REVIEW

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Pneumococcal vaccination in adults: Recommendations, trends, and prospects

ABSTRACT

The US Centers for Disease Control and Prevention recommends vaccination against *Streptococcus pneumoniae* for all people age 65 and older and also for younger people at high risk. However, experts continue to debate the efficacy of the vaccine; most observational studies found it beneficial, while clinical trials were inconclusive as a group. Although pneumococcal vaccination may or may not protect against pneumonia or death from any cause, it does significantly decrease the risk of invasive pneumococcal disease and is worthwhile for this reason.

KEY POINTS

The 23-valent vaccine induces an antibody response but not a T-cell-mediated or memory response. Antibodies persist for at least 5 years; hence, the interval between doses can be at least this long.

Serotype replacement (emergence of *S pneumoniae* serotypes not covered by the current vaccine) is a worrisome trend.

Physicians can boost their vaccination rates by setting up reminder systems and by writing standing orders.

Experimental pneumococcal vaccines do not target the polysaccharides contained in the current vaccine but rather bacterial proteins.

CURRENT VACCINES against *Streptococcus pneumoniae* may not be ideal, but they are worthwhile to give to elderly patients and others at risk, such as people with chronic cardiovascular disease, chronic pulmonary disease, diabetes mellitus, or those without a spleen.

Pneumococcal disease imposes a considerable burden in terms of deaths, hospitalizations, and health care costs. Whether vaccinating elderly people reduces the rate of death or even of pneumonia is not conclusively proven, but it does reduce the rate of invasive pneumococcal disease and for this reason is cost-saving.

In this paper we review the recommendations, trends, and future prospects regarding pneumococcal vaccination in adults.

THE SCOPE OF PNEUMOCOCCAL INFECTIONS

Each year, US hospitals log about 1.2 million admissions for pneumonia,[1] of which more than 900,000 are in people age 65 or older.[2] People in this age group also account for most excess deaths due to pneumonia.[2] In 2002, influenza and pneumonia together killed 59,000 people age 65 years and older,[3] and these illnesses remain the only infectious diseases among the top 10 causes of death in this age group in the United States.[4]

More than half of the more than $20 billion in direct health care costs attributed to pneumonia annually in the United States[1,2] is spent among people age 65 and older. These

numbers are all the more worrisome, given the anticipated growth of this age group in the coming decades.

S pneumoniae is the most common bacterial cause of pneumonia in the United States, accounting for up to 36% of cases of community-acquired pneumonia in adults and 50% of cases of hospital-acquired pneumonia[5]—more than 500,000 cases of pneumonia per year.[6]

S pneumoniae is also the most common bacterial cause of other respiratory tract infections, including otitis media and sinusitis, and is the primary bacterial pathogen in serious community-acquired invasive infections such as bacteremia and meningitis.[6] The latter two result in an additional 175,000 hospitalizations per year in the United States, and approximately 10,000 deaths in addition to those associated with pneumonia.[7,8]

People 65 years and older have a high rate of pneumococcal invasive disease, with an incidence in 1999 of 61.5 cases per 100,000 people per year.[9] Case fatality rates for invasive streptococcal disease increase with age to 20.6% among people 80 years or older.[8]

Rates of pneumococcal vaccination in people 65 and older:
1989: 15%
2003: 64%
Goal: 90%

Improvement is needed to meet goals of Healthy People 2010

In view of the tremendous burden of illness and death from pneumococcal disease, as well as its preventable nature, the US Department of Health and Human Services, in its Healthy People 2010 project,[10] has set goals for reducing pneumococcal infections. One of the goals is to reduce the incidence of invasive pneumococcal infections among adults age 65 years and older to less than 42 cases per 100,000 people per year. Goal vaccination rates are 90% among noninstitutionalized people age 65 and older and 60% among people age 18 to 64 at high risk.

