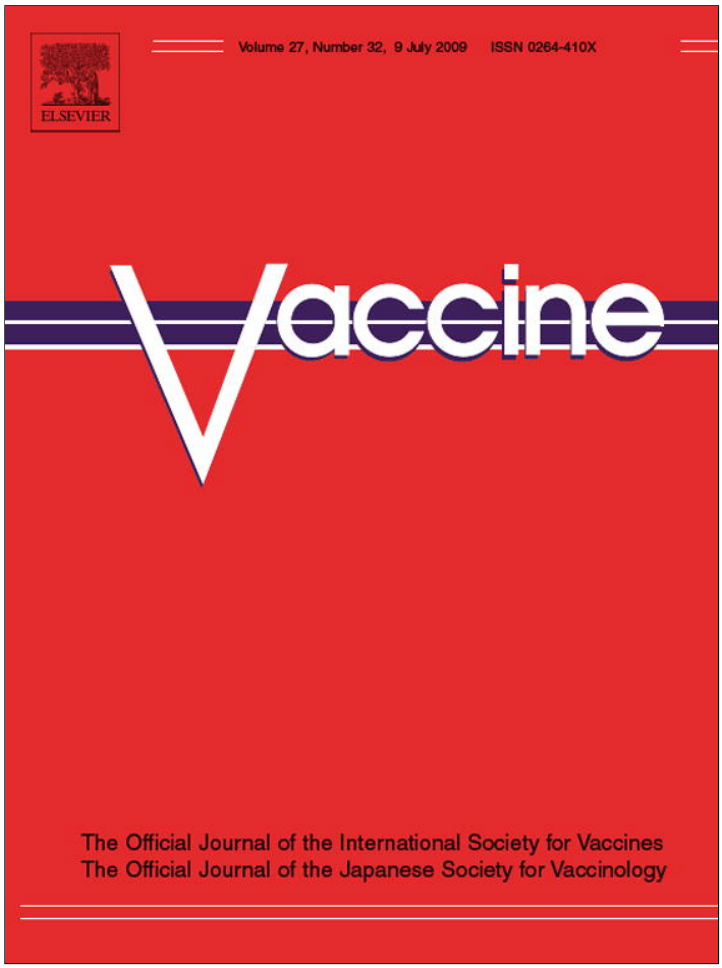

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Review

Pneumococcal vaccination in developing countries: Where does science end and commerce begin?

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ABSTRACT

Recently Pneumococcal vaccines have generated considerable interest in developing countries as an intervention for protecting children from pneumonia and thereby reducing childhood mortality. Many convincing scientific arguments have been put forward, although they are often based either on extension of information from developed countries, or estimation plus extrapolation of limited local data. In addition, there is also significant commercial pressure to prescribe/recommend Pneumococcal vaccine(s). Against such a background, it is important for developing countries to critically appraise the issues involved in order to make a rational choice. This brief paper explores these issues, showing that the current Pneumococcal vaccines have limited effectiveness in developing countries and the hype surrounding them is more commercial than scientific.

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1. Introduction

Recently, much has been written and said about the need to include the Pneumococcal conjugate vaccine in the national immunization schedule of developing countries. A lot of scientific data has been quoted and an even larger commercial thrust is evident. This article attempts to explore the facts pertaining to Pneumococcal vaccination with particular reference to the scientific and commercial issues behind it-hence the title. India accounts for 120 out of 478 million (>25%) under-five children (the largest number in any single country) and is seriously considering the inclusion of Pneumococcal vaccine in the childhood immunization programme. Hence the developments in India are particularly highlighted here. However the issues are relevant and applicable to all developing countries in general.

1.1. Burden of disease

The exact number of invasive Pneumococcal disease (IPD) in most developing countries including India is not known; even reliable local estimates are unavailable. Therefore data from various other sources are used to present a picture of high disease burden. These are summarised in Table 1, from which it is clear that the calculations are neither based on robust data nor likely to be

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Table 1
Burden of Pneumococcal disease.

