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☐ Review Article ☐

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

Young Mo Sohn

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

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Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea
Address reprint request to Dr. Y.M. Sohn, Department of Pediatrics, Yonsei University College of Medicine, Seoul 135-270, Korea. Tel: 82-2-3497-3354, Fax: 82-2-3461-9473, E-mail: youngmo@yumc.yonsei.ac.kr

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 (Cambell *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 polysaccaride capsules that play a fundamental role in the pathogenesis (Romero and Outschoorn, 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; Schneerson *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 mono- or bivalent 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

Vaccine	Carrier	Serotype
PncOMPC	Meningococcal OMPC	4,6B,9V,14,18C,19F,23F
PncCRM	CRM197	4,6B,9V,14,18C,19F,23F
PncD	Diphtheria toxoid	3,4,6B,9V,14,18C,19F,23
PncT	Tetanus toxoid	3,4,6B,9V,14,18C,19F,23

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

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

Vaccine	Type 6B		Type 14		Type 19F		Type 23F	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
PncOMPC	0.17	1.30	0.42	8.27	0.34	9.85	0.28	1.90
PncCRM	0.25	0.50	0.30	2.49	0.46	1.13	0.18	0.83
PncT	0.20	1.28	0.30	2.56	0.56	4.23	0.22	1.03
PncD	0.17	1.44	0.31	4.62	0.37	4.94	0.24	1.07

Modified from Käythy 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 prenatal 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 disases 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 anticapsular antibody may be temporary in the future. Fourth, human infants and infants of other vertebrates have established late maturation of their antipolysaccharide 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 antipolysaccharide 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. PspAs from different pneumococcal strains vary serologically. However, many PspA antibodies cross-react with PspAs 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.

REFERENCES

Adegbola RA, Mulholland EK, Secka O, Jaffar S, Greenwood BM: Vaccination with a *Haemophilus influenzae* type b conjugate vaccine reduces oropharyngeal carriage of *H. influenzae* type b among Gambian children. *J Infect Dis 177: 1758-1761, 1998*

Åhman H, Kåhty H, Tamminen P, Uistola A, Malinoski F, Eskola J: Pentavalent pneumococcal oligosaccharide conjugate vaccine PncCRM is well tolerated and able to induce an antibody response in infants. *Pediatr Infect Dis J 15: 134-139, 1996*

Barbour ML: Conjugate vaccines and the carriage of *Haemophilus influenzae* type b. *Emerg Infect Dis 2: 176-182, 1996*

Bisgard KM, Kao A, Leake J, Strebel PM, Perkins BA, Wharton M: *Haemophilus influenzae* invasive disease in the United States, 1994-1995: Near disappearance of a vaccine-preventable childhood disease. *Emerg Infect Dis 4: 229-237, 1998*

Briels DE, King JD, Gray MA, McDaniel LS, Swiatlo E, Benton KA: PspA, a protection-eliciting pneumococcal protein; immunogenicity of isolated native PspA in mice. *Vaccine 14: 858-867, 1996*

Briles DE, Tart RC, Swiatlo E, Dillard JP, Patricia S, Benton KA, Talph BA, Waiter AB, Crain M, Hollinshead SK, McDaniel LS: Pneumococcal diversity considerations for new vaccine strategies with emphasis on pneumococcal surface protein A (PspA). *Clin Microbiol Rev 11: 645-657, 1998*

Butler JC, Breiman RF, Cambel JF, Lipman HE, Broome CV, Facklam RR: Pneumococcal polysaccharide vaccine efficacy: an evaluation of current recommendations. *JAMA 270: 1826-1831, 1993*

Butler JC, Breiman RF, Lipman HE, Hofmann J, Facklam RR: Serotype distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978–1994: Implications for development of a conjugate vaccine. *J Infect Dis 1 71: 885-889, 1995*

Cambell WN, Hendrix E, Cryz S Jr, Cross AS: Immunogenicity of a 24-valent *Klebsiella* capsular polysaccharide vaccine and an eight-valent *Pseudomonas* O-polysaccharide conjugate vaccine administered to victims of acute trauma. *Clin Infect Dis 23: 179-181, 1996*