Pneumococcal vaccination rates have improved tremendously since 1989, when only 15% of noninstitutionalized people age 65 or older received the vaccine.[11] However, data from the Behavioral Risk Factor Surveillance System from 2003 suggest that the median coverage rate is still only 64% in people age 65 and older, indicating that substantial improvements are needed to meet the Healthy People 2010 goals.[12]

AT LEAST 90 SEROTYPES

S pneumoniae, a gram-positive facultative anaerobic bacterium, was first isolated in 1881 by Louis Pasteur. Some of the pneumococci are encapsulated with surface polysaccharides that are associated with pathogenicity in humans, leading to the mucosal, respiratory tract, and invasive diseases noted above.

At least 90 distinct *S pneumoniae* serotypes are known, classified by the chemical composition of their polysaccharide capsules.[13] These serotypes are further classified into 46 serogroups.[14] Up to 62% of invasive pneumococcal infections worldwide are due to 10 serotypes.[5]

These polysaccharides are used as antigens in our current vaccines, which induce serotype-specific antibodies that neutralize the organism and that interact with complement to opsonize it.

PNEUMOCOCCAL POLYSACCHARIDE VACCINE

The history of pneumococcal vaccines dates back to the early 1900s, preceding the discovery of antibiotics.[15] Once penicillin became available, interest in pneumococcal vaccine diminished. Interest revived as mortality rates from pneumococcal disease remained high despite broadly available and widely used antibiotics.[5]

Two six-valent vaccines (ie, active against six polysaccharide serotypes) were developed after World War II but were abandoned.[16] A 14-valent vaccine was licensed in the United States in 1977, followed in 1983 by the current 23-valent polysaccharide vaccine (PPV23).[6] Two 23-valent vaccines are licensed—Pneumovax 23 (Merck and Company, Inc.) and Pnu-Immune 23 (Lederle Laboratories)—although only the Merck vaccine is currently being manufactured for use in adults.

PPV23 contains 25 µg of each of 23 pneumococcal polysaccharide antigens (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F), with 0.25% phenol as a preservative. These 23 serotypes accounted for 85% to 90% of invasive pneumococcal infections in the United States at the time the vaccine was

developed,[17–19] and 86% to 98% of pneumococcal bacteremia in the industrialized world.[20] PPV23 is ineffective against serotypes not contained in the vaccine.[21]

PPV23 induces antibody to the capsular polysaccharides but not a T-cell-mediated or memory response. Therefore, when the patient later encounters a pneumococcus and is re-exposed to capsular antigen, his or her antibody levels will not rise again. However, vaccine antigen may remain in the lymphoreticular system for some time, and antibodies tend to remain elevated in healthy adults for at least 5 years after vaccination.

All other characteristics being equal, elderly recipients are more likely to have low or insufficiently persistent pneumococcal antibody levels than their younger counterparts; those at risk for more rapidly declining antibody levels include those age 65 years or older and many in the high-risk groups. However, whether antibody levels correlate optimally with the opsonophagocytic mechanisms that clear the offending pneumococcus is not clear.

A different vaccine is used in children younger than 5 years

The T-cell-independent response induced by PPV23 is ineffective in children younger than 2 years.[21] Therefore, a seven-valent pneumococcal conjugate vaccine (PCV7) containing purified antigens for polysaccharide serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to a nontoxic diphtheria protein (CRM197) was licensed in 2000 in the United States for use in children younger than 5 years.[22] These seven serotypes account for approximately 80% to 90% of invasive infections and a significant proportion of respiratory infections among children younger than 6 years in the United States.[5,23] Besides the number of antigens it contains, the PCV7 vaccine differs from the PPV23 vaccine in that in PCV7 the polysaccharides are combined or conjugated to a carrier protein (in this case CRM197), which enables a T-cell response to the conjugated polysaccharide.

