How Effective is Vaccination in Preventing Pneumococcal Disease?

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KEYWORDS

- *Streptococcus pneumoniae* • Pneumococcus • Vaccine • Pneumonia
- Community-acquired pneumonia

KEY POINTS

- Although some controversy persists, the 23-valent pneumococcal polysaccharide vaccine (PPV23) provides 50% to 80% protection in adults against pneumococcal infection, and vaccination with PPV23 is recommended for immunocompromised adults as well as all adults >65 years of age.
- Infants and toddlers do not make antibody after vaccination with PPV23, and this vaccine is not recommended for them.
- Vaccination with protein-conjugated pneumococcal polysaccharides (PCV) stimulates good antibody responses in infants and toddlers. Vaccination with PCVs also stimulates mucosal antibody and suppresses colonization.
- Beginning in 2000, widespread use of a vaccine containing 7 common PCVs (PCV7) greatly decreased disease caused by these vaccine serotypes, not only in those infants and children who were vaccinated but also in older children and in adults.
- Widespread vaccination with PCV13, which contains 13 PCVs is expected to greatly reduce disease caused by these serotypes in all sectors of the population at large.
- Based on evidence for modestly better antibody levels and possible better persistence of antibody in adults after PCV, as well as on the suggestion that PCV primes for enhanced response to PPV, the Centers for Disease Control and Prevention (CDC) have recently recommended that all immunocompromised adults aged 19 to 64 years receive PCV13 followed 8 weeks later by PPV23.
- Some experts predict that the use of PCV13 in adults will rapidly become irrelevant as the prevalence of these serotypes diminishes.

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AVAILABLE PNEUMOCOCCAL VACCINES

In the United States, the following 2 pneumococcal vaccines are currently approved for use:

1. PPV23, marketed as Pneumovax or Pnu-Immune, consists of capsular material from 23 pneumococcal types that have historically caused about 75% to 85% of pneumococcal disease in children or adults.
2. Protein-conjugate pneumococcal vaccine (PCV, initially marketed as Prevnar or Prevnar7 [PCV7], now replaced by Prevnar13 [PCV13]). PCV13 contains capsular polysaccharides from the 13 most common types that cause disease in children, covalently linked to a nontoxic protein that is nearly identical to diphtheria toxin. Many of the types covered by PCV13 are also common causes of adult infections.

PPV23 has been used in adults for decades and is not recommended for infants or toddlers. PCV7 was recommended of use in infants and toddlers in 2000; since 2011, PCV13 has been recommended in its place. PCV13 has also recently been recommended for limited use in adults. All these recommendations are discussed below.

INTRODUCTION

As has been shown in other articles within this issue, *Streptococcus pneumoniae* remains an important cause of community-acquired pneumonia (CAP), even though the proportion of CAP caused by pneumococcus has steadily decreased in the past 50 years. This section discusses the use of pneumococcal vaccination as a means of preventing pneumococcal pneumonia or, more broadly, as a means of preventing CAP. Clearly, the efficacy of pneumococcal vaccine in any given population will vary with the proportion of CAP cases that are attributable to *S. pneumoniae.*

BRIEF HISTORY OF PNEUMOCOCCAL VACCINATION

The understanding of humoral immunity arose from experiments performed by the Klemperers in the 1890s. This uncle and nephew team, members of the distinguished German-Jewish family that included conductor Otto Klemperer and pathologist Paul Klemperer, followed principles that had been elucidated by Pasteur. The team boiled pneumococci, injected them repeatedly into rabbits, and then challenged the rabbits with live organisms; these immunized animals were resistant to infection. The investigators transferred serum (the "humoral factor") from immunized rabbits to unimmunized ones, thereby conferring protection and showing that resistance could be transferred with serum from immune animals ("humoral immunity"). When immunized rabbits were challenged with certain other pneumococci, they were not protected, but they could be immunized with repeated injection of killed organisms from the new strain. This finding led to the concept of type-specific immunity; the first strain was called type (or serotype) I and the second was called type II. At first, all others were called type III. In the ensuing 100 years, some 91 distinct types of *S. pneumoniae* have been identified.

