ORIGINAL ARTICLE

Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults

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ABSTRACT

BACKGROUND

Pneumococcal polysaccharide conjugate vaccines prevent pneumococcal disease in infants, but their efficacy against pneumococcal community-acquired pneumonia in adults 65 years of age or older is unknown.

METHODS

In a randomized, double-blind, placebo-controlled trial involving 84,496 adults 65 years of age or older, we evaluated the efficacy of 13-valent polysaccharide conjugate vaccine (PCV13) in preventing first episodes of vaccine-type strains of pneumococcal community-acquired pneumonia, nonbacteremic and noninvasive pneumococcal community-acquired pneumonia, and invasive pneumococcal disease. Standard laboratory methods and a serotype-specific urinary antigen detection assay were used to identify community-acquired pneumonia and invasive pneumococcal disease.

RESULTS

In the per-protocol analysis of first episodes of infections due to vaccine-type strains, community-acquired pneumonia occurred in 49 persons in the PCV13 group and 90 persons in the placebo group (vaccine efficacy, 45.6%; 95.2% confidence interval [CI], 21.8 to 62.5), nonbacteremic and noninvasive community-acquired pneumonia occurred in 33 persons in the PCV13 group and 60 persons in the placebo group (vaccine efficacy, 45.0%; 95.2% CI, 14.2 to 65.3), and invasive pneumococcal disease occurred in 7 persons in the PCV13 group and 28 persons in the placebo group (vaccine efficacy, 75.0%; 95% CI, 41.4 to 90.8). Efficacy persisted throughout the trial (mean follow-up, 3.97 years). In the modified intention-to-treat analysis, similar efficacy was observed (vaccine efficacy, 37.7%, 41.1%, and 75.8%, respectively), and community-acquired pneumonia occurred in 747 persons in the PCV13 group and 787 persons in placebo group (vaccine efficacy, 5.1%; 95% CI, −5.1 to 14.2). Numbers of serious adverse events and deaths were similar in the two groups, but there were more local reactions in the PCV13 group.

CONCLUSIONS

Among older adults, PCV13 was effective in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic community-acquired pneumonia and vaccine-type invasive pneumococcal disease but not in preventing community-acquired pneumonia from any cause. (Funded by Pfizer; CAPITA ClinicalTrials.gov number NCT00744263.)

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Streptococcus pneumoniae, a major cause of community-acquired pneumonia in the elderly, results in considerable morbidity and mortality.[1-4] Pneumococcal community-acquired pneumonia most commonly presents as nonbacteremic disease.[3] Invasive pneumococcal disease, which involves infection of normally sterile sites, occurs in approximately 25% of cases.[3]

Immunologic protection against pneumococcal disease is mediated through opsonophagocytic antibodies directed against bacterial capsular polysaccharides that define the pneumococcal serotypes and serve as virulence factors.[5] Vaccines composed of purified capsular polysaccharides, which have been available for more than 50 years, are not immunogenic in young children.[6-8]

Although some studies have shown that purified capsular polysaccharides are effective against invasive pneumococcal disease in adults, their efficacy against noninvasive pneumonia is uncertain.[9-14] Pneumococcal polysaccharide conjugate vaccines (in which a bacterial polysaccharide is covalently conjugated to an immunogenic carrier protein) are effective in preventing pneumococcal pneumonia, invasive pneumococcal disease, and otitis media in children[15-20] and pneumococcal infections in adults and children with human immunodeficiency virus (HIV) infection.[17,21] The efficacy of pneumococcal conjugate vaccines for the prevention of vaccine-type invasive and noninvasive community-acquired pneumonia in adults 65 years of age or older has not been determined.

The assessment of efficacy became possible with the development of a serotype-specific urinary antigen detection assay.[22,23] Using this assay, we were able to evaluate a 13-valent pneumococcal conjugate vaccine (PCV13) for the prevention of vaccine-type invasive and noninvasive community-acquired pneumonia in adults 65 years of age or older.

METHODS

STUDY DESIGN AND OVERSIGHT

The Community-Acquired Pneumonia Immunization Trial in Adults (CAPITA) involved a collaboration between the University Medical Center Utrecht (UMCU) and the study sponsor, Wyeth (a Pfizer company). The study design has been published previously.[24] This study was a parallel-group, randomized, placebo-controlled, double-blind trial. Use of a placebo was appropriate because no pneumococcal vaccine is recommended in the Netherlands for routine use in older adults.[25,26] Details of the study methods and statistical analysis plan — including randomization, objectives, definition of end points, stopping criteria, and statistical analyses — are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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. The UMCU and Julius Clinical, an academic research organization affiliated with the UMCU, conducted the study and gathered all the data. The UMCU and the sponsor developed the study protocol, which is available at NEJM.org. The UMCU, Julius Clinical, and the sponsor provided study oversight and managed study logistics. The sponsor performed data management, urinary antigen tests, and the statistical analysis. The first author wrote the initial draft of the manuscript. All the authors participated in writing the final version of the manuscript and vouch for the accuracy and completeness of the reported data.