The vaccine is highly immunogenic and induces a T-cell response in infants and young children. Further characteristics of PCV7 and recommendations for its use are beyond the

TABLE 1

Recommendations for the use of pneumococcal vaccine

GROUPS FOR WHICH VACCINATION IS RECOMMENDED	STRENGTH OF RECOMMENDATION[a]	REVACCINATION[b]
Immunocompetent, age ≥ 65 years[c]	A	Second dose of vaccine if patient received vaccine ≥ 5 years previously and was younger than 65 years at the time of vaccination
Age 2–64 years with chronic cardiovascular disease,[d] chronic pulmonary disease,[e] or diabetes mellitus	A	Not recommended
Age 2–64 years with alcoholism, chronic liver disease,[f] or cerebrospinal fluid leaks	B	Not recommended
Age 2–64 years with functional or anatomic asplenia[g]	A	If age > 10 years, single revaccination ≥ 5 years after previous dose If age ≤ 10 years, consider revaccination 3 years after previous dose
Age 2–64 years living in a special environment or social setting[h]	C	Not recommended
Immunocompromised,[c] age ≥ 2 years, including those with HIV infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, or nephritic syndrome; those receiving immunosuppressive chemotherapy (including corticosteroids); and those who have received an organ or bone marrow transplant	C	Single revaccination if ≥ 5 years have elapsed since first dose If patient is age ≤ 10 years, consider revaccination 3 years after previous dose

[a]The following categories reflect the strength of evidence supporting the recommendations for vaccination:
A = Strong epidemiologic evidence and substantial clinical benefit support the recommendation for vaccine use
B = Moderate evidence supports the recommendation for vaccine use
C = Effectiveness of vaccination is not proven, but the high risk for disease and the potential benefits and safety of the vaccine justify vaccination.

[b]Strength of evidence for all revaccination recommendations is "C."

[c]If earlier vaccination status is unknown, patients in this group should receive pneumococcal vaccine.

[d]Including congestive heart failure and cardiomyopathies.

[e]Including chronic obstructive pulmonary disease and emphysema.

[f]Including cirrhosis.

[g]Including sickle cell disease and splenectomy.

[h]Including Alaskan Natives and certain American Indian populations, and those living in nursing homes and long-term care facilities.

DATA FROM ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES. PREVENTION OF PNEUMOCOCCAL DISEASE: RECOMMENDATIONS OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES. MMWR RECOMM REP 1997; 46(RR-8):1–24.

scope of this review but are discussed in detail elsewhere.[22,24]

RECOMMENDATIONS FOR VACCINATION

The current recommendations on pneumococcal polysaccharide vaccination in adults from the Advisory Committee on Immunization Practices (ACIP)[6] were issued in 1997, with an addendum[25] in 2002. The ACIP makes very clear the pneumococcal outcomes at which the vaccine is directed: "the focus of this report is the prevention of invasive pneumococcal disease (ie, bac-

teremia, meningitis, or infection of other normally sterile sites)."[6]

Who should be vaccinated?

The vaccine is recommended for everyone age 65 and older and for a number of specific groups at risk among people age 2 to 64 years (TABLE 1).

Patients receiving cochlear implants should receive either PCV7 or PPV23 depending on their age; this recommendation is based on data suggesting an increased risk of pneumococcal meningitis among these patients.[25] Healthy children attending day care facilities are specifically identified by the ACIP as being ineligible for the PPV23 vaccine,[6] as no data support the risk of invasive pneumococcal disease as increased in this setting.

Although the vaccine is less effective in immunocompromised than in immunocompetent people, immunocompromised people 2 years of age and older should be vaccinated.[6] HIV-positive patients should receive the PPV23 vaccine as soon as possible after the diagnosis of human immunodeficiency virus (HIV) is confirmed. Vaccination should be avoided during chemotherapy or radiation therapy, and an interval of at least 2 weeks should be allowed between vaccination and the start of immunosuppressive therapy (eg, chemotherapy, long-term corticosteroid therapy).

Stem-cell recipients have a poor response to PPV23, but the vaccine is recommended for use in these patients, as there may be "potential benefit among certain patients."[26]

The safety of PPV23 in pregnant women has not formally been evaluated. No adverse consequences attributable to the vaccine have been observed among newborns whose mothers received it during pregnancy, but eligible women should be vaccinated before pregnancy, when possible.[5]

Giving the vaccine

The ACIP indicates that all patients receiving the vaccine should be counseled on its risks and benefits, including the disclaimer that the vaccine does not protect against overwhelming pneumococcal infection.[6] Consent to receive the vaccine should be obtained from the patient, who should receive a record of the

immunization and a vaccine information sheet.[27]

The vaccine should be given intramuscularly or subcutaneously as a single 0.5-mL dose in the deltoid region. Intramuscular administration is recommended, as it decreases the rate of local side effects such as pain, swelling, induration, and erythema. The vaccine can be given at the same time (but in the other arm) as other vaccines, including those for influenza and poliovirus and the diphtheria-tetanus-pertussis combination, without significant impact on the incidence of adverse reactions or antibody response to PPV23.

