



Post-hoc analysis of a randomized controlled trial: Diabetes mellitus modifies the efficacy of the 13-valent pneumococcal conjugate vaccine in elderly



Susanne M. Huijts^{a,b,*}, Cornelis H. van Werkhoven^b, Marieke Bolkenbaas^b, Diederick E. Grobbee^{b,c}, Marc J.M. Bonten^{b,d}

^aDepartment of Respiratory Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

^bJulius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, The Netherlands

^cJulius Clinical, Zeist, The Netherlands

^dDepartment Medical Microbiology, UMC Utrecht, Utrecht, The Netherlands

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ABSTRACT

Background: The 13-valent pneumococcal conjugate-vaccine (PCV13) was effective in preventing vaccine-type Community-Acquired Pneumonia (VT-CAP) and Invasive Pneumococcal Disease (VT-IPD) in elderly subjects, but vaccine efficacy (VE) in patients with comorbidities at time of vaccination is unknown.

Methods: This is a post hoc analysis of the CAPiTAT study, a double blind, randomized controlled trial with 84,496 immunocompetent participants aged ≥ 65 years, receiving PCV13 or placebo vaccination. Presence of diabetes mellitus (DM), heart disease, respiratory disease, liver disease, asplenia, and smoking at the time of immunization was verified on medical records in 139 subjects developing the primary endpoint of VT-CAP. Presence of DM and respiratory disease based on International Classification of Primary Care (ICPC) coding was also determined in 40,427 subjects.

Findings: In the 139 subjects developing VT-CAP, DM caused significant effect modification (p -value 0.002), yielding VE of 89.5% (95%CI, 65.5–96.8) and 24.7% (95%CI, –10.4 to 48.7) for those with and without DM, respectively. Comparable effect modification (p -value 0.020) was found in the 40,427 subjects with and without ICPC-based classification of DM with VE of 85.6% (95%CI, 36.7–96.7) and of 7.0% (95%CI, –58.5 to 45.5) respectively. Effect modification through respiratory disease was not statistically significant, although the point estimate of VE was lower for those with respiratory disease in both analyses. There was no evidence of effect modification in subjects stratified by heart disease, smoking, and presence of any comorbidity.

Conclusions: Among immunocompetent elderly, VE of PCV13 was modified by DM with higher VE among subjects with DM. Significant effect modification was not observed for subjects with heart disease, respiratory disease, smoking, or presence of any comorbidity.

Conclusions: CAPiTAT trial registration number: www.ClinicalTrials.gov; trial number NCT00744263.

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1. Introduction

Community-Acquired Pneumonia (CAP) is a common infectious disease worldwide, with high incidences among young children and elderly [1,2]. The most frequent pathogen causing CAP is *Streptococcus pneumoniae*, a gram positive coccus of which over 90

different serotypes have been identified [3]. A minority of these serotypes cause the majority of the pneumococcal infections [3].

Pneumococcal conjugate vaccines (PCV), directed against some of those serotypes, have been available since the last decades and are reducing incidences of invasive pneumococcal disease (IPD), pneumonia and otitis media in children [4]. Recently, the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTAT) demonstrated vaccine efficacy (VE) of the 13-valent pneumococcal conjugate vaccine (PCV13) in the prevention of a first episode vaccine-serotype pneumococcal (VT) CAP and VT-IPD in immunocompetent adults aged 65 years and older [5].

* Corresponding author at: University Medical Center Utrecht, Department of Respiratory Medicine, Internal post: E.03.511, P.O. Box 85500, 3508 GA Utrecht, The Netherlands.

E-mail address: s.m.huijts@umcutrecht.nl (S.M. Huijts).

Some medical conditions, like diabetes mellitus (DM), heart disease or respiratory disease, are associated with an increased risk of pneumococcal infections [6–10] and PCV13 vaccination was calculated to be highly cost-effective among those adults with an increased risk [11]. This was mainly driven by the high incidences of CAP and IPD in these groups and under the assumption that VE was equal to those without increased risk. However, the efficacy of PCV in individuals with specific comorbidities is yet unknown. The only trial investigating PCV in adults with a specific comorbidity concerned a study in Malawi that demonstrated a VE of 74% (95% CI 30–90%) in prevention of VT-IPD in HIV-positive subjects [12].