PARTICIPANTS

The participants, who were 65 years of age or older, were enrolled in the study between September 15, 2008, and January 30, 2010, at 101 temporary community-based sites throughout the Netherlands. A subgroup of participants (the safety subgroup) was enrolled separately but was included in the overall study population. These participants were followed with home visits for 2 years to obtain additional safety data. Key eligibility criteria were no previous pneumococcal vaccination and an absence of protocol-defined immunocompromising conditions (see the exclusion criteria in the Supplementary Appendix). All the participants provided written informed consent.

During the first 2.5 months of study enrollment, trivalent inactivated influenza vaccine was administered concomitantly with the study vaccine or placebo in participants who were not in the safety subgroup; 30.4% of the participants received both vaccines at the vaccination visit.

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Rates of influenza vaccination in the Netherlands among people 65 years of age or older during the course of the study were reported to be 77.2 to 82.5%.[27]

The trial was completed in accordance with the protocol. All data were analyzed according to the vaccine administered. All participants who underwent randomization were vaccinated by investigators who were unaware of the study-vaccine assignments. Randomization was achieved by administration of vaccine from the next available syringe in a tray ordered in accordance with the randomization schedule. The schedule was generated with the use of a randomized block design in which study groups were randomly ordered within each block of 10 participants (i.e., each tray of 10 syringes, with six trays per shipment box). Further details are provided in the Supplementary Appendix. There were no post-randomization exclusions before vaccination.

INVESTIGATIONAL PRODUCTS

Participants were randomly assigned in a 1:1 ratio to receive PCV13 or placebo by intramuscular injection in the right deltoid. PCV13 contains polysaccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to a nontoxic diphtheria toxin cross-reactive material 197 protein. The vaccine contains 2.2 μg of each polysaccharide (except for 4.4 μg of serotype 6B), along with 5.0 mM succinate buffer, 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg of aluminum as aluminum phosphate per 0.5-ml dose.

The placebo contained 5.0 mM succinate buffer, 0.85% sodium chloride, 0.02% polysorbate 80, and 0.125 mg of aluminum as aluminum phosphate per 0.5-ml dose. It was identical in appearance to PCV13.

OBJECTIVES

The primary objective was to show the efficacy of PCV13 in the prevention of a first episode of confirmed vaccine-type community-acquired pneumonia (defined as the presence of ≥2 prespecified clinical criteria, findings on chest radiography consistent with community-acquired pneumonia, and a positive vaccine-type–specific urinary antigen test or isolation of vaccine-type *S. pneumoniae* from blood or another sterile site). The secondary objectives were to show the efficacy of PCV13 in the prevention of a first episode of confirmed nonbacteremic and noninvasive vaccine-type community-acquired pneumonia (i.e., an episode of vaccine-type community-acquired pneumonia for which the result of a blood culture and results of cultures of any other sterile site were negative for *S. pneumoniae*) and vaccine-type invasive pneumococcal disease (i.e., an episode in which the presence of *S. pneumoniae* is detected in a sterile site).

The following prespecified selected exploratory end points are also included in this article: all episodes of confirmed vaccine-type community-acquired pneumonia, a first episode of confirmed pneumococcal community-acquired pneumonia irrespective of serotype, a first episode of confirmed nonbacteremic and noninvasive pneumococcal community-acquired pneumonia irrespective of serotype, a first episode of invasive pneumococcal disease irrespective of serotype, a first episode of community-acquired pneumonia including nonpneumococcal pneumonia, and death. Analyses of all end points were prespecified in the study protocol.

The safety objective was an evaluation of the safety profile of PCV13 as measured by the incidence rates of serious adverse events for 28 days after vaccination among all participants and for 6 months after vaccination among participants in the safety subgroup. Additional safety objectives were evaluations of the frequency of local reactions, systemic events, and adverse events among participants in the safety subgroup and an assessment of the number of deaths from any cause among all participants.

