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Original Article

A post hoc assessment of duration of protection in CAPiTA (Community Acquired Pneumonia immunization Trial in Adults)

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ABSTRACT

Background: The Community Acquired Pneumonia immunization Trial in Adults (CAPiTA) was conducted to evaluate 13-valent pneumococcal conjugate vaccine (PCV13) for the prevention of vaccine-type community-acquired pneumonia (VT-CAP) and vaccine-type invasive pneumococcal disease (VT-IPD) in adults aged ⩾65 years. Plotting the cumulative number of episodes against time from vaccination demonstrated that efficacy was evident soon after vaccination and persisted throughout the duration of the study. This post hoc analysis was performed to quantify the persistence of vaccine efficacy (VE) of PCV13.

Methods: This was a parallel-group, randomized, placebo-controlled, double-blind trial. Subjects were enrolled between September 15, 2008 and January 30, 2010 at 101 sites in the Netherlands and randomized 1:1 to receive a single dose of PCV13 or placebo. The observed accumulation of episodes for VT-CAP, nonbacteremic/noninvasive VT-CAP (NB/NI-VT-CAP), and VT-IPD over the course of the study after vaccination was assessed. Post hoc time-to-event analyses of primary and secondary endpoints were performed. VE behavior over time was derived and effects of treatment, time, and time by treatment interactions were estimated.

Results: A total of 84,496 individuals were enrolled (PCV13, $n = 42{,}240$; placebo, $n = 42{,}256$). Cases of VT-CAP, NB/NI-VT-CAP, and VT-IPD were greater among placebo recipients compared with PCV13 recipients throughout the postvaccination observation period with a periodic rise in cases in the placebo group that was consistent with varied exposure and ensuing disease over time. There was a significant difference in disease-free survival among PCV13 recipients compared with placebo recipients for VT-CAP (log-rank test $P = 0.0005$), NB/NI VT-CAP ($P = 0.0051$), and VT-IPD ($P = 0.0004$). VE ranged from 42.9% to 50.0% for VT-CAP, 36.2% to 48.5% for NB/NI-VT-CAP, and 66.7% to 75.0% for VT-IPD.

Conclusions: The results of this post hoc analysis of the persistence of PCV13 VE in adults ⩾65 years, indicate that PCV13 was protective over the 5-year duration of the study, with no waning of efficacy observed.

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1. Introduction

The incidence of community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae* is higher in older adults [1–6], and the morbidity and mortality associated with pneumococcal disease increases with advanced age [3,5,7–9]. The natural diminution in the local/innate and adaptive immune systems or responses observed in

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older adults may render them more susceptible to infection with *S. pneumoniae* [10]. In addition, CAP exerts a substantial economic burden on national healthcare systems that has been documented in Europe [11] and in the United States [12]. Thus, a vaccine that reduces the prevalence of CAP and IPD in this population could have public health benefits.

The Community Acquired Pneumonia immunization Trial in Adults (CAPiTA; ClinicalTrials.gov identifier NCT00744263) was conducted to evaluate 13-valent pneumococcal conjugate vaccine (PCV13) for the prevention of vaccine-type community-acquired pneumonia (VT-CAP) and vaccine-type invasive pneumococcal disease (VT-IPD) in adults ⩾65 years of age [13]. This was an event-driven study that targeted at least 130 first episodes of VT-CAP in subjects who were randomized 1:1 to receive 13-valent pneumococcal conjugate vaccine (PCV13) or placebo. The per-protocol analysis vaccine efficacy (VE) results (with 95.2% confidence intervals [CIs]) were 46% (22–62%) for VT-CAP, 45% (14–65%) for non-bacteremic/noninvasive VT-CAP (NB/NI-VT-CAP), and 75% (95% CI: 41–91%) for first episodes of vaccine-type IPD (VT-IPD).

Although efficacy was demonstrated for all endpoints in both the per-protocol and modified intent-to-treat (mITT) populations, the long-term persistence of PCV13 efficacy in older adults is not currently known. Plotting the cumulative number of episodes against time after vaccination demonstrated that efficacy was evident soon after vaccination and persisted throughout the duration of the study [13]. Determination of VE over a longer period of time in adults ⩾65 years is of importance for guiding recommendations for revaccination. This post hoc analysis of data from the Community Acquired Pneumonia immunization Trial in Adults (CAPiTA) was performed to more precisely quantify the persistence of VE of PCV13 in adults ⩾65 years of age.

