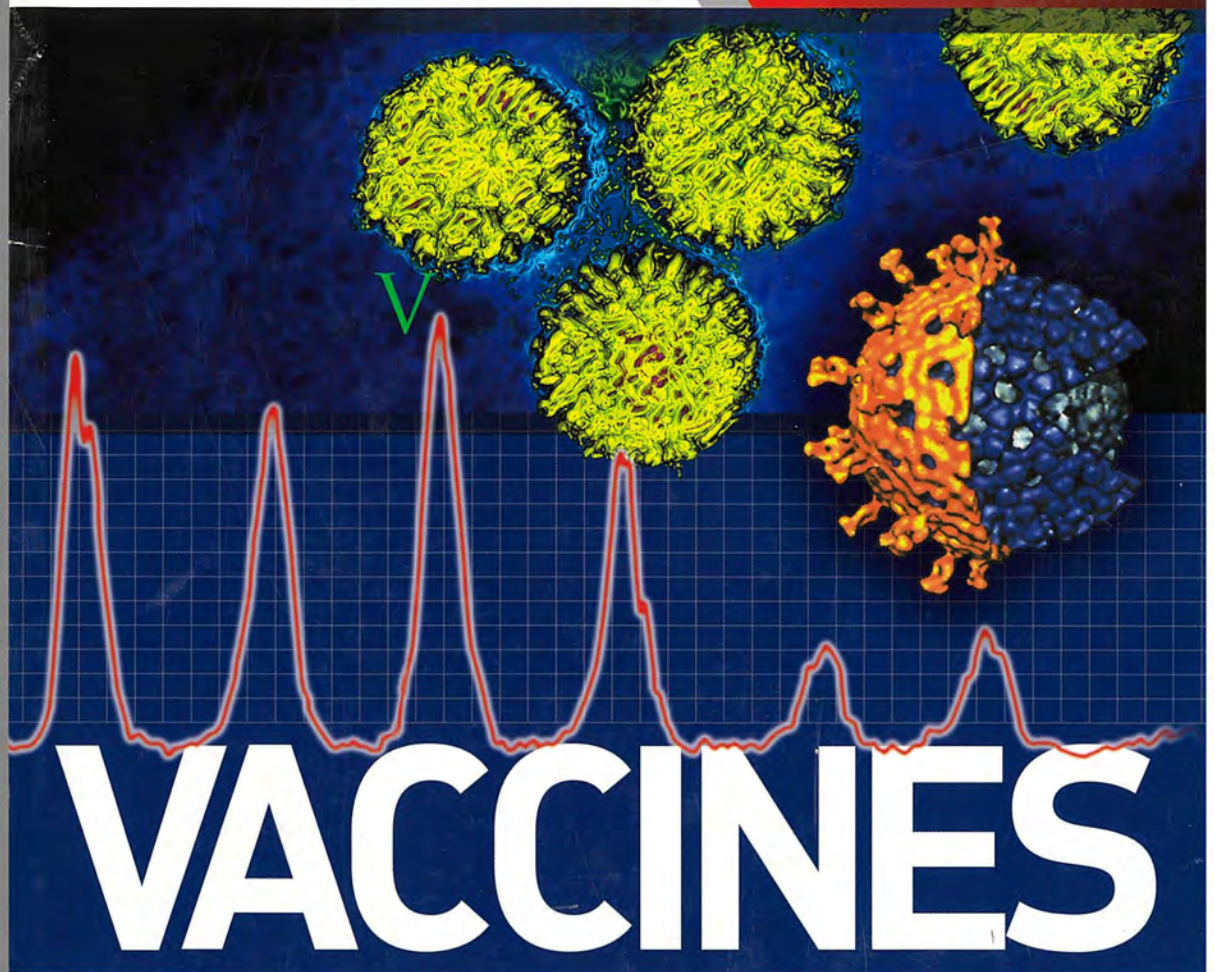


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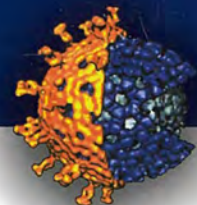
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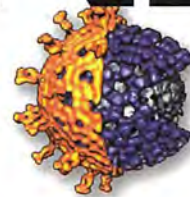
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Pneumococcal conjugate vaccine and pneumococcal common protein vaccines

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Introduction

The original demonstration by Avery and Goebel in 1929 that capsular polysaccharides were immunogenic when linked to a protein¹ and, 60 years later, the demonstrated efficacy of *Haemophilus influenzae* type b (Hib) conjugate vaccines in the 1990s (see Chapter 13) quickly led to the first phase of potentially one of the greatest ever public health interventions, when, in 2000, conjugated pneumococcal polysaccharide vaccines were introduced for the prevention of pneumococcal disease in infants. Acute respiratory infections are the major global cause of death in young children and lead, according to recent estimates, to 1.575 million deaths annually, with an uncertainty range of 1.046 million to 1.874 million deaths in 2008.² Advances in methodology to determine the global pneumococcal disease burden, using efficacy data from the trials of pneumococcal conjugate vaccination described below and conducted in both developed and developing countries, have allowed an estimate of 14.5 million episodes annually of serious pneumococcal disease in children younger than 5 years (uncertainty range 11.1-18 million episodes) and 826,000 deaths (uncertainty range 582,000-926,000 deaths) attributable to the pneumococcus, and thus these are potentially vaccine-preventable episodes/deaths. More than 60% of the deaths occur in 10 African and Asian countries, and more than 90% of the deaths in human immunodeficiency virus (HIV)-infected children from pneumococcal disease occur in Africa.³

This chapter reviews pneumococcal polysaccharide-protein conjugates and pneumococcal proteins as avenues for wider coverage and increased efficacy compared with the polysaccharide pneumococcal vaccine. The limited data on mucosal administration of pneumococcal vaccines has been evaluated in addition to traditional intramuscular administration of the antigens. Conjugate vaccines are the most advanced of these approaches; large randomized trials have confirmed efficacy against invasive disease⁴⁻⁹ and otitis media,^{10,11} and conjugate vaccines are now available and used in most developed countries, with a rollout in developing countries beginning to happen. The effectiveness of conjugate pneumococcal vaccines has been greatly enhanced by impact on vaccine serotype-specific carriage and thus reduced transmission of vaccine types in the community. In the United States, immunization of young children has led to the virtual elimination of vaccine-type disease in both children and adults,¹² and more than 90% of the reduction in hospitalization for nonbacteremic pneumonia attributable to the vaccine has been attributable to herd protection of adults.¹³ At the same time, as protection is largely limited to the specific vaccine serotypes, vaccine effectiveness has been reduced by replacement carriage resulting from nonvaccine serotypes

and replacement disease resulting from the disease potential of those serotypes. The impact of pneumococcal conjugate vaccines in developing countries and their impact (or lack thereof) on herd protection will be evaluated in the next decade. The development of protein antigens as vaccines is still at an early stage, and other approaches, such as vaccines targeting the development of T-cell immunity, are either in preclinical or in early clinical development. A vaccine that combines conjugated pneumococcal polysaccharides with additional nonconjugated pneumococcal proteins is approaching phase 3 trial.

Pathogenesis

With the exception of the great apes,¹⁴ humans are the only natural host of the pneumococcus. Other mammals, such as pets (horses, dogs, cats, and guinea pigs), zoo animals (dolphins), and laboratory animals (mice and rats)¹⁵ can acquire the organism in captivity from their handlers. The organism lives in the nasopharynx of humans, from whence it can be transmitted by respiratory droplets to other individuals. In most cases, pneumococci are carried asymptomatically before being cleared from the nasopharynx. The duration of carriage has been shown to be age- and serotype-dependent.¹⁶⁻¹⁸ In some cases, usually shortly after acquisition of carriage, pneumococci can cause mucosal disease by local spread to the middle ear (causing otitis media), the sinuses (causing sinusitis), or the lungs (causing pneumonia). In addition, pneumococci may cause systemic infections with considerable risk of mortality, including bacteremia and meningitis or, in rare cases, infections in remote foci, such as joints, bones, and soft tissues.

The pneumococcal capsular polysaccharide is the most important virulence factor of *Streptococcus pneumoniae*,^{19,20} although not the only one.²¹ The polysaccharide capsule significantly increases the resistance of pneumococci to phagocytosis by several mechanisms, including shielding from antibodies and complement. The capsule promotes adherence to epithelial cells in animal models. Strains of pneumococci that lack a detectable capsule can cause conjunctivitis²² and are also infrequently isolated in cases of invasive disease. Pneumococcal virulence depends in part on several serotype-specific characteristics, such as the chemical composition and molecular size of the capsular polysaccharide.^{18,23} The different pneumococcal serotypes vary in virulence depending on their ability to activate the alternative and classical complement pathway, to deposit and degrade the complement components on the capsule, and to resist phagocytosis;^{24,25} they also differ in their ability to induce antibodies. Antibodies to the capsular polysaccharides are protective, as has been amply demonstrated in animal models and also in clinical trials of conjugate vaccines.^{26,27}

Background

The reader is referred to Chapter 26, "Pneumococcal Polysaccharide Vaccines", for a discussion of the clinical and bacteriologic aspects of pneumococcal disease.

Epidemiology

Pneumococcal infections in unvaccinated children

Before the introduction of 7-valent PCV7 in the United States, *S. pneumoniae* caused approximately 17,000 cases of invasive disease per year in children younger than 5 years, resulting in 700 cases of meningitis and 200 deaths.²⁸ The annual incidence of invasive pneumococcal diseases was highest in children 6 to 11 months of age, at 235 per 100,000,²⁸ and declined to 35.2 per 100,000 between 2 and 4 years of age, reaching its lowest levels in older children, 5 to 17 years of age (3.9 per 100,000).²⁹ A similar distribution of incidence by age was seen in Canada, although the rates for the youngest children were somewhat lower, peaking at 161.2 per 100,000 for children 6 to 17 months of age.³⁰

In Europe, as well, the highest levels of infection were in children 2 years of age or younger (and were highest in the second 6 months of life), declining steadily thereafter into the teenage years.^{31,32} However, the incidence of pneumococcal infections has generally been reported to be much lower in Europe than in the United States.³³ For example, in England and Wales, the annual incidence of invasive pneumococcal diseases in infants between 6 and 11 months was 35.8 per 100,000 in the late 1990s,³⁴ compared with 235 per 100,000 in the United States. In Finland, the annual incidence of invasive pneumococcal diseases was 45.3 per 100,000 among those younger than 2 years.³² This difference in incidence is thought to be largely resulting from differences in blood culturing practices, in that children in Europe generally only get blood taken for culture if they are hospitalized for severe pneumococcal disease.³⁵

Bacteremia without focus is more common in young children than in older persons,^{28,31,32,36} and this diagnosis comprises 60% to 70% of invasive pneumococcal disease encountered in this age group in the United States.^{28,37,38} Pneumonia and meningitis are the next most common, but meningitis remains the diagnosis with the highest case fatality rate.^{31,36,39} After the introduction of the Hib vaccine, *S. pneumoniae* became the leading cause of bacterial meningitis and occult bacteremia in the United States.^{40,41} As children grow older, the proportions of pneumococcal infections classified as meningitis and

bacteremia without focus decline, and the proportion of pneumonia increases.^{37,39,42,43}

In the United States before conjugate vaccine introduction, there were about 15 million office visits annually as a result of acute otitis media (AOM),⁴⁴ and costs caused by otitis were estimated at US\$5 billion per year.⁴⁵ *S. pneumoniae* is the most commonly reported bacterial cause of AOM, with the proportion of the pneumococcus as an etiologic agent recovered from middle ear fluid varying from 18% to 55% in published studies.⁴⁶⁻⁴⁹

The burden of pneumococcal disease has been greatest for those populations in which the pneumococcal polysaccharide vaccine (PPV) vaccine is least immunogenic: children younger than 2 years; the elderly; immunocompromised individuals, including those infected with HIV, with functional or anatomic asplenia, or with malignancies; and individuals with chronic cardiovascular, pulmonary, or liver diseases.^{28,50-52} Among individuals without underlying illness, children younger than 2 years are most vulnerable to pneumococcal infections. There is evidence that this level of risk is increased further by spending time in crowded or communal settings, such as day-care centers.^{38,53}

Children from minority groups suffer disproportionately. Although the overall incidence of invasive pneumococcal disease in children younger than 2 years was 167 cases per 100,000 person-years in the United States before licensure of PCV7, black children of the same age had an incidence of 400, Alaskan Native children had an incidence of 624, and Native American children younger than 2 years had an overwhelming incidence of 2,396 cases per 100,000 (Table 25-1),²⁸ although rates in Navajo children were declining.⁴² Asians, blacks, and Hispanics also have a greater risk of pneumococcal pneumonia than whites.⁵⁴ Echoing what is seen in native populations in North America, indigenous people in Australia have much higher rates of pneumococcal disease than do nonnative populations; indigenous children younger than 2 years have an incidence of invasive pneumococcal diseases of 2,053 cases per 100,000 person-years,⁵⁵ whereas nonindigenous children have rates intermediate between those of Europe and the United States.⁵⁶ Minority populations in Israel also have a higher incidence of pneumococcal infections, although the difference is not as pronounced as in Australia and the United States.⁵⁷ This difference may be socioeconomically based because minority groups in Israel are not a single ethnic population but, as a group, have higher birthrates, more crowded living conditions, less education and lower socioeconomic status than the majority Jewish population.^{57,58}

Boys are more likely than girls to contract pneumococcal infections,^{42,58,59,61,62} and there are often seasonal peaks in incidence,^{45,57} with infection most likely in the winter months. Recent infection with influenza and other respiratory viruses may be a risk factor for severe pneumococcal pneumonia⁶⁴ and invasive disease.⁶⁵ In addition to attendance at a day-care center,

Table 25-1 Incidence of Invasive Pneumococcal Disease in Children in the United States, by Age and Ethnic Group before the Introduction of Pneumococcal Conjugate Vaccine

Age (yr)	Incidence per 100,000 person-years			
	All races	Blacks	Alaskan Natives	Native American (Navajo or Apache)
<2	167	400	624	2,396
2-4	36	116*	98†	227†
5-9	6	9	23	54
10-19	3	5	5	35

*Age 2-3 years.

†Age 2-5 years.

Modified from Advisory Committee on Immunization Practices. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Recomm Rep 49(RR-9):1-35, 2000.

recent ear infections and a lack of breastfeeding are associated with increased incidence of invasive pneumococcal diseases in children.³⁸ The association of invasive pneumococcal diseases with recent ear infections may indicate that the middle ear is an important route of *S. pneumoniae* invasion.³⁸

Children with cochlear implants have been identified as having a risk of pneumococcal meningitis approximately 40 times higher than the rate in the general population of children.⁶⁶ The risk was highest among children using a specific model of implant, which was subsequently discontinued, and in those with middle ear malformations associated with cerebrospinal fluid leaks. A study in Denmark suggested that deaf children without implants may have a fivefold increase in risk of meningitis relative to hearing children.⁶⁷

Globally, *S. pneumoniae* is responsible for the deaths of up to 800,000 children per year, most of which occur in developing countries.³ However, the true burden of disease is difficult to quantify in countries where disease surveillance systems and diagnostic facilities are lacking and most children with pneumococcal infections are diagnosed only if hospitalized.^{68,69} In these settings, carriage of pneumococci frequently occurs by less than 2 months of age⁷⁰ (by contrast, children in the United States acquire their first strain at 6 months of age, on average), a larger proportion of invasive diseases occur by 6 months of age than in industrialized countries,^{63,69,71} and neonatal infections after about 3 weeks of age are not uncommon.⁶⁹

A compromised immune system, whether caused by HIV infection, malignancy, asplenia, or primary immunodeficiencies, is a major risk factor for pneumococcal disease. Infection with *S. pneumoniae* occurs more than 100 times more frequently in HIV-infected individuals than among the general population.⁷²⁻⁷⁴ Meningitis or recurrent bacterial sepsis can be the first indicator of acquired immunodeficiency syndrome in pediatric patients,^{75,76} and otitis media has been reported to be 3 times more frequent in HIV-infected children than in uninfected children.⁷⁷ In the United States, rates of invasive pneumococcal diseases for HIV-infected children younger than 5 years are 2.8 times those of HIV-negative children of the same age; the rate is 12.6 times higher for HIV-infected children younger than 3 years.³ In both children and adults, the introduction of highly active antiretroviral therapy reduces the incidence of pneumococcal infections in HIV-infected patients, but rates remain elevated compared with HIV-uninfected persons.^{32,78-82}

In South Africa, the incidence of pneumococcal bacteremia was 36.9-fold higher in HIV-infected children than in HIV-negative children before introduction of antiretrovirals.⁸¹ Between 1997 and 1999, 5% of all children born in Soweto, South Africa, were infected with HIV.⁶⁸ In addition, many of these children have other predisposing conditions, including malnutrition and tuberculosis.^{69,82} The rates of pneumococcal bacteremia doubled between 1987 and 1997 as the rates of HIV infection rose.⁸² Overall, the disease spectrum is similar in HIV-positive and HIV-negative populations, except that pneumonia is more common in HIV-infected children.

Individuals with sickle cell disease and other hemoglobinopathies resulting in functional asplenia are also at increased risk for serious infections with *S. pneumoniae*.⁸³⁻⁸⁵

Without immunization, the rate of invasive pneumococcal disease in children with sickle cell disease is 30 to 100 times greater than that of healthy children and is greatest in children younger than 2 years. In the general population, most cases of bacteremia occur in children younger than 2 years, but bacteremia occurs more often in older children who also have HIV infection or sickle cell disease,⁸⁶ and pneumococcal infection accounts for as many as 25% of deaths from sickle cell disease.⁸⁷ Even with vaccination with the PPV vaccine, invasive pneumococcal disease among children with sickle cell disease who are younger than 5 years is 10-fold more frequent than in children without sickle cell disease,^{87,88} and the case-fatality rate is much higher in children with

sickle cell disease⁸⁹ or other forms⁸⁹ of anatomic or functional asplenia than in children with normal splenic function.

Children with nephrotic syndrome also are susceptible to pneumococcal disease, with the majority of infections occurring within the first 2 years after presentation. *S. pneumoniae* is responsible for 50% to 60% of sepsis and peritonitis in children with nephrotic syndrome, which accounts for a large portion of infective episodes in this population.⁹⁰ Patients who have received a bone marrow transplant are also more vulnerable to pneumococcal disease than the general public,⁹¹ in part because they often have impaired opsonization function and lose protection from previous immunizations because of T-cell and B-cell depletion;⁹² however, solid-organ transplant also confers a higher risk of invasive pneumococcal disease.⁹³ Of interest, the increased risk of pneumococcal infection in patients with Hodgkin disease can persist long after the underlying condition has been successfully treated.⁹⁴

Serotype distribution

Forty serogroups comprising 93 serotypes have been described for *S. pneumoniae*. Among this large number of serotypes, a relatively small number account for most of the invasive disease in young children around the globe⁹⁵ (Figure 25-1).

The PPV vaccine is made by combining purified polysaccharides from 23 pneumococcal serotypes, but it is complicated to combine so many antigens into one conjugate vaccine, in part because of the more technically difficult manufacturing process. Candidates for conjugate vaccines have therefore been designed based on knowledge about the relative importance of disease-causing serotypes. To date, conjugate vaccines containing the saccharides of 7, 10, and 13 serotypes have been licensed; the first to be licensed was a 7-valent vaccine (PCV7) sold under the trade name Prev(e)nar by Pfizer (New York, NY), representing the serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, which were selected based largely on pneumococcal epidemiology in the United States. The 10-valent vaccine (PCV10, Synflorix, sold by GlaxoSmithKline [GSK; Research Triangle Park, NC]) also includes serotypes 1, 5, and 7F, and the 13-valent (PCV13, Prevnar 13, Pfizer) includes those plus 3, 6A, and 19A.

Although comprehensive information about serotypes is not available for some regions, a recent systematic review summarized the information available from children younger than 5 years before introduction of pneumococcal conjugate vaccines.⁹⁵ The review included 169 studies in the final analysis, representing 70 countries and 60,090 serotyped isolates. According to this analysis, serotypes 14, 6B, 1, 23F, 5, and 19F, in that order, were the

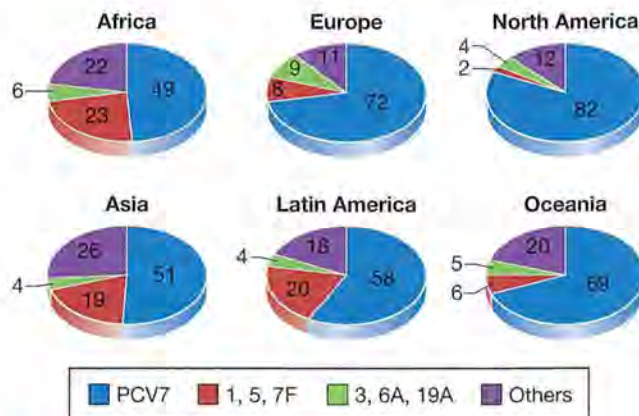


Figure 25-1 Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. (From Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS Med* 7(pii):e1000348, 2010. doi:10.1371/journal.pmed.1000348.)

most common serotypes found among sterile-site isolates from around the world. However, the distribution of disease-causing serotypes varied somewhat with location, age, and clinical presentation. Before the introduction of PCV7, serogroups in the 7-valent vaccine were responsible for more than 80% of invasive pneumococcal diseases in young children in the United States and Canada and for 50% or more in all other regions; 10-valent and 13-valent vaccine formulations covered more than 70% of invasive strains in all regions. The nonvaccine serotype 6A accounts for a substantial portion of disease, but within-serogroup cross-reactivity may allow PCV7 to provide protection against serotype 6A.⁹⁶⁻⁹⁹

Serotypes 1 and 5 are encountered much more frequently in the developing world than in the developed world, although in the last decade serotype 1 disease has increased in Western Europe and has also been found among children in Utah in the United States.^{100,101} Differences in blood culture practice may also affect the observed distribution of serotypes: virulent serotypes that are more likely to cause severe disease requiring hospitalization would have a higher apparent prevalence in regions that perform blood cultures only on hospitalized patients. This may be the case for serogroups 1, 5, and 7, which are isolated at similar (low) rates in the United States and Europe, although the most common serotypes/groups (14, 6, 19, 18, 23, 9, and 4) have a much higher incidence in the United States.³⁵ For example, serotype 1 causes 5% of reported invasive pneumococcal diseases in Western Europe and only 0.5% of invasive pneumococcal diseases in the United States before conjugate vaccine introduction, yet the rate of serotype 1 disease is about 0.9 per 100,000 person-years in each region.³⁵ This pattern indicates that serogroups 1, 5, and 7 cause severe rather than mild disease in both regions and supports the idea that certain serogroups are intrinsically highly virulent.³⁵ This could also account, in part, for the high prevalence of serotypes 1 and 5 in the developing world, where, as in Europe, blood cultures are rarely performed on an outpatient basis.

Serotype distributions change with age. A narrower range of serotypes are responsible for disease in young children^{102,103} than in older children and adults, and in most regions, 50% of invasive pneumococcal disease is caused by three serotypes in young children and by four to five serotypes in older children and adults.¹⁰² Serotypes 1 and 5 are responsible for a larger portion of invasive pneumococcal disease in children,^{42,58,104,105} and serotype 18C has also been reported to show this trend.¹⁰⁶

In addition to varying with age, certain serogroups are more likely to be associated with particular clinical presentations, although none of the most prominent serotypes is found exclusively in one clinical site, and all seem to have the potential to invade each of the normally sterile sites and to cause disease from those sites.¹⁰² Note that age and site of isolation may not be independent because, for example, young children are much more likely to present with meningitis than older children, and serotypes isolated from young children are therefore more likely to be found in the cerebrospinal fluid (CSF) than serotypes isolated from older children. Generally speaking, serogroups 6, 10, and 23 are more likely to be isolated from cerebrospinal fluid, whereas serogroups 1, 4, and 14 are more often isolated from blood than from CSF.^{86,102} Severe pneumonia is more likely to be associated with serotypes 1 and 3,¹⁰⁷ although both pneumonia and these serotypes are more common in older children than the very young. Serotypes 19F, 23F, 14, and 6B are consistently among the six serotypes most frequently isolated from children with AOM, although their relative frequency varies by study. Serotype 3 is also a frequent AOM isolate in some areas, but not others.^{43,62,108-111}

Antibiotic resistance

Antibiotic resistance also varies with age, race, and geographic location. Globally, the northern European countries of Norway, Sweden, Denmark, the Netherlands, and Switzerland have

consistently low rates of resistance; in contrast, France, Spain, Hong Kong, Singapore, and South Africa have high rates of resistance.¹¹² In the United States, resistant strains are found more frequently in the southern states of Tennessee and Georgia than elsewhere.^{113,114} The highest percentage of resistant strains occurs in children younger than 5 years, in whom antibiotic use also rose most quickly in the last decade.^{113,114} After 2000, increases in nonvaccine serotype 19A strains resistant to multiple antibiotics were seen in countries using 7-valent PCV7, such as the United States,^{114,115} but also in countries that had not yet introduced PCV7.¹¹⁶ The amount and types of antibiotics used have been correlated with increased resistance.^{114,117,118} The serotypes most likely to become resistant (6A, 6B, 9V, 14, 19A, 19F, and 23F)^{114,116,119} are those that are frequently carried and are most likely to cause AOM, and resistance rates are higher in isolates from middle ear fluid and sinuses than from sterile sites.¹²⁰ This may be because pneumococci in these regions are exposed to antibiotics more extensively than serotypes that cause invasive disease, both because they are carried for longer periods and because AOM is frequently treated with antibiotics. The serotypes with the highest rates of resistance were also either found in PCV7 or were within the same serogroups, and introduction of PCV7 has reduced disease caused by resistant infections in the United States, both among children and among older persons through reduced transmission.¹²¹

History of vaccine development and vaccine formulations

Over the past 25 years, several pneumococcal conjugate vaccine formulations have been tested in clinical trials; these vaccines differ in their included serotypes and carrier proteins.

The number of pneumococcal serotypes included in current vaccines and vaccine candidates in clinical development ranges from 7 to 15, fewer than the 23 serotypes included in the PPV vaccine. Although it would be preferable to include a larger number of different polysaccharides in a conjugate vaccine, doing so is technically challenging. Moreover, the total amount of carrier protein in the final vaccine may need to be limited because too much carrier protein can impair the antibody response to the polysaccharide antigen.¹²²⁻¹²⁴ In many countries, the incremental benefits in coverage for young children gained by increasing the number of serotypes remains low after seven serotypes have been included; however, the seven serotypes selected for inclusion may vary because the serotype distribution varies geographically and changes with time. It is therefore important to understand the seroepidemiology of disease in each country.

Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F are common to all of the vaccines developed so far. In general, the pneumococcal conjugates contain less polysaccharide per serotype than the licensed Hib conjugate vaccines. This most likely reflects both the desire to reduce the total amount of polysaccharide in the vaccine and a perceived greater immunogenicity for pneumococcal serotypes compared with Hib. Each 0.5-mL dose of the first licensed 7-valent vaccine, Prevnar (Prevenar outside North America; Wyeth Pharmaceuticals [Collegeville, PA]), now Pfizer Vaccines, contains 2 µg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F and 4 µg of serotype 6B per dose (16 µg total saccharide). Each of the serotypes is grown in soy peptone broth, and the polysaccharides are purified through centrifugation, precipitation, ultrafiltration, and column chromatography. The polysaccharides are chemically activated to form individual saccharides that are directly conjugated through reductive amination to CRM₁₉₇, a nontoxic mutant of diphtheria toxin that is also used in Hib and meningococcal conjugate vaccines. CRM₁₉₇ is isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in a casamino acids- and yeast extract-based

medium and purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography. The individual glycoconjugates are purified by ultrafiltration and column chromatography and are analyzed for saccharide-to-protein ratios, molecular size, free saccharide, and free protein. The vaccine has been available as a liquid preparation that contains 0.125 mg of aluminum per dose as aluminum phosphate adjuvant. After shaking, the vaccine is a homogeneous white suspension that is administered intramuscularly.¹²⁵ The use of this vaccine declined during 2011 as it was replaced by the 13-valent vaccine from Pfizer Vaccines (PCV13).

Several conjugate vaccines that were tested in clinical trials are no longer in development. Merck developed a 7-valent vaccine in which the saccharides were conjugated to a meningococcal outer membrane protein (OMPC) modified from *Neisseria meningitidis*, and Wyeth produced a CRM₁₉₇-conjugated 9-valent vaccine containing serotypes 1 and 5 in addition to the serotypes in the 7-valent vaccine. Sanofi Pasteur (Swiftwater, PA) developed an 11-valent vaccine that added serotypes 3 and 7F; in this vaccine (PncD/T), some of the saccharides (for serotypes 3, 6B, 14, and 18C) were conjugated to diphtheria toxoid and the others (for serotypes 1, 4, 5, 7F, 9V, 19F, and 23F) were conjugated to tetanus protein. Other potential carrier proteins that have been tested in animal studies include bovine serum albumin, human immunoglobulin G (IgG), complement C3d, keyhole limpet hemocyanin, flagellar protein of *Salmonella*, pertussis toxoid, and pneumolysin toxoid.¹²⁶⁻¹²⁹ The conjugation chemistry and manufacturing protocols vary for each preparation.

GlaxoSmithKline tested an 11-valent vaccine in which 1 µg of each saccharide was conjugated to protein D of *H. influenzae* (PncPD) or to a diphtheria or tetanus carrier protein. This vaccine protected against both pneumococcal and *H. influenzae* otitis media. However, serotype 3 proved not to be protective against AOM in the clinical trial,¹⁰ therefore, GlaxoSmithKline proceeded with the clinical development of a 10-valent version, containing serotypes 1, 5, and 7F in addition to those in the 7-valent vaccine. This 10-valent version (PCV10) is currently licensed in many countries globally and is prequalified by the World Health Organization (WHO). This vaccine uses protein D (9-16 µg per dose of vaccine) derived from nontypeable *Haemophilus influenzae* as a carrier protein for 8 of the 10 serotypes (1, 4, 5, 6B, 7F, 9V, 14, and 23F), while serotypes 18C and 19F are conjugated to tetanus toxoid (5-10 µg) and to diphtheria toxoid (3-6 µg), respectively. All conjugates are adsorbed onto 0.5 mg aluminum phosphate. It contains 1 µg of each polysaccharide except for serotypes 4, 18C, and 19F, each of which contain 3 µg.

Although Wyeth did not move ahead with its 9-valent vaccine, Pfizer currently has a 13-valent version that is licensed in Europe, the United States, and worldwide, and it contains serotypes 1, 3, 5, 7F, 6A, and 19A in addition to those in the original 7-valent vaccine. Merck (Whitehouse Station, NJ) has an investigational 15-valent vaccine that has completed phase 1 trials in adults and toddlers. A phase 2 trial in infants comparing immunogenicity to PCV13 is ongoing and the immunogenicity has been reported in infant macaques.¹³⁰ This vaccine is also conjugated to CRM₁₉₇, which includes, in addition to the serotypes in the 13-valent vaccine, serotypes 22F and 33F. The vaccine contains 2 µg of each serotype, except for 4 µg of serotype 6B, and has aluminium phosphate as an adjuvant.

Immunogenicity

Measurement of immunogenicity

Antibodies against capsular polysaccharides are protective against diseases caused by encapsulated bacteria. In pneumococcal infections, this has been demonstrated indirectly by the increased incidence of serious pneumococcal infections

in groups with lower antibody concentrations, for instance, infants and the elderly, patients with hypogammaglobulinemia or agammaglobulinemia and patients recovering from bone marrow transplantation. Direct evidence of the protective effect of anticapsular antibodies comes from studies where passively administered antibodies have provided protection from otitis media or invasive pneumococcal disease.^{131,132} Furthermore, vaccines that induce antibodies to pneumococcal capsular polysaccharides are protective against invasive pneumococcal infections (see Chapter 26).¹³³

The two most important serologic methods used to quantify and evaluate the function of antibodies induced by vaccination are IgG quantification by enzyme immunoassay (EIA) and measurement of opsonophagocytic activity (OPA) of antibodies from the sera of vaccinated individuals. The EIA method has been validated rather extensively, a link between antibody concentration and efficacy against invasive pneumococcal disease has been established, and a process for cross-laboratory standardization of the assay has been completed. The OPA assay provides important information about the functional activity of the antibodies and has also been the focus of intensive standardization efforts.

Additional tests, such as isotype and subclass analysis, determination of the avidity of antibodies and serotype cross-reactivity, provide qualitative information about the immune mechanisms evoked by the vaccines, but they have not yet been standardized, and their value in predicting protective efficacy still needs to be validated. Further information about the characteristics of the immune response to the vaccines can be obtained through demonstration of the induction of immunologic memory as well as by analyzing cellular and mucosal immune responses to the vaccination. Important information about immunity can also be obtained through protection studies in animal models.

Enzyme immunoassay

Immune responses to pneumococcal vaccines have been evaluated by radioimmunoassay (RIA) and EIA, both of which measure the binding of antibodies to pneumococcal polysaccharide antigens. The RIA technique is no longer in use.

EIA is a sensitive, convenient, and rapid method even for a large number of samples. Concentrations of IgA, IgM, and IgG isotypes,¹³⁴ as well as of IgG subclasses,¹³⁵ can be determined using a reference serum. The United States Food and Drug Administration (FDA) previously made available a reference serum from pooled human sera (89SF). More recently, a new serum pool has been formulated by the FDA (007Sp) and validated by the WHO. All major pneumococcal laboratories are now validating this reference to control for interlaboratory variation.

All current EIA protocols have an absorption step to remove anti-C-polysaccharide antibodies,¹³⁶⁻¹³⁹ whose presence was the main limitation of RIAs. However, it has recently been recognized that, to some extent, similar problems exist with EIA, in that some sera contain polyreactive antibodies that recognize pneumococcal polysaccharides of different serotypes.^{136,140,141} These antibodies are especially prevalent in the sera of individuals who have naturally acquired antibodies and are less prevalent in the sera of those immunized with pneumococcal vaccines. They are most probably directed to contaminants in the pneumococcal polysaccharide preparations that are used as antigens in the assays or directed to polyreactive epitopes present in the polysaccharide antigens. Inhibiting antibody binding using soluble polysaccharides of another serotype, eg, of serotype 22F, removes these polyreactive antibodies, improves the specificity,¹³⁶ and increases the linear correlation between anticapsular polysaccharide antibody concentration and OPA.^{136,142} Therefore, it is recommended that all

laboratories include the 22F neutralization step in the EIA protocol. This change has caused some confusion regarding the need to change threshold values for protection as discussed below. Further complicating the picture for the Merck 15-valent vaccine in development, which contains serotype 22F, an electrochemiluminescence assay has been developed using serotypes 25 and 72 for preadsorption.¹⁴³

The IgG antibody response in early infancy is mainly of the IgG1 subclass. After the booster dose in the second year of life, IgG2 antibodies also start to appear, and the response in adults to both pneumococcal polysaccharide and conjugate vaccines is mainly of the IgG2 subclass.^{135,144-146} In adults, some differences have been found in the IgG1:IgG2 ratio elicited after vaccination with pneumococcal polysaccharide and conjugate vaccines or after different conjugate vaccines.¹⁴⁵ However, the relevance of these findings for estimating the T-cell dependence of the response in infants and the functional activity of antibodies remains to be elucidated.

Avidity

Antibody avidity describes the strength with which an antibody binds to a complex antigen. Several methods have been described for determining relative antibody avidity to different types of antigens.¹⁴⁷⁻¹⁵⁷ In EIA techniques, the binding of antibody to the coated antigen may be prevented by competitive inhibition using decreasing concentrations of free antigen or, more usually, by eluting the antibody from the antigen by a dissociating agent, such as thiocyanate, urea, or diethylamine. Thiocyanate anion and urea interfere with the antibody-antigen binding primarily through disrupting the hydrophobic bonds; diethylamine is a protein-denaturing agent. Two avidity assays based on pneumococcal EIA and using sodium thiocyanate elution have been developed. Because the elution assays are based on dissociation of antibody-antigen complexes of low avidity, they allow the ranking of the antibodies by their avidity.

The avidity of antibodies induced in infants after pneumococcal conjugate vaccination increases from postprimary samples to prebooster samples and increases further over time.^{147,153,154} Experience with Hib conjugate vaccines suggest that measurement of antibody avidity is also useful in assessing the induction of memory.¹⁵⁰ Therefore, it has been suggested that avidity assays could be used to distinguish between those who are primed for memory and those who are not.

Opsonophagocytic activity

Because opsonin-dependent phagocytosis is the primary host defense mechanism against *S. pneumoniae*, a variety of techniques to measure the OPA of antibodies to pneumococci have been developed.^{142,155-157} The intent of measuring OPA is to assess the function of antibodies rather than just their quantity because a proportion of antibodies measured in EIA have no functional activity. In support of the likely improved utility of OPA over EIA is the observation in animal models that OPA provides better correlation with protection than the concentration of IgG antibodies as measured by EIA.^{158,159} In humans, sera from the Finnish otitis media trial, reanalyzed using an OPA assay, reveal that the OPA titers predict the observed low efficacy for serotype 19A, whereas the enzyme-linked immunosorbent assay (ELISA) titers did not.¹⁶⁰ Further, the cross-reactive IgG response to serotype 19A in the 7-valent vaccine, which was not associated with protection against invasive pneumococcal disease, lacks significant OPA activity.¹⁶¹ Of importance, EIA results may have limited relevance in older adults, who often have more nonfunctional anticapsular antibodies than infants and children. Interest in OPA has increased in recent years. It is the primary assay to evaluate the functional activity of the immune response to pneumococcal conjugate vaccine, and OPA responses are an essential part of the registration of new conjugate vaccines.

The classic OPA is an in vitro assay to determine the titers of sera that reduce the number of live bacteria by more than half because of opsonophagocytosis. Early studies were performed using human polymorphonuclear leukocytes as the effector cells, but recent assays have also been adapted to utilize cultivable phagocytes (eg, HL-60 or NB-4 cells). Romero-Steiner and associates¹⁵⁵ developed an OPA assay for pneumococcal antibodies, in which they used rabbit complement and HL-60 cells as phagocytes. This method has become a reference against which other assays are compared.

OPA techniques include radioisotopic, flow cytometric, microscopic, and viability (or killing) assays. The killing OPA method, which measures the killing of live bacteria by effector cells, is regarded to be the most biologically relevant.^{142,162} There is also more information about the validation and performance of the killing-type OPA than about the flow cytometric OPA. In general, the results obtained by the various techniques correlate well, and an assessment of assays from six laboratories showed acceptable agreement between their assays.¹⁶³

With increasing need for high-throughput and automated functional assays, multiplexed methods for OPA have been developed. The Romero-Steiner assay has been validated to measure up to seven serotypes simultaneously, using fluorescent dye to quantify the bacterial killing.¹⁶⁴ Another approach is to measure phagocytosis by flow cytometry, using fluorescently labeled bacteria or latex particles,¹⁵⁶ and a multiplexed phagocytosis assay for three to four different serotypes has been developed using bacteria or latex beads coated with different polysaccharides.¹⁶⁵ Still another type of multiplexed OPA is based on a killing-type OPA, using pneumococcal strains resistant to clinically irrelevant antibiotics.^{164,166-168}

The correlation between the IgG antibody concentration and OPA results is relatively strong in immune sera^{146,155,169,170} but is weaker at low antibody concentrations.^{145,158,169,171} In general, the correlation between antibody concentration and OPA seems to be good in infants who have been immunized with conjugate vaccines^{26,144} but is weaker in unimmunized children and in adults.^{145,172,173} Correlations between EIA and OPA results are high for vaccine serotypes but lower for cross-reacting serotypes such as 6A and 19A.¹⁷⁴ One reason for the poor correlation is antibodies that are detected by standard EIA but are not functionally active.^{140,172,176}

Immunologic memory

Memory is traditionally characterized by the presence of IgG antibody elicited in a previously naïve individual (such as an infant), by evidence of priming after immunization, or by affinity maturation. For the purposes of vaccine evaluation, the simplest method of demonstrating memory is often the increased concentration and IgG dominance of an antibody response after a booster dose.¹⁷⁵ The increase of geometric mean concentration (GMC) in a primed individual with immunologic memory is much stronger than that seen if the same vaccines were given at the same age without precedent priming.^{176,177-182}

The maturation of antibody avidity and increased OPA have also been evaluated in studies of pneumococcal vaccines.^{150,170} The avidity of antibodies is increased in children who receive a pneumococcal conjugate booster but not a polysaccharide vaccine booster.^{147,183} This suggests that the conjugate triggers a T-cell response, but the T-cell-independent pneumococcal polysaccharide vaccine only triggers the existing memory B cells.¹⁸³ There is also a shift of IgG subclass distribution after the booster dose that is not seen after primary immunization: the serotype-specific pneumococcal IgG antibody response is virtually restricted to the IgG1 subclass after primary immunization, but secondary immunization elicits antibodies of both IgG1 and IgG2 subclasses.^{145,180}

Antibody response is generally higher after the polysaccharide booster than after the conjugate booster.^{184,185} Whether this has any clinical advantage is not clear. Theoretically, a conjugate booster may stimulate the generation and expansion of high-affinity clones of B memory cells, whereas use of a polysaccharide booster could result in depletion of the memory pool.¹⁸⁶ Evidence in support of this idea has recently been found in a comparison of memory B cells following polysaccharide versus conjugate pneumococcal vaccination of adults.^{186a} Therefore, some have argued that boosting with a conjugate may prove important for the persistence of immunity, although this has not been conclusively shown. It is also important to note that the use of the polysaccharide booster may be associated with more pronounced reactogenicity.¹⁸⁴

The response to the booster dose is rather vigorous at 24 months of age, as seen in the increase in GMCs of anticapsular antibodies in samples taken 7 to 10 days (but not yet at 4 days) after immunization, provided the children had received primary doses with the conjugate.^{178,179,187} The priming effect is less impressive in healthy adults,^{129,188} maybe because adults often have already encountered the antigen and become primed, either through carriage of the bacterium or other, cross-reacting antigens. Some indications of priming can be seen also in HIV,^{189,190} bone marrow transplant,^{94,191} and sickle cell anemia patients.⁸³

Whether mucosal memory is induced by pneumococcal conjugate vaccines is still under examination. In one UK study, the salivary IgA concentrations against pneumococcal serotypes were only slightly higher than in the control group that did not receive PCV7, but there was a significant increase in mucosal antibodies after a booster dose of polysaccharide.¹⁹² Mean-fold rises after the polysaccharide vaccine were lower for serotypes not included in the conjugate, suggesting that the conjugate vaccine had primed children for memory responses.¹⁹² However, two other studies found no clear differences in salivary antibody responses between children primed with conjugates and those who received their first pneumococcal vaccine during the second year of life.^{176,193} Follow-up data from the Finnish Otitis Media Vaccine Trial (FinOM), an efficacy trial, showed that PCV7 induced both salivary IgG and IgA responses to the vaccine serotypes. By age of 4 to 5 years, IgA concentrations were similar in both the vaccinated group and the nonvaccinated control group,¹⁹⁴ most probably reflecting natural stimulation through repeated episodes of colonization.

Whether immunologic memory plays an important role in vaccine-induced protection against pneumococcal disease remains controversial. The experience with Hib immunization in infants supported the view that, in addition to the potent herd immune effect, priming may have provided some protection against disease because very young children were protected despite low antibody concentrations.¹⁹⁵ However, priming and memory to the Hib polysaccharide induced by natural exposure in the prevaccine era¹⁹⁶ or Hib conjugate vaccine^{197,198} may not be sufficient for protection against disease, as experience in the United Kingdom with Hib strongly suggests. An important rise in failures of the Hib vaccine was noted between 1999 and 2003 after the introduction of an acellular pertussis-containing Hib conjugate vaccine without a booster; this vaccine primed well but was associated with lower immunogenicity.^{199,200} In contrast, no such increase in failures was noted in countries that adopted this new vaccine but did not eliminate the booster dose. Similarly, studies of the serogroup C *N. meningitidis* conjugate vaccines in the United Kingdom have demonstrated lower effectiveness 1 year after vaccination, suggesting that priming of the immune response and memory responses may not be sufficient to prevent invasive disease.²⁰¹ It is possible that the lack of efficacy against serotype 1 pneumococcal disease in the PCV9 trials in Africa may also reflect failures in the second year of life after a primary vaccination schedule without a booster.²⁰² Because of the observed delay in antibody response in primed subjects after exposure, a memory

response may not be rapid enough to protect against an isolate that has the capacity to rapidly invade the bloodstream soon after establishing nasopharyngeal colonization. Thus, the role of immunologic memory in conferring long-term protection against invasive bacterial disease remains controversial.¹⁹⁸

Animal models

In addition to in vitro assays, many animal models have been developed to study the immunogenicity and efficacy of pneumococcal conjugate and novel protein vaccines, including rodent (mice and rats), rabbit, chinchilla, or infant monkey models.²⁰³⁻²¹² In the immunogenicity studies, animals are bled before and after active immunization with an experimental vaccine to obtain sera or cells for in vitro analyses.^{206-208,210,213} The functionality of antibodies can be evaluated in animal models.^{203,158,209,214-216} Animals may be passively or actively immunized and subsequently challenged with bacteria to determine protective efficacy.^{203,204,205,213}

Many different strains of pneumococci can be used for colonization and infection studies, although there are marked serotype-dependent differences with respect to their capacity to colonize the nasopharynx or cause invasive disease. Various routes of challenge have been employed, in attempts to mimic the situation in humans, including nasopharyngeal colonization, otitis media, bacteremia, pneumonia, and meningitis. For nasopharyngeal colonization, inocula using clinical isolates can result in sustained colonization for several days. Using the same challenge protocol but under anesthesia, mice aspirate the inoculum, which subsequently leads to lung infection and, depending on the strain used, possibly also sepsis. Adult and infant mice and rats have been used in passive protection models to determine the protective capacity of human antipneumococcal antibodies against bacteremia, meningitis, or death.^{158,159,213,217-219}

In addition, special mention should be made of a human model of intentional pneumococcal exposure that permits a safe evaluation of the immune responses that are either associated with resistance to colonization or response to exposure.^{220,221} Use of this model demonstrated the nasal inoculum required to establish colonization in healthy adults (50% colonizing dose estimated at 10^3 - 10^4 CFU), defined the duration of colonization (range 0-122 days) and analyzed the mucosal and systemic humoral response to a single carriage event. Such studies could be particularly useful in the future for testing of vaccines that target carriage.

