Use of Vaccine in the Era of Antimicrobial Resistance: Need of Effective Pneumococcal Vaccines

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Streptococcus pneumoniae is an important pathogen causing invasive infections particularly in children. Penicillin-nonsusceptible pneumococci are very prevalent in Korea and a difficult problem in antimicrobial treatment. Immunization with effective vaccines including viral and bacterial vaccines has proven to be the most effective and reliable method to prevent the target disease. Universal immunization to infants with Haemophilus influenzae type b conjugate vaccine has dramatically proven to be very effective in reducing invasive Hib diseases and also the carriage rate. The 23-valent pneumococcal polysaccharide vaccine is effective in preventing invasive diseases in young adults and covers most of the penicillin-nonsusceptible types. It has not proven very effective in the prevention of otitis media, and is unable to elicit adequate antibody response in children younger than 2 years of age. Recently a new polysaccharide-protein conjugate vaccine was developed which can elicit antibody response in children younger than 2 years of age. However, the vaccine is only 8-valent at the moment. Studies are required to determine the possible idiotypic modulation and nonproductive immune response when polysaccharide vaccine is administered to infants. Part of the problem of antimicrobial-resistant pneumococcal infection may be solved in the future with the use of improved vaccine. Preventing pneumococcal infections with safe and effective vaccines will not only reduce the development of antibiotic resistance, but could also be the most cost-effective method to control pneumococcal disease.

Key Word: Pneumococcal vaccines

Antimicrobial agents were believed to be miraculous drugs for the cure of various bacterial infections. However, with the increase of antimicrobial-resistant bacteria, it became difficult to cure some infections with antimicrobial agents alone. Methods other than antimicrobial agents have been sought and some, namely vaccines, have proved to be very effective these days. Although active or passive immunization was widely used to prevent or treat various infections before the antimicrobial era (Casadevall and Scharff, 1994), it soon became a less preferred method with the introduction of antimicrobial agents. However, interest in immunization with vaccines has been rekindled by the successful use of viral vaccines for the control of many serious viral infections. Viral vaccines eradicated smallpox from the world and virtually eliminated poliomyelitis from developed countries. Viral vaccines have also effectively limited the spread of many childhood diseases including measles, mumps, rubella and hepatitis B.

Confirming what we experienced in viral vaccine, bacterial vaccines are expected to be an effective method to eradicate and prevent target diseases. Hib conjugate vaccines have proven to be an effective
method for the prevention of *Haemophilus influenzae* type b (Hib) meningitis in children. Group B streptococci vaccines are being developed as the organism causes invasive infections which have become a major public health problem in both infants and adults (Wessles and Kasper, 1993). Even the effect of a vaccination for the prevention of infections due to *Klebsiella* and *Pseudomonas* in trauma patients has been investigated (Campbell et al. 1996). Vaccination against fungal agents has also become a current research interest, too (Deepe, 1997). Emergence of bacterial resistance to antimicrobial agents has prompted medical specialists to reconsider the importance of preventive measures. Vaccination may also be an effective method for the prevention of antimicrobial resistant pneumococcal infections (Munford and Murphy, 1994). The purpose of this article was to review the effect of Hib vaccination on the incidence of infection and the current development of pneumococcal vaccine.

**Experience with Hib vaccine against invasive infection**

Three species of organisms, *Neisseria meningitidis*, *H. influenzae* and *S. pneumoniae*, cause approximately 75% of the cases of bacterial meningitis and share the common characteristic of having polysaccharide capsules that play a fundamental role in the pathogenesis (Romero and Ouschoorn, 1994). Before the first Hib polysaccharide vaccine was introduced in 1985, *H. influenzae* was the most common cause of bacterial meningitis in children under 5 years of age in the United States, affecting approximately 12,000 children per year. The incidence of Hib invasive disease among children aged 4 years or younger has declined by 98% since the introduction of Hib conjugate vaccine (Bisgard et al. 1998). In other countries with established Hib vaccination programs, a sharp decline in the incidence of the disease was also reported (Peltola et al. 1992). The remarkable success of current vaccination programs against Hib has been due in part to the effect of Hib conjugate vaccine in decreasing carriage of the organism (Barbour, 1996). Pharyngeal carriage of Hib is important in the transmission of the organism, the pathogenesis of the disease, and the development of immunity to the bacterium. It was also reported that Hib polyribosylribitol phosphate-tetanus toxoid conjugate vaccine given during infancy reduced oropharyngeal carriage of Hib in fully-vaccinated children by 60% during the second year of life in a community in which exposure to the organism was likely to be much more intense than in industrialized countries (Adegbola et al. 1998). In much of Europe the incidence of Hib has declined by at least 90%, but not throughout all of Europe, because some countries such as Ukraine, Poland and Italy have not initiated large-scale vaccination programs (Peltola, 1998). Hib vaccination is currently recommended for children 12 months to 15 months in the United States (Gershon et al. 1997).

