
Abstract

Pneumococcal conjugate vaccines induce serotype specific protection, with cross-protection seen between serotypes within certain serogroups. Though most serious pneumococcal infections are caused by relatively small number of serotypes, choices need to be made on the serotypes to be included in the vaccine because of the complexity and cost related to developing and producing vaccines with increasing number of serotypes. The choice is rendered difficult because of differences in the distribution of serotypes causing serious disease between different geographic regions and age groups as well as changes over time. The World Health Organization convened an expert consultation to formulate a data-driven approach to determine the minimum or optimal formulation of pneumococcal conjugate vaccines, particularly keeping in mind the needs of developing countries as well as the epidemiologic, regulatory, formulation and manufacturing issues involved. The deliberations and conclusions of this meeting are summarized in this report.

Keywords: Vaccines; Conjugate; Streptococcus pneumoniae; Serotype composition

1. Background

A consultation was convened to lay out a data-driven process to evaluate the minimum or optimal serotype composition of pneumococcal conjugate vaccines (PCV) for use in developing countries. The specific objectives were to: (1) review the global epidemiology of pneumococcal disease in children and adults, with specific reference to serotypes causing serious disease in developing countries and changes in serotypes over time and in response to introduction of conjugate vaccines; (2) review the conjugation, formulation and production process for pneumococcal conjugate vaccines and identify bottlenecks and cost-escalating steps in the development, production, formulations and clinical evaluation of these vaccines; (3) review the regulatory requirements for pneumococcal conjugate vaccines; (4) review the pneumococcal vaccines pipeline, including multinational and emerging market suppliers, and conjugate and protein-based approaches to vaccine development. The expected outcome was to articulate principles on the basis of which a more detailed data-driven process could be undertaken to define alternative serotype composition of PCV that may provide significant benefit and be cost-effective, recognizing that the complexity of production and formulation and the risk of failure to new manufacturers increases with increasing number of serotypes in the vaccine.

The serotype composition of the first vaccine to be licensed (Prevnar™) was based on the common serotypes found in North America. The current vaccine development strategy is to add serotypes to the existing formulations to better meet the needs of other populations (i.e. a universally applicable serotype composition), leading to development of 10- to 13-valent vaccines. The complexity of vaccine production and of optimizing formulation of these multivalent vaccines, due to potential interference between individual conjugates, both related to the multiplicity of serotypes, might make it difficult for emerging manufacturers to enter the market. This raises the question as to whether vaccines with fewer serotypes, but targeted against the common serotypes in developing countries could be produced and constitute a relevant and economically viable public health alternative especially for developing countries. However, there are several issues that need to be carefully considered before such an approach can be supported.
2. Epidemiology of pneumococcal disease

Diseases caused by Streptococcus pneumoniae are a major cause of morbidity and mortality worldwide. They are estimated to cause 1.6 million deaths annually, particularly in young children and the elderly. In children under 5 years of age alone, an estimated 700,000 to 1 million deaths occur annually, the majority of these being in developing countries. Though there are 90 serotypes of pneumococcus described, relatively few of them are responsible for the majority of severe disease. Vaccines based on the capsular polysaccharide of pneumococcus are targeted against these serotypes, though the choice of serotypes in the currently available vaccines is based mainly on those causing invasive disease in North America and Western Europe. However, there are regional differences in pneumococcal serotypes causing severe disease. The most comprehensive review of serotype distributions by geographic regions was published by Hausdorff et al. in 2000 [1]. Based on serogroups causing invasive disease, this review showed that the serogroup coverage of the currently available 7-valent conjugate vaccine (PCV7) ranged from approximately 40% in Asia to 60% in Africa and Latin American to >80% in North America and Oceania. However, data are sparse in some regions. Asia has the lowest estimate of coverage for the PCV7 but this is based on the least amount of data. Furthermore, the data that are available may not be representative of all forms of invasive disease. For example, regions whose estimates are based almost solely on isolates from meningitis patients may have an inaccurate portrayal of all important serotypes if those that cause pneumonia differ. Prior use of antibiotics may skew the serotype prevalence to those that are more likely to be resistant to commonly used antibiotics. Certain serotypes are known to cause outbreaks and these serotypes may be over or under-represented if data are from a limited period of surveillance. Finally, serotype distribution also differs by age and this needs to be taken into consideration when designing vaccines for different target populations. Currently available data from some developing countries represent a broad age category that may not be representative of the main target age range, i.e. infants and young children.

