Review Article

A Review of Pneumococcal Vaccines: Current Polysaccharide Vaccine Recommendations and Future Protein Antigens

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This review describes development of currently available pneumococcal vaccines, provides summary tables of current pneumococcal vaccine recommendations in children and adults, and describes new potential vaccine antigens in the pipeline. *Streptococcus pneumoniae*, the bacteria responsible for pneumonia, otitis media, meningitis and bacteremia, remains a cause of morbidity and mortality in both children and adults. Introductions of unconjugated and conjugated pneumococcal polysaccharide vaccines have each reduced the rate of pneumococcal infections caused by the organism *S. pneumoniae*. The first vaccine developed, the 23-valent pneumococcal polysaccharide vaccine (PPSV23), protected adults and children older than 2 years of age against invasive disease caused by the 23 capsular serotypes contained in the vaccine. Because PPSV23 did not elicit a protective immune response in children younger than 2 years of age, the 7-valent pneumococcal conjugate vaccine (PCV7) containing seven of the most common serotypes from PPSV23 in pediatric invasive disease was developed for use in children younger than 2 years of age. The last vaccine to be developed, the 13-valent pneumococcal conjugate vaccine (PCV13), contains the seven serotypes in PCV7, five additional serotypes from PPSV23, and a new serotype not contained in PPSV23 or PCV7. Serotype replacement with virulent strains that are not contained in the polysaccharide vaccines has been observed after vaccine implementation and stresses the need for continued research into novel vaccine antigens. We describe eight potential protein antigens that are in the pipeline for new pneumococcal vaccines.

INDEX TERMS: 13-valent pneumococcal polysaccharide conjugate vaccine, 23-valent pneumococcal polysaccharide vaccine, pneumococcal vaccine protein antigens, *Streptococcus pneumoniae*

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INTRODUCTION

The gram-positive cocci *Streptococcus pneumoniae* causes pneumonia, otitis media, meningitis, and bacteremia in pediatric, elderly, and immunocompromised populations.[1] Pneumococcal infection is the leading cause of pneumonia in children, worldwide.[2] Pneumococcal infections also occur frequently in at-risk populations including individuals with diabetes, asthma, chronic obstructive pulmonary disease, cardiovascular disease, human immunodeficiency virus (HIV), and sickle cell disease. In developed countries, pneumococcal infection is responsible for approximately 30% of all adult pneumonia cases and has a mortality rate of 11% to 40%.[1]

Due to this organism's impact on both morbidity and mortality in adults and children, health care efforts have relied on vaccines to reduce the rate of pneumococcal disease over the past 30 years. Vaccine research has focused on using immunogenic proteins and carbohydrates found on the pneumococcal surface as antigens.[1] The goal of this review is to describe the evolution of current pneumococcal vaccines; the current guideline recommendations for their use in children, adults and special populations; and the new protein antigens in the pipeline, needed because of serotype replacement after introduction of polysaccharide vaccines.

POLYSACCHARIDE VACCINES

Capsular Polysaccharide

Pneumococci express chains of 1 of 92 immunologically distinct polysaccharide subunits

Table 1. Pneumococcal Vaccine Approval Dates, Serotypes, and General Effect on Pneumococcal Disease

Vaccine	FDA Approval	Serotypes Contained in Vaccine*†	Pneumococcal Disease Effect From Vaccine Serotypes
PPSV23	June 1983	1, 2,* 3, 4, 5, 6B, 7F, 8,* 9N,* 9V, 10A,* 11A,* 12F,* 14, 15B,* 17F,* 18C, 19A, 19F, 20,* 22F,* 23F, and 33F*	• Reduced invasive disease • No effect on carriage
PCV7	February 2000	4, 6B, 9V, 14, 18C, 19F, and 23F	• Reduced invasive disease • Reduced carriage • Protective herd effect • Increase in 19A infections
PCV13	February 2010	1, 3, 4, 5, 6A,† 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F	• Reduced invasive disease • Reduced carriage • Increase in 35B infections

PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine
*Serotypes in PPSV23 are unique to this vaccine.
†Serotype in PCV13 is unique to this vaccine.

anchored to the cell wall surface. These polysaccharide chains protect pneumococci from complement-mediated opsonophagocytosis, the main mechanism of clearance of pneumococci from the lung. Production of this polysaccharide chain is essential for pneumococcal colonization and virulence, making it an obvious early target antigen.[3] These polysaccharide subunits are highly immunogenic, producing antibodies that react with the homologous serotype. The prevalence of particular capsular serotypes can vary greatly among continents, providing differing levels of protection for vaccinated individuals depending on their location. Therefore, capsular serotypes have been monitored internationally since the beginning of their use as vaccine antigens.[4]

