

# A post-hoc analysis of serotype-specific vaccine efficacy of 13-valent pneumococcal conjugate vaccine against clinical community acquired pneumonia from a randomized clinical trial in the Netherlands

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## ARTICLE INFO

### Article history:

Received 11 December 2018

Received in revised form 22 May 2019

Accepted 23 May 2019

Available online 31 May 2019

### Keywords:

Community acquired pneumonia

Pneumococcal conjugate vaccine

Randomized controlled trial

Serotype

Vaccine efficacy

## ABSTRACT

**Background:** Serotype-specific vaccine efficacy (VE) against adult community acquired pneumonia (CAP) remains poorly defined, yet such data are important for assessing the utility of adult pneumococcal conjugate vaccine (PCV) programs.

**Methods:** We evaluated the Community Acquired Pneumonia Immunization Trial in Adults to assess serotype-specific VE for CAP. This parallel-arm randomized clinical trial assessed 13-valent PCV (PCV13) VE among community dwelling persons aged  $\geq 65$  years in The Netherlands. In the original analysis, PCV13 VE against first episodes of vaccine-type (VT) chest radiology confirmed CAP was 45.6% (95% confidence interval [CI] 21.8–62.5%). Unlike the original analysis, we included any subject that met a clinical definition of CAP regardless of radiographic findings. VT-CAP was identified by culture (sterile or non-sterile) or serotype-specific urinary antigen detection (SSUAD) test. Only the five serotypes with at least 10 episodes in the control arm, based on the original analysis, were included for VE assessment.

**Results:** Of 272 clinical CAP visits with VT serotypes identified, 253 (93%) were identified by SSUAD including 210 (77%) by SSUAD alone. VE was determined for serotypes 1, 3, 6A, 7F, and 19A, with total first episodes of, respectively, 27, 36, 25, 38, and 48. VE (95%CI) for the five evaluated serotypes against first clinical CAP episodes were: serotype 1, 20.0% (–83.1% to 65.8%); serotype 3, 61.5% (17.6–83.4%); serotype 6A, 33.3% (–58.6% to 73.2%); serotype 7F, 73.3% (40.5–89.4%); and serotype 19A, 45.2% (–2.2% to 71.5%).

**Discussion:** Statistically significant VE was observed for serotypes 3 and 7F for clinical CAP among elderly community dwelling adults. The VE point estimates and CIs for serotypes 1, 6A, and 19A were lower but consistent with the overall VT-CAP VE of 45.6% previously reported. These findings may be relevant in models to accurately account for the potential impact of adult PCV13 immunization.

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## 1. Introduction

The Community Acquired Pneumonia Immunization Trial in Adults was a double-blind, placebo-controlled, randomized study of 13-valent pneumococcal conjugate vaccine (PCV13) among

Dutch persons aged 65 years and older living in the community [1]. Subjects were enrolled from September 2008 through December 2010. The study took place in the context of 7-valent PCV (PCV7) use in the pediatric national immunization program starting in 2006, and a 10-valent PCV (PCV10) from 2011. Community acquired pneumonia (CAP) due to pneumococcal serotypes included in PCV13 (vaccine-type [VT] CAP) were identified in part using a serotype-specific urinary antigen detection (SSUAD) assay developed by Pfizer specifically to improve the sensitivity and

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specificity for detection of non-bacteremic CAP beyond blood and sputum culture [2]. In the original analysis, PCV13 vaccine efficacy (VE) against first episodes of VT chest X-ray confirmed CAP was 45.6% (95% confidence interval [CI] 21.8% to 62.5%) in the per-protocol population.

In this randomized controlled trial (RCT), there were 139 first episodes of chest X-ray confirmed VT-CAP (49 in the PCV13 group and 90 in the placebo group) in the per-protocol population. While not included in the published manuscript, the Clinical Study Report (Pfizer data on file) included per-protocol vaccine efficacy (VE) for the four most common serotypes [3]. In response to a request by the US Food and Drug Administration (FDA), a post-hoc analysis was done to calculate VE for each of the 13 vaccine serotypes among first episode of VT-CAP for both the per-protocol (Table 1a) and modified intention-to-treat (Table 1b) populations [4]. Lack of peer-reviewed publication and the limited statistical power of serotype-specific VE calculations have limited the ability of external authors to make inferences about PCV13 prevention of CAP due to the most prevalent vaccine serotypes in adults. In particular, serotype 3 and to a lesser extent 19A and 7F, have continued to cause adult pneumococcal disease despite robust childhood PCV13 programs [5,6].

**Table 1a**

Counts and vaccine efficacy of first case of confirmed vaccine type pneumococcal community acquired pneumonia by individual serotypes – per-protocol population (data reproduced from reference 4).

