Recommendations for the Use of Heptavalent Pneumococcal Vaccine

By

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Abstract

Why not immunize all children under the age of 59 months with pneumococcal vaccine? Vaccination for infants and children would provide an effective means for reducing the mortality and morbidity of pneumococcal disease. Pneumococcus (streptococcus pneumoniae) is responsible for infections such as otitis media, pneumonia, meningitis, and septicemia. According to the Centers for Disease Control and Prevention, pneumococcus is responsible for 40,000 deaths per year in the United States (Centers for Disease Control and Prevention [CDC], 1997). Pneumococcus is a nondiscriminatory infectious agent affecting all ages, sexes, and races. Children, by nature of their immature immunologic status, are susceptible to pneumococcal infections. Children in daycare centers with greater than ten children hold an even higher risk for infection. They are 6 to 36 times more likely to suffer from pneumococcal infection than their peers who are not in daycare (CDC, 1997). Vaccines are available that can provide up to 90% protection against the most common pneumococcal strains (O’Brien et al., 1996). Current recommendations limit their use to children under 2 years, and in certain select populations. Use of vaccines in children up to five years of age would provide an effective means of decreasing pneumococcal disease.
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Introduction

Early detection and antibiotic therapy has effectively reduced childhood pneumonia-related mortality by 50% and overall childhood mortality by 25%. However, drug resistance reduces the effectiveness of disease management. Pneumococcal vaccine offers an optimal approach to reduce morbidity and mortality for disease caused by pneumococcus. (Sniadack et al., 1995).

The American Academy of Pediatrics (AAP) recommend administration of Prevnar, a heptavalent pneumococcal vaccine for children younger than 24 months. Additionally, the guidelines include various at risk groups aged 24-59 months (American Academy of Pediatrics, 2000). Similarly, CDC criteria as of July 2000 suggest that all children under 24 months of age and children in certain high-risk groups above that age should be vaccinated with the heptavalent pneumococcal vaccine.

Despite the recent advent of an efficacious pneumococcal vaccination, the Advisory Committee on Immunization Practice (ACIP) of the Centers for Disease Control and Prevention (CDC), The American Academy of Pediatrics (AAP), and The American Academy of Family Physicians (AAFP) have not yet recommended coverage for all the pediatric population up to 59 months of age. The research literature confirms the significance of pneumococcal disease in children without a specific risk group designation. This manuscript analyzes the current literature and recommends coverage by heptavalent pneumococcal vaccine, Prevnar, to all children under the age of 59 months.
Epidemiology

Pneumococcus, a lancet shaped gram-positive diplococcus, commonly causes a wide range of infections, including otitis media, mild respiratory infections, pneumonia and severe invasive disease, such as bacteremia and meningitis (Ahman, Kaythy, Tamminen, Vuorela, Malinoski, Eskolal., 1996). Thirty percent of the bacterial related deaths in children under age five years are caused by pneumococcus (Butler, Breiman, Campbell, Lipman, Broome, Facklam., 1993).

Numerous serotypes of pneumococcus form a normal constituent of the bacterial flora of the upper respiratory tract (Austrian, 1989; AAP, 1997). If pneumococcus indicates normal flora, why do infections occur? One theory suggests a preceding upper respiratory viral infection or exposure to an alien pneumococcal serotype predisposes the child to an infectious process (AAP, 1997).

Some virulent pneumococcal serotypes demand a multivalent vaccine that specifically covers these serotypes. Unlike trying to vaccinate for the hundreds of common cold strains the relatively few virulent pneumococcal strains can be eradicated (Rennels et al., 1998). Although ninety serotypes exist, only a few are considered seriously virulent (CDC, 1997). The most virulent serotypes include groups 4, 6B, 9V, 14, 18C, 19F, and 23F are the most virulent in the U.S. (CDC, 1997).

Pneumococcus is the single most common bacterial infection in the United States (Jacobs & Guglielmo, 1999), and the most common invasive bacterial infection in children. The Morbidity and Mortality Weekly Report estimates 40,000 deaths per year can be attributed to pneumococcal infections (CDC, 1997). This number represents more deaths than any other vaccine-preventable bacterial disease (CDC, 1997).
Pneumococcus is the leading cause of fatal bacterial pneumonia in developing countries (CDC, 1997). Pneumonia accounts for up to 30% of all deaths in children <5 years old in developing countries. Seventy-five percent of all pneumonia deaths occur in infants under the age of 2 years (Garenne, Ronsmans, Campbell, 1992).

"Rates of pneumococcal disease are higher in the first two years of life and drop off sharply thereafter until they rise again in the elderly" (Steinhoff, 1998, p. 10). The incidence of reportable pneumococcal infection for children aged less than 2 years is 160 cases per 100,000 people (CDC, 1997).