Published scientific claim	Data sources quoted	Comments
There are an estimated 156 million annual childhood pneumonia cases worldwide [1,2].	• An estimate published in 2004 [3] based on analysis of 28 studies between 1969 and 1999. • The WHO-UNICEF document [1] quoted the above study [3] plus personal communication from the author of an unpublished paper [4]. • The paper subsequently published in May 2008[2] again quotes the original [3] paper with no new data presented.	• The critical estimation of disease burden rests on one publication quoted in different forms. • The calculation of total pneumonia cases worldwide is an extrapolation of numbers based on data from limited studies. • The impact of changes in health-care, economy, nutrition, etc. over the past four decades has not been taken into account.
There are 43–44 million annual childhood pneumonia cases in India [1,2].	• Refs. [3,4] above.	• The basis for arriving at this 'estimate' has not been presented in either document. • The latest paper [2] also mentions 43 million 'predicted' new cases among under-five children. • If this estimate and 'prediction' are correct, since India has about 120 million under-five children, it either means that every third child is affected by pneumonia or a smaller number have recurrent pneumonia. Clinical experience does not suggest either of these possibilities suggesting that the figure may be grossly inflated.
There are over 2 million pneumonia related deaths worldwide [1].	• Ref. [1] does not give the basis for this calculation. • The recent reference [2] cites a paper that arrived at this figure by calculating the mortality rate from 40 individual studies. The authors also quote another estimate [5] that gives a similar figure.	• Most of the studies quoted in Ref. [2] are over three decades old and largely limited to Latin American countries.
S. pneumoniae is responsible for 15–50% cases of childhood pneumonia [6].	• Ref. [2] quotes seven microbiology-based studies that attribute 30–50% cases to *S. pneumoniae* and 10–30% to *H. influenzae*. • The other method to arrive at this figure is from vaccine probe studies reporting the proportion of pneumonia cases prevented with specific vaccination and attributing to the organism against which the vaccine was used. This indirectly suggests the number of cases attributable to the organism. • Ref. [2] states that "future Pneumococcal vaccines may prevent 30 to 50% radiological and fatal pneumonia".	• *H. influenzae* is a fastidious organism that is difficult to isolate through culture techniques. Antigen based tests and PCR usually double and treble the yield of *H. influenzae* [7,8]. This suggests that *S. pneumoniae* and *H. influenzae* may be responsible for an approximately equal proportion of childhood pneumonia; therefore the large[r] proportion attributed to *S. pneumoniae* would be incorrect. • There is considerable data from developing countries highlighting the role of *S. aureus*, Gram negative organisms, *M. tuberculosis* and measles virus in causation of childhood pneumonia. • If other viruses are considered in the causation of childhood pneumonia, the proportion of *S. pneumoniae* cases will be even lower than quoted.
S. pneumoniae is responsible for 50% childhood pneumonia mortality [6].	• Ref. [1]. • WHO position paper 2007 [9] specifies that a "substantial" proportion of the "estimated" 2 million childhood pneumonia deaths are due to Pneumococcus. • The paper [9] also mentions that the total Pneumococcal deaths in under-five children [0.7 to 1.0 million] is about 50% of the total Pneumococcal mortality in all age-groups [1.6 million].	• Ref. [1] states "In Africa, *S. pneumoniae* may be responsible for over 50% of severe pneumonia cases, and probably a higher proportion of fatal cases". There is no cross-reference for this claim. • As Pneumococcus is responsible for other life-threatening clinical conditions besides pneumonia, if it kills 0.7 to 1.0 million children annually [9], it obviously cannot be responsible for 50% of the estimated 2 million deaths.
S. pneumoniae causes 6.6–22 million episodes of pneumonia in India annually [6].	• Ref. [1].	• This range has been arrived at by applying the 15–50% calculation (unproven) to 44 million [1] annual episodes (doubtful).
S. pneumoniae is responsible for 200,000 under-five deaths yearly [6].	• Ref. [1].	• This has been calculated by multiplying 410,000 estimated deaths in Ref. [1] by 50%. The basis for both these numbers is not clear.

as high as projected. However, this does not necessarily mean that IPD could not be a significant problem; a fact I have pointed out previously in the context of India [10]. This can only be resolved through multi-centric population-based surveillance studies, that are unfortunately cumbersome, time consuming and expensive.

1.2. Significance of Pneumococcal disease in developing countries

The significance of Pneumococcal disease in developed countries is based on (i) fairly accurate knowledge of disease burden, (ii) detailed knowledge of Pneumococcal serotypes causing invasive disease, (iii) control of other causes of pneumonia especially Hib and measles through efficient primary prevention, (iv) knowledge of etiology of childhood pneumonia including the proportion caused by viruses, (v) increasing antibiotic resistance among *S. pneumoniae*, and (vi) pre-existing high level of hygiene, sanitation, health-care delivery, etc.; which cannot be significantly improved further to reduce pneumonia morbidity and mortality. Based on these considerations, Pneumococcal vaccine is an intervention of choice in most developed societies. On the other hand, in most

developing countries (i) the burden of disease (total number of Pneumococcal cases in the population) is not clear, (ii) knowledge of serotypes causing invasive disease is limited, (iii) even if IPD is a significant cause of pneumonia morbidity and mortality, it is not likely to supercede other causes including *H. influenzae* and measles owing to poor immunization coverage, (iv) the contribution of viral pneumonia is not clear, (v) antibiotic (penicillin) resistance is not a significant problem in several countries [11,12], although limited information from some settings suggests otherwise [13,14], and (vi) there is ongoing as well as expected, scope for improvements in quality of life and hence morbidity/mortality. Therefore attempts to extrapolate the significance of Pneumococcal disease and practice(s) to control it in developed countries may not be appropriate in the scenario of developing countries.