Determination of PCV13 VE in patient groups with comorbidities may promote informed decision making for immunization strategies. We, therefore, determined VE of PCV13 in prevention of a first episode VT-CAP in elderly people with DM, respiratory disease or heart disease at the time of vaccination.

2. Methods

2.1. Study design

This was a post hoc analysis from the CAPIA-trial, in which 84,496 community dwelling immunocompetent individuals of 65 years and older were randomly allocated to receive either PCV13 or placebo vaccination [5,13]. The primary endpoint was a first episode of VT-CAP. The per-protocol analysis was restricted to subjects being still immunocompetent when the primary endpoint was met, and the modified-intention-to-treat analysis (mITT) included all subjects enrolled, i.e. including subjects that had developed immunodeficiency after study onset (Box 1). Subjects were included between September 2008 and January 2010 and follow-up for endpoint detection continued until August 2013. All participants provided written informed consent and the trial was approved by the Central Committee on Research Involving Human Subjects and by the Ministry of Health, Welfare and Sport in the Netherlands. Participants and investigators remained blinded for vaccination status until data collection was fully completed. Details of this trial, in- and exclusion criteria and main results were described earlier [5].

Subjects provided information on the presence of lung disease, asthma, heart disease, liver disease, DM with or without insulin use or asplenia at the time of study enrolment. These risk factors were selected on known associations with an increased risk on pneumococcal disease [6,8,10]. However, for the current analyses presence of comorbidities at the time of vaccination was based on documented comorbidity status in medical records instead of the self-reported comorbidity status. Two different approaches were used: In the first approach we investigated effect modification of comorbidities in the 139 subjects developing the primary endpoint (see below "VT-CAP"). Definition of the primary endpoint is summarized in the supplement and described in detail in Bonten et al. [5]. In the second approach subjects were stratified upon baseline comorbidities at the General Practitioner (GP) coded by the International Classification of Primary Care (ICPC) of 40,427 CAPIA participants (see below "GP-dataset").

2.2. VT-CAP

Detailed medical information was collected during the trial from the 139 per-protocol subjects developing VT-CAP (the primary endpoint) as part of adjudication of the immunological status. This included data from hospitals and GP medical records, including admission and discharge letters. For VT-CAP cases that did not fulfill the requirements for the per-protocol population based on data derived from the hospital records, medical records

Box 1: Definition per-protocol and modified intention-to-treat analysis.

Episodes with onset of symptoms within 14 days after vaccination were excluded from both analyses.

Episodes with onset of symptoms after the date of the following events were excluded from per-protocol analyses and included only in the modified intention-to-treat (mITT) analyses:

- Receipt of any pneumococcal vaccine subsequent to study vaccine.
- Diagnosis with bronchial obstruction due to primary lung cancer, another malignancy metastatic to the lungs, or a history of postobstructive pneumonia.
- Diagnosis with acquired immunodeficiency syndrome (AIDS), known or suspected Pneumocystis jiroveci pneumonia, or known or suspected active tuberculosis.
- Diagnosis with immune deficiency or suppression, defined as presence of 1 or more of the following conditions:
 - HIV infection
 - Leukemia^a
 - Lymphoma^a
 - Hodgkin disease^a
 - Multiple myeloma^a
 - Generalized malignancy^a
 - Chronic renal failure^b or nephrotic syndrome
 - Receipt of immunosuppressive therapy,^c
 - Receipt of an organ or bone marrow transplant
 - Assessment by the immune status committee that the subject was immunosuppressed.

Episodes in subjects who had been hospitalized or resided in a long-term care facility for more than 48 h immediately before the onset of symptoms were excluded from per protocol analyses and included only in the mITT analyses.

^aPresence defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years.

^bReceipt of renal dialysis or transplant.