Pneumococcus is responsible for 30% to 50% of cases of acute otitis media (AAP, 1997), accounting for 24 million pediatrician visits annually (CDC, 1997). Pneumococcus is now the leading cause of meningitis worldwide (Malley, 1998). The incidence of pneumococcal meningitis is highest among children aged 6-24 months (CDC, 1997). Data indicates that pneumococcus presents a major infectious bacterial concern for children up to age 10 years (Steinhoff, 1998). (See Table 1 for infections caused by pneumococcus).

**Resistance**

Antimicrobial treatments for pneumococcus most commonly utilize penicillin-based antibiotics. Six common serotypes include the most frequent isolates associated with penicillin resistant pneumococcus (AAP, 1997). Resistance mutation blocks the ability of beta-lactam antibiotics (penicillins and cephalosporins) to control infections. As a result multidrug resistant pneumococcal strains are rapidly emerging (Doern, Brueggemann, Holley & Rauch, 1996; CDC, 1998).

Non-susceptible strains of pneumococcus usually respond to 2nd and 3rd
generation antimicrobial products, such as Claforan (cefotaxime) or Rocephin (ceftriaxone). Vancocin (Vancomycin) and Rifadin (rifampin) also prove effective (AAP, 1997). However, many regions of the United States currently report severe pneumococcal resistance to penicillin, cefotaxime, and ceftriaxone (CDC, 1997). In some areas, as much as 35% of pneumococcal isolates are resistant (Butler, Hofman, Cetron, & Elliott, 1996).

Mark Steinhoff (1998) describes the process of building resistance to pneumococcus,

The current hypothesis [about resistance] is that penicillin resistance in pneumococci is related to the development of mutant Penicillin Binding Protein, (PBP) enzymes, which do not bind penicillins well but still bind their natural peptide substrates for cell wall synthesis. Random mutations alter the PBPs, allowing the organism to grow in the presence of penicillin. These mutations occur many times and in many sites. Cephalosporin resistance is mediated through a similar mechanism of change in PBPs. Once a pneumococcus acquires the advantageous enzyme, it may rapidly spread to other hosts, which accounts for rapid dispersal of resistant strains. (Steinhoff, 1998, p. 9)

Antibiotic resistance makes combating infections like acute otitis media more involved and costly. To treat resistant strains, the use of two or more antibiotics at the same time, or sequentially, has become common practice (CDC, 1997). If single therapy or first-line therapy fails, additional agents are added to attack and destroy pneumococcus. The CDC recommends amoxicillin as first choice and Augmentin as a
second choice. Amoxicillin costs approximately $12.00 per 10-day course of treatment while the cost of Augmentin is six times more expensive at $72.00. Although Augmentin is the current drug of choice for second line coverage of otitis media, other antibiotics also prove effective. An increased likelihood of creating resistance develops from multiple antibiotic exposure (Steinhoff, 1998).

Vaccinations have the inherent ability to provide enhanced immunity; thus vaccinations offer us the potential to reduce the over-usage of antibiotics. Heptavalent vaccine coverage of all children under five years could dramatically reduce the development of antibiotic resistant strains of pneumococcus by decreasing the use of antibiotics.

Risk factors and At-Risk Populations

Age and disease as risk factors

Transmission of pneumococcal disease is generally from person to person via aerosolized droplets (Ferri, 1999). Infection is spread by coughing, thus infecting persons in close contact.

Infants are immunologically immature at birth. Mature levels of immunoglobulins are not achieved until the age of 6 to 10 years of age (Austrian, 1989). Table 2 presents data identified by the CDC on various groups of children who represent those at highest risk for pneumococcal infection.

Children with Human Immunodeficiency Virus (HIV) and/or a positive antibody titer may present altered immune system response to infection, increasing their risk for infections (Wadwa & Feign, 1999). Children who are steroid dependent have a similar problem. Approximately, 5% of splenectomized children develop pneumococcus
bacteremia or meningitis with a mortality of 30-60% (Konradsen & Henrichsen, 1991).

Daycare as a risk

A Finish study revealed that daycare center children under the age of 2 years have a 6 to 36-fold increase of invasive pneumococcal infection when compared to the same aged population who did not attend daycare centers (Konradsen & Henrichsen, 1991). Daycare environment leads to exposure and transmission of different infectious agents when children gather in close proximity from a variety of environments with different pneumococcal serotypes.

Daycare children are also more prone to frequent infections due to the absence of, or decreases in breast-feeding in this population compared to their peer group who do not attend daycare. Failure to breastfeed results in a deficiency of passive immunoglobulin protection from mother to child, leading to decreased intrinsic protection (Levine, Farley, & Harrison, 1999; Zangwill, Vadheim, & Vannier, 1996).