In 1911, Lister and Wright began studies in which they injected killed pneumococci into South African miners, a group of men in whom the rate of pneumococcal disease was as high as 50 to 60 cases per 1,000 miners per year.[1,2] These attempts seemed to be quite successful in reducing morbidity and mortality of pneumococcal pneumonia, although later authorities criticized their lack of scientific rigor and interpretation of results.[3] By the 1930s, investigators at the Rockefeller Institute found that the capsular

material was the immunizing substance, and, soon thereafter, Felton succeeded in extracting sufficient amounts of capsular polysaccharide to use as a vaccine. In 1937, Smillie and colleagues[4] used Felton's preparation of capsular polysaccharide from *S. pneumoniae* type I as a vaccine to abort outbreaks of pneumococcal pneumonia in an institutional setting. Studies during the Second World War showed that vaccination with capsular polysaccharide from 4 prevalent serotypes could prevent outbreaks of pneumococcal infection in military recruits.[5]

Pneumonia had always been a major cause of death in persons of all ages, and many studies had shown that more than 90% of all recognized cases were caused by *S. pneumoniae*.[2] In the early 1960s, nearly all CAP was thought to be due to pneumococcus. Textbook chapters on pneumonia focused on pneumococcus, referring the reader to sections on other microorganisms to learn about other causes of pulmonary infection. For a variety of reasons, including but not limited to the aging of the population, the increasing prevalence of comorbid conditions and medications that reduce immunity predisposing to other kinds of pneumonia, and the use of pneumococcal vaccine, this is no longer the case. Recent studies suggest that about 30% to 50% of CAP leading to hospitalization is caused by pneumococcus, with *Staphylococcus aureus, Haemophilus influenzae*, respiratory viruses, and gram-negative bacteria causing most of the rest (see related articles within this issue for additional information).

PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPV)

The discovery of penicillin greatly reduced the frequency and serious complications of pneumococcal pneumonia in otherwise healthy adults, thereby reducing interest in pneumococcal vaccine. Only in the 1960s when it became clear that despite available antibiotic therapy pneumococcal disease remained a common and life-threatening problem[6] was there a renewed interest in pneumococcal polysaccharide vaccine (PPV). Austrian[7] worked to develop a vaccine consisting of capsular polysaccharides from the 14 serotypes (PPV14) that most commonly caused pneumonia; this vaccine

Group Studied	Percentage Reduction
Pneumococcal disease due to a vaccine type	
Invasive disease	82%
Bacteremic pneumonia	87%
Nonbacteremic pneumonia	73%
All pneumococcal disease	
Invasive disease	74%
Pneumonia	76%
Nonbacteremic pneumonia	53%
All-cause pneumonia	
All results	29%
Low-income countries	46%
High-income countries	26% (not significant)
All-cause mortality	
All results	13% (not significant)
Low-income countries	21%
High-income countries	0% (not significant)

Table 1
Incidence per 1000 person-years

	Vaccine $n = 502$	Placebo $n = 504$	Percentage Reduction
Condition observed			
Pneumococcal pneumonia	12	32	63.8% ($P = .002$)
Nonpneumococcal pneumonia	43	59	29.4% ($P = .08$)
All-cause pneumonia	55	91	44.8% ($P<.001$)
All-cause death	89	80	NS ($P = .46$)

Abbreviation: NS, nonsignificant.

was later expanded to include capsule from 23 types that, until the late 1990s, caused more than 85% of disease. PPV23 is currently marketed in the United States as PNEUMOVAX 23 (Merck) or Pnu-Immune 23 (Lederle).