**Impact of pneumococcal infection**

Pneumococci can cause invasive infections, including meningitis, bacteremia, pneumonia and other infections of the lower and upper respiratory tract. It is a major pathogen affecting particularly young children, the elderly and those with certain underlying medical conditions. In the United States, the estimated occurrence of annual pneumococcal infections were: 3,000 cases of meningitis, 50,000 bacteremia, 500,000 pneumonia, and 7 million otitis media (Center for Disease Control, 1984; Williams et al. 1988; Stool and Field, 1989; Jernigan et al. 1996).

Pneumococci were highly susceptible organisms to penicillin G, however penicillin-nonsusceptible pneumococci which started to increase in the 1980s, became very common in many countries. Presently, over 60% of pneumococci are either resistant or intermediate to penicillin in Korea (Chong et al. 1995; Lee et al. 1995; Song et al. 1997). Many penicillin-nonsusceptible pneumococci have shown reduced susceptibility to other β-lactams, including 3rd-generation cephalosporins. Many penicillin-nonsusceptible pneumococci are also resistant to erythromycin and trimethoprim-sulfamethoxazole.

Some invasive infections with penicillin- and multidrug-resistant pneumococci often complicate the management of infections due to the difficulty in choosing an antimicrobial agent (Kaplan and Mason, 1998). Treating patients infected with drug-resistant organisms may require the use of expensive
alternative antibiotics and may result in prolonged hospitalization, higher mortality, and increased medical costs.

**Pneumococcal polysaccharide vaccine: the possibilities and the limitations**

Ideal pneumococcal vaccine is the one which can protect against pneumonia, meningitis, otitis media and bacteremia in young children (Briles et al. 1998). Antibodies generated against the capsular polysaccharide were highly active against lethal infection. However, there are at least 90 capsular types of pneumococci, while only one type of *H. influenzae* causes most invasive infection.

The pneumococcal capsular vaccine was effective in young adults, but it was only 60% effective in preventing bacteremia in the elderly. A capsular polysaccharide vaccine has proven protective in immunocompetent adults and in some at-risk populations. However, its efficacy was only marginal in immunocompromised patients and in preventing acute otitis media (Makela et al. 1980). The vaccine was unable to elicit an adequate antibody response to most of the capsular polysaccharides in children younger than 2 years.

Capsular polysaccharide vaccines induce type-specific antibodies which enhance opsonization and kill pneumococci by phagocytic cells. It is impossible to include all of the known capsular types in a vaccine. Two vaccines are currently available, which include 23 purified pneumococcal capsular polysaccharide antigens (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). The penicillin-nonsusceptible pneumococci are mostly 1, 6B, 14, 19F and 23F in many countries including Korea (Chong et al. 1995). The 23-valent vaccines cover nearly 90% of penicillin-nonsusceptible pneumococci detected in the United States and 85–90% of the serotypes which cause invasive diseases in children and the elderly (Butler et al. 1993; Butler et al. 1995).

More than 80% of healthy young adults showed a two-fold or greater rise of serotype-specific antibody levels within 2–3 weeks of immunization, but the immune response was not consistent to all 23 antigens (Musher et al. 1990). It is possible to prevent most pneumococcal infection in children over two years of age by the utilization of pneumococcal vaccine. However, age-specific immune responses vary by serotype and the response to some common pediatric pneumococcal serotypes is poor and not promising in children aged 2–5 years (Douglas et al. 1983; Koskela et al. 1986; Leinonen et al. 1986). Unfortunately, the 23-valent pneumococcal vaccine failed to elicit adequate antibody responses to most of the capsular polysaccharides in children younger than 2 years of age (Malinoski et al. 1993).