Serotype	Cases		Vaccine efficacy % (95% CI)	P-value
	PCV13	Placebo		
1	9	11	18.18 (–117.18, 70.03)	0.8238
3	7	16	56.25 (–12.40, 84.78)	0.0931
4	2	3	33.33 (–481.98, 94.43)	>0.99
5	1	2	50.00 (–860.45, 99.15)	>0.99
6A	5	4	–25.00 (–529.95, 73.10)	>0.99
6B	4	3	–33.33 (–810.22, 77.44)	>0.99
7F	5	22	77.27 (38.49, 93.28)	0.0015
9V	1	1	0.00 (–7749.68, 98.73)	>0.99
14	2	2	0.00 (–1279.60, 92.75)	>0.99
18C	4	5	20.00 (–271.68, 84.13)	>0.99
19A	8	18	55.56 (–7.42, 83.28)	0.0755
19F	0	2	100.00 (–432.46, 100.00)	0.5000
23F	1	2	50.00 (–860.45, 99.15)	>0.99

**Table 1b**

Counts and vaccine efficacy of first case of confirmed vaccine type pneumococcal community acquired pneumonia by individual serotypes – modified-intention-to-treat population (data reproduced from reference 4).

Serotype	Cases		Vaccine efficacy % (95% CI)	P-value
	PCV13	Placebo		
1	11	12	8.33 (–126.93, 63.35)	>0.99
3	8	20	60.00 (5.19, 84.76)	0.0357
4	2	4	50.00 (–248.88, 95.48)	0.6875
5	2	3	33.33 (–481.98, 94.43)	>0.99
6A	7	8	12.50 (–176.14, 72.99)	>0.99
6B	5	3	–66.67 (–973.25, 67.57)	0.7266
7F	7	23	69.57 (26.74, 88.97)	0.0052
9V	2	2	0.00 (–1279.60, 92.75)	>0.99
14	4	2	–100.00 (–2110.97, 71.34)	0.6875
18C	4	5	20.00 (–271.68, 84.13)	>0.99
19A	11	20	45.00 (–20.41, 76.20)	0.1496
19F	1	3	66.67 (–315.14, 99.37)	0.6250
23F	2	3	33.33 (–481.98, 94.43)	>0.99

Note: For Tables 1a and 1b, subjects can be reported in more than one serotype category. Confidence intervals were derived using the Clopper-Pearson method. Type 1 error control for multiple comparisons across individual serotypes has not been applied. The lower limit of this confidence interval must exceed 0.0 to conclude efficacy for this analysis. p-value is for the null hypothesis that VE = 0.

In this study, CAP was defined based on both clinical and radiological criteria. Radiologic criteria were included with the goal of making the CAP diagnosis more specific. A recent analysis, however, suggested that restricting CAP episodes to persons with a radiographically confirmed pulmonary infiltrate may be no more specific and was substantially less sensitive in identifying CAP episodes preventable by PCV13 than CAP based on clinical criteria alone [7]. The reason for this remains unknown. Regardless, this raised the possibility that we could extend the analysis of serotype-specific data from the trial to include all CAP episodes regardless of radiological findings. In addition, and similar to a recent publication on 23-valent pneumococcal polysaccharide vaccine (PPSV23) vaccine effectiveness [8], we included serotype results from all sources, including SSUAD, sterile sites, and non-sterile sites.

## 2. Methods

### 2.1. Study design

The Community Acquired Pneumonia Immunization Trial in Adults study methodology has been described previously [1,9]. Briefly, this was a parallel-group, double-blind, placebo controlled clinical trial that enrolled 84,496 persons aged at least 65 years at 101 community-based sites across The Netherlands. Subjects were assigned to receive PCV13 or placebo in a 1:1 ratio. Participants were excluded if they had previously received a pneumococcal vaccine; resided in a nursing home or long-term care facility or required semi-skilled nursing care; had a contraindication for influenza vaccine or PCV13; or had immune deficiency or suppression [1].

Surveillance for suspected CAP and IPD was performed at 58 hospitals and one outpatient center located in the regions in which subjects were enrolled. All subjects who presented with suspected pneumonia had a medical history, physical examination, chest radiograph, laboratory tests, SSUAD, urinary pneumococcal antigen testing by BinaxNOW, sputum culture, and blood culture based on the subject's presenting medical status.

#### 2.1.1. Serotypes selected for vaccine efficacy analysis

For VE analysis, we selected the serotypes with at least 10 episodes in the placebo group (since the placebo group reflects the background disease incidence) based on the original VT-CAP all episodes analysis using a modified intention-to-treat (mITT) population (note, the data presented in Table 1b are first events, rather than all events). Based on this criterion, serotypes 1, 3, 6A, 7F, and 19A were chosen before the analyses were performed.