Polysaccharide Vaccines

Early vaccines developed against pneumococci contained purified polysaccharide capsules as antigens. Table 1 lists the serotypes contained in each vaccine, the US Food and Drug Administration (FDA) approval dates of the vaccine and each vaccine's overall effect on pneumococcal disease. The first vaccines developed contained 14 capsular polysaccharide serotypes and protected against pneumococcal disease. A 23-valent pneumococcal polysaccharide vaccine (PPSV23) was developed later, in 1983, to provide protection against 80% to 90% of the pneumococcal capsular serotypes causing disease. The current PPSV23 formulation contains the following capsular serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F (Table 1). It is supplied as either a single-dose of 0.5 mL or a multidose 5.0-mL vial to be administered either intramuscularly or subcutaneously into the deltoid muscle or lateral mid-thigh. Common side effects include mild site injection reactions (e.g., swelling), headache, fatigue, and myalgia.[5]

It is recommended that all adults 65 years of age and older receive one dose of PPSV23. Before 65 years of age, a single vaccination with PPSV23 is recommended for at-risk adults with some indications having recommendations for two doses of PPSV23 separated by at least 5 years. Recommendations for vaccination of at-risk children and adults 5 to 64 years of age are described in Table 2. It is important to note that cigarette-smoking patients alone require immunization with PPSV23, and immunization should be included as part of smoking cessation treatment. Additionally, if 1 or 2 doses before age 65 were received due to another indication, a final dose at or after age 65 should be administered, with at least 5 years between doses.[6] Adults should not receive more than two doses of PPSV23 before 65 years of age, and the maximum number of lifetime doses is three.

This vaccine's efficacy against pneumococcal infections with serotypes contained in the vaccine in immunocompetent persons was 65%.[7] Although the rate of invasive pneumococcal disease was reduced in PPSV23-immunized adults, the overall pneumococcal carriage rate was not reduced.[8] Unfortunately, the vaccine did not generate an immune response in the group with the highest rate of pneumococcal disease burden, children younger than 2 years of age.

Table 2. PPSV23 and PCV13 Vaccination Recommendations for Children and Adults 5 to 64 Years of Age With Medical Conditions

Condition	Number of Doses	
	PPSV23	PCV13
Chronic heart disease, chronic lung disease, diabetes mellitus	1	0
Sickle cell disease, functional or anatomical asplenia	2	1 administered before 23-valent
CSF leakage, cochlear implant, congenital immunodeficiency, HIV infection, chronic renal failure, cancer, transplant recipient	1	1 administered before 23-valent

CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine

The antibody response generated by PPSV23 is T-cell independent due to the fact that the repeating subunits of the capsular polysaccharide can stimulate an immune response in B-cells independent of T-cell help.[9] The theory is that their inability to mount a T-cell–independent immune response until this age prevented the vaccine from generating protective antibodies.[1]

Polysaccharide Conjugate Vaccines

In order to elicit a protective immune response in children under the age of 2, vaccines with the capsular polysaccharide conjugated to diphtheria toxin were developed. These conjugated antigens generated a T-cell–dependent antibody response that was effective in children under 2 years of age. They have also proven effective at generating higher antibody titers in high-risk individuals immunized with the unconjugated vaccine.

The first 7-valent pneumococcal polysaccharide conjugate vaccine (PCV7) developed in 2002 greatly reduced the rate of infections in children under 2 years of age and in unimmunized individuals in the same community through the herd effect.[10–12] In the decade after the introduction of PCV7, hospitalizations due to pneumonia have decreased significantly in both immunized children and the eldery.[13] PCV7 vaccination has also reduced pneumococcal carriage rates of serotypes covered by the vaccine for both vaccinated children and household members among whom a child was vaccinated.[14] Interestingly, vaccination has not reduced the rate of otitis media in vaccinated communities.[15] The second conjugate vaccine that was developed, the 13-valent pneumococcal conjugate vaccine (PCV13), contained the 7 serotypes in PCV7, 5 serotypes found in PPSV23, and 1 unique serotype found in neither PPSV23 nor PCV7, serotype 6A. Its increased coverage provided broader protective benefit against pneumococcal infection.[16] After PCV13 implementation, invasive and noninvasive pneumococcal infection rates from serotypes covered in the PCV7 vaccine and the six serotypes added to PCV13 again dropped.[12,16]