Adverse reactions to PPV23 are predominantly local, and 30% to 50% of recipients experience local pain, swelling or erythema that usually lasts for less than 48 hours. Systemic reactions such as fever or myalgia occur in fewer than 1% of PPV23 recipients, and more severe systemic reactions are rare.[5] Those who have had a severe allergic reaction to a component of the PPV23 vaccine or a previous dose of PPV23 should not be vaccinated.

Revaccination recommendations from the ACIP are outlined in TABLE 1. Although these recommendations for revaccination are relatively clear in practice, the logic behind them is somewhat less clear. One can thus imagine a scenario in which a person receiving a first dose at age 64 would be eligible for a second dose, while a person receiving his or her first dose at age 75 would technically not be eligible for a second dose.

Unlike the ACIP, the US Preventive Services Task Force recommends that all people be revaccinated with a single dose of PPV23 at the age of 75.[28]

HIV patients should receive the PPV23 vaccine as soon as possible after the diagnosis of HIV is confirmed

DOES THE PNEUMOCOCCAL VACCINE WORK?

Despite more than 20 years of experience with PPV23, controversy persists regarding its effectiveness and efficacy, fueled by a relative paucity of data on well-defined, conventionally accepted outcomes among the vaccine's target populations. Indeed, the number of reviews, systematic reviews, meta-analyses, and reviews of meta-analyses of observational studies and clinical trials of PPV23[29–46] almost appears to exceed the number of relevant studies themselves.

To summarize, the observational studies and the prospective trials appear to differ in their findings, not all of which can reasonably be cited or reviewed here. Compounding these differences, the studies varied widely in their populations, their generalizability to US target populations, the vaccines used (7-valent, 14-valent, 23-valent, or others), their strength of design and statistical power, and the validity and clinical relevance of their selected end points. These differences make direct comparison between the various studies complicated and, in some cases, invalid.

As clinical trials are the gold standard for assessing vaccine efficacy (and therefore for driving policy and clinical practice), they need to be much more rigorous in their design than they have been up to now. We urge investigators to:

- Accept the Consolidated Standards of Reporting Trials (CONSORT) guidelines (**http://www.consort-statement.org/Statement/revisedstatement.htm**) or other meaningful standards of trial practice and reporting
- Use consensus-driven clinical and vaccine-relevant end points
- Specify the study population, what comorbidities they had, and how the data were collected
- Register their trials to promote the awareness of negative studies.

As these practices become more common, there will be less confusion about how to interpret the results, and we will need to rely less on observational studies for decisions about policy and clinical practice.

Most observational studies found vaccination beneficial

In general, most of the observational studies found the pneumococcal vaccine to be beneficial, although estimates of its efficacy for preventing pneumonia and pneumococcal bacteremia vary widely (some studies found it ineffective), depending on the study design, vaccine examined, and populations evaluated.[6,19,47] Early observational studies in younger adults found it had efficacy against both pneumococcal pneumonia and invasive disease, while studies in people age 65 and

older found efficacy against invasive disease but not necessarily against pneumonia.[48,49]

A recent observational study (not included in reviews to date) examined more than 62,000 cases of hospitalization for community-acquired pneumonia in adults.[50] The rates of in-hospital mortality and of respiratory failure were significantly lower and length of stay was significantly shorter among vaccine recipients even after adjustment for age, medical comorbidity, and other factors—further strong evidence in support of PPV23 use.

