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Protein Conjugate Polysaccharide Vaccines: Challenges in Development and Global Implementation

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ABSTRACT

Pneumonia and meningitis caused by *Haemophilus influenzae type b*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* are among the leading causes of under five mortality and morbidity. Polysaccharide vaccines to prevent these infections are available since 1980s, but these are not effective in infants and children who are the common targets; therefore, protein conjugated were developed. The aim of this article is to understand the need for peumococcal protein conjugate vaccines, the challenges related to their development and global implementation, and the impact of these vaccines on global child health. Challenges in development of new vaccines are as follows:

1. While pneumonia is a major threat in developing countries, available vaccine 7-valent pneumococcal conjugate vaccine (PCV7) protects against only 30% of invasive disease.
2. Serogroup B of *Neisseria meningitidis causes* 32% of the cases in the USA and 45–80% or more in Europe. Due to similarity of its capsular polysaccharide with the cell surface glycoprotein on fetal brain tissue, developing a vaccine against this bacterium remains a challenge.

Challenges in implementation are as follows:

1. Replacement by nonvaccine serotypes;
2. capsule switching;
3. time duration of the antibody protective effect following vaccination;
4. costs of the vaccines, programme costs, lack of knowledge of the disease burden, and targeting population groups for vaccination.

Keywords: *Haemophilus influenzae type b*, meningococcus, pneumococcus, protein–conjugate polysaccharide, vaccine

Introduction

More than 10 million children under 5 years of age die worldwide yearly. Of these, 19% are due to pneumonia[1] and 95% of the burden is borne by developing countries.[2] There is annual incidence of 126,000 cases of meningitis in neonates with more than 50,000 deaths[3] and neurological impairment in survivors.[4] *Streptococcus pneumoniae* (pneumococcus) is accountable for approximately 800,000 deaths of children under five annually,[5] followed by *Haemophilus influenzae type b* (Hib) and *Neisseria meningitidis* (meningococcus) causing respectively, 386,000[6] and 50,000 deaths[5] yearly. In India, the burden of morbidity and mortality caused by these bacteria are as high as 60–100% among children under 5 years.[7-13] Studies show increased prevalence of multidrug resistant strains in India and other developing countries.[10,11,14,15]

Polysaccharide vaccines against these bacteria are available since 1980s, but these are not effective in infants

Access this article online

Quick Response Code:

Website: www.ijcm.org.in

DOI: 10.4103/0970-0218.96085

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Received: 24-01-10, **Accepted:** 06-01-12

and children who are the common targets. Therefore, protein-conjugate polysaccharide vaccines were developed.[5] However, development of these vaccines and their implementation have faced major challenges in terms of bacterial structures and their behaviors,[5] immune response of the host,[16] and cost aspects of these vaccines.[4,17] Further, adolescents are important carriers of meningococcal bacteria.[18]

The need for protein conjugate polysaccharide vaccines

Haemophilus influenzae, *Streptococcus pneumoniae*, and *Neisseria meningitidis* are encapsulated bacteria, the capsule being composed of polysaccharide. Destruction of the polysaccharide capsule which is the determinant of virulence in these bacteria is essential to protect against them. Normally, the capsule is destroyed by the complement system of the host along with antibodies produced by the B lymphocytes.[19] In infants and young children, this process is weak due to low complement activity.[19] Further, the capsular polysaccharide is presented directly to the B cell surface and not through the antigen-presenting cells (APC), the CD4+ T-cells are not stimulated, resulting in a weak proliferation of B cells to produce IgM and IgG2 without formation of memory cells.[20] Activation of CD4+ T-cells is also required to enhance affinity of antibody binding on subsequent exposure to the specific antigen.[20] For the same reasons, the polysaccharide vaccines developed against these bacteria were less immunogenic in children below 2 years of age even after repeated vaccinations.[16] The recognition of these limitations led to the development of the protein-conjugate polysaccharide vaccines. The carrier protein bound polysaccharide presents on the surface of the APC that further recruits CD4+ T-cells to co-stimulate the B-cells. This process leads to immunogenic and protective effects in young infants.[16] Thus, the conjugate vaccine has the potential to induce priming of B-cells and also produces affinity maturation.[16]