Irrespective of the observed differences in the prevalence of serotypes, available data suggest that an increase in valency to 10 or 13 serotypes in vaccines currently under development could increase coverage to near 80% of invasive disease in all regions. While the percent coverage of serotypes causing invasive disease can contribute importantly to country-specific estimates of the direct impact of vaccine, it is not reliable when used as the sole indicator of anticipated PCV impact. For example, in the United States, the baseline percent of invasive pneumococcal disease caused by serotypes in the 7-valent vaccine was 56% among American Indian children compared to 83% among the general US pediatric population [2]. However, vaccine-attributable declines in invasive pneumococcal disease incidence 3 years after vaccine introduction were markedly higher among American Indians than among the general US population (125 cases per 100,000 among American Indian children, compared to 73 cases/100,000 among the general US population of children <5 years of age) because of the substantially higher incidence of disease in the American Indian population prior to vaccine introduction [3,4]. Similarly, in Australia, the percent of invasive disease due to serotypes included in PCV7 was lower among the indigenous population than among the general Australian population (72% versus 86%) [5]. However, the incidence of invasive pneumococcal disease (relative risk 11.9, 95% CL 6.8, 14.9) and case fatality ratios (relative risk 22.7, 95% CL 7.2, 71.3) among indigenous children were an order of magnitude greater than for the general population, indicating that the benefit from PCV7 would be much greater in them, in spite of the lower proportion of disease caused by the PCV7 serotypes [6]. New data from Bangladesh and Africa suggest that the situation is similar to that seen in the indigenous populations in the USA and Australia [7] [Brooks A, personal communication]. Thus, in light of the high incidence of disease, PCV7 will provide a significant benefit in these populations despite the lower serotype coverage. However, a formulation with serotype composition more suited to local needs would be expected to provide even greater benefit. Thus, both the incidence of disease as well as the percent serotypes covered need to be considered when estimating the impact of a vaccine.

The issue of the optimal serotype composition of pneumococcal vaccines is complicated by the fact that serotypes causing disease change over time, both naturally as well as a consequence of health interventions, including vaccination. The best example of natural temporal variation of serotype specific disease is that caused by type 1 which is known to cause epidemics of disease in certain communities, recently exemplified by the reported outbreaks in the African meningococcal meningitis belt [8,9] and the disappearance of type 1 in the United States over the second half of the 20th century [10]. Sharp increases in 19A disease have been reported in the Republic of Korea even though vaccine usage was uncommon [11]. The reasons behind these changes are not fully understood. Changes in serotypes are also described following vaccine introduction. Decline in carriage and otitis due to vaccine types was almost completely replaced by non-vaccine types in clinical trials of the PCV7. Smaller increase in non-vaccine type invasive disease in young children and the elderly have been described following introduction of the PCV7 [12]. This replacement was mostly due to increase in serotype 19A disease, with evidence of a capsular switch from vaccine type strains to 19A [13]. Serotypes that colonize the nasopharynxx often and for longer duration and those that are antibiotic resistance are more likely to cause replacement disease. Replacement is also more common in immunosuppressed populations, including those with HIV/AIDS [14].
3. Serotype specific efficacy of pneumococcal conjugate vaccines

The currently available PCV7 was licensed on aggregate efficacy against the serotypes in the vaccine (i.e. vaccine serotypes). The pivotal clinical trial used for licensure could only document serotype specific efficacy against types 14, 18C, 19F and 23F [15]. Pooled analysis of data from this and subsequent clinical trials as well as post-marketing effectiveness analysis confirmed high efficacy against each of the seven serotypes in this vaccine as well as a related serotype, 6A [16]. Pooling of data from the two trials evaluating 9-valent vaccine could not document efficacy of serotype 1 antigen; for serotype 5, efficacy of 90% (1 case in vaccinated children versus 10 in controls) was demonstrated [17,18]. Thus, there is evidence for serotype specific efficacy for 8 of the 9 serotypes, evidence for efficacy against type 1 is lacking. The lack of such evidence does not justify a conclusion that serotype 1 antigen is ineffective because of the small numbers of cases in the two clinical trials.