Infants and young children

Infants are the main target group for pneumococcal conjugate vaccines, and most clinical trials have therefore focused on the safety and immunogenicity of candidate vaccines in infants. Various dosing schedules have been examined. Although aggressive schedules, starting with vaccination at birth, were studied,^{222,223} they have not been approved. In early infancy, passively acquired maternal antibodies seem to interfere with the response to the first doses of conjugates, although there is no evidence of interference for any serotype after the whole immunization series.²²⁴ In the Expanded Programme on Immunization (EPI) schedule, the conjugate is given at the ages of 6, 10, and 14 weeks. The schedule that has been studied most extensively is a three-dose primary immunization series either at 2, 3, and 4 months or at 2, 4, and 6 months of age, followed by a booster dose during the second year of life. Reduced vaccination schedules at 2, 4, and 12 months or at 3, 5, and 11 to 12 months of age have also been studied. Although three doses were originally considered necessary for an optimal immune response to conjugate vaccines,^{222,225} studies have indicated that even one dose of conjugate vaccine may be sufficient, at least in circumstances where carrier priming and early stimulation with high carriage of pneumococci is common.²²⁶⁻²²⁸ Direct studies comparing different schedules are few, but in general, some

conclusions can be drawn: (1) A short interval between doses (ie, 1 month) often results in lower antibody response than a longer one (ie, 2 months);²²⁹ (2) for some serotypes (in particular serotypes 6B and 23F), reduced schedules may show significantly lower immunogenicity, when immunogenicity prior to the booster dose in a two-dose regimen is compared with a three-dose regimen;²²⁸⁻²³⁰ and (3) although a single dose in infancy is immunogenic, it is inferior to a two- or three-dose regimen for all serotypes.²²⁸ Further evaluation of the quality of antibodies and induction of memory, as well as of the determination of the optimal age of vaccination, would be of interest.^{231,232} Although most of the existing data on immunogenicity are derived from the 7-valent and 9-valent CRM₁₉₇-conjugated vaccines (mainly PCV7 and PCV9), data on other PCVs (conjugated to diphtheria toxoid, tetanus toxoid, OMPC, *Haemophilus influenzae* protein D, or the 13-valent CRM₁₉₇ conjugate vaccine) suggest that they elicit antibody responses of the same order of magnitude as PCV7 in infants and toddlers (Table 25-2).^{4,10,11,161,185,233-241} Thus, the addition of PCV10 or PCV13 results in a wider spectrum of immune response without generally compromising the response of the seven serotypes in PCV7.

In general, anticapsular antibody GMCs increase 5-fold to 10-fold after the initial series, relative to the preimmunization concentrations. The antibody concentrations achieved are usually only sustained for a few months and decline thereafter to about the preimmunization levels. However, a dose of the pneumococcal vaccine, either polysaccharide or conjugate, administered during the second year of life to children primed with any of the conjugates, generally induces an approximately 10-fold increase in antibody concentrations. Typical ways to describe the immunogenicity results are reverse cumulative distribution curves (Figure 25-2) or radial diagrams ("lodosgrams") (Figure 25-3). Representative immunogenicity data after the primary immunizations from selected pivotal trials (either efficacy trials or trials used for licensure of new vaccines after PCV7 introduction [relevant to PCV10 and PCV13]) are compiled in Table 25-2.

Two doses of PCV7 given at either 2 and 4, 3 and 5, or 4 and 6 months of age as a primary series, together with a booster at 11 to 12 months, seem to induce an immune response and induction of immunologic memory comparable to those noted with the standard four-dose schedule in both normal and preterm infants.^{228,230,231,242-244} Thus, the marked booster response, after two doses in infancy, even for the least immunogenic serotypes, has led many countries to adopt a two-dose infant series and a booster rather than the initially licensed schedule of three infant doses and a booster.

In addition to the vaccination schedule and number of doses, the characteristics of the target population also affect the immune response. Direct comparisons are difficult, however, because both the vaccination schedules and the laboratories performing the serologic assays are usually different in different studies. Such comparisons were conducted with PCV7 vaccines containing either seven or nine serotypes, which were evaluated in studies conducted in the United States, Finland, and South Africa.^{4,245-247} Antibody responses elicited in Finnish infants to serotypes 4 and 19F were approximately two to three times higher than the responses in infants in the United States. In South African children, antibody concentrations against serotype 6B were approximately four-fold higher than either Finnish or United States populations.

A series of studies were performed in Finland, Israel, and the Philippines with the PncD/T vaccine. Filipino and Israeli infants had slightly, but significantly higher antibody GMCs than did Finnish infants. The ratio between Filipino and Finnish children varied from 1.8 to 6.7 in serotypes conjugated to tetanus protein and from 1.3 to 3.0 in those conjugated to diphtheria toxoid.²⁴⁸ The reasons for these differences could derive from many factors, such as the priming effect of tetanus

toxoid given to pregnant women, early pneumococcal acquisition, differences in concomitant vaccine administration, and genetic differences among populations.

Preterm infants

Preterm infants seem to respond to the pneumococcal conjugate vaccine satisfactorily.^{243,242,249} Very-low-birthweight premature infants, weighing less than or equal to 1,000 g at birth compared with larger premature infants, have similar antibody response to most, but not all, PCV7 vaccine serotypes.²⁵⁰ The Committee on Infectious Disease of the American Academy of Pediatrics therefore states in its guidance that pneumococcal conjugate vaccines should be given to preterm infants at their chronologic age, consistent with the schedule recommended for full-term infants.²⁵¹ It may be particularly important to offer a timely booster dose of PCV7 to such infants.^{248,252-254}

Older children, adults, and the elderly

GMCs for most serotypes among older infants and children receiving PCV7 were comparable to the immune responses of infants who received three doses of conjugate in the Northern California Kaiser Permanente (NCKP) efficacy study (Table 25-3).⁴ Based on these data, the official recommendation in the United States was to use PCV7 at 2, 4, 6, and 12 to 15 months of age. For children 12 to 23 months of age, two doses were recommended at least 2 months apart, and for those 24 months through 9 years of age, one dose was considered sufficient. Similar recommendations have been made for PCV13 for the primary schedule.²⁵⁴ Vaccination is recommended for all children 2 to 59 months of age and those 60 to 71 months of age with underlying medical conditions. Children who received one or more doses of PCV7 complete their schedule with PCV13. A supplemental dose of PCV13 was recommended for those children 14 to 59 years of age who had completed their four-dose PCV7 schedule. For children with underlying medical conditions, a supplemental dose of PCV13 was recommended up to age 71 months (the recommendation for PPV23 remains for children 2 to 18 years of age who have received their full schedule of PCV13).²⁵⁴ For older children not previously given PCV7, those 7 to 11 months of age are recommended to get three doses, the first two at least 4 weeks apart and the second two at least 8 weeks apart, with the third dose at 12 to 15 months. Such children, aged 12 to 23 months should receive two doses at least 8 weeks apart, and those 24 months of age or older should receive a single dose, or two doses at least 8 weeks apart if they have underlying medical conditions (Tables 25-4 and 25-5).²⁵⁵ To date, there is some evidence that conjugate vaccines are more immunogenic than the PPV vaccine in adults, although this has not been consistently shown.²⁵⁶ In early studies, a 5-valent PCV vaccine elicited a larger response than PPV to some serotypes (6B, 18C, and 23F) but not others (14 and 19F).^{128,188} In more recent studies, the IgG and opsonophagocytic responses to PCV7 and PCV13 were either similar or higher than those to PPV.^{257,258,259,260,261} In the Jackson study,²⁵⁷ dose ranging suggested an advantage of a 1-mL dose (double the infant dose), with no further immunologic advantage at fourfold the infant dose. In Alaska natives, PCV did not induce higher IgG and opsonophagocytic responses compared with PPV and provided no benefit to PPV responses when given before PPV.²⁶² There is also some evidence that the baseline level of antidiaphtheria antibodies is associated with the response to the PCV7 vaccine: adults with higher diphtheria antibody levels have higher responses to the conjugate.²⁶³ The duration of response to PCV adults is not yet clear, but repeated doses seem to induce comparable immunogenicity to the first dose.^{258,260} Receipt of PCV a year after PPV led to a diminished response to PCV compared with PPV-naïve adults.²⁵⁸

Table 25-2 Antibody Concentrations (GMCs, µg/mL) 1 Month After the Last Dose of the Primary Series of Pneumococcal Conjugate Vaccines

Company	Vaccine	Site/ Population	N	Schedule	1	3	4	5	6B	7F	9V	14	18C	19F	23F	6A	19A	Ref
Wyeth	PncCRM7	United States	88	2, 4, 6 mo			1.46		4.70		1.99	4.60	2.16	1.39	1.88			233
Wyeth	PncCRM7	United States	75	2, 4, 6 mo			1.34		2.14		1.23	5.04	1.88	1.52	1.20			4
Wyeth	PncCRM7	Finland	57	2, 4, 6 mo			1.70		2.00		2.50	6.30	3.60	3.30	2.50			11
Wyeth	PncCRM7	Navajo and Apache, United States	223	3 doses at age 6 wk-7 mo			3.21		8.25		2.47	6.81	2.60	2.74	2.59			*
Wyeth	PncCRM9	South Africa ¹	63	6, 10, 14 wk	7.55	3.45	4.09	5.79	1.76		3.35	3.62	4.55	6.02	3.15			234
Wyeth	PncCRM9	South Africa ²	30	6, 10, 14 wk	3.45		2.77	3.32	1.21		2.36	2.23	1.87	3.59	1.78			234
Wyeth	PncCRM9	The Gambia	217	2, 3, 4 mo	6.94		4.90	5.84	4.93		4.07	4.45	4.89	2.91	2.85			235
Merck	PncOMPC	Finland	376	2, 4, 6 mo			3.45		0.35		1.79	3.23	1.02	3.19	0.67			185
GSK	PncPD	Czech Republic	140	3, 4, 5 mo	1.58	3.78	2.16	1.92	0.62	2.34	1.60	3.00	1.49	2.60	0.90			10
GSK	PHiD-CV	Finland, France, Poland	1107	2, 3, 4 mo	1.05		1.45	1.70	0.33	1.72	1.32	2.90	1.66	1.84	0.53			236
GSK	PHiD-CV	Germany, Poland, Spain	173	2, 4, 6 mo	1.00		1.70	1.69	0.71	2.25	1.58	3.76	2.34	3.81	0.96			237
GSK	PHiD-CV	Philippines	285	6, 10, 14 wk	3.23		4.96	4.87	1.19	4.84	4.04	6.45	11.56	10.46	2.23			238
Pfizer	PncCRM13	United States	252	2, 4, 6 mo	2.03	0.49	1.31	1.73	2.10	2.57	0.98	4.74	1.37	1.85	1.33	2.19	2.07	161
Pfizer	PncCRM13	United States	258-264	3, 5 mo	2.30	1.15	2.38	1.27	0.41	2.06	1.68	2.84	1.72	3.42	0.61	1.17	2.87	239
Pfizer	PncCRM13	Germany	285	2, 3, 4 mo	1.83	1.55	2.18	1.31	0.98	2.59	1.65	4.14	1.94	1.73	1.26	1.33	3.26	240
Pfizer	PncCRM13	United Kingdom	107	2, 4 mo	1.69	0.63	1.37	0.95	0.26	2.14	0.87	1.83	1.37	2.38	0.53	0.86	1.90	241

*KL O'Brien, personal communication.

¹HIV-negative children only.²HIV-infected children only.

Blank entries indicate that the serotype was not present in the vaccine.

Data have been derived from pivotal trial (either efficacy trials or trials used for licensure of new vaccines after PCV7 introduction). Note that the studies have been conducted in different populations, at different time periods, and the antibody assays have been performed in different laboratories; results from separate studies are therefore not directly comparable.

GMCs, Geometric mean concentrations; GSK, GlaxoSmithKline; HIV, human immunodeficiency virus; OMPC, outer membrane protein conjugate; PHiD-CV, Haemophilus influenzae protein D conjugate vaccine; PncPD, pneumococcal protein D (conjugate); Ref, reference.

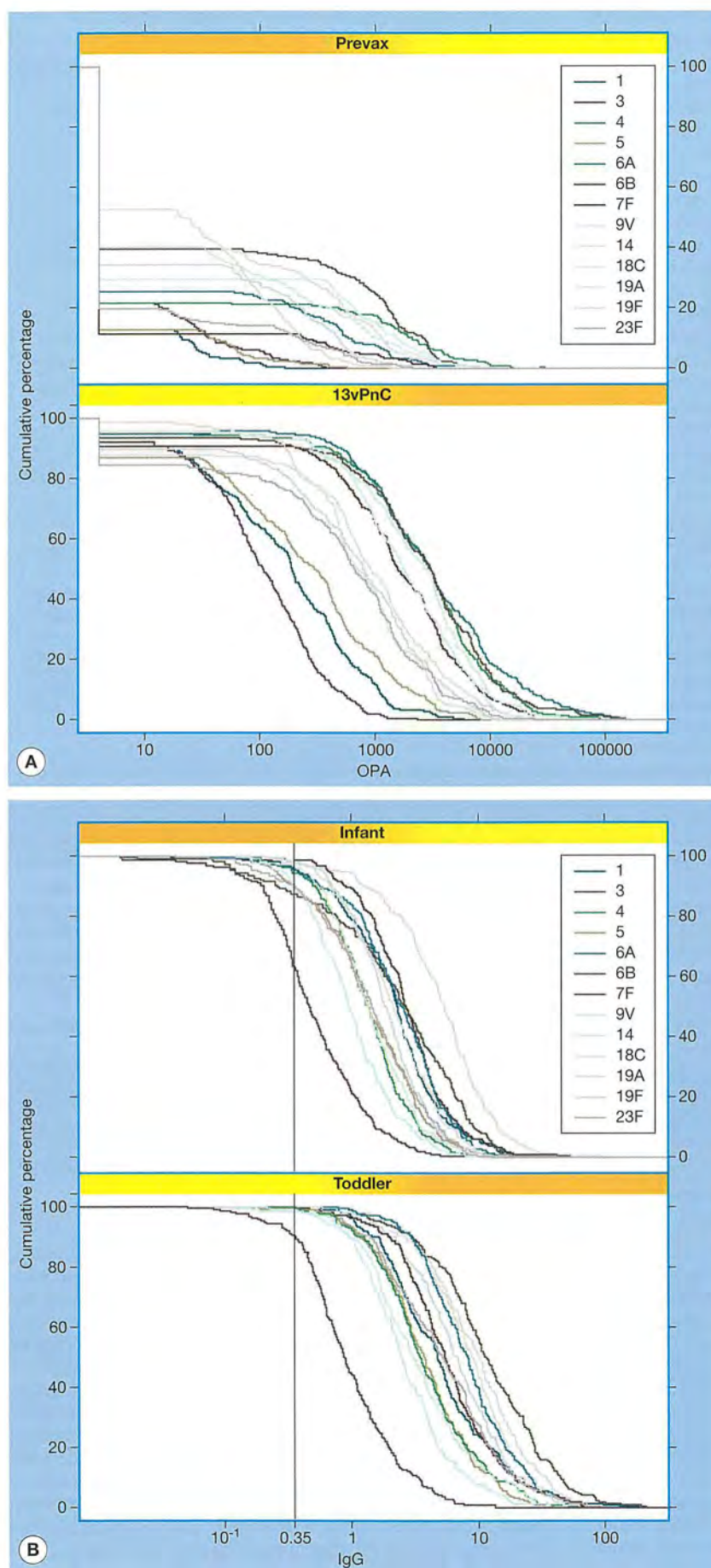
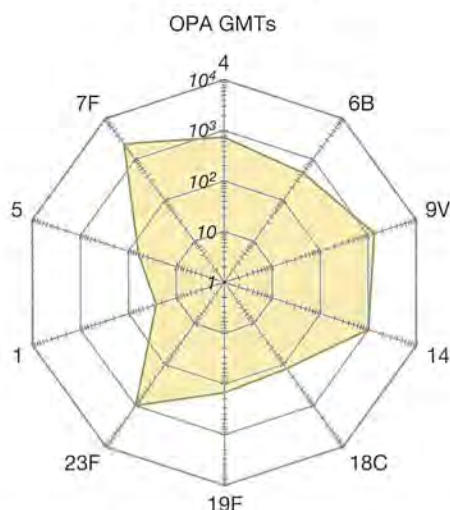


Figure 25-2 A and B, Reverse cumulative distribution curves of 13-valent vaccine. IgG, immunoglobulin G; OPA, opsonophagocytic activity. A. OPA values pre and post single dose PCV13 in adults. B. IgG post primary series in infants and toddlers. Pfizer data on file.

**Pivotal PHID-CV study*:
Post-primary OPA responses**

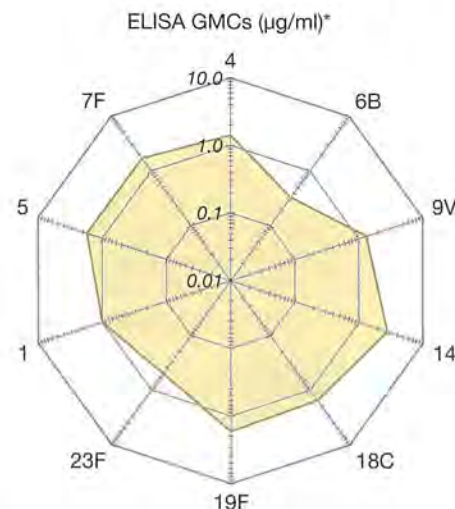


Study conducted in Finland, France and Germany, according to a 2-3-4 month of age schedule, with *Infanrix hexa*TM co-administered

*Study 10PN-PD-DIT-001, 2-3-4 mo
Vesikari et al., *Pediatr Infect Dis J*. 2009; 28(4):S66-S76

(A)

**Pivotal PHID-CV study:
Post-primary antibody responses**



*GSK 22F-inhibition ELISA study 10N-PN-DIT-001, 2-3-4 month
Vesikari et al., *Pediatr Infect Dis J*. 2009; 28(4):S66-S76

(B)

Figure 25-3 Spider web plots for licensed 10-valent study, conducted in Finland, France, and Germany, according to a 2-3-4 months of age schedule, with *Infanrix hexa* co-administered. (Modified from Vesikari T, Wysocki J, Chevallier B, et al. *Pediatr Infect Dis J* 28(suppl 4):S66-S76, 2009.)

Table 25-3 Geometric Mean Concentrations (μg/mL) of Pneumococcal Antibodies after Immunization of Children from 7 Months through 9 Years of Age with PCV7

Age group	Number of doses	Number of children	4	6B	9V	14	18C	19F	23F
7-11 mo	3 doses	22	2.34	3.66	2.11	9.33	2.31	1.60	2.50
		39	3.60	4.63	2.04	5.48	1.98	2.15	1.93
12-17 mo	2 doses	82-84	3.91	4.67	1.94	6.92	2.25	3.78	3.29
		33	7.02	4.25	3.26	6.31	3.60	3.29	2.92
18-23 mo	2 doses	52-54	3.36	4.92	1.80	6.69	2.65	3.17	2.71
		45	6.85	3.71	3.86	6.48	3.42	3.86	2.75
24-35 mo	1 dose	53	5.34	2.90	3.43	1.88	3.03	4.07	1.56
36-59 mo	1 dose	52	6.27	6.40	4.62	5.95	4.08	6.67	2.95
5-9 yr	1 dose	101	6.92	20.84	7.49	19.32	6.72	12.51	11.57

Wyeth Pharmaceuticals. Pneumococcal 7-valent conjugate vaccine.¹²⁵

Because most adults have preexisting antibodies to pneumococcal polysaccharides and to the carrier protein, the initial vaccination with the conjugate can, in fact, act as a booster.

Maturation of pneumococcal antibody avidity is prominent after the vaccination of infants, but the presence of mature antibodies before vaccination of adults results in only modest increases in avidity. In a study of different pneumococcal conjugates, the avidity index was stable in adults, whereas clear increases occurred in children after both primary and booster immunizations.¹⁴⁵ Other reports have noted no avidity maturation in elderly subjects vaccinated with PPV²⁶⁴ or young adults vaccinated with either PPV or PncD/T conjugate.²⁶⁵

Although both IgG and OPA responses to the PncT conjugate and to the polysaccharide vaccine appeared to be similar in a group of patients with chronic obstructive lung disease and

in healthy adults,²⁶⁶ in patients recovering from pneumonia, there was better persistence of antibody with PCV7 than with PPV23 6 months after immunization. This study also found little utility in combining PCV and PPV regimens.²⁶⁷ These data suggest that in nonimmunocompromised adults, there may be an advantage of PCV over PPV, particularly in the duration of antibody response and the response to revaccination. A conjugate vaccine of comparable valency to PPV23 would thus likely be a significant advance. The first large efficacy trial comparing PCV to placebo in adults is in progress²⁶⁸ and will provide additional insight into the benefits of PCV immunization of adults. Extensive herd protection associated with infant PCV immunization in the United States^{13,12} has reduced the potential benefits in that country of a PCV immunization program using an identical vaccine in adults.

Table 25-4 Underlying Medical Conditions that are Indications for Pneumococcal Vaccination Among Children, by Risk Group

Risk group	Condition
Immunocompetent children	Chronic heart disease* Chronic lung disease† Diabetes mellitus Cerebrospinal fluid leaks Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection Chronic renal failure and nephrotic syndrome Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid organ transplantation Congenital immunodeficiency‡

*Particularly cyanotic congenital heart disease and cardiac failure.

†Including asthma if treated with high-dose oral corticosteroid therapy.

‡Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1, C2, C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

From Advisory Committee on Immunization Practices, 2010.^{268a}

HIV, Human immunodeficiency virus.

Immunocompromised individuals

Pneumococcal conjugate vaccines have been tested in HIV-positive children in different populations. It appears that the immune status of the child (measured by the CD4 count) and the current viral load impact the response to the immunization.²⁶⁹ The responses after the first two vaccinations are rather modest in children with advanced HIV, but the antibody concentrations after the primary series were higher than those seen previously in a similar population with the polysaccharide vaccine.^{270,271} Three doses of PCV7 are immunogenic in young

HIV-infected children; children with milder disease tend to have better responses.^{234,270} Among HIV-infected infants with a CD4 percentage greater than 25, there was no impact of antiretroviral therapy on IgG responses, although functional responses may be better in those receiving antiretroviral therapy.²⁷² Functionality as measured by OPA is not however restored to that seen in HIV-unexposed, uninfected infants. There also may be some functional deficits in the quality of antibodies made by HIV-exposed but uninfected children.²⁷² One study suggested that more than one dose of conjugate vaccine may be needed to elicit immunologic memory in children with HIV infection (see Table 25-4).²⁷⁰

HIV-positive adults with a low CD4 count had only a modest response to primary vaccination with the PncOMPC vaccine as well as to a second dose 1 month later.¹⁹⁰ In contrast, HIV-positive individuals with a CD4 count greater than or equal to 200 cells/ μ L had a significant increase in antibodies, which was further increased with a PPV booster. In a Ugandan study,²⁷³ HIV-infected adults received two doses of the PCV7 vaccine. Postvaccination antibody concentrations were directly correlated with the CD4 cell count; this was especially true of the ability to generate a further increase after a second dose. Past receipt of PPV did not affect the response to the conjugate. In a trial among HIV-infected Malawian adults, the PCV7 vaccine was able to induce a response both systemically and mucosally in HIV-infected subjects, which was similar to the response in HIV-uninfected subjects. A second dose of conjugate did not provide any additional benefit.²⁷⁴ The antibodies were functionally active, as measured by OPA.²⁷⁵ If CD4 count really were a surrogate marker of B-cell count, and thus reflected the ability of the patient to respond to the conjugate, then establishing the effect of antiretroviral treatment and optional timing in relation to antiviral therapy would become important. Supplementation with zinc or vitamin A before immunization does not seem to change the response in HIV-positive adults.²⁷⁶ Although the strategy of a PCV prime has not met with significant success among nonimmunosuppressed patients, priming with PCV does increase the titer and duration of response to PPV among HIV-infected adults with CD4 counts 200 to 500/ μ L and a viral load less than 10,000 virus/mL.²⁷⁷ The enhanced response was correlated with Th1 lymphoproliferative responses to the CRM carrier.²⁷⁸ Conversely, immunization with PCV after previous PPV among HIV-infected adults resulted in higher IgG responses than those randomized to receive a second dose of

Table 25-5 Recommended Schedule for Administering Doses of 13-Valent Pneumococcal Conjugate Vaccine (PCV13) to Children Aged < 24 Months by PCV Vaccination History and Age: Advisory Committee on Immunization Practices, United States, 2010

Age at this visit (mo)	Vaccination history: total number of PCV7 and/or PCV13 doses received previously	Recommended PCV13 regimen
2-6 mo	0 doses	3 doses, 8 weeks apart; fourth dose at age 12-15 mo
	1 dose	2 doses, 8 weeks apart; fourth dose at age 12-15 mo
	2 doses	1 dose, 8 weeks after the most recent dose; fourth dose at age 12-15 mo
7-11 mo	0 doses	2 doses, 8 weeks apart; third dose at 12-15 mo
	1 or 2 doses before age 7 mo	1 dose at age 7-11 mo, with a second dose at 12-15 mo, $\geq$ 8 weeks later
12-23 mo	0 doses	2 doses, $\geq$ 8 weeks apart
	1 dose before age 12 mo	2 doses, $\geq$ 8 weeks apart
	1 dose at $\geq$ 12 mo	1 dose, $\geq$ 8 weeks after the most recent dose†
	2 or 3 doses before age 12 mo	1 dose, $\geq$ 8 weeks after the most recent dose†
	4 doses of PCV7 or other age-appropriate, complete PCV7 schedule	1 supplemental dose $\geq$ 8 weeks after the most recent dose

*Minimum interval between doses is 8 weeks except for children vaccinated at age < 1 year, for whom minimum interval between doses is 4 weeks.

†No additional PCV13 doses are indicated for children aged 12 to 23 months who have received two or three doses of PCV7 before age 12 months and at least one dose of PCV13 at age $\geq$ 12 months.

PCV7, 7-valent pneumococcal polysaccharide-protein conjugate vaccine.

PPV, but the duration of difference in antibody response was limited, with no differences between the groups 6 months post-vaccination.²⁷⁹ There was no variance in vaccine responses by black or white ethnicity among trial participants.²⁸⁰

In infants with sickle cell disease, the PCV7 vaccine induced significant increases in serum antibody concentration that appeared to be as high as in control infants.⁸⁷ In older children, two doses of the conjugate vaccine followed by a PPV booster resulted in higher GMCs and OPA titers than PPV alone.⁸³ Patients with ataxia-telangiectasia, who usually have low T-cell and B-cell counts, as well as low levels of pneumococcal antibodies, responded to PPV vaccination with a booster-type response if polysaccharide was given after a dose of the conjugate. However, the antibody concentrations were lower than those observed in control subjects.^{281,282}

Two studies have examined the immune response to PncOMPC in patients previously treated for Hodgkin disease. Although the response to a single dose of 7-valent PncOMPC vaccine was lower than to a polysaccharide vaccine,⁹⁴ the conjugate seems able to induce immunologic priming even in this patient group.¹⁹⁰ In adults with chronic lymphocytic leukemia, responses to PCV were detected in 40% of cases before the onset of hypogammaglobulinemia associated with chemotherapy.²⁸³

Patients with hematopoietic cell transplantation and allogeneic or autologous hematopoietic stem cell transplantation have a satisfactory antibody response to a three-dose schedule of PCV7.²⁸⁴ Immunization of the donor before transplantation (or the patient before stem cell collection) enhances at least the early antibody responses,^{285,286} and revaccination post-transplantation induces a greater than 80% immune response to PCV7.²⁸⁷ Among adult allogeneic bone marrow transplant recipients, responses to PCV and PPV are generally poor, but PCV resulted in prolongation of detectable antibody responses compared with PPV.²⁸⁸ Early immunization with PCV at 3 months post-transplant is as immunogenic as waiting for 9 months, so earlier vaccination may be recommended.²⁸⁹ In pediatric solid-organ transplant recipients, two doses of PCV7, followed by one dose of pneumococcal polysaccharide vaccine, increases pneumococcal antibody concentrations. The first conjugate dose seemed to do the job; neither the second dose of conjugate nor the dose of polysaccharide increased the levels further. Final responses were, however, significantly lower in solid-organ transplant recipients than in the control group.²⁹⁰ In renal transplant recipients, PCV7 was marginally more immunogenic than PPV; OPA responses were not different,²⁹¹ antibodies wane significantly over 3 years, and over that time period, PCV did not increase the durability of the immunogenicity compared with PPV in these patients.²⁹² The prime boost strategy was no better than PPV alone in terms of immunogenicity among liver transplant recipients.²⁹³ There may be some heterogeneity in responses after differing types of solid-organ transplants because multiple doses of PCV and the prime boost strategy seem to have been associated with additional immunogenicity after cardiac transplantation.²⁹⁴

Duration of immunity

Over a 5.3-year follow-up after immunization with PCV9 of South African infants who did not receive a booster in the second year of life, antibodies to the 7 valent vaccine serotypes remained significantly elevated compared with control subjects.²⁹⁵ Titers greater than 0.35 µg/mL were detected among 44% to 95% of control subjects depending on serotype. The lowest percentage was to serotype 4 suggesting that long-term immunogenicity to types rarely carried, such as types 1, 4, and 5, should be further investigated, particularly in the absence of a booster dose in the second year of life. Even among HIV-infected children, higher antibody titers were detected 5.3 years postimmunization than in HIV-infected control subjects, but the percentage of children with titers greater than 0.35 µg/mL was lower than among HIV-uninfected children and ranged from 19% to 81%.²⁹⁵

Variables influencing the immunogenicity of conjugate vaccines

Composition of the vaccine

The immunogenicity of a conjugate vaccine is dependent on its chemical characteristics.²⁹⁶⁻²⁹⁹ In pneumococcal conjugates, polysaccharides seem to be more immunogenic than oligosaccharides.^{180,300,301} Other variables influencing immunogenicity include the inherent properties of carrier proteins, the nature of the chemical linkage of the carbohydrate to the protein carrier,^{302,303} conformational changes in epitopes after conjugation,²⁹⁶ the availability of antigenic structural components,^{298,300} the presence of free polysaccharides or carrier proteins in the vaccine,^{304,305} and the carbohydrate:protein ratio.³⁰⁶

It has recently been shown for group B streptococcal type III polysaccharide conjugated to ovalbumin that the carbohydrate itself is presented to major histocompatibility class II receptors suggesting that peptide conjugates with multiple links to the polysaccharide chain may be more effective conjugate structures.^{306a} This exciting observation may open the way to more rational design of conjugates including pneumococcal conjugates. Clear-cut differences exist in the antibody responses to different capsular-type polysaccharides in the conjugate vaccines.^{11,187,233,247,306,307} In studies with Finnish children, the magnitude of the IgG response to serotype 6B appears to be rather consistent between the different vaccines, but large differences can be found for other serotypes, particularly 14 and 19F.³⁰⁸ In general, in infants, serotypes 6B and 23F appear to be poor immunogens in spite of conjugation, whereas serotype 19F induces a relatively high antibody concentration, although these antibody concentrations to serotype 19F may not be associated with higher OPA titers. Serotypes 3 and 18C are usually satisfactory immunogens even after the first dose, although a poor booster response is seen for serotype 3 antibodies. No marked increase in anti-6B IgG can be seen in infants after a single dose, and even two doses are markedly inferior to three doses.²²⁸⁻²³⁰ For serotype 4, there is a marked response after the first dose and a further increase after the second dose, but not after the third dose. Serotype 19F induces an antibody response after the second dose, and the third dose does not increase the mean antibody concentrations.

Dose-response evaluation results have been published for 4-valent PncT and PncD vaccines (1, 3, or 10 µg of each polysaccharide). For PncT vaccine, no dose dependency was seen after the primary immunization, whereas the booster response was highest in the group primed with the lowest dose of the conjugate vaccine.¹⁸² In contrast, the highest dose of PncD induced the strongest response after primary immunization, but, as with the PncT vaccine, the booster response was greatest in the group primed with the lowest dose.¹⁸¹ When a tetravalent *H. influenzae* protein D pneumococcal conjugate vaccine was tested in three doses (0.1, 1.0, and 10.0 µg of each polysaccharide), the 0.1 µg dose was superior to the 10 µg dose; for serotype 14, the response increased with increased polysaccharide content, and for serotype 19F the 1.0 and 10.0 µg were equal and superior to that of the 0.1 µg.³⁰⁹ Thus, the dose response in the various PCVs is not always predictable and depends on the carrier and the serotypes.

The optimal carrier may be different for each serotype. Thus far, direct comparisons have been made only between diphtheria and tetanus carriers. Polysaccharides from serotypes 3, 9V, and 14 evoke a better response in infants when conjugated to diphtheria toxoid, and polysaccharides from serotype 4 induce a stronger response when conjugated to tetanus protein.^{246,310} No carrier-specific differences in immunogenicity have been shown for serotypes 6B, 18C, 19F, and 23F. Furthermore, the conjugates seem to have different capacities to induce a mucosal immune response: whereas diphtheria toxoid conjugates induce a better mucosal response, tetanus conjugates seem more efficient in inducing systemic responses.¹⁷⁶

Immunity to carrier proteins is beneficial for the improved immunogenicity of conjugate vaccines. Early priming with

carrier proteins enhances the immune response to polysaccharides in subsequent immunizations with conjugates.^{305,311–313} In a study in the Philippines, antibody concentrations at 9 months of age were similar after one dose or three doses.²²⁵ The most plausible explanation for the good immunogenicity and persistence of antibodies, despite the lower number of doses, is carrier priming with previous diphtheria-tetanus-pertussis (DTP) vaccine. Although the T-cell immunity against carrier proteins is essential for responses to polysaccharides, B-cell immunity to carrier protein may become detrimental upon induction of anticarrier antibodies.^{314,315} In a situation where polysaccharide- and protein-specific B cells compete to capture conjugates, high amounts of antibodies to carrier proteins may result in a suppressed immune response to polysaccharides.^{304,305,313,315–317} This is a valid argument for minimizing the amount of antigen and for developing mixed-carrier vaccines.

Adjuvants, which bias the immune system to a Th2 response, are often part of the formulation of conjugate vaccines. In most cases, they enhance the immune response. Aluminum adjuvants are currently used in all marketed conjugate products, except in two stand-alone Hib vaccines. The addition of an aluminum hydroxide adjuvant to the PncT/PncD vaccine has increased the IgG response and functional activity of antibodies in studies in Finland and Israel.³¹⁸

Table 25-6 describes the composition of the three PCVs licensed in 2012.

Concurrent administration with other vaccines

High coverage of infant and toddler populations with PCVs and Hib-conjugated vaccines has partly been fostered by their ability to be co-administered or mixed together with other routinely administered vaccines, including other conjugate vaccines. However, the potential of conjugate vaccines to induce immune interference (enhancement or impairment), of humoral immune responses to co-administered antigens, is increasingly recognized.^{316,317} Two common interference mechanisms are (1) carrier-induced epitopic suppression, whereby preexisting immunity to a carrier (conjugate protein) suppresses subsequent responses to a hapten/saccharide linked to the same carrier and (2) bystander interference, whereby co-administration and/or combinations of vaccines containing a given conjugate protein induce interference that extends to unrelated antigens that are part of the combinations in use.³¹⁶

The best recognized form of immune enhancement occurs when vaccines using tetanus toxoid (TT) as the conjugate protein are co-administered with Hib-TT. Anti-PRP (polyribosyl-ribitol-phosphate) antibody concentrations increase when Hib-TT is co-administered with meningococcal serotype C TT conjugate (MenC-TT), or with protein D pneumococcal conjugate vaccine.^{319–324} On the other hand, immune responses to TT-conjugated pneumococcal polysaccharides and MenC-TT decrease in the presence of excessive amounts of co-administered TT through carrier-induced epitopic suppression.^{325,326} Immune enhancement mechanisms also contribute to optimal responses to vaccines that use diphtheria toxoid variant (CRM₁₉₇) as conjugate proteins. In general, CRM₁₉₇ and TT, when engaged as carrier, lead to higher antipolysaccharide responses than does DT, as exemplified by Hib-TT/CRM versus Hib-DT,³²⁷ and meningococcal ACWY-TT/CRM versus ACWY-DT.^{327–329} However, unlike TT, DT/CRM₁₉₇ conjugates need T-cell enhancement via DT/CRM₁₉₇ priming or co-administration to maximize immune response.²²⁷

Conjugate vaccines using CRM₁₉₇, although less likely than those using TT or DT to reduce responses to polysaccharides through carrier-induced epitopic suppression, are more likely to induce interference through another yet unclear mechanism, termed bystander interference.^{316,317} This phenomenon affects vaccines co-administered with the CRM₁₉₇ conjugate vaccines, and Hib-TT and Hepatitis B vaccines are particularly vulnerable to this interference. Bystander effects are probably

mediated by T-cell mechanisms shared between DT and CRM₁₉₇ and are spreading to other co-administered antigens.

Immune interference in general, and that observed with conjugate vaccines in particular, are most marked when vaccines are co-administered with combination vaccines acellular pertussis (ie, DTaP), as compared with whole-cell pertussis combinations (ie, DTwP).^{316,317,325} PncD/T has proved to be sufficiently immunogenic during infancy when given in the presence of DTwP.^{248,330} However, when DTaP was present in the concomitantly administered vaccine, a reduction in the primary immunogenicity of the pneumococcal polysaccharides conjugated to tetanus toxoid was observed.³²⁵ No similar reduction was seen in relation to the polysaccharides conjugated to diphtheria toxoid in the same vaccine. The phenomenon was attributed to a disturbance in the rather complicated balance between the immunogenic properties and amounts of carrier protein and the adjuvant effect of whole pertussis cells, which was removed when switching to acellular pertussis vaccines.³²⁵ Because of this finding, Sanofi Pasteur decided to abandon the development of the PncD/T vaccine.

When studies are compared, CRM₁₉₇-conjugated vaccines co-administered with DTaP vaccines and Hib-TT, consistently demonstrate reduced anti-PRP responses compared with schedules where CRM₁₉₇ is not co-administered, as can be exemplified in Table 25-7. In contrast, with co-administration of Hib-TT with conjugate vaccines that do not contain CRM₁₉₇, anti-PRP GMCs remain unaffected or are enhanced.^{319–323}

In addition to the potential interference induced by the introduction of PCV into the infant immunization program, the effect of increasing DT or TT component of pneumococcal vaccine immunogenicity needs to be considered, especially when introducing extended-spectrum PCVs with additional conjugated polysaccharides. Head-to-head studies of PCV13-CRM (34 µg CRM₁₉₇) versus PCV7-CRM (20 µg CRM₁₉₇) show a reduction in post-dose-three antipneumococcal GMCs in PCV13-CRM for at least four of the seven serotypes in PCV7, in particular serotype 6B.^{239,240,331} These observations suggest dose-dependent carrier-induced epitopic suppression in the pneumococcal response by CRM₁₉₇. The complex effect of co-administration has still not been totally elucidated, and the various mechanisms involved in such a complex intervention are far from being fully explained. Table 25-8 depicts some of the observed interference phenomenon related to conjugate vaccines.

In addition to the complexity of multiple vaccine co-administered in infants, it has recently been observed that some co-administered drugs can also interfere with the immune response of PCVs, as well as other vaccines.³³² The most striking example is the finding that prophylactic administration of acetaminophen before vaccination markedly reduced response to PCV, Hib and diphtheria, and tetanus and pertussis vaccines.³³²

With the introduction of new conjugated vaccines with CRM₁₉₇ epitopes, there is a need to further evaluate potential interference either by carrier-induced epitope suppression or by the bystander interference mechanism. However, the multitude of studies needed for the licensure of each of the new vaccines with a variety of co-administered vaccines has shown that although interference may often be seen when vaccines are co-administered in infancy, it is rarely of clinical importance. Nevertheless, a potential interference is now taken into consideration when national immunization plans are considered.

In the setting of less immunogenic vaccine combinations and co-administrations, the importance of the booster dose becomes paramount. The value of the booster dose in the second year of life in Hib disease control has been highlighted in postmarketing surveillance studies³³³ and by public health experience in the United Kingdom. However, the extent to which carrier-induced epitopic suppression or bystander effects are negated or persist upon boosting is not well studied. Creative use of available vaccines can limit these issues without substantially impacting either the number of antigens administered, or number of injections required to protect young children.

Table 25-6 Composition of the Three Pneumococcal Conjugated Vaccines Licensed in 2011*

Vaccine	Commercial name	Polysaccharide content (µg) and protein carrier												Adjuvant	
		1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	
PCV7 (CRM197 conjugate)	Prevnar/Prevenar	(-)	(-)	2.0	(-)	(-)	4.0	(-)	2.0	2.0	2.0	(-)	2.0	2.0	Aluminum phosphate
PCV13 (CRM197 conjugate)	Prevnar13/Prevenar13	2.2	2.2	2.2	2.2	2.2	4.4	2.2	2.2	2.2	2.2	2.2	2.2	2.2	Aluminum phosphate
PHID-CV (serotypes 1, 4, 5, 6B, 9V, 14, 23F conjugated to nontypable Haemophilus influenzae-derived protein D; serotype 18C conjugated to tetanus toxoid; serotype 19F conjugated to diphtheria toxoid)	Synflorix	1.0	(-)	3.0	1.0	(-)	1.0	1.0	1.0	1.0	3.0	(-)	3.0	1.0	Aluminum phosphate
*Information as described in product monographs presented for licensure.															
PHID-CV. Haemophilus influenzae protein D conjugate vaccine.															

*Information as described in product monographs presented for licensure.
 PHID-CV, Haemophilus influenzae protein D conjugate vaccine.

Table 25-7 Effect of CRM197 Bystander Interference on the Immune Response to Co-Administered Hib-TT

Vaccines administered	Schedule (months)	Number of participants	Anti-PRP response		Ref
			(µg/mL)		
			% ≥ 0.15	GMC (95% CI)	
DTaP5-IPV-Hib-TT	2, 4, 6	324	97.9	4.86 (4.21, 5.62)	597
DTaP5-IPV-Hib-TT+MenC-TT	2, 3, 4	53	94.2	5.17 (3.53, 7.58)	319
DTaP5-IPV-Hib-TT+MenC-CRM	2, 3, 4	50	87.6	2.17 (1.34, 3.53)	319
DTaP5-IPV-Hib-TT+MenC-CRM+PCVCRM7*	2, 3 or 2, 4	126	89	1.75 (1.29, 2.38)	320
DTaP5-IPV-Hib-TT+MenC-CRM+PCVCRM7†	2, 3 or 2, 4	126	85	1.76 (1.29, 2.39)	320
DTaP5-IPV-Hib-TT+MenC-CRM+PCVCRM	2, 3, 4	53	85	0.77 (0.51, 1.16)	598
DTaP5-IPV/Hib-TT+PCVCRM7	2, 3, 4	248	91	1.38 (1.14, 1.66)	599
DTaP3-HBV-IPV/Hib-TT	2, 3, 4	138	95.7	2.27 (1.78, 2.90)	600
DTaP3-HBV-IPV/Hib-TT+PHiD-CV	2, 3, 4	542	97.4	2.13 (1.93, 2.36)	323
DTaP3-HBV-IPV/Hib-TT+PCVCRM7	2, 3, 4	141	93.6	1.59 (1.23, 2.05)	600
DTaP3-HBV-IPV/Hib-TT+PCVCRM7	2, 3, 4	178	97.2	1.18 (0.97, 1.42)	323
DTaP3-IPV/Hib-TT+PCVCRM7	2, 3, 4	242	80.8	0.59 (0.49, 0.71)	599
DTaP3-IPV-HBV/Hib-TT+PCVCRM13	2, 3, 4	285	89.5	1.23 (1.03, 1.46)	240

*Manufactured by Wyeth.

†Manufactured by Novartis.

Anti-PRP measured by enzyme-linked immunosorbent assay.

CRM, Carrier protein in conjugate vaccine; DTaP, diphtheria-tetanus-acellular pertussis vaccine; DTaP3, 3-component DTaP vaccine; DTaP5, 5-component DTaP vaccine; GMC, geometric mean concentration; HBV, hepatitis B virus; Hib, Haemophilus influenzae type b; IPV, inactivated polio virus; PCV, pneumococcal conjugate vaccine; PHiD-CV, Haemophilus influenzae protein D conjugate vaccine; PRP, polyribosyl-ribitol-phosphate; Ref, reference; TT, tetanus toxoid.

Table 25-8 Observed Immune Interference Phenomena After Conjugate Vaccination in Children and Suggested Mechanisms

DTP vaccine	Co-administered conjugates	Direction of effect	Mechanism	Ref
DTaP3, DTaP5	Hib-TT + MenC-TT	↑ PRP	Enhancement via TT	319
DTaP3	Hib-TT + PHiD-CV	↑ PRP	Enhancement via TT or neutral	323
DTaP3	Hib-TT + PCVCRM7	↓ PRP	Bystander interference	221,323,600
DTaP3	PCVCRM7	↑ Pn	Enhancement via DT	244,323
DTaP3	PCVCRM13	↓ Pn	Carrier-induced epitopic suppression	239,240,331
DTaP5	PCV-TT + MenC-TT	↓ Pn ↓ MenC	Carrier-induced epitopic suppression	124,313,325
DTaP5	Hib-TT + MenC-CRM	↓ PRP	Bystander interference	317,319
DTaP5	Hib-TT + PCVCRM7 + MenC-CRM	↓↓ PRP ↓ Pn ↓ MenC	Bystander interference	229,598
DTaP2	PCVCRM7	↓ HBs (unconfirmed)	Bystander interference	316
DTwP	PCVCRM9 - MenC-CRM	↓ MenC	Carrier-induced epitopic suppression	601

CRM, Carrier protein in conjugate vaccine; DTaP2, DTaP3 or DTaP5 refers to 2-component, 3-component or 5-component diphtheria-tetanus-acellular pertussis vaccines, respectively; DTwP, diphtheria-tetanus-whole-cell pertussis vaccine; HBs, antihepatitis B surface antibody; Hib, Haemophilus influenzae type b; MenC, meningococcal C; PCV, pneumococcal conjugate vaccine; Pn, pneumococcal polysaccharide; PRP, polyribosyl-ribitol-phosphate; Ref, reference; TT, tetanus toxoid.

Correlates of protection

Challenges in the search for correlates

Determination of serologic correlates or surrogates of protection against pneumococcal diseases has proven complicated. First, even if the level of a specific antibody is considered to be an adequate surrogate in a particular setting,^{175,334} the level may vary between serotypes and the disease in question. Secondly, the quantitative assessment of immune response alone may be insufficient, and measurement of the qualitative characteristics of antibodies should also be included in the analyses.^{308,335–338} Finally, induction of immunologic memory has to be taken into consideration^{150,199,336,339,340} because immunologic memory can be induced even after a weak antibody response.

Traditionally, methods for assessing the association between immunogenicity and the prevention of disease have relied on comparisons of aggregate measures, such as comparison of vaccine efficacy and GMCs of antibodies. An alternative possibility for the definition of a protective level is to combine information about the incidence of disease and antibody concentrations in different subgroups of the study population. Correlates of protection should ideally be sought on the individual level by collecting longitudinal follow-up data on children who contract pneumococcal infection in spite of vaccination. They should also be sought in populations by comparing cross-sectional information on antibody concentrations and estimates of protection in the same group of subjects.

Two comprehensive reviews have been published on the principles and methods of correlates of protection and their use in the licensure of pneumococcal conjugate vaccines. One was written by WHO experts and academic researchers,¹⁷⁵ the other by scientists from the FDA and National Institutes of Health.³⁴¹

Serologic correlates

Once an effective vaccine has been licensed and placed into widespread use, it is difficult, no longer feasible, or ethically challenging to perform additional controlled studies to demonstrate the efficacy of new vaccines against *S. pneumoniae*. In this case, immunologic correlates of protection then become critical for predicting the efficacy of new vaccines.³⁴²

For this purpose, noninferiority of immunologic correlates based on efficacy against invasive pneumococcal disease (IPD) was chosen. Establishing noninferiority based on serologic criteria becomes difficult, however, because there is no clear agreement on the concentration of antibody or titer in vaccines that may be used in a noninferiority model to predict whether vaccine is effective.

Pneumococcal disease is multifaceted. Invasive pneumococcal disease is the first outcome against which the PCVs were aimed, and efficacy against IPD is considered the gold standard when calculating or assuming serologic correlates. However, the most common pneumococcal disease outcome is not IPD, but mucosal infections such as pneumonia or otitis media. Furthermore, nasopharyngeal carriage is the main player in pneumococcal spread and development of antibiotic resistance. Even if serologic correlates of efficacy against IPD are established, they do not predict accurately efficacy against mucosal infections. Effectiveness of PCVs is greatly dependent on reduction of carriage and spread; therefore again, correlates that predict protection against IPD may not necessarily accurately predict effectiveness, because effectiveness is heavily dependent on reduction of carriage and spread of *S. pneumoniae*.

