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Pneumococcal Prevention Gets Older and Wiser

Anne Schuchat, MD

National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.

Pneumococcus, or *Streptococcus pneumoniae*, the "captain of the men of death" in the parlance of Sir William Osler, has killed millions of people while repeatedly frustrating clinicians, vaccine experts, and epidemiologists. The advent of effective antibiotics did not eliminate deaths from pneumococcal disease. Pneumococcal morbidity has remained substantial among the elderly population even though most have received the 23-valent pneumococcal polysaccharide vaccine (PPSV-23). Diagnostic tests for pneumonia are relatively insensitive and nonspecific.[1] Thus, it is difficult to evaluate the efficacy of pneumococcal vaccines against pneumonias that do not lead to detectable bloodstream infection.

The Multivalent Polysaccharide Vaccines

Multivalent pneumococcal polysaccharide vaccines against 14 and later 23 capsular types were licensed in the United States in 1977 and 1983, respectively. The PPSV-23 was recommended for people 2 years or older with medical conditions putting them at high risk (eg, sickle cell disease) and for all those 65 years or older. Since the 1990s, when reimbursement for administration of pneumococcal vaccine was added to the Medicare beneficiary program, 60% to 70% of people in the United States 65 years or older have been vaccinated with PPSV-23.

The PPSV-23 provides moderate protection against invasive pneumococcal disease in people who are immunocompetent. It is unclear, however, whether polysaccharide vaccines have any effect on nonbacteremic pneumonia. Studies suggest that efficacy wanes over time and may decrease with age at vaccination. Disease incidence in adults increases with age. Before 2014, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended that people in their 65th year of life receive a single dose of PPSV-23 as well as an annual influenza vaccination.

Polysaccharide-Protein Conjugate Vaccines

Conjugation of capsular polysaccharide to carrier proteins in vaccines has led to improved immunologic response to pneumococcus in infants and young children compared with that induced by polysaccharide vaccines; it has also induced immunologic memory and reduced

Corresponding Author: Anne Schuchat, MD, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Mailstop A-27, Atlanta, GA 30333, (aschuchat@cdc.gov).

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acquisition of nasopharyngeal colonization. Since licensure in the United States in 2000, pneumococcal polysaccharide-protein conjugate vaccine has revolutionized the prevention of pneumococcal disease among children. Conjugate vaccines have high efficacy in young children against disease caused by the capsular types included in the vaccine and also reduce transmission of vaccine-type pneumococci from immunized children to others. The 7-valent (introduced in 2000) and the 13-valent (introduced in 2010) conjugate vaccine formulations dramatically reduced invasive and noninvasive pneumococcal infections in children[2,3] and were estimated to prevent about 2 invasive infections indirectly for each 1 directly prevented.[4]

Although substantial reductions in invasive pneumococcal disease caused by the 7-valent types were seen in the elderly population following uptake of the 7-valent conjugate vaccine in children, nonbacteremic pneumococcal pneumonia has remained common in people older than 65 years.[3] The advent of conjugate vaccines targeting more capsular types raised hope that direct vaccination of seniors might provide important additional benefits against pneumococcal pneumonias, including cases that are nonbacteremic. On December 30, 2011, the US Food and Drug Administration (FDA) approved a 13-valent pneumococcal conjugate vaccine (PCV-13), manufactured by Pfizer (Prevnar 13), for use in adults 50 years or older. Approval of PCV-13 for adults was based on detection of noninferior vaccine-induced antibody levels against vaccine types compared with levels observed following administration of PPSV-23. In June 2012, the ACIP voted to recommend PCV-13 use in adults at very high risk—eg, those with conditions such as human immunodeficiency virus infection, which increases risk of developing invasive pneumococcal disease more than 20-fold.

