

A Simple Approach to Pneumococcal Vaccination in Adults

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Abstract

Streptococcus pneumoniae is a bacterium responsible for a spectrum of diseases including lobar pneumonia, meningitis, otitis media, and sinusitis. Invasive pneumococcal disease is responsible for significant morbidity and mortality across the world. Concerted efforts led to the development of two vaccinations, Pneumova × 23 and Prevnar 13, for the prevention of pneumococcal disease. The Advisory Committee on Immunization Practices of the US Centers for Disease Control and Prevention provides vaccination schedules for predisposed adults, but the proposed schedules remain a challenge to health-care providers. We performed a systematic review in PubMed and these specialty group websites to present the pathophysiology of pneumococcal disease, outline different pneumococcal vaccinations, and condense recommendations for vaccination administration.

Keywords: PCV13, PPSV23, *Streptococcus pneumoniae*, vaccination

INTRODUCTION

Since its identification in the late 19th century by Pasteur and Stenberg, the pneumococcus (*Streptococcus pneumoniae*) has been associated with an entire spectrum of clinical manifestations, ranging from simple colonization to invasive pneumococcal disease (IPD).^[1-4] In the United States, it is the most common cause of lobar pneumonia; a major cause of meningitis, sinusitis, and otitis media; and a less frequent cause of endocarditis, septic arthritis, and peritonitis.^[1,5-7] Predisposing factors for IPD are numerous and include the extremes of age, crowding, antecedent viral infections, both anatomic and functional asplenia, chronic disease states such as diabetes mellitus, and frank immunosuppression. Penicillins have been and remain the standard of care; however, drug-resistant *S. pneumoniae* is now well described in the literature, with acquisition of high-grade resistance thought to originate from spontaneous mutations, horizontal transfer of genetic material across bacterial species, and selective pressure resulting from the indiscriminate use of antibiotics.^[8-10] The emergence of such drug-resistant strains has, for example, led the Infectious Disease Society of America to update their practice guidelines for the management of bacterial meningitis, recommending adjunctive vancomycin when empirically treating presumptive pneumococcal meningitis with a third-generation cephalosporin such as ceftriaxone or cefotaxime.^[11]

Given the high burden of IPD, two inactivated, but nonequivalent, vaccines have been developed and marketed for routine vaccination against pneumococcus in adults in the United States: Pneumovax 23 (PPSV23) and Prevnar 13 (PCV13). The Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) provides guidelines on vaccination scheduling for predisposed adults unvaccinated with either one or both vaccines, but the proposed schedules remain a challenge to health-care providers. The aims of this paper are to clarify the pathophysiology of pneumococcal disease, to provide a balanced overview of different pneumococcal vaccines, and to perform a systematic review to summarize the latest recommendations for pneumococcal vaccination.

MICROBIOLOGY

S. pneumoniae is a Gram-positive, catalase-negative diplococcus able to be cultured from the human oral mucosa as a commensal but opportunistic organism. The bacterium is fastidious, but routine microbiological identification can be

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achieved based on *in vitro* observation of α -hemolysis on blood agar, susceptibility to the chemical optochin, and solubility in bile salts.^[1] Most pneumococcal strains are encapsulated, but all have within their cell wall the pneumococcal common antigen (C-polysaccharide), and this antigen can be detected with relative ease in the urine, aiding in the rapid diagnosis of IPD.^[12]

Despite conservation of this antigen across pneumococcal strains, sequence variations in capsular antigens have led to the identification of >90 pneumococcal serotypes with distinct differences in their virulence and immunogenicities.^[1,13] Importantly, most are uncommon, and only a small fraction of these cause most cases of invasive disease. Nontypeable (serotype negative) strains are extremely rare in IPD and cause disease in patients with underlying immune defects.^[14,15] Historically, the lower-numbered serotypes have been the most implicated in human disease and both polysaccharide vaccines incorporate capsular material from these prevalent pneumococci.^[1] More specifically, PPSV23 and PCV13 share serotypes 1, 3–5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23, whereas PPSV23 also contains serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F.^[16,17] Serotype 6A is unique to PCV13.^[1,16,17]

Two Inactivated but Nonequivalent Vaccines

Irrespective of some shared serotypes, PPSV23 and PCV13 also differ in their abilities to generate an effective immune response. Both polysaccharide vaccines generate antibodies against pneumococcal capsular antigens in a T-independent and B-cell-mediated fashion, but only PCV13 can induce a T-cell-dependent response.^[13] PCV13, unlike PPSV23, contains a protein conjugate, allowing for a more robust immunogenicity with enhanced avidity and memory for pneumococcal polysaccharide antibodies.^[1,18] Covalent attachment of this nontoxic protein conjugates to the vaccine also allows B-cells to produce antibodies in sufficient amounts to control infection and even reduce or suppress nasopharyngeal colonization with certain vaccine serotypes.^[1,19–23] Even more, unvaccinated adults have also shown comparable reductions in colonization, suggesting an indirect protection from conjugate vaccines through mechanisms also seen in herd immunization.^[1,3,18]

