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Prevention of adult pneumococcal pneumonia with the 13-valent pneumococcal conjugate vaccine: CAPiTA, the community-acquired pneumonia immunization trial in adults

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The aging of the world population is expected to be accompanied by increased pneumococcal pneumonia in older adults. To address this, the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), a large, randomized, placebo-controlled trial conducted to assess the 13-valent pneumococcal conjugate vaccine (PCV13) in adults ≥65 years, found statistically significant vaccine efficacy for first episodes of vaccine-type community-acquired pneumonia (VT-CAP; 46%), nonbacteremic/noninvasive VT-CAP (45%), and VT invasive pneumococcal disease (75%), along with an acceptable safety profile. Study results were presented to the US Advisory Committee on Immunization Practices in June 2014, which subsequently recommended sequential PCV13 and 23-valent pneumococcal polysaccharide vaccination for adults ≥65 years. Thus, appropriate protection of adults at risk for pneumococcal CAP will include vaccination with PCV13.

With the aging of the world population, pneumococcal pneumonia places a significant and increasing burden on global public health. The medical community, vaccine regulatory agencies, and health authorities recognize that studies evaluating the efficacy and effectiveness of 23-valent pneumococcal polysaccharide vaccine published to date do not demonstrate consistent results regarding the ability of this vaccine to prevent pneumococcal pneumonia, particularly nonbacteremic pneumococcal pneumonia, the most common clinical manifestation of pneumococcal disease in adults. The unmet medical need for a vaccine with confirmed efficacy for the prevention of pneumococcal pneumonia supported the clinical development of the 13-valent pneumococcal conjugate vaccine (PCV13) for use in older adults. To address this unmet need, the US Food and Drug Administration approved PCV13 in 2011 for use among adults 50 years of age and older under an accelerated approval pathway, which requires verification of clinical benefit. Thus, as agreed with regulatory agencies in the United States and Europe, Pfizer conducted the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), one of the largest prospective, double-blind, randomized, placebo-controlled vaccine efficacy trials ever done in adults.[1]

The study evaluated the safety and efficacy of PCV13 for prevention of first episodes of confirmed vaccine-type pneumococcal community-acquired pneumonia (VT-CAP), for prevention of first episodes of confirmed nonbacteremic/noninvasive VT pneumococcal CAP (NB/NI VT-CAP), and for prevention of confirmed VT invasive pneumococcal disease (VT-IPD). A total of 84,496 immunocompetent adults aged ≥65 years were enrolled and were vaccinated with a single dose of PCV13 (n=42,240) or placebo (n = 42,256). The study continued until a prespecified number of VT-CAP episodes occurred; CAP and IPD episodes were identified using a PCV13-serotype–specific urinary antigen detection (UAD) assay or by isolation of VT pneumococcus from a normally sterile site using standard laboratory methods.

Study randomization resulted in a balanced distribution of age, gender, and comorbidities between the treatment groups. The primary and secondary endpoint efficacy results for the per-protocol population were statistically significant. Vaccine efficacy (VE) was

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45.56% (95.2% confidence interval [CI]: 21.82, 62.49, $P = 0.0006$) for first episode of VT-CAP; 45.00% (95.2% CI: 14.21, 65.31, $P = 0.0067$) for first episode of NB/NI VT-CAP, and 75.00% (95% CI: 41.43, 90.78, $P = 0.0005$) for VT-IPD. VE for the exploratory endpoint of first episode of pneumococcal CAP (all serotypes) was 30.56% (95% CI: 9.75, 46.74, $P = 0.0077$). In a post hoc analysis of the cumulative number of episodes plotted against time from vaccination for the primary and secondary endpoints, efficacy began shortly after vaccination and persisted throughout the duration of the trial (mean of approximately 4 years), without evidence of waning. All PCV13 serotypes were identified among first episodes of confirmed VT pneumococcal CAP throughout the course of the study. The study results are biologically plausible, likely reflecting the robustness of antipneumococcal immune responses as well as the development of T cell–dependent memory by PCV13-immunized subjects.

The PCV13 safety profile was acceptable and consistent with findings from previous studies.[2-5] Expected differences were observed between the PCV13 and placebo groups in the frequency of inoculation site reactions and muscular pain. There were no significant differences in frequencies of newly diagnosed medical conditions or deaths, and no vaccine-related serious adverse events were reported.