Serotype Replacement

After the introduction of PCV7, serotype replacement of pneumococcal infections from serotypes not contained in PCV7 was noted only 5 years after vaccine implementation. Additionally, pneumococcal infection rates returned to pre-vaccine levels in groups at high risk for pneumococcal disease.[17] Of particular concern is the observation that levels of antibiotic resistance increased in non-vaccine isolates responsible for infections after the vaccine was introduced.[18] PCV13 was introduced to cover six of the most prevalent serotypes that were not included in PCV7. Since the introduction of PCV7 and PCV13, a longitudinal surveillance program of 43 medical centers in the United States has observed that the only serotype that has increased in infection rates is one not covered in any current vaccine, 35B.[12] Currently, the long-term effects of PCV13 on serotype replacement of isolates causing pneumococcal disease remain unclear. Given the rise of infections from serotype 35B, it could be hypothesized, however, that infections from serotype replacement strains will continue to occur as observed after the introduction of PCV7.

IMPACT ON PEDIATRIC DISEASE

PCV13 has provided substantial benefits since its introduction in 2010. To date, these benefits have been primarily in reduction of the incidence of invasive pneumococcal disease. Multisite population-based surveillance analyses revealed an overall reduction of 64% in invasive pneumococcal disease in children younger than 5 years of age. Additionally, a reduction in invasive pneumococ-

Table 3. PCV13 Vaccination Catch-up Dose Recommendations for Healthy Children Under 5 Years of Age*

Previous PCV7 dose	Age (mo)	Number of Doses to Complete Primary Series	Booster Dose
None	<6	3	Yes
None	7–11	2	Yes
None	12–23	2	No
–	24-59	–	Yes
1 or 2	7–11	1	Yes
None or 1 given <12 mo	12–23	2	No
1 given >12 mo	12–23	1	No
2–3 doses given <12 mo	12–23	1	No

PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine
*Minimum interval between doses depends on age at which the first dose was administered. Refer to the CDC website for complete information regarding minimum interval recommendations.

cal disease was found to be 93% when researchers removed serotypes that were not contained in PCV7 from the analysis.[19] The introduction of and subsequent vaccination in children with PCV13 resulted in a spillover effect as reductions in invasive pneumococcal disease were also seen in adults.[19] The most recent Cochrane review of the effects of pneumococcal conjugate vaccines for preventing otitis media found modest beneficial effects in healthy infants given PCV7. This review encompassed 1995 to 2013 and reported that there were several ongoing randomized clinical trials studying the newly licensed PCV13 to establish its effects on acute otitis media.[20]

GUIDELINE RECOMMENDATIONS

PCV13 Vaccination

The recommendation for PCV13 vaccination of children and adults 5 to 64 years of age with medical diagnoses and healthy children under 5 years of age are described in Tables 2 and 3. Currently, the Centers for Disease Control and Prevention (CDC) recommend that all children younger than 2 years of age undergo a series of PCV13 immunizations. If the child is less than 6 months old, 4 doses of the vaccine are recommended, with the doses 8 weeks apart (minimum interval of 4 weeks). The fourth dose is considered a booster and should be given between 12 and 15 months of age. Catch-up schedules for children older than 6 months who have not received PCV13 and children who previously received PCV7 are described in Table 3.[21] For children 2 to 5 years of age, vaccination with PCV13 is also recommended for those with certain medical diagnoses (Table 4). [21]

PCV13 is supplied as a prefilled single-dose 0.5-mL syringe for intramuscular injection in the anterolateral aspect of the thigh in infants and in the deltoid muscle of the upper arm in infants, children, and adults. The most common side effects reported include irritability, injection site reactions, decreased appetite and sleep, fever, fatigue, headache, muscle and joint pain, chills, or rash.[22]

PPSV23 Vaccination in At-Risk Children

It is recommended that at-risk children receive immunization with PPSV23 after they finish an immunization series with conjugated vaccines. In sickle cell pediatric patients, higher titers of the 7 serotypes contained in PCV7 were observed in patients receiving immunization with PCV7 series followed by PPSV23 compared to patients who received the PCV7 series alone.[23] In HIV-positive pediatric patients receiving highly active antiretroviral therapy, a series of two PCV7 vaccinations followed by a PPSV23 vaccination increased antibody titers.[24] Due to increased titers from PPVS23 vaccination, children who are immunocompromised should receive a single immunization with PPSV23 after the PCV13 vaccination series. For children who have sickle cell disease and/or functional or anatomical asplenia, two doses of PPSV23 are recommended. The first dose is recommended 8 weeks after finishing the PCV13 vaccine series. The second dose is recommended 3 to 5 years after the first dose according to the 2002 National Heart Lung and Blood Institutes Management of Sickle Cell Disease guidelines or 5 years after the first dose according to the 2010 Advisory Committee on Immunization Practices (ACIP) guidelines.[21,25]