The poor antibody response in children is thought to be due to the nature of the polysaccharide antigens. Bacterial capsular polysaccharides are type 2 T-cell independent (TI) antigens, which stimulate mature B cells and induce antibodies by T-cell-independent mechanisms. Human infants as well as other infant vertebrates have been known for late maturation of their antipolysaccharide immune responsiveness compared to their responsiveness to protein antigens. The B cells of newborns do not respond to most polysaccharide antigens. Responsiveness only develops slowly during the first years of life. Furthermore, the TI antigens do not induce immunogenic memory or the maturation of the immune response; antipolysaccharide antibodies have low avidity and the switch from one isotype to another does not occur even after repeated immunizations. The lack of memory has some important implications for the vaccination and because of the rapid decline of antibodies, booster vaccination is often necessary. A more effective vaccine for pneumococcal infection is a priority.

**Pneumococcal polysaccharide-protein conjugate vaccines**

The 23-valent polysaccharide vaccine does not contain adjuvant. Studies have shown that polysaccharides could be rendered more immunogenic by conjugating them to proteins. Pneumococcal conjugates have been prepared by coupling capsular polysaccharides to several carriers including tetanus toxoid, diphtheria toxoid, CRM197 (a nontoxic variant of diphtheria toxin), pneumolysin, and meningococcal outer membrane proteins (Shell et al. 1997).
The polysaccharide antigens in a conjugate vaccine seem to benefit at least partly from the immunologic character of the carrier protein. The carrier protein is presented as peptides in association with the major histocompatibility complex class II molecules on the surface of the antigen-presenting cells. Table 1 shows four pneumococcal conjugate vaccines which were prepared by the same basic approaches as for the Hib conjugate vaccine.

The polysaccharide-protein conjugate vaccine is at present 7- or 8-valent. Apart from these formulations, several other candidate vaccines have been tested in animals, which include conjugates using pneumolysoid, pertussis toxoid, and salmonella protein as a carrier (Van de Wijgert et al. 1991; Schoenerson et al. 1992; Lee et al. 1994). Preclinical data showed that all of these conjugates were immunogenic and protective in animals, including mice, infant monkeys, and chinchillas (Giebink et al. 1993). However, so far no animal model can mirror human immunogenicity and efficacy studies. The first human studies were done in adults with monovalent conjugates and showed that the conjugates were at least as immunogenic as the polysaccharide vaccine. Since then, up to 8-valent vaccines have been used in human studies, including infants. Table 2 shows the antibody response of Finnish infants to pneumococcal conjugate vaccine administered at 2, 4, and 6 months of age.

There have been several efficacy trials evaluating pneumococcal conjugate vaccines. The end points of these trials vary considerably, from otitis media to invasive disease. Giebink et al. vaccinated women of childbearing age with 23-valent pneumococcal polysaccharide vaccine and 7-valent PS-CRM197 conjugate vaccine (Giebink et al. 1998). Both conjugate and polysaccharide vaccine produced moderate to high levels of anti-polysaccharide IgG2 antibody. It was considered that passive antibody transfer to the fetus may be possible, but neither conjugate vaccine nor polysaccharide vaccine produced high levels of anti-polysaccharide IgG1 antibody, the subclass preferentially transported across the placenta. Therefore, the infant of an immunized mother may be more likely to derive benefit based on serotype coverage of the vaccine administered during pregnancy than from an immunogenicity difference between conjugate vaccine and polysaccharide vaccine. Since conjugate vaccine covers 65% of serotypes and polysaccharide vaccine covers 85%, it is considered that

Table 1. New pneumococcal polysaccharide-protein conjugate vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Carrier</th>
<th>Serotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>PncOMPC</td>
<td>Meningococcal</td>
<td>4,6B,9V,14,18C,19F,23F</td>
</tr>
<tr>
<td></td>
<td>OMPC</td>
<td></td>
</tr>
<tr>
<td>PncCRM</td>
<td>CRM197</td>
<td>4,6B,9V,14,18C,19F,23F</td>
</tr>
<tr>
<td>PncD</td>
<td>Diphtheria toxoid</td>
<td>3,4,6B,9V,14,18C,19F,23F</td>
</tr>
<tr>
<td>PncT</td>
<td>Tetanus toxoid</td>
<td>3,4,6B,9V,14,18C,19F,23F</td>
</tr>
</tbody>
</table>

OMPC, outer membrane protein complex; CRM1, CRM197, a nontoxic variant of diphtheria toxin; D, diphtheria toxoid; T, tetanus toxoid.