PROCEDURES

Surveillance for suspected pneumonia and invasive pneumococcal disease was conducted from September 15, 2008, through August 28, 2013; the study surveillance period ended after a prespecified number of first episodes of vaccine-type community-acquired pneumonia had been identified. Surveillance was conducted at 59 sentinel centers located in the regions in which participants were enrolled.

A diagnostic routine reflecting standard of practice was used for all patients who presented to sentinel centers with symptoms of lower respiratory tract infection. If pneumonia was suspected, the staff at the sentinel center determined whether the patient was a participant in the trial by searching a participant database. If

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the patient was a study participant, an aliquot of urine was obtained for the serotype-specific urinary antigen detection, and BinaxNOW assays were performed by the sponsor (Table S7 in the Supplementary Appendix). Results of chest radiography were read centrally to provide consistent interpretation. The radiologists were unaware of the participants' vaccination status. Surveillance for invasive pneumococcal disease was conducted by regular review of laboratory culture results.

Surveillance for death, loss to follow-up, and receipt of any nonstudy pneumococcal vaccine was conducted in the same time period by means of a regular review of records from general practitioners. Physicians reviewed available documents to determine the cause of each death and to assess whether the death was due to community-acquired pneumonia or invasive pneumococcal disease.

POPULATIONS FOR ANALYSIS

The modified intention-to-treat efficacy population included participants who had an episode of community-acquired pneumonia or invasive pneumococcal disease with the onset of symptoms at least 14 days after vaccination. The modified intention-to-treat population was further categorized into two subgroups according to the participant's immune status at the time of presentation with community-acquired pneumonia or invasive pneumococcal disease: one comprising immunodeficient or immunosuppressed persons, and the other comprising immunocompetent persons. Participants who became immunodeficient or immunosuppressed after enrollment were those who met the criteria for immunodeficiency or immunosuppression specified for study eligibility (see the Supplementary Appendix) or were assessed by physicians who were experienced in clinical immunology and could determine whether the patients were immunosuppressed to the degree represented by the list of conditions in the study eligibility criteria.

The per-protocol population included participants who met the criteria for the modified intention-to-treat population, were eligible for the study, received a vaccination, and had no other major protocol violations. Episodes of community-acquired pneumonia or invasive pneumococcal disease were excluded from the per-protocol analyses if the onset of symptoms occurred after receipt of any nonstudy pneumococcal vaccine or after any of the following diagnoses: immunodeficiency or immunosuppression (as defined in the eligibility criteria or by physician assessment that the participant was immunosuppressed), bronchial obstruction due to primary lung cancer, another cancer that was metastatic to the lungs, postobstructive pneumonia (not including chronic obstructive pulmonary disease), the acquired immunodeficiency syndrome, or known or suspected *Pneumocystis jiroveci* pneumonia or active tuberculosis.

SAFETY ASSESSMENT

Participants in the safety subgroup used electronic diaries to record any local reactions, systemic events, or the receipt of medications for fever or pain for 7 days after vaccination. Study nurses conducted home visits at which they collected information about other adverse events and newly diagnosed chronic medical conditions (e.g., asthma, emphysema, hypertension, and cardiac failure) in these participants. Surveillance for serious adverse events and deaths in all participants was conducted by regular review of records from general practitioners and of information reported by participants, relatives, and general practitioners.

All participants who received the study vaccine were included in the safety analysis unless safety data were lacking. Deaths, serious adverse events, and adverse events were categorized according to the *Medical Dictionary for Regulatory Activities*, version 16.1. All safety data were summarized according to study group.

STATISTICAL ANALYSIS

The per-protocol population was the primary population for the analysis of the primary and secondary end points and most exploratory end points. The analysis of all episodes of community-acquired pneumonia (which included nonpneumococcal pneumonia) was based on the modified intention-to-treat population.

A total of 130 primary end-point events were required to have sufficient statistical power for the final analysis; this number was determined with the use of the conditional binomial approach described by Breslow and Day,[28] taking the specificity and sensitivity of the serotype-specific urinary antigen detection assay into account. The interim analysis by the data and safety monitoring committee approximately midway through the study did not result in discontinuation of the

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study. The efficacy estimates and two-sided confidence intervals were derived with the use of the Clopper–Pearson method[29] with alpha adjustment for interim analysis. Study personnel remained unaware of the study-group assignments until the database was finalized.