4. Review of polysaccharide conjugation technologies and improving yields

The ability to induce a protective immune response to polysaccharides in young children was greatly improved by covalently attaching a bacterial polysaccharide or oligosaccharides to protein carriers. This conjugate can induce protective antibodies in infants through immune stimulation utilizing helper T cells.

Native polysaccharides will not covalently link to a protein without chemical modification. This modification (activation) is often achieved by creation of reactive aldehyde groups on the polysaccharide using sodium periodate. The other usual means of polysaccharide activation is to use 1-cyano-4-dimethylaminopyridinium tetrafluoroborate (CDAP) activation reagent to randomly change some of the many –OH groups to active cyano groups (–CN). The activated polysaccharide or oligosaccharide can then be conjugated to the carrier protein of choice; tetanus toxoid, diptheria toxoid, and CRM 197 being the most common. Other bacterial proteins that have been used include pseudomonas exotoxin A and Haemophilus influenzae protein D. In each case, free amino groups, principally those on lysine, are used to couple the protein to the activated polysaccharide. Whatever the method used, conjugation reaction conditions must be carefully controlled to consistently obtain conjugates with the same characteristics.

The efficiency of the conjugation reaction and ease of conjugate purification impacts the yield of conjugate. This said, it has been very difficult to compare reported yields, because many different ways of calculating yield have been used. For example, some report high yields based upon recovery of the conjugate protein, but the critical measure is the quantity of conjugated polysaccharide present. Using the chemistries described above between 10 and 30% of the starting polysaccharide becomes conjugated. Conjugate yields can be greatly improved by activating both the polysaccharide and protein. One method of protein activation is to use hydrazine to convert some –COOH groups on the protein to hydrazide groups, which will rapidly condense with aldehyde groups on the activated polysaccharide with formation of a hydrazone. In actual manufacturing practice yields using hydrazide chemistry have been over 50%.

A possible approach for production of pneumococcal conjugates for developing countries could use high yield conjugation technology in combination with a reduced number of serotypes, covering the most prevalent serotypes in a given geographic region. Pneumococcal proteins such as pneumolysin or PspA, known to induce protective antibody, may be used as the carrier protein to further expand the spectrum of protection. Of note is the fact that intellectual property right issues may complicate access of emerging manufacturers to the latter carrier proteins.

5. Pneumococcal conjugate vaccine economics

The optimal number of serotypes in a pneumococcal conjugate vaccine depends on the balance between the disease reduction potential of the formulation and the development and production costs of such a formulation. The latter includes the actual cost of manufacture as well as other costs associated with the research and development, risks and time-line of the process.

A model was presented by representatives of Mercer Management Consulting, Chicago, USA that evaluated the drivers of cost for production, and which included vaccine characteristics, the production process, manufacturing location, and demand. For the base case with a single serotype, 1 mcg dose, conjugate yield of 35%, a 10-dose presentation, manufacturing in a low labor cost setting, and demand of 100 million doses, the cost per dose was estimated to be $0.26. The costs of adding additional serotypes are highly dependent on the productivity of the process and product efficiencies. With a highly efficient process the incremental costs of adding serotypes would be small. With less efficient processes and higher dosage requirements the cost of production becomes sensitive to increasing valency of the vaccine. In addition, costs become more sensitive to the location of production (due to local wage rate environments and construction costs) in manufacturing systems where the conjugation process does not allow high yields of conjugated product. The model did not include costing of the risk of production failures, which increases with the number of serotypes included.

Importantly, pricing of vaccines is generally not based solely on the cost of production but on willingness to sell (lowest margin of return) on the part of the manufacturer and willingness to pay on the part of the buyer. Where pricing ultimately falls in the “willingness-to-sell” and “willingness-to-pay” spectrum is determined by many other factors,
including competitiveness of supply base, importance of buyer and seller to one another, negotiating position, and terms of tender, etc.