^cIncluding steroids within 3 months before the onset of symptoms. For corticosteroids, this meant prednisone, or equivalent, 0.5 mg/kg/day for 14 days or more. Inhaled, intra-articular, and topical steroids were not considered immunosuppressive.

were not available. For each subject presence of comorbidities at the time of study enrolment was classified retrospectively as respiratory disease (i.e. any lung disease, including asthma, COPD, chronic bronchitis and bronchial hyper reactivity), DM (either with or without insulin use), heart disease (defined as ischemic heart disease, heart valve disorder or heart failure), liver disease, asplenia, and active smoking by two investigators (SH, CHvW or MBol) blinded for the subjects' vaccination status and self-reported comorbidities. If two investigators disagreed, this was solved by discussion. If the presence of a comorbidity was documented in medical records without a start date or with a first date within one year after study enrolment, the subjects' self-reported comorbidity status was leading. We considered that the absence of documentation of smoking status would not exclude active smoking, therefore, in these cases the self-reported smoking status was leading. The diagnoses that were classified as DM, respiratory disease

or heart disease and corresponding vaccination status are listed in **Tables S1–S3 in the supplement**.

2.3. GP-dataset

In the Netherlands every inhabitant is registered with one single GP who keeps a patient specific medical record in which diagnoses are coded according to the ICPC [14]. As part of the Eti-CAP study, an observational study conducted in parallel with the CAPITA trial to investigate etiology of CAP and impact of PCV13 in primary care, medical records of 40,427 subjects from 876 GP-practices (38.8%) that participated in CAPITA were studied. Selection of these GP-practices was based on the use of one of four of the most common GP information systems. The presence of respiratory disease or DM was based on ICPC codes R95 (COPD), R91.1 (chronic bronchitis), R96 (asthma), R96.1 (bronchial hyper reactivity) and R96.2 (allergic asthma) for 'respiratory disease' and T90 (DM), T90.1 (DM type 1) and T90.2 (DM type 2) for DM. Information on the presence of heart disease, liver disease, and asplenia was not collected. The registration date of a code was considered the start date of the comorbidity and if more codes per disease group were present the first registration date was used. When a comorbidity code was registered without a start date, the subjects' self-reported status for that disease was leading.

The informed consent of the CAPITA-trial covered the data-collection of the Eti-CAP study and the study was approved by the Central Committee on Research Involving Human Subjects (Dutch: CCMO).

2.4. Analyses

The number of VT-CAP episodes, stratified by vaccine group and comorbidity status as defined in the VT-CAP dataset, was used to evaluate VE in people with and without each comorbidity. Because of the large sample size and randomized study design the denominators, representing the number of placebo or PCV13 vaccinated individuals in a certain comorbidity group, were assumed to be comparable and only the nominators were used to calculate VE. VE was calculated by $(1 - \text{Relative Risk}) * 100\%$ using a Poisson regression model. To evaluate the presence of effect modification the comorbidity, the vaccine group and their interaction term were used as determinants. Effect modification was considered present if the interaction term had a significant contribution to the model ($p < 0.05$). This was repeated separately for respiratory disease, DM, heart disease, smoking status, and for presence of any of the

comorbidities. Due to the low numbers, VE was not stratified for liver disease (1 VT-CAP episode) and asplenia separately (no VT-CAP episodes).

To evaluate the impact of other factors on the effect modification the interaction effects were also determined when adding all other comorbidities, age at vaccination, gender, and self-reported smoking status, including all interactions with vaccination status, to the model. To perform this adjusted analyses, assumptions about the distributions and correlations of the comorbidities in the baseline population had to be made. For this we used the self-reported comorbidity status, assuming that misclassifications had occurred equally often in both directions and independent of PCV13 vaccination status.