### 2.2. CAP definitions

The original analysis defined CAP as a clinical illness that included both clinical and radiological findings. The former was defined as at least two of the following symptoms: cough, production of purulent sputum or a change in the character of sputum; temperature >38 °C or <36.1 °C; auscultatory findings consistent with pneumonia; leukocytosis (>10 × 10<sup>9</sup> white blood cells/liter or >15% bands); C-reactive protein value >3 times the upper limit of normal; or hypoxemia with a partial oxygen pressure >60 mm Hg while breathing room air. The radiological component of the CAP definition was based on adjudication by an independent and blinded four-person committee whereby two of three agreed that a radiograph (lateral and posterior-anterior chest radiograph if the clinical condition permitted and otherwise an anterior-posterior image) was consistent with CAP. For the current analysis, we focused on clinical CAP [7], defined as persons that met the

clinical part of the CAP definition regardless of radiographic findings.

2.3. VT-CAP identification

The original study defined confirmed VT-CAP as: (1) culture of vaccine serotypes from blood, pleural fluid, or other sterile sites; or (2) vaccine serotypes from SSUAD, among patients with radiographically confirmed CAP. Additionally, if SSUAD identified a vaccine serotype but a non-*S. pneumoniae* pathogen was confirmed from culture of sterile sites, this episode was excluded as VT-CAP. For the current analysis, we classified VT-CAP as any clinical CAP (regardless of radiographic findings) with a PCV13 serotype identified from culture of sterile or non-sterile (sputum and respiratory tract) sites, or from SSUAD.

2.4. Case definition

We included all visits for which a PCV13 serotype was identified. Consistent with the original case identification, cases were included only if the clinical pneumonia visits occurred a minimum of 14 days after vaccination and at least 6 weeks apart between two separate episodes. These rules were applied to each serotype independently. For example, serotype 1 cases included all clinical pneumonia visits that had serotype 1 identified either from culture (sterile or non-sterile) or SSUAD. A new case of serotype 1 specific clinical CAP required that at least 6 weeks passed between hospitalizations involving serotype 1 and the first episode was the earliest episode with serotype 1 clinical CAP.

2.5. Statistical analysis

Both all episodes and first episodes were included in this post-hoc analysis, with the latter the basis for our primary analysis (consistent with the originally published primary endpoint) [1]. We analyzed the mITT population because the per-protocol analysis, as defined in the original study protocol, required radiological con-

firmation of CAP episodes and the strict rule of identifying VT serotypes.

We used the same statistical approach as was used for the original primary objective, namely VE against VT-CAP. Specifically, VE was estimated as 1-RR (relative risk), assuming an equal total person-years of observation between PCV13 group and placebo groups. To estimate 2-sided 95% CIs for the VEs and p-values, we employed the conditional exact test based on the conditional binomial distribution of the number of VT-CAP cases in the PCV13 group given the total number of VT-CAP cases in both groups. Finally, false discovery rate was used to adjust multiple comparisons for p-values based on the exact method.

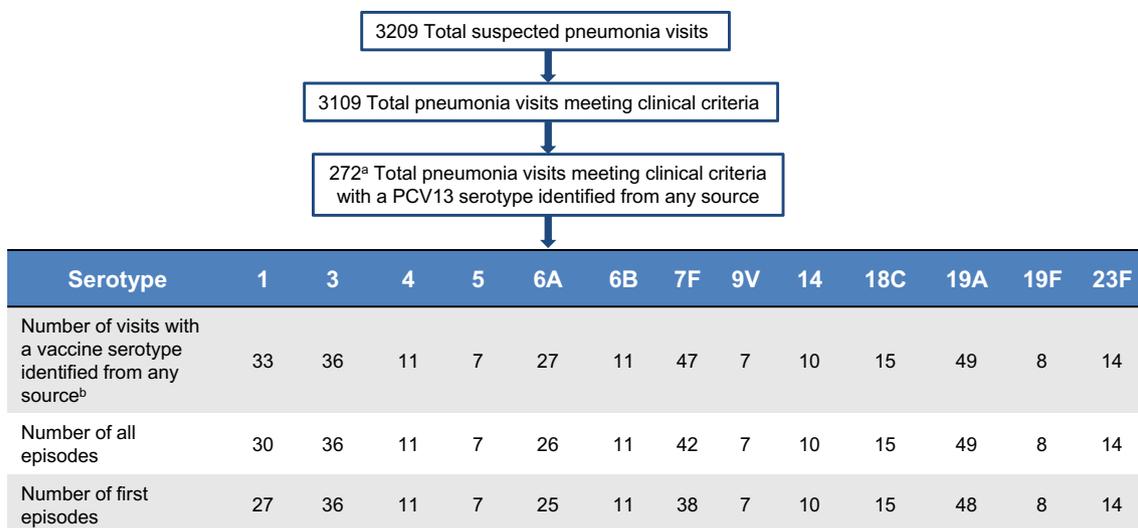
2.6. Role of the funding source

Pfizer employees were involved in study design, analysis, and interpretation; wrote the first manuscript draft; and provided substantial input into the final manuscript.