Currently used licensed vaccines are *Haemophilus influenzae type b* (Hib), the 7-valent *pneumococcal conjugate vaccine* (PCV7) which covers the serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; PCV10 which in addition to the serotypes covered by PCV7 also covers 1, 5, and 7F. Apart from these, PCV-11 and PCV-13 are undergoing efficacy trials.[5] Meningitis C (MenC) vaccine is being used in United Kingdom (UK) since 1999 and MenACYW, a quadrivalent vaccine containing serotypes A, Y, C, and W135 conjugated with diphtheria toxoid is being used in the United States of America (USA) since 2005. Other combinations like A, C, Y, and W135–CRM197 and A, C, Y, and W135–tetanus toxoid are in the process of development.[5]

Further requirements and challenges in the development of protein conjugated vaccines

Despite substantial progress made by developing new and effective vaccines, challenges still remain. Each of the three causative bacteria has large number of serotypes classified according to their polysaccharide capsule. Currently available licensed vaccines do not protect against all serotypes. Following the introduction of Hib vaccine, the incidence of pneumonia and meningitis has considerably decreased.[21] However, it does not protect against the noncapsular variants, known as *Nontypable Haemophilus influenzae* (NTHi),[21] which have the potential to cause acute upper respiratory tract infection, otitis media, exacerbation of chronic bronchitis, and pneumonia.[22] High heterogeneity of NTHi and their potential to act as platelet activating factor[22] make it difficult to identify a single vaccine candidate even after sequencing of the genome.

While pneumonia is a major threat in developing countries, PCV7 protects against only 30% of invasive disease in Asia.[2] Pneumococcus has more than 40 serogroups which are further divided into 91 serotypes.[5] At present 5–11 serogroups account for 75% of invasive disease and of these the ones responsible for causing pneumonia in Africa and Asia are not included in PCV7.[2] It is difficult to develop a vaccine covering all serotypes which requires conjugating each capsular polysaccharide individually with a protein carrier through a complex process.[2] There are also concerns regarding the number of carriers that can be administered at a time and cross reactivity between the serotypes leading to reduced efficacy.[2] However, PCV10 may resolve this problem to certain extent.

An effective vaccine against Hib being available, *Neisseria meningitidis* now remains as the major cause of bacterial meningitis worldwide. Meningococcus has about 13 serogroups but bacterial isolates collected from cases around the world have shown the presence of only 5 serogroups, namely A, B, C, Y, and W135.[5] Different serogroups are found in different regions of the world.[23] The quadrivalent vaccine is promising; however, its uptake was found to be slow in the USA and its effectiveness and potential for herd immunity are yet to be established.[5] The major challenge is serogroup B which causes 32% of the cases in the USA and 45–80% or more in Europe.[2] In contrast to serogroup C, which mainly causes focal outbreaks among teenagers and young adults, group B causes widespread epidemics and predominantly targets infants and young children.[4] Development of vaccines against serogroup B is difficult due to the similarity of its capsular polysaccharide with the cell surface glycoprotein on fetal brain tissue leading to tolerance and decreased immunogenicity.[4,22] Following sequencing of the bacterial genome, several

vaccine candidates have been studied including lipo-oligosaccharides, outer membrane vesicles (OMVs), transferring binding protein B, etc. However, the problem is that these candidates are not conserved across the numerous phenotypic and genotypic variants of serogroup B.[4] An OMV-based vaccine for controlling group B outbreaks in New Zealand was developed under the initiative of the World Health Organization and the Ministry of Health, New Zealand.[4] However, the challenge of identifying a single membrane protein conserved in all group B serotypes still remains.