However, the committee opted to delay consideration of PCV-13 recommendations for people 65 years or older, a much larger population, until 2 key pieces of additional data could be reviewed. First, the committee sought data on the effect that ongoing PCV-13 use in children was having on 13-valent type invasive pneumococcal infections in adults. Second, the committee awaited results of the CAPITA study—a randomized, placebo-controlled trial of PCV-13 efficacy against pneumococcal pneumonia in about 85 000 people 65 years or older conducted in the Netherlands from 2008 to 2013.[5] Lack of similar randomized clinical trial data for pneumococcal polysaccharide vaccine in community-dwelling adults 65 years or older may have contributed to the long-standing controversy over the efficacy of this vaccine. In August 2014, the ACIP held an extraordinary meeting to consider the results of the CAPITA trial, which had yet to be published, and to deliberate on recommendations for routine use of PCV-13 among the elderly population.[6] In this trial, the results of which were published in 2015,[5] PCV-13 prevented 75% of vaccine-type invasive pneumococcal disease and 45% of vaccine-type nonbacteremic pneumonia. In the United States, an estimated 50 000 hospitalizations occur annually in people 65 years or older for community-acquired pneumonia caused by the 13-valent type pneumococci.

Emergence of Vaccine Guidelines

The resulting ACIP guidance was issued by the CDC in September 2014[6]; it was intended to provide the public and clinicians with updated practice recommendations in time for

vaccination in the fall of 2014 and as soon as possible after the CAPITA trial[5] data were reviewed. The urgency arose from the approach of the winter season, when pneumonia and influenza rates peak, especially among seniors. The ACIP recommended a dose of the PCV-13 conjugate vaccine for all those 65 years or older followed by a dose of the PPSV-23 formulation 6 to 12 months later. This recommendation was prompted by the continued occurrence of invasive disease related to pneumococcal types not covered by PCV-13 but covered by PPSV-23.

For people who never received a pneumococcal vaccine, the ACIP recommended that the conjugate vaccine should be administered first because the immune response is better than when the polysaccharide vaccine is given first. Most people 65 years or older have already received the polysaccharide vaccine, however. Therefore, to increase protection against nonbacteremic pneumonia, the ACIP recommended administration of the conjugate vaccine at least 12 months after the prior vaccination. On the basis of the CDC ACIP recommendations,[6] the Centers for Medicare & Medicaid Services (CMS) revised the coverage of pneumococcal vaccines for Medicare beneficiaries, allowing reimbursement for 2 doses (ie, 1 conjugate and 1 polysaccharide dose) when given at least 12 months apart.[7]

Continued Controversy Over Vaccine Guidelines

Some critics have stated that the CDC and the ACIP waited too long to recommend the use of PCV-13 in adults older than 65 years. Others have questioned whether PCV-13 should have been recommended for adults at all. And some were confused by the different dosing intervals in the 2014 recommendations.

This last concern has now been addressed. In June 2015, ACIP voted to set the interval between conjugate and polysaccharide vaccine doses for seniors at 12 months or more, regardless of order of receipt, consistent with the CMS reimbursement policy. The longer dosing interval for the conjugate vaccine followed by the polysaccharide vaccine is supported by evidence of lower reactogenicity, adequate immune response, and very small incremental risk of invasive disease caused by nonconjugate vaccine types during the additional 6 months between doses.[8]

The 2014-2015 winter was one of the worst in recent history for severe respiratory infections in the elderly population in the United States. The H3N2 influenza strains that had drifted away from the 2014-2015 influenza vaccine dominated, leading to the highest rates of laboratory-confirmed influenza hospitalizations among people 65 years or older observed since CDC’s surveillance of influenza hospitalizations began in 2005.[9] The effectiveness of influenza vaccine against H3N2 influenza strains was very low.[10] However, while influenza vaccines likely provided little benefit to the elderly population during the 2014-2015 flu season, those who had received a pneumococcal conjugate vaccine in addition to earlier polysaccharide vaccines were likely at lower risk for pneumococcal infections complicating influenza.

Conclusions

The ACIP's 2015 guidance is unlikely to end debate about optimal ways to defeat the pneumococcus. The ACIP will review its recommendations for the use of pneumococcal conjugate vaccine in the elderly population in 2018. Until the recommendations are reviewed, the evidence from the CAPITA trial[5] suggests that widespread vaccination of older adults with the PCV-13 vaccine can prevent an important proportion of nonbacteremic pneumonias attributable to the pneumococcal types covered by the vaccine.

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