2. Methods

2.1. Study design

The Community Acquired Pneumonia immunization Trial in Adults (CAPiTA) was a parallel-group, randomized, placebo-controlled, double-blind trial. Subjects were enrolled between September 15, 2008 and January 30, 2010 at 101 sites in the Netherlands. Cases of suspected pneumonia and IPD were acquired between September 15, 2008 and August 28, 2013 at 59 sentinel centers. Study surveillance ended after identification of at least 130 per-protocol, first episodes of VT CAP. The complete study design and procedures were previously published [13,14].

2.2. Study participants

Eligible subjects were adults ⩾65 years of age with no previous pneumococcal vaccination and who were not immunocompromised. The study was conducted in compliance with Good Clinical Practice guidelines and was approved by the Central Committee on Research Involving Human Subjects and by the Ministry of Health, Welfare and Sport in the Netherlands. Written informed consent was obtained from all subjects before the performance of any study-related procedures. The per-protocol population included participants who had an episode of CAP or IPD with an onset of symptoms at least 14 days after vaccination, were eligible for the study, received a vaccination, were still immunocompetent at the time of the CAP or IPD episode, and had no other major protocol violations.

2.3. Study procedures

Subjects were randomized 1:1 to receive a single dose of PCV13 or placebo. Cases of pneumonia were diagnosed using standard procedures including X-rays and laboratory analysis (BinaxNOW® and serotype-specific urinary antigen detection [UAD]). Samples from sterile and non-sterile sites were assessed by laboratory culture and positive samples were serotyped. CAP was confirmed radiologically together with 2 predefined clinical criteria as described by Bonten and colleagues [13]; IPD was defined as the presence of *S. pneumoniae* in a normally sterile site using laboratory culture techniques.

2.4. Statistical methods

An interim analysis was planned at the time of at least 65 per-protocol first episodes of confirmed VT-CAP. The study was to be stopped at the time of the interim analysis if harm was demonstrated (i.e., an adjusted upper confidence bound of VE <0), or if clinically significant VE was demonstrated for first confirmed VT CAP (i.e., an adjusted lower confidence bound >20%) and for first confirmed NB/NI VT CAP (i.e., an adjusted lower confidence interval >0). The observed accumulation of episodes for VT-CAP, NB/NI-VT-CAP, and VT-IPD over the course of the study following vaccination was plotted. Post hoc Kaplan–Meier time-to-event analyses of the primary and secondary endpoints were performed. Behavior of VE over time was also derived, and Poisson regression was used to estimate the effects of treatment, time, and time by treatment interaction. Analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC). Graphical representations of first episodes of vaccine-type pneumococcal disease over calendar time and cumulative episodes of vaccine-type pneumococcal disease over time since vaccination were produced using S-Plus 8.2 (Tibco Spotfire, Boston, MA).

3. Results

3.1. Study population

A total of 84,496 individuals were enrolled in the study (PCV13, $n = 42{,}240$; placebo, $n = 42{,}256$) [13]. Baseline characteristics were similar between the two vaccine groups and were described previously [13]. Subjects were followed for a mean of approximately 4 years.

3.2. Interim analysis

At the interim analysis, which was conducted for the 74 episodes for which data were available, the VE for the first episode of per-protocol confirmed VT-CAP was 49.0% (99.48% CI: −2.4%, 75.9%; $P = 0.007$), which did not meet the requirements for stopping the study (a lower confidence interval exceeding 20%) and CAP and IPD data acquisition continued until at least 130 per-protocol, first episodes of VT-CAP were observed.

3.3. First episodes of vaccine-type pneumococcal disease over time

The number of cases of VT-CAP, NB/NI-VT-CAP, and VT-IPD were higher among subjects who received placebo compared with the number of cases among subjects who received PCV13 throughout the postvaccination observation period (Fig. 1). There was a periodic rise in the number of cases in the placebo group that was consistent with exposure to pneumococcus and ensuing disease over time with most cases of pneumococcal disease occurring between September and April. However, these data do not take into consideration the time of vaccination (September 2008–January 2010).