3. Results

A total of 42,240 persons received PCV13 and 42,256 received placebo, corresponding to 167,874 and 167,748 person years of observation, respectively. Among 3209 visits for suspected pneumonia, 3109 met clinical CAP criteria (Fig. 1). Of the 3109 clinical CAP visits, 1935 (62%) had radiologic confirmation and 1174 (38%) were not confirmed (Table 2).

Using the current study definitions, we identified 272 visits that had a PCV13 vaccine serotype identified from any source, with three visits having two PCV13 serotypes identified at the same time (serotypes 18C and 7F; serotypes 5 and 19A; and serotypes 4 and 5 – all from SSUAD). Of the 272 VT-clinical CAP visits, 253 (93%) were identified by SSUAD including 210 (77%) by SSUAD alone; 33 (12%) were identified by sterile site culture including 7 (3%) by sterile site culture alone; and 30 (11%) were identified by sputum culture, including 12 (4%) by sputum culture alone (Table 3).



<sup>a</sup>We identified 272 visits that had a PCV13 vaccine serotype, with 3 visits having 2 PCV13 serotypes identified at the same time (serotypes 18C and 7F; serotypes 5 and 19A; and serotypes 4 and 5 — all from SSUAD).

<sup>b</sup>Any source includes sterile culture, sputum culture, or SSUAD

Fig. 1. Flow chart for identification of first episodes of serotype specific clinical community acquired pneumonia.

**Table 2**  
Serotype distribution by vaccine group and chest radiography (CXR) criteria among all clinical community acquired pneumonia (CCAP) visits (N = 3109).

Serotype	PCV13 (N = 1486)		Placebo (N = 1623)		Total (N = 3109)	
	Radiologically Confirmed (CXR+ CCAP) (N=934)	non-Radiologically Confirmed (CXR- CCAP) (N=552)	Radiologically Confirmed (CXR+ CCAP) (N=1001)	non-Radiologically Confirmed (CXR- CCAP) (N=622)	Radiologically Confirmed (CXR+ CCAP) (N=1935)	non-Radiologically Confirmed (CXR- CCAP) (N=1174)
PCV13	79	27	131	35	210	62
1	14	2	16	1	30	3
3	9	1	24	2	33	3
4	3	2	4	2	7	4
5	2	0	3	2	5	2
6A	7	3	11	6	18	9
6B	5	1	4	1	9	2
7F	11	1	29	6	40	7
9V	2	3	2	0	4	3
14	4	3	3	0	7	3
18C	4	3	6	2	10	5
19A	14	4	22	9	36	13
19F	1	1	5	1	6	2
23F	3	3	5	3	8	6

Note: All suspected pneumonia visits that met the clinical case definition were included. Radiologically confirmed visits were based on study designated centralized reading by an adjudication committee. The sum of case counts for each individual serotype is not equal to the case count for the PCV13 row because three subjects had two serotypes identified from UAD, and the three subjects were counted separately for each of the two individual serotypes, but only counted once for the PCV13 row.

**Table 3**  
Serotype distribution by source of identification among all clinical community acquired pneumonia visits (N = 3109); UAD = serotype specific urinary antigen detection test.

Serotype	Total serotypes	Serotypes identified from any source			Serotype Identified from a single source			Serotype identified from two sources			Serotype identified from all 3 Sources
		Sterile site culture	Sputum culture	UAD <sup>a</sup>	Sterile site only	UAD only <sup>a</sup>	Sputum culture only	Sterile site culture and UAD	Sputum culture and UAD	Sterile site and sputum cultures	
PCV13	272	33	30	253	7	210	12	25	17	0	1
1	33	6	2	31	2	26	0	3	1	0	1
3	36	4	6	31	2	26	3	2	3	0	0
4	11	3	1	10	0	7	1	3	0	0	0
5	7	1	0	7	0	6	0	1	0	0	0
6A	27	3	1	26	0	23	1	3	0	0	0
6B	11	2	2	10	0	7	1	2	1	0	0
7F	47	8	1	46	1	38	0	7	1	0	0
9V	7	1	1	7	0	5	0	1	1	0	0
14	10	1	0	9	1	9	0	0	0	0	0
18C	15	1	1	15	0	13	0	1	1	0	0
19A	49	3	12	44	1	34	4	2	8	0	0
19F	8	0	2	7	0	6	1	0	1	0	0
23F	14	0	1	13	0	13	1	0	0	0	0

Note: All suspected pneumonia visits that the clinical case definition were included. The sum of case counts for each individual serotype is not equal to the case count for the PCV13 row because three subjects had two serotypes identified from UAD, and the three subjects were counted separately for each of the two individual serotypes, but only counted once for the PCV13 row.