6. Technology transfer in the development of polysaccharide conjugate vaccines—the MVP experience

The Meningitis Vaccine Project (MVP) is a 10-year partnership between WHO and the Program for Appropriate Technologies in Health (PATH) to develop a vaccine to control epidemic group A meningococcal meningitis in Africa. A deliberate decision was made to pursue a single valent conjugate, even though epidemics due to other serogroups were known to occur, because it would be a low risk venture, address 80% of the disease burden and address demand in addition, it could be made available at prices that the affected countries were willing to pay.

The product is developed through a consortium that included SynCo Biopartners who produce raw polysaccharide, Serum Institute of India (SII) that produces the carrier protein and manufactures the final product and the USFDA who transferred the conjugation technology to SII. Commitment, contracts, communication, and excellent staff were key factors for the success of the endeavor.

It was proposed that a similar process might be applicable for the development of a monovalent type 1 pneumococcal conjugate vaccine for control of outbreaks of type 1 disease, though it was recognized that clinical evaluation of such a vaccine in the absence of a serological correlate of protection would be challenging. However, there was no consensus that such an approach could be used to produce a vaccine for the control of endemic pneumococcal disease in infants and young children.

7. Immunological interference between conjugates in a multivalent vaccine

Combining conjugate vaccines with other childhood vaccines has in some instances led to a reduction in the immune response to the polysaccharide moiety of the conjugate and the vaccine antigens given at the same time. The initial description of a reduction in the antibody responses to glycoconjugate vaccines occurred when Hib-tetanus toxoid conjugate vaccines were co-administered with acellular pertussis containing DTP combinations [19,20]. The reduced response was initially thought to be due to the adjuvant aluminum hydroxide [21]; more recently, the absolute amount of carrier proteins is thought to have played a role, with relatively large amounts of tetanus or diphtheria toxoid able to inhibit response to the carbohydrate [22]. Meningococcal C conjugate vaccine is also similarly sensitive to carrier overload. In a trial of 9V pneumococcal conjugate combined with meningococcal C vaccine, a lower response was observed, as compared to that induced by the meningococcal C conjugate vaccine alone, perhaps due to CRM overload [23]. The adjuvant effect of whole cell pertussis can offset carrier induced hypo responsiveness of tetanus toxoid conjugates.

In studies of pneumococcal conjugate vaccines that evaluate immune responses to 5-valent, 7-valent and 9-valent formulations, no reduction in antibody levels were seen with serotypes 4, 6B, 9V, 14 and 18C, but some reduction with others.

In summary, Hib, meningococcal C, and pneumococcal conjugate vaccines are all vulnerable to reduced antibody response as a result of carrier protein overload in combination vaccines or when given concomitantly. Some data indicate that overload effects are observed mainly in infants, with responses in toddlers and older vaccinees less affected by the number of conjugated components in the combination. Whole cell pertussis acts as an adjuvant and may offset this effect. Some decrease in immunogenicity is also observed for some serotypes in vaccines with increasing number of serotypes in the formulation. In general, this effect is more of a problem when tetanus toxoid is used as the carrier, and it was suggested that 7–8 components might be the threshold for tetanus toxoid conjugates. However, small differences in geometric mean titres are unlikely to be relevant and proportions above putative thresholds may be more critical.

8. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants

WHO has published guidelines for the clinical evaluation and licensure of new pneumococcal conjugate vaccines that propose that evaluation of newer formulations of conjugate vaccines be based on the demonstration of non-inferiority, in a head-to-head comparison with existing 7-valent vaccine, in the proportion of subjects developing antibody concentrations (using ELISA without 22F absorption) above a defined threshold (0.35 mcg/ml) 4 weeks following a primary series of vaccination [24]. These criteria were derived on the basis of pooled analysis of data from the Northern California, Navajo and South Africa efficacy and immunogenicity trials of the 7- or 9-valent conjugate vaccine [25]. The threshold level derived from each individual trial varied significantly and had wide confidence limits. The pooling of data allowed narrowing of the confidence limits of the efficacy estimates and a more precise definition of the threshold. Adding the data from The Gambia trial may further improve the precision of the threshold antibody concentration. Non-inferiority to all 7 serotypes was not an absolute requirement; cases of failure of 1 or more serotypes would need to be considered on an individual basis based on the epidemiological and public health importance of the serotype(s) concerned [24]. Additional criteria include the demonstration of functional antibodies measured with OPA after three doses and a test of
immune memory such as avidity or ability to induce a booster response.