RESULTS

STUDY PARTICIPANTS

Of the 84,496 persons who were enrolled in the study, 42,240 received PCV13 and 42,256 received placebo (Fig. 1). The mean follow-up time was 3.97 years in each group. The rates of discontinuation over the course of the study were 12.4% in the PCV13 group and 12.6% in the placebo group; discontinuations were due primarily to deaths (7.1% in each group) and loss to follow-up (4.8% in the PCV13 group and 5.1% in the placebo group). Baseline characteristics were balanced between the two groups (Table 1).

EFFICACY

There were 3232 visits (by 1552 participants in the PCV13 group and 1680 in the placebo group) to sentinel centers for suspected pneumonia or invasive pneumococcal disease. A total of 2842 of these participants (88%) had received the influenza vaccine in the previous year; the proportion was balanced between study groups (88% in each group). Results of serotype-specific urinary antigen detection tests were available for 95% of the visits, and results from blood cultures or cultures from other sterile sites were available for 79% of the visits. These percentages were similar in the two study groups. A total of 46 participants (20 in the PCV13 group and 26 in the placebo group) were excluded from the analysis because of prior receipt of pneumococcal vaccination.

We found that the vaccine had significant efficacy in the per-protocol population against first episodes of confirmed vaccine-type community-acquired pneumonia, confirmed nonbacteremic and noninvasive vaccine-type community-acquired pneumonia, and vaccine-type invasive pneumococcal disease (Table 2). A first episode of confirmed vaccine-type community-acquired pneumonia was documented in 49 participants in the PCV13 group and 90 participants in the placebo group (vaccine efficacy, 45.6%; 95.2% confidence interval [CI], 21.8 to 62.5; P<0.001). A first episode of confirmed nonbacteremic and noninvasive vaccine-type community-acquired pneumonia was documented in 33 participants in the PCV13 group and 60 participants in the placebo group (vaccine efficacy, 45.0%; 95.2% CI, 14.2 to 65.3; P=0.007), and a first episode of vaccine-type invasive pneumococcal disease was documented in 7 participants in the PCV13 group and 28 participants in the placebo group (vaccine efficacy, 75.0%; 95% CI, 41.4 to 90.8; P<0.001).

We also found that the vaccine had significant efficacy with respect to the same three end points in the modified intention-to-treat population (Table 2). Tables S4, S5, and S6 in the Supplementary Appendix summarize the vaccine efficacy for these three end points in subgroups defined according to immune status. The lower vaccine efficacy with respect to confirmed vaccine-type pneumococcal community-acquired pneumonia that was observed in the modified intention-to-treat population, as compared with the vaccine efficacy in the per-protocol population, may reflect the distribution of episodes between the two study groups in the immunodeficient or immunosuppressed subgroup of participants, in whom immunocompromising conditions (such as hematologic or generalized cancers) developed or who began to receive active immunosuppressive therapy (Table S4 in the Supplementary Appendix).

For all first and subsequent episodes of confirmed vaccine-type community-acquired pneumonia, the vaccine also had significant efficacy in both the per-protocol and modified intention-to-treat populations (Table 2). Vaccine efficacy against a first episode of confirmed pneumococcal community-acquired pneumonia and against a first episode of invasive pneumococcal disease, both of which included non–vaccine-type or undetermined serotypes, was also observed. The vaccine did not have significant efficacy against a first episode of confirmed nonbacteremic and noninvasive pneumococcal community-acquired pneumonia when non–vaccine-type serotypes were included (P=0.11 in the per-protocol population) or against a first episode of all-cause community-acquired pneumonia, which included nonpneumococcal as well as pneumococcal pneumonia (vaccine efficacy, 5.1%; 95% CI, −5.1 to 14.2).

The vaccine was not shown to have significant efficacy for the prevention of death from

