The Impact of Age on the Efficacy of 13-valent Pneumococcal Conjugate Vaccine in Elderly

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In a post hoc analysis of the Community-Acquired Pneumonia (CAP) immunization Trial in Adults the model-predicted 13-valent pneumococcal conjugate vaccine efficacy for preventing vaccine-type specific CAP and Invasive Pneumococcal Disease declined from 65% to 40% for subjects being 65 and 75 year olds at the time of vaccination, respectively.

Keywords. pneumococcal conjugate vaccine; community-acquired pneumonia; invasive pneumococcal disease; vaccine efficacy; immunosenescence.

The humoral, cell-mediated, and innate immune system are affected by increasing age, independent of comorbidities, which may impair immunogenicity of vaccines [1–4]. Indeed, antibody concentrations and opsonophagocytic activity after receipt of 23-valent pneumococcal polysaccharide vaccine (PPSV23) were lower in elderly compared to young adults [5]. In contrast to polysaccharide vaccines, conjugate vaccines induce a T-cell dependent immune response and, therefore, enable B-cell memory. In elderly, immunogenicity of pneumococcal conjugate vaccines was higher than of polysaccharide vaccines [6], although opsonophagocytosis assay (OPA) levels after 12 months were not significantly different in adults receiving 13-valent pneumococcal conjugate vaccine (PCV13) compared to PPSV23 [7]. The effect of increasing age on the efficacy of pneumococcal conjugate vaccines has not been established. We therefore analyzed the impact of age on the observed vaccine efficacy (VE) of PCV13 in the prevention of vaccine-type community-acquired pneumonia (VT-CAP) and invasive pneumococcal disease (VT-IPD) in immunocompetent subjects aged 65 years and older.

METHODS

This is a post hoc analysis of the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), a randomized, double-blind, placebo controlled study, in which 84 496 immunocompetent subjects aged ≥65 were randomized to receive either PCV13 or placebo [8]. The primary endpoint of this trial, CAP caused by any of the 13 vaccine-serotypes (VT-CAP), was determined in 84 492 subjects (the safety population, excluding 4 patients with missing safety information) through identifying hospitalizations for CAP in 58 participating hospitals and one diagnostic center. Within 24–48 hours after presentation, urine was collected for serotype-specific urinary antigen detection (UAD) [9]. Blood cultures were collected as part of routine clinical care, and isolated *Streptococcus pneumoniae* strains were serotyped. CAP was defined as the presence of at least 2 clinical criteria (cough, production of sputum or change in character of sputum, temperature >38°C or <36.1°C, auscultatory findings consistent with pneumonia, leucocyte count $>10\times10^9$/L, CRP >30 mmol/L, and arterial pO2 <8 kPa) and abnormalities on chest X-ray consistent with pneumonia. VT-CAP was defined as CAP with detection of vaccine-serotype *S. pneumoniae* in blood culture, other sterile cultures, or serotype specific UAD and subjects were classified as having VT-IPD when a vaccine-serotype *S. pneumoniae* strain was isolated from normally sterile body fluids, independent of CAP criteria (see Supplementary Material for more detailed definition). Urine samples collected more than 48 hours after the admission were not used, and the serotype-specific UAD was considered false-positive if another pulmonary pathogen or another pneumococcal serotype was isolated from a sterile body fluid. Events occurring within 42 days of a previous episode were considered the same episode, unless a different pathogen or different serotype was detected. The modified intention-to-treat (mITT) population consisted of CAP and IPD episodes occurring more than 14 days after vaccination. In the per protocol population subjects who had become immunocompromised, had received another pneumococcal vaccine before event onset, or were hospitalized or

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resided in a long-term care facility at the time of symptom onset, were excluded.