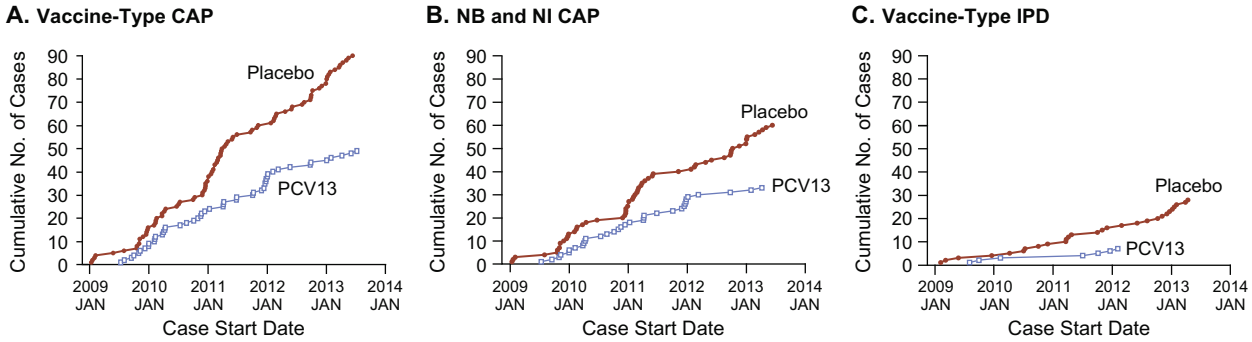

Fig. 1. First episodes of vaccine-type pneumococcal disease over calendar time. NB/NI-VT-CAP = nonbacteremic/noninvasive-vaccine-type community-acquired pneumonia; PCV13 = 13-valent pneumococcal conjugate vaccine; VT-CAP = vaccine-type community-acquired pneumonia; VT-IPD = vaccine-type invasive pneumococcal disease.

3.4. Cumulative episodes of vaccine-type pneumococcal disease over time

The total number of pneumococcal disease episodes increased from 34 to 139, from 25 to 93, and from 8 to 35 for VT-CAP, NB/NI-VT-CAP, and VT-IPD from 1 to ⩽5 years since vaccination (Table 1). Accounting for time since vaccination, cumulative episodes of VT-CAP, NB/NI-VT-CAP, and VT-IPD were higher among subjects who received placebo compared with subjects who received PCV13 throughout the postvaccination observation period (Fig. 2). The number of disease episodes among placebo recipients increased to a greater extent than among PCV13 recipients shortly after vaccination and remained greater throughout the postvaccination period.

3.5. Estimated disease-free survival

The estimated disease-free survival function is the estimate of the distribution in time in which subjects in the trial were free from disease since vaccination. By approximately day 700, the distributions were separated as indicated by the lack of overlap of 95% confidence intervals between the PCV13 and placebo groups (see Supplementary figures in Bonten et al. [13]). At the end of the study, 99.9% of subjects in the PCV13 group remained disease-free, whereas <99.7% of subjects in the placebo group remained disease-free. This analysis was performed to account for the effect of censoring, with the Kaplan–Meier analyses including the censored observations as well as the uncensored observations to evaluate any shifts in subjects who received PCV13 relative to those who received placebo. Potential sources of censoring in this study included death, confirmed loss to follow up, withdrawal, and the timing of the enrollment periods. There was a significant difference in time to the first episode among PCV13 recipients compared with placebo recipients for VT-CAP (log-rank test $P = 0.0005$), NB/NI VT-CAP ($P = 0.0051$), and VT-IPD ($P = 0.0004$) confirming that the interpretation remains consistent when censoring of the data is accounted for in the analysis [13].

