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Pneumococcal disease prevention among adults: Strategies for the use of pneumococcal vaccines

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ABSTRACT

Use of the pneumococcal conjugate vaccines among children in the US since 2000 has dramatically reduced pneumococcal disease burden among adults. Significant vaccine-preventable morbidity and mortality from pneumococcal infections still remains, especially among older adults. The US Advisory Committee on Immunization Practices (ACIP) has recently recommended the routine use of both pneumococcal conjugate (PCV13) and polysaccharide vaccines (PPSV23) for adults ≥65 years. These recommendations were based on the remaining burden of illness among adults and the importance of non-bacteremic pneumonia prevention in light of new evidence confirming the efficacy of PCV13 to prevent pneumococcal pneumonia among older adults. This paper reviews the evidence that led the ACIP to make recommendations for PCV13 and PPSV23 use among adults, and highlights potential gaps to be addressed by future studies to inform adult vaccination policy. The changing epidemiology of invasive pneumococcal disease and pneumonia should be closely monitored to evaluate the effectiveness and continued utility of the current vaccination strategy, and to identify future directions for pneumococcal disease prevention among older adults.

1. Background

Streptococcus pneumoniae is a leading cause of disease and death among older adults in the United States. Pneumococcus causes invasive disease – bacteremia and meningitis – as well as pneumonia. Use of polysaccharide vaccine since the late 1970s should have resulted in the decline of invasive pneumococcal disease (IPD) among older adults but uptake has been slow, and the declines at a population level have not been documented [1–3]. Conversely, use of the conjugate vaccines (7-valent conjugate vaccine (PCV7) and 13-valent conjugate vaccine, (PCV13)) in children since 2000 has dramatically reduced vaccine-type invasive infections in older adults as a result of indirect, "herd" effects [4,5]. Reductions in community-acquired pneumonia (CAP) among adults have also been documented since PCV7 introduction among children [6]. Despite these dramatic indirect benefits of PCV7 and PCV13 use in pediatric populations, significant morbidity and mortality still result from pneumococcal infection in older adults. In 2013, approximately 20–25% of IPD [7] cases and approximately 10% of all CAP [8] cases among adults ≥65 years old were caused by PCV13 serotypes and, therefore, many of these might have been prevented through direct use of PCV13 among adults. This paper will review the evidence that led the Advisory Committee on Immunization Practices (ACIP) to recommend PCV13, and continued use of PPSV23 for adults, and highlight potential gaps to be addressed by future studies to inform adult vaccination policy.

2. Pneumococcal vaccines

2.1. Pneumococcal polysaccharide vaccine—PPSV23

The currently available pneumococcal polysaccharide vaccine, manufactured by Merck, Inc. (Pneumovax® 23), includes 23 purified capsular polysaccharide antigens of *S. pneumoniae* (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). This vaccine was licensed in the United States in 1983 and replaced an earlier 14-valent formulation that was licensed in 1977.

The first PPSV licensed in the US was PPSV14. Capsular polysaccharides included in the current polysaccharide vaccine, PPSV23, induce antibodies primarily by T-cell—independent mechanisms, and therefore, induce an immune system response that is neither long-lasting nor characterized by an anamnestic (i.e., booster)

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response upon subsequent challenge with native polysaccharides. Therefore, antibody response to PPSV is poor in children aged <2 years whose immune systems are immature. In addition, polysaccharide vaccine does not reduce nasopharyngeal carriage of *S. pneumoniae* in children, and, therefore, is not associated with indirect (herd) effects.

PPSV23 has been recommended for adults ≥65 years old since 1983. Through 2012, a single dose of PPSV23 has been recommended for adults <65 years old with chronic medical conditions, as well as those with asthma or those who smoke cigarettes. A single revaccination with PPSV23 5 years after the initial dose was recommended before age 65 years for adults with immune compromise or those with functional or anatomic asplenia. In addition, a single dose of PPSV23 was recommended for all adults ≥65 of age regardless of previous history of PPSV23.

2.2. Pneumococcal conjugate vaccine—PCV13

The first pneumococcal conjugate vaccine, PCV7, was licensed in 2000 and recommended for use in infants and young children with a 4-dose schedule. Conjugate pneumococcal vaccine includes purified capsular polysaccharides of *S. pneumoniae*, each coupled with a nontoxic variant of diphtheria toxin, CRM197. Conjugation of polysaccharides to proteins changes the nature of the immune response to polysaccharide antigens from T-independent to T-dependent. This antigen complex stimulates a T-helper-cell response, leading to a substantial primary response among infants and a strong booster response at re-exposure.