The first assumption needed to establish a threshold concentration of antibody that predicts protection is that antibody concentration after the primary series of the vaccine predicts protection. The second assumption is that the relationship between risk of disease and antibody concentration is expressed in a stepwise manner rather than as a continuous function. Neither of these assumptions actually holds completely true. The multiplicity

of antigens in the current vaccines and the fact that newer formulations contain additional antigens for which no licensed product is available for comparison adds complexity to the decision process.¹⁷⁵ One proposed possibility for addressing the multiple immunologic end-point comparisons is to assign a weighted average based on the ranking of serotypes by their epidemiologic and clinical significance.³⁴³ This resulted in a pooled model based on three efficacy studies, the Northern California Kaiser Permanente (NCKP) PCV7 study in the United States,⁴ the American Indian PCV7 study,⁵ and the PCV9 South Africa study.⁷ These three studies showed efficacy of 97.3%, 78.8%, and 90%, respectively, and the lowest estimate for PCV7 serotype protection was 0.2, 1.0, and 0.68 µg/mL, respectively. The pooled estimated antibody concentration was 0.35 µg/mL.^{342,343} A subsequent controlled PCV9 study from the Gambia showed vaccine efficacy of 86% for IPD, with protective antibody estimate of 1.20 µg/mL. The three studies in high-risk populations (American Indians, South Africa, and the Gambia) suggest that such populations may require higher antibody levels to achieve an equivalent protective efficacy against IPD than do Californian infants, or that more antibody is needed to protect against meningitis and pneumonia cases among IPD than is needed to protect from bacteremia without a focus.³⁴² Variations between laboratories and different analysis caused some disagreement with regard to the pooled antibody concentration cut-off for the protective antibody levels. Thus, some use the value of 0.35 µg/mL, but others use the cut-off value of 0.20 µg/mL.³⁴⁴

The practical approach for licensure of new PCVs containing additional serotypes beyond the PCV7, is as follows: For the common 7 serotypes, noninferiority is established for each serotype by direct comparison of the response in the new PCV compared with the licensed vaccine. For each of the six additional serotypes, the difference in proportions above the cut-off level between the new vaccine and the established vaccine is calculated using the serotypes with the lowest proportion above the cut-off level (usually for serotype 6B) among the established vaccine as the reference group. For each serotype, noninferiority would be described if the lowest boundary of the 95% confidence interval for the difference is greater than -0.10.³⁴³

The protective level is best applied to population rather than the individuals; thus, if a high proportion of individuals in a population achieves anticapsular antibody concentrations above the protective threshold, one can predict a high level of protection for IPD in that population. In a particular individual, the outcome of an encounter with the pneumococcus may vary depending on multiple host and pathogen factors.³⁴²

As stated above, the situation with mucosal infections and carriage is not identical to that of IPD. Several studies suggest that there is a need to achieve higher concentration after primary immunization series to protect against AOM and carriage than against IPD. In AOM, generalized linear modeling has been used to study the association between the antibody concentrations to serotypes 6B, 19F, and 23F and the risk of AOM caused by the homologous serotypes in the 5 months after immunization.²⁶ The association was most clear-cut for serotype 23F and poorest for serotype 19F. Even low concentrations (GMC 0.5 µg/mL) predicted vaccine efficacy of 50% for serotype 6B, while a GMC of 2 µg/mL was required for the same efficacy for serotype 23F. For serotype 19F, the results suggested that much larger concentrations (GMC > 10 µg/mL) might be required to achieve protective efficacy. Thus, these results indicate different behavior for different serotypes, discouraging the setting of a unique serologic correlate of protection for all serotypes. In addition, the concentration needed to protect against AOM seems to be higher than the concentration that is protective against IPD.

For protection against carriage, it has been clearly demonstrated, like the case of AOM, that the concentrations needed for protection are higher than those needed for IPD. Furthermore, complete protection may be associated with concentrations higher than those attained after PCV administration with the

current vaccines.^{27,345} In addition, serotype-to-serotype variation in protection, in relation to achieved antibody concentrations, was observed.

To date, no studies have been able to demonstrate any correlation of antibody concentrations of protection against pneumonia, or nonpneumonia lower respiratory infections.

In summary, although correlates of protection were drawn in IPD, and have been used for licensure, many questions still remain. To date, no correlations have been determined for mucosal disease and carriage responsible for most of *S. pneumoniae* pneumococcal disease burden. Furthermore, post-PCV introduction effectiveness is greatly dependent on indirect protection conferred by reduced carriage and spread of vaccine-serotype *S. pneumoniae*, but no correlates predicting such an effect are known. However, it is suggested that if higher functional antibody concentrations are achieved after the primary immunization series, a higher reduction in mucosal disease carriage will take place, resulting in higher and faster population protection through herd immunity.

Mucosal antibody response

Although it is generally assumed that host defense at mucosal sites contributes to protection, it has been difficult to determine the relative importance of mucosal antibodies in preventing pneumococcal invasive disease and/or colonization. Nonetheless, analysis of mucosal immunity has been an important focus for the understanding of the protection provided by conjugate³⁴⁶ and is being evaluated for protein-based or whole-cell vaccines (see section Human experiences with natural or vaccine-derived pneumococcal protein antigens). These antibody responses can be analyzed either by measuring anticapsular or noncapsular antibodies from mucosal membranes and secretions, or through demonstration of specific antibody-secreting cells (ASCs) in lymphatic tissues or in the peripheral blood.

Enzyme-linked immunosorbent assays can be applied to the measurement of antipneumococcal antibodies from mucosal secretions and saliva. Two specific challenges present themselves: one is the instability of samples caused by the degradative action of enzymes present, especially in saliva; the other is the wide individual variation and the unknown magnitude of dilution of samples. The first challenge can be dealt with through the use of enzyme inhibitors and by storing the samples at -70°C and the second by relating the concentration of specific antibodies to the total antibody concentration in the sample.

Parenterally administered pneumococcal capsular vaccines, both polysaccharide and conjugate, induce mucosal antibody responses. Serotype-specific salivary antibodies are found rarely after primary immunization but more frequently after a booster either with the conjugate or with polysaccharide vaccine.^{176,193,347-349} The IgG detected in saliva is thought to be derived from serum, with high serum IgG concentrations leading to leakage of the antibodies into mucosal secretions. Serum and salivary IgG concentrations indeed correlate strongly, in accordance with this concept.

As B cells are continuously circulating through the lymphatics and blood and back to the peripheral tissues, cells committed to mucosal sites are also present in the peripheral blood for a limited period of time before homing to different sites. The appearance of these antigen-specific ASCs can be measured with an enzyme-linked immunospot assay (ELISPOT) in peripheral blood after an antigen challenge, and the magnitude of this response is thought to reflect the immune response in mucosal membranes.³⁵⁰⁻³⁵⁵

A high number of IgA ASCs detected with an ELISPOT is considered to be an indicator of the mucosal IgA response after parenteral pneumococcal vaccination. The response to parenteral protein vaccines is generally dominated by IgG-producing cells,³⁵⁴ whereas the response to polysaccharide antigens is

dominated by IgA-producing cells.³⁵⁴⁻³⁵⁶ The IgA/IgG ratio of the ASC response to a polysaccharide that is conjugated to a protein carrier is altered toward a pattern typical of T-cell-dependent antigens.^{350,356} For the PPV vaccine, the response is dominated by the IgA ASCs,³⁵² but after the conjugate vaccines, the IgG ASC responses are higher.^{205,353} The ASC responses to the PncT and PncD vaccines in toddlers are lower than those seen in adults after conjugate vaccine but comparable to those in adults after PPV vaccine. In toddlers, the ASC response is clearly dominated by IgA-secreting cells.³⁵²

Cellular responses

The improved immunogenicity of the conjugates compared with the pure polysaccharide vaccines is thought to be due to the engagement of CD4⁺ lymphocytes because of the presence of the carrier protein. This cellular response has been evaluated by measuring lymphocyte proliferation and the production of different cytokines (eg, interferon- γ and various interleukins [ILs]) after in vitro stimulation with the polysaccharide and protein components of the conjugated vaccines.^{307,358} These studies have demonstrated, as expected, that conjugate vaccines can induce proliferative and cytokine responses to the carrier proteins but not to the polysaccharide components.

The importance of the cellular component is well illustrated by animal experiments and more recent human studies. Age-dependent Th2-cytokine responses can be observed in mice immunized with the conjugate; the lack of response to the polysaccharide in neonatal mice seems to be associated with absence of carrier-specific IL-5 production. These results suggest that immunization with pneumococcal conjugate induces carrier-specific T-cell responses that increase with age and determine the levels of the antibody response to the polysaccharide component.³⁵⁹ A randomized controlled trial in Papua New Guinea demonstrated that neonatal immunization with the 7-valent conjugate primes T-cell responses to the protein carrier and polarized T-cell responses toward Th2.²²³

At the same time, data from humans and animal models have emerged to provide support for the existence of an antibody-independent, T-cell response that confers resistance to pneumococcal colonization. In adult patients with chronic obstructive pulmonary disease (COPD), naturally acquired and vaccine-induced antibodies to pneumococcal antigens (capsular and noncapsular) do not predict resistance to pneumococcal colonization, suggesting the existence of other mechanisms.³⁶⁰ In mice, acquired immunity to colonization after mucosal exposure to either live or killed unencapsulated whole-cell pneumococcal vaccine³⁶¹ is antibody independent and CD4⁺ T-cell dependent. Mice that genetically lack antibodies, IFN- γ , or IL-4 maintain whole-cell vaccine-induced immunity to colonization, but mice treated with neutralizing anti-CD4 or genetically lacking the IL-17A receptor are not protected by these exposures. A likely effector cell is the IL-17A-producing CD4⁺ Th17 cell,^{362,363} which has previously been implicated in resistance to pathogens such as *Bordetella pertussis*³⁶⁴ or *Mycobacterium tuberculosis*³⁶⁵ and has been shown to be absent in individuals with autosomal dominant hyperimmunoglobulin E (Job) syndrome.³⁶⁶ A proposed mechanism of protection involves the release of IL-17A, IL-22, and other related cytokines, which help recruit and activate neutrophils to the site of infection, enhancing clearance of the organism.³⁶⁷ Whether such cellular responses demonstrated in mice also mediate protection to pneumococcal colonization in humans remains to be formally proven. It is worthy of note, however, that systemic and mucosal IL-17A responses to pneumococcal antigens have been demonstrated in humans^{362,368} and that IL-22 responses to pneumococcal antigens correlate with resistance to colonization in adults with COPD.³⁶⁹

Schedules

Schedules of PCV are an area of intense debate, and the arguments around selecting them—in terms of immunogenicity, impact on carriage and effectiveness in prevention of IPD, and pneumonia and otitis media—are made under the relevant headings of this chapter. The gold standard regimen of 3 + 1 has been defined by the US licensure trials.^{4,5} This schedule is three doses in infancy, generally 2 months apart with a booster in the second year of life. A dose-sparing schedule of 2 + 1 with the two infant doses, generally two or more months apart and the third in the second year of life, has been widely studied for effectiveness and appears effective in conferring protection, with the caveat that before herd protection is established, there may be a period of increased susceptibility to some serotypes, between 6 and 12 months of age, that are less immunogenic after two doses, such as serotype 6B. A variant of 2 + 1 is to bring the booster in line with the WHO scheduled visit of 9 months because there is no further visit around 12 months in the WHO infant EPI schedules. This could also be described as a prolonged variant of the 3 + 0 schedule, which is the final schedule that has been tested in large efficacy trials, based on the efficacy of the African trials of three doses in the first year of life, which were given at 6, 10, and 14 weeks of age in the South African study but at 2, 4, and 6 months because of delays in presentation for vaccination in The Gambia.^{6,7} A limitation of the shortened 3 + 0 schedule for countries with a significant burden of disease caused by serotype 1 is that the extended period of susceptibility to serotype 1 and the invasive nature of that serotype may require prolonged levels of antibody in the second year of life, especially after 18 months of age, so that at least a 6-week, 14-week, plus 9-month schedule may be needed,²⁰² but the effectiveness of this schedule or other prolonged schedules in protection against serotype 1 remains under investigation.

Efficacy and effectiveness

Invasive disease

Several studies have now examined the efficacy of pneumococcal conjugate vaccines in preventing invasive disease. In a double-blind study conducted at NCKP medical centers before licensure of the PCV7, 37,868 infants were randomized to receive either the pneumococcal conjugate vaccine or a meningococcus group C conjugate vaccine as a control.⁴ Study vaccine was given at 2, 4, 6, and 12 to 15 months of age, along with other routine childhood vaccines. The primary outcome measure was the incidence of invasive pneumococcal disease caused by vaccine serotypes. To be included in the main efficacy analysis, invasive disease must have been caused by a vaccine serotype, occurred more than 14 days after the third dose of the vaccine, and occurred in a subject vaccinated according to protocol. Children younger than 16 months were considered to be fully vaccinated if they had received three or more doses of vaccine; children 16 months old or older were considered to be fully vaccinated after receipt of a fourth dose. In addition to the per-protocol analysis, an intent-to-treat (ITT) analysis was performed that included all invasive disease caused by any pneumococcal serotype occurring after randomization, regardless of vaccination status.

In the per-protocol analysis, 40 cases of invasive pneumococcal diseases were seen in the study population. Of these, 39 were in the control group. This represents a vaccine efficacy of 97% (95% confidence interval (CI), 83%-100%; $P < .0001$; Table 25-9). The one vaccine failure was a child who had received four doses of vaccine, yet developed bacteremic pneumonia caused by serotype 19F. In the ITT analysis, there were 52 cases of vaccine-serotype invasive pneumococcal diseases, three of which were in vaccinated children, representing a vaccine efficacy of 94%. The three failures

included the one described above, a case of serotype 19F disease in a child who developed leukemia after vaccination and was receiving immunosuppressive chemotherapy, and a partially vaccinated child who developed a serotype 6B infection 317 days after a single dose of vaccine. Point estimates of serotype-specific efficacy were obtained for four vaccine serotypes and ranged from 85% for serotype 19F to 100% for serotypes 14, 18C, and 23F.

In the prelicensure study, there was no evidence of an increased risk of disease caused by nonvaccine serotypes. Nine cases of invasive pneumococcal diseases caused by nonserotype pneumococci occurred during the study, six in the control group and three in vaccinated children. Only one case was caused by a potentially cross-reactive serotype in a vaccinated child. Overall, in an ITT analysis, including disease caused by both vaccine and nonvaccine serotypes, an 89.1% reduction was seen in the burden of invasive pneumococcal diseases in children who had received at least one dose of conjugate vaccine.

Efficacy of PCV7 also was analyzed separately for the low-birthweight and preterm infants who had been included in the NCKP study.²⁴⁹ Although the study protocol required that patients be vaccinated at outpatient clinics, healthy low-birthweight and preterm infants were eligible once they were discharged from the hospital. No difference in mean age of administration of vaccine resulted for low-birthweight and preterm infants compared with normal-birthweight and full-term infants. For low-birthweight infants who received the control vaccine, the relative risk of invasive pneumococcal diseases was 2.6 compared with normal-birthweight infants, and for preterm infants, the relative risk was 1.6 compared with full-term infants. However, no low-birthweight or preterm recipient of pneumococcal vaccine contracted an invasive pneumococcal disease, as compared with six low-birthweight infants and nine preterm control subjects who received the meningococcal vaccine; the pneumococcal vaccine was therefore 100% efficacious for both groups.

A community-randomized, controlled efficacy trial of PCV7 was conducted between April 1997 and October 2000 among Navajo and White Mountain Apache children,⁵ who have some of the highest rates of invasive pneumococcal disease in the world. As in the NCKP study, meningococcal vaccine was used as a control. A per-protocol analysis was performed of the 5,792 children younger than 2 years who were enrolled in the primary efficacy portion of the study. Eight cases of vaccine-serotype invasive disease occurred in the control group, compared with two in the PCV7 group, yielding an efficacy of 76.8% (95% CI, -9.4% to 95.1%). In an ITT analysis, 11 cases of vaccine-serotype disease occurred in the control group, compared with 2 cases in the PCV7 group, for an efficacy of 82.6% (95% CI, 21.4%-96.1%). This study was stopped early when PCV7 was approved for licensing in the United States, resulting in lower statistical power than planned; however, these efficacy estimates demonstrate that the vaccine provided significant benefit, even in this high-risk population.

The efficacy of PCV9 containing serotypes 1 and 5 in addition to the serotypes in the 7-valent vaccine was tested in a large randomized, double-blind study in South Africa in children with and without HIV infection.⁷ A total of 39,836 children received vaccine or placebo at approximately 6, 10, and 14 weeks of age, and follow-up was continued until 15 cases of vaccine-serotype invasive pneumococcal disease occurred in fully vaccinated HIV-negative children. The vaccine was highly efficacious in this per-protocol analysis: 13 of the cases were in children who received placebo, and two were in children who received PCV7, for an efficacy of 85% (95% CI, 32%-98%). The efficacy was similar in an ITT analysis (83%; 95% CI, 39%-97%; $P = .003$). Efficacy was lower but still highly significant against vaccine-serotype invasive pneumococcal disease in HIV-infected children (65%; 95% CI, 24%-86%; $P = .006$) and against any invasive pneumococcal disease in all children (50%; 95% CI, 23%-68%)

Table 25-9 Efficacy of PncCRM Vaccines Against Invasive Pneumococcal Disease and Efficacy Against Pneumonia

Study	Efficacy estimate (%)	95% CI	Notes
Invasive disease caused by 7-valent vaccine serotypes			
NCKP	94	80 to 98	7-valent PCV7
Intent to treat			
The Gambia	77	49 to 89	9-valent PCV7
Intent to treat			
Navajo and Apache	83	22 to 96	7-valent PCV7
Intent to treat			
South Africa	77	19 to 93	9-valent PCV7
HIV-negative children			
Intent to treat, prolonged follow-up			
Meta-analysis of above five studies	85	75 to 91	Types in 7- valent
Intent to treat			
South Africa	28	– 22 to 58	9-valent PCV7
HIV-infected children			
Intent to treat, prolonged follow-up			
Invasive disease caused by any serotype			
NCKP	89	75 to 95	7-valent PCV7
Intent to treat			
The Gambia	45	19 to 62	9-valent PCV7
Intent to treat			
Navajo and Apache	46	– 6 to 73	7-valent PCV7
Intent to treat			
South Africa	35	– 31 to 68	9-valent PCV7
HIV-negative children			
Intent to treat, prolonged follow-up			
Meta-analysis of above five studies	58	45 to 68	Types in 7- valent
Intent to treat			
South Africa	46	19 to 64	9-valent PCV7
HIV-infected children			
Intent to treat, prolonged follow-up			
Radiographically defined pneumonia			
NCKP	26	7 to 40	7-valent PCV7
Intent to treat			
The Gambia	37	27 to 45	9-valent PCV7
Per protocol			
South Africa	20	3 to 35	9-valent PCV7
HIV-negative children intent to treat			
Navajo and Apache	-21	– 62 to 9	7-valent PCV7
Intent to treat			
Philippines	23	– 1 to 41	11-valent PncD/T
Per protocol			

CI, Confidence interval; HIV, human immunodeficiency virus; NCKP, Northern California Kaiser Permanente; PCV, pneumococcal conjugate vaccine; PncD/T, pneumococcal diphtheria-tetanus vaccine.

Data for Philippines from Lucero MG, Nohynek H, Williams G, et al. HP Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo-controlled trial. *Pediatr Infect Dis J* 28:455-462, 2009. Invasive pneumococcal disease data from Klugman KP, Cutts F, Adegbola RA, et al. Meta-analysis of the efficacy of conjugate vaccines against invasive pneumococcal disease. In: Siber GR, Klugman KP, Makela PH, eds. *Pneumococcal Vaccines*. Washington, DC: American Society for Microbiology Press; 317-326, 2008. Pneumonia data from Madhi SA, Klugman KP. Efficacy and safety of conjugate pneumococcal vaccine in the prevention of pneumonia. In: Siber GR, Klugman KP, Makela PH, eds. *Pneumococcal Vaccines*. Washington, DC: American Society for Microbiology Press; 327-337.

and HIV-positive children (53%, 95% CI, 21%-73%). The incidence of invasive pneumococcal disease caused by antibiotic-resistant pneumococci also decreased by 56% (95% CI, 21%-77%). The decrease was most prominent in HIV-infected children, who nonetheless continued to have a higher rate of infection with resistant strains than HIV-negative children. In a further analysis of long-term efficacy after 6.16 years of follow-up, efficacy remained high at 77.8% (95% CI, 34%-93%) but declined from 65% to 39% among HIV-infected children (95% CI, -8% to 65%). Vaccine efficacy was, however, retained overall against serotype 6A, and this protection was clear even in the HIV-infected children (vaccine efficacy [VE] 79%; 95% CI, 39%-93%).²⁹⁵

The same 9-valent vaccine was tested for its efficacy against invasive pneumococcal disease in a large, randomized, double-blind study in the Gambia.⁶ Infants between 6 weeks and 1 year of age were given three doses of vaccine or placebo mixed with DPT/Hib vaccine; hepatitis B and oral polio vaccines were given concurrently. Vaccine efficacy against any vaccine-serotype invasive pneumococcal disease was 77% (95% CI, 51%-90%) and against vaccine-serotype meningitis or sepsis was 92% (95% CI, 44%-100%). Efficacy against invasive pneumococcal disease of all serotypes was 50% (95% CI, 21%-69%), reflecting an absolute reduction of about two episodes per 1,000 child-years. Although there was a relative reduction in invasive pneumococcal disease caused by vaccine-related serotypes and a relative increase caused by nonvaccine serotypes, neither difference was significant. In the placebo group, 65% of invasive pneumococcal disease was caused by vaccine serotypes and 48% was caused by serotypes contained in the 7-valent vaccine.

At the time this chapter goes to press the first results of the PCV10 conjugate vaccine against IPD were presented from a large double-blind cluster randomized trial in Finland. There were 78 clusters within which 47,369 children less than 19 months of age were enrolled. Among children less than 7 months of age at enrollment, the children in 26 control clusters received hepatitis B vaccine as a control and in surveillance to January 31, 2012 there were 12 cases of IPD due to vaccine types among them for an incidence of 56.4 cases of vaccine type IPD/100,000 children. Among 30,528 vaccinated children in the 52 clusters where PCV10 was given, there were no cases among vaccinees in 26 clusters receiving 3 + 1 doses and only 1 case of serotype 7F disease among the 26 clusters receiving a 2 + 1 schedule at 3, 5 and 12 months. The single failure was just 12 days after the first dose of vaccine. These data translate to a vaccine efficacy of the 3 + 1 schedule of 100% (95% CI 83%-100%). The efficacy of the 2 + 1 schedule was 92% in the intent-to-treat analysis (95% CI 58%-100%).^{295a}

Pneumonia and other respiratory infections

Several of the invasive pneumococcal disease studies also examined vaccine efficacy against pneumonia (see Table 25-9). In the NCKP trial, pneumonia was a secondary outcome measure. Cases of pneumonia were identified by the presence in the NCKP database of a diagnosis of pneumonia, "bronchopneumonia", or "viral pneumonia" by the treating physician in the outpatient, emergency room, or hospital setting in which the patient was seen. Based on the interpretations of radiologists at the point of care, the conjugate vaccine was found to significantly reduce the number of episodes of pneumonia in which there was a positive film to 8.3 per 1,000 person-years, for an estimated efficacy of 17.7% (95% CI, 4.8-28.9; $P = .01$).⁵⁴ Radiographs obtained for this study were then reevaluated using the criteria established by the WHO in 2001 for interpreting chest radiographs, which are intended to standardize radiologic diagnoses for epidemiologic purposes.³⁷⁰ Of the 2,841 original sets of radiographs, 2,446 were digitized and analyzed according to the WHO criteria. The standardization increased the vaccine efficacy estimate to 25.5% (95% CI, 6.5%-40.7%; $P = .011$).⁸

In the South African trial of PCV9,⁷ the efficacy of the vaccine in reducing radiographically defined pneumonia was a primary end point and was 20% (95% CI, 2%-25%; $P = .03$) in the intent-to-treat analysis and 25% in fully immunized children without HIV infection (95% CI, 4%-41%). This reduction was in addition to any protection afforded by the Hib vaccine, which was provided to all subjects. The vaccine efficacy did not reach statistical significance in children infected with HIV (13%; 95% CI, -7% to 29%; $P = .19$), but subsequent secondary analyses showed that only 39% of the pneumonia prevented by the vaccine was included in the radiographically defined end point. In an intent-to-treat analysis of clinical pneumonia excluding bronchiolitis, vaccine efficacy among HIV-infected children remained at 15%, but because of the larger number of children meeting this definition (379 vaccinees vs. 446 control subjects), the protection was significant (95% CI, 5%-24%; $P = .004$).³⁷¹

Pneumonia was also a primary outcome measure of the Gambian trial of PCV9.⁶ Pneumonia was defined radiographically as the presence of a dense or fluffy opacity that occupied some or all of the lung, presence of fluid in the lateral pleural space, or both and defined clinically as a history of cough or breathing difficulty of less than 14 days' duration, with a raised respiratory rate or chest-wall in-drawing. Overall, the vaccine reduced first episodes of radiologic pneumonia by 37% (95% CI, 27%-45%) and reduced first episodes of clinical pneumonia by 7% (95% CI, 1%-12%). The absolute reduction in radiographic pneumonia was to 15 cases (95% CI, 10%-19%) per 1,000 child-years in the per-protocol analysis, more than seven times higher than the absolute reduction in invasive pneumococcal disease (≈ 2 per 1,000 child-years), indicating that there is a high burden of preventable pneumonia in this population. In addition, the vaccine resulted in a 16% reduction in mortality in young children, suggesting that pneumococcal pneumonia and bacteremia contribute to more deaths than is generally recognized.

The PCV9 has also been shown to reduce respiratory infections other than pneumonia. In a study of children 12 to 35 months old attending day care in Israel,³⁷² vaccinated children had a relative risk of upper respiratory infection, including rhinorrhea, pharyngitis, and sinusitis, of 0.85 (95% CI, 0.76-0.96; $P = .009$) and of lower respiratory infection, including bronchitis, cough, and asthma as well as pneumonia, of 0.84 (95% CI, 0.72-0.98; $P = .024$). The effectiveness of the vaccine in preventing these infections indicates that *S. pneumoniae* plays a role in diseases more commonly associated with viral infection. This role has been supported by evidence from the large South African efficacy trial^{373,374} in which vaccination with PCV9 significantly lowered the risk of confirmed viral pneumonia by 22% to 58%, depending on the causative virus, presumably because pneumococcal coinfection contributes to the pathogenesis of a large proportion of pneumonias thought to be viral. The vaccine prevented 45% of confirmed hospitalizations caused by influenza,³⁷³ which suggests a potential role for PCV in protection from pandemic influenza, in which postinfluenza pneumococcal mortality may be significant.³⁷⁵ Another secondary analysis of the South African trial data suggests that children with culture-confirmed tuberculosis may also be at increased risk of pneumococcal pneumonia, which is also prevented by the PCV9 vaccine.³⁷⁶

In the only randomized trial to date of pneumococcal conjugate vaccination in Asia, an 11-valent investigational vaccine conjugated to tetanus and diphtheria toxoid, which has not been licensed but was manufactured for the trial by Sanofi Pasteur, was compared with placebo in 12,191 children in Bohol, Philippines. The vaccine efficacy against radiologically confirmed pneumonia in fully immunized children (three doses at least 1 month apart between 6 weeks and 6 months of age) was 23% (95% CI, -1% to 41%; $P = .06$). Significant protection was seen in the first year of life (34%) but not the second year (3%).⁹ The PCV10 vaccine conjugated to protein D has been subject to a clinical trial in Argentina, Colombia, and Panama. The results have not been published at the

time this chapter goes to press but numerous presentations have shown an efficacy against the WHO confirmed definition of pneumonia³⁷⁰ by intent-to-treat analysis of 23.4% (95% CI 9%–36%) and 26% (95% CI 8%–40%) in fully immunized children.³⁷⁷

Acute otitis media

Streptococcus pneumoniae, together with nontypeable *Haemophilus influenzae* (NTHi), is the most commonly reported bacterial pathogens in acute otitis media (AOM). *Streptococcus pneumoniae* is isolated from the middle ear fluid (MEF) of less than 20% to 60% of patients.^{46,47,378} By choosing 7 to 13 common serotypes, AOM pneumococcal serotypes could be covered from $\approx$ 50% to greater than 90% of cases.³⁷⁸ Thus in theory, pneumococcal vaccines could cover between 10% to greater than 50% of all cases of AOM. However, the reality is more complex, because several, sometimes contradictory factors play a role in the overall effectiveness of PCV against AOM.

PCV large-efficacy trials were conducted in three sites, each with different designs, and thus not comparable for many outcomes. One trial was conducted in the Northern California Kaiser Permanente (NCKP) Health Services,^{4,379} using PCV7-CRM conjugate. The second was conducted in Finland (the FinOM study) with two vaccines: PCV7-CRM and PCV7-OMPC.^{11,185} The third was conducted in the Czech Republic, using PCV11-protein D vaccine (PHiD-CV) (the POET study).¹⁰ All three studies were double blinded, randomized, controlled studies, with an arm that did not receive any PCV. In all three studies, healthy infants received three PCV doses during the first 6 months of life and a booster early in the second year of life (2, 4, 6, and 12 months or 2, 4, 5, and 12 to 15 months of age).

In the NCKP trial, infants were enrolled over a period of $\approx$ 3 years and were followed between 8 months to 3.5 years of age. Although the trial was not primarily intended to look at AOM, computerized data on AOM visits could be used to assess the effect of PCV7-CRM on AOM visits. In contrast, the FinOM and POET studies were designed primarily to determine the effect of PCV on AOM. In the FinOM study, the children were followed up to age 24 months, and diagnosis of AOM was standardized. The FinOM study was somewhat complex because one arm received PCV7-CRM, another arm received PCV7-OMPC, and a third arm received no PCV (the control arm). Furthermore, the PCV7-OMPC arm was further randomized after three PCV7-OMPC doses to receive either a fourth PCV7-OMPC or a 23-valent polysaccharide vaccine (PS-23) dose as a booster.^{11,185} In the POET study, follow-up continued until age 24 to 27 months. The diagnosis of AOM was standardized, but the follow-up in the POET study was passive because parents were advised to consult their pediatrician if the child was sick, had ear pain, or had spontaneous ear discharge. Furthermore, the trigger to be defined as a case was a tympanocentesis after the child was referred to the ear-nose-throat (ENT) physician, thus probably enriching the outcome cases with severe, recurrent, or nonresponsive AOM. Therefore, because of the very different methodology in the POET study compared with the NCKP and the FinOM studies, the POET study results cannot be directly compared with the two former ones.³⁸⁰

The NCKP and FinOM studies showed that PCV7-CRM could reduce overall AOM by $\approx$ 6% to 7% (see Table 25-10). In contrast, the PCV7-OMPC did not show any reduction in overall AOM. The POET study, which is probably measured by a different outcome than the FinOM and NCKP studies in several aspects, showed an overall reduction of 34% in AOM episodes with the PCV11-protein D vaccine. The reduction in AOM caused by vaccine-type serotypes, as measured by tympanocentesis or culture of spontaneous draining ears, was quite similar between the studies, ranging between 56% to 67%. PCV7-CRM and PCV11-protein D vaccines also reduced the cross-reactive serotype 6A, while the PCV7-OMPC did not show

any cross-protection. In the FinOM study, the administration of both PCV7-CRM and PCV7-OMPC was associated with a tendency to increase occurrence of AOM caused by *Moraxella catarrhalis* and *H. influenzae*. This was not the case in the POET study, where AOM caused by NTHi decreased by 35%.¹⁰ Whether the reduction of NTHi otitis was related to the peculiar study design or is a direct effect of the *H. influenzae* protein D used for the conjugation of the pneumococcal polysaccharides still remains to be determined. PCV7-CRM had an efficacy of $\approx$ 9% in reducing recurrent AOM,^{4,11} with a trend to an even higher reduction in children showing frequent recurrences. The greatest effect of PCV7-CRM was seen on middle ear effusion, necessitating insertion of ventilation tubes: it reached a 20.1% reduction (95% CI, 1.5–34.2) in the NCKP study⁴ and 39% in the FinOM study.³⁸¹ The PCV11-protein D showed a 56% reduction in recurrent AOM, but this finding was not statistically significant and could be also attributed to the particular study design of the POET study. The PCV11-protein D vaccine did not protect against AOM caused by serotype 3, and this was the reason behind changing the formulation of the protein D conjugate vaccine to contain 10 instead of 11 serotypes.

An additional trial was conducted in an underprivileged and somewhat more compromised population in the United States: the Navajo and White Mountain Apache population.³⁸² In this double-blind study, infants were randomized to receive either PCV7-CRM or meningococcus C-CRM vaccine. The methodology of the study did not allow it to reach statistically significant conclusions, but its findings support those of the three larger-scale studies conducted with PCV7-CRM described above. The intention-to-treat efficacy findings were overall otitis media, -3.3% (95% CI, -21.4 to 12.0); number of medical visits resulting from severe episodes, 13.7% (95% CI, -3.4 to 49.5); and ventilation tube insertion (22.2% [95% CI, -215.7 to 83.0]). Thus, although not statistically significant, the trend toward higher efficacy with severe outcome was kept in this study, as in the previously described studies. Furthermore, when cultures were taken from spontaneously draining ears, 11 isolates were of vaccine-type (VT) serotypes, and 8 were in the control group (64% efficacy, 95% CI, -34% to 90%), again in the order of magnitude observed for VT-serotype efficacy in the other studies.

Three prelicensure efficacy trials were conducted in toddlers. The first was a double-blind, randomized study in healthy Israeli day-care center toddlers attendees who received PCV9 or meningococcus C-CRM vaccine (two doses for toddlers 12–17 months old and one dose for toddlers 18–35 months old) and had $\approx$ 18 encounters per child during the successive 2 years (monthly visits in first year and bimonthly visits the year after).¹² The parents responded to a questionnaire that included data on respiratory infections, as well as AOM episodes. Although the AOM diagnosis was not confirmed by study physicians and not standardized, the double-blind approach permitted a comparison between the two arms. There was a 17% reduction in the number of episodes in the PCV9 recipients and a reduction of 20% in the length of time the children were on antibiotic treatment for AOM.³⁷² Two additional studies were conducted in the Netherlands and in Belgium in toddlers and young children (aged 1–7 years) with a history of greater than or equal to two AOM episodes in the year before enrollment.^{383,384} The children were randomized in a double-blind manner to receive either PCV7-CRM (two doses in children 1–2 years old and one dose in children 3–7 years old, followed by PPV23 6–7 months later) or hepatitis A and B vaccines. The children were followed for 24 weeks by the family physicians or specialists, when symptomatic. In both studies, PCV7-CRM did not reduce AOM cases, despite the reduction seen in pneumococcal AOM.³⁸⁴ In the Dutch study, there was a reduction of 33%, with a 56% reduction in vaccine serotypes and a 17% reduction in nonvaccine serotypes. However, none of these values were

Table 25-10 Double-Blinded Efficacy Studies Against Acute Otitis Media Before the Introduction of Vaccine to Widespread Use

Author	Ref	Location	Vaccine	Subjects	Reduction in vaccine-type serotypes (95% CI)	Reduction in pneumococcal AOM (95% CI)	Reduction in overall AOM (95% CI)	Cross-reacting (95% CI)	Nonvaccine serotype (95% CI)	Recurrent AOM	Remarks
Black	4	California	PCV7-CRM7	Healthy infants	67% (P = .077); PP 65% (P = .035); ITT	ND	ND	ND	ND	9% (3, 15); PP: 9% (4, 14); ITT	
Eskola	11	Finland	PCV7-CRM	Healthy infants	57% (44, 67); PP 54% (41, 64); ITT	34% (21, 45); PP	6% (-4, 16); PP	51% (27, 67); PP	-33% (-80, 1); PP	16% (-6, 35); PP: 9% (-12, 27); ITT	
Fireman	379	California	PCV7-CRM7	Healthy infants	ND	ND	7% (4, 9); PP: 6% (4, 8); ITT	ND	ND	ND	
Kilpi	185	Finland	PCV7-OMP7	Healthy infants	56% (44, 66); PP	25% (11, 37); PP	-1% (-12, 10); PP	5% (-47, 25); PP	27% (-70, 6)	ND	
Pymula	10	Czech Republic	PCV11-protein D	Healthy infants	58% (41, 69); PP	52% (37, 63); PP	34% (21, 44); PP	66% (22, 85); PP	9% (-64, 49); PP	56% (-2, 8); PP	Outcome measured in children attending an otorhinolaryngologist for tympanocentesis
Dagan	385	Israel	PCV9-CRM	Toddlers attending day-care centers	ND	ND	17% (-2, 33); ITT	ND	ND	ND	
Veenhoven	384	Netherlands	PCV7-CRM	Toddlers and young children with recurrent AOM	52% (P = -.21)	34% (P = .02); PP	-29% (-62, -2); PP: -25% (-57, 1); ITT	ND	21% (P = .44); PP	ND	
Van Kempen	383	Belgium	PCV7-CRM	Toddlers and young children with recurrent AOM	ND	ND	-16% (-96, 3); PP	ND	ND	ND	

AOM, Acute otitis media; CI, confidence interval; CRM, protein carrier in conjugate vaccine; ITT, intention to treat; ND, not determined; PCV, pneumococcal conjugate vaccine; PP, per protocol; Ref, reference.

statistically significant, probably because of the small numbers. The findings of the Dutch and Belgium studies suggest that when a recurrent AOM is established, PCVs may not be effective against disease, or even against development of effusion.³⁸⁵

It is not easy to assess the reduction of AOM burden once PCVs are implemented, for several reasons. First, AOM is a disease caused not only by pneumococcus and, in most cases, tympanocentesis is not performed, and thus the role of pneumococcal reduction cannot be assessed in most studies. Second, AOM is difficult to diagnose with the current skills of the practicing physicians, and overdiagnosis as well as underdiagnosis are common. Third, because tympanocentesis is not accepted as a routine procedure in most practices, it is often performed in selected cases (ie, nonresponsive AOM or complicated AOM). The reduction in pneumococcal AOM caused by the vaccine serotypes results in a *relative* increase in the proportion of other pathogens (ie, non-VT pneumococcus, *H. influenzae*, and *M. catarrhalis*), leading to the often false perception of replacement disease. The complex process described above led to confusing observations in the short-term post-PCV7-CRM implementation period in the United States. Several studies looking at AOM during that period reported reduced proportions of VT serotypes, increased proportions of non-VT serotypes and nonpneumococci (ie, *H. influenzae* and *M. catarrhalis*), and reduction of antibiotic-resistant pneumococci.^{46,386-388} However, because of the limitation mentioned above, the studies could not appropriately document the true vaccine effect on AOM incidence. Similar observations were made in France.^{389,390} On the other hand, a national study in the United States, showed that already by 2002 to 2003 (2-3 years post-PCV7-CRM introduction), rates of otitis media-related outpatient medical care visits of children younger than 2 years had decreased by 20% compared with rates before vaccine introduction.³⁹¹ For some high-risk populations, such as the American Indians and Alaska natives, the figures were a bit more confusing: The rates decreased overall for these children in the US from 138 per 100 children/year (in 1994-1996) to 89 per 100 children/year (during 2003-2005); however, for the Alaska region, no decrease was seen during the period (the number of episodes increased from 158 to 181, respectively, per 100 children/year).³⁹² Another study found a 17% and 28% decline in frequent AOM in two birth cohorts from Tennessee and upstate New York shortly after PCV7-CRM introduction.³⁹³ A study comprising greater than 500,000 person-years of children younger than 2 years found a reduction of 42.7% and 41.9% in ambulatory visits related to AOM and antibiotic-prescribing related to this entity, respectively.³⁹⁴

The much higher benefits observed in the postimplementation large studies,^{391,393,394} compared with the benefits found in the efficacy trials in the prevaccine implementation period, may be explained by several factors. First, rapid reduction to the near elimination of the circulation of VT serotypes by the PCV7 in the United States reduced the risk for AOM caused by these serotypes to almost nil.³⁹⁵ Second, these studies measured *all visits associated* with AOM rather than *incidence* of AOM (the latter was the outcome in the efficacy studies). Because even in the efficacy studies, PCV7-CRM prevented complicated AOM more successfully than simple AOM,^{379,381,396} it is understandable that the complicated cases were associated with a significantly higher frequency of medical service use, such as clinic visit, otorhinolaryngology visits, ventricular tube insertion, and more. Third, the disappearance of VT serotype from the circulation could be associated with a significant reduction of very early AOM cases in children too young to be vaccinated,^{395,397} reducing early damage to the middle ear, potentially reducing the resulting recurrent AOM.³⁹⁸

PCV7 was introduced in countries other than the United States a few years later than in the United States, but results from these countries support the post-PCV7 implementation findings from the United States. In Canada, a 13.2% reduction in claims for otitis media attributable to PCV7 was reported

3 years after implementation of PCV7 in children younger than 5 years.³⁹⁹ In Italy, PCV7 was implemented in the Liguria administrative region in 2003, with a 38% reduction in hospitalizations associated with AOM in children younger than 2 years.⁴⁰⁰ In Australia, in the 2.5 years after routine PCV7 introduction, a significant adjusted reduction in myringotomy with ventilation tubes insertion was seen in 23%, 16%, and 6% of children younger than 1, 1, and 2 years old, respectively.⁴⁰¹ Thus, there is growing evidence that widespread implementation of PCV7 reduced AOM disease burden, at least in developed populations.

Despite the apparent success of PCV7, there are several outstanding problems and uncertainty with regard to the current situation. First, the extent of replacement disease is not yet determined in AOM. Numerous reports point to at least two important serotypes that have been important in AOM even before PCV7 implementation and which became dominant postimplementation: serotypes 19A and 3.^{378,386,390,395,397,402-404} Furthermore, serotype 19A is now often multidrug resistant. The association of PCV7 with the increase observed in serotype 19A and 3 could be derived either from the replacement phenomenon (meaning that vaccine is associated with increasing rates of AOM caused by this serotype) or by accentuating the importance of these serotypes because of the decrease of VT serotypes by the vaccine. The potential of new generation vaccines with extended serotype spectrum in further reducing AOM burden is obvious.

Effect on carriage

Direct effect of PCVs on colonization

The first study demonstrating that a PCV could reduce colonization of the serotypes included in the vaccine was conducted in Israel and published in 1996.⁴⁰⁵ In this study, one and two doses of PCV-OMPC7 were compared with a single PPV23 dose in toddlers 12, 15, or 18 months of age. The PPV23 group did not have any effect on carriage, in contrast to the group receiving PCV-OMPC7, in which a marked reduction was observed in a follow-up that lasted 1 year. An increase in carriage of serotypes not included in the vaccine (non-VT) was observed 1 year after vaccination. This study led to the assumption that PCVs can reduce carriage of VT serotypes and may increase the carriage of non-VT serotype (replacement phenomenon). The study also supported previous observations that nonconjugate polysaccharide vaccines are not capable of reducing carriage.⁴⁰⁶ Further clinical trials confirmed that observation, using a variety of conjugates, age groups, locations, and schedules. Some representative studies are summarized in Table 25-11.^{235,245,407-409} The overall pattern that could be observed in these studies is a reduction in VT carriage, sometimes seen only after the booster dose, and an increase in the carriage of non-VT, so that the overall carriage rate did not change significantly or was slightly reduced.

Several trials were conducted in toddlers in the 1990s using either PCV7 or PCV9. In a series of studies in day-care center attendees in Israel,^{27,410,411} a reduction in both acquisition and prevalence of VT (and serotype 6A) serotypes were seen in PCV9 recipients, compared with control subjects [receiving meningococcus-C-CRM vaccines]. At the same time, a marked increase of prevalence and acquisition of non-VT serotypes was also observed. No effect on duration of carriage was seen. The effect of the vaccine on carriage persisted for the duration of the follow-up (2 years). Serotype-specific protection against increased carriage of serotypes 6A, 6B, 9V, 14, and 23F could be demonstrated.²⁷ In the Netherlands and Belgium,^{383,384} PCV7, followed by a PPV23 booster, administered to children 1 to 7 years old with recurrent AOM resulted in a marked reduction of VT carriage, with an increase in non-VT carriage.

Table 25-11 Clinical Trials Testing PCV Effect on Colonization when Administered in Infancy

Location	Reference	Vaccine	Schedule	Assessed (months postprimary)	n Children			Colonization VT (%)			Colonization non-VT (%)		
					PCV	Control	Vaccine	Controls	P value	Vaccine	Controls	P value	Comments
Israel	407	PnTT4	2, 4, 6, 12 mo*	1, 6, 7 combined	25	25	10	27	.014	No clear pattern	11	(-)	VT including 6A
Israel	407	PnDT4	2, 4, 6, 12 mo*	1, 6, 7 combined	25	25	5	27	.001	No clear pattern	11	(-)	VT including 6A
United States	409	PCVCRM7	2, 4, 6, 12 mo	1	54	31	11	7	NS	17	11	NS	
				6	54	31	17	18	NS	17	11	NS	
				7	54	31	10	21	NS	10	7	NS	
The Gambia	235	PCVCRM9	2, 3 mo	1	102	100	54	64	NS	45	33		
			4 mo	5	102	100	61	74	NS	28	16		
South Africa	245	PCVCRM9	6, 10, 14 wk	1	242	239	No difference	No difference		No difference			
				6	242	239	18	36	.001	36	25	.007	
The Gambia	408	PCVCRM5	2, 3, 4, 18 mo*	20	26	160	50	90	<.001	77	43	NS	
Czech and Slovakian Republics	10	PCV-protein D-10	2, 3, 18 mo* 3, 4, 5, 12 mo	20 10-13	30 177	160 175	67 6	90 11	.002 NS	43 7	43 8	NS NS	

*Booster with a PPV23.

PnTT4 = Tetraivalent PCV (6B, 14, 19F, 23F) conjugated to tetanus toxoid.

PnDT4 = Tetraivalent PCV (6B, 14, 19F, 23F) conjugated to diphtheria toxoid.

PCVCRM5 = Pentavalent PCV (6B, 14, 18C, 19F, 23F) conjugated to CRM197.

NS, Not significant; VT, vaccine type.

Recently, because of the trend to reduce the number of doses of PCVs in various universal programs, an interest in the potential effect of a regimen with a lower number of doses (compared with the gold standard of three doses in infancy and one booster dose) in second year led to several studies. The shortened schedules could be of concern because two studies conducted in Israeli toddlers²⁷ and in American Indian infants and toddlers^{34,5} showed an inverse correlation between serotype-specific anti-capsular IgG and the risk for nasopharyngeal acquisition of the corresponding pneumococcal serotype. Two pivotal randomized studies with PCV7 versus no vaccine were conducted in the Fiji Islands and in Israel. In the Israeli study, children were randomized to receive either a gold standard regimen of 2, 4, 6, and 12 months (3 + 1), a reduced-dose regimen of 4, 6, and 12 months (2 + 1), and a no-booster regimen of 2, 4, and 6 months (3 + 0).^{230,412} The children were seen at ages 2, 4, 6, 7, 12, 13, 18, 19, 24, and 30 months, and a nasopharyngeal culture was obtained at each visit. The 2 + 1 regimen showed a marked reduced immune response in infancy, especially to serotype 6B, associated with significantly higher acquisition rates of serotypes 6B and 6A before the booster. The overall effect on VT (+ serotype 6A) was a slight increased acquisition during infancy in the 2 + 1 group. However, the effect was seen no longer after booster administration. On the other hand, when the 3 + 0 regimen was compared with that of the 3 + 1 regimen (without a booster vs. with a booster), no differences in carriage prevalence or acquisition rates were observed during the entire study period (until age 30 months). This study suggested that regimens with only two infant doses (of CRM-containing vaccine) may be successfully introduced to universal vaccination programs without a significantly reduced effect on carriage (and therefore on herd immunity) on condition that a booster is given at the beginning of the second year of life. On the other hand, the study suggested that if a three-dose regimen (when the three doses are given at a 2-month interval) is applied, a booster dose may not be needed, at least when the serotypes included in the PCV7 are considered.