Apart from these challenges an important issue is the burden of vaccines on infants. To reduce this burden there is increasing focus on combination vaccines, but studies have shown decreased immunogenicity of the protein conjugate vaccines in combination forms. For example, MenC when combined with PCV7 not only showed decreased immunity but was also associated with reduced serum antibody level of the concomitantly administered Hib and diphtheria vaccine.[5]

Challenges in global implementation of protein conjugate polysaccharide vaccines

In addition to the challenges in development of protein-conjugate polysaccharide vaccines for bacterial pneumonia and meningitis there are also implementation challenges concerned with the behavior of these bacteria,[5] duration of immunity,[16] and vaccination programmes. The first unresolved issue associated with the bacteria is replacement by nonvaccine serotypes. Several different serotypes of each bacterium may colonize the nasopharyngeal mucosa at the same time.[18] Vaccination against a few of them may lead to replacement by nonvaccine serotypes whose pathogenesis is largely unknown.[24] This raises concerns at both individual and population levels due to the probability of transmission and the potential to cause infection by these nonvaccine serotypes.[25]

Second issue related to bacterial behavior is "capsule switching." Genetic variations, shown through modeling in Hib, can undergo change in the length of its repetitive DNA units leading to diversity.[22] This phenomenon is far enhanced in meningococcal bacteria and capsular switching is an unresolved problem.[26] Evidence dates back to the latter half of the twentieth century when capsular switching occurred from serogroup B to C.[27,28] This evokes the fear that wide coverage of MenC vaccination will cause immune pressure leading to capsule switching.[26] An example is the outbreak in Haj pilgrims; W135 serogroup was isolated from the returning pilgrims in France and England. This strain is a variant of ET-37 clone[29] and is otherwise commonly found in the serogroup C isolates in U. K.[29,30]

Third problem is the unknown time duration of the antibody protective effect following vaccination. Studies with serological markers for immunity showed that the antibody levels wane off following primary immunization and even the booster at 12 months may not infer a long-lasting protection.[26] The concern of waning antibody level and efficacy is more for MenC because the second peak of meningococcal invasive disease is among the teenagers.

Finally, introduction of these vaccines in the national immunization programmes in developing countries including India has been hindered by costs of the vaccines,[4] programme costs, lack of knowledge of the disease burden,[17,10] and targeting of population groups for vaccination. The effectiveness of Hib vaccine is known for more than a decade now, but the decline in incidence of bacterial meningitis globally has been only 6%.[21] In India, the National Technical Advisory Group on Immunization (NTAGI) and the Indian Academy of Pediatrics recommend the introduction of Hib vaccine into the Universal Immunization Programme (UIP) schedule,[31] but presently this vaccine and other protein-conjugate polysaccharide vaccines are available only to those who can afford them.[7]

Conclusion

Introduction of Hib in the USA has decreased the incidence of bacterial meningitis by 73%.[21] PCV7 covers approximately 80% of invasive disease and PCV10 is expected to cover the serotypes predominant in Africa and South-East Asia and thereby contribute substantially to decrease the burden of bacterial pneumonia and meningitis in these regions. It is estimated that a global introduction of PCV will help prevent 5.4–7.7 million deaths among children by 2030 and will help in achieving goal-4 of the "Millennium Development Goals."[17] Considering this, WHO has recommended the introduction of Hib and PCV7 in the national immunization schedules of all countries.[17] However, there are challenges left to overcome in vaccine development to cover all variants of Hib, pneumococcus, and meningococcus. The challenges of reaching all infants and children in the developing countries are even great considering the burden of the disease that they bear.

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How to cite this article: Nair M. Protein conjugate polysaccharide vaccines: Challenges in development and global implementation. Indian J Community Med 2012;37:79-82.

Source of Support: This CME article has been drafted from a course work successfully submitted for MSc in Global Health Science, University of Oxford, United Kingdom. MSc was sponsored by the Future Faculty Programme scholarship of Public Health Foundation of India,
Conflict of Interest: None declared.