If the figures presented in Ref. [1] are believed, in India the case-fatality rate of pneumonia is 0.93% (410,000 deaths among 44 million cases). This relatively low case-fatality suggests that either the 44 million pneumonia cases are fairly 'mild' and/or amenable to treatment with whatever medication (antibiotics or otherwise) is currently used [15,16]. The fact that only two-thirds of these children are taken to an appropriate health-care provider [1] again suggests a mild disease. If this is the case, it would not merit a large-scale and expensive vaccination programme.

However, "pneumonia is the leading killer of children worldwide" [1] and the "leading cause of death" suggesting that it cannot be regarded as a mild disease. This apparent paradox therefore stems from the large denominator of 44 million used to demonstrate high disease burden. As this figure appears to be incorrect, all the calculations based on this premise also become suspect. The same argument holds true for other developing countries also [1].

1.3. Role of Pneumococcal vaccines

It is clear that young infants are at great risk of IPD and amenable to protection through routine immunization. Therefore, vaccination should be efficacious and effective in this age-group. Since the 23-valent Pneumococcal polysaccharide vaccine is not recommended for young infants, it cannot be used for routine immunization. The 7-valent Pneumococcal conjugate vaccine (PCV-7) covers only a limited proportion of serotypes causing IPD in most developing countries, hence at best would be "something better than nothing". It should be pointed out that PCV-7 was designed to protect children in developed countries; and hence serotype coverage is 90% for USA and Canada, 78% for Australia and 75% for Europe. It is much lower for Africa (67%) and Latin America (63%), though this is still much better than for Asia (43%) and India (53% or lower) [17,18].

1.4. Efficacy versus effectiveness

Proponents of PCV-7 [6,19,20] are at pains to point out that despite limited serotype coverage, the vaccine is very efficacious (judged by antibody response to vaccination). However, in the context of vaccination for public health, one is more interested in effectiveness than efficacy. Effectiveness addresses the question, "Will the vaccine do what it is supposed to viz protect children from IPD?" In the context of PCV-7, the answer is no because (i) it does not guarantee protection from IPD, but can only reduce the risk and (ii) economic forces dictate that those who need vaccination the most would not get it, and those who do get it may not need it as much. This inequity will reduce the effectiveness even further, despite high efficacy.

1.5. Administration and logistics

The vaccination schedule of PCV can be linked with that of DPT in routine immunization programmes, making it an attractive option logistically. However, it cannot be mixed in the same syringe with other vaccines and the WHO estimates the need for a "substantially increased capacity in the cold chain" to the extent of 300% [2]. Administration would necessitate use of separate syringes and injection sites. Therefore safety data comparing both vaccinations against DPT alone would need to be generated prior to usage. These factors make vaccination less attractive than one is led to believe.

1.6. Role of the WHO

The WHO and its recommendations are generally given great importance in developing countries, though not as much in most developed countries which prefer to base their decisions on scientific data generated locally. As on previous occasions with other vaccines, the WHO issued a position paper [9] recommending PCV-7 in developing countries, that temporally coincided with aggressive marketing of the same. This has given a substantial boost to sales of PCV-7.

The WHO paper states, "WHO considers that it should be a priority to include this vaccine in national immunization programmes, particularly in countries where mortality among children aged <5 years is >50/1000 live births or where >50,000 children die annually". It is intriguing that no explanation is offered for choosing these particular cut-off criteria. It is even more intriguing that rather than using the word, "and" to include both criteria, WHO has used "or" giving the option of using either of the two criteria. Table 2 shows the impact of these "considerations". The option permits the additional inclusion of seven countries that would otherwise not have been considered if only the criterion of under-five mortality >50/1000 or both criteria together are used. It is significant that these countries together account for 161 million under-five children; of these Brazil and China alone account for 104 million. It is even possible that the cut-off criteria have been chosen to ensure that these countries are included in the 'consideration'. As currently there is only one brand of PCV available in the market (PCV-10 and PCV-13 are at the clinical trials stage), it is obvious who will benefit the most from these statements. Despite these facts, owing to the respect and respectability of WHO statements, even the carefully worded 'consideration' is accorded the status of 'recommendation' in most developing countries like India.

