, for example, indicates that the vaccine's health impacts may extend well beyond the target population. With financial support from GAVI, India also has the chance to access life-saving pneumococcal vaccines at a minimal cost. The WHO position statement provides guidance to reassure decision-makers that vaccine introduction is a sensible health policy.

On the other hand, and disappointingly, the burden of childhood pneumonia and pneumococcal disease remain high in India - as high as six years ago. Together, the availability of a life-saving vaccine and attractive financing combined with a stubbornly high burden of childhood pneumonia provide a compelling rationale for India to take action to introduce pneumococcal vaccination into its national immunization program.

Based on the available data and policy options before it, India can take several important steps to prevent pneumonia and improve child survival through the expanded use of life-saving pneumonia vaccines. First, India can add *Hemophilus influenzae* type b (Hib) vaccine to its universal childhood immunization program beginning in 2008. Together, Hib and *S. pneumoniae* are responsible of the majority of serious and fatal pneumonia worldwide. If needed, India can apply as early as September 2007 through the GAVI Alliance to procure the vaccine. Second, the Government should formulate a timetable for the introduction of pneumococcal vaccine into the national immunization program. This timetable should address directly how it will utilize the life-saving pneumococcal vaccines from multinational companies that are currently available or soon to be licensed, and how it would simultaneously encourage the involvement of Indian suppliers over time.

With more than 400,000 child deaths from pneumonia each year in India, the consequences of inaction and indecision can be calculated in lives lost. As advocates for child health, individual pediatricians and the Indian Academy of Pediatrics, should urge the government to develop a process and timeline for introducing pneumococcal and Hib vaccines.

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## REFERENCES

1. Mulholland K. Pneumococcal conjugate vaccine--relevance for developing countries. Indian Pediatr 2001; 38:453-460.
2. Thacker N. Integrated management of neonatal and childhood illnesses: a new hope for child survival. Indian Pediatr 2007; 44:169-171.
3. Cherian T, Lalitha MK, Manoharan A, Thomas K, Yolken RH, Steinhoff MC. PCR-Enzyme immunoassay for detection of *Streptococcus pneumoniae* DNA in cerebrospinal fluid samples from patients with culture-negative meningitis. J Clin Microbiol 1998; 36:3605-3608.
4. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, *et al*. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infec Dis J 2000; 19: 187-195.
5. Hansen J, Black S, Shinefield H, Cherian T, Benson J, Fireman B, *et al*. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. Pediatr Infect Dis J 2006; 25: 779-781.
6. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N, *et al.* A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. New Eng J Med 2003; 349: 1341-1348.
7. Cutts FT, Zaman SMA, Enwere G, Jaffar S, Levine OS, Okoko JB, *et al*. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in the Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005; 365: 1139-1146.
8. O'Brien KL, Moulton LH, Reid R, Weatherholtz R, Oski J, Brown L, *et al*. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet 2003; 362: 355-361.
9. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, *et al*. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003; 348: 1737-1746.
10. Poehling KA, Talbot TR, Griffin MR, Craig AS, Whitney CG, Zell E, *et al*. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. JAMA 2006; 295: 1668-1674.
11. Kellner JD, Church DL, MacDonald J, Tyrrell GJ, Scheifele D. Progress in the prevention of pneumococcal infection. CMAJ 2005; 173: 1149-1151.
12. Flannery B, Schrag S, Bennett NM, Lynfield R, Harrison LH, Reingold A, *et al*. Impact of childhood vaccination on racial disparities in invasive Streptococcus pneumoniae infections. JAMA 2004; 291: 2197-2203.
13. Hennessy TW, Singleton RJ, Bulkow LR, Bruden DL, Hurlburt DA, Parks D, *et al*. Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization in Alaska Natives: progress towards elimination of a health disparity. Vaccine 2005; 23: 5464-5473.
14. Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: A time-series analysis. Lancet 2007; 369: 1179-1186.
15. Grijalva CG, Poehling KA, Nuorti JP, Zhu Y, Martin SW, Edwards KM, *et al*. National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. Pediatrics 2006; 118: 865-873.
16. Poehling KA, Szilagyi PG, Grijalva CG, Martin SW, LaFleur B, Mitchel E, *et al*. Reduction of frequent

otitis media and pressure-equalizing tube insertions in children after introduction of pneumococcal conjugate vaccine. Pediatrics 2007; 119: 707-715.

17. Whitney CG, Klugman KP. Vaccines as tools against resistance: the example of pneumococcal conjugate vaccine. Semin Pediatr Infect Dis 2004; 15 :86-93.

18. Anonymous. Prospective multicentre hospital surveillance of Streptococcus pneumoniae disease in India. Invasive Bacterial Infection Surveillance (IBIS) Group, International Clinical Epidemiology Network (INCLEN). Lancet 1999; 353(9160): 1216-1221.

19. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, *et al*. Efficacy of a pneumococcal conjugate vaccine against otitis media. New Eng J of Med 2001; 344: 403-409.

20. Kilpi T, Ahman H, Jokinen J, Lankinen KS, Palmu A, Savolainen H, *et al*. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. Clin Infect Dis 2003; 37: 1155-1164.

21. Flannery B, Heffernan RT, Harrison LH, Ray SM, Reingold AL, Hadler J, *et al*. Changes in invasive Pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. Ann Intern Med 2006; 144 :1-9.

22. Pai R, Moore MR, Pilishvili T, Gertz RE, Whitney CG, Beall B. Postvaccine genetic structure of Streptococcus pneumoniae serotype 19A from children in the United States. J Infect Dis 2005; 192: 1988-1995.

23. Singleton RJ, Hennessy TW, Bulkow LR, Hammitt LL, Zulz T, Hurlburt DA, *et al*. Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. JAMA 2007; 297: 1784-1792.

24. World Health Organization. Pneumococcal conjugate vaccine for childhood immunization: WHO position paper. Wkly Epidemiol Rec 2007; 82: 93-104.

25. Levine OS, O'Brien KL, Knoll M, Adegbola RA, Black S, Cherian T, *et al*. Pneumococcal vaccination in developing countries. Lancet 2006; 367: 1880-1882.