Many studies have examined the efficacy of PPV, and a range of results has been observed, depending on the end point being investigated. In general, the more specific the end point, the better is the efficacy. A 2008 Cochrane review by Moberley and colleagues[8] analyzed the protective effects of PPV in published randomized control trials as follows (reductions in disease were significant unless otherwise noted):

These data show that PPV clearly reduces the rate of pneumococcal infection, whether invasive (positive blood cultures or isolation of the organism from a normally sterile site) or noninvasive, due to vaccine strains. Substantial protection, albeit to a somewhat lesser degree, is still apparent if infecting strains have not been typed. In fact, these results are precisely what might be expected if PPV23 contains capsular material from types that cause about 80% of all pneumococcal disease. Because all-cause pneumonia comprises an umbrella diagnosis with many potential causes, it is not surprising that a protective effect is not so clearly discernible. It is also reasonable to expect that the overall socioeconomic conditions and a higher rate of vaccination in high-income countries have reduced the frequency of pneumococcal disease, thereby blunting the efficacy of PPV23, when compared with developing countries. A subsequent review by Huss and colleagues[9] found that the PPV was not protective, but this review was seriously flawed, as has been shown elsewhere.[10]

More recent studies have essentially confirmed these results. In a prospective study involving 8 Japanese nursing homes, subjects were randomized to receive PPV23 or placebo[11]; the incidences of pneumonia and death were then studied, with the results given in **Table 1**.

A cohort study of community-living adults in the Kaiser Permanente system[12] showed similar results, but it should be noted that a case-control study of persons hospitalized in Edmonton, Alberta, Canada[13] found no significant protection. The investigators of this last-named study reported separately that even though PPV did not prevent hospitalization for CAP, it reduced complications and mortality from that disease,[14] a result also reported by Fisman and colleagues.[15]

Many case-control studies of PPV have also been reported, showing protection rates of 50% to 60% (range 40%–90%).[16–22] Some results have suggested that PPV23 protects against invasive pneumococcal infection (defined as pneumococcal disease with isolation of the infecting organisms from a normally sterile body site), but not against nonbacteremic pneumococcal pneumonia.[20,21] However, this concept is not biologically plausible and results are opposed by those cited above.

In an important case-control study, Shapiro and colleagues[18] showed that the benefit of PPV23 decreases with age and with time after vaccination. The investigators found that PPV23 was about 90% protective in adults aged 50 to 60 years, with protection persisting for 5 years. With aging, and presumably in the face of comorbid and/or immune-compromising conditions, the initial rate of protection is much lower and falls off far more rapidly, so that in persons older than 90 years, the rate of protection was about 20% in the first year after vaccination and was not detectable after that.

POLYSACCHARIDE VACCINE IN IMMUNOCOMPROMISED PERSONS

Unfortunately, patients who, because of an immunocompromising condition, are most in need of protection against pneumococcal infection are the least likely to benefit from PPV. Hodgkin disease, multiple myeloma, and lymphoma block the ability of the immune system to respond appropriately to new antigenic stimuli, especially to polysaccharides, and patients with these diseases respond to few or no capsular polysaccharides contained in PPV23. Drugs that are immunosuppressive also suppress responses to PPV23, and patients who have received a solid-organ or a bone marrow transplant do not respond well,[23] hence the recommendation that transplant candidates be vaccinated before transplantation. Even persons with advanced heart failure and those who have increasing age and frailty respond only poorly to PPV23, with no response to a varying number of antigens and a low antibody level to the rest.[24] Patients who recover from pneumococcal pneumonia also respond very poorly to PPV23.[25] Even when persons with all these conditions make antibody in response to PPV, the antibody may not be as effective in opsonizing bacteria and, therefore, in protecting the vaccinated subject.[24,26] Patients with untreated human immunodeficiency virus (HIV) infection and low CD4 counts also respond poorly or not at all to PPV23[27]; once effective antiviral treatment has been given, responses are partially restored, but are still not normal.[28]

RECOMMENDATIONS FOR USE OF POLYSACCHARIDE VACCINE

The CDC's Immunization Practices Advisory Committee[29] recommends PPV23 for all persons older than 2 years who are at substantially increased risk of developing pneumococcal infection and/or of having a serious complication of such an infection. Perhaps most important are those with anatomic or functional asplenia. Others include persons (1) older than 65 years; (2) with cerebrospinal fluid (CSF) leak, diabetes mellitus, alcoholism, cirrhosis, chronic renal insufficiency, chronic pulmonary disease, or advanced cardiovascular disease; (3) who have an immunocompromising condition associated with increased risk of pneumococcal disease, such as multiple myeloma, lymphoma, Hodgkin disease, HIV infection, organ transplantation, or chronic use of glucocorticoids; or (4) who live in environments in which outbreaks are particularly likely to occur, such as nursing homes. Recommendations for pneumococcal vaccination for adults are summarized in **Table 2**.