As a group, clinical trials were inconclusive

On the other hand, the clinical trials as a group have been inconclusive in demonstrating a significant benefit of PPV23 for the elderly. However, these trials have been criticized as lacking sufficient power to demonstrate moderate but clinically relevant protective effects against pneumonia or invasive disease in this age group.[29,44,46,51–54] Therefore, it is difficult to interpret the clinical trials or subsequent meta-analyses as clearly demonstrating that the vaccine has no benefit in the elderly or in high-risk adults.

We have reasonably effective vaccines, and new ones on the horizon

What can we conclude? People 65 years and older receiving pneumococcal vaccine may or may not be significantly protected against broadly defined pneumonia or all-cause mortality, although this should not be surprising since many cases of pneumonia and death in the clinical trials may have been due to causes other than *S pneumoniae*.

Nonetheless, vaccination with PPV23 significantly decreases the risk of invasive pneumococcal disease, and this benefit, even in the absence of consistent results between clinical trials and observational studies, has made the vaccine cost-saving when used in people age 65 or older and in high-risk groups.[29,55–59]

VACCINATION MAY BE CAUSING SEROTYPE REPLACEMENT

Interestingly, introduction of the PCV7 vaccine in children appears to have resulted in beneficial reductions in pneumococcal disease caused by PCV7-related serotypes in the elderly.

The Active Bacterial Core surveillance (ABCs) group prospectively collected data to evaluate the incidence of invasive pneumococcal disease among people age 50 and older in eight geographical areas of the United States.[60] The incidence of all invasive pneumococcal disease decreased by 28% from 1998–1999 to 2002–2003, but the incidence of invasive disease caused by the seven PCV7 serotypes decreased by 55%. In contrast, disease caused by the 16 serotypes covered by PPV23 but not by PCV7 did not change in incidence, while disease caused by serotypes not covered by either vaccine increased from 1.7% to 5.6% of total cases, a phenomenon known as serotype replacement.

Similar trends were also observed in HIV-infected adults living in seven ABCs areas.[61]

These observations speak to the value of broad population-level vaccination coverage and resulting herd immunity, which likely contribute to decreased community transmission of PCV7 serotype pneumococci.[62] However, serotype replacement is worrisome.

In children who received PCV7, the pneumococci colonizing the nasopharynx shifted to serotypes not included in the PCV7 vaccine.[63] This is good in that it shows that the vaccine is effective, but the shift complicates population-level management of pneumococcal disease in that it potentially increases the risk of illness from serotypes not included in the vaccine in populations at risk, and of subsequent lower clinical efficacy or diminished cost-benefit of existing vaccines.

In fact, in a recent study in which nasopharyngeal swabs were collected in eight Alaskan villages,[64] the percentage of adult carriers of *S pneumoniae* who carried serotypes covered by PCV7 decreased from 28% in 1998–2000 to only 4.5% in 2004. The proportion of penicillin-resistant pneumococcal carriage in this group decreased as well, an observation that also supports serotype replacement, since five of the seven serotypes in PCV7 accounted for 78% of penicillin-resistant isolates in the United States in 1998.[65] ABCs data[66] also showed that rates of penicillin-resistant pneumococcal disease declined from 1999 to 2004 in people age 65 and older.

Serotype replacement needs to be addressed by bringing effective vaccines to

market more rapidly and applying them in a coordinated and logical manner, not only in people at high risk but also in those who transmit disease to people at risk. Serotype replacement issues may also affect US Food and Drug Administration expectations that new vaccines demonstrate equivalent immunogenicity to existing available vaccines, complicating the development of potentially promising new vaccines and biologics. Clearly, serotype distribution and population carriage may need to be taken into account in the evaluation of trial results in the near future.

OPPORTUNITIES FOR FUTURE PNEUMOCOCCAL DISEASE PREVENTION

New vaccines on the horizon

A pneumococcal conjugate vaccine for adults would be attractive, because in theory it could confer more effective or longer-lasting protection than a polysaccharide vaccine, but conjugate vaccines in general are limited by the number of serotypes that can be practically included in a formulation.[67] Giving both a conjugate and a polysaccharide vaccine in a combined schedule raises concerns about increased incidence and severity of adverse effects.