3.6. Cumulative vaccine efficacy estimates

Over the five years of the study, VE ranged from 42.9% to 50.0% for VT-CAP, 36.2–48.5% for NB/NI-VT-CAP, and 66.7–75.0% for VT-IPD (Table 1). Poisson regression showed statistically significant treatment effects for VT-CAP ($P = 0.008$), NB/NI-VT-CAP ($P = 0.0048$), and VT-IPD ($P = 0.0002$), and years since vaccination effects ($P < 0.05$ for all endpoints except VT-IPD, $P = 0.2339$) consistent with vaccine efficacy estimates and natural variation in observed disease incidence over time. However, time by treatment interaction was not significant (VT-CAP, $P = 0.8565$; NB/NI-VT-CAP, $P = 0.1541$; VT-IPD, $P = 0.6352$) showing that no significant evidence of vaccine waning was observed.

Table 1
Cumulative vaccine efficacy estimates in the per-protocol population.

	Years since vaccination (total observed episodes)	Vaccine efficacy (%)	*P*-value
VT-CAP	1 (34)	45.5	0.1214
	⩽2 (69)	50.0	0.0076
	⩽3 (110)	42.9	0.0054
	⩽4 (131)	44.1	0.0016
	⩽5 (139)	45.6	0.0006
NB/NI-VT-CAP	1 (25)	43.8	0.2295
	⩽2 (50)	48.9	0.0328
	⩽3 (77)	36.2	0.0675
	⩽4 (88)	40.0	0.0246
	⩽5 (93)	45.0	0.0067
VT-IPD	1 (8)	66.7	0.2890
	⩽2 (15)	75.0	0.0352
	⩽3 (24)	66.7	0.0227
	⩽4 (33)	73.1	0.0013
	⩽5 (35)	75.0	0.0005

NB/NI-VT-CAP = nonbacteremic/noninvasive-vaccine-type community-acquired pneumonia; VT-CAP = vaccine-type community-acquired pneumonia; VT-IPD = vaccine-type invasive pneumococcal disease.

4. Discussion

This post hoc analysis of PCV13 VE in the Community Acquired Pneumonia immunization Trial in Adults (CAPiTA) confirmed that cases of VT-CAP, NB/NI-VT-CAP, and VT-IPD over the postvaccination study period were greater in subjects who received placebo compared with subjects who received PCV13. The benefits of PCV13 vaccination in older adults was further demonstrated by the significant difference in disease-free survival between PCV13 and placebo recipients for the outcomes of VT-CAP, NB/NI VT-CAP, and VT-IPD. As the primary and secondary outcomes of the study described the prevention of first episodes of CAP (and IPD), the data presented in this post hoc analysis provide a fuller picture of the effectiveness of PCV13.

The prevention of VT-CAP, NB/NI-VT-CAP, and VT-IPD in subjects was observed shortly after PCV13 vaccination. Interim analysis (at approximately 2 years) did not meet the extremely stringent requirements for stopping the study, and resulted in the study continuing until at least 130 per-protocol, first episodes of VT-CAP were observed. This allowed for this post hoc study of the persistence of protection and demonstration of persistence of VE throughout the remainder of the study. A waning of VE would be observed if the frequency of pneumococcal disease episodes for PCV13 recipients increased to the same extent as those that were

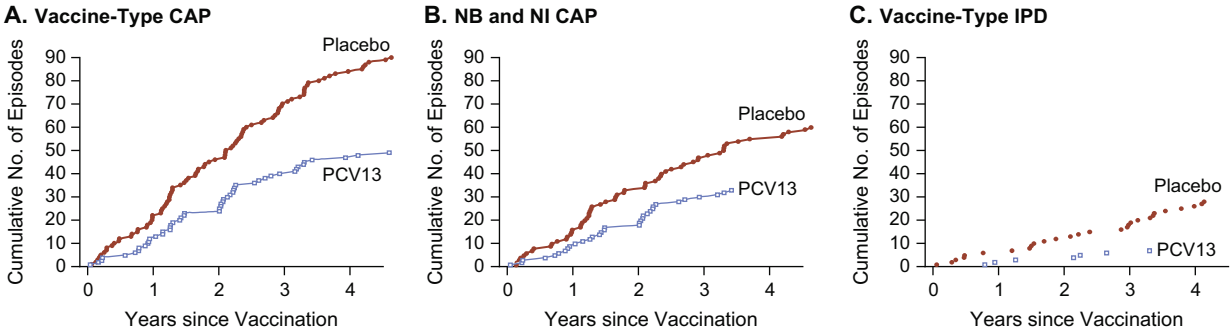

Fig. 2. Cumulative episodes of vaccine-type pneumococcal disease over time since vaccination. NB/NI-VT-CAP = nonbacteremic/noninvasive-vaccine-type community-acquired pneumonia; PCV13 = 13-valent pneumococcal conjugate vaccine; VT-CAP = vaccine-type community-acquired pneumonia; VT-IPD = vaccine-type invasive pneumococcal disease. From *N Engl J Med*, Bonten et al., Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults, 372:1114–1125. Copyright© Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