REVACCINATION WITH POLYSACCHARIDE VACCINE

After healthy adults older than 50 years of age are vaccinated, antibody levels peak at 1–2 months, thereafter declining rapidly over a 1- to 2-year period, persisting at very low levels for 5 to 10 years.[30,31] It is not known what level of antibody is protective. The CDC recommends that "All persons should be vaccinated with PPV23 at the age of 65 years. Those who have received PPV23 before the age of 65 years for any indication

Table 2
Indications for administration of PPV23 and PCV13 in adults aged 19 to 64 years

Risk Group	Medical Condition	PCV13	PPV23	PPV23 Revax[a]
Presumed Immunocompetent	Asplenia (including hemoglobinopathies)	X	X	X
	CSF leaks	X	X	—
	Cochlear implant	X	X	—
	Chronic heart disease	—	X	—
	Cigarette smoking	—	X	—
	Chronic lung disease	—	X	—
	Diabetes	—	X	—
	Alcoholism	—	X	—
	Chronic liver disease	—	X	—
Immunocompromised	Congenital or acquired immunodeficiencies	X	X	X
	HIV infection	X	X	X
	Chronic renal failure	X	X	X
	Nephrotic syndrome	X	X	X
	Leukemia	X	X	X
	Lymphoma	X	X	X
	Hodgkin disease	X	X	X
	Generalized malignancy	X	X	X
	Iatrogenic immunosuppression	X	X	X
	Solid organ transplant	X	X	X
	Multiple myeloma	X	X	X

[a] Single revaccination 5 years after a prior vaccination.

should receive another dose of the vaccine at the age of 65 years or later if at least 5 years have passed since the previous dose. Those who receive PPV23 at or after the age of 65 years should receive only a single dose."[29]

Patients who have undergone splenectomy are under special risk for overwhelming pneumococcal infection, and some experts think that such patients should be revaccinated at 5- to 6-year intervals.[32] The same might be said for adults in their 70s and 80s who were vaccinated at the age of 65 years. The concern, largely theoretical, that repeated vaccination may lead to hypresponsiveness[33] does not seem to be relevant if vaccine is given at less than 5-year intervals[31,34,35]; administration at closer intervals has been shown in selected groups of patients to be successful.[36]

PROTEIN-CONJUGATE POLYSACCHARIDE VACCINE (PCV)

Children younger than 2 years do not respond well to polysaccharide antigens. However, when a polysaccharide is covalently conjugated to a carrier protein, the resulting antigen is recognized as T-cell dependent, stimulating a good antibody response in children younger than 2 years and inducing immunologic memory. In the 1990s, a study of PCV7 in 38,000 infants and toddlers in the Kaiser Permanente system yielded spectacular results, showing a 98% reduction in bacteremia and meningitis[37] and a 67% reduction in otitis media due to vaccine serotypes. Within a few years after PCV7 was marketed in 2000 as Prevnar 7, its widespread use in the United States brought about the near disappearance of serious disease caused by vaccine strains in children nationwide (**Fig. 1**).[38] A 13-valent vaccine, marketed as Prevnar 13, was approved in 2010, and is expected to cause the same kinds of decreases in incidence of infection due to these strains.