The use of total serotype specific antibody measured by ELISA has limitations and measurement of functional antibody (e.g. opsonophagocytic antibody) may be a better option, though such assays need to be further standardized before they can be used as the primary endpoint for vaccine evaluation.

9. The use of nasopharyngeal carriage as an endpoint for efficacy trials and registration of new formulations

Herd immunity effects have been one of the most important benefits of pneumococcal conjugate vaccines [12]. Herd effects occur because of reduction in nasopharyngeal carriage and transmission of vaccine type pneumococci [26]. Replacement of vaccine type pneumococci by non-vaccine types have been observed following vaccination and may lead to replacement disease, particularly diseases caused by contiguous spread of pneumococci from the nasopharynx (e.g. otitis media). Therefore, understanding carriage is important to predicting how conjugate vaccines will benefit a population and nasopharyngeal carriage effects might be a useful endpoint for clinical trials.

10. The PneumoCarr initiative

This initiative aims to establish endpoints based on reduction of colonization and correlates of protection for colonization. This will be achieved by gathering multi-site longitudinal data on colonization and concomitant serum and salivary antibodies; the information will be used for models of dynamics of colonization, to correlate serologic data and colonization, and develop models of transmission.

While there was agreement that colonization was important for vaccine evaluation and understanding vaccine effectiveness, more data are needed before this parameter could be used as an endpoint for regulatory purposes. This endpoint may be used for supporting and supplementing the immunological criteria for regulatory purposes.

11. Regulatory pathways for licensure of regional formulations

In the past, vaccines were mostly developed in industrialized countries, and licensed by the national regulatory authorities (NRA). If these vaccines were then used in developing countries, their NRAs relied on the regulatory review conducted by the NRA of the producing country. In recent years, regulatory pathways have become more complicated as vaccines may be bulk-produced in one country and finished in another, and each process might take place either in developed countries or developing countries. Licensure may be by the national regulatory agency (NRA) of the country of manufacture or the user country, or might be pre-qualified by WHO for countries without an NRA, if the product will be purchased through UNICEF or other U.N. agencies. Some NRAs might be unwilling to review a product that is not used in its home country, even though it is manufactured there. Article 58 of Regulation (EC) No. 726/2004 1 (“the Regulation”) allows the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) to give opinions, in cooperation with the World Health Organization (WHO), on medicinal products for human use that are intended exclusively for markets outside of the EU, but an equivalent process is not in place in North America.

Recognizing the complexity of the regulatory environment and to ensure that the vaccine needs of developing countries are adequately addressed, WHO has been exploring a variety of regulatory pathways. Global and regional networks of regulators, such as African Vaccine Regulatory Forum (AVAREF), Developing Country Vaccine Regulators Network (DCVRN), and Association of South East Asian Nations/Vaccine Chapter ASEAN-Vax) are being established to discuss regulatory approaches and criteria and to facilitate collaboration among regulators and WHO to allow novel regulatory pathways for licensure of vaccines intended for specific populations that are different from the country of manufacture or licensure.

12. Regulatory issues related to periodic strain changes in vaccine formulations

Several multivalent vaccines are licensed in the United States. In order to broaden protection and respond to changing epidemiology, some vaccines have been modified by increasing the number of strains or serotypes comprising the vaccine (e.g., pneumococcal polysaccharide and meningococcal vaccines). Only influenza vaccines replace component strains on a periodic basis, often yearly, in response to changing epidemiology. The choice of strains to be included in the trivalent influenza vaccine is based on updated worldwide epidemiologic surveillance data, and is made with participation by the World Health Organization, the US Centers for Disease Control, and with advice of FDA’s expert advisory panel. There are differences in the approaches used by different regulatory agencies. For example, the European Medicines Agency (EMEA) requires studies in about 200 adults whereas the USFDA requires animal data, manufacturing inspection, and a label update.