The second pivotal study was conducted in Fiji.^{228,414} In that study, infants were randomized to receive either no PCV7 or PCV7 at one dose (14 weeks of age); two doses (6 and 14 weeks); or three doses (6, 10, and 14 weeks of age). Nasopharyngeal cultures were obtained at 6, 9, 12, and 17 months of age. When compared with no PCV, any of the regimens showed reduction of carriage, but the carriage prevalence was lower as higher numbers of doses were given. The cumulative proportion of infants carrying PCV7 serotypes was greater than 50% with no dose and $\approx$ 35%, $\approx$ 28%, and $\approx$ 20% with one, two, and three doses, respectively.⁴¹⁴ Of interest, the children in each group were randomized to receive a PPV23 booster at 12 months or no booster. No effect on carriage of the PPV23 was seen in any regimen, despite a marked response in antibody titer.^{414,415} This study thus suggested that for the fastest effect on herd immunity a three-dose PCV regimen should be given, but any regimen of PCV (including even a one-dose regimen) may have herd immunity effect if the vaccine is universally used. On the other hand, the study suggests that a PPV23 booster may not be useful in reducing carriage even in children primed with a PCV. Support for the notion that a regimen using a lower number of doses can successfully reduce carriage was also found in a study from the Netherlands.⁴¹⁶ In that study, both a 2 + 1 regimen (2, 4, and 11 months of age) or a 2 + 0 dose (2 and 4 months of age) of PCV7 successfully reduced VT serotypes carriage compared with no vaccination. At 18 months of age the 2 + 1 group had lower carriage than the 2 + 0 group, but by age 24 months of age, no difference in carriage rates between the 2 + 0 and 2 + 1 group was seen, and both groups had significantly lower rates than the group that was not vaccinated.

The question with regard to the duration of protection from carriage acquisition is still not fully answered. A study

was conducted in the United Kingdom to assess whether the reduction in nasopharyngeal carriage of VT serotypes induced by PCV7 to infants persisted beyond age 2 years of age. The study was conducted as an unblinded controlled study in children 2 to 5 years old who received three PCVCRM7 doses in infancy and a PPV23 booster at 13 months of age versus unimmunized control subjects. Nasopharyngeal cultures were taken in the summer and the winter. In the summer, the rates of VT-serotype carriage in vaccinated and control subjects were 10.0% and 13.5%, respectively, and in the winter, the rates were 30.0% and 31.5%, respectively. Thus, no real difference could be found between vaccinated and control subjects in VT serotypes (or overall pneumococcal) carriage at this age. However, the role of PPV23 versus a PCV as booster was not assessed. In South Africa, long-term carriage after a primary series of three doses (6, 10, and 14 weeks of age) of PCVCRM9 or placebo was assessed. A random subset of children, who had received three doses of study vaccine per protocol during the trial, was enrolled to the long-term carriage study in a fashion blinded to the study personnel. It was found that by age 5.3 years, the PCV9 no longer reduced nasopharyngeal colonization by VT serotypes. In addition, HIV-infected children had a higher prevalence of colonization by *S. pneumoniae* (71.6%) than did HIV-negative children (50.9%). A nested study in American Indian children 1 to 7 years of age who had participated in a group-randomized efficacy trial reported that 27 months postvaccination children from communities randomized to receive PCV7 had a lower carriage prevalence than the control subjects: 10.3% versus 17.1% ($P = .01$).⁴¹⁷ Thus, it seems that protection from acquisition of carriage can be achieved for some limited time (probably 2-3 years) after a full PCV schedule, but additional studies are needed.

PCV impact on carriage seems to be mediated by protection against acquisition or perhaps density of carriage by antibody and perhaps mucosal memory B cells.⁴¹⁸ Duration of carriage may be antibody-independent, Th17 cell-mediated immunity, at least in the mouse.³⁶⁸

Thus, as for direct effect of PCV7s on carriage, an overall reduction of carriage of VT serotypes can be attributed to PCVs, with a parallel increase in non-VT serotypes (termed replacement). This phenomenon is expected to be of great magnitude, resulting in herd immunity against vaccine serotype disease on the one hand, but a potential for replacement disease on the other hand. It is understandable that the magnitude of the effect is dependent on vaccination coverage.

Indirect effect of PCV on pneumococcal colonization

The reduction of VT serotypes and the replacement by non-VTs, instigated in the nasopharyngeal flora by vaccination do not exist in isolation.⁴⁰⁶ Pneumococci are constantly on the move in the population, being transmitted and acquired at high rates, especially in young children. These dynamics in the effect of vaccine were first demonstrated in Israel in a series of studies where vaccination of day-care center attendees reduced carriage of VT pneumococcus in their younger siblings.^{411,419} In a randomized double-blind study, 262 day-care center toddler attendees, aged 12 to 35 months, each received a PCV9 vaccine or a meningococcus C-CRM vaccine. The children were followed for carriage of *S. pneumoniae* for 2 years. Forty-six younger siblings of the day-care attendees who were younger than 18 months were also enrolled, and nasopharyngeal cultures were obtained monthly for *S. pneumoniae*. Of 306 cultures obtained from the younger siblings, 151 (49%) were positive for *S. pneumoniae*. In siblings of PCV9 recipients, 21% of all cultures were positive for VT serotypes versus 34% of the siblings of control vaccine recipients ($P = .017$). For non-VT serotypes, a trend for the reverse picture was seen: 19% versus 13% in the PCV9

recipients versus control vaccine, respectively ($P = .15$). The acquired VT serotypes were carried for a shorter period of time among siblings of PCV9 recipients than among the siblings of control vaccine recipients (1.6 ± 0.75 child-months vs. 2.21 ± 1.53 child-months), serotype 6A (1.33 ± 0.52 vs. 2.33 ± 2.31) but not for non-VT (1.38 ± 0.74 vs. 1.31 ± 0.7). There was a significantly reduced carriage rate and duration for antibiotic-resistant *S. pneumoniae*.

A group-randomized efficacy trial of PCV7 was conducted in the Navajo and Apache reservations.⁴²⁰ The randomization was done by clusters defined by geography and population size to allocate communities with significant social interactions of adults and children to the same randomization unit and to allocate communities with minimal social interaction to different randomization units. Each of the entire communities (units rather than individuals) was randomized to receive either PCV7 or meningococcus C-CRM vaccine in a double-blind manner. There was a significantly lower carriage rate of VT serotypes among the vaccinated children compared with the placebo recipients in the communities allocated to no vaccination.⁴²⁰ Furthermore, even when the vaccinated children were carriers of VT serotypes, they were less densely colonized with VT serotypes than control vaccinees [odds ratio (OR) 0.61 [95% CI, 0.38-0.99]].⁴²¹ In these children, the highest density degree of VT carriage was found in 53.6% of vaccinated children versus 67.5% among control children; 22.8% and 11.6%, respectively, were colonized with the lowest degrees of density. Adults and unvaccinated children younger than 5 years living in households with a PCV7 vaccinee were less likely to be colonized with VT serotypes (OR for adults 0.57 [95% CI, 0.33-0.99]; OR for children 0.57 [95% CI, 0.26-0.98]) than were those living in a household with control vaccinees. No such effect was seen in children age 5 to 17 years. Decreases in VT serotypes were offset by increases in carriage of non-VT. Among adults, those living in a household with a trial participant who was colonized with vaccine-type pneumococcus and randomized to receive PCV7 were less likely to be colonized with the same serotype than those in the households randomized to receive the control vaccine (OR 0.34 [95% CI, 0.11-0.99]), suggesting that even with carriage of VT, children receiving PCV7 were less infectious than unvaccinated children.

A study in the Gambia investigated the effect of PCV9 on carriage in vaccine recipients and their younger siblings.⁴²² In this very crowded population, no reduction of carriage of VT-related serotype or no increase in carriage of non-VT serotypes was seen in the younger siblings of PCV9 recipients compared with siblings of placebo recipients (RR 0.95 [95% CI, 0.78-1.16], 0.97 [95% CI, 0.73-1.29], and 1.03 [95% CI, 0.87-1.22] for VT serotypes, VT-reduced serotypes, and non-VT serotypes, respectively). This may suggest that in areas with extensive *S. pneumoniae* colonization and very high transmission rate, indirect protection of young infants may not be as effective as in industrialized countries. A follow-up study in the Gambia has, however, provided evidence of herd immunity in adults when the children received PCV7.⁴²³

With time elapsed after introduction of PCV vaccination, a new postvaccination type of flora becomes prevalent in the population and spreads beyond the vaccinated age group to younger infants and adults. After the introduction of PCV7 in the United States, the first demonstrations of indirect effect on a population level were published from Massachusetts and Alaska.⁴²⁴⁻⁴²⁶ In each study, the overall pneumococcal carriage among children younger than 5 years remained fairly constant throughout the time period, lower in Massachusetts (23%-26%) and higher in rural Alaska (5%-60%); but the percentage of VT pneumococci among them decreased by 60% to 80%. The decrease of VT carriage was greatest in children younger than 5 years (the majority of whom would have received PCV).

Additional studies from various sites showed a decline in carriage of VT serotype and increase in non-VT serotypes in children younger than 5 years, after introduction of PCV7.⁴²⁷⁻⁴³¹ However, post-PCV introduction, it is difficult to separate direct effect on carriage from indirect effect even in vaccinated children, because the vaccine efficacy is not complete, and reduced exposure to VT serotype, through indirect protection is also important. Later reports show extensive effects of PCV7 introduction on all age groups in the United States and other countries in which the vaccine was introduced. Postvaccine, dramatic reduction in carriage in older children and adults was reported in several reports from the United States^{425,432} and Canada.⁴³⁰ Similarly, reduction in carriage of VT in neonates and infants too young to be vaccinated was also reported.⁴³³ In addition, unvaccinated children in the age targeted for vaccination also showed similar trends.⁴³¹ In all the reports of indirect effects of PCVCRM7 on reduction of VT serotypes, increase in carriage of non-VT was seen at the same time.

The serotypes found as replacement colonizers largely represent the non-VTs seen in the area before vaccination, that is, the pneumococcal reservoir available to be transmitted. The non-VT serotypes/groups 3, 11A, 15 (A, B, and C), 35B, and the vaccine-related serotype 19A are among types commonly seen in replacement.^{115,427,428,430} However, there is much variation between study sites, apparently reflecting the relatively modest transmission/colonization ability of the less common serotypes. It remains to be seen whether some serotypes or clones within them evolve new variants capable of global spread to overtake the now common serotypes, be they included or not in the vaccine.

Effect of dosing schedule on pneumococcal vaccine effectiveness

PCV7, PCV10, and PCV13 are licensed in the United States, Europe, and elsewhere on four-dose schedules, including three primary doses plus a booster at about 1 year of age.^{434,435} In Europe, PCV13 is approved for use on a schedule of two primary doses plus a booster at 1 year of age when part of a "routine immunization program". All three conjugate vaccines are prequalified by the WHO for use in developing countries, and the WHO recommends that conjugate vaccines be used on a schedule of three doses without a booster, the standard Expanded Programme on Immunization schedule.⁴³⁶

In practice, schedules used in routine programs differ. In the United States and most Canadian provinces, the vaccine is given to infants on a four-dose schedule, with doses at 2, 4, 6, and 12 to 15 months, identical to the schedule used in the United States vaccine trials.⁴⁵ In other settings, three doses are used, either given during the first 6 months of life without a booster (eg, Australia) or as two doses during that period, followed by a booster after 1 year of age (eg, Quebec Province in Canada and many Latin American and European countries). In Africa, schedules of three doses given at 6, 10, and 14 weeks (eg, Rwanda) or at 6 and 14 weeks and 9 months (South Africa) are used.

The number and timing of doses that will provide optimal prevention of disease is unclear, and may be different for different settings.⁴³⁷ Data from early adopting countries all show substantial disease reduction with different schedules. Three doses given at 6, 10, and 14 weeks were efficacious, except for serotype 1, in clinical trials in Africa.^{6,7} The Australian schedule of three doses at 2, 4, and 6 months without a booster has been shown to quickly reduce invasive disease both in young children and in adults through herd effects.⁴³⁸ Likewise, the four-dose schedule led to rapid and sustained reductions in the United States and Canada,^{12,439} and marked reductions in pneumonia hospitalizations in children occurred quickly after introducing a

"2 + 1" (two primary doses plus a booster) schedule in Quebec Province in Canada.⁴⁴⁰ In these settings, the true effect of the routine schedule on its own is difficult to discern because the initial national programs included catch-up campaigns that offered vaccine to all children younger than 2 years, which likely helped to quickly reduce disease burden. Data are not yet available on the effectiveness of different schedules in developing-country settings.

Comparable to immunogenicity studies, studies of disease from the United States shortly after 7-valent conjugate vaccine introduction found small but statistically significant differences between the effectiveness of a two- or three-dose primary series. A study of cases of invasive disease occurring in vaccinated children found a disproportionate number of cases caused by serotype 6B among children who had only received one or two primary doses compared with cases that occurred among children receiving three primary doses or a full four-dose series.⁴⁴¹ A study of lower respiratory tract infections found that compared with children who had received two primary doses, children who had received three doses had 7.8 fewer hospitalizations and 57 fewer outpatient visits (per 1,000 children) among those born in 2002; no difference in hospitalization rate was seen after the booster dose for the 2002 birth cohort or at any time for the 2003 birth cohort, a finding the authors attributed to herd effects that were likely more substantial in the later period as more children became vaccinated.⁴⁴² Other studies also found a booster dose to be beneficial, including a large case-control study from the United States. In this study, a variety of schedules were found to be protective against invasive disease compared with no vaccine, but a schedule of three doses plus a booster dose after 12 months was significantly more protective than three doses without a booster.⁹⁹

Safety

Children younger than 2 years

The safety of pneumococcal conjugate vaccines has been most extensively examined in children younger than 2 years because most of the pivotal licensure trials were performed in this age group. For 7-valent conjugate vaccine, local reactions, including swelling, redness, and induration were not observed uncommonly but were generally mild and self-limiting. The rates of local reactions after receipt of PCV13 were similar to the rates observed in recipients of PCV7,³³¹ whereas the rates of local reactions after PCV10 vaccine were somewhat higher than seen for PCV7.⁴⁴³

Fever is generally more frequent in infants receiving pneumococcal conjugate vaccine than in control subjects.^{4,249,300,331,457} The incidence of fever (> 38° C) after receipt of pneumococcal conjugate vaccines varies widely but appears to be somewhat higher with both PCV10 and PCV13 than PCV7.^{341,457} Generalized systemic symptoms, such as irritability, drowsiness, and crying more than usual, have been seen in recipients of all three licensed conjugate vaccines,^{341,443,444} but these symptoms have usually been mild. Other events that could possibly be attributed to conjugate vaccine include urticaria, rash, excessive crying, hypotonic-hyporesponsive episodes, cyanosis, and transient granulocytopenia.^{223,247,11,445}

In the NCKP efficacy trial of PCV7,⁴ the frequency of uncommon events requiring medical attention after vaccination was evaluated through the use of comprehensive hospitalization and emergency room utilization databases. The incidence of events in 92 diagnostic categories was followed for 30 days after vaccination for events in hospitalized children and for 60 days for events seen in the emergency department.

Adverse events that were severe, unexpected, or possibly had been caused by the study vaccine were followed up through chart review, parent contact, or both. Significant differences were seen only for febrile seizures and elective admissions. Febrile seizures requiring hospitalization were more common in recipients of PCV7 than control subjects, but only in those patients who had received DTwP at the same time; there was no difference in rate of seizure between recipients of PCV7 and infants in the control group, who had received a concomitant DTaP vaccine. There was no clustering of febrile seizures within the 3-day period after vaccine administration, and the rates of seizure in this study were below the historical rates of seizure seen after DTwP vaccination.²⁸ Rates of sudden infant death syndrome (SIDS) also were similar to or lower than those expected from historical data. Elective admissions, including ventilatory ear tube placement, occurred more frequently in the control group.⁴ In an analysis of selected categories of outpatient clinic visits, control subjects had significantly more seizures overall than PCV7 recipients; no seizure subcategory was different between the two groups, and there was no temporal clustering of the seizures relative to vaccination. Similarly, although there was an excess of generalized seizures among vaccinees in the South African trial, there were less seizures in the "unspecified" seizure category and no excess of seizures overall.⁷ In the trial in South Africa, hyperactive airway disease and asthma were noted 79% more frequently in recipients of PCV9 (nominal $P = .009$), but no temporal association to receipt of vaccine was apparent.⁷ This was not observed in another trial of PCV9 in the Gambia nor in the Kaiser Permanente or Navajo trials for PCV7.⁴⁴⁷

There was an excess of visits to the clinic or hospital associated with respiratory infections in the first week post-PCV dose-one vaccination in the South African, Gambian, and Philippine trials,^{6,7,9} but this excess was not noted in the Navajo⁵ or in the NCKP trial.⁴

Seizures were also specifically examined among cases reported to the Vaccine Adverse Event Reporting System (VAERS), a repository for reports of adverse events that are possibly related to vaccinations given in the United States. The reports are voluntarily submitted by manufacturers, health care workers, and patients and, as such, must be interpreted with caution. Wise and colleagues⁴⁴⁸ reported on data submitted to VAERS in the first 2 years after licensure of PCV7, during which time an estimated 31.5 million doses of the vaccine were administered in the United States. Of 4,154 reports made within 3 months of PCV7 vaccination of children 17 years and younger, there were 393 reports of seizures; 159 of these were considered serious (including three deaths). Fifty-seven (14.5%) of the total seizures and 15 of the serious seizures (9.4%) occurred in children who had received PCV7 alone, without concurrent vaccinations. Additional details of case history and follow-up were obtained for the first 98 reports of seizure. Seventy-nine of these cases (80.6%) either had fever at the time of the seizure or had a history of seizure. The three children who died had seizures without known cause, although one had a previous diagnosis of "gross motor delay"; the other two were fraternal twins. More recently, an excess of febrile seizures (of concern but associated with a good prognosis) has been reported to the Vaccine Safety Datalink in the United States when the 2010/2011 trivalent influenza vaccine has been given together with PCV13 to children 6 months to 2 years of age, and the Centers for Disease Control and Prevention (CDC) have estimated an excess of 60 such seizures per 100,000 children receiving both vaccines simultaneously, with the seizures typically occurring the day after immunization.⁴⁴⁹

The 4,154 reports in the VAERS database represent a rate of 13.2 adverse events per 100,000 vaccinations temporally, though not necessarily causally related to receipt of the vaccine. Serious adverse events comprised 14.6% of these reports

($n = 608$, including 117 deaths). This is consistent with the rate of serious adverse events, 14.2%, reported for other vaccines.⁴⁵⁰ The majority of reports involved minor adverse events that had been observed in clinical trials. In 23 cases, rechallenge with a subsequent dose of vaccine produced the same event encountered after a previous dose, suggesting a causal relationship; these included seven cases of fever, irritability, or other nonspecific symptoms; four cases of respiratory symptoms; four cases of prolonged or abnormal crying; three cases of gastrointestinal (GI) disturbance; two possible allergic reactions; two seizures; and one case of alopecia. In addition, there were 14 reports of anaphylactic reactions, 78 cases with possible thrombocytopenias (12 with platelet counts less than 20,000/mm³), and 6 cases of serum sickness. For each of these categories, alternative explanations were present in some cases but not all. Of the 117 deaths, 73 (62.4%) did not have an identified cause, although 59 of these were classified as sudden infant death syndrome (SIDS) or possible SIDS. Of the 44 deaths in which the cause was identified, seven were due to pneumococcal infections (six in partially vaccinated children).

Older children and adults

In the United States and some other countries, catch-up vaccination is recommended for healthy children up to 23 months of age who did not receive pneumococcal vaccine as infants,²⁸ but vaccination of older children without previous vaccination or who did not respond to vaccination with PPV could prevent considerable additional disease. In 115 Spanish children who received a single dose of vaccine between 24 and 36 months of age,⁴⁵¹ local reactions of erythema, induration, and tenderness occurred in 32% to 40% of the vaccinees. About one third of these reactions were severe, but most resolved within 3 days of vaccination. Eight children (7%) had fever greater than or equal to 38°C within 72 hours of vaccination, a lower rate than seen in younger children.^{4,223,445}

Pain at the injection site was the most common adverse reaction in two groups of children aged 2 to 18 years, occurring in 20% to 56% of patients,^{263,452} but there were no significant differences between those receiving conjugate vaccines and those receiving control vaccines. The incidence and severity of local reactions may be reduced by using a deep intramuscular route to inject the vaccine,²⁵² and eliminating alum adjuvant from the vaccine appears to decrease the incidence of local reactions in toddlers,²⁵² although it increases the incidence in adults.⁴⁵³ Reactogenicity does not increase with repeated doses.^{452,454} Fever is seen more frequently in children receiving PPV vaccine than conjugate vaccines, but temperature greater than 38°C is infrequent in any group.^{59,286,452}

The safety of various doses of PCV7 was studied in older adults who had previously received PPV.^{455,258} Increases in PCV7 dose were associated with increases in both local and systemic adverse events, but among systemic symptoms, only general muscle aches and pains were significantly different between lower and higher doses. Swelling, pain, and limited movement all increased significantly with dose of PCV7 but tended to be encountered less frequently after PCV7 than after PPV vaccination. Earlier studies^{128,188} found no differences in symptoms produced by PCV7 and PPV in older adults, although younger adults experienced more pain and headache after PCV7 than after PPV.¹⁸⁸ Thirteen-valent conjugate has been evaluated in adults. In this population, fever was infrequent, and the most common reaction observed was mild local tenderness.²⁵⁹

Special groups

Several studies have examined reactogenicity of pneumococcal conjugate vaccines in children with immunodeficiencies. In a study of children infected with HIV, those receiving PCV7 did not have significantly more reactions than those receiving control

vaccine,⁴⁵⁷ but swelling, redness, pain, fever, and irritability of at least moderate severity were significantly more frequent after the first and second doses of PCV7 than after the corresponding doses of placebo (56.7% vs. 20.0% [$P = .02$] and 53.3% vs. 13.3% [$P = .01$], respectively). Among the 30 HIV-positive children randomized to receive PCV7, 3 had severe reactions to vaccination (severe induration, erythema, and limited leg movement; limited leg movement and high-pitched crying; and temperature of 39.9°C). Among 15 HIV-positive children randomized to placebo, 1 had a fever of 39.5°C. All 4 children with severe symptoms had symptomatic HIV disease at baseline. In an earlier study of 5-valent PCV vaccine in HIV-positive and HIV-negative children older than 2 years,²⁷¹ only minor adverse reactions were observed.

The reactogenicity of PCV7 is not different between children with and without sickle cell disease,^{83,87} however, children with sickle cell disease who had a three-dose primary series of PCV7 had slightly stronger reactions to a PPV booster than those who had a single dose at 12 months.¹⁰⁶ Children with solid-organ transplants experienced less pain at the injection site than healthy control children, but no serious adverse events were seen in either group.²⁷⁷

Preterm infants receiving PCV7 had fever greater than 38°C, swelling, tenderness at injection site, irritability, loss of appetite, vomiting, diarrhea, and hives more frequently than preterm infants receiving control meningococcal vaccine.²⁵³ However, these reactions were not severe enough to preclude the use of PCV7 in preterm infants. A smaller study²⁴² found no significant differences between preterm and full-term infants in local or systemic reactions when vaccine was given at 3, 5, and 11 months after birth, although both groups had fewer adverse events after the third (booster) dose than after either of the two primary doses.

Public health considerations

Epidemiologic effects of vaccination

Effect of vaccination in children younger than 5 years

Use of pneumococcal conjugate vaccine has had a profound effect on pneumococcal disease in the United States, the first country to include pneumococcal conjugate vaccine as part of the routine childhood immunization schedule. The effects were seen very quickly after vaccine introduction in 2000. In a multicenter study of children requiring hospitalization for invasive pneumococcal disease, investigators noted 77% fewer cases in 2002 in children younger than 2 years when disease was caused by vaccine serotypes, compared with the average number of cases during 1994 to 2000.⁴⁸⁴ Surveillance in the NCKP population identified no cases of invasive disease caused by vaccine serotypes among children younger than 1 year between April 2002 and March 2003, compared with rates between 51 and 98 cases per 100,000 person-years before vaccine licensure.⁴⁵⁹ According to the CDC's Active Bacterial Core Surveillance (ABCs), a population-based system measuring invasive pneumococcal disease in approximately 20 million people in eight states, overall rates of total incidence of invasive pneumococcal disease (both vaccine type and nonvaccine type) among children aged younger than 5 years had dropped 75% from prevaccine levels by 2003. Rates of disease caused by all serotypes fell from 96.7 cases per 100,000 population during 1998 and 1999 to 23.9 cases per 100,000 population in 2003; disease caused by vaccine-type strains fell 94% from 80.0 cases per 100,000 population to 4.6 (Figure 25-4).⁴⁶⁰ Since 2004, overall disease rates among children younger than 5 years have remained stable (23.6 cases per 100,000 in 2007); invasive disease caused by vaccine serotypes has become very unusual (0.4 cases per

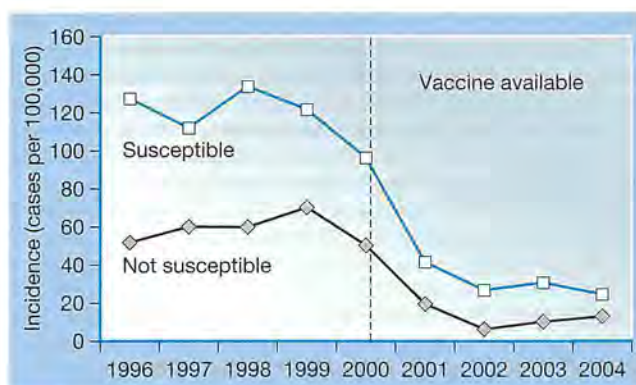


Figure 25-4 Effect of pneumococcal conjugate vaccine introduction in 2000 on rates of penicillin-susceptible and nonsusceptible invasive pneumococcal infections in the United States in children younger than 2 years. (From Kyaw MH, Lynfield R, Schaffner W, et al. Effect of pneumococcal conjugate vaccine introduction on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med* 354:1455-1463, 2006.)

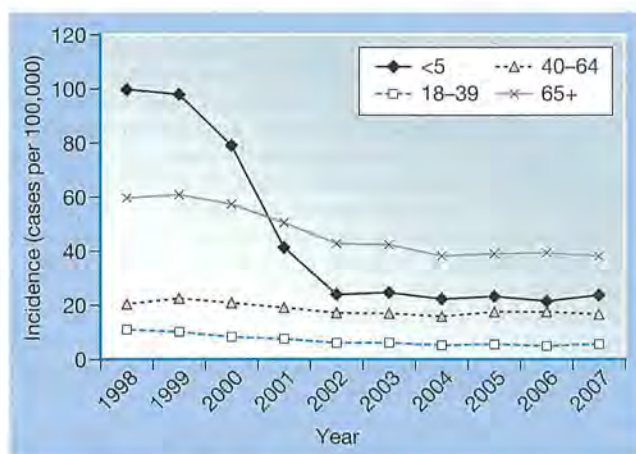


Figure 25-5 Overall disease rates of invasive disease caused by vaccine serotypes among children younger than 5 years, 1998-2007.

100,000 population in 2007), and an increase in disease caused by nonvaccine serotype 19A has occurred, which accounts for the lack of change in overall disease rates between 2004 and 2007¹² (Figure 25-5, see Table 25-5).

Use of conjugate vaccine in children has also reduced the differences in risk of invasive pneumococcal disease between certain racial and ethnic groups. According to ABCs data, rates of invasive disease fell 77% overall in white children younger than 2 years between 1998 and 2002 and fell 89% in black children in the same interval; incidence among black children younger than 2 years went from 3.3 times the rate among white children in the prevaccine period to 1.6 times higher in 2002.⁴⁶¹ Among Navajo children living in the American Southwest, rates of vaccine serotype disease were 210 and 263 cases per 100,000 children younger than 1 and 1 to 2 years of age, respectively, in 1995 to 1997, the time period before a vaccine trial was conducted in the population; in 2004 through 2006, no vaccine serotype cases occurred in this age group.⁴⁶² In addition, rates of disease caused by nonvaccine serotypes did not change significantly after vaccine introduction. In Alaska, surveillance by CDC's Arctic Investigations Program identified a large drop in disease caused by vaccine serotypes among the Alaska Native population.⁴²⁵ After vaccine introduction, vaccine-type invasive disease fell 91% among Alaska Native children younger than 2 years (from 275 cases per 100,000 children to 25 cases per 100,000) and by 80% among non-Natives the same age (from

101 cases per 100,000 to 20 cases per 100,000), eliminating the disparity in disease caused by vaccine serotypes. After this first report, an increase in non-vaccine-serotype disease was seen among Alaska Natives, primarily among those living in the rural Yukon-Kuskokwim region; these increases reduced the overall benefits of pneumococcal vaccination in this population.⁴⁶³

The amount of data on vaccine impact from outside the United States is growing. Surveillance from 12 centers across Canada (the IMPACT Program) found a 56% decrease in the number of cases among children younger than 5 years, from 269 in 2000 to 119 in 2007, including a 92% decrease in PCV7 cases in children younger than 5 years.⁴³⁸ In Australia, incidence of invasive disease decreased 74% between 2002 and 2007 (from 98.1 to 25.1 per 100 000); the reduction was more pronounced in nonindigenous children (84.7 to 19.5 per 100 000) than indigenous children (129.1 to 82.3 per 100 000).⁴⁶⁴ In Europe, results of studies from the first few years after vaccine introduction are now coming available for several countries, and generally, findings have been similar to those seen in other regions,⁴⁶⁵ although in some settings, the emergence of serotype 1 disease has in part offset reductions seen by vaccine implementation.⁴⁶⁶

Studies from multiple countries now also show that changes have occurred in the epidemiology of noninvasive pneumococcal syndromes, in particular pneumonia, after vaccine introduction. A study using the Nationwide Inpatient Sample, the largest available inpatient database in the United States, and an interrupted time-series analysis found large reductions in hospitalizations coded as all-cause and pneumococcal pneumonia among children when comparing 1997-1999 (pre-PCV7 years) to 2001-2004 (post-PCV7 years).⁴⁸³ By the end of 2004, all-cause pneumonia hospitalization rates had declined 39% in children aged younger than 2 years, a drop of 506 hospitalizations per 100,000 children younger than 2 years, or about 41,000 pneumonia hospitalizations prevented per year. Pneumococcal pneumonia rates (2% of episodes) declined by 65% in children younger than 2 years, or approximately 17 fewer hospitalizations per 100,000 children per year. In Australia, hospital discharges with the primary diagnosis of pneumonia fell 38% (95% CI, 36%-40%) and 29% (26%-31%), respectively, among children younger than 2 and 2 to 4 years during the 30 months after universal funding for 7-valent conjugate vaccine, representing about 4,700 fewer hospitalizations for pneumonia over the 30-month period.⁴⁶⁸ Likewise, hospitalizations fell 69.4% for lobar pneumonia and 8.2% for all-cause pneumonia in children younger than 2 years in the 15-month period after provision of 7-valent vaccine for all children younger than 5 years in Quebec Province in Canada.⁴⁴⁰

Indirect effects

Pneumococci are generally transmitted from persons carrying pneumococci in the nasopharynx to others who become carriers and who may go on to develop disease. As expected from reports of clinical trials,^{236,411,469} routine use of pneumococcal conjugate vaccines as part of the US vaccination schedule has reduced nasopharyngeal carriage of vaccine serotypes. In Massachusetts, a study of nasopharyngeal carriage among children younger than 7 years visiting primary care practices found that vaccine-serotype pneumococci accounted for only 14% of colonizing strains in 2004, a decrease from 36% in 2001, while non-PCV7 serotypes increased from 34% to 55% of strains; overall, carriage did not change substantially (from 26% to 23% of all children).³⁶⁹ Similar findings have been noted elsewhere.^{426,470,425} The reduction in carriage of vaccine serotypes in children who have received pneumococcal conjugate vaccine means that fewer vaccine-serotype pneumococci are circulating among families, day-care centers, and in the community, which should also reduce carriage and disease caused by vaccine

serotypes in unvaccinated persons. This concept—protection of unvaccinated persons from disease by vaccinating a subset of the population—is known as “herd” or “indirect” effects.

Several studies show that herd effects are an important part of the public health benefit of pneumococcal conjugate vaccine use. The first report demonstrating herd effects was from the NCKP population early after vaccine licensure in the United States. Data from this population indicated that the reduction in disease was greater than the percentage of children who had been vaccinated.³⁹⁶ By early 2001, only 34% of children younger than 5 years had received one or more doses of conjugate vaccine, and only 14% were fully vaccinated. In spite of this low coverage, disease caused by vaccine serotypes had dropped to 18 cases per 100,000 children from a baseline incidence of 42 to 60 cases per 100,000 in this age group. A later report from this group, tracking disease rates through March 2003, noted that disease caused by vaccine serotypes was dropping among persons too old to have received pneumococcal conjugate vaccine.⁴⁵⁹ Among persons 5 to 19 years of age, incidence fell from 2.6 to 2.1 cases per 100,000 person-years, in those 20 to 39 years of age from 5.7 to 2.4, in those 40 to 59 years from 10.2 to 8.7, and in those 60 years of age and older, the incidence fell from 35 to 30 cases per 100,000 person-years.

The indirect effect of infant vaccination on disease among persons 5 years of age and older reported by ABCs have been generally similar to those seen in the NCKP population (Figure 25-5).^{460,471} Analyses of ABCs data through 2007 show that invasive disease caused by vaccine serotypes had dropped by 87% to 94% among age groups 5 years of age and older.¹² Overall disease rates fell 43%, 40%, 18%, and 37% among persons 5 to 17 years, 18 to 49 years, 50 to 64 years, and 65 years and older, respectively, between the 1998/1999 baseline years and 2007. The rate was 62% among persons 5 years and older between 1998/1999 and 2003, with the largest absolute rate reduction occurring in persons 65 years and older (33.6 cases/100,000 in 1998/1999 and 11.9 during 2003).⁴⁶⁰ An examination of older adults in the conjugate vaccine era indicated that disease was more likely than before conjugate vaccine introduction to occur in persons with comorbid conditions and to result in death, indicating that the population of adults benefiting from herd effects were somewhat healthier than those who continued to get invasive disease.⁴⁷¹ Infants too young to be vaccinated have also been shown to be protected through herd effects.⁴⁷²

Most studies conducted in locations that use pneumococcal vaccine routinely for all children report a drop in invasive disease caused by vaccine serotypes among older children and adults after vaccine implementation, but data have been mixed on whether there is an overall benefit for disease rates when disease caused by both vaccine-type and non-vaccine-type serotypes is evaluated. A recent World Health Organization review of data from Australia, Canada, England and Wales, South Africa, and the United States evaluated serotype-specific rates of invasive disease among persons too old to have been vaccinated; Australian and US datasets included information on both indigenous and nonindigenous populations.⁴⁷³ This study found that, among people too old to have received pneumococcal conjugate vaccine, observed rates of PCV-serotype disease in most datasets were noted to have declined. However, variable increases in non-vaccine-serotype invasive disease led either to no change or, in one location, an increase in the overall rate of invasive disease. Explanations for the lack of overall disease reductions in adults after conjugate vaccine introduction for children, for some studies, include a low baseline percentage of invasive disease caused by conjugate vaccine serotypes, such as is seen among Alaska Native or Navajo adults^{425,462} and a large disease outbreak caused by a non-vaccine-type serotype.⁴⁷⁴ A recent study from the United States was the first to document significant herd effects for prevention of noninvasive pneumonia in older adults.¹³ In this study, which used a very large administrative database,

investigators found a reduction of 54% (95% CI, 53%-56%) for nonbacteremia pneumonia hospitalizations among adults 65 years of age and older. A model included in this report estimated a total reduction of 788,838 [95% CI, 695,406 to 875,476] hospitalizations for pneumococcal pneumonia between 2000 and 2006, with 90% of the reduction in hospitalizations attributed to herd effects among adults 18 years of age and older.

Effect on resistance

There are several mechanisms by which widespread use of the new conjugate vaccine might have an effect on antibiotic-resistant pneumococci. Serotypes included in the vaccine cause the majority of disease caused by resistant strains,⁴⁷⁵ so reducing infections caused by these serotypes reduces resistant infections⁷. In addition, the vaccine reduces acquisition of carriage of vaccine serotypes in the nasopharynx,^{236,393,411,408} reducing the opportunity for vaccine-serotype strains to be exposed to the selective pressures of antibiotics. As the vaccine reduces transmission of vaccine-serotype strains from vaccinated children to others, vaccinating a subset of the population reduces the overall number of infections caused by resistant vaccine-serotype strains.⁴⁷⁶ Finally, by preventing infections, vaccination has been shown to reduce the need for antibiotics^{372,379} and therefore reduces the selective pressure that antibiotic use provides. On the other hand, the acquisition of nonvaccine types in carriage exposes these types to the selective pressure of antibiotics, and resistance emerges in the residual disease because of nonvaccine types. Overall, the burden of resistance is reduced, but the extent of resistance emergence in non-vaccine types may return the resistance proportion in these residual strains to the same or even higher levels than previously encountered.⁴⁷⁵

Initial reports after PCV introduction in the United States demonstrated a reduction in the proportion of resistant strains in both children and adults.^{474,122} In Northern California, penicillin nonsusceptible strains with minimum inhibitory concentrations (MICs) greater than or equal to 2 µg/mL were seen in 15% of pneumococcal isolates causing disease in all age groups in 2000, compared with 5% of strains in 2003; erythromycin resistance was prevalent in 28.9% of strains at baseline, compared with 15% after vaccine introduction³⁰⁷. Stephens and associates⁴⁹³ evaluated trends in macrolide-resistant invasive disease in the Atlanta, Georgia, the ABCs site. Large decreases in the incidence of macrolide-resistant disease were seen in children younger than 2 (82%) and 2 to 4 years (71%) after vaccine introduction. The predominant clone causing macrolide-resistant disease in Atlanta had a *meffE*-mediated mechanism for resistance and was serotype 14, a 7-valent PCV7 serotype; the decrease in macrolide-resistant pneumococcal disease was largely due to a reduction in disease caused by this clone.

Data from the ABCs Emerging Infections Program Network found that rates of invasive pneumococcal disease caused by penicillin-nonsusceptible strains dropped 78% in children younger than 5 years from a peak of 33.8 cases per 100,000 in 1999, before conjugate vaccine introduction, to 7.5 cases per 100,000 in 2004 (Figure 25-4).¹²¹ Rates of invasive disease caused by penicillin-nonsusceptible strains and strains not susceptible to multiple antibiotics among persons older than 65 years peaked in 1999 at 16.4 per 100,000 and then decreased by 49% to 8.4 cases per 100,000 in 2004; effects on resistance were most pronounced among children <2 years of age (Figure 25-4). Although the incidence of nonsusceptible strains fell as vaccine-type pneumococci began to disappear from the community, the proportion of resistance among residual strains causing disease in children began to increase.¹²¹

In Alaska, rates of disease caused by penicillin-resistant, cotrimoxazole-resistant, erythromycin-resistant, and multi-drug-resistant strains dropped in children younger than 5

years, consistent with the reduction in disease caused by vaccine-serotype strains.⁴²⁵ Studies of carriage in young children in Alaska however, showed that although carriage of cotrimoxazole-resistant strains in children fell after vaccine introduction, carriage of penicillin-nonsusceptible strains was not significantly affected.⁴²⁶

In a multisite study, the proportion of pneumococcal strains from children with otitis media caused by vaccine serotypes dropped from 76% in 1999 to 52% in 2002, but no change was seen in the proportion of isolates that were resistant to penicillin over time.³⁸⁶

The reversal in the trend to a reduction in the proportion of resistant strains in the United States and elsewhere after PCV7 introduction has been related to the emergence of a small number of antibiotic-resistant nonvaccine serotypes. The most important of these types has been serotype 19A, the burden of which increased from 0.8 to 2.5 cases per 100,000 per year from 1998 to 2003 in the United States.¹¹⁵ The emergence of serotype 19A is associated in the United States with a global clone that has undergone a capsular switch from 19F to 19A, acquired the *ermB* gene in addition to *mefA*, conferring high-level macrolide resistance, and has, in addition, high-level resistance to beta-lactams, including injectable third-generation cephalosporins such as ceftriaxone.¹¹⁵ The only oral agents that can be used to treat otitis media caused by these resistant strains are fluoroquinolones.¹⁰⁷ Multiresistant serotype 19A post-PCV7 introduction is also a problem in other parts of the world, for example, in France.^{477,478-479} Other serotypes not included in the PCV7 vaccine have also emerged as antibiotic-resistant in the United States, including serotype 6C⁴⁸⁰ as well as serotypes 15A, 23A, and 35B.⁴⁸¹ Although the emergence of antibiotic-resistant pneumococci has occurred over the past half century independent of PCV selection, and will continue to do so, the changes in serotypes carried in the nasopharynx of PCV-immunized children has contributed to the opportunity for selection of resistance in these serotypes.

Serotype replacement

At best, conjugate vaccines as currently designed can only protect against a limited number of the 93 known pneumococcal serotypes. Carriage studies have shown that vaccination has reduced carriage of vaccine-type pneumococci among children in the community.^{470,425,424,426} The concomitant increase in carriage among children of pneumococcal serotypes not covered by the vaccine means that nonvaccine serotypes may be transmitted and potentially cause disease more often than they did before routine use of conjugate vaccine. An increase in disease caused by nonvaccine serotypes in the wake of a reduction in vaccine-type disease is known as "replacement disease". To what extent replacement disease occurs likely depends in part on the ability of the nonvaccine serotypes to cause disease; studies of invasiveness that have analyzed distributions of serotypes from carriage and invasive disease have shown that certain serotypes are much more likely to cause invasive disease than others.⁴⁸²

The first evidence for replacement disease came from a clinical trial in Finland evaluating two conjugate vaccines for prevention of AOM among children younger than 2 years. The first analysis evaluated the 7-valent PCV7; compared with a control group receiving hepatitis B vaccine, children receiving pneumococcal conjugate vaccine had 57% fewer otitis media episodes caused by serotypes in the vaccine and 51% fewer episodes caused by cross-reactive serotypes, but these changes were accompanied by a 33% increase in episodes caused by other pneumococcal serotypes and an 11% increase in those caused by *H. influenzae*.¹¹ In the second analysis, which evaluated efficacy of 7-valent PncOMPc, the efficacy against otitis media caused by vaccine serotypes was similar (56%).¹⁸⁵ More

episodes of otitis media caused by non-vaccine-serotype pneumococci and *H. influenzae* occurred among children receiving pneumococcal vaccine (121 and 315 episodes, respectively) than receiving hepatitis B vaccine (95 and 287 episodes, respectively), but the differences were not statistically significant between the two groups. A shift in pneumococci causing otitis media was also seen in Pennsylvania, where in 2001 children receiving at least two doses of pneumococcal conjugate vaccine were noted to be more likely to have acute otitis media caused by nonvaccine types (47%) than children who had not received conjugate vaccine (21%).⁴⁸³

The first report of significant replacement invasive disease among children came from an eight-center study monitoring hospitalizations for invasive disease among children younger than 2 years in the United States.⁴⁸⁴ While noting a 77% decrease in vaccine-type disease between baseline (1994-2000) and 2002, they also found a 66% increase in non-vaccine-serotype disease. Isolates of nonvaccine serogroups 15 and 33 had the largest increases. In Utah, an increase in cases caused by serogroup 3 was noted among child members of a large health care system, along with an increase in the incidence of empyema and severe invasive disease from 2001 to 2003 compared with prevaccine years.¹⁰¹

Data from the CDC's ABCs program have shown that rates of invasive disease caused by nonvaccine-types in children younger than 5 years increased 128% between the 1998/1999 average and 2007.¹² In this large sample, the main serotype causing replacement disease in children has been serotype 19A, a type somewhat structurally similar to vaccine serotype 19F but for which the vaccine provides no cross-protection.⁴⁸⁵ An analysis comparing pneumococcal genotypes before and after conjugate vaccine introduction noted that the increase in serotype 19A was due to the serotype 19A clone most prevalent in the United States becoming more common as a cause of disease and also to the emergence of new clones with capsular serotype 19A that were previously identified as having only vaccine serotypes.⁴⁸⁵ This analysis suggests that pneumococci may be adapting to vaccine use by acquiring genetic material that allows a switch in expressed capsular type.

Surveillance data from Alaska Native children indicate that this group may be more susceptible to replacement disease than other populations. Recent data indicate that an increase in non-vaccine-type disease among Alaska Native children aged younger than 2 years began as early as 2003, 2 years after universal introduction of PCV7. Between baseline (1995-2000) and 2004 to 2006, among children aged younger than 2 years, rates of invasive disease caused by nonvaccine serotypes increased from 95 to 229 cases per 100,000, substantially reducing the overall benefit of PCV7.⁴⁸⁶ In contrast, replacement disease has not been as evident among non-Native Alaskans, suggesting that environmental, socioeconomic, or genetic factors may explain some of the differences seen in the two groups. Replacement disease has not been problematic among other indigenous populations, such as Australian Aboriginals⁴⁸⁷ or Navajo residing in the American Southwest.⁴⁶³ Although disease rates among Alaska Native children are among the highest reported, the overall size of the population is small, such that rate calculations are based on relatively few cases; therefore, more data are needed to better understand the trends in this population.

Evidence suggests that nonvaccine serotypes are more likely to cause disease in persons with immune system disorders. Some of the most dramatic increases in nonvaccine serotypes documented after conjugate vaccine introduction have been among adults 18 to 64 years of age with HIV or acquired immunodeficiency syndrome (AIDS).⁴⁸⁸ In this very-high-risk population, overall rates of invasive pneumococcal disease (all serotypes) declined 25% between 1998/1999 and 2007. The overall decline was the result of an 88% reduction in disease caused by the seven serotypes in the vaccine and a 60% increase in disease caused

by nonvaccine serotypes. A comparison group of adults 18 to 64 years of age without HIV or AIDS noted a very similar percent reduction in vaccine-serotype disease (91%), but this group had a smaller (28%) increase in non-vaccine-type disease.