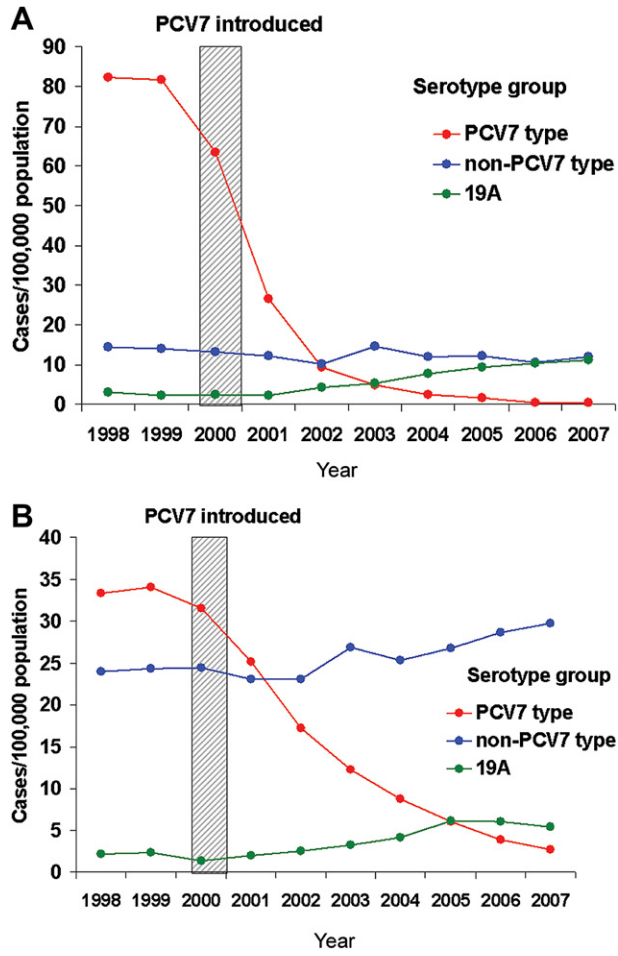

Fig. 1. Infections due to serotypes of pneumococcus included in PCV7 occurring in children younger than 5 years (*A*) or adults older than 65 years (*B*) between 1998 and 2007. (*Data from* Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010;201:32–41.)

OTHER EFFECTS OF CONJUGATE PNEUMOCOCCAL VACCINE

Indirect Effect

A second property of PCV that distinguishes it from PPV23 is that it stimulates mucosal immunity, protecting against pneumococcal colonization.[39] In an Alaskan village, after administration of PCV7, carriage of vaccine strains decreased remarkably, not only in vaccinated children but also in adults.[40] This effect on colonization explains the very important indirect effects of conjugate vaccine (sometimes called the "herd effect"). As shown in **Fig. 1**, widespread vaccination of infants and toddlers with PCV7 has also led to a remarkable decrease in pneumococcal infection in older persons who did not, themselves, receive the vaccine. This decrease resulted from a lower rate of colonization among infants and toddlers who had received the vaccine and a consequent lower rate of spread to the rest of the population. At present, in the

United States, the incidence of pneumonia in adults caused by pneumococcal types included in PCV7 has been reduced by more than 90%.[38] These same direct and indirect effects are anticipated for the 13 serotypes contained in PCV13, as a result of the widespread use of this vaccine since 2010,[41] a factor that must be considered in any discussion of PCV13 for adults.

Comparison of PCV with PPV in Adults

Many investigators have postulated that, by altering the nature of the antigenic stimulation, PCV might stimulate higher levels of antibody that persist longer than those after PPV. The author and his colleagues recently reviewed all comparative studies of PPV and PCV, whether in normal or immunocompromised adults, that were published through 2010.[42] All studies were based on in vitro assays of antibody levels or antibody opsonic activity. It was concluded that up to 6 months after PCV, antibody levels were similar or slightly higher than those after PPV, but no definitive or consistent advantage was demonstrated. In 2 reports of antibody persistence 1 year after vaccination, antibody levels were similar and opsonic activity was slightly greater after PCV.[43,44] Data, as yet unpublished, obtained by the manufacturer of PCV13 are based on study of 924 subjects who were randomized to receive PPV23 or PCV13. This large study seems to show slight but significant differences favoring PCV13 1 month after vaccination; whether these differences are clinically meaningful is entirely unknown.

As far as the actual efficacy of PCV is concerned, only 1 study has been carried out. PCV7 was clearly protective against pneumococcal infection when given to patients with AIDS in Malawi[45]; however, the efficacy waned dramatically after the first year. Although the investigators did not directly compare PCV7 to PPV23, they had previously reported that PPV23 failed to protect patients with AIDS in Uganda.[46] Taken together, these 2 studies by the same group of investigators influenced the Advisory Council on Immunization Practices (ACIP) of the CDC to make its recommendations, released in October 2012, that are summarized in **Table 2**.