Proportions of patients with blood cultures and serotype specific UAD tests were compared over age groups and between the vaccine and placebo group. The interaction effect of age at enrolment was assessed using a Cox proportional hazard model, with the first episode of either VT-CAP or VT-IPD as the outcome variable. This combined endpoint, although not protocol specified, was chosen to increase statistical power and because both are relevant vaccine preventable diseases. Subjects that had died were censored at time of death. Because subjects that were lost to follow-up could still be identified as CAP or IPD case if they presented in a participating hospital, loss to follow-up was ignored. Vaccination status, age, and an interaction term of vaccination status and age were included as independent variables. For example, a hazard ratio (HR) for the interaction of 1.05 means that the HR for vaccination increases with 5% for each year of age. VE, defined as 1-HR, than declines with increasing age. The analysis was repeated using VT-CAP and VT-IPD separately and using the per protocol population. Adjustment was performed for gender, and self-reported presence of chronic pulmonary disease, chronic cardiac disease, diabetes, and smoking at the time of vaccination. All models were checked for the proportional hazards assumption and for nonlinearity. Graphical representation of model-predicted VE with 95% confidence intervals as a function of age was generated using 2000 bootstrap samples. The analyses were performed in R version 3.0.2 [10].

RESULTS

Age was similarly distributed in the vaccine and placebo group with a median of 71.6 years (IQR 68.2–76.4). A total of 32 933 (39.0%) subjects were <70 years old, 25 145 (29.8%) were 70–74 years old, 15 758 (18.7%) were 75–79 years old, 7715 (9.1%) were 80–84 years old, and 2941 (3.5%) were 85+. The mean follow-up duration was 3.9 years (IQR 3.8–4.8 years). During follow-up 6011 subjects (7.1%) died and 4571 subjects (5.4%) were lost to follow-up.

Urine for serotype specific UAD was collected slightly more often in CAP episodes of subjects below 70 years (93%) compared to those over 85 years (90%, *P*-value for trend .03). Blood culture collection was performed in 78% of cases, with no effect of age (*P*-value: .62). There were no differences in microbiological tests between the vaccine and placebo group.

There were 184 first episodes of VT-CAP or VT-IPD in the mITT population. A statistically significant vaccine-age interaction effect was observed (HR for interaction 1.057, 95% confidence interval [CI], 1.008–1.109, $P = .023$). The model-predicted that VE declined from 65% (95% CI, 38% to 81%) in 65 year-old subjects to 40% (95% CI, 17%; 56%) in 75 year-old subjects (Figure 1). Point estimates of the vaccine-age interaction effect were similar for VT-CAP and VT-IPD separately, for the per protocol analyses and after adjustment for covariates (see Supplementary Material). In all models, the proportional hazards assumptions were met, except for the direct effect of age in the models with IPD. The regression model may be not optimally fitted for subjects above 85 years of age, as shown by the residuals plot (see Supplementary Material). However, they were not improved with different transformations of age.

Numbers of events per serotype and per age group in the primary analysis are displayed in Supplementary Appendix Figure 3. Of the most common serotypes, serotypes 3 and 7F were most associated with lower age groups and VE against these serotypes was higher than the average VE. Yet within these serotypes, VE also tended to decrease with increasing age.

DISCUSSION

In this study of immunocompetent elderly subjects, aged ≥65 years, efficacy of PCV13 in preventing VT-CAP or VT-IPD, was highest among those subjects aged 65 at the time of randomization, and VE declined with increasing age. A similar finding was obtained in the per protocol analysis, which was limited to subjects that were immunocompetent at the time of their first CAP or IPD episode. Although we used data from a randomized controlled trial, the vaccine-age interaction could have been biased by other baseline characteristics, such as comorbidities associated with age and with different VE.