1.7. Role of the Indian Academy of Pediatrics (IAP)

The recent IAP guidelines [6] recommend the use of PCV-7 in infants through routine immunization after one-to-one discussion; this means that only those who are willing to pay for a vaccine with limited effectiveness should be vaccinated. The IAP further recommends that the Government of India should seriously consider PCV-7 for routine immunization. Since this is impossible owing to the huge expense involved, IAP recommends that Government could offset the cost by availing the GAVI offer of subsidized vaccine till 2015 [6]. It is not clear what the Government is expected to do when/if GAVI pulls the rug from under it after 2015.

1.8. Role of the Government of India

The Government of India has shown unusual alacrity with respect to Pneumococcal vaccination. The Ministry of Health and Family Welfare (MOHFW) set up an expert committee under the chairmanship of the Director General, Department of Biotechnology (DBT) to study the matter. Within a period of 2 weeks, the committee was able to recommend that PCV should be included in the routine immunization programme and the Health Secretary, MOHFW rapidly confirmed that PCV would be introduced within 1 year [21]. This is indeed impressive considering that a

Table 2
Countries where PCV could be used based on the WHO 'consideration' [9]. Data are derived from [1].

Criterion	Countries	Total number of under-five children, hence 'eligible' for vaccination
Both criteria (38 countries, mostly in Africa).	Afghanistan, Angola, Bangladesh, Benin, Burkina Faso, Burundi, Cambodia, Cameroon, Chad, Democratic Republic of Congo, Cote d'voire, Ethiopia, Ghana, Guinea, India, Iraq, Kenya, Madagascar, Malawi, Mali, Mozambique, Myanmar, Nepal, Niger, Nigeria, Pakistan, Papua New Guinea, Rwanda, Senegal, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Uganda, Yemen, Zambia, Zimbabwe.	298,810,000 (298 million).
Only U5MR >50/1000 (32 countries).	Azerbaijan, Bhutan, Bolivia, Botswana, Central African Republic, Comoros, Congo, Djibouti, Equatorial Guinea, Eritrea, Gambia, Guinea-Bissau, Guyana, Haiti, Kazakhstan, Kiribati, DPR Korea, Kyrgyzstan, Lao PDR, Liberia, Marshall Islands, Mauritania, Mongolia, Namibia, Solomon Islands, Swaziland, Tajikistan, Timor-Leste, Togo, Turkmenistan, Tuvalu, Uzbekistan.	17,979,000 (18 million).
Only total U5 deaths >50,000 (7 countries).	Brazil, China, Egypt, Indonesia, Iran, Mexico, Phillipines.	160,998,000 (161 million).

rational policy over Hib, hepatitis B and measles vaccines has not emerged over several years. On the other hand, the expert committee recommended that a vaccine covering at least 70% serotypes be introduced; since this is not available it is unclear how the recommendation will be fulfilled. Meanwhile, these actions have boosted sales of currently available PCV-7.

1.9. Role of industry

In recent years, unprecedented economic growth in many developing countries notably India and China, has led industry to view these countries as potentially profitable markets. This is why these countries are flooded with a wide variety of vaccines and other pharmaceutical products. The current heightened interest in Pneumococcal disease (judging by the WHO 'consideration', IAP recommendations, publications in scientific and lay press, numerous presentations at scientific fora, and statements from senior Government personnel) is not related to increase in scientific knowledge of the epidemiology of Pneumococcal disease or vaccine/vaccination related issues, but the thrust by industry. This includes manufacturers and marketers of the vaccine, as well as all those who stand to gain through the widespread sale of the vaccine.

Industry has been using a two-pronged strategy to increase sales of PCV-7. The first is the 'academic channel' through organization of countless sponsored lectures by 'experts'; many of these for a fee. The other is the 'commercial channel' through extensive marketing, advertising and providing the vaccine to physicians at about 20% less than the retail price. These practices encourage physicians to be oriented in favour of a vaccine whose effectiveness is limited in the local setting.

1.10. What is the solution?

In the context of Pneumococcal vaccine(s), each developing country has to take a decision on using the vaccine (or otherwise) based on actual or expected burden of disease, likely effectiveness of available vaccines and existing health-care priorities; it must not be based solely on efficacy, safety, availability or affordability. Accordingly, it is probable that many developing countries need a Pneumococcal vaccine for young infants; however the currently available vaccines are not suitable. Knowledge of locally relevant serotypes and indigenous manufacture of tailor-made vaccines should be encouraged. This will make the vaccine effective, affordable and sustainable in the long term. At the current time, India and China appear most suited to shoulder this enormous responsibility.

2. Summary and conclusion

The current hype over Pneumococcal vaccines is largely commercial in origin, character and content. This commercial thrust is boosted directly and indirectly through the loud and/or quiet acquiescence of professionals in individual, institutional and organizational capacities. The relegation of scientific considerations to the back-seat is the most unfortunate outcome of these strategies. Such events are likely to be witnessed with increasing regularity in the future as well. A way out of the current situation has been proposed herewith.

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