In July 2010, the World Health Organization convened a meeting of experts to discuss the issue of replacement disease and review data on invasive disease trends from several countries that had introduced conjugate vaccine.⁴⁹¹ The latest data were reviewed from Australia, Canada, England and Wales, South Africa, and the United States and included information from both indigenous and nonindigenous populations. The data were collected through systems that varied in size, methods, background incidence rates, the prevaccination proportion of invasive disease caused by vaccine serotypes, vaccination schedules, and the use of catch-up programs for older children. In each setting, children benefited overall from vaccine introduction; the overall incidence of invasive pneumococcal disease among children targeted for vaccination declined after vaccine introduction. The overall reductions in each case was the result of large declines in vaccine-serotype disease and, in some but not all datasets, smaller increases in disease caused by serotypes not covered by conjugate vaccine. The increases in non-vaccine-serotype disease were seen mostly with cases requiring hospitalization. Among older children and adults, an overall indirect benefit was not seen in all settings. In some sites, overall rates were lower after conjugate vaccine introduction; all sites saw reductions in vaccine-serotype invasive disease, but increases of variable size in non-vaccine-serotype disease resulted in either no change or an increase (one site) in the overall rate of invasive pneumococcal disease in others. After reviewing the data, participants concluded that vaccine-induced serotype replacement likely explains some of the observed increases in non-PCV-serotype disease but that other factors, such as population immunity, secular trends in disease,

and changes in surveillance system sensitivity, also contributed to the pattern observed. The group concluded that they could not discern the relative contribution of vaccine-induced replacement disease versus observed trends in non-vaccine-serotype disease related to these other factors and that more data are needed as the newer conjugate vaccines are implemented.

Disease control strategies

Pneumococcal disease is endemic globally. Nearly all young children will have one or more mild infections caused by *S. pneumoniae*, and severe infections most often occur sporadically rather than in outbreaks of infections clustered together by place and time. Therefore, including pneumococcal conjugate vaccine in the routine childhood vaccination schedule is likely the optimal strategy for controlling pneumococcal disease.

In 2000, the first year 7-valent PCV7 was licensed, the United States introduced the vaccine for all children younger than 2 years.⁵⁰⁶ Demand for vaccine quickly outpaced supply; vaccine shortages began in 2001 and persisted until mid-2004.^{489,490} Beginning in 2006, with expansion of supply, a large number of countries began introducing 7-valent PCV7. With the licensure of PCV10 and PCV13, beginning in late 2009, national programs using 7-valent PCV7 began switching to PCV10 or PCV13 as they became available, and additional national programs are adopting the newer vaccines. As of December 2010,⁴⁹¹ 42 countries included pneumococcal conjugate vaccine in their routine infant immunization programs (Table 25-12). Several other countries have programs limited to providing vaccine for high-risk children, and in many countries that do not routinely provide pneumococcal vaccine to all children through governmental health programs, vaccination can often be obtained through the private sector. A critical next step is to begin using pneumococcal conjugate vaccines in developing countries.

Table 25-12 Countries Routinely Using Pneumococcal Conjugate Vaccine as Part of their Routine Infant Immunization Program by World Health Organization Region (Updated to May 14, 2012)

Africa	Americas	Eastern Mediterranean	Europe	Western Pacific
Benin	Barbados	Bahrain	Albania	Australia
Burundi	Brazil	Jordan	Andorra	Japan
Cameroon	Canada	Kuwait	Belgium	Marshall Islands
Central African Republic	Cayman Islands	Morocco	Bulgaria	Micronesia
Democratic Republic of Congo	Colombia	Oman	Czech Republic	New Zealand
Ethiopia	Costa Rica	Qatar	Cyprus	Niue
Gambia	Ecuador	Saudi Arabia	Denmark	Palau
Kenya	El Salvador	United Arab Emirates	Finland	Singapore
Malawi	Guyana	Yemen	France	
Rwanda	Honduras		Germany	
Sierra Leone	Mexico		Greece	
South Africa	Nicaragua		Hungary	
	Panama		Ireland	
	Peru		Israel	
	United States		Italy	
	Uruguay		Kazakhstan	
			Latvia	
			Luxembourg	
			Netherlands	
			Norway	
			Slovakia	
			Spain	
			Sweden	
			Switzerland	
			Turkey	
			United Kingdom	

Globally, an estimated 800,000 children younger than 5 years die of pneumococcal disease each year.³ Nearly all of these deaths occur in developing countries. As of early 2011, six low-income countries—Guyana, Nicaragua, Sierra Leone, Rwanda, Gambia, and Yemen—were using pneumococcal conjugate vaccines, but 16 countries had introduced the vaccines by the end of 2011, using funding from a unique donor program called the Advance Market Commitment: <http://www.gavialliance.org/results/goal-level-indicators/vaccine-goal-indicators/> (accessed 17 March, 2012).

Outbreaks of severe pneumococcal disease, including bacteremia, sepsis, and pneumonia, can occur. Most outbreaks occur in closed settings where people are in prolonged close contact, such as jails, long-term care facilities, child-care centers, or homeless shelters.⁴⁹² In these settings, control measures include making improvements in infection control coupled with vaccination; conjugate vaccine or 23-valent polysaccharide vaccine might be appropriate, depending on the serotype and ages of persons involved. Use of antibiotic prophylaxis might be helpful, depending on the susceptibility profile of the strain causing the outbreak and whether the nature and timing of cases suggests that the at-risk population requires protection while vaccines are taking effect. Care must be taken with use of antibiotic prophylaxis, however, because widespread antibiotic use has led to circulation of resistant strains.⁴⁹³ In some outbreaks, the presence of a viral cofactor may suggest that other prevention measures might be helpful, such as use of influenza vaccine.

PCV immunization of adults

As this chapter is being written, adult PCV13 vaccination has been under consideration for licensure in some countries that already have PCV13 licensed for infants. In the US the vaccine was licensed for use in adults over age 50 but no recommendation has as yet been made for its use. There is significant debate about the advantages of conjugate vaccine use in adults in terms of immunogenicity and potential effectiveness compared with PPV vaccination.²⁵⁶ A large-scale randomized double-blind trial in the Netherlands, the CAPITA trial, will report soon and may provide data on the efficacy of PCV in adults.²⁶⁸ In the interim, there are data supporting the efficacy of PCV in the prevention of IPD in HIV-infected adults who have already experienced a previous episode of IPD.⁴⁹⁴ Because the PCV7 serotypes have almost disappeared as a cause of IPD in adults in the United States after PCV immunization of adults, the impact of PCV13 immunization in infants on the preventable disease burden of PCV13 immunization in adults in the United States may be time limited. Recommendations for use in adults will be made once the residual burden of vaccine-preventable disease is clarified. As the burden of disease in immunocompromised adults may be up to 100-fold higher than that in immunocompetent adults there may be an indication for PCV13 vaccination of these groups until the burden of disease in these groups is deemed to be negligible. The impact of PCV13 on herd protection of the additional six serotypes will therefore require further study. Little is currently known about the risks of imported carriage of PCV7 serotypes on disease among susceptible adults in the United States or other countries where these types are close to elimination. The risks of travel by susceptible adults to countries where these serotypes remain common have also not yet been evaluated. These factors will need to be considered both in the licensure decisions around PCV13 vaccination of adults and in its potential indications for use.

Cost-benefit information

The cost of pneumococcal conjugate vaccine was considered quite high when it was initially introduced, although since that time, other vaccines of higher cost, such as HPV vaccine,

have been introduced. In the developing world, the unit cost remains high compared with EPI vaccines, and only subsidies through the Global Alliance on Vaccines and Immunizations (GAVI) and other programs have allowed its use in this setting.

Vaccine cost-effectiveness is dependent on many factors, including disease incidence, vaccine efficacy, herd effects, disease sequelae, number of doses, and cost per dose of the vaccine. Any of these factors may change over time as prices change, as more is learned about vaccine efficacy or herd effects, or when standards of medical care improve. Any determination of cost-effectiveness therefore is limited by the time- and place-specific variables that were used for the analysis. In addition, there are significant non-medical costs associated with pneumococcal disease, most notably the cost of work-time lost by parents caring for ill children.⁴⁹⁵

Lieu and associates⁴ initially analyzed the potential cost-effectiveness of the 7-valent pneumococcal conjugate vaccine using data from the NCKP randomized trial as well as the opinions of a panel of experts.⁴⁹⁵ The analysis was based on a comparison of "vaccination" with "no vaccination", assuming the use of four doses for routine vaccination of healthy infants and one dose for catch-up vaccination of children older than 2 years. In addition, the conservative assumption was made that a vaccinated infant would experience reductions in pneumococcal diseases only until his or her fifth birthday and that vaccination of children would not protect unvaccinated persons (no herd effects). From the societal perspective, vaccination of healthy infants would result in savings if the vaccine cost \$46 or less per dose. From the health care payer perspective, net savings would occur if the vaccine cost \$18 or less per dose.

An updated analysis looked at cost-effectiveness in the United States for the first 5 years of routine use and showed that the actual cost-effectiveness has been better than that predicted by this earlier estimate because of the "herd effect" and consequent reduction in disease among unvaccinated children and adults.⁴⁹⁶ Without incorporating herd effects in this more recent model, conjugate vaccine was estimated to have averted 38,000 cases of invasive disease during its first 5 years of use, at a cost of \$112,000 per life-year saved. After incorporating the reductions in invasive disease for unvaccinated persons, the vaccine prevented 107,000 cases of invasive disease at a cost of \$7,800 per life-year saved. Similar analyses have been performed for other countries, which have demonstrated similar results.^{497,498} An analysis of PCV cost-effectiveness in developing countries suggests the vaccine would greatly reduce mortality and be highly cost-effective at between one and five dollars per dose.⁴⁹⁹

A recent analysis was conducted of the impact of the PCV10 manufactured by GSK as compared with PCV7.^{500,501} This simulation model predicted, as expected for a higher-valency vaccine, that there would be a higher impact of PCV10 on invasive disease than has been observed for PCV7. For otitis media, the contribution of protection against nontypable *H. influenzae* increased the impact of this vaccine against otitis media significantly. Because nontypable *H. influenzae* in the developed world is a major cause of otitis media, and the vaccine impact on otitis media, because of its frequency in this setting, has been the most important cost-saving determinant of the vaccine in children, if these projections of the impact of PCV10 against both the pneumococcus and nontypable *H. influenzae* are borne out, one would anticipate that PCV10 may be a more cost-effective vaccine than PCV7 in the developing world setting. In another study comparing the impact of PCV13 against both PCV10 and PCV7, PCV13 was predicted to be most cost-effective.⁵⁰² However, this study did not take into account the potential impact of the 10-valent PHiD-CV vaccine against otitis media caused by nontypable *H. influenzae*. In reality, whether the 13-valent or 10-valent vaccine is more cost-effective will depend on the relative importance of the

additional serotype coverage provided by the 13-valent vaccine versus the impact of PHiD-CV against nontypable *H. influenzae*. At this point, it is too soon after the introduction of these two vaccines to reliably make this assessment.

Efforts are underway to find financing to cover costs of introducing new vaccines, including pneumococcal conjugate vaccine, in developing countries. In an analysis that estimated the funding needs for childhood immunization in developing countries during the 2004 to 2014 period, the total costs of providing immunization for the poorest countries would be approximately US\$14 to \$17 billion, accounting for phasing in of new vaccines. Vaccine-related costs represented the largest share of this amount (US\$7.1–\$9.3 billion), with US\$4.3 to \$6.5 billion for a set of new vaccines, including pneumococcal conjugate vaccine. These estimates were for all 75 countries eligible for support from GAVI and covered existing vaccines that are considered priorities (diphtheria/tetanus/pertussis, hepatitis B, Hib, and yellow fever) as well as future vaccines likely to be available during 2004 to 2014 (meningococcal A and C, rotavirus, human papillomavirus, malaria, *S. pneumoniae*, and tuberculosis).⁵⁰³ The sustainability of these programs will depend both upon the ability of developing countries to assume responsibility for paying for pneumococcal conjugate and the ability of manufacturers to supply vaccine to these countries at an affordable price.

Future vaccines

Problems with conjugates

Despite the good safety record of pneumococcal conjugate vaccines and their demonstrated high efficacy against invasive infections, several limitations remain. One of the issues is that conjugate vaccines are only capable of protecting against infection with bacteria that express polysaccharide capsule types that are included in the vaccine. Current formulations in use or in clinical development cover up to 75% to 90% of strains prevalent in children.^{33,35,102,107,95} This figure is lower in certain geographic areas and in older age groups. Another potential problem is that the potential for replacement disease with nonvaccine serotypes may attenuate the overall benefit seen from reduction in disease caused by vaccine serotypes. The third major issue is the complexity of conjugate vaccines production. This complexity is the main reason why only a limited number of companies are manufacturing conjugate vaccines and in part explains why their prices are often higher than those for other vaccines.

To improve and expand the immunogenicity of the conjugate vaccines, new components in the conjugate and novel adjuvants have been tested in animal studies.^{27,504–506} New administration routes have also been evaluated: it appears that intranasal immunization with various adjuvants induces strong antibody responses both in serum and on mucous membranes in mice and can protect them against lethal infections.^{203,504,505} Even though these strategies may circumvent some of the problems of conjugates, they do not address the issues of coverage, replacement, or complexity of vaccine production. Therefore, other types of immunogens, including whole-cell pneumococcal bacteria, DNA vaccines, and protein antigens, are being evaluated as candidates for novel pneumococcal vaccines. One whole-cell-based vaccine has proven effective in a mouse model⁵⁰⁶ and is now in a phase 1 clinical trial in healthy adult volunteers, as this chapter goes to press; attempts to develop pneumococcal DNA vaccines are still limited by the generic problems of immunogenicity associated with naked DNA in humans. In contrast, work with protein vaccine candidates has been intense during the past few years and will be discussed in more detail below.

Protein antigens

Protein-based vaccines are attractive for several reasons. They are expected to be immunogenic in early infancy and in the elderly because of their T-cell-dependent nature and, if the proteins are well conserved across all pneumococcal strains, their coverage could in theory be broader than that of conjugate vaccines. Enhanced protection against colonization and avoidance of the replacement phenomenon are also potential advantages. In addition, the cost of goods would likely be lower than that of conjugates because they would have fewer components than multivalent conjugate vaccines; thus protein-based vaccines are expected to be less expensive, allowing wide use in all areas of the world.

The list of pneumococcal proteins that have been evaluated for their potential as vaccine candidates is extensive. Although exceptions can be found, these candidates tend to have several characteristics in common: significant contribution to bacterial virulence, conservation across all sequenced pneumococcal strains, and little homology to human proteins. In general, the candidate antigens also show promising data when used as immunogens in a rodent model of invasive disease, colonization, or both. These proteins have been studied alone, in combination with other candidates, or sometimes as carrier proteins for pneumococcal conjugates. Some examples are provided below.

Pneumococcal surface protein A (PspA) is a surface protein with variable molecular size, ranging from 67 to 99 kDa in different pneumococcal strains. It is present on the surface of pneumococci and is required for full virulence.^{507,508} It is serologically highly variable, and the structure of the *pspA* gene has been shown to be mosaic.⁵⁰⁹ The high degree of variability exhibited by PspA may indicate the importance of this surface protein as a natural target for host defense. Based on the relatedness of the nucleotide and amino acid sequences, the different PspA molecules are grouped into three families, which are further subdivided into clades.⁵⁰⁹ More than 98% of the PspA molecules typed to date are members of families 1 and 2.

The mechanism of action of PspA has been carefully investigated. The amino-terminal region of PspA functions as a specific receptor for lactoferrin. It has been suggested that by binding lactoferrin, pneumococci are able to interfere with the host's immune functions.⁵¹⁰ PspA inhibits activation of complement by *S. pneumoniae*. The interference of complement activation by PspA facilitates pneumococcal survival and host invasion.

PspA is immunogenic and has been shown to elicit protective immunity against pneumococcal infection in mice.^{511–515} It can elicit protection against pneumococcal carriage and subsequent invasive disease in mice after intranasal immunization.⁵¹⁶ Animal models have shown that PspA has the ability to elicit cross-protection against heterologous strains.^{508,513,515} In addition, human antisera from a phase 1 vaccine trial were competent for protecting mice against challenge with pneumococcal strains of various PspA types.⁵¹⁷ Because of the variability of the PspA protein, a potential PspA-based vaccine may need to contain PspAs of more than one pneumococcal strain or be based on conserved regions of the molecule to be able to protect against all pneumococci.⁵¹⁸

Pneumococcal surface protein C (PspC) plays an important role in pneumococcal pathogenesis by functioning as an adhesin.⁵¹⁹ It also binds soluble host factors, such as the secretory component, the third component of complement, and complement factor H.^{520–523} The gene for this protein is present in approximately 75% of *S. pneumoniae* strains.

Pneumococci harbor a dozen proteins that are attached to the bacterial surface by docking noncovalently with the phosphorylcholine of the cell wall. These pneumococcal choline-binding proteins (CBPs) include several important surface molecules, including PspA, PspC, CbpA, SpsA [*S. pneumoniae* secretory IgA

binding protein), Hic (factor *H*-binding inhibitor of complement) and LytA (major pneumococcal autolysin).^{519,520,524,525} Sequence analysis has shown that PspC, CbpA, Hic, PbcA (C3-binding protein A), and SpsA are variants of the same CBP.⁵²⁶

When used as an immunogen in a mouse model, PspC has shown promise.⁵²⁷ Immunization of mice with a proline-rich domain of the PspC molecule results in protection against challenge with pneumococcal strains expressing both PspA and PspC, as well as those expressing only PspA, suggesting cross-protection.⁵²⁶

Pneumococcal surface adhesin A (PsaA) is a 37-kDa surface lipoprotein that contributes to pneumococcal virulence. Initially, PsaA was thought to be a pneumococcal adhesin, but genomic sequence comparison⁵²⁸ and studies on the crystal structure of PsaA⁵²⁹ revealed that it is a component of an ATP-binding cassette-type (ABC-type) permease membrane transport system. It is thought that PsaA is responsible for the uptake of Mn^{2+} (and possibly Zn^{2+}) into the bacterium.⁵³⁰ Many genes for such metal transporters exist in the pneumococcal genome. Some of these proteins, such as Adc and PsaA, are particularly important for pneumococcal virulence.⁵³⁰

The loss of host adhesion observed in PsaA- mutants is thus probably indirect. PsaA appears to have a regulatory role in adhesion by affecting the expression of CBPs on the surface of pneumococci: mutants lacking the *psa* operon demonstrate a complete absence of PspC/CbpA.⁵³¹ It has been suggested that PsaA might play an important role in regulating the expression of oxidative-stress response enzymes and intracellular redox homeostasis.⁵³²

In animal models, PsaA has been shown to be immunogenic and protective against invasive pneumococcal disease.⁵³³⁻⁵³⁵ It has been found to be highly effective against nasopharyngeal carriage in mice when administered intranasally; however, as has been shown with other proteins, combinations of antigens containing PsaA are far more effective than when PsaA is used alone.⁵³⁶

Pneumolysin (Ply) is a 53-kDa intracellular toxin produced by all clinical pneumococcal isolates. This toxin has several properties that may contribute to virulence: Ply inhibits neutrophil bactericidal activity by reducing chemotaxis, phagocytosis, and the respiratory burst.⁵³⁷ It also inhibits the lymphocyte proliferation response to mitogens, the synthesis of all Ig classes,⁵³⁸ and the beating of cilia on the human respiratory tract epithelium.^{539,540} Ply is able to induce separation of the tight junctions of the alveolar epithelial cells.⁵⁴¹ Ply also activates the classic complement pathway, thus leading to complement consumption. The activation of complement at a distance may allow pneumococci to evade opsonophagocytosis, the essential mechanism for clearance of pneumococci from the lung.⁵⁴² Pneumolysin also induces Toll-like receptor 4-dependent inflammatory responses and apoptosis in eukaryotic cells.⁵⁴³ What role each of these properties plays in pathogenesis is unclear; a serotype 1 strain causing invasive disease in Scotland was found to express a nonhemolytic pneumolysin.⁵⁴⁴

Mutants negative for Ply are less virulent than parental wild-type strains in some animal models.⁵⁴⁵ Immunization with Ply prolongs the survival of mice after challenge with pneumococci of different serotypes.⁵⁴⁶⁻⁵⁴⁸ Mice immunized with combinations of pneumococcal virulence proteins, including Ply, have significantly longer survival times than those immunized with any of the antigens alone.⁵⁴⁵ Conjugation of pneumolysin toxoids or recombinant Ply with pneumococcal capsular polysaccharides may confer broader protective immunity than conjugates using nonpneumococcal proteins.^{126,200,201,549,550} Constructs of pneumolysin-pneumococcal protein fusions conjugated to polysaccharides have also been shown to confer enhanced protection against pneumococcal disease and colonization.⁵⁵¹

Neuraminidase enzymes (NanA and NanB) cleave sialic acid residues from host glycolipids and gangliosides, causing damage to host tissues. This action may reveal new receptors for pneumococcal adhesins, facilitating both adhesion and invasion.⁵⁵² NanA is a cell surface-associated enzyme with sialidase activity produced by all clinical isolates of pneumococcus.^{553,554} NanA has the potential to cause great damage to the host by cleaving the terminal sialic acid residues from a wide variety of glycoproteins, glycolipids, and oligosaccharides present on host cell surfaces.⁵⁵⁵ It has been suggested that NanA plays a role in pneumococcal carriage and AOM. NanA may enhance pneumococcal colonization by decreasing the viscosity of mucus⁵⁵⁶ or by exposing new host cell receptors for pneumococcal adherence.⁵⁵⁶⁻⁵⁵⁸ More recently, it has been shown that NanA promotes brain endothelial cell invasion.^{559,560} Immunization of mice with purified NanA has conferred a limited degree of protection against challenge with virulent pneumococci.⁵⁶¹ In a chinchilla model, immunization with NanA resulted in significant reduction in nasopharyngeal colonization as well as in the incidence of otitis media with effusion.⁵⁶²

The more recently described group of pneumococcal vaccine candidates are a family of *pneumococcal histidine-triad proteins*. These are similar surface-exposed proteins capable of protecting mice against fatal pneumococcal infection. Distinct research groups have designated this protein family with various names on the basis of a conserved histidine triad motif (HxxHxH) repeated several times in the proteins. The proteins have been named the Php family (for pneumococcal histidine protein; PhpA, PhpB, PhpC),⁵⁶³ the Pht family (for pneumococcal histidine triad; PhtA, PhtB, PhtD and PhtE),⁵⁶⁴ and BVH3 and BVH11.⁵⁶⁵

The proteins of the Pht/Php/BVH family are immunogenic and protective against pneumococcal challenge in animal models. The immunization of mice with PhtA (BVH11-3), PhtB/PhpA (BVH11), or PhtD (BVH11-2) induced protection against invasive pneumococcal disease.⁵⁶⁴ Immunization of mice with recombinant PhpA protein significantly reduced nasopharyngeal colonization and protected mice against bacteremia and death after intranasal challenge with pneumococci.⁵⁶³ A previous study reported that immunization of mice with the recombinant proteins BVH3 and BVH11 elicited protection against both experimental pneumococcal sepsis and pneumococcal pneumonia.⁵⁶⁶ In a recent study, it was shown that natural anti-PhtD human antibodies transferred to mice protected against lethal intranasal challenge.⁵⁶⁷

The discovery of a mobile genetic element encoding a *pilus-like* structure in pneumococcus and the demonstration of a role for the pilus in virulence in mouse models have led to the consideration of pilus antigens as vaccine candidates.^{568,569} In *S. pneumoniae*, pili are encoded by two genomic islets (pilus islet 1 and 2), but these are present in only a subgroup of pneumococcal isolates. Mutants of the type 1 pilus demonstrate reduced virulence in different models. The pilus appears to be an inflammatory structure, but it remains to be determined whether the resulting inflammation promotes or reduces the ability of the bacterium to colonize or invade.⁵⁶⁹

The type 1 pilus was found to be associated with certain serotypes and correlates very tightly with genotype.⁵⁷² After the introduction of the conjugate vaccine in the United States, the prevalence of the type 1 pilus in clinical isolates dropped dramatically⁵⁷⁰ but rebounded to pre-PCV7 prevalence levels in Massachusetts within 7 years.⁵⁷³

Mice immunized with the three structural proteins that constitute the type 1 pilus (encoded by *rrgA*, *rrgB*, and *rrgC*) were protected against invasive disease resulting from pilated strains.⁵⁷⁴ The low prevalence of pilated pneumococci may limit the usefulness of these antigens, but it has been proposed that they may be used in combination with more conserved pneumococcal proteins in a multicomponent vaccine.⁵⁷⁵

Two more recent antigenic discovery approaches have been described. In one instance, investigators screened protein libraries for immunogenic targets. This approach was used to identify antigens recognized by antibody from convalescent sera of patients recovering from IPD,⁵⁷⁶ including the two antigens “protein required for cell wall separation of group B streptococcus” (PcsB) and serine/threonine protein kinase (StkP). Another strategy used a proteomic approach to identify antigens recognized by CD4⁺ Th17 cells from murine or human hosts that have been exposed to pneumococcus. The targets identified by this work appear to be different from those selected by antibody-mediated approaches and protect animals from colonization in a CD4⁺ T-cell and IL-17A-dependent manner.³⁶⁸

In general, because different virulence factors of *S. pneumoniae* may act at different stages of pneumococcal colonization and/or infection, it is likely that immunization with a combination of proteins may be the best approach. Another strategy that has been proposed would be to use a combination of a conjugate and a protein vaccine to achieve the optimal protection and the widest coverage, while simultaneously reducing the risk of replacement with strains not included in the conjugate vaccine.

An extension of this idea involves the possibility of using a killed whole-cell pneumococcal vaccine, where a large number of pneumococcal antigens would be presented at once. Published reports of numerous trials using this type strategy date back as early as 1911.⁵⁷⁷ Work in mice, has demonstrated that immunization with killed whole cells, using a variety of routes (intranasal, oral, sublingual, transcutaneous, subcutaneous, and intramuscular) and adjuvants (enterotoxins, enterotoxin mutants, or nontoxic subunits or Toll-like receptor agonists by the mucosal route, and aluminum hydroxide by the parenteral route), provides robust and reproducible protection against nasopharyngeal colonization (via CD4⁺ T cells) and invasive disease (via antibodies).⁵⁷⁸ Most recently, a good manufacturing practices (GMP)-grade whole-cell vaccine administered parenterally with aluminum hydroxide was shown to confer protection in mouse models of carriage or aspiration pneumonia/sepsis.²¹³

Human experiences with natural or vaccine-derived pneumococcal protein antigens

Over the past few years, there have been numerous reports on the natural development of antibodies to many of these pneumococcal proteins in humans, including children.^{579–585,586–588} Concentrations of antibodies to PsaA are lower in children with pneumococcal AOM than in those with nonpneumococcal AOM⁵⁸⁰ and in children with pneumococcal carriage than in noncarriers.⁵⁷⁹ Similarly, a low concentration of PspA antibodies was detected in children with invasive pneumococcal infection as compared with children with nonpneumococcal

invasive infection.⁵⁸⁴ The presence of salivary IgA antibodies (but not serum IgG antibodies) to PspA was associated with a decreased risk of pneumococcal otitis media during the following 6 months.⁵⁸⁹ Increases in anti-PsaA and anti-Ply concentrations are seen in adults with pneumococcal pneumonia, the increase being more evident in those with bacteremic pneumonia. On the other hand, anti-PspA levels showed a twofold increase in only 15% of Finnish children with invasive pneumococcal diseases. Studies in Filipino children did not support the notion that natural immunity protects against otitis media, although there were some hints that antibodies to Ply were associated with a reduction of pneumococcal carriage.⁵⁹⁰

Human adults have been shown to naturally produce antibodies to PhtA and PhtB.⁵⁶⁶ Likewise, pneumococcal contacts have been shown to induce the development of natural antibodies in infants.⁵⁹¹ Antibodies to PhtA and PhtD have been detected in convalescent-phase sera from patients with pneumococcal bacteremia.⁵⁶⁴

McCool and associates²²⁰ provided evidence that serum IgG and/or secretory IgA targeting the variable terminal region of PspA were associated with reduced likelihood of carriage and that experimentally induced nasal colonization in human adults induces serum IgG antibodies to both PspA and CbpA.²²¹ Finnish researchers showed that high serum anti-PsaA levels predicted low risk of progression to otitis media in colonized children older than 9 months, but in younger infants, it predicted greater likelihood of subsequent otitis media.⁵⁸⁰ In a British study, anti-CbpA and anti-Ply serum levels and salivary IgG antibody levels were higher in children undergoing adenoidectomy who were culture negative than in those obtained from children who were colonized.⁵⁹²

Whether these antibodies provide protection to children against pneumococcal colonization or are just associated with resistance to colonization remains uncertain. As described above, data in mice and humans have suggested the possibility that, independently of antibodies, CD4⁺ T cells directed against pneumococcal antigens may provide resistance to colonization.^{362,363} Adenoidal cells of children colonized with pneumococcus at the time of surgery have lower CD4⁺ T-cell proliferative responses to pneumolysin,⁵⁹³ and lower IL-22 responses to pneumococcal antigens were noted to be a risk factor for pneumococcal colonization in patients with chronic obstructive lung disease.³⁶⁹ Despite decades of research in this area, there have been very few trials of pneumococcal proteins in humans, with even fewer published to date. A phase 1 clinical trial demonstrated that the PspA vaccine, a recombinant family 1 PspA protein, is safe and elicits persistent antibodies in vaccinated volunteers.^{594,595} These antibodies, when transferred to immunocompromised mice, protected against challenge with pneumococci expressing either family 1 or family 2 PspAs. Studies of some of the other proteins mentioned above have been either completed and not yet published or are ongoing.



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Pneumococcal polysaccharide vaccines

Lisa A. Jackson

Introduction

Since the late 19th century, the study of *Streptococcus pneumoniae* and pneumococcal infections has occupied a central position in the development of a scientific basis for the control of infectious diseases.¹⁻³ The organism was first isolated and grown in the laboratory almost simultaneously by Sternberg and Pasteur in 1881. During the next decade, the pneumococcus was shown to be the chief cause of lobar pneumonia. In the early 20th century, the importance of humoral immunity in prevention of infectious diseases was recognized, in large measure as a result of studies of *S. pneumoniae*, and there was the beginning of an understanding of the potential protective effects of antiserum and vaccines.

The first large-scale clinical trial of a pneumococcal vaccine, which evaluated a crude whole-cell formulation, was conducted in 1911, at a time when the importance of serotype-specific immunity was not understood. During the next two decades, the experimental foundation was laid for understanding the importance of serotype-specific antibody to pneumococcal capsular polysaccharides and for developing an effective polyvalent pneumococcal polysaccharide vaccine. The first clinical trial of a tetravalent vaccine was reported at the close of World War II. Two hexavalent vaccines were marketed in 1946, only to be withdrawn within a few years, at least in part because physicians had little interest in a vaccine to prevent a disease they could now treat successfully with penicillin.

It remained for Austrian and Gold⁴ to demonstrate, in the early 1960s, that pneumococcal infections were still lethal in spite of appropriate antimicrobial therapy. Led by Austrian, efforts to develop a modern pneumococcal capsular polysaccharide vaccine were undertaken once again. Within a decade, the efficacy of pneumococcal polysaccharide vaccine (PPSV) was demonstrated in clinical trials conducted among gold miners in South Africa.^{5,6} In 1977, a 14-valent capsular polysaccharide vaccine was licensed in the United States for persons 2 years of age and older, which was replaced by the current 23-valent formulation in 1983.

Pneumococcal polysaccharide vaccines are poorly immunogenic in children younger than 2 years, who are at high risk of invasive pneumococcal infections. To improve the immune response to the capsular polysaccharide in young children, second-generation vaccines in which capsular polysaccharides are conjugated to one of several different proteins were developed and tested.⁷ These efforts culminated in the development of a 7-valent pneumococcal conjugate vaccine (PCV) that was demonstrated to be highly efficacious against vaccine-type invasive pneumococcal disease (IPD) in infants,⁸ which led, in 2000,

to the universal recommendation of this vaccine for all children younger than 24 months in the United States and older children with certain high-risk conditions. Since the introduction of the 7-valent pneumococcal conjugate vaccine into the routine childhood immunization schedule, remarkable declines in IPD have been documented in children and adults as a result of a herd immunity effect.⁹⁻¹³ In 2010, a 13-valent pneumococcal conjugate vaccine was licensed for children in the United States and replaced the 7-valent vaccine in the childhood immunization schedule.¹⁴

As in the prior edition of this book, pneumococcal conjugate vaccines are discussed in a separate chapter (see Chapter 25). Pneumococcal conjugate vaccines are routinely recommended for children, and so, that chapter also includes a discussion of pneumococcal infections in children. This chapter focuses on the use of unconjugated pneumococcal polysaccharide vaccines and pneumococcal infections in adults.

Background

Clinical pneumococcal infections

Streptococcus pneumoniae is an asymptomatic colonizer of the nasopharynx and is a major cause of a diverse array of infections, including pneumonia, meningitis, bacteremia, sinusitis, and otitis media. The organism causes infection either by direct extension from the nasopharynx, leading, for example, to pneumonia or otitis media, or by invasion into normally sterile fluids, leading to syndromes such as bacteremia or meningitis. Invasive pneumococcal disease (IPD) is defined by the isolation of *S. pneumoniae* from a normally sterile site, such as blood, cerebrospinal fluid (CSF), pleural fluid, or synovial fluid.

Bacteriology and pathogenesis

The microorganism initially observed by Sternberg and Pasteur was called *Pneumococcus* by Fraenkel in 1886.¹ It was renamed *Diplococcus pneumoniae* in 1920 because of its distinctive morphology. Its name was changed to *Streptococcus pneumoniae* in 1974 because of its many similarities to other streptococci. Historically, the demonstration in 1944 by Avery, MacLeod, and McCarty that DNA is the active substance responsible for the genetic transformation of pneumococci from rough (non-encapsulated) to smooth (encapsulated) cells is one of the cornerstones of modern molecular biology.¹⁵⁻¹⁷ Other biologic markers, such as type specificity and antibiotic resistance, are also genetically transferable.

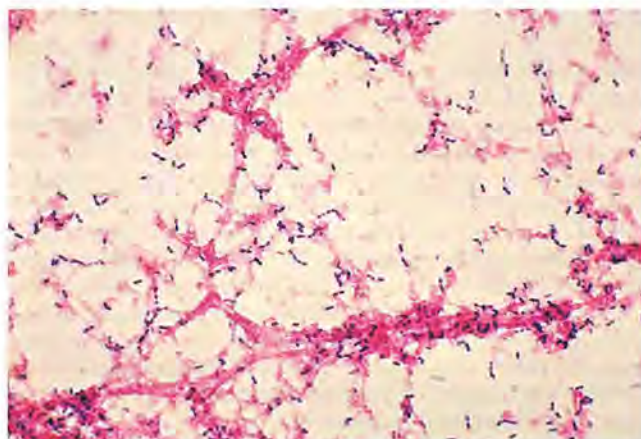


Figure 26-1 Photomicrograph of *Streptococcus pneumoniae* bacteria isolated from a blood culture. (Obtained from the Public Health Image Library [PHIL; <http://phil.cdc.gov/phil/details.asp>]; in the public domain.)

Pneumococci are relatively fastidious, facultative anaerobic organisms that grow in short chains in broth culture and appear as lancet-shaped gram-positive diplococci or chains of cocci when examined microscopically (Figure 26-1). Growth requires a source of catalase, obtained by adding red blood cells to the growth medium, to neutralize the large amounts of hydrogen peroxide produced by the bacteria. On blood agar, colonies characteristically produce a zone of alpha (green) hemolysis, which differentiates *S. pneumoniae* from the group A (beta hemolytic) streptococcus, but not from alpha hemolytic (viridans) streptococci. Pneumococci are distinguished from other alpha hemolytic streptococci by two key reactions: optochin susceptibility and solubility in deoxycholate (bile). Pneumococci, but not most other streptococci, are inhibited by optochin and undergo lysis by bile salts. Some pneumococcal isolates, however, are resistant to optochin,¹⁸ and therefore solubility of the colony in bile is usually regarded as definitive for routine diagnostic purposes. More recently available molecular methods for identification of isolates of pneumococci include a commercially available deoxyribonucleic acid (DNA) probe hybridization test (AccuProbe, San Diego, CA).¹⁹

The capsular polysaccharide on the cell surface (Figure 26-2) is one of the primary factors responsible for the virulence of *S. pneumoniae* in the normal host.²⁰⁻²² The capsule interferes with phagocytosis by preventing complement C3b opsonization of the bacterial cells. Antibodies to the capsular polysaccharides are protective. More than 90 pneumococcal serotypes have been identified on the basis of antigenic differences in the capsular polysaccharide. Traditionally, capsular serotypes were defined by the Quellung reaction, using polyclonal rabbit sera. The Quellung reaction is, however, not sufficiently sensitive to distinguish serotypes with small structural differences, and more recently, molecular techniques have been used to identify new pneumococcal serotypes, such as 6C, which was indistinguishable from serotype 6A using the Quellung reaction.²³ Antipneumococcal vaccines are based on formulations of various capsular (polysaccharide) antigens derived from the selected serotypes.

The cell wall of *S. pneumoniae* is roughly six layers thick, and peptidoglycan and teichoic acid are the principal components. Cell wall (C-) polysaccharide consists of teichoic acid that is covalently linked to a peptidoglycan backbone on the outer surface of the cell wall and is present in all isolates.²⁰⁻²² C-polysaccharide plays a major role in stimulating the inflammatory response associated with pneumococcal infections^{24,25} and is responsible for serologic cross-reactivity between *S. pneumoniae* and other streptococci. It reacts with a specific β -globulin in human serum (C-reactive protein) in the early

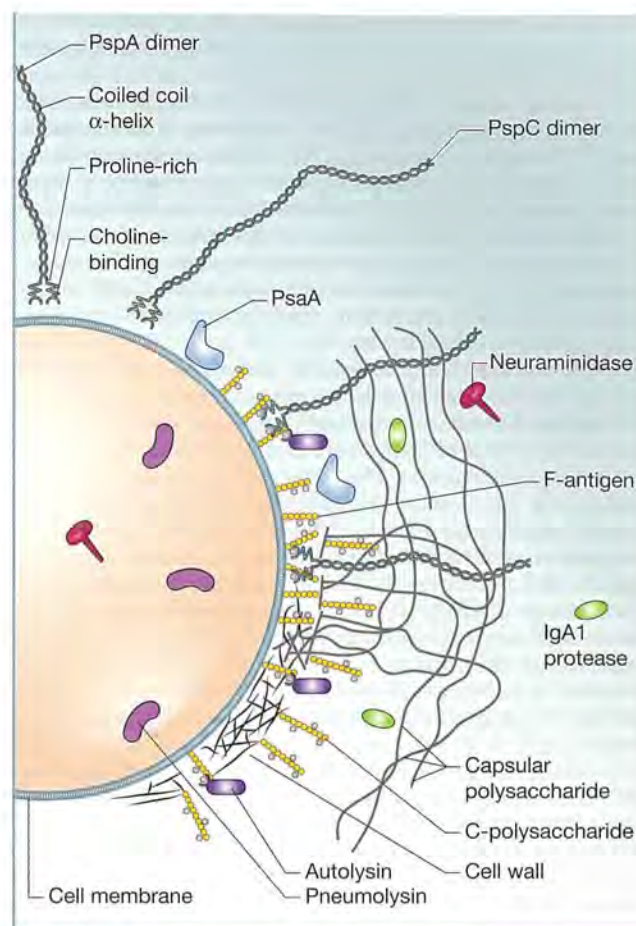


Figure 26-2 A representation of the cell membrane, cell wall, and capsule of *Streptococcus pneumoniae*. (Modified from Brille DE, et al. PspA and PspC: their potential for use as pneumococcal vaccines. Microb Drug Resist 3:401-408, 1997.)

stages of the inflammatory response and activates the alternative complement pathway. Antibody to C-polysaccharide appears early in life and can be found in virtually all children and adults, but antibodies directed against C-polysaccharide do not protect against pneumococcal infection.²⁶

On the basis of functional genomic analysis, it is estimated that the pneumococcus contains more than 500 surface proteins. The role of several pneumococcal proteins in the pathogenesis of *S. pneumoniae* infections is being increasingly elucidated. These proteins, including pneumolysin, pneumococcal surface protein A (PspA), pneumococcal surface protein C (PspC), pneumococcal surface antigen A (PsaA), neuraminidase enzymes, and histidine-triad proteins, are the targets for a new generation of protein-based vaccines.^{20,21,24,27-57} The potential advantages of such vaccines include greater cross-protection among different capsular serotypes, and enhanced immunogenicity compared with current vaccines.⁵⁸⁻⁶² More information on these virulence proteins and the current state of pneumococcal protein vaccine development may be found in Chapter 25 "Pneumococcal conjugate vaccine and pneumococcal common protein vaccines".

Diagnosis

The diagnosis of invasive pneumococcal disease is definitively established by isolation of the organism from blood or another normally sterile site (eg, cerebrospinal, pleural, or synovial fluid). Culture may, however, be negative in patients with

IPD because the sensitivity of culture is reduced with delays in specimen collection and transport and with prior administration of antibiotics.^{63,64}

The diagnosis of non-IPD pneumococcal infections, such as nonbacteremic pneumococcal pneumonia, is more complicated. The majority of cases of pneumococcal pneumonia are not associated with bacteremia, and so the etiology of those cases cannot be determined by blood culture. In addition, cases of bacteremic pneumococcal pneumonia may not be identified by blood culture if the culture is falsely negative for the reasons indicated above. For these reasons, a negative blood culture from a patient with pneumonia does not exclude the pneumococcus as the causative agent.

In patients with pneumococcal pneumonia, other microbiologic studies may also be falsely negative, or, if positive, the results difficult to interpret.^{20,65–69} Significant limitations of diagnostic tests of sputum are that at least 40% of patients are unable to produce an adequate expectorated sputum specimen, and if an adequate specimen is available, the diagnostic value is significantly reduced by prior antibiotic treatment.^{63,70} In patients with community-acquired pneumonia who have not received antibiotics and who can submit an adequate sputum specimen, identification of pneumococci in the sputum specimen is not optimally specific because the presence of the organism could be due to respiratory colonization rather than infection. For this reason, identifying the pneumococci as the etiology of community-acquired pneumonia presents particular challenges.

Considerable attention has been given to identifying alternative techniques that would overcome the limitations of sputum testing in patients with community-acquired pneumonia.⁷¹ A rapid immunochromatographic assay for the detection of *S. pneumoniae* antigen became commercially available in 1999. The test, BinaxNOW *S. pneumoniae*, detects the *S. pneumoniae* C polysaccharide cell wall antigen, which is common to all strains of *S. pneumoniae*. The assay was originally developed to detect pneumococcal antigen in urine, and that method is associated with a sensitivity of 70% to 80% and a specificity of greater than 90% for identification of *S. pneumoniae* as the etiology of pneumonia.^{72–74} Its main advantages are its rapidity, simplicity, high specificity in adults, and the ability to detect the antigen, even with lower bacterial counts resulting from prior antibiotic therapy. The urinary test is less specific for the diagnosis of pneumococcal pneumonia in children, who are more likely to have false-positive results resulting from respiratory colonization with *S. pneumoniae*.^{75–78} The BinaxNOW test is also approved for the rapid diagnosis of pneumococcal meningitis by testing of CSF samples, with a sensitivity of at least 95% and a specificity of 100%.^{79–81} The test has also been used to detect *S. pneumoniae* antigen in pleural fluid specimens,^{82–84} bronchoalveolar lavage fluid samples,⁸⁵ and blood cultures.⁸⁶

The newest approach to diagnosing pneumococcal infections has been to use nucleic acid–amplification techniques.⁸⁷ Although polymerase chain reaction (PCR)-based assays are highly sensitive, their use for detection of *S. pneumoniae* in respiratory samples can be limited by nonspecificity of the gene targets, some of which may also be present in other organisms, such as *S. pseudopneumoniae*⁸⁸ and nonpneumococcal viridans group streptococci that are oropharyngeal colonizers, which can lead to false-positive results. The test may also detect asymptomatic colonization with *S. pneumoniae*, and so a positive test may not be indicative of pneumococcal infection.^{89–97} The first concern may be addressed by the use of gene targets found only in *S. pneumoniae*.⁹⁸ The second concern may potentially be addressed by the use of quantitative real-time PCR methods to prevent false-positive results resulting from colonization with small numbers of organisms.^{99,100} In patients with meningitis, PCR is highly sensitive and specific for detection of *S. pneumoniae* in CSF samples.^{101,102}

Treatment and resistance

The breakpoints for susceptibility when testing penicillin against *S. pneumoniae* for infections other than meningitis were revised in January 2008.¹⁰³ The revised susceptibility breakpoint is less than or equal to 2 µg/mL for nonmeningeal infections and remains unchanged at less than or equal to 0.06 µg/mL for pneumococcal meningitis. As a consequence of this revision, the proportion of nonmeningeal pneumococcal isolates defined as nonsusceptible to penicillin has dramatically decreased, and greater than 95% of pneumococcal isolates are expected to be defined as susceptible based on the revised definition.¹⁰⁴ Infections outside the central nervous system that are known to be caused by the pneumococci may therefore be treated with parenteral penicillin, if appropriate, or other recommended antibiotics.

Epidemiology of pneumococcal infections

Invasive pneumococcal disease

Invasive pneumococcal disease is defined by isolation of *S. pneumoniae* from a normally sterile site, such as blood or CSF. As with many other infectious diseases, rates of IPD are highest at the extremes of age. In 2010, the Centers for Disease Control and Prevention (CDC) Active Bacterial Core Surveillance (ABCs) program estimated the following rates (per 100,000 population) by age in the United States: 34.2 for children younger than 1 year, 26.6 for one year olds, 3.1 for 2 to 4 year olds, 2.2 for 5 to 17 year olds, 3.8 for 18 to 34 year olds, 10.5 for 35 to 49 year olds, 18.8 for 50 to 64 year olds, and 36.4 for persons 65 years of age and older.¹⁰⁵ Case fatality is much higher in older adults. In 2010, the case fatality rate of IPD in persons 65 years of age and older was 15% compared with less than 1% in children younger than 5 years. A total of 39,750 cases and 4,000 deaths resulting from IPD are estimated to occur in the United States annually. Pneumonia with bacteremia accounts for the majority (70%) of cases of IPD. Bacteremia without focus and meningitis account for 17% and 6%, respectively. Rates of IPD increase in the winter, but this seasonal variation is not clearly attributable to lower temperature and may be due to factors such as photoperiod-dependent variation in host susceptibility.^{106,107} Although most IPD is community acquired, IPD can be nosocomially acquired. A population-based study in Finland reported that nosocomial pneumococcal bacteremia accounted for 10% of hospitalized pneumococcal bacteremia cases.¹⁰⁸

In the United States, the overall rates of IPD in persons of all ages declined substantially after the introduction of the 7-valent pneumococcal conjugate vaccine into the recommended childhood immunization schedule in 2000.^{9–11,109–112} Similar reductions have been reported from other countries where PCV7 is routinely used in infants, including Canada¹¹³ and England.¹¹⁴ In the United States, in the ABCs network, the overall incidence of IPD for persons of all ages declined by 45%, from 24.4 per 100,000 population during 1998 to 1999 to 13.5 cases per 100,000 population in 2007.¹¹ Rates of IPD caused by PCV7 serotypes among persons of all ages declined by 94%, from 15.5 per 100,000 population in 1998 to 1999 to 1.0 per 100,000 population in 2007. Among adults, the greatest absolute declines in both overall IPD rates and rates of IPD caused by the PCV7 serotypes were among those 65 years of age and older. Conversely, there were consistent, but smaller, increases in the rates of IPD caused by serotypes not contained in PCV7, with an overall increase of 29%, from 6.1 cases per 100,000 population in 1998 to 1999 to 7.9 per 100,000 in 2007. Most of this increase, termed a replacement effect, has been due to increased rates of disease caused by serotype 19A.