observed among placebo recipients, at which time the curves would become parallel, or if the rate of episodes for PCV13 recipients increased so that the PCV13 curve approached that of the placebo curve. However, waning of vaccine-type protection was not observed during the mean follow-up time of approximately 4 years. The pattern of VE observed over time is as expected given the natural behavior of test statistics (statistical significance is not expected until an appropriate minimum number of events are observed). At the time of study design, it was anticipated that at least 2 years of follow-up would be required with the expected number of events in the study.

The analysis of the persistence of vaccine efficacy is of particular importance in older adults as some age-related decreases in post-vaccination antibody concentrations have been documented for tetanus and tick-borne encephalitis vaccines [15]. Another post hoc analysis of the CAPiTA study data suggested a lower VE for the combined endpoint of VT-CAP and VT-IPD in elderly subjects [16].

In many countries, the 23-valent polysaccharide vaccine (PPSV23) has been recommended for administration to older adults for the prevention of pneumococcal diseases. Although PPSV23 is considered to be protective against IPD [17] little evidence exists for protection against nonbacteremic pneumonia in older adults [18] and meta analyses do not provide evidence for protection in against all-cause pneumonia in this age group [17,19]. In contrast to the extended vaccine effectiveness of PCV13 demonstrated in this post hoc analysis, the vaccine effectiveness of PPSV23 has been shown to wane over time after vaccination particularly in the oldest adults (46%, 22% and −13% in individuals vaccinated <3 years, 3–5 years, and >5 years previously) [20,21].

Strengths of the study and therefore, for this post-hoc analysis, included the large size and the length of the follow-up time. Limitations included those associated with post hoc analyses. Additional limitations included the restriction of the study to inhabitants of a single country, and the potential overestimation of VE with the use of the highly-sensitive serotype-specific UAD assay [13]. The study used a passive data collection mechanism, and active follow-up of the 84,496 subjects over the course of the 5-year study for competing risks was not performed.

As older adults are at increased risk for contracting CAP and for experiencing more serious morbidity from CAP, the reduction in pneumococcal disease afforded by PCV13 vaccination may provide clinical and economic benefits, depending on the remaining burden of vaccine-type disease [22]. The results of this post hoc analysis of the persistence of PCV13 VE in adults ⩾65 years, indicate that this vaccine was protective over the duration of the study. No clear evidence of waning of VE was observed. This finding may have implications for revaccination strategies in the elderly, and additional immunogenicity data from the Community Acquired Pneumonia immunization Trial in Adults (CAPiTA) will help to further guide future vaccination recommendations.

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Role of the sponsor

The sponsor was involved with study concept and design, analysis and interpretation of the data, and drafting the manuscript.

Conflict of interest statement

MJMB reports receiving consulting fees from Pfizer. SH reports receiving financial support from Pfizer for thesis printing. WD is an employee of inVentiv Health Clinical LLC, a company contracted by Pfizer Inc. SP, CW, MP, WCG, and DAS are employees of Pfizer Inc. MB reports no conflict of interest.

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Contributors: Study concept and design: SP, CW, MP, MB, WCG, DAS, and MJMB; acquisition of data: SP, CW, MP, MB, WCG, DAS, and MJMB; analysis and interpretation of data: SP, CW, WD, MP, MB, WCG, DAS, MJMB; drafting of the manuscript and critical revision of the manuscript for important intellectual content: all authors; statistical analysis: WD and SP. All authors approved the final manuscript for submission. The authors wish to acknowledge the contributions of James Trammel, Dan Creswell, and Brian Tucker of inVentiv Health Clinical for their work in support of this statistical analysis.

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