Randomized clinical trials, as well as post-licensure observational studies have demonstrated that PCV7 prevents not only vaccine-type invasive pneumococcal disease but also pneumonia and acquisition of nasopharyngeal carriage of vaccine-type strains among children. This latter characteristic of PCV7 contributed to reduced transmission of vaccine-type strains to adults and, consequently, reductions in disease burden among adults (herd effects). The use of PCV7 among children has changed the epidemiology of pneumococcal disease in the United States. Although the vaccine was only recommended for children initially, its administration has resulted in dramatic declines in invasive pneumococcal disease in all age groups due to herd effects. As the serotypes in PCV7 declined, there was some replacement observed with increases in disease burden caused by non-vaccine serotypes [4]. In 2010, PCV13 replaced PCV7 for the vaccination of children. PCV13 contains the seven serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and six additional serotypes (1, 3, 5, 6A, 7F, and 19A). By 2013, there were declines in invasive disease caused by the serotypes unique to PCV13 observed among all age groups similar to what was seen for PCV7 serotypes following PCV7 introduction [5]. The ability to demonstrate reduction in IPD due to several individual serotypes (1,3,5,6A) was limited because their incidence was too low or too inconsistent.

3. Recent changes in recommendations

In 2011, PCV13 was approved by the FDA for use among adults ≥50 years old to prevent pneumonia and invasive disease caused by the serotypes in the vaccine. It was approved under the FDA's accelerated approval pathway based on non-inferior immunogenicity compared to PPSV23. As a condition of licensure, the vaccine manufacturer agreed to conduct a randomized controlled trial of PCV13 against pneumococcal pneumonia in adults ≥65 years old [9]. The ACIP elected to recommend PCV13 for immunocompromised adults in 2012, but postponed making general recommendations in adults pending the results of the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) [8] and additional data regarding the impact of PCV13 use in children on adult disease [5]. In 2014, after review of the results of CAPiTA and the impact of PCV13 indirect (herd) effects, ACIP recommended routine use of PCV13 in series with PPSV23 among adults ≥65 years [7]. In addition, in June 2015, ACIP revised the recommended intervals between PCV13 and PPSV23 for adults 65 years or older.

In adults ≥65 years of age who have not previously received a pneumococcal vaccine, the ACIP recommended the use of PCV13 followed by PPSV23 1 year or later. The ACIP further recommended that those who had previously received PPSV23 at age ≥65 receive PCV13 at least one year following the PPSV23 dose. Those who received PPSV23 before age 65 years who are now ≥65 years of age at the time of their visit should receive a dose of PCV13 at least one year after their last PPSV23, followed by a dose of PPSV23 at least a year after the PCV13 dose and at least 5 years following the previous PPSV23 dose. The recommendations for immunocompromised individuals passed by the ACIP in 2012 remained unchanged [10].

The ACIP further stated that recommendations for routine use of PCV13 among adults aged ≥65 will be reevaluated in 2018 and revised as needed. The recommendations for vaccine use are routinely reevaluated by the ACIP. There are already ample data to show that the herd effect of PCV13 vaccination in children will likely result in a diminished frequency of the vaccine serotypes in circulation and, therefore, diminished need for routine PCV13 vaccination among adults in the next few years.

4. Evidence supporting PCV13 use among adults

4.1. Immune response to PCV13

FDA approval of PCV13 in 2011 for adults was based on immunogenicity studies that compared antibody responses to PCV13 with antibody responses to PPSV23. In two randomized, multicenter, immunogenicity studies conducted in the United States and Europe, adults aged 50 years and older received a single dose of PCV13 or PPSV23. Functional antibody responses were measured 1 month after vaccination using an opsonophagocytic activity (OPA) assay. In adults aged 60 through 64 years naïve to pneumococcal vaccines, PCV13 elicited OPA geometric mean antibody titers (GMTs) to the 12 serotypes common to both vaccines that were comparable to, or higher than, responses elicited by PPSV23 [11]. For serotype 6A, which is unique to PCV13, OPA antibody responses were higher after PCV13 vaccination than after PPSV23 vaccination. OPA GMTs elicited by PCV13 in adults aged 50 through 59 years for all 13 serotypes were comparable to the corresponding GMTs elicited by administration of PCV13 in adults aged 60 through 64 years. In adults aged 70 years and older who previously had been immunized with a single dose of PPSV23 at least 5 years before enrollment, PCV13 elicited OPA responses that were comparable to or higher than those elicited by PPSV23 for the 13 serotypes. For 10 of 12 serotypes in common, the PCV13 responses were significantly greater than the PPSV23 responses [12]. At 1-year follow up, OPA levels were lower both in PCV13 and in PPSV23 recipients than at 1 month after immunization.

Four studies of PCV7 immunogenicity were conducted in the United States and Europe involving 699 HIV-infected subjects, all with CD4 counts of >200 cells/μl [13–16]. Response to a single dose of PCV7 was non-inferior or superior to PPSV23 for the serotypes evaluated. In an open label study among HIV-infected adults ≥18 years of age who previously received ≥1 doses of PPSV23, antibody response was measured following the receipt of 3 doses of PCV13 given 6 months apart [17]. The results of this study demonstrated that anticapsular polysaccharide immunoglobulin G concentrations and OPA titers were measured 1 month after each of the 3