To calculate the VE stratified by ICPC defined respiratory disease and DM in the GP-dataset, a Cox-regression model was used with time to the first VT-CAP episodes as outcome parameter and the vaccine group as determinant. VE was calculated as $(1 - \text{Hazard ratio}) * 100\%$, stratified by comorbidity group. The comorbidity, the vaccine group and their interaction term were used as determinants and effect modification was considered present if the interaction term had a significant contribution to the model ($p < 0.05$). This was repeated separately for respiratory disease and DM. To correct for other factors the adjusted VE (aVE) was also calculated by adding ICPC defined respiratory disease/DM, age at vaccination, gender, self-reported heart disease and smoking status at vaccination to the model. All analyses were performed with the per-protocol and mITT VT-CAP endpoints in the GP-dataset of 40,427 subjects.

To estimate the accurateness of the self-reported comorbidities, the ICPC-defined respiratory disease and DM were compared with the self-reported asthma or lung disease, i.e. self-reported respiratory disease, and self-reported DM, either with or without insulin use.

The Poisson regression model was performed in R Version 3.0.2 [15] and all other analyses were performed in IBM SPSS Statistics version 21.0 (IBM corp, USA).

3. Results

The presence of respiratory disease, heart disease, and DM at the time of study enrolment was reported in 79 (56.8%), 53 (38.1%), and 32 (23.0%) of the 139 VT-CAP cases. Of these, presence of respiratory disease, heart disease, and DM was based on documented evidence in medical records in 65, 49 and 27 and on self-reported comorbidity status in fourteen,

Table 1
Distribution of VT-CAP cases among comorbidity groups.

Comorbidity ^a	PCV13 VT-CAP	Placebo VT-CAP	VE (95% CI)	p-value interaction (crude model)	p-value interaction (adjusted model) ^b
Total population	49	90	45.6 (22.7–61.7)		
Lung disease	33	46	27.2 (−13.8 – 53.5)	0.0605	0.0542
No lung disease	16	44	63.7 (35.7–79.5)		
Heart disease	18	35	48.4 (9.0–70.8)	0.8087	0.8476
No heart disease	31	55	43.7 (12.5–63.7)		
Diabetes	3	29	89.5 (65.5–96.8)	0.0020	0.0020
No diabetes	46	61	24.7 (−10.4 – 48.7)		
Smoking	9	21	57.4 (6.9–80.5)	0.4878	0.4615
No smoking	40	69	42.0 (14.3–60.7)		
Any comorbidity \$	41	75	45.3 (19.9–62.6)	0.9567	0.9757#
No comorbidities	8	15	46.7 (−25.8–77.4)		

Abbreviations used: PCV13 = 13-valent pneumococcal conjugate vaccine; VT-CAP = vaccine serotype pneumococcal community acquired pneumonia; VE = vaccine efficacy; CI = confidence interval; adj. = adjusted; NA = not applicable; DM = Diabetes Mellitus.

^a Comorbidity groups are defined by the status at enrolment as documented in hospital medical records.

^b Adjusted for the presence of other listed comorbidities, age (binary split at age 73), gender, and smoking status. \$ comorbidities include lung disease, heart disease, diabetes mellitus, liver disease, splenectomy, and smoking. # adjusted for age (binary split at age 73) and gender.

four, and five subjects, respectively. Active smoking was present at baseline in 30 (21.6%) subjects. This was derived from medical records in 20 and based on self-reported smoking status in 10 subjects. Of the subjects developing VT-CAP, 116 (83.5%) had at least one of the documented comorbidities at study enrolment.

The distribution of VT-CAP episodes in PCV13 and placebo vaccinated subjects among the various comorbidity groups is presented in Table 1. DM caused significant effect modification of

the VE (p-value 0.002), with a VE of 89.5% (95%CI 65.5–96.8) in those with DM, compared to 24.7% (−10.4 to 48.7) for those without. The interaction terms of the other comorbidities were not significant, although there was a trend towards effect modification for respiratory disease, with the VE for patients with respiratory disease being lower (27.2%, 95%CI −13.8 to 53.5) compared to those without (63.7%, 95%CI 35.7–79.5, p-value for interaction 0.061). Adding other baseline factors and interactions to the models did not change the size or statistical significance of effect modification.

Table 2
Baseline characteristics of GP-dataset.