The study demonstrated that PCV13 is safe and efficacious in adults aged 65 years and older for the prevention of VT-CAP and VT-IPD. Diagnosis of nonbacteremic pneumococcal CAP was possible by the use of the UAD assay. Therefore, the Community-Acquired Pneumonia immunization Trial in Adults is the first study to demonstrate efficacy in the prevention of VT nonbacteremic CAP.

There were some study limitations. Although it was conducted in 59 centers, all were in a country of low incidence of pneumococcal pneumonia and high uptake of PCV7 (introduced in 2006), followed by PCV10 (March 2011) in children, which may have impacted the magnitude of observed VE. The study was not designed to evaluate VE in subjects who became immunocompromised after enrollment, and these subjects were excluded from the primary analysis. The numbers of subjects who developed immunosuppression after vaccination, as well as the number of subjects in the older cohorts, were too low to draw efficacy conclusions in these subpopulations. Prevention of all-cause CAP and mortality were exploratory endpoints, and the study was neither designed nor powered to assess the difference between the vaccine and placebo groups for these endpoints.

Data from the study will be important when considering any potential new or updated recommendations for PCV13 in adults. Another key factor to consider is the burden of pneumococcal CAP in adults, particularly in relation to the use of PCV13 in pediatric populations. Profound reductions in adult IPD from pediatric PCV7 and PCV13 National Immunization Programs (NIPs), through herd protection, have been regularly described.[6-9] For nonbacteremic pneumococcal CAP, however, the data do not permit similar conclusions. In fact, recent work from the United Kingdom,[10] United States,[11,12] and Spain,[13] as well as data from the Community-Acquired Pneumonia immunization Trial in Adults document persistent circulation of PCV7 and PCV13 serotypes in patients with confirmed pneumococcal CAP several years after successful NIP implementation, suggesting that IPD cohorts are not accurate surrogates for CAP. Current understanding of the disease-causing potential of *Streptococcus pneumoniae* in adults is complex and incomplete. Analyses of adult IPD rates may underestimate the true incidence of nonbacteremic pneumococcal CAP preventable by PCV13 vaccination of adults. Thus, indirect effects alone may not be sufficient to confront the public health burden of pneumococcal CAP in adults. Continuous monitoring of both IPD and CAP, including nonbacteremic pneumococcal CAP, is essential to fully understand the real impact of direct and indirect protection afforded by PCV13.

The results of the Community-Acquired Pneumonia immunization Trial in Adults were presented to the US Advisory Committee on Immunization Practices (ACIP) in June 2014. In September 2014, ACIP recommended routine sequential administration of PCV13 and the 23-valent pneumococcal polysaccharide vaccine to all adults 65 years of age and older.[14] These recommendations will be reassessed in 2018. Because the recommendations for routine use of PCV13 in adults aged 19 years and older living with immunocompromising conditions, asplenia, cerebrospinal fluid leak, or cochlear implants remain in place, immunocompetent adults aged 19 to 64 years living with chronic medical conditions such as heart disease, lung disease, and diabetes mellitus, among others, are the only individuals at increased risk of pneumococcal disease not to be routinely recommended PCV13. Furthermore, rates of all-cause pneumonia in these cohorts are comparable to or higher than those noted in adults aged 65 years and older. The proportion of all-cause CAP due to PCV13 serotypes was similar between the periods 2010–2011 and 2013–2014 with no apparent change in prevalence despite high uptake of the vaccine in US infants (Pfizer Inc., data on file). By design, the study included individuals who were judged immunocompetent at randomization, but had underlying medical conditions that may have increased the risk of pneumococcal pneumonia, with 42% of subjects having at least 1 chronic medical condition. Based on experience from prior immunogenicity trials, these populations are able to respond to PCV13[15,16] and are likely to benefit from direct vaccination.

Early evidence of emergence of nonvaccine serotypes in IPD after the introduction of PCV13 in the United States and Europe is limited,[8,17–19] but the role of these strains as causative agents of CAP in adults is unknown. The UAD assay was developed specially for the Community-Acquired Pneumonia immunization Trial in Adults study. Wider use of current and future UAD tests, incorporating additional serotypes, will be needed to prospectively understand the changing epidemiology of CAP in adults and the need for higher-valency PCVs. Proof of concept for a protein serotype-independent vaccine has proved elusive. For the foreseeable future, appropriate protection of adults at risk for pneumococcal CAP relies on vaccination with PCV13, which, as demonstrated by the study, is safe and effective in older adults for prevention of VT pneumococcal CAP.

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