Perhaps through immunologic priming, PCV13 also allows for a more enhanced immune response to PPSV23 when administered as the initial vaccine in the vaccination series.^[16] Two large, randomized studies demonstrated increased antipneumococcal opsonophagocytosis activities in unvaccinated individuals who were vaccinated with PCV13 but then received PPSV23 12 months later.^[1,19,24,25] In contrast, those who first received PPSV23 had a blunted response when later challenged with PCV13, suggesting an immunological advantage seen with the conjugate but not standard polysaccharide vaccine.^[1,18,24,25] Based on these observations, the ACIP recommends administering the

conjugate vaccine before the standard polysaccharide vaccine in patients who need both.^[13,26]

SYSTEMATIC REVIEW OF INDICATIONS FOR VACCINATION METHODS

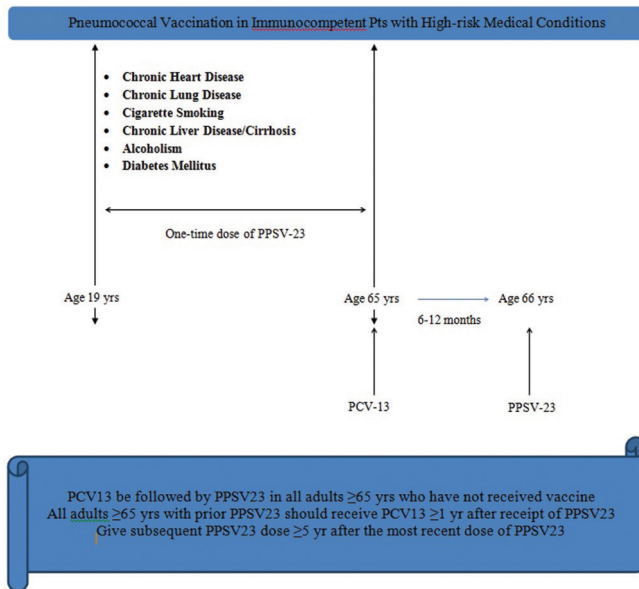
A systematic review was performed adhering to the guidelines established by the PRISMA statement.^[27] A bibliographic search was performed in the PubMed from January 2000 to June 2017 using combinations of the following medical subject heading search terms: “pneumococcal vaccine” or “pneumococcal vaccination.” No prepublished protocol is accessible. Other sources of information were the websites of ACIP and CDC. Four authors (C. G., C. M., A. M., and K. B.) reviewed the articles and achieved consensus. The study was exempt from approval by the Scientific Ethics Committee of Copenhagen Capital Region because the analysis involved only de-identified data. There was no source of funding for this review or preparation of the manuscript.

RESULTS

Although both PCV13 and PPSV23 are FDA approved for use in all adults 50 years and older, the ACIP currently recommends the routine use of the two vaccines in all unvaccinated persons age 65 years or older, with preferential receipt of PCV13 as the initial vaccine followed by administration of PPSV23 6–12 months later.^[13,16–18,25] Those who have received PPSV23 before the age of 65 but who are now age 65 or older should receive PCV13 at least 1 year later after the initial dose of PPSV23 and an additional dose of PPSV23 no sooner than 5 years after the initial dose of PPSV23; however, the second dose of PPSV23 should not be administered until at least 12 months after PCV13 vaccination.

The guidelines for patients with certain underlying medical conditions are more complex. Current ACIP recommendations also call for all adults with chronic medical conditions including tobacco use, alcoholism, diabetes mellitus, and chronic heart, lung, or liver diseases, to receive one dose of PPSV23 between 19 and 65 years [Flowchart 1].^[18,26]

Immunocompromised adults ages 19 or older, including those with functional or anatomic asplenia, should receive both pneumococcal vaccines using a sequential two-dose regimen with PCV13 administered first, followed by a dose of PPSV23 at least 8 weeks later [Flowchart 2]. Other examples of immunocompromised patients at risk for IPD include those with HIV, chronic renal failure or nephrosis, patients with multiple myeloma or generalized malignancies, and those receiving iatrogenic immunosuppression such as solid organ transplant recipients or those receiving prolonged courses of corticosteroids (20 mg of prednisone or its equivalent daily for at least 2 consecutive weeks).^[3,13,28] Given the increased prevalence of recurrent pneumococcal meningitis in immunocompetent persons with cerebrospinal fluid leaks or cochlear implants, the ACIP also recommends early vaccination