With these issues in mind, researchers are looking into protein-based pneumococcal vaccines,[68,69] trying to identify a common pneumococcal protein or proteins that are present in all serotypes of the organism. If developed as a conjugate vaccine, such a vaccine could combine the individual benefits of existing conjugate vaccines, which confer improved and longer-lasting immune response, with the broad coverage of a multivalent polysaccharide vaccine through the use of a common protein without suffering the relative detriments of either vaccine type.

A number of candidate pneumococcal proteins are being explored, including pneumococcal surface proteins A and C, autolysin, pneumolysin, putative proteinase maturation protein A, and others.[69,70] To date, no single protein identified confers ubiquitous protection, but the approach is promising and merits support, and these vaccines should be cautiously brought to human testing with close monitoring.

Controlling risk factors

Even without new vaccines, many opportunities exist for improving the practical benefits of pneumococcal vaccine.

Medical conditions that predispose to pneumococcal infection include diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and chronic kidney disease. By doing what we can to prevent and manage these conditions, we may shrink the population at risk of pneumococcal illness. Wider and more aggressive use of smoking cessation programs may also provide benefit, as smoking and second-hand smoke exposure are risk factors for pneumococcal illness.[71,72]

Writing standing orders for vaccination

System-based opportunities exist as well. Many studies have shown that standing orders increase the rate of vaccination,[73–75] and computer-based standing orders have proven useful as well.[75]

Lindenauer et al[76] used Medicare and Medicaid data to examine vaccine delivery in the hospital and found that physicians who care for more pneumonia patients may actually do significantly (35%–40%) worse than their lower-volume colleagues in vaccinating their hospitalized patients, further supporting the rationale for taking vaccine delivery out of physicians' hands and using standing orders.

A vaccine not given is a health risk ignored

The National Immunization Program (NIP) encourages the use of standing orders and other evidence-based strategies to improve the rate of vaccine delivery.[77] Additional information on standing order templates and programs can be found at **http://www.cdc.gov/nip/home-hcp.htm**. This Web site also provides valuable information to help in developing simple protocols to address vaccine receipt.

Using reminder systems

Nowalk et al[78] observed that, in 25% to 85% of patient contacts in primary care practices, physicians missed the opportunity to address eligibility for influenza, pneumococcal, and tetanus vaccination. Recall and reminder systems are effective tools that can be implemented in your practice and will help to avoid missed opportunities that otherwise may occur in busy patient encounters.

Start vaccinating at age 50?

Several authors have suggested that the timing of vaccinations could be better coordinated by changing the age of universal pneumococcal vaccination to that for influenza: age 50 years.[59,79] Roughly 30% of Americans age 50 to 64 already qualify for pneumococcal vaccination, and 20% of this age group is composed of minorities also considered at high risk.[79] We agree with this suggestion.

TO MEET THE HEALTHY PEOPLE 2010 GOALS

We have less than 4 years to meet the Healthy People 2010 goals for better prevention and control of pneumococcal illness. We have reasonably efficacious vaccines, and new ones are on the not-too-distant horizon. An acceptable incidence of invasive disease in the elderly has been achieved, although the rate should continue to be pushed downwards.

Our vaccination rates are not nearly as inspiring. A vaccine not given is a health risk ignored, which is unacceptable in an age of inexcusable health disparities and illness and death from pneumococcal illness. Mixed messages from controversial and dissonant interpretations of existing data may be a factor in the failure or unwillingness of health care providers to give PPV23; better-designed clinical trials should begin to address these data-related uncertainties in the future. Many strategies, such as recall and reminder systems and vaccination standing orders, exist to make delivery more complete.

The provider remains key: remember that the most important factor in determining whether or not an individual chooses to receive vaccine is the recommendation of the primary provider.

An update of current pneumococcal vaccine recommendations would assist in influencing practice in this regard; it has been a decade since the last publication of ACIP recommendations. New data on risk factors and populations at risk are available, old data are less relevant, and a clear message informing providers to evaluate the data and their own practices may help us to determine the best way to reach appropriate goals for minimizing pneumococcal illness after all. ■

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