The combination of immature immune function and increased exposure to various foreign serotypes provides a reservoir for infection. The at-risk daycare population needs protection with pneumococcal vaccine (Levine, Farley, & Harrison, 1999; Zangwill, Vadheim, & Vannier, 1996).

Twenty-three valent vaccine

Two suppliers of 23-valent pneumococcal vaccines in the United States include (Drug Facts and Comparisons, 1999). Pneumovax 23, manufactured by Merck and Company, Inc. and Wyeth-Lederle, manufacture Pnu-Immune 23. The 23-valent vaccine was licensed in the United States in 1983. A “valence” represents a specific serotyping of bacteria. Thus, a 7-valent vaccine designates 7 specific and different serotypes. In
February 2000 the heptavalent pneumococcal vaccine, Prevnar, was licensed by the FDA as a seven valent vaccine.

Pneumovax vaccine is composed of capsular polysaccharide antigens of 23-streptococcus pneumoniae. The wholesale cost of pneumovax is $1.10 per a one-time injection. Pneumovax is recommended for adults and children over 10 years with specified risk factors. Recommendations for use of the 23-valent vaccine are listed in table 3.

The six serotypes most often associated with invasive drug-resistant pneumococcal infection in the United States include 6B, 9V, 14, 19A, 19F, and 23F. These six serotypes are contained in the 23-valent Pneumo-Vaccine licensed in 1983 (Hofmann et al, 1995). After vaccination with the 23-valent vaccine, the antigen-specific antibody response produces a 200% increase in serotype specific antibody response 2-3 weeks post vaccination in greater than 80% of healthy adults (CDC, 1997). Levels of antibody after pneumococcal vaccination appear to be sustained for three to five years (CDC, 1997). Revaccination after 3 to 5 years is recommended for children over age 10. Adults need a booster approximately six years after the initial vaccination. The 23-valent pneumococcal vaccine has not proved efficacious for children under two years of age. The 23-valent pneumococcal vaccine appears to have a 60-70% efficacy for the prevention of pneumococcal meningitis among immunocompetent persons (Shapiro, Berg & Austrian, 1991). Children with HIV and other types of immunosuppression have a poorer response of measurable antibody levels to the 23-valent vaccine (King et al., 1996).
Seven Valen Vaccine

Prevnar, produced by Wyeth-Lederle, is the first conjugate pneumococcal vaccine to be approved for use in infants. The 7-valent conjugate vaccine is approved for use in the prevention of invasive disease, bacteremia, and meningitis caused by the serotypes contained in the vaccine. The cost of the Prevnar is approximately $58.00 per administration and costs $232.00 for the series four injections. The current recommendation states that children in the previously identified high-risk groups (Table 2) and all children under 24 months should routinely receive Prevenar vaccine.

Prevnar™ heptavalent (7-valent) conjugated vaccine contains serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. The 7 valences covered by the vaccine account for 85% of bacteria responsible for pneumococcal disease (Ahman et al., 1996). Prevnar has proven immunogenicity in the under 24-month-old group (Rennels et al., 1998).

An analysis of all acute otitis media episodes during a randomized, double-blind clinical trial on greater than 38,000 children was conducted by the Kaiser Permanente Vaccine Study Centers. The study (Rennels et al., 1998) utilized the heptavalent pneumococcal vaccine to determine efficacy in infants. The vaccine was administered four times at 2, 4, 6, and 12 to 15 months of age to determine safety and immunogenicity. After three doses, more than 92% of patients recorded a 50% to 90% serotype specific antibody level (Ahman et al., 1996). A booster dose resulted in a rapid and effective response to all seven serotypes and stimulation of memory-T-cells resulted (O'Brien et al., 1996). The heptavalent vaccine appears to have an immunogenic response with both a primary and secondary booster administration (O'Brien et al., 1996; Rennels et al., 1998).
The Kaiser Permanente study determined that children receiving the heptavalent pneumococcal vaccine had a 7% greater reduction in otitis media versus the placebo group (Black & Shinefield, 1997). The study also included a review of the records of the study groups. Children in the vaccine group were 20% less likely to require tympanostomy tubes and 23% less likely to have frequent ear infections. Frequent ear infections were defined as five episodes in six months, or six episodes in twelve months. Finally, the vaccine group recorded 9 less clinical visits per vaccinated patient than the control group (no vaccine) during the three-year study time frame (Black & Shinefield, 1997).