Flowchart 1: Pneumococcal vaccination in immunocompetent patients with high-risk medical conditions

in this patient population using the same sequential two-dose regimen as recommended in the immunocompromised.^[1,11,28,29]

ADVERSE REACTIONS AND CONTRAINDICATIONS

The most common adverse reaction to PPSV23 and PSV13 is noted to be pain or tenderness at site of injection in approximately 60% of patients, progressing to swelling or induration in 20%.^[16,17]

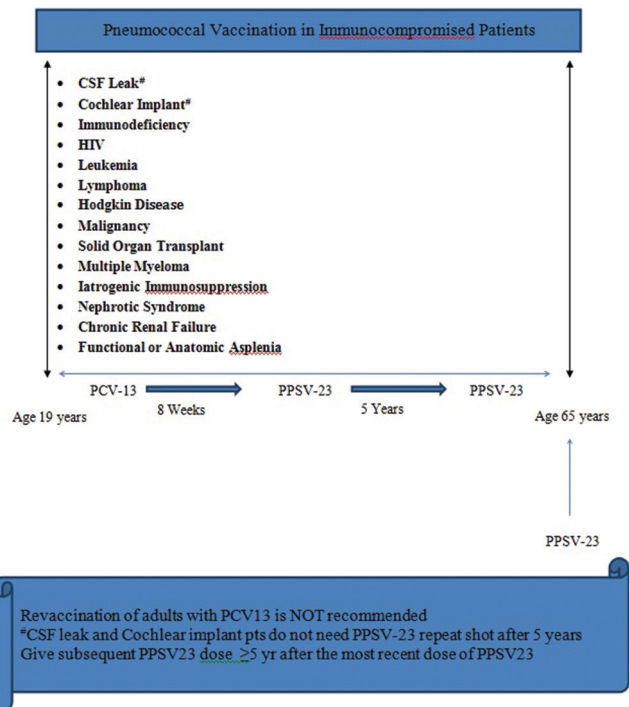
Severe allergic reactions to PPSV23 and PSV13 are contraindication to both the vaccines, whereas a severe allergic reaction to any diphtheria toxoid-containing vaccine is a contraindication for PSV13 only.^[16,17,30,31]

FUTURE EXPECTATIONS

With the introduction of PCV7 in early 2000, overall IPD incidence declined by 45% (from 24.4 to 13.5 cases per 100,000), and incidence of IPD due to PCV7 strains declined by 94% (from 15.5 to 1.0 cases per 100,000), but incidence of IPD caused by non-PCV7 types (especially *S. pneumoniae* type 19A) increased marginally, leading to introduction of PCV13 in 2010, which covers a broader range of serotypes.^[32,33]

Now, with the routine use of PCV13 in children aged 2, 4, 6, and 12–15 months of age, there is emergence of non-PCV13 serotypes (for example, 15B, 23A, 23B, and 35B) that appear as colonizers of nasopharynx and as causes of pneumococcal disease, highlighting the need for continued surveillance and updated vaccine.^[34,35] Currently, an additional 15-valent vaccine is undergoing preclinical trial.^[36-38]

The routine use of pneumococcal conjugate vaccine in infants has effectively eradicated nasal colonization of *S. pneumoniae* vaccine serotypes, not only in vaccinated infants but also in



Flowchart 2: Pneumococcal vaccination in immunocompetent patients

older unvaccinated children and adults due to a phenomenon called “herd immunity.” This has resulted in >90% decline in pneumococcal disease due to serotypes contained in PCV7 among older children and adults who did not receive vaccines.^[32] A similar trend has been observed with PCV13 in the United States since 2010 with the same degree of decline in pneumococcal infections in unvaccinated adults. This questions the recommendation for routine use of PCV13 in all adults >65 years of age.^[39] Most developed countries (Germany, France, Italy, United Kingdom, etc.) do not recommend the routine use of PCV13 in all adults >65 years of age.^[40] The ACIP will reevaluate these in 2018 and revise the guidelines to adjust according to the changing health-care needs of the population.

CONCLUSION

In this article, we reviewed the basic microbiology and disease spectrum of *S. pneumoniae*, along with the recent guidelines for vaccination in adults. We hope to improve clinical decision-making and reduce morbidity and mortality in the offices and hospitals. In this study, we observe the evolution of guidelines over the past few years. The trend seen points in the direction that to prevent infections in the general population, to really make a significant difference, the goal is herd immunity, the means to which is achievable through a universally acceptable system of vaccines in the form of vaccination guidelines that are efficient and easily adaptable in day-to-day practice.

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Conflicts of interest

There are no conflicts of interest.

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