Among the 272 VT-CAP visits, 210 (77%) had radiologic confirmation and 62 (23%) were not confirmed. Among these 272 VT-CAP visits, the number of visits associated with the five serotypes that were prespecified to be included in the VE analysis were 33 (serotype 1), 36 (serotype 3), 27 (serotype 6A), 47 (serotype 7F), and 49 (serotype 19A) (Fig. 1). These were also the most frequent serotypes based on the prespecified selection criteria. The majority of visits also met our criteria for independent episodes based on the case algorithm (14 days after vaccination and a 6 week gap between visits). Specifically the number of all-episodes and first-episodes of clinical CAP for these five serotypes were: serotype 1 (n = 30 for all episodes and 27 for first episodes), serotype 3 (n = 36/36), serotype 6A (n = 26/25), serotype 7F (n = 42/38), and serotype 19A (n = 49/48) (Fig. 1).

VE was positive for all five serotypes that were prespecified to be included in the VE analysis with point estimates ranging from 20.0% to 73.3% for the first episode analysis (Table 4). After adjusting for multiple testing, VE for two serotypes (3 and 7F) had a lower 95% CI above zero and these two serotypes also had the high-

est VE point estimates. The VE point estimates and CIs for serotypes 1, 6A, and 19A were lower but consistent with the overall VT-CAP VE of 45.6% previously reported. When evaluating case accrual over time, we found no evidence that protection was concentrated in the period immediately after vaccination, particularly for the serotypes with larger sample sizes and more stable patterns (Fig. 2). Data were consistent when assessing the division of cases by the source of pneumococcal identification (sterile site, sputum, or UAD) and vaccination status (Supplemental Table); vaccine efficacy was not calculated due to small numbers for most cells.

For serotypes 1, 3, 7F, and 19A, VE was similar to that obtained from the original analysis presented in response to a request from the US FDA (comparison of Tables 1a, 1b, and 4). For serotype 6A, VE was negative in the original analysis and 33% in the current analysis, with the first analysis containing 9 cases (Table 1a) and the latter 25 (Table 4), the greatest proportionate increase of any of the analyzed serotypes. Little difference was seen between the first- and all-episodes analyses, since few subjects had multiple episodes of clinical CAP due to a single serotype.

**Table 4**

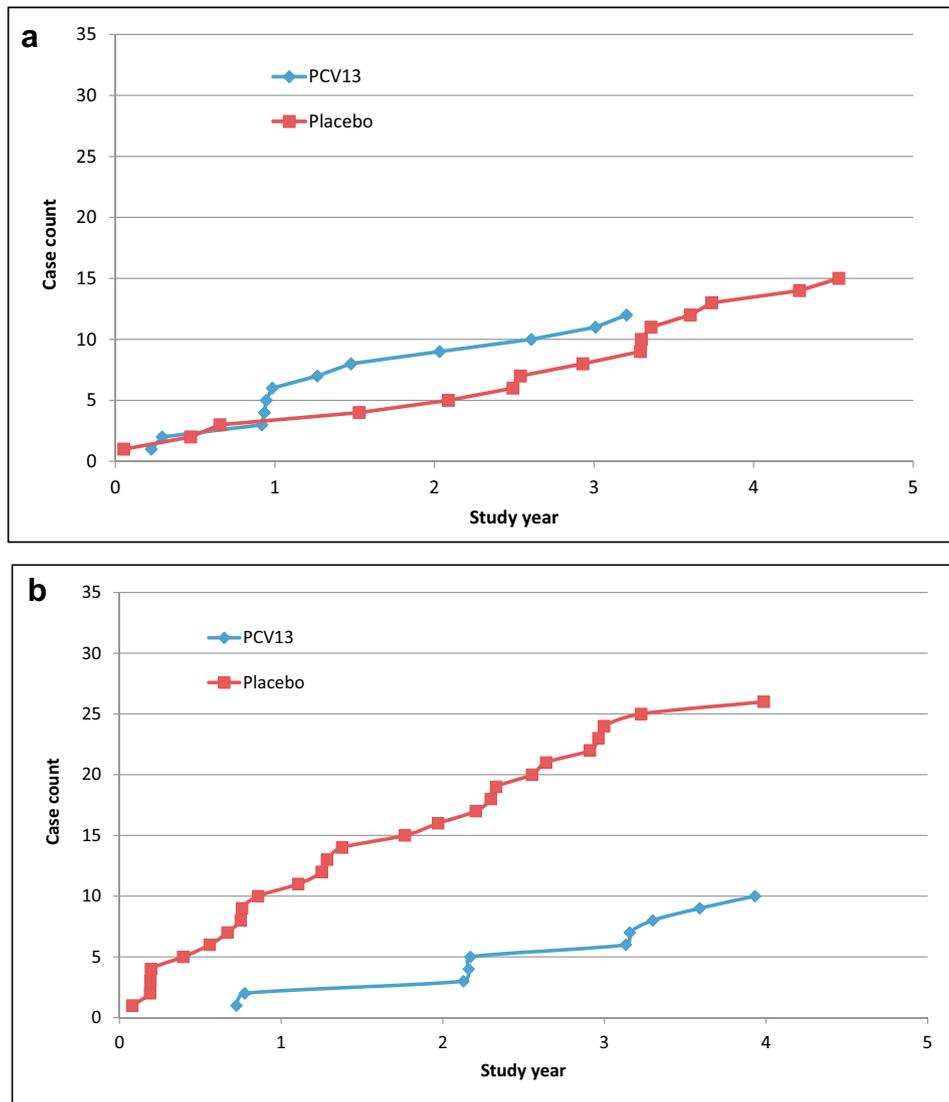
Vaccine efficacy (VE) of 13-valent pneumococcal conjugate vaccine (PCV13) against serotype specific clinical community acquired pneumonia (CAP).