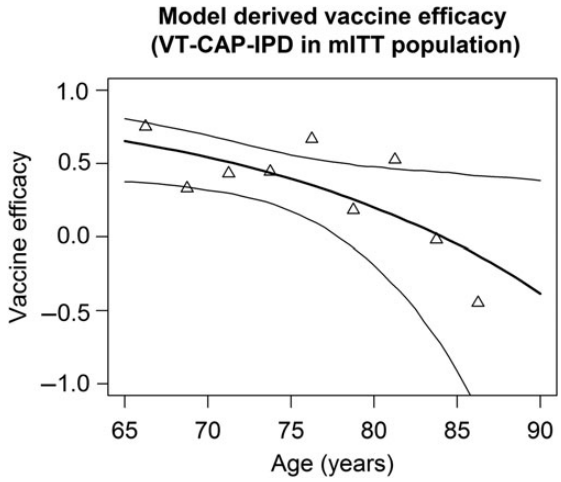

Figure 1. Model derived vaccine efficacy by age for first episode of vaccine-type community-acquired pneumonia (VT-CAP) or vaccine-type invasive pneumococcal disease (IPD) in modified intention-to-treat (mITT) population using a Cox proportional hazards model. Triangles represent crude estimates of age groups of 2.5 years each. The solid bold line represents the model derived vaccine efficacy. The 95% confidence interval (thin lines) was derived using 2000 bootstrap samples.

However, after adjustment for gender and self-reported baseline comorbidities, effect estimates remained unchanged, minimizing the risk of this form of bias in the present study.

The differences in VE may be caused by age-related decreases in antibody avidity. Reduced antibody responses in subjects above 75 years of age, compared to subjects between 60 and 75 years have been reported for the PPSV23 and the 7-valent pneumococcal conjugate vaccine [11]. Antibodies following immunization with PPSV23 had lower avidity and opsonophagocytic activity in elderly compared to young adults, and these low avidity sera were less protective in mice [5]. However, immunogenicity data in a subset of the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) collected at 1, 12, and 24 months post vaccination showed only small differences in immunoglobulin G antibody levels and OPA titers in the very old, compared to younger subjects, which could not fully explain the observed effects (A. M. M. van Deursen et al, manuscript in preparation; see also https://idsa.confex.com/idsa/2014/webprogram/Paper47279.html). Other age-related changes in the immune system, such as reduced phagocytic function of macrophages, may also explain the observed decline in VE despite the absence of age-related differences in antibody and OPA titer levels [3]. Similar age-vaccine interactions on clinical outcomes have been observed in conjugate and polysaccharide meningococcal vaccines and hepatitis B vaccine [12, 13]. Two of the most prevalent PCV13 serotypes (3 and 7F) were less common in the highest age group and had a higher overall VE. Yet VE also tended to decrease with age for these serotypes. Due to the low numbers, it is not possible to determine whether the observed higher VE against these serotypes is causing the age effect, or rather that it is the result of it.

Several aspects of the study need to be considered. Measurement of the outcome events relied on identification of CAP and IPD episodes requiring hospitalizations and on timely collection of blood cultures and urine samples in any of the 58 participating hospitals. Therefore, episodes will have been missed. Because this is a randomized trial and subjects and investigators were blinded for vaccination status, missing outcome events can be considered as independent of vaccination status. However, identification of episodes and collection of urine samples and blood cultures might be associated with age, potentially inducing bias. Indeed, serotype specific UAD testing was performed less frequently in older age groups. Age effects were accounted for by adjusting for age at baseline.

Naturally, the trial was not designed to study vaccine-age interaction, and the study contained 2941 subjects over 85 years of age, with only 12 endpoints in this subgroup. Although the VE point estimate suggests no efficacy of PCV13 in this age group, a relevant effect could not be excluded. Also, there was a poor model fit in this age group in 4 of the models. The estimate of decreasing VE should therefore be interpreted as an averaged decrease and should not be used for per age prediction of the VE. Nevertheless, overall there was a statistically significant decline in VE by increasing age.

In conclusion, in immunocompetent subjects aged ≥65 years, VE of PCV13 in the prevention of clinical outcomes decreased with increasing age.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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