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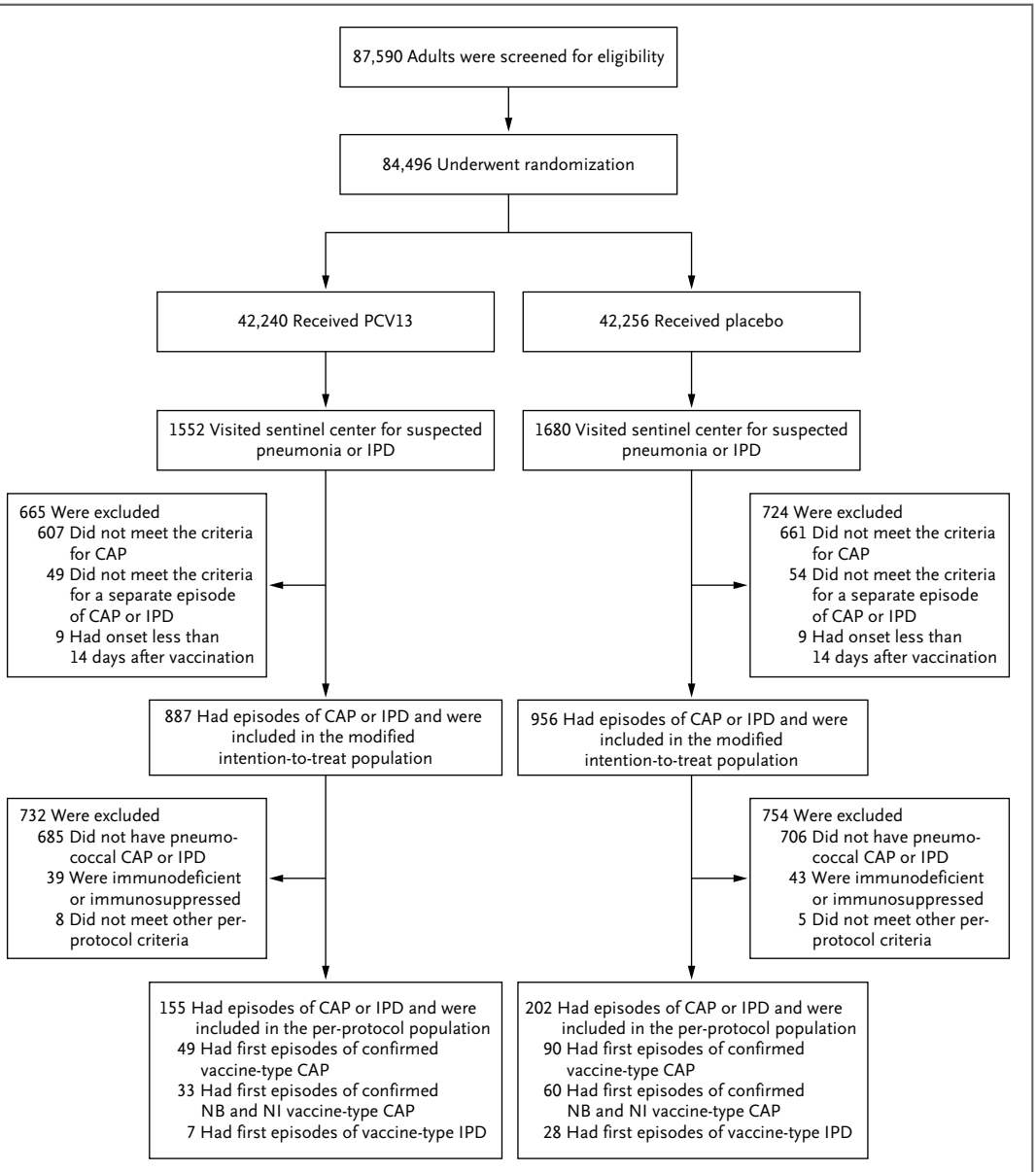

Figure 1. Enrollment and Outcomes in the Per-Protocol Population.

CAP denotes community-acquired pneumonia, IPD invasive pneumococcal disease, NB and NI nonbacteremic and noninvasive, and PCV13 13-valent pneumococcal conjugate vaccine.

any cause. The number of deaths associated with pneumococcal disease during this study was too small to permit a meaningful analysis of the effect of the vaccine (Table S8 in the Supplementary Appendix).

Analyses of the primary and secondary end points according to serotype are summarized in Tables S10, S11, and S12 in the Supplementary Appendix. In addition, the results of the analysis of vaccine efficacy according to age against first episodes of vaccine-type community-acquired pneumonia are shown in Table S3 in the Supplementary Appendix.

Post hoc analyses of the primary and secondary end points in which the cumulative number of episodes were plotted against the time from vaccination provided evidence of efficacy beginning shortly after vaccination. They also showed

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Table 1. Baseline Characteristics of the Participants.*