Group	Serotype	Cases		Vaccine Efficacy % (95% CI) <sup>a</sup>	p-Value	
		PCV13	Placebo		Raw <sup>a</sup>	Adjusted <sup>b</sup>
First episode	1	12	15	20.0% (-83.1%, 65.8%)	0.7011	0.7790
	19A	17	31	45.2% (-2.2%, 71.5%)	0.0595	0.1189
	3	10	26	61.5% (17.6%, 83.4%)	0.0113	0.0283
	6A	10	15	33.3% (-58.6%, 73.2%)	0.4244	0.5304
	7F	8	30	73.3% (40.5%, 89.4%)	0.0005	0.0047
All episodes	1	14	16	12.5% (-91.3%, 60.4%)	0.8555	0.8555
	19A	18	31	41.9% (-7.1%, 69.4%)	0.0854	0.1424
	3	10	26	61.5% (17.6%, 83.4%)	0.0113	0.0283
	6A	10	16	37.5% (-46.5%, 74.6%)	0.3269	0.4671
	7F	10	32	68.8% (34.8%, 86.3%)	0.0009	0.0047

Note: A serotype-specific clinical case was defined first by identifying any clinical CAP visit with that serotype identified (either SSUAD or culture from any specimen). To be considered a new case, any subsequent clinical CAP visit with the same serotype identified should be at least 42 days after resolution of the previous clinical CAP visit with that serotype.

<sup>a</sup> 95% CI and p-value (2-sided) were based on exact method.

<sup>b</sup> p-values from Exact test was used and adjusted with False Discovery Rate due to multi-comparison adjustment (across all comparisons).



**Fig. 2.** (a) Serotype 1 clinical community acquired pneumonia case accrual by study year and 13-valent pneumococcal conjugate vaccine (PCV13) receipt. (b) Serotype 3 clinical community acquired pneumonia case accrual by study year and 13-valent pneumococcal conjugate vaccine (PCV13) receipt. (c) Serotype 6A clinical community acquired pneumonia case accrual by study year and 13-valent pneumococcal conjugate vaccine (PCV13) receipt. (d) Serotype 7F clinical community acquired pneumonia case accrual by study year and 13-valent pneumococcal conjugate vaccine (PCV13) receipt. (e) Serotype 19A clinical community acquired pneumonia case accrual by study year and 13-valent pneumococcal conjugate vaccine (PCV13) receipt.