The declines in IPD caused by the PCV7 serotypes among adults has been attributed to herd immunity effects, whereby

the decreased presence and circulation of PCV7 serotypes leads to a decline in pneumococcal transmission from vaccinated children to unvaccinated children and adults. Among older adults in the United States, the declines in IPD since 2000 cannot be attributed to the modest increases in PPSV23 vaccination rates that have occurred since that time, because the incidence of IPD caused by the 16 serotypes included in PPSV23 but not in PCV7 has increased, by 26% among persons 65 years of age and older and by 48% in 18 to 64 year olds.¹¹ In 2010, a 13-valent pneumococcal conjugate vaccine that includes serotype 19A was licensed in the United States and replaced the 7-valent vaccine in the childhood immunization schedule.¹⁴ Ongoing surveillance is needed to assess whether reductions in the IPD caused by the PCV7 serotypes are sustained, whether reductions in disease caused by the six additional serotypes in PCV13 occurs after routine use of that vaccine in young children, and whether replacement disease caused by non-PCV13 serotypes will impact the benefits derived from the herd immunity effect.

Risk factors for invasive pneumococcal disease

In general, rates of IPD in adults are higher in males and increase with age. Certain racial and ethnic groups are at increased risk, and several studies in the United States document substantially higher rates of invasive pneumococcal disease in blacks than in whites.¹¹⁵⁻¹²⁴ These findings apply to both elderly persons and younger adults, regardless of human immunodeficiency virus (HIV) status. Even higher rates of invasive disease have been reported among the White Mountain Apaches in Arizona,^{125,126} the Alaskan Native population,¹²⁷⁻¹²⁹ and aboriginal populations in Australia.¹³⁰⁻¹³³

Certain chronic conditions, in particular immunocompromising conditions, are also associated with an increased risk of IPD, independent of age. One study that identified cases of IPD in adults in 1999 and 2000 found that adults with chronic conditions were at substantially elevated risk of disease compared with healthy adults.¹²³ For example, the rate of IPD, in cases per 100,000 person-years, was 9 among healthy adults compared with rates of 51 among adults with diabetes, 63 among adults with chronic lung disease, 94 among adults with chronic heart disease, and 100 among adults who abused alcohol. Among immunocompromised adults, disease rates are even higher, with rates of 300 among adults with solid cancer, 423 among adults with HIV/acquired immunodeficiency syndrome (AIDS), and 503 among adults with hematologic cancer. Among the latter group, another study found that adults with multiple myeloma appear to be at particularly high risk.¹³⁴

An evaluation of IPD cases from the Toronto area found similarly high rates among transplant recipients, with an overall incidence of 146 cases of IPD per 100,000 adult transplant recipient person-years, which was about 13-fold higher than the rate in the general adult population.¹³⁵ The risk was highest in liver (354 cases per 100,000 person-years) and lung (239 cases per 100,000 person-years) transplant recipients. Children and adults with functional or anatomic asplenia are also at greatly increased risk of pneumococcal bacteremia, which is associated with a high fatality rate.¹³⁶⁻¹⁴¹

More recently, an increased risk of pneumococcal meningitis has been identified in persons of all ages with cochlear implants.¹⁴²⁻¹⁴⁴

HIV infection

Persons with HIV infection are at substantially increased risk of pneumonia and bacteremia caused by *S. pneumoniae*.¹⁴⁵⁻¹⁴⁸ Among HIV-infected persons, as in the general population, *S. pneumoniae* is the most common cause of bacterial pneumonia.¹⁴⁹ Pneumococcal infections often occur earlier in the course of HIV disease than do other opportunistic infections,^{150,151} and recurrences are more common in HIV-infected adults compared with immunocompetent adults.^{121,150-154} The risk of pneumococcal infection is inversely related to CD4⁺ count, and persons with

CD4⁺ T-cell counts less than 200 are at highest risk.^{155,156} Among HIV-infected adults in the United States, the risk of invasive pneumococcal disease is higher in blacks than whites.^{121,123,155,157} Rates of invasive pneumococcal disease in HIV-infected persons not on antiretroviral therapy are 50 to 100 fold higher than in age-matched uninfected adults.^{121,152} Surveillance studies in the United States and Spain have documented significant declines in the rates of invasive pneumococcal disease in HIV-infected persons after introduction of highly active antiretroviral therapy (HAART).^{153,158} More recent studies have documented further declines in rates of IPD in HIV-infected adults after introduction of PCV7 for children.^{159,160} In the United States, rates of IPD in HIV-infected persons declined by half to two thirds after widespread use of HAART, and rates declined another 25% following introduction of PCV7 for children.¹⁶⁰ However, even with these declines, adults with HIV infection are still at much higher risk of invasive pneumococcal disease than adults without HIV infection.^{123,147,153,158,160,161}

Asthma and cigarette smoking

In 2008, the Advisory Committee on Immunization Practices (ACIP) recommendations for use of PPSV23 for prevention of invasive pneumococcal disease were revised to add asthma and cigarette smoking as indications for PPSV23 for adults 19 to 64 years of age.¹⁶² There is consistent evidence from observational studies that cigarette smoking is a strong and independent risk factor for IPD in adults. A case-control study of immunocompetent adults 18 to 64 years of age found a 4-fold higher risk of IPD in current smokers and a 2.5-fold higher risk of IPD in those with passive exposure to smoke compared with adults who had never smoked and had no passive exposure.¹²² In that study, 51% of IPD cases were attributable to smoking. Two other population-based studies of adults, which compared the prevalence of smoking in adults with IPD with the estimated prevalence of smoking among adults in the source population, also found about a 2-fold higher risk of IPD in smokers.^{119,124} These data indicate that smoking is the strongest risk factor for IPD in immunocompetent nonelderly adults.

Before 2008, the ACIP guidelines recommended PPSV23 vaccination for persons with chronic pulmonary diseases (such as chronic obstructive pulmonary disease [COPD] and emphysema) and for those immunocompromised by high-dose, long-term corticosteroid therapy, but asthma alone was not an indication for vaccination.¹⁶³ Asthma was added as an adult vaccine indication on the basis of data suggesting that asthma may be a risk factor for IPD, but the evidence supporting asthma as a risk factor, independent of smoking, among adults younger than 65 years who lack the vaccine indications of COPD, emphysema, or chronic corticosteroid treatment is not as well defined as that regarding smoking as a risk factor for IPD in adults. Two population-based studies of nonelderly adults, one in Tennessee and one in Finland, identified about a twofold higher risk of IPD in persons with asthma, but those studies lacked accurate information on smoking status and so could not determine whether the association of asthma with disease risk was independent of smoking.^{164,165} A third population-based study, from Pennsylvania, compared the characteristics of adults 18 years of age and older with IPD, as defined by medical record review, with the characteristics of the source population, as determined by a regional health survey, and found that smoking, but not asthma, was associated with a higher risk of disease.¹²⁴ Two other studies evaluated the association of asthma and risk of pneumococcal pneumonia, with or without IPD, in adults; one found a higher risk among adults with asthma¹⁶⁶ while the other found no association.¹⁶⁷

Pneumococcal pneumonia

S. pneumoniae is a predominant cause of community-acquired pneumonia, but the exact burden of pneumococcal pneumonia is difficult to accurately define because routine diagnostic

tests are not optimally specific or sensitive for nonbacteremic pneumococcal pneumonia, which accounts for the majority of cases of pneumococcal pneumonia. In most studies of the etiology of hospitalized community-acquired pneumonia in adults, *S. pneumoniae* is ranked first among all known causes.^{138,168–201} Historically, however, an etiologic agent is not identified for a relatively large proportion of pneumonia cases, typically about half. Application of molecular diagnostic methods has the potential to improve the diagnostic yield. A study of adults hospitalized with pneumonia in Sweden, which included traditional diagnostic testing methods as well as PCR testing of sputum and BinaxNOW testing of urine samples, identified a microbial etiology for 89% of patients with complete sampling.²⁰² Among that group, *S. pneumoniae* was identified in 63%, and, of those with *S. pneumoniae* identified, a second microbial agent, most commonly a respiratory virus, was found in half.

An assessment of the clinical and economic burden of pneumococcal disease in older US adults identified the burden of community-acquired pneumonia (outpatient and hospitalized) in adults 50 years of age and older in the United States from published studies and then assumed that 30% of such cases were caused by *S. pneumoniae*. This study estimated that *S. pneumoniae* accounts for about 500,000 cases of nonbacteremic pneumococcal pneumonia (and an additional 29,500 cases of IPD) in adults 50 years of age and older in the United States each year, leading to \$3.7 billion in direct costs annually.²⁰³

Reservoirs of infection: the carrier state

The human nasopharynx is the only natural reservoir for *S. pneumoniae*, and colonization of the nasopharyngeal epithelium represents the first step in the pathogenesis of pneumococcal infections.^{204,205} Thus, it is not surprising that the greater incidence of pneumococcal infections in young children compared with adults is paralleled by higher carrier rates. Carriage studies provide an estimate of the baseline pneumococcal serotypes, to provide information for vaccine composition and to monitor changes induced by biologic pressure derived from antibiotic therapy or vaccinations.

Colonization studies have been conducted in many locales, and demonstrate much higher carriage among children than adults.^{20,206–224} After acquisition, the duration of carriage is also longer in children compared with adults, and *S. pneumoniae* may be introduced into households by children and is then spread to other family members.²²⁴ Among adults, carriage rates may be much higher among certain populations, including adults with AIDS, military personnel, cigarette smokers, and native Alaskans,^{218–222} but are lower in elderly persons.²²⁵

Pneumococcal conjugate vaccines provide serotype-specific protection and also reduce carriage of vaccine-related serotypes in the vaccinated individual. Since the introduction of PCV7 in the United States, numerous studies have documented declining rates of colonization with PCV7 serotypes in vaccinated children.^{226,227} Data from vaccine trials and from observational studies conducted soon after the introduction of PCV7 have suggested that replacement of vaccine serotypes by nonvaccine serotypes in the nasopharynx could occur after widespread vaccination.^{227–229} A study among native Alaskan adults demonstrates that pediatric vaccination with conjugate vaccines has resulted in changes in dynamics of adult carriage as well, with decreases in vaccine serotypes and increases in nonvaccine serotypes.²¹⁹ Similarly, a household carriage study conducted in the context of a clinical trial of PCV7 vaccine among children in southwestern American Indian communities found that vaccination of children in the household was associated with lower rates of carriage with PCV7 serotypes in the parents, which was offset by increased rates of carriage of serotypes not included in the vaccine.²³⁰ Unlike pneumococcal conjugate vaccines, vaccination with PPSV23 does not appear to reduce nasopharyngeal carriage of vaccine type strains of *S. pneumoniae*.

Passive immunization

Human immune globulin intravenous (IGIV) preparations commercially available in the United States contain varying amounts of antibody to pneumococcal capsular polysaccharides.^{231–233} Chronic prophylaxis with IGIV is used to prevent infections with encapsulated bacteria in patients with primary immunodeficiency disorders. This therapy has also been shown in randomized controlled trials to reduce the risk of serious bacterial infections in patients with secondary immunodeficiency resulting from chronic lymphocytic leukemia²³⁴ and multiple myeloma.²³⁵ The generally low levels of anticapsular polysaccharide antibodies present in commercially available IGIV preparations require that relatively high doses be given, usually 400 mg/kg every 28 days.

During the pre-HAART era, IVIG was effective in preventing serious bacterial infections in symptomatic HIV-infected children, but this effect was restricted to children who were not receiving concurrent trimethoprim-sulfamethoxazole prophylaxis.²³⁶ Currently, immune globulin intravenous prophylaxis is recommended for primary prevention of serious bacterial infections only in HIV-infected children who have hypogammaglobulinemia (IgG < 400 mg) or functional antibody deficiency.²³⁷

Active immunization with pneumococcal polysaccharide vaccine

History

Vaccines to prevent pneumococcal infection were first evaluated in the early 1900s. Several heat- or formalin-inactivated whole-cell pneumococcal vaccines were initially studied,²³⁸ followed by the development and evaluation of more purified capsular polysaccharide vaccines.²³⁹ Two hexavalent pneumococcal capsular polysaccharide vaccines were licensed in the United States shortly after World War II, but the promise of newly available antimicrobials effective against pneumococcal infections led to diminished interest in the use of vaccines, and those two vaccines were eventually withdrawn from the market. In the 1960s, recognition of continued morbidity and mortality from pneumococcal infections despite the use of appropriate antibiotics⁴ led to renewed interest in prevention of disease by vaccination. A 14-valent vaccine, containing 50 µg of each capsular polysaccharide per dose was licensed in 1977, and in 1983, this vaccine was replaced by 23-valent vaccines containing 25 µg of each polysaccharide per dose.²⁴⁰

Vaccine and administration

The 23-valent vaccine formulations currently available contain capsular polysaccharides of 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.¹⁶³ Selection of the vaccine serotypes was based primarily on the distribution of strains causing invasive pneumococcal disease. Before the introduction of 7-valent pneumococcal conjugate vaccine for children in the United States in 2000, the 23 serotypes in pneumococcal polysaccharide vaccine accounted for more than 85% of strains that caused invasive disease in adults in the United States.^{110,163} After introduction of 7-valent pneumococcal conjugate vaccine for children, and the resulting herd immunity effect, rates of invasive pneumococcal disease caused by the seven serotypes included in the 7-valent pneumococcal conjugate vaccine (and also contained in the 23-valent pneumococcal polysaccharide vaccine) have declined in older adults.^{11,110} In the years 2006 and 2007, the 23 pneumococcal polysaccharide vaccine serotypes accounted for 65% of cases of invasive pneumococcal disease in adults 65 years of age and older in the United States.¹¹

Two vaccine manufacturers produce 23-valent pneumococcal vaccines, and Pneumovax 23 (Merck, Whitehouse, NJ) and Pneumo 23 (Sanofi Pasteur, Swiftwater, PA) formulations are available in Canada and Europe. In the United States, only Pneumovax 23 is available. These vaccines consist of polysaccharides dissolved in isotonic saline, with either phenol (0.25%, Pneumovax 23) or thimerosal (0.01%, Pneumo 23) added as a preservative. They contain no adjuvants. They should be stored at 2° C to 8° C and should not be frozen. Under those conditions, they are stable for 24 months. Techniques that simultaneously measure the consistency of molecular size and the antigenicity of individual polysaccharides have helped to ensure uniformity between different lots of vaccine.²⁴¹

Pneumococcal polysaccharide vaccine should be administered as a single 0.5-mL dose. The vaccine is approved for intramuscular or subcutaneous administration.¹⁶³ Intramuscular administration is believed to be less reactogenic and so is the preferred route. The vaccine should not be administered intradermally because this can cause severe local reactions. Pneumococcal polysaccharide vaccine can be administered simultaneously with influenza vaccine.²⁴² Administration of PPSV23 concomitantly with zoster vaccine does not impact the response to PPSV23 but, in a trial of concomitant administration, anti-varicella-zoster virus antibody levels were significantly lower after concomitant administration of PPSV23 and zoster vaccine compared with levels after administration of zoster vaccine alone.²⁴³ The Zostavax package insert advises that administration of the two vaccines separated by at least 4 weeks should be considered. An observational study reported no difference in risk of medically attended herpes zoster after Zostavax in persons who received Zostavax concomitant with PPSV23, compared with persons who received Zostavax alone.²⁴⁴

Immunogenicity of vaccine

Laboratory methods to assess antibody response

Pneumococcal antibody assays can be broadly divided into two groups. Antibody-mediated killing of *S. pneumoniae* by phagocytes involving complement is generally the primary mechanism of protection against pneumococcal infections, and the ability of a serum sample to opsonize pneumococci can be measured by in vitro opsonophagocytosis assays (OPAs), also called functional assays. In contrast, antibody binding assays, which include the older radioimmunoassays (RIAs) and the more modern enzyme-linked immunosorbent assays (ELISAs), are used to quantify the amount, but not the function, of circulating antibodies to pneumococcal capsular polysaccharide.

In general, OPAs are believed to provide the best functional correlate of vaccine-induced protection in humans. Opsonophagocytic assays include four components: the serum specimen, pneumococcal bacteria, a standardized source of complement (human or rabbit), and culturable phagocytes.²⁴⁵ The classic OPA, or killing-type OPA, determines the titers of sera that reduce the number of live bacteria by more than half because of opsonophagocytosis. Traditionally, the number of surviving bacteria was measured by manually counting bacterial colonies, and the assay was extremely labor intensive, which limited its use. More recently, assay efficiency has been improved by modifications such as the use of an optical readout to measure surviving bacteria. The labor requirements of the standard OPA have also led to the development of other types of OPAs. Phagocytosis-type OPA methods measure the phagocytosis of fluorescently labeled bacteria by flow cytometry.²⁴⁶ Multiplexed OPAs are also being developed to overcome the limitation in traditional OPAs, which could assess only one serotype-specific antibody at a time.²⁴⁷ These

technical innovations that improve testing efficiency will likely allow more widespread use of OPAs in clinical studies.

Measures of antibody avidity are also believed to correlate with functional activity. The avidity of capsule-specific antibodies correlates with their ability to mediate complement-dependent killing of the organism.^{248,249} Avidity is measured by incubation of antibodies bound to the solid phase with the mild denaturing agent ammonium thiocyanate.²⁵⁰ Results can be expressed as the avidity index, which is equal to the molar concentration of ammonium thiocyanate required to elute 50% of antibody bound under conditions of antigen excess.

Several antibody binding assays for measuring serotype-specific pneumococcal antibody concentrations have been developed, with the ELISA, being the method now most commonly used.^{251–254} Nearly all contemporary studies of the immune response to pneumococcal polysaccharide vaccine report ELISA results. Enzyme-linked immunosorbent assays measure total serotype-specific antipneumococcal antibody levels, including both functional and nonfunctional antibodies, and so the antibody concentrations measured by ELISA do not necessarily correlate with functional antibody activity.²⁴⁸

To improve the specificity of ELISAs, the original ELISA methods developed in the 1980s have since been modified to include two absorption steps to remove cross-reactive antibodies that are not serotype specific. The first modification was to add an absorption step to remove antibodies to pneumococcal cell wall polysaccharide. All persons, regardless of vaccination status, have antibodies to the cell wall polysaccharide, and in unimmunized persons, the antibody levels to cell wall polysaccharide may exceed those of antibody to the type-specific polysaccharide. Once this problem was recognized, second-generation ELISAs were developed in the late 1980s, which reduced the impact of nonspecific antibody binding in the ELISA by including a preadsorption step to neutralize cell wall polysaccharides in serum samples before the ELISA measurement. It was more recently discovered that even after antibodies to cell wall polysaccharide are removed from test sera, a substantial amount of nonspecific antibodies may still be measured by ELISA.^{255–258} This is probably due to the presence of nonspecific antibodies that bind to novel epitopes that contaminate commercial preparations of capsular polysaccharides. A heterologous type 22F pneumococcal polysaccharide can be used to adsorb out antibodies to these common epitopes.^{259,260} Serotype 22F was chosen for this purpose because the capsular polysaccharide is readily available and, although it is included in the 23-valent pneumococcal polysaccharide vaccine, is not likely to be included in future conjugate vaccines. Absorption with 22F capsular polysaccharide has improved the correlation between IgG levels determined by ELISA and opsonophagocytic titers in some^{259,261} but not all²⁵⁵ studies. A guidance protocol for third-generation pneumococcal IgG antibody ELISAs has been developed,²⁶² and the details can be found at www.vaccine.uab.edu.

Correlates of protection

There is considerable interest in establishing correlates of protection in children at the population level, to facilitate evaluation and licensure of new pneumococcal conjugate vaccine formulations. A World Health Organization (WHO) working group used data from three clinical efficacy trials of PCVs in infants to propose a protective threshold in infants of 0.35 µg/mL, when sera are tested with the serotype-specific ELISA with C polysaccharide absorption but not with 22F absorption.²⁶³ This is believed to correlate with a threshold of 0.32 µg/mL when double absorption is used.

Data derived from randomized vaccine trials in children are not useful in establishing a correlate of protection for adults and seniors, however. Adults and seniors generally have baseline antibody levels that are higher than levels being considered

possible correlate thresholds in children, and data from randomized controlled trials demonstrating vaccine efficacy in adults to support identification of correlates of protection are not available. Therefore, although the results of ELISA and opsonophagocytic assays can be used to identify the relative magnitude of the immune response to vaccination in adults, these markers cannot be used to define individuals as protected or susceptible to pneumococcal infection.

Immunogenicity in adults

In immunocompetent adults, vaccination with the 23-valent pneumococcal vaccine induces significant increases in serotype-specific anticapsular antibody levels as measured by ELISA, as well

as functional activity as measured by an OPA assay.^{248,250,261,264–278} The magnitude of the immune response varies by serotype and, at the individual level, the magnitude of response to any given serotype varies widely.²⁷⁹ Some of the individual variation in vaccine response may be due to genetic factors.^{280–284}

Among adults, the magnitude of the immune response diminishes with age. In general, most studies comparing ELISA IgG antibody responses between younger and older adults report lower postvaccination geometric mean titers (GMTs) in the older group, but these differences tend not to be substantial.^{250,266,268,273,274} In contrast, OPA titers are generally markedly lower in elderly adults compared with young adults (Figure 26-3).^{248,277,285,286} The lower OPA titers in elderly persons appear to be correlated with lower avidity of the IgG antibody

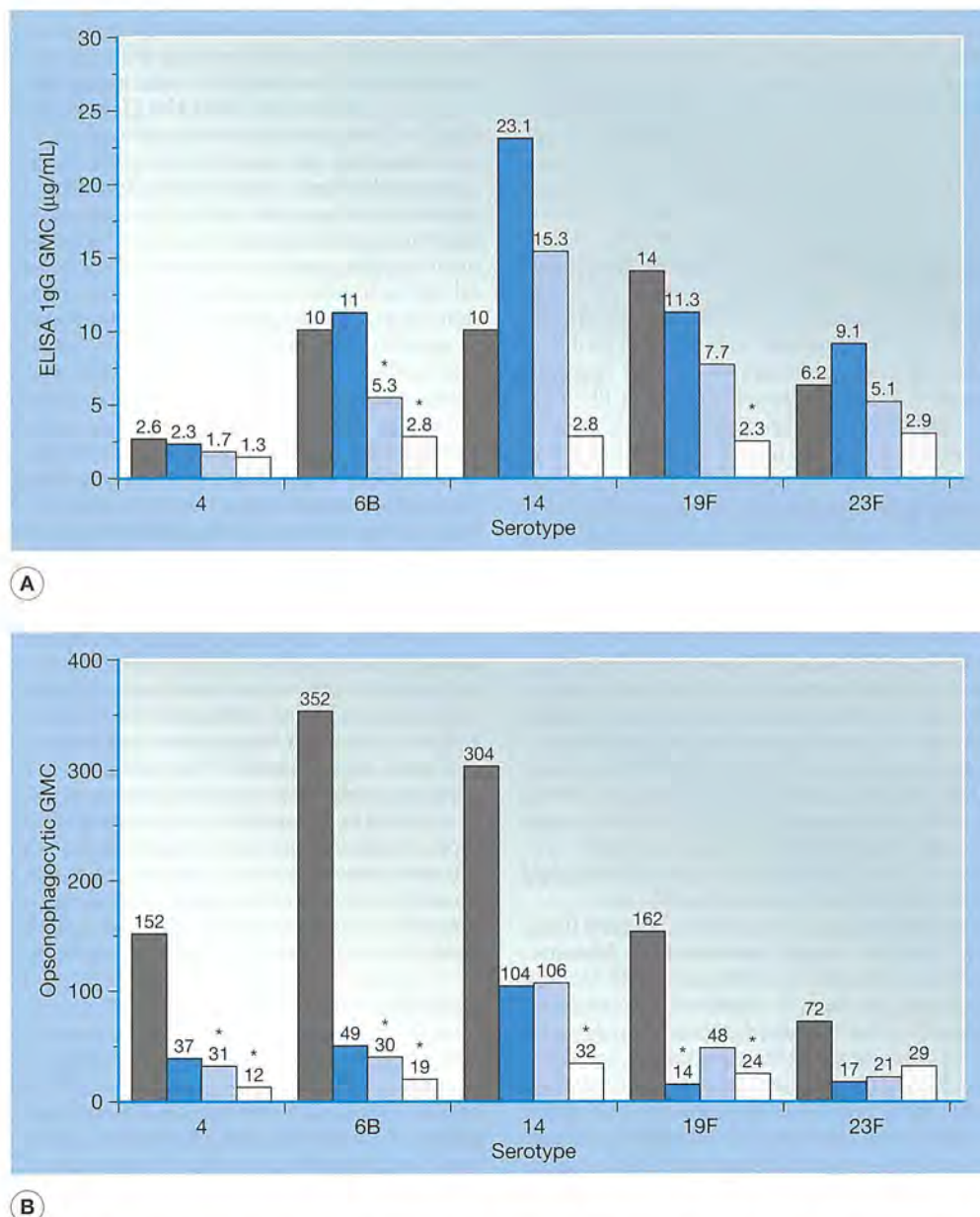


Figure 26-3 Comparison of serotype-specific enzyme-linked immunosorbent assay (ELISA) IgG geometric mean concentrations and opsonophagocytic antibody geometric mean titers in young adults and elderly adults. A, Geometric mean concentration (GMC, $\mu\text{g/mL}$) of IgG pneumococcal capsular polysaccharide-specific serum antibody, as determined by ELISA, for young control subjects (22–46 years of age; $n = 12$; black bars) and for elderly age groups (1) (63–79 years of age; $n = 10$, dotted bars), (2) (80–89 years of age; $n = 22$, striped bars), and (3) (≥ 90 years of age; $n = 14$, open bars) after vaccination with PPSV23. B, Geometric mean opsonophagocytic titer (GMT, reciprocal serum dilution) for the young control subjects and elderly age groups shown in panel A after vaccination. An asterisk designates a significant difference ($P < .05$) from values for the younger control subjects, per the Wilcoxon sample test. (Reproduced with permission from Romero-Steiner S, Musher DM, Cetron MS, et al. Reduction in functional antibody activity against *Streptococcus pneumoniae* in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. Clin Infect Dis 29:281–288, 1999.)

for pneumococcal polysaccharide.²⁴⁸ In addition, recent studies have found that, although postvaccination concentrations of serotype-specific IgG antibodies are relatively comparable between young adults and elderly adults, concentrations of IgM antibody are much lower in the elderly group.^{286,287} Further, after absorption of IgM antibody, the differences in OPA titers between the young adults and the elderly adult groups disappears, suggesting that because IgM antibodies are more efficient at fixing complement than IgG, the observed decline in functional OPA activity with advancing age is due at least in part to decreases in IgM levels with aging.²⁸⁶ Older adults also exhibit a diminished clonal expansion of B cells in response to vaccination compared with younger adults.^{287,288}

In general, the immune response, as measured by ELISA, to pneumococcal polysaccharide vaccine in immunocompetent persons with chronic medical conditions, such as heart disease, lung disease, or diabetes, is comparable to that of age-matched healthy control subjects.²⁸⁹⁻²⁹² In patients with chronic lung disease, the antibody response to vaccination does not appear to be affected by concurrent treatment with oral or inhaled steroids.²⁹³ Patients with chronic alcoholism and cirrhosis can usually mount an antibody response to pneumococcal vaccine.^{294,295} Older persons with low serum vitamin B₁₂ levels may have antibody responses to pneumococcal vaccination that are significantly lower than those of age-matched normal control subjects.²⁹⁶

Antibody persistence

In older adults, anticapsular antibody levels induced by a first pneumococcal polysaccharide vaccination tend to decline significantly in the year after vaccination,^{271,276,297} and to approximate prevaccination levels within 4 to 7 years after initial vaccination (Figure 26-4).²⁹⁷⁻³⁰¹ The clinical significance of this decline is not well defined because there are limited data regarding the duration of clinical protection induced by a first PPSV23.

Immune response to revaccination

Multiple studies have documented that older adults who receive a second PPSV23 several years after an initial vaccination demonstrate a significant increase in anticapsular antibody levels.^{297,299,302-307} Significant antibody responses to revaccination have also been documented in renal dialysis and renal transplant patients,³⁰⁸ postsplenectomy patients,^{309,310} and adults with spinal cord injury.³¹¹ Whether the degree of protection induced by revaccination is comparable to that induced by first vaccination is not clear. Pneumococcal polysaccharide vaccine induces a T-cell-independent response, and so, there is no anamnestic, or booster, response to revaccination. Given that revaccination is not expected to induce an augmented response to pneumococcal polysaccharide vaccination, the question then is whether the immune response to revaccination is comparable to that after a first vaccination. There is concern that a first vaccination with plain polysaccharide antigens may blunt the immune response to subsequent vaccination with the same polysaccharide antigens.^{276,312,313} This phenomenon of hyporesponsiveness on revaccination has been well documented, for example, in persons receiving a second dose of meningococcal serogroup C polysaccharide vaccine.³¹⁴⁻³¹⁶

The relative magnitude of the immune response to a second compared with a first pneumococcal polysaccharide vaccination has been evaluated two ways. Several studies have compared the postvaccination antibody response in persons being revaccinated with a concurrent group of persons being vaccinated for the first time. Most of those studies have demonstrated trends toward lower responses in older adults receiving a second PPSV23 compared with adults of similar age receiving a first PPSV23.^{305,306,317} A large study ($n = 981$) that followed adults 50 years of age and older, after either a first or second PPSV23, found that serotype-specific ELISA antibody geometric mean concentrations at 30 days postvaccination tended to be lower in the revaccination group compared with the first vaccination group, although the differences were generally not statistically

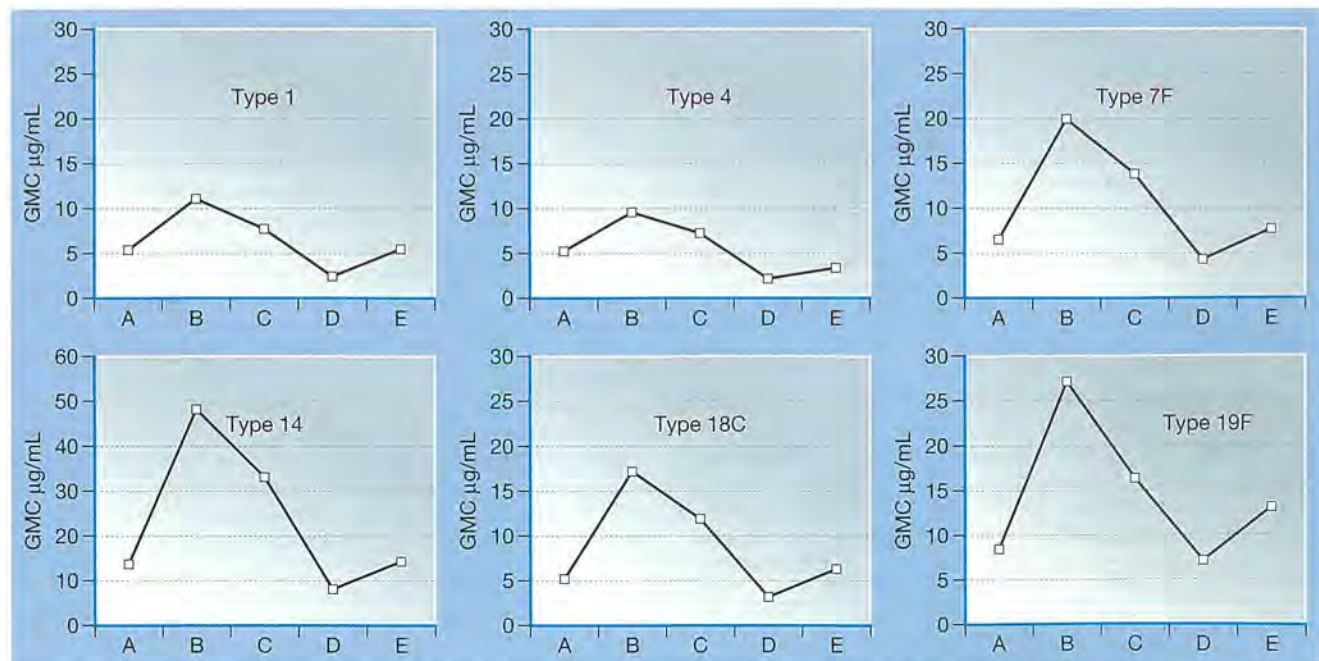


Figure 26-4 Geometric mean concentrations (GMC) of serotype-specific antibody measured by enzyme-linked immunosorbent assay (ELISA) in adults 50 years of age and older followed through their first and second pneumococcal polysaccharide vaccinations. Note that the y-axis for serotype 14 differs from the other serotypes. Time points are designated as A, Before first vaccination. B, Four weeks after first vaccination. C, One year after first vaccination. D, Immediately before revaccination 4 to 7 years after first vaccination. E, Four weeks after revaccination. (From Torling J, Hedlund J, Konradsen HB, et al. Revaccination with the 23-valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated for pneumonia. *Vaccine* 22:96-103, 2003.)

significant.³⁰⁵ Antibody levels declined over time, and at 5 years after the study vaccination, the ELISA geometric mean concentrations were similar in both groups. A substudy that tested samples by OPA, obtained from a subgroup of 120 subjects 65 years of age and older, reported similar findings.³⁰⁶ In contrast, a large study of primarily Alaska Native/Native American older adults found comparable postvaccination responses, as measured by ELISA or an OPA assay, in adults receiving their first PPSV ($n = 123$) compared with those receiving a second ($n = 121$) and those receiving a third or fourth PPSV ($n = 71$) (minimum interval of 6 years after a previous PPSV23).³⁰⁷

The immune response to revaccination has also been evaluated in longitudinal studies following the same persons through their first and second vaccinations. One assessment of eight healthy older adults who received a first pneumococcal polysaccharide vaccination at a mean age of 65 years and a second vaccination 6 years later found that the postrevaccination ELISA levels were comparable to the levels observed after the first vaccination for six of the eight serotypes evaluated, and were substantially lower after revaccination than following first vaccination for the other two serotypes.³⁰¹ A larger study evaluated 61 seniors who were first vaccinated after a hospitalization for pneumonia in conjunction with a clinical trial,³¹⁸ and who then received a second pneumococcal polysaccharide vaccination an average of 5 years later.²⁹⁷ For all six serotypes evaluated, the serotype-specific geometric mean antibody concentration was lower after revaccination than after first vaccination (see Figure 26-4). Most recently, a clinical trial designed to evaluate PCV13 also included a group of 189 subjects, 60 to 64 years of age, who received a first dose of PPSV23 at study enrollment and a second dose of PPSV23 approximately 3.5 years later.³¹⁹ OPA GMTs to 12 of the PPSV23 serotypes were assessed at 1 month after each vaccination. The GMTs after the second PPSV23 were significantly lower than those after the first vaccination for 8 of

those 12 serotypes, indicating a diminished immune response to a second PPSV23 (Table 26-1).

In the longitudinal studies, the study participants were, of course, older at the time of revaccination than at first vaccination, and so it is possible that some of the differences in the immune response to revaccination were due to an age effect rather than to an effect of prior receipt of pneumococcal polysaccharide vaccine. In addition, it should be noted that because the quantity of antibodies that correlate with protection against pneumococcal disease has not been clearly defined, for all of these studies, it is unknown if the lower antibody levels seen on revaccination correlate with inferior protection.

Immunogenicity in children

Pneumococcal capsular polysaccharides are T-cell-independent antigens, and therefore most are poor immunogens in babies. Although highly immunogenic serotypes, such as type 3, can induce antibodies in infants as young as 3 months of age,³²⁰ antibody responses to most other pneumococcal capsular polysaccharides are generally poor in children younger than 1 year. A recent study of children in Fiji who received PPSV23 at 12 months of age indicated children of this age are capable of mounting an adequate response to the free polysaccharide antigen, with response varying substantially by serotype.³²¹ Older studies generally indicate a poor response to the PPSV23 antigens in children younger than 2 years.^{163,320,322-325} Children 2 years of age and older typically have a significant antibody rise to vaccination.³²⁶⁻³²⁹

Two publications have reported the results of evaluations of the immunogenicity of pneumococcal polysaccharide vaccine alone among children 2 years and older with cochlear implants.^{326,327} Administration of pneumococcal polysaccharide vaccine was associated with a rise in the mean concentration of IgG antibodies to the majority of the seven serotypes evaluated, even in the youngest age group of children, 2 to 5 years of age.

Table 26-1 Opsonophagocytic Antibody Geometric Mean Titers 1 Month after a First PPSV23 and 1 Month After a Second PPSV23 Given a Mean of 3.5 Years Later to 189 Adults 60 to 64 Years of Age at the Time of First Vaccination

Serotype	GMT after the second PPSV23			GMT after the first PPSV23			GMFR (response to second PPSV23/response to first PPSV23) and 95% CI	
	N*	GMT	95% CI	N*	GMT	95% CI	GMFR	95% CI
1	181	95	75-122	181	115	88-149	0.8	0.68-1.02
3	177	53	43-65	177	103	84-128	0.5	0.44-0.59
4	162	725	543-968	162	1437	1069-1933	0.5	0.40-0.64
5	173	71	52-97	173	152	112-206	0.5	0.39-0.56
6B	168	915	659-1272	168	1133	804-1599	0.8	0.62-1.04
7F	174	174	336-645	174	440	302-643	1.1	0.81-1.37
9V	157	157	118-277	157	669	458-978	0.3	0.18-0.41
14	165	165	474-809	165	823	608-1113	0.8	0.60-0.95
18C	165	165	602-1124	165	1096	778-1544	0.8	0.60-0.94
19A	177	177	287-454	177	374	292-478	1.0	0.83-1.12
19F	158	158	307-533	158	596	447-795	0.7	0.57-0.81
23F	165	165	39-81	165	91	62-134	0.6	0.50-0.76

*N = Number of subjects with a determinate OPA antibody titer to the specified serotype who were included in the analysis of that serotype.

CI, Confidence interval; GMFR, geometric mean fold ratio; GMT, geometric mean titer; OPA, opsonophagocytic antibody; PPSV, pneumococcal polysaccharide vaccine.

Modified from Khoie T, Tiernan R, deVore N; Vaccines and Related Biological Products Advisory Committee. Prevnar 13™ (PCV13): Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein). FDA Briefing Document. Applicant: Wyeth Pharmaceuticals Inc. November 16, 2011. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM279681.pdf. Accessed December 8, 2011.

The postvaccination antibody response was, however, higher in children older than 5 years compared with younger children. Among children 5 years of age and older, the antibody response tended to be greater in children 8 years of age and older compared with the younger age group.

Immunogenicity in immunocompromised persons

HIV infection

A large number of studies have evaluated the immunogenicity of pneumococcal polysaccharide vaccine in HIV-infected persons.³³⁰⁻³⁴⁸ These studies were conducted to determine whether pneumococcal polysaccharide vaccination induces a significant increase in anticapsular antibody levels in HIV-infected persons and whether the antibody response is influenced by factors such as the CD4⁺ level at the time of vaccination or the use of antiretroviral therapy. Interpretation of the findings from this group of studies is complicated by differences in the characteristics of the study populations evaluated and, to some extent, by differences in the serologic and analytic methods used.

In HIV-infected persons not on HAART, the immunologic response to pneumococcal polysaccharide vaccination is generally diminished when compared with healthy control subjects.³³⁰⁻³⁴⁶ In those studies, postvaccination antibody levels in the HIV-infected groups did not consistently correlate with CD4⁺ T-cell counts,^{336,337,339,341,342,344-346,349} but some studies reported that patients with higher CD4 counts^{340,347,350} or those vaccinated soon after seroconversion³³⁸ may have a better response to vaccination than other groups. In HIV-infected adults, ELISA IgG antibody levels to most serotypes decline more rapidly than they do in healthy control subjects, and, after 1 to 3 years, have been reported to approximate prevaccination levels.^{341,351,352} The functional antibody response also appears to be reduced in HIV-infected persons compared with uninfected control subjects.^{348,342,345,346}

Preservation or reconstitution of immune function with antiretroviral therapy may be associated with an improved immunologic response to pneumococcal polysaccharide vaccination in HIV-infected persons. In the pre-HAART era, one study showed that HIV-infected adults who were treated with zidovudine had better antibody responses after pneumococcal vaccination than did comparable persons not receiving antiretroviral therapy.³³⁴

In the HAART era, one study comparing the response to vaccination in HIV-infected adults on HAART therapy with HIV-seronegative healthy control subjects found comparable levels of serotype-specific antibody levels at 1 and 12 months after pneumococcal polysaccharide vaccination in both groups.³⁵³ In contrast, three evaluations have reported little evidence of an improvement in the postvaccination antibody response in HIV-infected adults on HAART.^{344,350,354}

Before the introduction of HAART, HIV-infected children demonstrated poor response to pneumococcal polysaccharide vaccination.³⁵⁵ A study conducted in the post-HAART era documented an improved response, although the response in HIV-infected children was still lower than in healthy control subjects.³³⁰ In that study, a better antibody response in the HIV-infected children was correlated with a higher CD4 count at the time of vaccination.

There are few studies evaluating the response to revaccination with pneumococcal polysaccharide vaccine in HIV-infected populations. In one assessment, persons with HIV infection who were initially vaccinated within 1 year of HIV seroconversion and were revaccinated 5 or more years later had a diminished antibody response when compared with recently HIV-seroconverted patients receiving their first dose of vaccine.³⁴³ In another study, revaccination of HIV-infected individuals who failed to respond to their initial dose of vaccine had

no effect.³⁵¹ A third study found that revaccination 3 to 8 years after first vaccination was associated with significant increases in serotype specific IgG concentrations.³⁵⁶

Several studies in the pre-HAART era reported transient increases in viral load in HIV-infected children and adults after pneumococcal polysaccharide vaccination,^{357,358} however, multiple other studies have failed to demonstrate this effect in HIV-infected persons on HAART as well as those not on HAART.^{343,344,356,359-362} For example, one placebo-controlled trial of pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine in HIV-infected persons found no increase in viral load in vaccine recipients at 2, 4, or 6 months after vaccination, and no difference in those results when subjects were stratified by HAART treatment status.³⁶²

Hematopoietic stem cell transplant

Among hematopoietic stem cell transplant (HSCT) recipients, the antibody response to PPSV23 improves with increasing time since transplantation,³⁶³⁻³⁶⁵ and so in the past, an initial PPSV23 vaccination was recommended at 12 months after HSCT, with a second vaccination 12 months later. The antibody response to PPSV23 vaccination is limited, however,³⁶⁵⁻³⁶⁸ particularly in patients receiving corticosteroid treatment for graft-versus-host disease,³⁶⁹ and is not improved with the second vaccination.³⁷⁰

More recent trials indicate that 7-valent pneumococcal conjugate vaccine is more immunogenic in autologous and allogeneic bone marrow transplant recipients than PPSV23,^{371,372} and current recommendations call for a three-dose series of pneumococcal conjugate vaccine, starting 3 to 6 months after transplant.³⁷³ PPSV23 given after the pneumococcal conjugate vaccine series can broaden serotype coverage for serotypes not included in the pneumococcal conjugate vaccine and potentially also improve the response to serotypes common to the two vaccines.^{374,375}

Solid-organ transplant

Solid-organ recipients can respond to pneumococcal vaccine,³⁷⁶⁻³⁷⁸ but the immune response may be less intense³⁷⁹ and of shorter duration²⁹⁵ than in normal control subjects. In adult renal transplant recipients, serotype-specific ELISA antibody levels and opsonophagocytic titers increase after pneumococcal polysaccharide vaccination.^{377,380} Antibody levels decline rapidly after vaccination, however.³⁸¹ Revaccination leads to modest increases in antibody levels, but they seldom reach those seen initially.³⁰⁸ In a randomized trial of adult renal transplant recipients, the opsonophagocytic antibody response to pneumococcal conjugate vaccine was comparable to that of pneumococcal polysaccharide vaccine.³⁸⁰ At 3 years after vaccination, serotype-specific antibody titers had declined significantly compared with 8 weeks postvaccination, but geometric mean titers at 3 years after vaccination were comparable between the two vaccine groups.³⁸²

Renal disease

Children with nephrotic syndrome^{328,383} and children and adults with other chronic renal diseases and those on dialysis usually respond adequately to vaccination.³⁸⁴ However, in most of these patients, antibody levels rapidly decline.^{383,385} Revaccination 1 year later leads to good antibody responses in about half of renal disease patients, but levels decline rapidly over the next few months.³⁸⁴

Hematologic neoplasms

Several factors influence the immune responses to PPSV23 among patients with hematologic neoplasms, such as chronic lymphocytic leukemia, Hodgkin disease, and multiple myeloma, including the stage of disease, whether or not a splenectomy has been performed, the extent of previous radiation therapy or chemotherapy, and the time between completion of treatment and vaccination.³⁸⁶

Few patients with chronic lymphocytic leukemia respond to pneumococcal vaccine, even when they are not receiving chemotherapy.^{387,388} Those who do respond have less advanced disease and higher levels of IgG, IgG2, and IgG4.³⁸⁸ Administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) does not improve the immune response to PPSV23 in this population.³⁸⁹ Children with acute leukemia who are on maintenance chemotherapy have poor antibody responses.³⁹⁰ In contrast, those who have been in remission for 2 or more years respond well to pneumococcal vaccination.³⁹¹

Patients with Hodgkin disease who are vaccinated before the onset of treatment have immune responses to PPSV23 that are comparable to those of healthy persons.^{392,393} Once treatment begins, antibody responses to vaccination are reduced.³⁹⁴ In some patients, antibody levels fall below prevaccination levels, and in others, the response is delayed for several months. After completion of treatment, antibody levels may not return to pretreatment levels, and patients seldom respond to revaccination.³⁹⁵ These findings indicate that they should be vaccinated as soon as possible after the diagnosis is established, before treatment begins.

Patients with multiple myeloma have low antibody levels before vaccination. After vaccination, antibody responses are poor, although a few patients respond to a few serotypes.^{235,396} The capacity to respond does not correlate with the severity of the disease or the timing of chemotherapy, and antibody levels are seldom sustained.

Functional or anatomic asplenia

Antibody responses to pneumococcal polysaccharide vaccine in postsplenectomy patients vary, largely because some patients are immunocompromised and others are not. After splenectomy for trauma, antibody responses to pneumococcal polysaccharide vaccine that are similar to those in normal control subjects can be documented.³⁹⁷⁻⁴⁰⁰ In splenectomized patients with hematologic disease, response may be more variable,³²⁸ antibody levels may decline rapidly after vaccination, and persons who do not respond to an initial vaccination may also have a poor response to revaccination.⁴⁰¹ In one study of postsplenectomy trauma patients who were randomized to receive pneumococcal polysaccharide vaccine at 1, 7 or 14 days postoperatively, opsonophagocytic antibody titers were significantly higher in the group vaccinated at day 14 compared with the groups vaccinated on days 1 or 7.³⁹⁸ In a follow-up study by the same investigators, no difference in antibody titers was found in persons vaccinated at 28 days compared with 14 days postoperatively, suggesting no advantage to delaying vaccination for longer than 14 days.³⁹⁷ In a study in Denmark that involved serologic testing of previously splenectomized patients, persons vaccinated more than 14 days postoperatively were found to have a higher pneumococcal antibody level index than persons vaccinated within 14 days after the procedure.⁴⁰²

Other conditions

Patients with systemic lupus erythematosus,⁴⁰³⁻⁴⁰⁵ rheumatoid arthritis,⁴⁰⁴ Felty syndrome,⁴⁰⁶ and celiac sprue⁴⁰⁷ are at increased risk for pneumococcal infections. Patients with systemic lupus erythematosus or rheumatoid arthritis may have a diminished response to pneumococcal polysaccharide vaccine compared with healthy persons.^{404,408} Patients with celiac sprue respond normally to pneumococcal vaccine.⁴⁰⁷ Vaccination of patients with systemic lupus erythematosus does not trigger the generation of autoantibodies.⁴⁰⁹

In patients with rheumatologic conditions, such as rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis, anti-tumor necrosis factor therapy (adalimumab, etanercept, infliximab) does not appear to impair the antibody response to pneumococcal vaccination, while methotrexate therapy, given

with or without anti-tumor necrosis factor therapy, reduces this response.⁴¹⁰⁻⁴¹⁶ Other immunomodulatory agents used for the treatment of rheumatologic conditions may also influence the immune response to pneumococcal vaccine. In healthy volunteers, a single dose of abatacept, a selective costimulatory modulator that inhibits CD28-dependent T-cell activation, reduced the immune response to pneumococcal polysaccharide vaccine.⁴¹⁷ Similarly, rituximab, a monoclonal antibody that targets CD20⁺ B cells, reduces the immune response to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis.⁴¹⁸ Together, these results suggest that, if possible, PPSV23 should be given to patients with rheumatologic disorders before initiation of treatment with agents such as methotrexate, abatacept, and rituximab, which diminish the immune response to vaccine.