	PCV13 (n = 20,196)		Placebo (n = 20,231)		With DM (n = 5886)	Without DM (n = 34,541)	With resp. dis. (n = 4810)	Without resp. dis. (n = 35,617)
	N (%)	Missing, N (%)	N (%)	Missing, N (%)	N (%)	N (%)	N (%)	N (%)
Age	71.4 ^a (68.1–76.1)	—	71.4 ^a (68.1–76.1)	—	71.0 ^a (68.0–76.0)	71.0 ^a (68.0–76.0)	72.1 ^a (68.5–76.6)	71.3 ^a (68.0–76.0)
Male gender	11,257 (55.7)	—	11,400 (56.3)	—	3478 (59.1)	19,179 (55.5)	2864 (59.5)	19,793 (55.6)
Caucasian race	19,911 (98.6)	6 (0.0)	19,955 (98.6)	4 (0.0)	5755 (97.8)	34,111 (98.8)	4751 (98.8)	35,115 (98.6)
Respiratory disease – ICPC ^b	2393 (11.8)	—	2417 (11.9)	—	772 (13.1)	4038 (11.7)	—	—
Self reported resp. disease	2829 (14)	33 (0.1)	2837 (14)	39 (0.2)	840 (14.3)	4826 (14.0)	3255 (14.0)	2411 (6.8)
Diabetes Mellitus – ICPC ^c	2928 (14.5)	—	2958 (14.6)	—	—	—	772 (16.0)	5114 (14.4)
Self reported DM	2548 (12.6)	21 (0.1)	2592 (12.8)	19 (0.1)	4576 (77.7)	564 (1.6)	653 (13.6)	4487 (12.6)
Self-reported heart disease	5038 (24.9)	55 (0.3)	5167 (25.5)	59 (0.3)	1996 (33.9)	8209 (23.8)	1422 (29.6)	8783 (24.7)
Self-reported smoking	2484 (12.3)	3 (0.0)	2427 (12.0)	3 (0.0)	641 (10.9)	4270 (12.4)	934 (19.4)	3977 (11.2)

^aMedian and IQR are presented.

PCV13 = 13-valent pneumococcal conjugate vaccine; Resp. = respiratory; Dis. = disease; ICPC = International Classification of Primary Care.

^a Median and interquartile ranges.

^b Defined as ICPC codes R95, R91.1, R96, R96.1 and R96.2.

^c Defined as ICPC codes T90, T90.1 and T90.2.

Table 3
Vaccine efficacy stratified by ICPC defined comorbidities at enrolment in GP-dataset.

	PCV13		Placebo		Crude VE (95% CI)	p-value crude VE	p-value crude interact.	Adj. ^a VE (95% CI)	p-value Adj. ^a VE	p-value adj. ^a interact.
	VT-CAP	Total	VT-CAP	Total						
Per protocol										
Total population GP-dataset	28	20,196	42	20,231	33.2% (−7.7–58.6)	0.098	NA	32.1% (−9.5–57.9)	0.112	NA
With respiratory disease ICPC ^b	17	2393	20	2417	13.5% (−65.2–54.7)	0.661		11.8% (−68.4–53.8)	0.703	
No respiratory disease ICPC ^b	11	17,803	22	17,814	50.0% (−3.1–75.8)	0.060	0.268	49.9% (−3.4–75.7)	0.062	0.257
With DM ICPC ^c	2	2928	14	2958	85.6% (36.7–96.7)	0.010		85.1% (34.3–96.6)	0.012	
No DM ICPC ^c	26	17,268	28	17,273	7.0% (−58.6 to 45.5)	0.790	0.020	6.1% (−60.2–44.9)	0.817	0.022
Modified intention-to-treat										
Total population GP-dataset	37	20,196	48	20,231	22.8% (−18.6 to 49.7)	0.238	NA	21.5% (−20.6 to 48.9)	0.270	NA
With respiratory disease ICPC ^b	21	2393	23	2417	7.1% (−67.9 to 48.6)	0.808		5.2% (−71.3 to 47.6)	0.859	
No respiratory disease ICPC ^b	16	17,803	25	17,814	36.0% (−19.9 to 65.8)	0.163	0.397	35.9% (−20.1 to 65.8)	0.165	0.378
With DM ICPC ^c	4	2928	17	2958	76.3% (29.6–92)	0.010		75.5% (27.1–91.8)	0.011	
No DM ICPC ^c	33	17,268	31	17,273	−6.6% (−74.1 to 34.7)	0.798	0.013	−7.8% (−76.1 to 34)	0.763	0.014