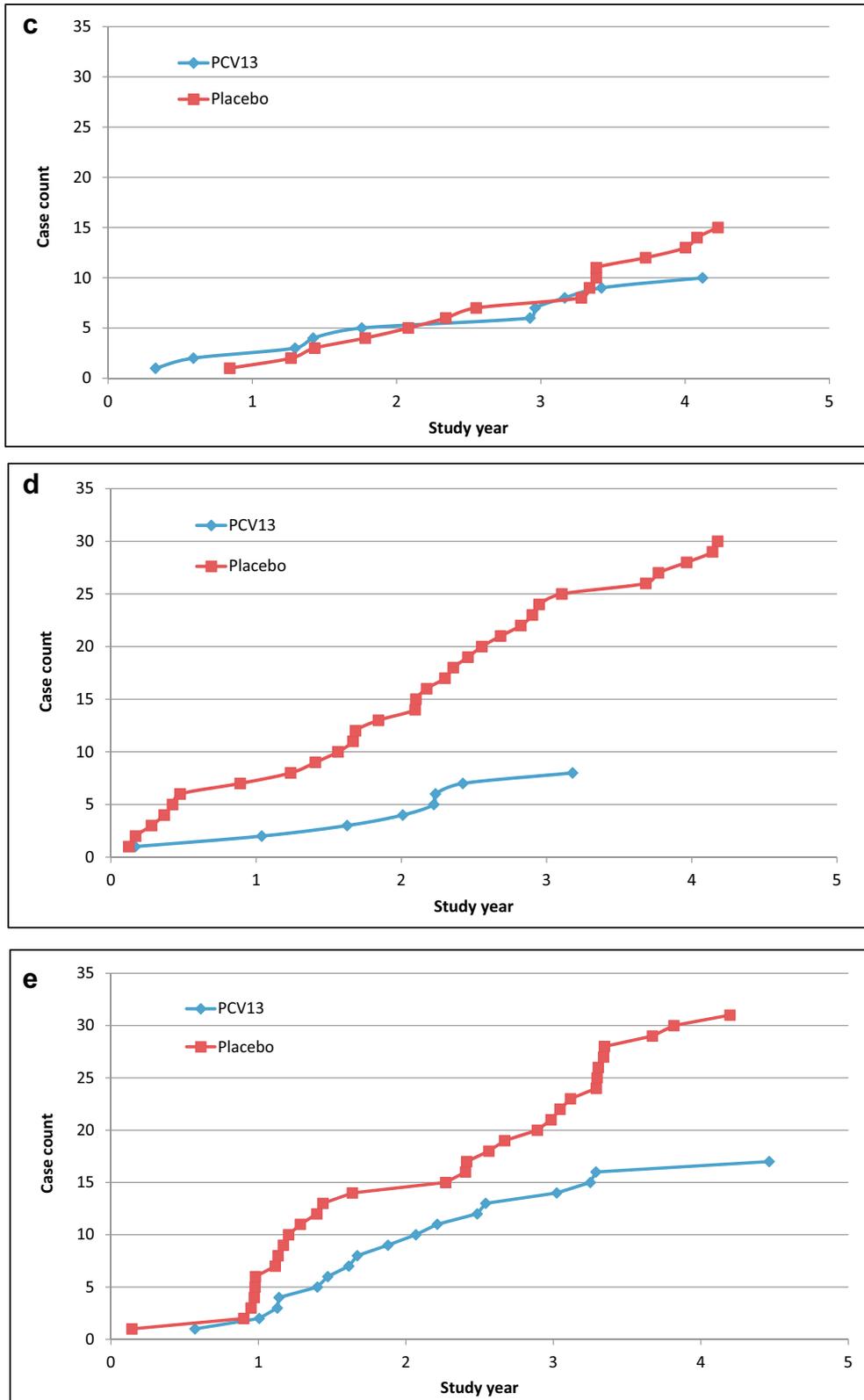


Fig. 2 (continued)

4. Discussion

PCV13 provides direct protection against IPD due to all vaccine serotypes in children [6,10]. Nevertheless, among adults, serotypes 3 and to a lesser extent 19A, 19F, and 7F have persisted as causes of IPD [6,11,12,13] and CAP [1,5] in the era of routine childhood

PCV13 programs. For serotypes 7F, 19A, and 19F, this phenomenon has occurred despite the ability of PCV13 to provide direct protection against carriage acquisition in children [14]. It may be that transmission dynamics for some serotypes differ. For example, transmission pathways may exist that do not depend on young children or the ability of direct vaccination to reduce carriage

density or acquisition may be insufficient to interrupt transmission. Regardless, for PCV13 to have a role in adult immunization programs, it will need to provide direct protection against the most common serotypes contributing to the current adult disease burden.

Similar to an earlier unpublished analysis prepared for the US FDA, the current analysis demonstrated relatively high VE point estimates for serotypes 3, 7F, and 19A with the current analysis narrowing the confidence interval around these estimates. Moreover, we found no evidence that the difference in case accrual between vaccinated and unvaccinated persons was concentrated in the earlier part of the study, and no indication that – for the most common serotypes – the relative division of cases by PCV13 versus placebo receipt differed by source of pneumococcal identification. Consistent with VE against all VT-CAP being sustained for at least five years [15], this suggests that waning of immunity did not occur for individual serotypes, although a larger sample size would be needed to definitively assess immune duration.