Table 4. PCV13 Vaccination Recommendations for Children <72 Months of Age With Medical Conditions*

Previous PCV7 Dose	Number of Doses to Complete the Primary Series	Booster Dose
None	2	–
<3 Doses	2	–
3 Doses	–	Yes
Complete course	–	Yes

PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine
*Chronic heart disease, chronic lung disease, asthma, diabetes mellitus, cochlear implant, cerebrospinal fluid leakage, functional or anatomical asplenia, human immunodeficiency virus (HIV) infection, chronic renal failure, and immunodeficiency

Decreased duration between revaccination with PPSV23 has led to increased occurrences of mild vaccine-related adverse events in adults (and sickle cell pediatric patients) and should be considered when deciding PPSV23 revaccination scheduling in pediatric sickle cell patients.[26-28]

NEW VACCINE ANTIGENS

The incidence of serotype replacement in both carriage and infection isolates after implementation of conjugate vaccines and the increase in antibiotic resistance among serotype replacement strains stress the need for pneumococcal vaccines with broader coverage against pneumococci. Due to the large diverse pool of capsular polysaccharide serotypes that pneumococci can express, research has focused on finding a more conserved protein-based antigen that could offer protection against pneumococcal disease.[4] The following section describes research for potential protein antigens for pneumococcal vaccines.

Pneumococcal Surface Protein A

Pneumococcal surface protein A (PspA) is an antibody-accessible surface protein attached non-covalently via binding to choline residues in lipoteichoic acid and cell wall teichoic acid on the pneumococcal surface.[29] PspA has been found on all clinical isolates and is necessary for pneumococcal virulence.[30] It aids pneumococcus in escaping complement-dependent immune phagocytosis both by inhibiting the deposition of complement on the surface of the bacterium and by inhibiting the killing of pneumococcus by the innate immune molecule lactoferrin.[31,32] The N-terminal coiled-coil region of the protein can be divided into seven immunologically unique families.[29] This region has been studied extensively for its ability to elicit an antibody-mediated, protective immune response against pneumococcal infection in mice.[33] Immunization with this protein in humans elicits antibodies that are capable of passively protecting mice against infection.[34] Vaccine antigen research has focused on this portion of the protein because it is farthest from the C-terminal choline-binding repeats that anchor the protein and was thus hypothesized to be the most accessible to antibodies.

Another conserved region of PspA that is more closely located to the C terminus has also been studied for its ability to elicit a protective immune response. Between the choline-binding repeat anchors and the N-terminal coiled-coil region, is a conserved proline-rich region found in all PspAs. It consists of a series of repeat units with a proline amino acid found every 3 or 4 residues. The proline repeats can be interrupted by a highly conserved sequence of amino acids lacking proline residues termed the "non-proline block." Approximately 50% of PspAs contain a non-proline block within their proline-rich region.[29] This antigen was shown to elicit antibody-mediated protection in mice against invasive pneumococcal disease.[35] Its conservation in PspAs suggests it could increase protection when used as an antigen in a protein-based vaccine. Recently, a vaccine delivering the PspA antigen via an attenuated, orally administered Salmonella vector has demonstrated safety in phase I clinical trials in healthy adults.[36]

Pneumolysin

Another potential protein vaccine antigen is pneumolysin, a thiol-activated toxin expressed by almost all clinical isolates of pneumococci. Pneumolysin interferes with neutrophil function during the immune response and inhibits proliferation and antibody-production by immune cells, ciliary pulmonary cell beat, and toxicity to alveolar epithelial cells.[37] Due to its wide array of effects on both pulmonary tract cells and immune cells, the protein is too toxic to be used in human vaccines in its native form. However, site-directed mutagenesis has been used to create