In one small study, patients with solid tumors had an antibody response to vaccination that was similar to healthy control subjects.⁴¹⁹ The response to pneumococcal vaccination in persons with HTLV-II infection is comparable to the response in healthy adults in terms of magnitude, quality, and functional activity.⁴²⁰

In a prospective trial of PPSV23 in patients with inflammatory bowel disease, the response to vaccination, as measured by ELISA, was lower in patients who were receiving anti-TNF therapy and concomitant immunomodulator therapy (6-mercaptopurine, azathioprine, or methotrexate) compared with patients not receiving immunosuppressive therapy and healthy control subjects.⁴²¹ Those with inflammatory bowel disease, but not receiving immunosuppressive therapy, had responses similar to the healthy control group. In one small study of adults with treated panhypopituitarism, who were on glucocorticoid replacement as well as other conventional replacement therapy, a lower response to PPSV was found in the patients with panhypopituitarism compared with healthy control subjects of similar age.⁴²²

Vaccine efficacy and effectiveness

Clinical trials: non-HIV-infected adults

South African gold miners

Clinical trials of whole-cell pneumococcal vaccine formulations were initiated in the early 20th century, but interpretation of the results of many of the earlier studies is limited by methodologic issues, such as small sample size or lack of an appropriate comparison group.^{239,423,424} Of interest, a recent reanalysis of data from trials of whole-cell killed bacterial vaccines given during the 1918 influenza pandemic suggests that whole-cell bacterial vaccines containing pneumococci may have reduced the risk of pneumonia and mortality among patients with pandemic influenza infection.⁴²⁵

Evidence of the efficacy of more contemporary capsular polysaccharide pneumococcal vaccines emerged in the 1970s from randomized controlled trials conducted among young adult South African gold miners (Table 26-2).^{5,6} These men were known to be at very high risk of pneumococcal pneumonia, which facilitated the conduct of adequately powered clinical trials. Smit⁵ reported the results of two randomized trials, one of a 6-valent and the other of a 12-valent vaccine, conducted with novice gold miners in South Africa. The primary outcome of vaccine-type pneumococcal pneumonia was defined as radiographically confirmed pneumonia, with onset 14 days or more after vaccination and with a vaccine-type pneumococci identified from sputum, nasopharyngeal, or blood specimens. In the control groups, this laboratory-defined outcome accounted for 64% (6-valent study) and 89% (12-valent study) of all cases of radiographically confirmed pneumonia.

Table 26-2 Randomized Clinical Trials of Pneumococcal Polysaccharide Vaccine Efficacy in Adults Reported Since 1970, Excluding Evaluations of HIV-Infected Persons.

Author year ^{ref} Vaccine valency	Study population	Outcome	VE, %	95% CI	No. events/no. vaccinated	No. events/no. unvaccinated
Smit 1977 ⁵ 6	Gold miners in South Africa	Vaccine type pneumococcal pneumonia All-cause pneumonia Bronchitis	76 37 8	53 to 88 9 to 56 - 17 to 28	9/983 37/83 84/983	78/2036 121/2036 190/2036
Smit 1977 ⁵ 12	Gold miners in South Africa	Vaccine type pneumococcal pneumonia All-cause pneumonia Bronchitis	92 32 42	38 to 99 - 42 to 68 - 7 to 68	1/540 9/540 13/540	25/1135 28/1135 47/1135
Austrian 1976 ⁶ 6 or 13	Gold miners in South Africa	Vaccine type pneumonia and/or vaccine type bacteremia	79	65 to 87	17/1493	160/3002
Riley 1977 ⁴⁵⁶ 14	Papua New Guinea highlanders ≥ 10 years of age	All-cause mortality Respiratory mortality Death from pneumonia uncomplicated by chronic lung disease All-cause pneumonia Cough illness Cough illness with pneumococci isolated from blood culture or lung aspirate	21 27 43 26 19 86	1 to 37 0 to 46 6 to 66 - 13 to 52 - 3 to 36 48 to 97	133/5946 68/5946 23/5946 36/2713 114/2713 2/2714	170/6012 94/6012 41/6012 48/2660 138/2660 14/2660
Austrian 1980 ^{430*} 12	Inpatients at the Dorothea Dix Psychiatric hospital in Raleigh, HNC	All-cause pneumonia	- 22	- 49 to 0	154/607	144/693
Austrian 1980 ^{430*} 12	Members ≥ 45 years of age of the Kaiser Permanent Health Plan in San Francisco	Vaccine type bacteremia Vaccine type pneumonia Non vaccine type infections All-cause pneumonia	100 15 - 15 2	$P = .06$ - 47 to 51 - 135 to 44 - 16 to 7	0/6782 24/6782 16/6782 268/6782	4/6818 28/6818 14/6818 274/6818
Gaillat 1985 ^{433†} 14	Residents of 48 long-term care institutions in France	All-cause pneumonia	79	53 to 91	7/937	27/749
Simberkoff 1986 ⁴³⁵ 14	US Veterans, immunocompetent, and either ≥ 55 years or with renal, hepatic, cardiac or pulmonary disease, alcoholism, or diabetes mellitus	Pneumococcal pneumonia or bronchitis Pneumococcal pneumonia All-cause pneumonia All-cause mortality	- 15 - 0.8 - 39 - 28	- 48 to 11 - 29 to 43 - 110 to 8 - 57 to - 5	43/1145 17/1145 56/1145 211/1145	28/1150 16/1150 41/1150 171/1150
Koivula 1997 ⁴³⁶ 14	Resident ≥ 60 years of age of a small town in Finland	All-cause pneumonia Pneumococcal pneumonia	- 17 15	- 66 to 17 - 43 to 50	69/1364 26/1364	64/1473 33/1473

Continued

Table 26-2 Randomized Clinical Trials of Pneumococcal Polysaccharide Vaccine Efficacy in Adults Reported Since 1970, Excluding Evaluations of HIV-Infected Persons—cont'd

Author year ^a Vaccine valency	Study population	Outcome	VE, %	95% CI	No. events/no. vaccinated	No. events/no. unvaccinated
Örtqvist 1998 ³¹⁸ 23	Immunocompetent persons 50-85 years of age who had been previously discharged from a hospitalization for community-acquired pneumonia in Sweden	All-cause pneumonia Pneumococcal pneumonia All-cause mortality Vaccine type bacteremic pneumonia	-20 -28 -5 79	-72 to 11 -150 to 34 -88 to 38 -77 to 98	63/339 19/339 29/339 1/339	57/352 16/352 28/352 5/352
Honkanen 1999 ³¹⁷ 23	Persons ≥ 65 years of age in northern Finland	All-cause pneumonia Pneumococcal pneumonia Vaccine type bacteremia	-20 -20 60	-50 to 10 -90 to 20 -40 to 90	145/13980 52/13908 2/13980	116/12945 40/12945 5/12945
Alfageme 2006 ³¹⁶ 23	Immunocompetent COPD patients 61-73 years of age in Seville, Spain	Community-acquired pneumonia due to pneumococcal infection or of unknown etiology Pneumococcal pneumonia Community-acquired pneumonia due to organisms other than pneumococci All community-acquired pneumonia	24 100 -7 3	-24 to 54 $P = .06$ -62 to -0.01 -52 to 38	25/298 0/298 8/298 33/298	33/298 5/298 1/298 34/298
Furumoto 2008 ⁴⁴¹ 23	Persons 40 to 80 years of age with chronic lung disease in Japan	Pneumonia Acute pulmonary disease exacerbation	0 30	-105 to 52 9 to 46	13/87 42/87	12/80 55/80
Maruyama 2010 ⁴³⁹ 23	Nursing home residents in Japan	All-cause pneumonia Pneumococcal pneumonia	45 64	22 to 61 32 to 81	63/502 14/502	104/04 37/504
Kawakami 2010 ⁴⁴⁰ 23	Persons ≥ 65 years of age in Japan	All-cause pneumonia All-cause pneumonia hospitalization	25 27	-18 to 53 -16 to 56	67/391 60/391	81/387 76/391

^aStudy results obtained from Broome CV. Efficacy of pneumococcal polysaccharide vaccines. Rev Infect Dis 3(suppl):S82-S96, 1981.

¹Study results obtained from Fedson DS, Liss C. Precise answers to the wrong question: prospective clinical trials and the meta-analyses of pneumococcal vaccine in elderly and high-risk adults. Vaccine 22:927-946, 2004. CI, Confidence interval; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; VE, vaccine effectiveness, which is calculated based on the formula $VE = 1 - \text{relative risk of disease in vaccinated versus unvaccinated}$. A negative VE estimate indicates a higher risk in vaccinated compared with unvaccinated person, a zero VE estimate indicates no difference in risk between vaccinated and unvaccinated person, and a positive VE indicated a lower risk in vaccinated compared with unvaccinated person. If the confidence intervals for the VE estimate cross zero, that is, extend from negative to positive, or include zero, the VE estimate is not statistically significant.

Table 26-3 Retrospectively Calculated Sample Size Requirements for Detection of Vaccine Efficacy against All-Cause Pneumonia in Clinical Trials in the United States and Europe

Author year ^{ref}	Actual reported person-years of observation in the study vaccine and control groups	Retrospectively calculated person-years of observation required for 80% power to detect a vaccine efficacy of XX% or greater against all-cause pneumonia			
		VE ≥ 15%	VE ≥ 25%	VE ≥ 35%	VE ≥ 45%
Austrian 1980 ⁴³⁰	2913	13400	4700	2300	—*
Austrian 1980 ⁴³⁰	34462	118000	28000	—*	—*
Gaillat 1985 ⁴³³	3372	58000	25000	12200	7000
Simberkoff 1986 ⁴³⁵	6656	87400	37600	18400	10600
Koivula 1997 ⁴³⁶	7944	54600	30000	12700	6800
Örtqvist 1998 ⁴³⁸	1666	18100	6800	3200	1920
Honkanen 1999 ⁴³⁷	38037	175700	75500	32000	—*

*Person years of observation in the vaccine and control groups exceeded that required to detect a lower level of vaccine efficacy.

VE, Vaccine efficacy.

Adapted from Fedson DS, Liss C. Precise answers to the wrong question: prospective clinical trials and the meta-analyses of pneumococcal vaccine in elderly and high-risk adults. *Vaccine* 22:927-946, 2004.

In both trials reported by Smit, pneumococcal vaccine was associated with a significant reduction in the risk of vaccine-type pneumococcal pneumonia. Vaccine efficacy was estimated to be 76% in the 6-valent study and 92% in the 12-valent study. In the 6-valent study, there was also a significant reduction in risk of all radiographically confirmed pneumonia, while in the 12-valent trial, the reduction in risk of this outcome in the vaccine group was not statistically significant. In the 6-valent study, there was no difference in risk of nonvaccine type pneumonia (relative risk [RR], 1.40; 95% confidence interval [CI], 0.88-2.22). In the 12-valent study, vaccination was associated with an increased risk of nonvaccine type pneumonia (RR, 5.60; 95% CI, 1.49-21.04), but this estimate is based on only eight cases in the vaccine group and three in the placebo group.

The results of three other trials, evaluating either 6-valent or 13-valent vaccines, in South African gold miners were reported by Austrian.⁶ In an analysis of all three trials together, pneumococcal vaccine was reported to reduce the risk of vaccine-type pneumococcal bacteremia by 82%. Pneumococcal vaccine was also reported to reduce the risk of all-cause radiographically confirmed pneumonia by approximately 50%, and to significantly reduce the risk of radiographically diagnosed pneumonia in which pneumococci were not isolated.⁶

Papua New Guinea trial

In the 1970s, another large randomized, double-blind, placebo-controlled clinical trial, in this case of a 14-valent vaccine, was conducted in Papua New Guinea.⁴²⁶ Study participants were rural highlanders who lived in poorly ventilated longhouses and had frequent respiratory infections. A total of 11,958 persons 10 years of age and older were enrolled in the trial and were followed for 3 years for mortality outcomes. Among all participants, a reduction in risk of death from any cause was documented, and there was also a trend toward a lower risk of death attributed to any respiratory cause in the vaccinated group compared with the placebo group. The risk of death more specifically attributed to pneumonia without chronic lung disease (a subset of all respiratory deaths) was significantly lower in the vaccinated group (0.4%) compared with the placebo group (0.7%).

In addition, half of the study population was followed more intensively for 16 months after enrollment to identify episodes of cough illness. Of those, 252 (5%) had an identified cough illness, which was, when possible, further evaluated by chest radiograph and laboratory testing. There was no difference in

risk of clinically or radiographically defined all-cause pneumonia in the vaccine compared with the placebo group. However, the risk of cough illness with pneumococci isolated from blood culture or lung aspirate was significantly lower in the vaccinated group compared with the placebo group, for an estimated vaccine efficacy against that outcome of 86% (see Table 26-2).

Trials in the United States, Europe, and Japan since the 1970s

The results of the South Africa trials provided the primary evidence supporting licensure of the 14-valent vaccine in the United States in 1977, which was then replaced by the 23-valent vaccine in 1983. Those trials provide consistent evidence of vaccine efficacy against pneumococcal pneumonia and pneumococcal bacteremia in a unique population of young adults at very high risk of pneumococcal infection. However, those findings are not sufficient to establish vaccine efficacy in other, very different, populations, such as older adults or persons with chronic illness. In addition, because the contribution of nonbacteremic disease to all pneumococcal pneumonia in the South African trials is not well defined, it is not clear whether the reported reductions in risk of the outcome of pneumococcal pneumonia reflect vaccine efficacy against both nonbacteremic and bacteremic disease.

Since the mid 1970s, 14 randomized trials of pneumococcal polysaccharide vaccines have been conducted among adults in the United States, Europe, and Japan. Three of those trials were small studies of patients with lung disease or lung cancer that included a total of only 339 participants and were primarily intended to evaluate vaccine safety and immunogenicity.⁴²⁷⁻⁴²⁹ The remaining 11 trials, summarized in Table 26-2, evaluated vaccine efficacy against pneumonia outcomes. Because pneumococcal bacteremia is relatively uncommon in adults in developed countries, and as a consequence, very large sample sizes would be required to detect a vaccine effect, this was not the primary outcome evaluated in those trials, but this outcome has been evaluated in observational studies.

In the 1970s, Austrian conducted two clinical trials sponsored by the National Institutes of Health (NIH). One trial included 1300 residents of a long-term care institution in North Carolina, and the other included 13,600 enrollees of a managed-care organization in California. The results of these trials were never published but were included in a report to NIH⁴³⁰ and have been summarized in other publications.^{423,424,431,432} There was no significant difference in risk of all-cause pneumonia in

the vaccine compared with the placebo group in either study. In the larger study, all four bacteremic infections caused by vaccine-type *S. pneumoniae* were in the unvaccinated group, which resulted in a point estimate of vaccine efficacy against vaccine-type bacteremia of 100% ($P = .06$). In both studies, pneumonias associated with an increase in pneumococcal antibody levels detected in paired serum specimens were more common in the unvaccinated group. However, this method of classification of pneumococcal infection has not been validated, and could be biased if vaccinees are less likely to demonstrate an antibody rise after pneumococcal infection than would unvaccinated persons.

In France, a randomized, nonblinded, clinical trial was conducted among 1686 residents of 48 long-term care institutions.⁴³³ The investigators concluded that 14-valent pneumococcal vaccine significantly reduced the risk of all-cause pneumonia. The validity of that finding has been questioned because many of the presumptive pneumococcal events were not radiographically confirmed, the randomization process generated study groups of markedly uneven size, clinical follow-up by the more than 80 study physicians was highly variable, and approximately one third of subjects either died during the study period or were lost to follow-up.⁴³⁴

In the Veterans Administration Cooperative Study conducted in the United States, 2295 immunocompetent veterans who were defined as high-risk on the basis of age (≥ 55 years) or the presence of chronic cardiac, pulmonary, renal or hepatic disease, diabetes mellitus, or alcoholism were randomized with equal probability to receive 14-valent pneumococcal polysaccharide vaccine or placebo.⁴³⁵ Only one case of vaccine-type invasive pneumococcal infection occurred in each group. The frequency of probable pneumococcal pneumonia, defined as radiographically confirmed pneumonia with pneumococci isolated from sputum, was also balanced between the groups. Vaccine efficacy against the composite primary study outcome of invasive pneumococcal infection, probable pneumococcal pneumonia, or probable pneumococcal bronchitis (cough and sputum production without radiographic evidence of pneumonia and with pneumococci isolated from sputum) was -15% (95% CI, -48% to 11%), indicating a nonsignificant excess of events in the vaccine group. In survival analysis, adjusting for age and the presence of chronic medical conditions, there was a significantly increased risk of all-cause mortality in the pneumococcal vaccine group.

Two clinical trials conducted in Finland^{436,437} and one conducted in Sweden³¹⁸ assessed pneumococcal vaccine efficacy against all-cause pneumonia and against an outcome of pneumococcal pneumonia that was defined at least in part on the basis of serologic testing for antibodies to pneumolysin. In the first Finnish study,⁴³⁶ investigators used a health database to identify the 4213 residents of a small town who were at least 60 years of age and then sent them a letter inviting them to attend a study enrollment visit in September or October 1982. Before the enrollment visits, residents were assigned to receive 14-valent pneumococcal vaccine plus influenza vaccine or influenza vaccine alone. A total of 2837 persons attended a study enrollment visit, and of those, 1364 had been assigned to receive pneumococcal and influenza vaccines, and 1473 had been assigned to receive influenza vaccine alone. During the 3-year follow-up period there was a higher incidence of all-cause pneumonia in the pneumococcal vaccine group that was not statistically significant (see Table 26-2). There was no significant difference in risk of the study outcome of pneumococcal pneumonia between the study groups.

In the study in Finland, a significant reduction in risk of pneumonia was demonstrated in one of the 13 subgroup analyses reported. Among the 30% of participants categorized as at increased risk for pneumonia on the basis of age (≥ 70 years), heart disease, lung disease, bronchial asthma, alcoholism,

institutionalization, or being permanently bedridden, there was a significant 59% reduction in risk of pneumococcal pneumonia [odds ratio [OR], 0.41; 95% CI, 0.18-0.94]. However, in that subgroup, pneumococcal vaccination was associated with a trend toward a higher risk of nonpneumococcal pneumonia (crude OR, 1.80; 95% CI, 0.95-3.57), and there was no difference in risk of all-cause pneumonia between the pneumococcal vaccine and comparison groups (OR, 0.99; 95% CI, 0.60-1.62).

In the second Finnish trial,⁴³⁷ seniors in northern Finland were invited to attend study clinics at their local health center, at which time they were allocated to receive either 23-valent pneumococcal vaccine plus influenza vaccine, if they were born in an even year, or influenza vaccine alone, if they were born in an odd year. Among the 26,925 study participants, there was a higher risk of all-cause radiographically confirmed pneumonia and of serologically defined pneumococcal pneumonia in the pneumococcal vaccine group, but these differences were not statistically significant (see Table 26-2). There were two cases of vaccine-type pneumococcal bacteremia in the pneumococcal vaccine group, and five in the comparison group, but this reduction in risk in the vaccine group was not statistically significant.

The third trial was a randomized, blinded, placebo-controlled trial of 691 immunocompetent older adults who were enrolled after discharge from a hospitalization for community-acquired pneumonia in Sweden.³¹⁸ In this study, pneumococcal pneumonia was defined by isolation of pneumococci from blood, pleural fluid, or sputum or by serologic testing for pneumolysin antibody. The study design stipulated that participants would be followed until 60 cases of pneumococcal pneumonia had accrued in the placebo group. However, the study was stopped for futility by an external monitoring committee after only 16 pneumococcal pneumonia cases had been identified in the placebo group. The study found a nonsignificantly higher risk of all-cause pneumonia and of pneumococcal pneumonia in the vaccine group. Six cases of bacteremic pneumococcal pneumonia were identified, five of which were in the placebo group, for a 79% reduction in risk of this outcome in the vaccine group that was not statistically significant ($P = .2$).

In an open trial of 23-valent pneumococcal polysaccharide vaccine, elderly outpatients with chronic obstructive pulmonary disease in Seville, Spain were randomly assigned to receive pneumococcal polysaccharide vaccine or no vaccine.⁴³⁸ The study design was not optimal in that the investigators and participants were not blinded and, although the method used to generate the randomization sequence was specified, whether allocation was concealed before randomization was not reported. Participants were followed for 3 years to identify the primary study outcome of a first episode of community-acquired pneumonia caused by pneumococcal infection or of unknown etiology. Of the 67 first episodes of community-acquired pneumonia identified in the 596 study participants, 5 were defined as pneumococcal by isolation of *S. pneumoniae* from sputum or bronchoscopy specimens, 53 were of unknown etiology, and the remaining 9 were attributed to organisms other than pneumococci (for example, gram-negative bacilli).

There was a nonsignificant 24% reduction in risk of the primary outcome in the vaccine group that was due to the absence of cases of pneumococcal pneumonia in that group. In contrast, vaccine recipients were at significantly higher risk of pneumonia because of organisms other than *S. pneumoniae* (RR, 8.00; 95% CI, 1.01-63.57), and so the risk of all-cause community-acquired pneumonia was equivalent between the vaccine and nonvaccine groups (vaccine efficacy [VE], 3%; $P = 1.00$). No cases of pneumococcal bacteremia were identified, and there was no difference in the risk of all-cause mortality or pneumonia deaths between the two groups.

Most recently, a randomized, placebo-controlled, observer-blind trial was conducted among nursing home residents (mean age, 85 years) in Japan.⁴³⁹ The primary end points were all-cause

pneumonia and pneumococcal pneumonia (defined by isolation of *S. pneumoniae* from blood, pleural fluid or sputum, or by a positive urine antigen test). The rate of all-cause pneumonia was very high, with 17% of participants having a pneumonia diagnosis during the 2.3-year follow-up period, which may have been due in part to the routine use of chest computed tomography (CT) scans for diagnostic confirmation. Unlike most other trials, a vaccination effect was observed, with a significantly lower risk of pneumonia and of pneumococcal pneumonia in the vaccine group compared with the placebo group.

Two other open-label randomized trials of PPSV23 among older adults in Japan have been recently reported. One did not find a difference in risk of all-cause pneumonia in the primary analysis, but did find some trends toward a vaccine effect in subanalyses.⁴⁴⁰ The other trial, which included patients with chronic lung disease, did not find an association between pneumococcal vaccination and risk of pneumonia but did report a reduction in risk of infectious acute exacerbations of chronic lung disease.⁴⁴¹

Interpretation of clinical trial results

Many of the clinical trials of pneumococcal polysaccharide vaccine included an end point of pneumococcal pneumonia, which is an intuitively logical outcome for a pneumococcal vaccine trial. However, an important limitation of that approach is that most episodes of pneumococcal pneumonia are not associated with bacteremia, and the diagnostic methods traditionally used to identify nonbacteremic pneumococcal pneumonia lack sensitivity and specificity. In the clinical trials from Finland and Sweden^{318,436,437} the definition of pneumococcal pneumonia was based at least in part on detection of rising antibodies to pneumolysin or detection of IgG antibody to pneumolysin in circulating immune complexes precipitated from patient serum. Subsequent studies suggest that these assays may not be optimally sensitive and specific.^{442,443} In most of the other trials, the diagnosis of nonbacteremic pneumococcal pneumonia was based on the identification of pneumococci by sputum culture or Gram stain. Sputum assays also lack sensitivity and specificity, and therefore, some misclassification of pneumococcal pneumonia likely occurred in all trials that attempted to assess this outcome. In the recent trial by Maruyama and colleagues in Japan,⁴³⁹ nearly all of the cases of pneumococcal pneumonia were defined by urine antigen testing.

The outcome of all-cause pneumonia is not dependent on an etiologic diagnosis and is an outcome of public health relevance. This outcome is nonspecific, however, and the degree to which a vaccine efficacious against pneumococcal pneumonia could impact all-cause pneumonia is a function of both vaccine efficacy against pneumococcal pneumonia and the contribution of pneumococcal infection to all-cause pneumonia. For example, pneumococcal vaccination could reduce the risk of all-cause pneumonia by 25% if the vaccine reduces the risk of pneumococcal pneumonia by 50% and if pneumococcal pneumonia accounts for 50% of all-cause pneumonia. The nonspecificity of the outcome of all-cause pneumonia dilutes study power to detect a true vaccine effect. For this reason, relatively large sample sizes are required for adequate power to detect an effect that may be moderate yet clinically relevant. A null finding in a pneumococcal vaccine trial evaluating the outcome of all-cause pneumonia could therefore be found if vaccination does not reduce the risk of pneumococcal pneumonia, or if the vaccine reduces the risk of pneumococcal pneumonia but the combination of the magnitude of that reduction and the incidence of pneumococcal pneumonia is insufficient to lead to a statistically significant difference in the risk of all-cause pneumonia in the vaccine compared with the nonvaccine group.

Interpretation of the results of pneumococcal vaccine trials must therefore take into account the adequacy of the trial

design, the study outcomes evaluated, the method of ascertainment of the study outcomes, and whether the sample size was sufficient to detect a clinically meaningful reduction in risk of disease. Regarding the latter question, Fedson and Liss⁴³⁴ identified the rate of all-cause pneumonia in the control group of each of the US and European trials reported before 2004 and used that estimate to retrospectively calculate the sample size that would have been required for the trial to have had 80% power to detect a 15%, 25%, 35%, or 45% or greater reduction in risk of all-cause pneumonia in the vaccine group.

Based on those calculations, they estimated that between 13,400 and 175,500 person-years of observation in the vaccine and control groups combined would have been required for adequate power to detect a 15% or greater reduction in risk of all-cause pneumonia in those trials, and none of the trials met that criterion (see Table 26-3). The Austrian trial in healthy adults included 34,462 person-years of follow-up, which exceeded the estimated sample size needed to detect a 25% or greater reduction in risk. In that trial, the point estimate of vaccine efficacy against all-cause pneumonia was 2% (95% CI, -16% to 7%). For the Austrian trial in the psychiatric hospital patients and the Honkanen Finnish trial, the trial sample sizes approximated the estimates required for power to detect a vaccine efficacy of 35% or greater. In both of those trials, there was a nonsignificantly higher risk of all-cause pneumonia in the vaccine group, and the upper limit of the confidence interval for the estimate of vaccine efficacy was zero for the Austrian trial and 10% for the Honkanen trial.

Taken together, the findings from these three trials do not support a vaccine efficacy against all-cause pneumonia of 25% or greater in older adults. Based on the sample-size calculations, a true vaccine effect leading to a smaller reduction in risk of all-cause pneumonia cannot be excluded. However, the point estimates of vaccine efficacy in those three trials are not suggestive of a trend toward a lower event rate in the vaccinated group. Of the two trials reporting a significant reduction of risk against all-cause pneumonia, one, the Gaillat study⁴³³ was not blinded, and there are questions regarding allocation concealment and the method of randomization. Nonblinded trials and those with inadequate allocation concealment have been found to overestimate intervention effects,⁴⁴⁴ and so, there is the possibility that bias influenced the reported findings. The Maruyama trial in Japan⁴³⁹ remains the only randomized, blinded trial to demonstrate efficacy of PPSV23 against all-cause pneumonia. Reasons why a lower risk of all-cause pneumonia was seen in this relatively small study ($n = 1006$) of nursing home residents at very high risk of pneumonia and not in other randomized trials are not clear.

Observational studies in non-HIV-infected persons

Effectiveness against invasive pneumococcal disease

In contrast to the data obtained from randomized controlled trials, postlicensure epidemiologic studies have provided consistent evidence supporting the effectiveness of pneumococcal polysaccharide vaccine in immunocompetent adults (Table 26-4).⁴⁴⁵⁻⁴⁶⁴ These studies, in aggregate, provide evidence supporting a protective effect of pneumococcal polysaccharide vaccine against invasive pneumococcal disease in immunocompetent adults. Vaccination was associated with a significant reduction in risk of invasive pneumococcal disease in 14 of the 18 adult studies, with estimates of vaccine effectiveness ranging from 44% to 81%.

These evaluations have included the traditional case control and cohort observational designs. In addition, several studies have used a novel indirect cohort methodology.^{460,461,463,465} In that design, only cases of invasive pneumococcal disease

Table 26-4 Observational Studies of Pneumococcal Polysaccharide Vaccine Effectiveness Against Invasive Pneumococcal Disease in Non-HIV-Infected Populations

Author year ^{ref}	Design	Study population	Subgroup	No. cases of invasive pneumococcal disease	VE, %	95% CI, %
Shapiro 1984 ⁴⁴⁵	Case control	Adults with an indication for pneumococcal vaccine admitted to Yale–New Haven hospital in Connecticut	All Immunocompromised	90 20	67 0	13 to 87 – 1228 to 93
Forrester 1987 ⁴⁴⁹	Case control Indirect cohort	Persons ≥ 55 years of age admitted to the Denver Veterans Administration hospital	All	89 89	– 34 – 21	– 176 to 35 – 221 to 55
Sims 1988 ⁴⁵⁷	Case control	Immunocompetent persons ≥ 55 years of age admitted to one of five hospitals in Pennsylvania	All	122	70	36 to 86
Shapiro 1991 ⁴⁴⁶	Case control Indirect cohort	Adults with an indication for pneumococcal vaccine admitted to one of 11 hospitals in Connecticut	All Immunocompetent Immunocompromised All	983 808 175 932	56 61 21 48	42 to 67 47 to 72 –55 to 60 3 to 72
Butler 1993 ⁴⁵⁴	Indirect cohort	Persons ≥ 5 years of age in the United States	All Immunocompetent ≥ 65 years of age Anatomic asplenia, excluding persons with sickle cell disease	2837 525 166	57 75 77	45 to 66 57 to 85 14 to 95
Farr 1995 ⁴⁴⁸	Case control	Persons ≥ 2 years of age with an indication for pneumococcal vaccination admitted to the University of Virginia Health Sciences Center in Virginia	All	85	81	34 to 94
Fiore 1999 ⁴⁵⁵	Indirect cohort	Children 2-5 years of age with chronic illness* in the United States	All Sickle cell disease Other chronic illness	173 46 127	63 62 84	8 to 85 – 294 to 98 40 to 96
Benin 2003 ⁴⁵⁰	Case control Indirect cohort	Navajo adults ≥ 18 years of age with an indication for vaccination Navajo adults ≥ 18 years of age	All All	108 278	26 35	– 29 to 58 – 33 to 69
Jackson 2003 ⁴⁴⁷	Cohort	Community-dwelling members of a Washington State health plan ≥ 65 years of age	All Immunocompetent Immunocompromised	61 39 22	44 54 22	7 to 67 13 to 76 – 87 to 68

Table 26-4 Observational Studies of Pneumococcal Polysaccharide Vaccine Effectiveness against Invasive Pneumococcal Disease in Non-HIV-Infected Populations—cont'd

Author year ^{ref}	Design	Study population	Subgroup	No. cases of invasive pneumococcal disease	VE, %	95% CI, %
Hedlund 2003 ⁴⁵²	Cohort	Residents of Stockholm County, Sweden ≥ 65 years of age who were invited to receive influenza and pneumococcal vaccines in the fall of 1998	All	40	48	3 to 72
Adamkiewicz 2003 ⁴⁵⁶	Indirect cohort	Children < 18 years of age with sickle cell disease at eight centers in the United States	All	79	64	– 6 to 88
Andrews 2004 ⁴⁵⁸	Indirect cohort	Persons ≥ 65 years of age in Victoria, Australia	All	98	79	– 14 to 96
Dominguez 2005 ⁴⁵³	Case control	Persons ≥ 65 years of age admitted to 12 hospitals in Catalonia, Spain	All	149	70	48 to 82
			Immunocompetent	103	76	51 to 88
			Immunocompromised	31	50	– 44 to 82
Vila-Córcoles 2006 ⁴⁵¹	Cohort	Community-dwelling seniors ≥ 65 years of age in Catalonia, Spain	All	22	40	– 165 to 78
Singleton 2007 ⁴⁶⁰	Indirect cohort	Alaska Native adults	All	300	75	27 to 91
			20-39 years	111	100	78 to 100
			40-54 years	86	73	< 0 to 96
			≥ 55 years	103	< 0	< 0 to 78
Bliss 2007 ⁴⁵³	Indirect cohort	White Mountain Apache adults ≥ 18 years of age	All	92	68	3 to 90
			Persons without alcoholism	NR	96	47 to 100
			Persons with alcoholism	NR	25	– 241 to 82
Mooney 2008 ⁴⁶²	Screening method	Persons ≥ 65 years of age in Scotland [†]	All	135	62	45 to 73
Moberley 2010 ⁴⁶¹	Screening method	Indigenous adults 15-49 years of age in the Northern Territory of Australia	All	385	3	– 43 to 35
	Indirect cohort		All	342	57	15 to 78
Vila-Córcoles 2009 ⁴⁶⁴	Case control	Community-dwelling seniors ≥ 50 years of age in Catalonia, Spain	All	94	66	34 to 83
Vila-Córcoles 2010 ⁴⁵⁹	Case control	Community-dwelling seniors ≥ 60 years of age in Catalonia, Spain	All	88	66	37 to 82

*Chronic illness included sickle cell disease, malignancy, leukemia, nephrotic syndrome, HIV infection, organ transplant, CSF leak, congenital anomalies, asplenia, and immunosuppressive medications.

[†]Excluded persons with asplenia, hematologic malignancies, and nonhematologic malignancies on chemotherapy.

CI, Confidence interval; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; NR, not reported.

are evaluated; there is no comparison group of uninfected persons. The cases are classified according to their vaccination status and the serotype of the infecting pneumococcal isolate. Vaccine effectiveness is estimated by comparing the distribution of pneumococcal serotypes in the vaccinated and unvaccinated groups. This serotype distribution method is based on the assumption that, if the vaccine is effective, vaccine serotypes will be less common among vaccinated persons with invasive pneumococcal disease than among unvaccinated persons. An advantage of this method is that, because infected persons are not being compared with uninfected persons, the estimates of effectiveness are less likely to be influenced by bias resulting from factors that are related both to vaccination status and risk of infection, such as the presence of underlying conditions. In the three studies that utilized both the indirect cohort and case-control methodologies,^{446,449,450} the results of the two methods were very similar.

The largest case-control study included 983 cases of invasive pneumococcal disease identified at 11 hospitals in Connecticut from 1984 to 1990.⁴⁴⁶ Cases were eligible for enrollment only if they had a recognized indication for receipt of pneumococcal polysaccharide vaccine, and most were elderly, with a mean age of 68 years. Control subjects were selected from among the group of patients admitted to the same hospital as the case patient and were matched to the case patient by age, date of hospitalization, and chronic condition that represented an indication for vaccination. In this study, the effectiveness of pneumococcal vaccination in preventing invasive pneumococcal disease caused by vaccine and vaccine-related serotype organisms was 56%, and it was 47% effective in preventing invasive pneumococcal disease caused by all serotypes. Vaccination was not associated with a decreased risk of infection caused by non-vaccine-type organisms.

The largest indirect cohort study included 2837 persons, 5 years of age and older, with pneumococcus isolated from blood or cerebrospinal fluid at one of 58 hospitals in the United States participating in a CDC surveillance system from 1978 to 1992.⁴⁵⁴ The overall vaccine effectiveness estimate was 57%. In subgroup analyses, vaccine effectiveness was documented for persons with diabetes mellitus, coronary vascular disease, congestive heart failure, chronic pulmonary disease, and anatomic asplenia but was not documented for persons with alcoholism/cirrhosis. Vaccination was not associated with a significant reduction in risk of invasive pneumococcal disease in the smaller subgroups of persons with immunocompromising conditions other than anatomic asplenia, including sickle cell disease, chronic renal failure, immunoglobulin deficiency, leukemia/lymphoma, or multiple myeloma.

One of the four studies in adults that did not find a protective effect of vaccination evaluated 89 adults, 55 years of age and older, hospitalized with pneumococcal bacteremia at a Veterans Administration hospital in Denver, Colorado.⁴⁴⁹ The vaccination status of cases and hospital-based control subjects was ascertained from hospital records, and so may have been misclassified. In addition, 30% of cases were nosocomial, defined as having a positive blood culture 2 weeks or more after hospital admission, which may imply that this study population differed from other groups. In this study, there was no significant association of vaccination and risk of pneumococcal bacteremia, either in the case-control analysis or in the indirect cohort analysis.

The second study that did not find a protective effect of vaccination was a rigorously conducted case control study that included 108 Navajo adults with invasive pneumococcal disease during 1996 and 1997.⁴⁵⁰ Navajo adults are at substantially increased risk of invasive pneumococcal infection,⁴⁶⁶ and this population also has a relatively high prevalence of comorbidities. In this study, 43% of case patients had alcoholism and 41% had diabetes. There was no significant association

of vaccination and risk of pneumococcal bacteremia, either in the case control or the indirect cohort analyses of all subjects. Effectiveness was also not demonstrated in subgroup analyses of persons without alcoholism or diabetes. It is possible that these findings may not be entirely generalizable to other populations if Native American adults respond less well to polysaccharide antigens⁴⁶⁷ than other groups.

The other two studies that did not report a significant reduction in risk of invasive pneumococcal disease in association with vaccination included a cohort study of seniors that was designed to evaluate vaccine effectiveness against pneumonia and that identified only 22 cases of pneumococcal bacteremia in the study population,⁴⁵¹ and there was an indirect cohort study that reported a point estimate of vaccine effectiveness of 79%.⁴⁵⁸

Duration of effectiveness

There are limited data on the duration of effectiveness of pneumococcal polysaccharide vaccine. The results of the large case-control study in Connecticut suggest that vaccine effectiveness declines with time and with advanced age.⁴⁴⁶ In that study, vaccine effectiveness could not be documented more than 5 years after vaccination in persons 65 years of age and older (Table 26-5). Similarly, in an indirect cohort analysis of Alaska Native adults, vaccine effectiveness was demonstrated in the first 5 years (77%; 95% CI, 38%-92%) but did not appear to persist past 5 years (36%; 95% CI, < 0%-92%).⁴⁶⁰ In contrast, two other observational studies did not document a significant decline in vaccine effectiveness over time. In the indirect cohort study by Butler and associates⁴⁵⁴ of persons 5 years of age and older (see Table 26-4), in which the majority of subjects were older than 50 years, vaccine effectiveness 5 to 8 years after vaccination was 71% (95% CI, 24%-89%), and 9 or more years after vaccination, it was 80% (95% CI, 16%-95%). In the cohort study of persons 65 years of age and older,⁴⁴⁷ vaccine effectiveness within 5 years of vaccination was 48% (95% CI, 6%-71%); in the 5 to 7 years after vaccination, it was 36% (95% CI, -41% to 71%), and more than 7 years after vaccination, it was 42% (95% CI, -70% to 80%) (author's unpublished data).

Effectiveness of revaccination

Two published studies have evaluated the effectiveness of revaccination. In a case-control study of risk of invasive pneumococcal disease in Navajo adults, the risk of disease in persons who had received two or more pneumococcal polysaccharide vaccinations was compared with that in unvaccinated persons.⁴⁵⁰ In that analysis, revaccination was not associated with a reduction in risk of invasive pneumococcal disease (VE, 40%; 95% CI, -27% to 72%). However, that study also did not document an overall effectiveness of pneumococcal polysaccharide

Table 26-5 Pneumococcal Polysaccharide Vaccine Effectiveness against Invasive Pneumococcal Disease in Adults, by Age and Time Since Vaccination

Age (years)	Time since vaccination		
	< 3 years	3-5 years	> 5 years
Vaccine effectiveness, % (95% CI)			
< 55	93 (82 to 97)	89 (74 to 96)	85 (62 to 94)
55-64	88 (70 to 95)	82 (57 to 93)	75 (38 to 90)
65-74	80 (51 to 92)	71 (30 to 88)	58 (-2 to 83)
75-84	67 (20 to 87)	53 (-15 to 81)	32 (-67 to 72)
≥ 85	46 (-31 to 78)	22 (-90 to 68)	-13 (-174 to 54)

Modified from Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 325:1453-1460, 1991.

vaccination, and the estimate of effectiveness after revaccination was not significantly different from that after any vaccination. In a study of Alaska Native adults, the point estimates of vaccine effectiveness, as determined by the indirect cohort method, were similar for the first dose of PPSV23 (73%; 95% CI, 19%-92%) and for revaccination (74%; 95% CI, <0%-94%), although the confidence limits around the estimate of the efficacy of revaccination overlapped zero.⁴⁶⁰

Effectiveness in immunocompromised persons

Immunocompromised persons are at disproportionately high risk of invasive pneumococcal disease. In the observational studies of pneumococcal polysaccharide vaccine effectiveness against invasive pneumococcal disease in non-HIV-infected populations, persons defined as immunocompromised accounted for 12%,⁴⁵⁴ 15%,⁴⁵⁰ 18%,⁴⁴⁶ 22%,⁴⁴⁵ 24%,⁴⁵³ 33%,⁴⁵⁹ and 36%,⁴⁴⁷ respectively, of invasive pneumococcal disease cases. In most of those studies, pneumococcal polysaccharide vaccine was not associated with a reduction in risk of IPD in immunocompromised persons. The one study to find a significant reduction defined the immunocompromised subgroup as persons with immunodeficiency, asplenia, any solid-organ or hematologic cancer, chronic nephropathy, or long-term corticosteroid therapy.⁴⁵⁹ Nearly all of the IPD case patients defined as immunocompromised met the definition because of existence of solid-organ cancers (stage not defined) or non-dialysis-dependent chronic renal failure. In the immunocompromised group, PPSV23 vaccine effectiveness was estimated to be 88% (47% to 97%).

Effectiveness against pneumonia

Observational studies of the effect of pneumococcal polysaccharide vaccine on risk of community-acquired pneumonia have yielded divergent results. Of the seven cohort studies of non-institutionalized seniors that have evaluated the association of pneumococcal polysaccharide vaccine and risk of pneumonia (Table 26-6), five found no association and two found a lower risk of pneumonia among vaccinated persons. Of the five negative studies, one, a retrospective cohort study of seniors enrolled in a health maintenance organization in western Washington State,⁴⁴⁷ found that pneumococcal vaccination did not alter the risk of ambulatory or hospitalized community-acquired pneumonia but was associated with a 44% reduction in risk of pneumococcal bacteremia (see Table 26-4). In that study, the risk of hospitalized community-acquired pneumonia (validated by medical record review), was slightly higher in vaccinated compared with unvaccinated persons in an analysis of all subjects (see Table 26-6) but was not significantly elevated in an analysis restricted to subjects with known smoking status, which also adjusted for current smoking (RR, 1.11; 95% CI, 0.98-1.26). In the subgroup of 3126 immunocompetent persons with chronic lung disease, defined by diagnosis codes and prescriptions for pulmonary medications, vaccination was also not associated with risk of hospitalized or ambulatory pneumonia or with risk of death.

Another of the negative studies was a case cohort study of adults 65 years of age and older that found no association between PPSV23 and risk of hospitalized community-acquired pneumonia.⁴⁶⁸ The third negative study included seniors with chronic respiratory disease and found no association with ambulatory or hospitalized pneumonia or with hospitalized pneumonia alone (although this association was of borderline statistical significance).⁴⁶⁹ The fourth negative study was primarily directed toward the evaluation of pneumococcal vaccination and risk of pneumonia among HIV-infected adults but included a relatively small control group of HIV-uninfected adults.⁴⁷⁰ Among that group, there was no association of PPSV23 and risk of pneumonia. The last study used claims data to evaluate the association of receipt

of PPSV23, within a 2 year window, with risk of mortality and hospitalization outcomes among dialysis patients.⁴⁷¹

In contrast, reductions in risk of pneumonia in vaccinated compared with unvaccinated persons were reported by the other two cohort studies. A prospective study of 11,241 community-dwelling seniors in Catalonia, Spain identified 473 cases of community-acquired pneumonia in the 3-year study period.⁴⁵¹ In multivariate analysis, vaccination was associated with reductions in risk of all community-acquired pneumonia, hospitalized community-acquired pneumonia, and pneumonia mortality. An evaluation of 1898 seniors enrolled in a health maintenance organization in Minnesota, who were defined as having chronic lung disease on the basis of diagnosis codes, reported that vaccination was associated with a 43% reduction in risk of hospitalization assigned pneumonia or influenza diagnosis code and a 29% reduction in risk of all-cause mortality.⁴⁷² There was no significant association of vaccination with risk of the control outcome of nonpneumonia hospitalizations (RR, 0.91; 95% CI, 0.77-1.07).

A case control study of 489 seniors hospitalized with community-acquired pneumonia (CAP) in Spain found that PPSV was associated with a lower risk of CAP in analysis of all subjects (VE, 24%; 95% CI, 1%-41%) but was not associated in analyses of the two subgroups of immunosuppressed subjects (VE, 21%; 95% CI, -19% to 47%) and immunocompetent subjects (VE, 24%; 95% CI, -7% to 46%).⁴⁷³ Another case-control study from Spain identified adults with radiographically confirmed pneumococcal pneumonia, defined by isolation of pneumococcus from blood culture or by sputum culture, or by a positive BinaxNOW *S. pneumoniae* antigen test.⁴⁶⁴ PPSV23 was associated with a significantly lower risk of all pneumococcal pneumonia (VE, 48%; 95% CI, 27%-63%) as well as bacteremic pneumococcal pneumonia (see Table 26-4).