Immunologic Priming by PCV

The third property of PCV is that, by virtue of stimulating long-lived memory cells,[47] this vaccine may prime for a better response to a second administration of vaccine than does PPV. Studies to date do not strongly support this suggestion; some have found a priming effect, whereas others have not.[42] However, it is possible that the antibody persists better after PCV, and it seems well established that PCV primes the immunologic system for better responses to subsequent challenge with PPV.

Replacement Serotypes

An undesired effect of vaccination with PCV has been an increase in infection caused by serotypes that are not included in the vaccine (called replacement serotypes). Unlike PPV, PCV stimulates mucosal immunity and therefore prevents colonization by vaccine types. In doing so, an ecological niche for colonization by nonvaccine strains is created. The result has been the emergence of new serotypes as common causes of pneumococcal disease. For example, the most common cause of pneumococcal infection in persons of all ages in the past few years has been type 19F, which rose to prominence as a replacement strain after implementation of routine vaccination with PCV7. This type is contained in PCV13, but it seems very likely that other replacement strains will emerge as PCV13 is widely used.

RECOMMENDATIONS FOR USE OF PCV13 IN ADULTS

The basic recommendation has been that adults older than 65 years receive a single dose of PPV23. If they have previously been vaccinated within 5 years and are now older than 65 years, physicians should wait 5 years before recommending revaccination. This recommendation is unchanged.

In October, 2012, the ACIP of the CDC recommended[48] the following:

1. Adults 19 years or older with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants and those who have not previously received PCV13 or PPSV23 receive a single dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later.
2. Adults 19 years or older with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants and those who have previously received one or more doses of PPSV23 receive a dose of PCV13 1 or more years after the last PPSV 23 dose. For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years since the most recent dose of PPSV23. These recommendations are given in **Table 2**.

CONTROVERSIES AND UNRESOLVED PROBLEMS

There are several problems with the official recommendation. First, as noted above, it is not at all clear that PCV stimulates better antibody responses than PPV. Second, the importance of pneumococcal pneumonia has steadily diminished in recent years. Third, emphasis on PCV13 for the pediatric population will almost certainly lead to the near disappearance of these vaccine strains from the adult population, so a program based on vaccinating adults with PCV13 may be unimportant. Fourth, the cost analysis[49] that showed significant (albeit modest) benefit to the final recommendations was based on projected figures derived from a Delphi analysis, in which experts estimate a predicted efficacy for various approaches. The experts who comprised the Delphi panel had generally accepted the view of Huss and colleagues[9] that PPV23 only prevented bacteremic, but not nonbacteremic, pneumococcal pneumonia. Finally, PCV13 is recommended for the groups of patients for whom there is simply no evidence that they will respond, for example, those with multiple myeloma.

For these reasons, the author is unenthusiastic about recommendations that advocate a set of 2 vaccinations—conjugate followed by unconjugated polysaccharide vaccine. Much greater effort needs to be expended on new approaches to pneumococcal vaccination involving common conserved proteins (see next section) (**Box 1**).

Box 1
Potential problems with new ACIP recommendations

- Logistical
  - Compliance with 2 vaccinations 8 weeks apart
  - Costs (to individual patients and to society)
- Usefulness
  - Data on which recommendations are based are not solid
  - Continuing decline in prevalence of vaccine strains in the population
  - No data that some of the most severely immunosuppressed persons will respond

NEWER VACCINES

The principal advantage of the conjugate vaccine seems to be that it primes for a better immunologic response with revaccination, but a multiple vaccine approach greatly increases the cost of vaccination while decreasing the likelihood of compliance, and one is still left with the issue of replacement strains now that PCV13 has been adopted. With all the concerns over indirect effects and replacement strains following the use of polysaccharide vaccines, it seems appropriate to direct efforts toward developing vaccines that use highly conserved pneumococcal proteins such as detoxified pneumolysin, pneumococcal histidine triad protein D, pneumococcal surface protein A, or other surface-expressed proteins as their basis. Several such vaccines are currently under study,[50–52] and any discussion of new approaches should address their use.

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