The USFDA and EMEA have adapted the WHO guidelines for licensure of newer formulations of pneumococcal conjugate vaccines. However, these guidelines were intended for formulations that build on the existing PCV7, and they
might have to be revised for other formulations of pneumococcal conjugate vaccines, especially if the serotypes in the new formulation are substantially different from those in the existing licensed formulation.

13. Pneumococcal conjugate vaccine pipeline and projections on supply of multivalent conjugate vaccines

The pneumococcal conjugate vaccine pipeline is strong in part because the scientific hurdles are largely overcome and in part because there is a large global market. There is a robust pipeline for pneumococcal vaccines that is largely driven by the strong demand in high- and middle-income countries and also private markets in low-income countries. The pipeline includes not only multinationals committed to supplying developing countries but emerging market suppliers who are committed to R&D activities to provide an affordable vaccine for their markets as well. This is a prime example of markets driving supply and innovation, which will also result in availability of new products for developing markets.

Based on an analysis developed by GAVI’s PneumoADIP, using differential pricing of vaccines (ranging from $5 per dose in the public sector of low income countries to $65 per dose in the private sector of industrialized countries), the global market for pneumococcal conjugate vaccines is estimated to be approximately $7 billion; high income markets account for 43 million doses at $2.3 billion, and low and middle income markets account for 309 million doses at $4.7 billion.

Between 2008 and 2012 the 10-valent and 13-valent products will be launched; by 2012–2015, third generation vaccines may be ready and emerging market suppliers may be able to provide additional products. Manufacturers in Cuba and India have vaccine development plans, with initial plans to produce formulations that contain serotypes prevalent in their populations, e.g. Latin America, Africa and Asia.

14. Conclusions

Based on the data presented and the discussion that followed, the following conclusions were made.

14.1. Serotype composition

- There is recognition of the substantial value of the currently available 7-valent (PCV7) in addressing the burden of pneumococcal disease, including in developing countries. The 10-valent and 13-valent pneumococcal conjugate vaccines under development are likely to cover most serotypes causing serious disease worldwide. While these vaccines will be available in the short term and are likely to meet the initial demand, additional supply may be required to meet the eventual global demand.
- There is a role for multivalent vaccines with serotype composition different from that in the currently licensed PCV7. Different formulations for different country groupings are acceptable in principle:
  - The focus of new formulations should be the impact of the new product for disease prevention in infants and young children through routine immunization.
  - The basis of evaluation should be the potential of such formulations to reduce disease and their cost-effectiveness. The exact composition of such vaccines should be left to individual manufacturers, based on the populations that they target and in discussion with country decision-makers.
  - WHO and its global partners will assist with doing a review of the published and unpublished data on the geographic distribution of serotypes to estimate the incremental benefit of adding serotypes, by sub-region/country groups.
- A monovalent type 1 vaccine may have a significant public health value but given the different epidemiology of type 1 disease, it may require a different strategy—probably directed against epidemic control to deploy this vaccine.

14.2. Clinical evaluation of new vaccine formulations

The current WHO criteria for evaluation of pneumococcal conjugate vaccines were prepared for formulations that built upon the existing PCV7 vaccine that has undergone clinical efficacy trial:

- Current criteria are adequate for the 10v and 13v formulation currently under development; the licensure and use of these vaccines will generate effectiveness data that may allow more flexibility for use of current criteria for the newer formulations.
- The current criteria need to be reviewed as and when new formulations with different serotypes are proposed.
- The use of OPA for clinical evaluation of conjugate vaccines needs to be explored and included in the revised guidelines.
- The use of nasopharyngeal carriage as an efficacy endpoint is an important proposition as the frequency of acquisition events allows rapid evaluation of vaccine efficacy against this endpoint. Currently regulatory agencies do not consider this as a sole effectiveness endpoint for regulatory purposes. This should be explored further and may provide an alternative method for evaluating the potential impact of non-conjugate vaccines.

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