Two other studies have evaluated the association of pneumococcal vaccination and risk of pneumonia. A prospective study of 475 residents in five nursing homes in Toronto, Canada included active surveillance for radiographically confirmed pneumonia over the 3-year study period.⁴⁷⁴ Pneumococcal vaccination status was assessed at baseline and updated yearly. In the analysis, pneumococcal vaccination was "treated as intervals by considering the number of years that residents were exposed". By that definition, subjects with pneumonia had a lower mean number of years of pneumococcal vaccine exposure (1.2 years) than subjects without pneumonia (1.5 years), but this variable was not significantly associated with pneumonia risk in multivariate analysis. An assessment of vaccinated seniors in Genoa, Italy that compared rates of hospitalization before and after vaccination reported a reduction in risk of pneumonia after vaccination.⁴⁷⁵

Lastly, four studies have evaluated cohorts of adults hospitalized with pneumonia to identify the association between prior PPSV23 with subsequent outcomes such as mortality.⁴⁷⁶⁻⁴⁷⁹ Three studies reported that patients who had received PPSV23 were less likely to die or be admitted to the intensive care unit, or to have a prolonged hospital stay, than unvaccinated patients,^{476,477,479} although some issues with study methodology have been noted.⁴⁸⁰ Two of the studies did not find an association between vaccination and length of survival after hospital discharge.^{478,479}

Association of PPSV and risk of myocardial infarction

Several studies have evaluated the association of PPSV vaccination and risk of cardiovascular events such as myocardial infarction. A self-control case series study found no association between PPSV and risk of myocardial infarction or stroke.⁴⁸¹ A subsequent hospital-based case-control study found that patients admitted for treatment of myocardial infarction (cases)

Table 26-6 Cohort Studies of 23-Valent Pneumococcal Polysaccharide Vaccine Effectiveness against Pneumonia in Noninstitutionalized Seniors

Author year ^a	Senior population	Person-years of follow-up	Outcome	Association of vaccination and risk of the outcome		
				Number of events	Adjusted for age and sex	Adjusted for age, sex, and participant characteristics
						Relative risk (95% CI)
Nichol 1999 ⁴⁷²	1898 members of a HMO in Minnesota with a diagnosis code of COPD assigned during the baseline year	Not reported	Hospitalization assigned a pneumonia or influenza diagnosis code All-cause mortality	174 275	Not reported Not reported	0.57 (0.38-0.84) 0.71 (0.56-0.91)
Jackson 2003 ⁴⁴⁷	47,365 members of a HMO in Washington	127,180	Ambulatory and hospitalized community-acquired pneumonia Hospitalized community-acquired pneumonia All-cause mortality	4489 1428 5690	Not reported 1.21 (1.08-1.35) 0.88 (0.84-0.93)	1.07 (0.99-1.14) 1.14 (1.02-1.28) 0.96 (0.91-1.02)
Vila-Córcles 2006 ⁴⁵¹	11,241 seniors assigned to one of eight primary care centers in Tarragona, Catalonia, Spain	33,905	Ambulatory and hospitalized community-acquired pneumonia Hospitalized community-acquired pneumonia All-cause mortality Pneumonia mortality	473 355 1497 60	1.03 (0.86-1.24) 0.96 (0.78-1.19) 0.83 (0.75-0.92) 0.55 (0.33-0.91)	0.79 (0.64-0.98) 0.74 (0.59-0.92) 0.97 (0.86-1.09) 0.41 (0.23-0.72)
Skull 2007 ^{468*}	1952 cases and 2927 cohort members of hospitalized seniors in Victoria, Australia	NA	Hospitalization assigned a pneumonia diagnosis code	1952	Not reported	1.01 (0.87-1.16)
Rodríguez-Barradas 2008 ⁴⁷⁶	934 participants in the Veterans Aging Cohort 5-Site Study	Not reported	Outpatient or inpatient encounter with a pneumonia or pneumococcal ICD9 code	12	Not reported	0.85 (0.25-2.95)
Ochoa-Gondar 2008 ⁴⁶⁹	1298 seniors assigned to one of eight primary care centers in Tarragona, Catalonia, Spain who had a diagnosis of chronic respiratory disease.	3676	Ambulatory and hospitalized community-acquired pneumonia Hospitalized community-acquired pneumonia All-cause mortality	171 137 275	0.93 (0.68-1.28) 0.87 (0.61-1.23) 1.22 (0.92-1.62)	0.77 (0.56-1.07) 0.70 (0.48-1.00) 1.20 (0.91-1.59)
Gilbertson 2011 (B)	118,533 hemodialysis patients	Not reported	Hospitalization assigned a pneumonia diagnosis code All-cause mortality	Not reported Not reported	Not reported Not reported	≈ 0.95 (not significant) [†] 0.94 (0.90-0.98)

*Case cohort study design.

[†]Extrapolated from figure.

COPD, Chronic obstructive pulmonary disease; HMO, health maintenance organization; ICD, international classification of diseases; NA, not applicable.

were less likely to have been vaccinated with PPSV than the control group of patients admitted for surgery (OR, 0.53; 95% CI, 0.40-0.70).⁴⁸² The apparent protective effect increased with more remote vaccination. A more recent cohort study of more than 80,000 men, which included assessment of participant characteristics by surveys, found no evidence of an association between pneumococcal vaccination and reduced risk of myocardial infarction (MI) (hazard ratio [HR], 1.09; 95% CI, 0.98-1.21) or stroke (HR, 1.14; 95% CI, 1.00-1.31).⁴⁸³

Some support for the hypothesis that PPSV may be associated with a reduced risk of outcomes, such as acute MI, was derived from one paper that reported that injection of hypercholesterolemic mice with whole *S. pneumoniae* organisms, as a surrogate for vaccination, induced high levels of IgM autoantibodies to oxidized low-density lipoprotein (LDL) and decreased the extent of atherosclerosis.⁴⁸⁴ Subsequent studies evaluating the immune response in humans injected with PPSV23 have not, however, identified an increase in circulating IgM antibodies to oxidized LDL,^{485,486} suggesting that PPSV23 does not have an antiatherogenic effect in humans.

Summary of vaccine studies in non-HIV-infected adults

The randomized, controlled trials of pneumococcal polysaccharide vaccines in South African gold miners provided convincing evidence for vaccine efficacy against pneumococcal pneumonia in that population. Since that time, 14 observational studies have reported a significant reduction in risk of invasive pneumococcal disease in vaccinated compared with unvaccinated immunocompetent older adults in the United States, Europe, and Australia. Taken together, these studies provide evidence supporting an effect of pneumococcal polysaccharide vaccine on reduction of risk of invasive pneumococcal infection in immunocompetent adults. In the United States, pneumococcal polysaccharide vaccine is recommended for seniors and persons with certain chronic medical conditions, based on the evidence for vaccine effectiveness against invasive pneumococcal disease. There is, however, a lack of evidence supporting an effect of vaccination on risk of invasive pneumococcal infection in immunocompromised adults, who are at increased risk of pneumococcal infection.

The impact of vaccination on risk of nonbacteremic pneumonia is difficult to evaluate because *S. pneumoniae* accounts for only a fraction of all-cause pneumonia cases, and defining the etiology of nonbacteremic pneumonia remains problematic.

The results of clinical trials performed in the United States, Europe, and Japan since the 1970s do not support, in general, an effect of vaccination on reduction of all-cause pneumonia in adults, although two trials, including a recent trial conducted in Japan, found an association of PPSV23 with reduction in risk of all-cause pneumonia in nursing home residents. The lack of association between PPSV23 and risk of all-cause pneumonia reported in most of the clinical trials is consistent with either a lack of effect of vaccination against nonbacteremic pneumococcal pneumonia or an effect of vaccination in reducing the risk of nonbacteremic pneumococcal pneumonia that does not lead to a significant reduction in overall risk of pneumonia. The latter could occur if the vaccine effect was only modest and/or pneumococcal infection accounted for a relatively small proportion of all pneumonia cases. In observational cohort studies in the elderly, vaccine effectiveness estimates vary considerably, with the largest of these studies demonstrating no reduction in risk of all-cause pneumonia in vaccinated persons—consistent with the results of most of the clinical trials. It is possible that increased use of newer-generation diagnostic tests may allow more accurate identification of cases of nonbacteremic pneumococcal pneumonia and, therefore, a more complete assessment of this outcome in future vaccine evaluations.

Clinical trials in HIV-infected adults

The efficacy of pneumococcal polysaccharide vaccination in HIV-infected adults has been evaluated in one randomized, controlled trial conducted in Uganda.⁴⁸⁷ The results of this trial did not support a benefit of vaccination in protection against invasive pneumococcal infection or pneumonia in this population. In the trial, initiated in 1995, 1392 HIV-infected adults in Uganda were randomized to receive 23-valent pneumococcal polysaccharide vaccine or placebo. The primary study end point was the first event of invasive pneumococcal disease, and secondary end points included vaccine serogroup-specific invasive disease, all-cause pneumonia, and death. Approximately half of study participants had a CD4⁺ cell count less than 200 at the time of enrollment.

During the prespecified 2.5-year study follow-up period, there was no significant difference between the vaccine and placebo groups in the risk of all invasive pneumococcal disease or of vaccine-specific invasive pneumococcal disease (Table 26-7). Participants randomized to pneumococcal polysaccharide vaccine had a significantly higher risk of all-cause pneumonia, and in the first 6 months of follow-up, receipt of pneumococcal

Table 26-7 Relative Risk of Invasive Pneumococcal Infection, Pneumonia, and Death Associated with Receipt of 23-Valent Pneumococcal Polysaccharide Vaccine in a Randomized Placebo-Controlled Trial in HIV-Infected Adults in Uganda, by Study Follow-up Interval

Outcome	Original trial period		Extended follow-up period		
	Enrollment through 6 months	7 months-2.5 years	Enrollment through 2.5 years	2.6-6.0 years	Enrollment through 6.0 years
Relative risk (95% CI) of outcome in vaccinated versus placebo					
Invasive pneumococcal disease, all serotypes	2.45 (0.77-7.82)	0.82 (0.25-2.68)	1.48 (0.65-3.32)	1.13 (0.5-2.4)	1.28 (0.7-2.2)
Vaccine-type invasive pneumococcal disease	4.91 (1.07-22.39)	0.98 (0.28-3.39)	2.14 (0.86-5.31)	0.88 (0.3-2.4)	1.43 (0.7-2.8)
All-cause pneumonia	2.82 (1.19-6.66)	1.43 (0.72-2.83)	2.02 (1.19-3.45)	0.92 (0.4-2.1)	1.56 (1.0-2.4)
Death	1.01 (0.72-1.40)	0.98 (0.75-1.27)	1.08 (0.87-1.33)	0.70 (0.6-0.9)	0.84 (0.7-1.0)

CI, Confidence interval; HIV, human immunodeficiency virus.

Modified from French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet* 355:2106-2111, 2000; Wataha C, Nakiyingi J, Miro G, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. *AIDS* 18:1210-1213, 2004.

polysaccharide vaccine was also associated with a significant elevation in the risk of vaccine-specific invasive pneumococcal disease that did not persist after that period. The risk of death was similar in the two groups. These results indicate that, in this study population of HIV-infected adults, pneumococcal vaccine may have been associated with a transiently increased risk of nonfatal pneumococcal infection.

In response to those findings, follow-up of trial participants was continued for an additional 3.5 years.⁴⁸⁸ During the extended follow-up period, the risk of vaccine-specific invasive pneumococcal disease and of all-cause pneumonia was comparable in vaccine and placebo recipients (see Table 26-7). However, in the 2.6 to 6.0 years after the trial was initiated, vaccine recipients were at significantly lower risk of death. During the entire 6-year period following enrollment, there was no difference in the risk of vaccine-type invasive pneumococcal disease in the vaccine compared with the placebo group, but there were trends toward a higher risk of all-cause pneumonia and a lower risk of death in vaccinated compared with unvaccinated persons.

In subgroup analyses of risk of all-cause pneumonia during the 6-year period after enrollment that were stratified by CD4 count at the time of vaccination, there was a trend toward a greater increase in risk of all-cause pneumonia in vaccinated compared with unvaccinated persons in the subgroups with higher CD4 counts. The relative risk (95% CI) of all-cause pneumonia associated with vaccination was 0.94 (0.5-1.7) in participants with CD counts less than 200, 2.34 (1.1-4.9) in participants with CD4 counts of 200 to 500, and 5.88 (0.7-47.8) in those with CD4 counts greater than 500.⁴⁸⁸ A similar trend was observed in the original 2.5-year study follow-up period.⁴⁸⁷

The investigators hypothesized that pneumococcal polysaccharide vaccination may have caused polysaccharide-responsive memory B cells to terminally differentiate into short-lived antibody-producing plasma cells and thereby induced a specific defect in the humoral response to rechallenge with pneumococcal capsular polysaccharide antigens. The disproportionate increase in risk in persons with higher CD4 counts at the time of vaccination appeared to support this hypothesis, because a vaccine-induced defect in antipneumococcal immunity might have a greater effect in the group with relatively preserved baseline immune function. This hypothesis does not, however, explain the trend toward a decreased risk of death in the vaccinated group over the 6-year period after enrollment.

To evaluate the ability of trial participants to respond to a pneumococcal polysaccharide challenge, 6 years after the original trial, the investigators conducted another evaluation in which they administered two doses of 7-valent conjugate pneumococcal vaccine to trial participants still under follow-up.⁴⁸⁹ This study was designed to evaluate the response to rechallenge with pneumococcal polysaccharide antigen in participants who had previously received pneumococcal polysaccharide vaccine compared with those who had previously received placebo. There were significant increases in anticapsular IgG concentrations after conjugate vaccination in both groups, and there was no effect of past receipt of pneumococcal polysaccharide vaccine on antibody response to the conjugate vaccine. These findings do not support the hypothesis that pneumococcal polysaccharide vaccination led to selective defects in humoral response to pneumococcal capsular polysaccharide antigens. However, this trial included only 8% of the participants enrolled in the original trial, because most had died in the interval between the two studies, and so the group evaluated in the conjugate vaccine study was not representative of the original trial cohort.

More recently, a randomized, placebo-controlled trial of two doses of a 7-valent pneumococcal conjugate vaccine in predominantly HIV-infected Malawian adolescents and adults who had

recovered from documented IPD found that the PCV7 vaccine was associated with a significantly lower risk of IPD due to the vaccine serotypes (plus 6A).⁴⁹⁰

Observational studies of vaccine effectiveness in HIV-infected adults

The Uganda trial is the only reported randomized trial of pneumococcal polysaccharide vaccine efficacy in HIV-infected persons, and so estimates of vaccine effectiveness for populations outside of eastern Africa are derived exclusively from nonrandomized studies. As with other observational studies, there is the possibility that the estimates of vaccine effectiveness from nonrandomized evaluations of pneumococcal polysaccharide vaccine in HIV-infected persons are biased by differences in the characteristics of the vaccinated and unvaccinated groups. Potentially important factors that are associated with risk of pneumonia and IPD, and that may also be associated with likelihood of pneumococcal vaccination, include CD4 cell count, HIV ribonucleic acid (RNA) level, history of pneumonia, injection drug use, smoking, sex, race, age, and receipt of antiretroviral therapy.⁴⁹¹

The results of 14 published nonrandomized studies of pneumococcal vaccine effectiveness in HIV-infected persons are summarized in Table 26-8.^{148,155-158,470,492-499} Of those 14 studies, two^{148,495} were very small, including only 7 or 12 pneumococcal outcome events. The remaining 12 studies evaluated a variety of outcomes, including invasive pneumococcal disease, invasive and noninvasive pneumococcal infection, and all-cause pneumonia.

Four studies evaluated an outcome of invasive pneumococcal disease (or pneumococcal bacteremia).^{156,158,492,498} Two found no association of receipt of PPSV23 and risk of IPD,^{156,498} one found a significant reduction in risk of pneumococcal bacteremia in vaccinated compared with unvaccinated persons,¹⁵⁸ and one found that vaccination was associated with a reduction in risk of IPD in whites but not blacks.⁴⁹²

Five other studies evaluated the nonspecific outcome of all-cause pneumonia.^{470,493,494,496,497} By far the largest study was an assessment of 23,255 HIV-infected adults enrolled in the Adult/Adolescent Spectrum of HIV Disease project.⁴⁹⁷ In that study, receipt of PPSV23 was associated with a lower risk of pneumonia. Vaccine effectiveness was associated with viral load at vaccination, and vaccine effectiveness was not documented for persons vaccinated with a viral load of 100,000 copies per milliliters or greater.

The other three studies evaluated an outcome of pneumococcal infection, the definition of which varied between studies. The studies by Gebo and Dworkin^{155,157} found a beneficial effect of vaccination that was restricted to a subgroup with a higher (≥ 200 or ≥ 500) CD4 count at the time of vaccination. In contrast, a more recent study by Penaranda⁴⁹⁹ found a significantly lower risk of pneumococcal infection in vaccinated persons, even in analyses of persons with a CD4 count less than 200. Limitations of that study were that vaccination status in cases was defined by vaccine received before the pneumococcal disease onset date, while vaccination status in the control group was defined as receipt at any time during the study period, which may have led to a bias toward a higher vaccination rate in the control group and thus an inflated estimate of vaccine effect.

Interpretation of the observational studies of PPSV23 effectiveness in HIV-infected adults is complicated by variations in study designs, outcomes, and the possibility of a healthy user bias. In aggregate, they provide some support for a protective effect of PPSV23, particularly if the vaccine is administered when the CD4 count is not suppressed or the viral load is not elevated.

Table 26-8 Observational Studies of 23-Valent Pneumococcal Polysaccharide Vaccine Effectiveness in HIV-Infected Adults

Author year ^{ref}	Study population	Study period	Design	Outcome	No. of events	Subgroup	Relative risk in vaccinated compared with unvaccinated	95% CI
Gebo 1996 ¹⁵⁷	Cohort of outpatients in Baltimore, Maryland	1990-1994	Case control	Invasive pneumococcal disease (42%) or pneumococci isolated from respiratory secretions	85	CD4 > 200 at vaccination	0.22	0.05-0.98
Guerrero 1999 ¹⁵³	Outpatients in Los Angeles, CA	1990-1998	Case control	All-cause pneumonia	127	All CD4 < 100 at vaccination CD4 100-199 at vaccination CD4 > 200 at vaccination	0.31 0.36 0.23 0.22	0.16-0.62 0.16-0.84 0.08-0.67 0.09-0.54
Navin 2000 ¹⁵⁶	Hospitalized patients in Atlanta, GA	1994-1996	Case control	All-cause pneumonia	211	All	0.63	0.41-1.15
Breiman 2000 ¹⁵²	Hospitalized patients in San Francisco, California and Atlanta, GA	1992-1995	Case control	Invasive pneumococcal disease	176	White race Black race	0.24 0.76	0.09-0.65 0.39-1.50
Dworkin 2001 ¹⁵⁵	Adult and Adolescent Spectrum of Disease Project cohort in the United States	1990-1998	Cohort	Pneumococcal infection	585	CD4+ < 200 at vaccination CD4+ 200-500 at vaccination CD4+ ≥ 500 at vaccination	1.0 1.0 0.5	0.7-1.4 0.8-1.4 0.3-0.9
Lindenburg 2001 ¹⁵⁴	48 injection drug users in Amsterdam who seroconverted to HIV during follow-up	1994-1998	Cohort	All-cause pneumonia	65	All	1.01	0.53-1.91
Hung 2004 ¹⁵⁵	Prospectively identified group of 305 patients who consented to receive PPSV and 203 patients who did not in Taiwan	2000-2002	Cohort	Pneumococcal infection	7	All	0.08	0.01-0.73

Continued

Table 26-8 Observational Studies of 23-Valent Pneumococcal Polysaccharide Vaccine Effectiveness in HIV-Infected Adults—cont'd

Author year ^{a†}	Study population	Study period	Design	Outcome	No. of events	Subgroup	Relative risk in vaccinated compared with unvaccinated	95% CI
Lopez-Palomo 2004 ¹⁴⁸	Cohort of 300 outpatients in Cadiz, Spain	1997-2000	Cohort	Pneumococcal pneumonia	12	All	0.28*	0.07-1.06
Grau 2005 ¹⁴⁹	Cohort of outpatients in Barcelona, Spain	1997-2002	Case control	Pneumococcal bacteremia	122	All	0.39	0.15-0.97
Barry 2006 ¹⁵⁰	Cohort of outpatients in Baltimore, Maryland	1990-2003	Case control	Pneumococcal bacteremia	67	CD4 < 300 at vaccination CD4 > 300 at vaccination	0.7 0.8	0.4-1.3 0.4-1.7
Penaranda 2007 ^{149b}	Hospitalized patients in Spain	1995-2005	Case control	Pneumococcal infection	184	All	0.39	0.24-0.65
Veras 2007 ^{149b}	Inpatients and outpatient in Brazil	2000-2004	Case control	Invasive pneumococcal disease	69 95	CD4 < 200 CD4 ≥ 200	0.15 0.55	0.04-0.50† 0.31-0.99
Rodriguez-Barradas 2008 ⁴⁷⁰	692 participants in the Veterans Aging Cohort 5-Site Study	2001-2004	Cohort	All-cause pneumonia	85	All	0.65	0.42-1.00
Teshale 2008 ⁴⁹⁷	Adults in the Adult/Adolescent Spectrum of HIV Disease (ASD) project	1996-2003	Cohort	All-cause pneumonia	4135	All	0.8	0.8-0.9

*Results of univariate analysis are reported. The authors noted that in multivariate analysis pneumococcal vaccination was not associated with risk of pneumococcal pneumonia or all community-acquired pneumonia but the estimates of those associations were not reported.

†These numbers represent a correction supplied by the author to the confidence interval reported in the publication.

Number of events = number of cases in a case-control study.

CI, Confidence interval; HIV, human immunodeficiency virus; PPSV, pneumococcal polysaccharide vaccine.

Vaccine evaluations in children

Clinical trials in immunocompetent children

Several randomized controlled trials in the 1980s assessed the efficacy of 8-valent or 14-valent pneumococcal polysaccharide vaccines in preventing otitis media in children younger than 6 years.⁵⁰⁰⁻⁵⁰⁹ In Australia, a randomized, blinded trial showed no difference in the risk of acute otitis media in children younger than 2 years (RR, 1.01; 95% CI, 0.81-1.25) and a possible trend toward a reduction in risk in children older than 24 months (RR, 0.83; 95% CI, 0.69-1.01).⁵⁰⁰ A recent meta-analysis of these trials found no evidence for an overall effect across all age groups or for a reduction in risk of otitis in children younger than 24 months who received pneumococcal polysaccharide vaccine, but in the pooled analysis of children older than 24 months, there was evidence of a vaccine effect (RR, 0.78; 95% CI, 0.63-0.97).⁵⁰⁸ These results of these trials have been interpreted as evidence for a lack of efficacy in prevention of otitis media in children younger than 24 months and, at best, a moderate effect in older children.

Pneumococcal polysaccharide vaccine has been associated with a reduction in risk of death attributed solely to acute lower respiratory infection (ALRI) in young children in Papua New Guinea.⁵¹⁰⁻⁵¹² A clinical trial of more than 7000 children, 4 months to 5 years of age, randomized children either individually or by hamlet cluster to receive a 14-valent or 23-valent pneumococcal polysaccharide vaccine or placebo. Vaccination was reported to have reduced ALRI mortality by 59% overall (95% CI, 19%-79%) and by 50% (95% CI, 1%-75%) in children vaccinated at 2 years of age or younger.

Clinical trials in children with sickle cell disease

Only one randomized trial⁵¹³ has evaluated the efficacy of pneumococcal polysaccharide vaccination for prevention of pneumococcal infection in children with sickle cell disease. In that trial, 242 Jamaican children aged 6 months to 3 years of age were randomized to one of four study groups: 14-valent pneumococcal vaccine with penicillin prophylaxis ($n = 97$), 14-valent pneumococcal vaccine without penicillin prophylaxis ($n = 62$), *Haemophilus influenzae* b (Hib) vaccine with penicillin prophylaxis ($n = 46$), and Hib vaccine without penicillin prophylaxis ($n = 37$ [which was misreported as 27 in a table in the original paper⁵¹⁴]). Eleven children in the pneumococcal polysaccharide vaccine groups developed pneumococcal infection compared with only 3 in the Hib vaccine groups (odds ratio [OR], 3.01; 95% CI, 0.65-13.91). There was also no evidence of pneumococcal vaccine efficacy in an analysis restricted to children who did not receive penicillin prophylaxis. A limitation of this trial was that the majority of the participants were younger than 2 years, and so the results are not necessarily generalizable to older children, in whom the vaccine is more immunogenic.

A nonrandomized, nonblinded study of persons with sickle cell disease, 2 to 25 years of age, evaluated 68 patients who were given an 8-valent pneumococcal polysaccharide vaccine and a nonconcurrently enrolled comparison group of 106 unimmunized patients. During the 2-year follow-up period, 8 of the unimmunized patients developed pneumococcal bacteremia compared with none of the immunized patients, which was interpreted as evidence for a protective effect of vaccination.⁵¹⁵

Observational studies of vaccine effectiveness in children

Two observational studies of pneumococcal vaccine effectiveness against invasive pneumococcal disease included both children and adults,^{448,454} but neither presented results of subgroup analyses of persons less than 18 years of age. Two other indirect cohort studies included only children and have yielded varying

estimates of the effectiveness of 23-valent pneumococcal polysaccharide vaccination against invasive pneumococcal infection in children with sickle cell disease in the era before the availability of pneumococcal conjugate vaccine (see Table 26-4).

The first study, an indirect cohort analysis of data from a national surveillance system conducted by Fiore and colleagues,⁴⁵⁵ included children 2 to 5 years of age with chronic illnesses considered to be a risk factor for pneumococcal infection and who had pneumococcus isolated from blood or cerebrospinal fluid during 1984 to 1996. Of the 173 children included in the study, 46 had sickle cell disease, and vaccine effectiveness was not demonstrated in that subgroup. A significant 84% reduction in risk of invasive pneumococcal disease was, however, found in the subgroup of children without sickle cell disease, the majority (62%) of whom had malignancy, nephrotic syndrome, HIV infection, or organ transplant.

The second study, conducted in conjunction with a multisite study of regional pediatric sickle cell programs and which included only children with sickle cell disease, reported no significant association of ever-receipt of pneumococcal vaccine with risk of invasive pneumococcal disease.⁴⁵⁶ However, an alternate analysis that defined vaccinated children as only those who had received pneumococcal polysaccharide vaccine within the previous 3 years compared that group with a combined group of unvaccinated children and children vaccinated 3 or more years earlier and found an estimated effectiveness of 80% (95% CI, 40%-94%).

Vaccine evaluations of persons with asplenia

Evidence supporting pneumococcal polysaccharide vaccine efficacy in persons with anatomic asplenia is provided by one observational study and one ecologic study. In the indirect cohort study by Butler and colleagues,⁴⁵⁴ vaccine efficacy was 77% (95% CI, 14%-95%) in persons with asplenia. The characteristics of the patients, in terms of their indication for splenectomy, time since splenectomy, number of previous pneumococcal vaccinations, and time since last vaccination, were not reported. An ecologic assessment in Denmark found no cases of pneumococcal bacteremia in 292 children with splenectomies performed in 1979 to 1987, when pneumococcal polysaccharide vaccine was used routinely, compared with six cases per 1,000 person-years in children splenectomized in 1969 to 1978, before the availability of pneumococcal polysaccharide vaccine.⁵¹⁶ The possible impact of the recommended use of antimicrobial prophylaxis on the Denmark study findings could not be determined.

A retrospective study of 879 postsplenectomy patients in Canada found no association between PPSV and risk of all-cause mortality.⁵¹⁷

Vaccine safety

Common reactions

Local reactions are the most common adverse events after administration of pneumococcal polysaccharide vaccine (Table 26-9).^{317,432} These reactions usually resolve within 2 days of vaccination and are typically mild. Fever is uncommon after pneumococcal polysaccharide vaccination. The safety profile of a first pneumococcal polysaccharide vaccination in children is similar to that in adults.^{328,355}

Rare reactions

There are two published reports of apparent anaphylactic reactions to 23-valent pneumococcal polysaccharide vaccine. The first was a 2-year-old nonatopic boy who had small bowel and

Table 26-9 Local Reactions Reported by 901 Adults 50-74 Years of Age Receiving a First 23-Valent Pneumococcal Polysaccharide Vaccination and 513 Adults 50-74 Years of Age Receiving a Second 23-Valent Pneumococcal Polysaccharide Vaccination 5 or More Years after Their First Vaccination

Reaction reported postvaccination	First vaccination, %	Revaccination, %
Maximal diameter of redness or swelling in the vaccinated arm		
Any	21	38
≥ 5.08 cm [2 in]	10	25
≥ 7.62 cm [3 in]	6	18
≥ 10.2 cm [4 in]	3	11
Arm soreness	57	74
Any limitation of arm movement caused by pain	18	32
Cannot raise arm above head caused by pain	3	10
Cannot raise arm above shoulder caused by pain	1	5

P < .001 for all comparisons of first vaccination versus revaccination.
From Jackson LA, Benson P, Sneller VP et al. Safety of revaccination with pneumococcal polysaccharide vaccine. JAMA 281:243-248, 1999.

liver disease and was awaiting liver transplantation and who developed bronchospasm and cutaneous and laryngeal edema immediately after vaccination, which resolved with appropriate treatment.⁵¹⁸ A diagnostic evaluation demonstrated immunoglobulin E (IgE) antibodies specific for pneumococcal polysaccharides, suggesting that previous nasopharyngeal carriage or occult infection with *S. pneumoniae* induced IgE-dependent sensitization. The second was a 3 year old girl who had received three doses of 7-valent pneumococcal conjugate vaccine before the age of 1 year, who had a severe anaphylactic reaction within minutes of receipt of PPSV23 at age 3 years.⁵¹⁹ Immediate responses to intradermal skin testing with both 7-valent pneumococcal conjugate vaccine and PPSV23 were noted, suggesting that administration of 7-valent pneumococcal conjugate vaccine may have induced sensitization to antigens in PPSV23.

Safety of revaccination

In the early 1980s, revaccination was contraindicated because of safety concerns.⁵²⁰ Those concerns were prompted by the findings of two studies conducted in the 1970s that reported a higher-than-expected frequency and severity of local injection-site reactions after revaccination of healthy adults within 2 years of their first vaccination.^{521,522} Other reports also documented limb swelling and other large local reactions in healthy adults and children vaccinated within 3⁵²³ or 4 years⁵²⁴ of a first vaccination. However, several more recent studies evaluating the safety of revaccination of older adults at intervals of approximately 5 years between vaccinations indicate that revaccination tends to be associated with a higher frequency of local reactions but is generally well tolerated.^{297,299,302,303,317,525,526}

In a prospective study of adults 50 years of age and older, which included 901 participants receiving their first PPSV23 and 513 participants receiving a second PPSV23 greater than or equal to 5 years after their prior vaccination, local reactions were more frequent in the group given a second vaccination

(see Table 26-9), but the reactions were not severe and were self-limited.³¹⁷ Participants who received their second vaccination were more likely than participants who were given a first vaccination to report an injection-site reaction with a diameter of 4 inches or greater (11% vs. 3%) and to report tenderness, soreness, and limitation of movement of the vaccinated arm. In both first vaccinees and revaccinees, higher prevaccination pneumococcal antibody levels were correlated with an increased risk of larger injection-site reactions. In the revaccination group, the risk of larger local reactions did not vary significantly by number of years since the prior vaccination. Only one participant, who was in the revaccination group, sought medical evaluation for an injection site reaction, and serious adverse events associated with either a first vaccination or revaccination were not identified.

Similarly, another study of adults 50 years of age and older given either a first PPSV23 (*n* = 444) or a second PPSV23 at least 3 years after the prior vaccination (median, 3.9 years) (*n* = 1008) also found a higher frequency of local reactions in participants receiving a second compared with a first PPSV23.³⁰⁵ In that study, a severe injection-site reaction, defined as greater than or equal to 4 inches of erythema or induration or severe pain, was reported by approximately 16% of revaccinated subjects compared with 4% of subjects receiving a first vaccination. Higher prevaccination antibody levels were correlated with a greater risk of local reactions.

A prospective study of Alaskan adults 55 to 74 years of age that included persons receiving a first PPSV23 (*n* = 121), persons receiving a second PPSV23 after an interval of at least 6 years (*n* = 119), and persons receiving a third or fourth PPSV23 at least 6 years after the prior vaccination (*n* = 69) also found that a first vaccination was associated with a lower frequency of swelling at the injection site and limitation of movement of the vaccinated arm.³⁰⁷ In that study, revaccination was also associated with a higher frequency of some systemic symptoms, including joint pain, fatigue, and headache.

The available data from two published retrospective studies indicate that a third pneumococcal polysaccharide vaccination is not associated with an increased risk of medically attended adverse events in adults.^{527,528}

Indications for vaccine

General recommendations in the United States

Adults

In the United States, ACIP recommends pneumococcal polysaccharide vaccine for all persons 65 years of age and older and for adults 19 to 64 years who are at increased risk of IPD (Table 26-10).^{162,163,529} Indications for vaccination of adults 19 to 64 years of age include cigarette smoking, chronic lung disease (including asthma), chronic cardiovascular diseases, diabetes mellitus, chronic liver disease, cirrhosis, chronic alcoholism, residence in a nursing home or long-term care facility, functional or anatomic asplenia (eg, sickle cell disease and other hemoglobinopathies or splenectomy [if elective splenectomy is planned, vaccinate at least 2 weeks before surgery]), immunocompromising conditions (including HIV infection, chronic renal failure, nephrotic syndrome, certain congenital immunodeficiency disorders, and diseases associated with treatment with immunosuppressive drugs or radiation therapy [including malignant neoplasms, leukemias, lymphomas, and solid-organ transplant]), cochlear implants, and cerebrospinal fluid leaks. As of 2008, routine use of PPSV23 is no longer recommended for otherwise healthy American Indian or Alaska Native (AI/AN) persons under 65 years of age. This change from the prior recommendation for routine use of PPV23 in AI/AN persons

Table 26-10 Recommendations for Pneumococcal Polysaccharide Vaccination and Revaccination in the United States

Indicates for initial Vaccination	Revaccination
≥ 65 years of age	All adults should receive a single dose of PPSV23 vaccination on or after the 65th birthday, regardless of whether they received PPSV23 before age 65. For adults who received one or more doses of PPSV23 before age 65 years, another dose of PPSV23 is recommended on or after the 65th birthday (and at least 5 years after the most recent prior PPSV23).
2 through 64 years of age* with:	
chronic lung disease (including asthma), chronic cardiovascular diseases, diabetes mellitus; chronic liver diseases, cirrhosis, chronic alcoholism, cerebrospinal fluid leaks, cochlear implants, residents of nursing homes or long-term care facilities), smokers	Routine revaccination before age 65 years is not recommended.
HIV infection; congenital immunodeficiency; leukemia; lymphoma; Hodgkin disease; multiple myeloma; generalized malignancy; immunosuppressive therapy or high-dose, long-term corticosteroid therapy; and organ or bone marrow transplantation	One-time revaccination after 5 years is recommended if prior to age 65 years.
Functional or anatomic asplenia (e.g., sickle cell disease or splenectomy)*	One-time revaccination after 5 years is recommended if prior to age 65 years.
Chronic renal failure or nephrotic syndrome	One-time revaccination after 5 years is recommended if prior to age 65 years.

*Children aged ≥ 2 years with underlying medical conditions should receive PPSV23 after completing all recommended doses of PCV13. These children should be administered one dose of PPSV23 at age ≥ 2 years and at least 8 weeks after the most recent dose of PCV13.

HIV, Human immunodeficiency virus; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.

Modified from Centers for Disease Control and Prevention (CDC): 2012 Child, Adolescent and Adult Immunization Schedules, United States. www.cdc.gov/vaccines/recs/schedules/default.htm. Accessed 18 May 2012.

2–64 years of age was made in recognition of the fact that while those groups may have disproportionately higher rates of IPD, the bulk of the disease burden is among those with medical indications for PPV23.^{529a} However, in special situations, public health authorities may recommend PPSV for American Indian or Alaska Native adults 50 to 64 years of age who are living in areas where the risk of IPD is increased.

Similar recommendations for vaccination of older adults and younger persons with high-risk conditions are in place in the majority of countries in the European Union, although in France, the Netherlands, and Sweden vaccination is recommended only for adults with high-risk conditions and not for healthy adults 65 years of age and older (Table 26-11).⁵³⁰ In England, a risk group–only policy was implemented in 1992, and in 2003, the recommendations were extended to include all adults 65 years of age and older. In March 2011, the UK Department of Health Joint Committee on Vaccination and Immunisation (JCVI) issued a statement indicating that the program of routine vaccination of adults 65 years of age and older was ineffective and advised that it be discontinued.⁵³¹ The JCVI statement cited surveillance data showing no detectable reduction in incidence of IPD among adults 65 years and older in the years after initiation of the routine vaccination program and other evidence suggesting that PPSV23 is poorly effective and provides a limited duration of protection in older adults. The JCVI statement also noted that decreases in IPD in older adults had been observed after introduction of PCV7 in children, and further declines are expected with the switch to PCV13 in 2010.

Children and adolescents

Children younger than 19 years with underlying medical conditions that are associated with an increased risk of IPD should receive 13-valent pneumococcal conjugate vaccine according to current recommendations of the ACIP and the American Academy of Pediatrics, which may indicate a supplemental dose of PCV13.^{14,532} Underlying medical conditions that are an

indication for pneumococcal vaccination in children include chronic heart disease, chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, cerebrospinal fluid leaks, cochlear implant, functional or anatomic asplenia (eg, sickle cell disease or splenectomy), and immunocompromising conditions.

Children 2 to 18 years of age who have an indication for pneumococcal vaccination, including cochlear implant,⁵³³ should also receive one dose of PPSV23.^{532,534} Receipt of PPSV is associated with a diminished immune response to subsequent PCV (hypo-responsiveness);^{276,319} therefore, all recommended doses of PCV should be given before the dose of PPSV, which should be given a minimum of 8 weeks after the last dose of PCV. Routine use of PPSV is not recommended for Alaska Native or American Indian children. However, in special situations, public health authorities may recommend the use of PPSV after PCV for Alaska Native or American Indian children aged 24 to 59 months who are living in areas in which risk of IPD is increased.¹⁶²

The US Recommended Immunization Schedules for children, adolescents, and adults are updated annually and available at www.cdc.gov/vaccines.

Revaccination

Revaccination with PPSV23 is not generally recommended, with the exception of certain subgroups of immunocompromised persons younger than 65 years. A one-time revaccination after 5 years is recommended for children and adults younger than 65 years who have chronic renal failure or nephrotic syndrome, functional or anatomic asplenia (eg, sickle cell disease or splenectomy), or another immunocompromising condition, but no more than two doses of PPSV are recommended.

All adults should receive a PPSV23 vaccination on or after the 65th birthday, regardless of whether they received PPSV23 before age 65 years. For adults who received PPSV23 before age 65 years, a single dose of PPSV23 is recommended on or after the 65th birthday (and at least 5 years after the prior PPSV23).

Table 26-11 Pneumococcal Polysaccharide Vaccine Recommendations in Selected Industrialized Nations

	Vaccine licensed	National recommendation for risk groups	≥ 65- year- olds	Number of risk groups*	Booster dose recommended
Australia	Yes	Yes	Yes	12	NA
Austria	Yes	Yes	Yes	9	NA
Belgium	Yes	Yes	Yes [†]	11	NA
Canada	Yes	Yes	Yes	12	After 5 years [‡]
Czech Republic	Yes	Yes	Yes	6	NA
Cyprus	Yes	Yes	Yes	11	NA
Denmark	Yes	Yes	Yes	9	NA
England	Yes	Yes	Yes [§]	8	No [¶]
Estonia	Yes	Yes	Yes	9	NA
Finland	Yes	Yes	Yes	12	After 3-5 years [¶]
France	Yes	Yes	No	5	NA
Germany	Yes	Yes	Yes [†]	7	After 6 years
Ireland	Yes	Yes	Yes	11	NA
Italy	Yes	Yes	Yes	NA	NA
Latvia	Yes	Yes	Yes	2	NA
Lithuania	Yes	Yes	Yes	9	NA
Luxembourg	Yes	Yes	Yes [†]	12	NA
Netherlands	Yes	Yes	No	5	NA
New Zealand	Yes	Yes	Yes	NA	NA
Norway	Yes	Yes	Yes	9	NA
Portugal	Yes	No	No	0	—
Slovak Republic	Yes	Yes	NA	NA	After 3-5 years
Slovenia	Yes	Yes	Yes	10	NA
Sweden	Yes	Yes	No	10	NA
Switzerland	Yes	Yes	Yes	9	After 5 years

*Of the following 12 risk groups: splenectomised, cardiovascular disease, chronic pulmonary disease, diabetes mellitus, alcoholism, chronic liver disease, cerebrospinal fluid leaks, immunosuppressed, HIV-infected, > 65 years of age, nursing home resident, and other.

[†]> 60-year-olds targeted.

[‡]Some risk groups.

[§]In 2011, the Joint Committee on Vaccination and Immunisation (JCVI), an independent expert advisory committee to the UK Department of Health, recommended cessation of the program of routine vaccination of adults ≥ 65 years of age. A change to the official policy recommending routine vaccination of persons ≥ 65 years of age is under consideration by the Department of Health.

[¶]For immunocompromised only.

HIV, Human immunodeficiency virus; NA, not available.

Modified from Pebody RG, Leino T, Nohynek H, et al. Pneumococcal vaccination policy in Europe. *Euro Surveill* 10:174-178, 2005 and the 2006 Canadian Immunization Guide: www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php. Accessed 8 December 2011.

Vaccination of specific risk groups

Persons with functional or anatomic asplenia

Pneumococcal polysaccharide vaccine is recommended for asplenic persons 2 years of age and older. Patients scheduled for elective splenectomy should receive indicated vaccinations, which in children may include pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine, at least 2 weeks before the procedure. After emergent splenectomy, pneumococcal polysaccharide vaccine may be administered as early as 1 day postoperatively, but there may be an advantage to delaying vaccination for 14 days postoperatively.

Persons with cochlear implants

In June 2002, the Food and Drug Administration received reports of bacterial meningitis in persons with cochlear implants, which are surgically implanted devices that include

an electrode array that is inserted into the cochlea. As of May 2003, 118 cases of bacterial meningitis in children and adults with cochlear implants worldwide had been identified.⁵³⁵ A subsequent investigation of 4264 children in the United States who received cochlear implants when they were younger than 6 years identified a rate of pneumococcal meningitis in the study population that was more than 30 times higher than that of children in the general US population.¹⁴⁴ The risk of meningitis was significantly higher for patients with implant devices that included an electrode positioner, and those devices were estimated to account for about 50% of the cases of bacterial meningitis. A follow-up study found that children with implants with positioners remain at elevated risk of bacterial meningitis beyond 24 months after implantation, whereas a continued increase in risk was not found in children with implants without positioners.⁵³⁶ Implant devices with electrode positioners were voluntarily recalled in 2002 and are no longer used.

Because of the documented increase in risk of pneumococcal meningitis, the ACIP recommends that all persons with cochlear implants receive age-appropriate pneumococcal vaccination with pneumococcal conjugate vaccine, pneumococcal polysaccharide vaccine, or both, according to the schedules for persons at high risk.^{533,534} The dose of PPSV should be given at least 2 months after the last dose of PCV13, and for maximal benefit, the doses of PCV13 and PPSV should be completed at least 2 weeks before implant surgery. Administration of more than one dose of PPSV to children with cochlear implants is not recommended.

Persons infected with HIV

In the United States, pneumococcal polysaccharide vaccination has been recommended for HIV-infected persons since 1989.⁵³⁷ In their most recent guidelines, the HIV Medicine Association/ Infectious Diseases Society of America recommended that adolescents and adults with HIV infection who have a CD4⁺ T-lymphocyte count of greater than 200 cells/ μ L should be administered a dose of 23-valent polysaccharide pneumococcal vaccine, unless they have received this vaccine during the previous 5 years.⁵³⁸ Revaccination every 5 years may be considered.

HIV-infected adults and adolescents who have a CD4⁺ count of less than 200 cells/ μ L can be offered PPSV. Revaccination can be considered for persons who were initially vaccinated when their CD4⁺ counts were less than 200 cells/ μ L and whose CD4⁺ counts have increased to greater than 200 cells/ μ L in response to antiretroviral therapy (ART).

Other immunocompromised persons

Pneumococcal vaccination is recommended for immunocompromised persons because of their increased risk of disease, although because of poor immunogenicity, many of these patients are likely to derive little benefit.^{123,163} Persons who are being considered for immunosuppressive therapy should be vaccinated at least 2 weeks before treatment begins or, if this is not possible, 3 months after treatment stops because the antibody response to vaccination during or shortly after chemotherapy or radiation therapy is poor.

Contraindications and precautions

There are no contraindications to administering pneumococcal polysaccharide vaccine other than known hypersensitivity to a vaccine component or a previous severe reaction to the vaccine.

Children for whom both pneumococcal polysaccharide vaccine and pneumococcal conjugate vaccine are recommended should not receive these vaccines concurrently because there is limited information on the safety of concurrent administration.^{539,540}

Public health considerations

In the United States, achieving 90% coverage with pneumococcal polysaccharide vaccine for noninstitutionalized adults 65 years of age and older was a Healthy People 2010 objective and is now a Healthy People 2020 objective (www.healthypeople.gov). Additional Healthy People 2020 objectives for pneumococcal polysaccharide vaccine include achieving 60% coverage for noninstitutionalized high-risk adults 18 to 64 years of age and achieving 90% coverage for institutionalized adults 18 years of age and older. Current coverage rates with PPSV23 have increased substantially over the past 20 years, particularly among adults 65 years of age and older, but, in all groups, remain below these target goals.

Among noninstitutionalized adults in the United States who are 65 years of age and older, PPSV23 coverage increased from 14% in 1989 to 60% in 2008.⁵³⁴ In all years, vaccination rates among non-Hispanic blacks and Hispanics were substantially lower than among non-Hispanic whites. Analyses of 2008 data revealed that vaccination coverage is higher among women (63%) than men (56%) and is also associated with health care access. Racial disparities in PPSV23 coverage also exist among nursing home residents.⁵⁴¹ Coverage rates for PPSV-23 are even lower among high-risk persons younger than 65 years. In 2002, the National Health Interview Survey estimated that only 19.1% of persons aged 18 to 64 years with one or more vaccine indications had received pneumococcal polysaccharide vaccine.⁵⁴²

PPSV23 coverage rates vary widely by population and geographic location, and in certain groups, relatively high coverage rates have been attained. For example, PPSV23 coverage in an American Indian community reached 96% among adults 65 years of age and older and 61% among high-risk younger adults in 2007; both rates were higher than the Healthy People 2010 goals.⁵⁴³ Among adults enrolled in four managed-care organizations, PPSV23 coverage in 2006 was 82% among adults 65 years of age and older and ranged from 58% to 67% among younger adults with high-risk medical conditions, including diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease.⁵⁴⁴

Because increased PPSV23 coverage is an important public health goal, evidence-based evaluations of interventions to improve coverage are relevant. Evidence-based reviews support that certain interventions improve vaccination coverage.^{542,545} Both the ACIP and the Task Force on Community Preventive Services recommend the use of standing order programs in both inpatient and outpatient settings to improve pneumococcal vaccination coverage. Standing orders programs, where allowed by state law, authorize nurses and pharmacists to administer vaccinations according to an institution- or physician-approved protocol without the need for a physician's examination or direct order.⁵⁴⁶

Risk-based interventions, such as the targeting of younger adults with high-risk conditions for PPSV23 vaccination, are more difficult to implement than age-based recommendations, such as universal vaccination of adults 65 years of age and older. The Task Force on Community Preventive Services conducted systemic reviews to evaluate the effectiveness of interventions to improve risk-based vaccination coverage (ie, coverage with vaccines recommended for some, but not all, persons in an age range) among adults younger than 65 years. The Task Force found evidence that provider-reminder interventions, even when implemented alone, improved targeted vaccination coverage. Provider-reminder interventions are used to inform those who administer vaccinations that individual clients are due for specific vaccinations. The Task Force also recommended combinations of other interventions to improve vaccination rates. These combinations included one or more interventions to enhance access to vaccination services (eg, expand availability of vaccines in medical or other settings, or reduce out-of-pocket costs) with one or more provider- or system-based interventions and/or one or more interventions to increase client or community demand for targeted vaccination services. Examples of provider- or system-based interventions, in addition to provider reminders and standing orders, include assessment and feedback for vaccination providers and provider education. Interventions to increase community and client demand include client reminders, clinic-based education, community-wide education and policies or laws that require vaccination or other documentation of immunity as a condition of school attendance, residence, or employment.⁵⁴²



Access the complete reference list online at <http://www.expertconsult.com>

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