Characteristic	PCV13 Group (N=42,237)†	Placebo Group (N=42,255)†	All Participants (N=84,492)†
Sex — no. (%)			
Male	23,447 (55.5)	23,801 (56.3)	47,248 (55.9)
Female	18,790 (44.5)	18,454 (43.7)	37,244 (44.1)
Race — no. (%)‡			
White	41,600 (98.5)	41,614 (98.5)	83,214 (98.5)
Black	146 (0.3)	140 (0.3)	286 (0.3)
Asian	277 (0.7)	292 (0.7)	569 (0.7)
Other	205 (0.5)	199 (0.5)	404 (0.5)
Unknown	9 (<0.1)	10 (<0.1)	19 (<0.1)
Age at vaccination — yr			
Mean	72.8±5.7	72.8±5.6	72.8±5.7
Median (range)§	71.6 (61.9–101.1)	71.5 (63.3–99.5)	71.6 (61.9–101.1)
Age group — no. (%)			
<75 yr	29,006 (68.7)	29,064 (68.8)	58,070 (68.7)
≥75 and <85 yr	11,727 (27.8)	11,753 (27.8)	23,480 (27.8)
≥85 yr	1504 (3.6)	1438 (3.4)	2942 (3.5)

* Plus–minus values are means ±SD. Additional characteristics are listed in Table S2 in the Supplementary Appendix. PCV13 denotes 13-valent pneumococcal conjugate vaccine.
† The numbers of participants who received the study vaccine and for whom any safety data were available are shown. Four participants (three in the PCV13 group and one in the placebo group) were excluded because no safety data were available.
‡ Race was self-reported.
§ A total of 18 participants who were enrolled in the PCV13 group and 16 who were enrolled in the placebo group were younger than 65 years of age.

the persistence of efficacy throughout the duration of the trial (mean follow-up, approximately 4 years) without evidence of waning (Fig. 2).

SAFETY

The frequencies of prespecified local reactions and systemic events (Tables S13 and S14, respectively, in the Supplementary Appendix) reported by participants in the safety subgroup were higher in the PCV13 group than in the placebo group. Most local reactions and systemic events were mild or moderate in severity.

There was no significant difference between the two groups in the frequencies of newly diagnosed chronic medical conditions, serious adverse events, or deaths (Table 3). The significant difference in the percentage of participants who reported an adverse event reflects differences between the groups with respect to the prevalence of injection-site reactions and of muscular pain. No vaccine-related serious adverse events were reported.

DISCUSSION

In this study, we found that PCV13 had significant efficacy for the prevention of vaccine-type community-acquired pneumonia and vaccine-type invasive pneumococcal disease among adults 65 years of age or older, and the efficacy persisted for at least 4 years. In the per-protocol population, vaccine efficacy was 46% for the prevention of a first episode of vaccine-type community-acquired pneumonia, 45% for the prevention of nonbacteremic and noninvasive vaccine-type community-acquired pneumonia, and 75% for the prevention of vaccine-type invasive pneumococcal disease.

PCV13 had significant efficacy with respect to all three end points in the modified intention-to-treat population but not with respect to community-acquired pneumonia from any cause. Given that approximately 13% of the first episodes of community-acquired pneumonia observed in the placebo group were episodes of vaccine-type

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Table 2. Vaccine Efficacy.*

End Point and Analysis†	Episodes‡	PCV13 (N=42,240)	Placebo (N=42,256)	Percent Vaccine Efficacy (CI)§	P Value¶
		number			
First episode					
Infection with vaccine-type strain					
Confirmed community-acquired pneumonia					
Per-protocol analysis	139	49	90	45.6 (21.8 to 62.5)	<0.001
Modified intention-to-treat analysis	172	66	106	37.7 (14.3 to 55.1)	0.003
Confirmed nonbacteremic and noninvasive community-acquired pneumonia					
Per-protocol analysis	93	33	60	45.0 (14.2 to 65.3)	0.007
Modified intention-to-treat analysis	116	43	73	41.1 (12.7 to 60.7)	0.007
Invasive pneumococcal disease					
Per-protocol analysis	35	7	28	75.0 (41.4 to 90.8)	<0.001
Modified intention-to-treat analysis	41	8	33	75.8 (46.5 to 90.3)	<0.001
Infection with any pneumococcal strain					
Confirmed pneumococcal community-acquired pneumonia					
Per-protocol analysis	244	100	144	30.6 (9.8 to 46.7)	0.008
Modified intention-to-treat analysis	309	135	174	22.4 (2.3 to 38.5)	0.05
Confirmed nonbacteremic and noninvasive pneumococcal community-acquired pneumonia					
Per-protocol analysis	153	66	87	24.1 (–5.7 to 45.8)	0.11
Modified intention-to-treat analysis	199	90	109	17.4 (–10.2 to 38.2)	0.25
Invasive pneumococcal disease					
Per-protocol analysis	83	27	56	51.8 (22.4 to 70.7)	0.004
Modified intention-to-treat analysis	100	34	66	48.5 (20.9 to 67.0)	0.006
Community-acquired pneumonia					
Modified intention-to-treat analysis	1534	747	787	5.1 (–5.1 to 14.2)	0.32
All episodes of confirmed vaccine-type community-acquired pneumonia					
Per-protocol analysis	145	53	92	42.4 (18.4 to 59.7)	0.004
Modified intention-to-treat analysis	182	70	112	37.5 (15.0 to 54.3)	0.006
Death‖					
From confirmed vaccine-type pneumococcal community-acquired pneumonia or vaccine-type invasive pneumococcal disease	4	2	2	0 (–1279.6 to 92.8)	>0.999
From confirmed pneumococcal community-acquired pneumonia or invasive pneumococcal disease	13	6	7	14.3 (–197.9 to 76.2)	>0.999