In the present study, VE for serotype 3 specific adult clinical CAP was 61.5% (95%CI: 17.6–83.4%). This finding is consistent with a recent systematic review and meta-analysis which found a serotype 3 vaccine effectiveness for pediatric invasive pneumococcal disease (IPD) of 63.5% (95%CI: 37.3–89.7%) [16]. Some authors have questioned the ability of PCV13 to provide direct or indirect protection against serotype 3 [17]. However, this conclusion has been based primarily on surveillance data, which have shown a relatively minor or no change in serotype 3 incidence over time among different age cohorts, compared with substantial declines for other prevalent serotypes. This logic is faulty for several reasons. First, comparing incidence before and after vaccine introduction can be confounded by serotype specific issues such as antibiotic resistance, changes in the capsular polysaccharide structure, and the proportion of persons with underlying chronic illness. For example, a recent global genomic analysis of serotype 3 isolates found that a new antibiotic resistant clade is replacing the former clade that infrequently demonstrated antibiotic resistance, and that – at the country level – variation in PCV13 use did not predict which clade predominated [18]. This raises the possibility that an imperfect serotype 3 vaccine combined with reduced population impact of community antibiotic use against serotype 3 have combined to contribute to observed surveillance trends. Second, surveillance data represent the combined effect of direct and indirect protection. For serotype 3, a randomized controlled trial found no VE against serotype 3 carriage acquisition in children [14] although the upper confidence bound of 52% leaves substantial margin for effect. Measureable effectiveness against disease but not carriage may be because PCV13 generates sufficient immune responses to provide direct protection against disease but less so against carriage acquisition, which may require higher levels of antibodies or other immunologic mediators. Regardless of the reason, if PCV13 provides inadequate protection against carriage among children, who represent the primary source of pneumococcal transmission, population-based transmission and risk for unvaccinated persons may increase, even while vaccinated persons remain protected. Third, the correct counterfactual for assessing PCV13 impact from surveillance data is not data from the pre-PCV13 era, but data from countries that have introduced PCV10, which does not contain serotype 3. Recently, just such an evaluation was carried out in six countries using PCV13 in their pediatric immunization program and four using PCV10. From 2011 through 2015, pooled serotype 3 incidence remained below baseline in PCV13 countries and increased 50% above baseline in PCV10 countries [13]. In summary, data are consistent with substantial direct PCV13 VE against serotype 3 IPD and pneumonia, less protection against carriage, and the influence of non-vaccine factors such as increasing serotype 3 antibiotic resistance.

VE was relatively low for serotype 1, but the upper limit of the 95% CI was within the range of the previously reported overall VE against all VT-CAP of 45.6% [1]. In the original analyses, serotype-specific VE for IPD was not reported, but in the per-protocol population there were five first episodes of serotype 1 IPD in the placebo group and only one in the PCV13 group [1]. Moreover, surveillance data have shown a rapid decline in serotype 1 IPD following PCV13 introduction in children [6,19], surveillance data in Israel have shown reductions in serotype 1 acute otitis media following PCV13 introduction [20], and an RCT in Israel found significant VE of PCV13 against serotype 1 carriage among children [14]. Consequently our findings for serotype 1 may reflect statistical variation due to small numbers.

Our study had several limitations. First, it may be argued that CAP requires positive radiographic confirmation of a pulmonary infiltrate. However, the radiographic criteria used in this RCT may have excluded minor infiltrates; some persons may have presented relatively early in the course of their illness before an identifiable infiltrate developed; and there are no validated findings for defining an infiltrate consistent with adult CAP and inter-observer variability is high [21–23]. Furthermore, we previously demonstrated that in this RCT, PCV13 prevented a substantial burden of disease due to clinically defined CAP regardless of radiologically confirmed infiltrates, indicating that clinical CAP is a relevant outcome for identifying serious disease preventable by PCV13 [3]. A second limitation is that despite expanding the case definition of pneumonia, the sample size for individual serotypes was small, and in most cases prevented definitive conclusions on VE.

Overall, our study provides strong evidence that PCV13 provides direct protection against adult CAP due to the most common vaccine serotypes contributing to the current adult disease burden in the United States and elsewhere. Additionally, we found no evidence that PCV13 had a lower VE against serotype 3 CAP. These data can inform economic and impact models to investigate the utility of directly vaccinating elderly adults in the setting of strong childhood PCV programs. Future studies should continue to evaluate trends in serotype-specific adult IPD and pneumonia, and where PCV13 is used, assess impact against VT disease.

#### Author contributions

Contributors: Study concept and design: BDG, QJ, HLS, CW, DS, WCG and LJ for current analysis and CHVW, CW, DS, DEG, MJMB for original Community Acquired Pneumonia Immunization Trial in Adults (CAPI<sub>T</sub>A); acquisition of data: CHVW, DEG, MJMB for original Community Acquired Pneumonia Immunization Trial in Adults (CAPI<sub>T</sub>A); analytic plan and statistical analysis of data: BDG, QJ; interpretation of data: BDG, QJ, CHVW, HLS, CW, DS, WCG, DEG, MJMB, and LJ. All authors reviewed and approved the final manuscript for submission.

#### Funding support and role of funder/sponsor

This study was sponsored by Pfizer Inc. The sponsor was involved with study concept and design, conduct, analysis and interpretation of the data, drafting of the manuscript, and the decision to submit the manuscript for publication. The corresponding author had full access to the study data and had final responsibility for the decision to submit for publication.

#### Funding

The original study and the current analysis were funded by Pfizer.

## Declaration of Competing Interest

BDG, QJ, HLS, CW, DS, WCG and LJ are employees of Pfizer Inc. MJMB reports research grant funding for vaccine related studies from Pfizer, Arsanis, Johnson and Johnson and Janssen Vaccines and advisory board and speaker fees from Pfizer and Janssen Vaccines. The remaining authors report no conflicts of interest.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.05.065>.

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