Casadevall A, Scharff MD: Serum therapy revisited: Animal models of infection and development of passive antibody therapy. *Antimicrob Agents Chemother 38: 1695-1702, 1994*

Center for Disease Control: Pneumococcal polysaccharide vaccine. *MMWR 33: 273-276, 281, 1984*

Chong Y, Lee K, Kwon OH, Henrichsen J: Capsular types and antimicrobial resistance of *Streptococcus pneumoniae* isolated in Korea. *Eur J Clin Microbiol Infect Dis 14: 528-531, 1995*

Dagan R, Gradstein S, Janco J, Sikuler-Cohen M, Chang I, Kimura A, Hackell J: Tolerability and immunogenicity of a 9-valent pneumococcal CRM197 vaccine (PncCRM9) vs. meningococcal group C CRM197 vaccine (MncCRM-C) during 2nd and 3rd year of life: A double blind randomized study, abstr. G51. In abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C., American Society for Microbiology, *1998, 298-299*

Dagan R, Muallem R, Yagupsky P: Reduction of nasopharyngeal carriage of penicillin-resistant pneumococci by pneumococcal-OMPC conjugate vaccine during second year of life, abstr. G2. In abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C., American Society for Microbiology, *1995*

Deepe GS Jr: Prospects for the development of fungal vaccines. *Clin Microbiol Rev 10: 585-596, 1997*

Douglas RM, Paton JC, Duncan SJ, Hansman DJ: Antibody response to pneumococcal vaccination in children younger than five years of age. *J Infect Dis 148: 131-137, 1983*

Gershon AA, Gardner P, Peter G, Nichols K, Orenstein W: Quality standards for immunization. Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis 25: 782-786, 1997*

Giebink GS, Englund JA, Liebeler C, Le CT, Glezen WP: Pneumococcal conjugate vs. polysaccharide vaccine in women of child-bearing age, abstr. G55. In abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C., American Society for Microbiology, *1998, 300*

Giebink GS, Koskela M, Vella PP, Harris M, Le CT: Pneumococcal capsular polysaccharide-meningococcal outer membrane protein complex conjugate vaccines; immunogenicity and efficacy in experimental pneumococcal otitis media. *J Infect Dis 167: 347-355, 1993*

Hayrinen J, Jennings H, Raff HV, Rougon G, Hanai N, Gerardy-Schahn R, Finne J: Antibodies to polysialic acid and its N-propyl derivative: binding properties and interaction with human embryonal brain glycopeptides. *J Infect Dis 171: 1481-1490, 1995*

Jernigan DB, Centron MS, Breiman RF: Minimizing the impact of drug-resistant *Streptococcus pneumoniae* (DRSP): a strategy from the DRSP working group. *JAMA 275: 206-209, 1996*

Kaplan SL, Mason EO Jr: Management of infections due to antibiotic-resistant *Streptococcus pneumoniae. Clin Microbiol Rev 11: 628-644, 1998*

Käythy H, Eskola J: New vaccines for the prevention of pneumococcal infections. *Emerg Infect Dis 2: 289-298, 1996*

Koskela M, Leinonen M, Haiva V-M, Timonen M, Makela PH: First and second dose antibody responses to pneumococcal polysaccharide vaccine in infants. *Pediatr Infect Dis 5: 45-50, 1986*

Lee CJ, Lock RA, Andrew PW, Mitchell TJ, Hansman D, Paton JC: Protection of infant mice from challenge with *Streptococcus pneumoniae* type 19F by immunization with a type 19F polysaccharide-pneumolysoid conjugate. *Vaccine 12: 785-878, 1994*

Lee HJ, Park JY, Jand SH, Kim JH, Kim EC, Choi KW: High incidence of resistance to multiple antimicrobials in clinical isolates of *Streptococcus pneumoniae* from a university hospital in Korea. *Clin Infect Dis 20: 826-835, 1995*

Leinonen M, Sakkinen A, Kalliokoski R, Luotonen JJ, Timonen M, Makela PH: Antibody response to 14-valent pneumococcal capsular polysaccharide vaccine in preschool age children. *Pediatr Infect Dis* 5: 39-44, 1986