* The numbers of participants who received the vaccine in each study group are shown. CI denotes confidence interval.

† The modified intention-to-treat population included participants who had an episode of community-acquired pneumonia or invasive pneumococcal disease, with the onset of symptoms at least 14 days after administration of either PCV13 or placebo. Episodes of community-acquired pneumonia or invasive pneumococcal disease were excluded from per-protocol analyses if the onset of symptoms occurred after the participant received any nonstudy pneumococcal vaccine or after the participant received any of the following diagnoses: immunodeficiency or immunosuppression, bronchial obstruction due to primary lung cancer, another cancer with metastasis to the lungs, postobstructive pneumonia (not including chronic obstructive pulmonary disease), the acquired immunodeficiency syndrome, or known or suspected *Pneumocystis jiroveci* pneumonia or active tuberculosis.

‡ Some participants may have had more than one episode.

§ The definition of vaccine efficacy is provided in the Supplementary Appendix. Confidence intervals were derived with the use of the Clopper–Pearson method. The confidence intervals for the end points of confirmed vaccine-type community-acquired pneumonia and confirmed nonbacteremic and noninvasive vaccine-type community-acquired pneumonia were adjusted to 95.2% to account for the assessment of these two end points at the interim and final analyses; 95% confidence intervals are shown for the other end points.

¶ P values for exploratory end points were adjusted for multiple comparisons with the use of the Benjamini–Hochberg false-discovery-rate procedure within each population group.

‖ The number of deaths shown are those that were determined by the mortality assessment committee to be due to community-acquired pneumonia or invasive pneumococcal disease and for which there was an episode detected by the sentinel system with a date of resolution of symptoms of the episode within 7 days before death. These deaths were related to episodes of community-acquired pneumonia and invasive pneumococcal disease in participants who were members of the per-protocol case-level population (i.e., participants with episodes that met all of the criteria for community-acquired pneumonia).

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Table 3. Safety Outcomes.*

Event	Safety Subgroup		P Value†	All Participants		P Value†
	PCV13 (N=1006)	Placebo (N=1005)		PCV13 (N=42,237)	Placebo (N=42,255)	
	no. (%)			*no. (%)*		
Adverse event within 1 mo after vaccination	188 (18.7)	144 (14.3)	0.01			
Chronic medical condition diagnosed 1–6 mo after vaccination‡	17 (1.7)	12 (1.2)	0.46			
Serious adverse event						
Within 6 mo after vaccination	70 (7.0)	60 (6.0)	0.41			
Within 1 mo after vaccination				327 (0.8)	314 (0.7)	0.61
Death				3006 (7.1)	3005 (7.1)	0.98

* The numbers of participants who received study vaccine and for whom any safety data were available are shown. Four participants (three in the PCV13 group and one in the placebo group) were excluded because they had no safety data. Listed are events that occurred at least once in any participant.

† A two-sided Fisher's exact test was used to calculate the P value for the difference between percentages of participants who reported an event in each of the study groups.

‡ Newly diagnosed chronic medical conditions (including autoimmune or neuroinflammatory disease) were identified in subgroup participants by site staff members who conducted home visits; chronic medical conditions included conditions such as asthma, emphysema, hypertension, and cardiac failure.

pneumococcal community-acquired pneumonia, the nonsignificant 5.1% vaccine efficacy observed against a first episode of community-acquired pneumonia from any cause was consistent with the observed 46% reduction in vaccine-type pneumococcal community-acquired pneumonia.