Table 2. Geometric Mean of the Anti-Pneumococcal polysaccharide (μg/mL)*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type 6B</th>
<th>Type 14</th>
<th>Type 19F</th>
<th>Type 23F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>PncOMPC</td>
<td>0.17</td>
<td>1.30</td>
<td>0.42</td>
<td>8.27</td>
</tr>
<tr>
<td>PncCRM</td>
<td>0.25</td>
<td>0.50</td>
<td>0.30</td>
<td>2.49</td>
</tr>
<tr>
<td>PncT</td>
<td>0.20</td>
<td>1.28</td>
<td>0.30</td>
<td>2.56</td>
</tr>
<tr>
<td>PncD</td>
<td>0.17</td>
<td>1.44</td>
<td>0.31</td>
<td>4.62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
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<tr>
<td>Type 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 19F</td>
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<td></td>
</tr>
<tr>
<td>Type 23F</td>
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</table>

Modified from Käyhty and Eskola, 1996.
PncOMPC, tetravalent conjugate vaccine with a meningococcal outer membrane protein complex; PncCRM, petavalent oligosaccharide conjugate vaccine with CRM197 protein; PncT, octavalent conjugate vaccine with tetanus toxoid carrier; PncD, octavalent conjugate vaccine with diphtheria toxoid.

*Serum samples are taken before immunization (pre) and at 7 months (post).
polysaccharide vaccine should be the favoured pre-natal vaccine. The Hib conjugate vaccines induce good responses in mothers and, consequently, long-lasting protective concentrations in infants born to these mothers.

Impact of vaccination on nasopharyngeal colonization

The problem of antimicrobial-resistant pneumococcal infection may be solved by active immunization, as we have experienced in Hib conjugated vaccines. Our experience with Hib conjugate vaccines suggests that pneumococcal conjugate vaccines could also reduce the number of carriers of the capsular types and in this way decrease the spread of bacteria. Vaccination was considered to be an effective method of preventing nasopharyngeal colonization and infection in children by drug-resistant pneumococci (Munford and Murphy, 1994). It was reported that the pneumococcal outer membrane protein complex (PncOMPC) vaccine decreased the carriage rate of pneumococci, including the antibiotic resistant ones among toddlers, while the pneumococcal polysaccharide vaccine did not. A 7-valent pneumococcal conjugate vaccine was reported to significantly reduce pneumococcal nasopharyngeal colonization rates among children (Dagan et al. 1995). Also the PncCRM9 conjugated vaccine was reported to cause a continuous reduction in the nasopharyngeal carriage of vaccine type pneumococci, but simultaneously increased the carriage of non-vaccine type strains. No change in total pneumococci carriage was observed within an 8-month period analyzed so far (Dagan et al. 1998). The emphasis will be on invasive diseases as well as the impact of conjugate vaccines on colonization. Many of the new conjugate vaccines will contain as many as 11 serotypes (serotypes 1, 3, 4, 5, 6, 7, 9, 14, 18, 19, 23).