Lock RA, Paton JC, Hansman D: Comparative efficacy of pneumococcal neuraminidase and pneumolysin as immunogens protective against *Streptococcus pneumoniae. Microb Pathog 5: 461-467, 1988*

Makela PH, Sibakov M, Herva E, Henricksen J: Pneumococcal vaccine and otitis media. *Lancet 2: 547-551, 1980*

Malinoski F, Hogerman D, Ginsberg H, Madore D: Safety and immunogenicity of pentavalent *S. pneumoniae* conjugate vaccines in healthy adults, abstr. 168. In abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washing-

ton, D.C., American Society for Microbiology, *1993, 150*

McDaniel LS, Sheffield JS, Delucchi P, Briles DE: PspA, a surface protein of *Streptococcus pneumoniae*. *Infect Immun 59: 222-228, 1983*

Munford RS. Murphy TV: Antimicrobial resistance in *Streptococcus pneumoniae*; can immunization prevent its spread? *J Intest Med 42: 613-621, 1994*

Musher DM, Luchi M, Watson DA, Hamilton R, Baughn RE: Pneumococcal polysaccharide vaccine in young adults and older bronchitis: determination of IgG response by ELISA and the effect of serum with non type-specific cell wall polysaccharide. *J Infect Dis 16l: 728-735, 1990*

Paton JC, Lock RA, Hansman DJ: Effect of immunization with *Streptococcus pneumoniae*. *Infect Immun 40: 548-552, 1983*

Peltola H: Only slightly declined burden of Hib (*Haemophilus influenzae* type b) disease in Europe, abstr. G54. In abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C., American Society for Microbiology, *1998, 299*

Peltola H, Kilpi T, Anttila M: Rapid disappearance of *Haemophilus influenzae* type b meningitis after routine childhood immunization with conjugate vaccine. *Lancet 340: 592-594, 1992*

Romero JD, Outschoorn IM: Current status of meningococcal group B vaccine candidates: Capsular or noncapsular? *Clin Microbiol Rev 7: 559-575, 1994*

Sampson JS, O'Connor SP, Stinson AR, Tharpe JA, Russell H: Cloning and nucleotide sequence analysis of PsaA, the *Streptococcus pneumoniae* gene encoding a 37-kilodalton protein homologous to previously reported *Streptococcus* sp. Adhesins. *Infect Immun 62: 319-324, 1994*

Schneerson R, Levi L, Robbins JB, Bryla DM, Schiffman G, Lagergard T: Synthesis of a conjugate vaccine composed of pneumococcus type 14 capsular polysaccharide bound to pertussis toxin. *Infect Immun 60: 3528-3532, 1992*

Shell MA, Jacoby H, Riley GJ, Graves BT, Pichichero M, Treanor JJ: Comparison of pneumococcal polysaccharide and CRM197 conjugated pneumococcal oligosaccharide vaccines in young and elderly adults. *Infect Immun 65: 242-247, 1997*

Song JH, Yang JW, Peck KR, Kim S, Lee NY, Jacobs MR, Appelbaum PC, Pai CH: Spread of multiresistant *Streptococcus pneumoniae* in South Korea. *Clin Infect Dis 25: 747-749, 1997*

Stool SE, Field MJ: The impact of otitis media. *Pediatr Infect Dis J 8(suppl): 11-14, 1989*

Tart RC, McDaniel LS, Ralph BA, Briles DE: Truncated *Streptococcus pneumoniae* PspA molecules elicit cross-protective immunity against pneumococcal challenge in mice. *J Infect Dis 173: 380-386, 1996*

Van de Wijgert JHHM, Verheul AFM, Snippe H, Check IJ, Hunter RL: Immunogenicity of *Streptococcus pneumoniae* type 14 capsular polysaccharide; influence of carriers and adjuvants on isotype distribution. *Infect Immun 59: 2750-2757, 1991*

Wessels MR, Kasper DL: The changing spectrum of group B streptococcal disease. *N Engl J Med 3238: 1843-1844, 1993*

Williams WW, HicksonMA, Kane MA, Kendal AP, Spika JS, Hinman AR: Immunization policies and vaccine coverage among adults; the risk for missed opportunities. *Ann Intern Med 108: 616-625, 1988*