Table 5. Protein Vaccine Antigens in the Pipeline

References	Protein Antigen	Mechanisms of Virulence	Current Trials
Briles et al[34] Frey et al[36]	Pneumococcal surface protein A (PspA)	Inhibits complement deposition Inhibits killing by apolactoferrin	Phase I clinical trials conducted in adults Immunized human sera protects mice against infection Humans immunized orally with *Salmonella* expressing PspA developed PspA antibody titers
Daniels et al[35] Frey et al[36]	Proline-rich-region of PspA and Pneumococcal Surface Protein C (PspC)	Role in virulence unknown Identified in the proteome scan of protein antigens	Contained in some PspA vaccines studied Protects mice against invasive pneumococcal infection
Hirst et al[37] Briles et al[39]	Pneumolysin	Aids surface adhesion and forms pores in target cells Interferes with neutrophil function Inhibits antibody cell proliferation and antibody generation Inhibits ciliary epithelial cell beat Toxicity for alveolar epithelial cells	Phase I study showed safety, immunogenicity, and efficacy using enzymatically inactivate pneumolysin Protection from combination vaccine with PspA
Harfouche et al[41] Moschioni et al[42]	Pneumococcal pilus proteins	Aids in bacterial adherence to epithelial cells	Protected mice against pneumococcal infection Antibodies to this performed as well as PCV7 antibodies in surrogate in vitro assay of vaccine efficacy
Giefing et al[43] Olafsdottir et al[44]	Trivalent protein antigen vaccine	Pneumococcal surface adhesion protein A is involved in bacterial adhesion to host cells PcsB and StkP were identified in screen of pneumococcal a proteome against sera of healthy adult donors	Trivalent vaccine demonstrated protection in animal models and is in early stage clinical evaluation

PCV7, 7-valent pneumococcal conjugate vaccine; PcsB, PspA, pneumococcal surface protein A; PspC, pneumococcal surface protein C; StkP, serine-threonine protein kinase

variants that are not toxic but are still immunogenic. Vaccination with the variant protects mice against infection.[38] Additionally, inclusion of this antigen along with PspA has shown to be protective against pneumococcal infection, suggesting again that a protein-based vaccine with multiple antigen targets may be an effective future vaccine.[39] A phase I clinical trial completed in Switzerland has demonstrated immunogenicity, safety and efficacy of human vaccination with the inactivated pneumolysin antigen.[40]

Fusion pneumococcal pilus proteins

Pneumococcal pilus 1 is an epithelial cell adhesion virulence factor composed of three separate proteins. This pilus structure, which has been associated with increased adherence to epithelial cells and plays a role in lung infection, is present on the surface of half of pneumococcal isolates. A recombinant protein formed by the fusion of the three subunits elicited antibodies that were capable of binding to the pneumococcal surface and protecting mice against pneumococcal isolates containing a pilus.[41] This protection was observed against strains that had both high and low levels of pilus expression.[42] Additionally, sera generated from the fusion antigen displayed efficacy equal to that of sera from PCV7 immunization in the established in vitro antisera-dependent, complement-mediated opsonization phagocytosis assay.[41]

Protein antigen combination vaccines

In order to determine novel protein antigens, a

proteome of pneumococcal proteins was screened using sera from individuals with pneumococcal exposure who lacked an active pneumococcal infection. This proteome was generated by adhering small amino acid fragments of pneumococcal proteins on a slide to represent all potential proteins pneumococcus can make. This array was then screened against the collected sera by determining which amino acid fragments on the array bound antibodies in the sera. The parent proteins of the amino acid fragments identified represent potential vaccine antigens. This screen identified two surface proteins as potential antigens, a protein required for cell wall separation (PcsB) and a serine-threonine protein kinase (StkP). These 2 proteins were highly conserved among clinical isolates, and vaccination with these 2 proteins protected mice against infection with multiple, lethal strains of pneumococci.[43] Additionally, they have been included with the protein pneumococcal surface adhesion protein A (PsaA) in a trivalent protein vaccine that has demonstrated protection in animal models and is in early stage clinical evaluation.[44]

CONCLUSIONS

Polysaccharide pneumococcal vaccines have evolved over the past 20 years, using both unconjugated polysaccharides and polysaccharides conjugated to toxins to elicit a protective immune response in groups at risk for pneumococcal infection. Current CDC immunization guidelines for these vaccines have reduced the rates of pneumococcal infections within immunized communities. However, the rise of antibiotic resistance in serotype replacement strains observed after implementation of current vaccines stresses the need for research into new, non-polysaccharide vaccines with broader coverage. Surface proteins expressed on pneumococci offer hope for potential new vaccines that can provide further protection against pneumococcal infections.

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Abbreviations ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; FDA, Food and Drug Administration; HIV, human immunodeficiency virus; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PspA, pneumococcal surface protein A

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