Limitations of polysaccharide-protein conjugate vaccines

The use of polysaccharide-protein conjugate vaccines still involves a number of problems. First, In *H. influenzae* b polysaccharide vaccine, only a single conjugate is necessary, however, for pneumococcal vaccine, it must contain as many types of polysaccharide conjugates as possible. Since each conjugate requires unique conjugation substrates and reaction conditions, individual conjugates must be separately constructed. Due to the amount of conjugated protein required to elicit immunity to a single polysaccharide, the number of different conjugates included in a vaccine will of necessity be limited. The immunity induced by pneumococcal conjugate vaccines may be short-lived, especially in infants, but such a limitation would require repeat vaccinations through the first several years of life. This will necessitate increased costs even in wealthy countries. Second, some variations exist in the common pneumococcal serotypes in different parts of the world. This could be addressed by further increasing the number of polysaccharides in the vaccine or by making different mixtures of polysaccharides and conjugates for different regions of the world. Such modifications are not only technologically difficult, but also exceedingly expensive. Third, pneumococci are able to change their capsular serotype as a result of insert heterologous DNA. There will be a possibility that protection of an anti-capsular antibody may be temporary in the future. Fourth, human infants and infants of other vertebrates have established late maturation of their antipoly saccharide immune responsiveness in comparison to their responsiveness to protein antigens. Since the ability to make antibodies to polysaccharides would confer the capability to protect the infection from encapsulated bacteria, the absence of antipoly saccharide responsiveness in infants raises the possibility that there is some selective immunologic or developmental disadvantage in making such responses (Hayrinen et al. 1995). This suggests that the absence of responsiveness to bacterial polysaccharide antigens in children may prevent the production of antibodies reactive to developing tissues. Fifth, another suggested problem with early vaccination with polysaccharides came from deleterious modulation of the antibody response (Musher et al. 1990). The mouse model is well demonstrated by the response to phosphocholine. Phosphocholine is present both in F-antigen (lipoteichoic acid) and C-polysaccharide (teichoic acid), and it is an immunodominant determinant molecule in the mouse (Van de Wijgert et al. 1991; Åhman et al. 1996).
It has been proven that pretreatment with deceased pneumococci resulted in an anti-phosphocholine response in 7-week-old mice that was largely deficient in antibodies of the T15 idiotype. In contrast, nonimmunized control mice were able to mount a primarily T15 response when immunized at 7 weeks of age with deceased pneumococci. In other words, exposure of neonatal mice to polysaccharide antigens can lead to idiotypic modulation and nonprotective-immune responses. If this is also proven in human infants, rigorous removal of nonconjugated tolerogenic polysaccharide fragments might be necessary to minimize any immunomodulatory effects of polysaccharide-protein vaccines (Briles et al. 1998). Although millions of infants have been immunized at 3 months of age with Hib polysaccharide-protein conjugate vaccines, there have been no reports of deleterious immunologic developmental effects. However, as five or more different conjugates would be required for pneumococcal vaccines, it may possibly increase the risk of deleterious consequences (Briles et al. 1996).

Pneumococcal protein vaccine candidates

All of these considerations of pneumococcal polysaccharide protein conjugate vaccines lead to the conclusion that new generations of pneumococcal vaccines will be developed to address these problems. In addition to the capsule, a number of protein antigens are either exposed on the surface or released from the pneumococci. These surface proteins have been considered as promising vaccine candidates or as carrier proteins in pneumococcal conjugate vaccines. The prime vaccine candidates are enzymes and toxins that are excreted or released after the bacterium has autolyzed, or surface proteins whose exact functions are not known. These include neuraminidase, autolysin, pneumolysin, pneumococcal surface protein A (PsPA), and pneumococcal surface adhesin A (PsAA) (Lock et al. 1988; Sampson et al. 1994; Tart et al. 1996). PsPA is a surface protein present in all clinically relevant pneumococcal strains. PsPA is from different pneumococcal strains vary serologically. However, many PsPA antibodies cross-react with PsPA from unrelated strains. Furthermore, active immunization of mice with PsPA generates a protective immune response against diverse pneumococcal strains (McDaniel et al. 1983). Pneumolysin is a cytolytic toxin produced by all types of pneumococci. In mice, immunization with inactivated pneumolysin or recombinant pneumolysin toxoid offers at least partial protection or enhanced survival when challenged with pneumococci (Paton, et al. 1983).

CONCLUSIONS

In the near future, pneumococcal protein-conjugate vaccines may be included in universal childhood immunization programs. The price of the conjugate vaccines has been too high for use throughout the world. The development of new pneumococcal vaccines may reduce the cost so that a global immunization program can give all children the benefit of vaccines. Preventing pneumococcal infections with vaccines will not only reduce the development of antibiotic resistance, but it will also be the most cost-effective method to control pneumococcal diseases.

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