This trial also did not identify any safety concerns associated with the use of PCV13 in more than 42,000 patients who were vaccinated. These findings are consistent with observations from previous studies of PCV13 vaccination in adults.[30-34]

Post hoc analyses provided evidence of efficacy beginning shortly after vaccination. This efficacy was sustained throughout the duration of the trial (mean follow-up, approximately 4 years) without evidence of waning. The immunologic basis for this persistent efficacy against both vaccine-type community-acquired pneumonia and vaccine-type invasive pneumococcal disease requires further study but may reflect both the quantity and quality of the elicited functional antibacterial immune response, as well as establishment of immune memory mediated by PCV13.[30-32,35]

Our study showed the efficacy of PCV13 for the prevention of vaccine-type nonbacteremic and noninvasive pneumococcal community-acquired pneumonia in older adults. This evaluation was made possible by the serotype-specific urinary antigen detection assay, which detects vaccine-type *S. pneumoniae* polysaccharides in the urine of persons with suspected pneumonia. Previously, diagnosis was dependent on assays that relied on isolation of the organism (culture) or that had insufficient sensitivity and specificity (such as BinaxNOW).[36] Most earlier randomized studies of vaccination with either free polysaccharide vaccines in older adults[37] or pneumococcal conjugate vaccines in HIV-infected adults[21] were underpowered to show efficacy against vaccine-type community-acquired pneumonia; results of these studies and other observational studies have been inconsistent.[11-14]

Our study had several limitations. The study was performed in a single country in a homogeneous population of participants among whom there was a low incidence of pneumococcal disease.[24] The degree of vaccine efficacy observed may vary in other populations depending on the epidemiologic characteristics of the vaccine-associated serotypes and the susceptibility of the population to pneumococcal infections and disease. The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in the Netherlands in 2006 for use in all newborns and was replaced by the 10-valent pneumococcal conjugate vaccine (PCV10) in March 2011. In 2008, a total of 68.4%

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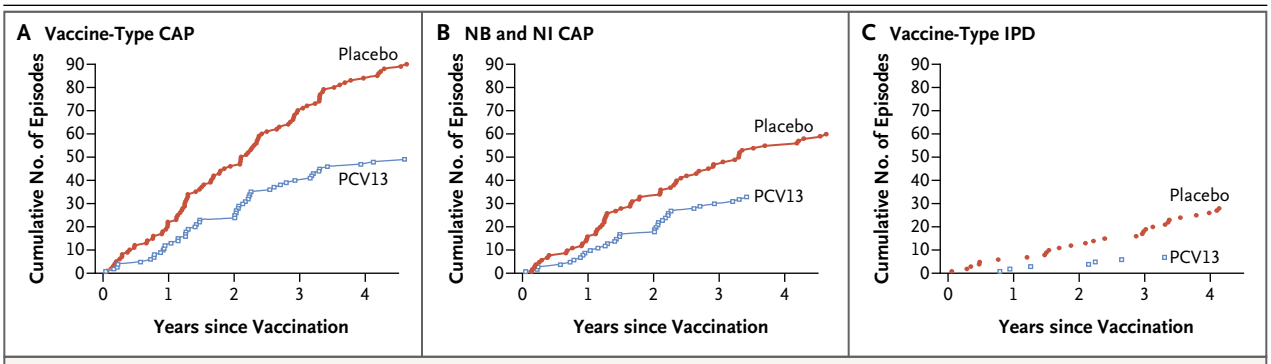

Figure 2. Post Hoc Analysis of the Cumulative Episodes of the Primary and Secondary Efficacy End Points in the Per-Protocol Population.

of the episodes of invasive pneumococcal disease among patients 65 years of age or older were caused by PCV13 serotypes (49.7% by PCV7 serotypes and 5.3% by serotype 19A).[38] During the study period, in 2013, this percentage decreased to 42.3% caused by PCV13 serotypes (6% by PCV7 serotypes and 11.4% by serotype 19A).

In addition, the study was not designed to show efficacy among patients in whom an immunosuppressing condition developed after enrollment. Such events that occurred after randomization were excluded from the per-protocol analysis. These episodes were included as part of the analyses based on the modified intention-to-treat population; however, the numbers of immunosuppressed participants were too low to draw a meaningful conclusion regarding efficacy in this subpopulation.

Finally, the higher sensitivity of the serotype-specific urinary antigen detection assay to detect vaccine-type *S. pneumoniae* may have led to marginal overestimation of the proportion of vaccine-type serotypes and, therefore, the efficacy of the vaccine with regard to all pneumococcal community-acquired pneumonia. Nonetheless, the 46% reduction in vaccine-type community-acquired pneumonia that was seen after PCV13 immunization indicates that PCV13 immunization in adults may contribute to a reduction in pneumococcal pneumonia in older adults.

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APPENDIX

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