Disadvantages of Universal Immunization of Children under the age of Five

One stance against coverage with pneumococcal vaccine argues that children already receive more than a dozen shots during their early childhood (CDC, 1997). Future combined vaccines may minimize pain and fear associated with multiple injections.

Comparisons of the risks and side effects of this immunization to other immunizations suggest there is a notable absence of risks and only mild local discomfort at the injection site (King et al., 1996). Common mild side effects from heptavalent pneumococcal vaccination include pain, induration, and erythema at the site of injection. Severe systemic reactions and moderate complaints of fever, myalgia and local reactions are rare. No findings report long-term sequelae from receiving the protein-conjugate vaccine (King et al., 1996).

Cost is also a deterrent to beginning a new vaccine. The CDC and National Immunization Program (NIP) are currently negotiating a contract for this vaccine through
Vaccines for Children (VFC), a federal program that pays for immunizations for eligible groups. No additional funds are currently available or designated for this vaccine (Bette Pollard & Rick Nelson, National Immunization Program, Personal Communication, March 2000).

Implications

Pneumococcus statistics reveal profound morbidity and mortality with severe economic costs upon society (CDC, 1997). Prevnar is established as an effective vaccine against pneumococcal infection (Black & Shinefield, 1997). Treating medical and surgical complications of otitis media costs between three to four billion dollars annually (Byrns, Bondy, Glazner, & Berman, 1997).

The utilization of the heptavalent vaccine for all children under 59 months could potentially result in a 50% reduction of deaths, totaling 20,000 per year, saving 5 billion dollars per year in health care (Black & Shinefield, 1997). Compliance with the ACIP recommendation to immunize all children under 24 months will not eliminate the need for vaccinating older age groups.

The following summarizes the ACIP discussions February 17, 2000:

The vaccine has the potential to reduce more than 2 million physician visits a year (Rennels et al., 1998). At an average of $50.00 per visit, this reduction of clinical visits could save the economy over 100 million dollars per year. The economy could potentially realize cost savings of five billion dollars per year with the reduction of pneumococcal infections (Black & Shinefield, 1997).
Summary

Prevnar and Pneumovax are effective in prevention of pneumococcal disease. As with the utilization of vaccines like Diptheria-tetanus-pertussis and Haemophilus influenzae type B to prevent the spread of infectious disease among the pediatric population, health care providers are finding that pneumococcal vaccines can arrest the spread of disease (Black & Shinefield, 1997). Due to research on the with protein conjugated vaccine Prevnar helps improve the quality of life for the pediatric population. Practitioners can assess for high-risk young children, inform parents when pneumococcal vaccine is indicated, and be current to future research on the long-term efficacy, safety, and use of the vaccine for additional age groups of children.

The primary care provider can reduce the confusion and potential for missed administrations of pneumococcal vaccines. Recommendations should soon provide universal pneumococcal coverage to all children under five years.
Table 1: Percentage of Infections caused by pneumococcus

<table>
<thead>
<tr>
<th>Infection</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>85%</td>
</tr>
<tr>
<td>Bacterial Pneumonia</td>
<td>40-60%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>50%</td>
</tr>
<tr>
<td>Otitis Media</td>
<td>40%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>40%</td>
</tr>
</tbody>
</table>

Table 2: CDC “at high risk children” for pneumococcal infection

- Chronic illness
- Sickle cell disease
- Nephrotic syndrome
- Asplenic anatomy
- Cardiovascular disease
- HIV positive
- Compromised immune system
- Pulmonary disease

Centers for Disease Control, 1997
Table 3: Guidelines for Immunization

The Advisory Committee of Immunization Practice, American Academy of Pediatrics, Centers for Disease Control, and the American Academy of Family Physicians recommend the following guidelines as criteria to justify immunization with the 23-valent-pneumococcal vaccine. The vaccine should be administered to:

1. Children 2 years and older with increased risk of acquiring systemic pneumococcal infection, anatomic or functional asplenia, chronic renal failure or nephrotic syndrome.

2. Children with sickle cell disease conditions that suppress the immune system. This could be a case of functional asplenia.

3. Children with HIV infection, parents, care givers, and daycare providers who are around children with functional or anatomical asplenia.

4. Children greater than 2 years of age with chronic cardiovascular disease, chronic pulmonary disease, or chronic liver disease. Revaccination after 3 to 5 years is recommended for children aged greater than 10 years. Adults need a booster approximately six years after vaccination. It is currently not recommended to vaccinate against the prevention of otitis media or any pneumococcal infection during the first year.

5. Alaskan Natives and at-risk American Indian populations should be vaccinated. These groups have a higher incidence of invasive pneumococcal bacterial infections (Davidson et al., 1993).

Centers for Disease Control, 1997.
References


Phone Conversations