PCV13 = 13-valent pneumococcal conjugate vaccine; CI = Confidence Interval; VT-CAP = vaccine serotype pneumococcal community acquired pneumonia; Adj. = Adjusted; VE = Vaccine efficacy; interact. = interaction term; ICPC = International Classification of Primary Care; DM = Diabetes Mellitus.

^a Adjusted for age and gender and the presence of ICPC defined respiratory disease/DM, self-reported heart disease and smoking status.

^b Defined as ICPC codes R95, R91.1, R96, R96.1 and R96.2.

^c Defined as ICPC codes T90, T90.1 and T90.2.

The 40,427 subjects in the GP-dataset had a median age of 71.4 years (IQR 68.1–76.1) and 22,657 (56.0%) were male, resembling the characteristics of those subjects for which ICPC codes were not available (Table S4). At the time of study enrolment there were 4810 (11.9%) and 5886 (14.6%) subjects with an ICPC defined diagnosis of respiratory disease and DM, respectively, with equal distribution of those comorbidities among the two treatment groups (Table 2). Among these, the presence of respiratory disease and DM was based on self-reported comorbidity at the time of study enrolment in 118 and 108 subjects, respectively. In this cohort there were 70 per-protocol VT-CAP cases (28 PCV13 and 42 placebo) and 85 mITT VT-CAP cases (37 PCV13 and 48 placebo), yielding a VE of 33.2% (95% CI –7.7 to 58.6) for the per protocol endpoints and of 22.8% (95%CI –18.6% to 49.7%) for the mITT endpoints.

Stratification by respiratory disease and DM based on ICPC codes demonstrated that DM was an effect modifier, both for the per-protocol as for the mITT endpoints (p-values for interaction being 0.020 and 0.013, respectively). Point estimates for VE with the per protocol cases were 85.6% (95%CI 36.7–96.7) and 7.0% (95%CI –58.5 to 45.5) for subjects with and without DM at study enrolment, respectively, with a similar pattern for the mITT population and the adjusted analyses (Table 3). ICPC defined respiratory diseases at study enrolment was not associated with effect modification (p-value for interaction 0.268). Stratified respiratory disease status yielded VE of 13.5% (95%CI –65.2 to 54.7) and 50.0% (95%CI –3.1 to 75.8) in the per protocol population for subjects with and without respiratory disease, respectively, with similar findings for the mITT population and the adjusted analyses (Table 3).

Analyses stratified for different comorbidities consistently yielded higher VE for patients with DM compared to patients without DM in both datasets (Tables S5 and S6). For respiratory disease, the trend was confirmed in 9 of 10 strata in the VT-CAP dataset and in 8 of 10 strata in the GP-dataset (Tables S5 and S6).

There was a high level of congruence between self-reported DM at the time of study enrolment and the disease presence based on ICPC-coded DM (95.4%), but this was lower for respiratory disease (90.2%) and the presence of self-reported respiratory disease could only be confirmed in 56.8% (Tables S7 and S8).

We also explored associations between insulin use and VE. However, insulin use among DM patients could not be reliably collected in the VT-CAP dataset and the low numbers of VT-CAP episodes in the GP-dataset did not allow stratification of the results for diabetes type. Based on self-reported DM type VE was 82.2% (95% CI 39.0–100%) and 93.1% (95%CI 72.2–100%) for subjects with and without insulin use, respectively.

4. Discussion

In this post hoc analysis of the CAPiTA study VE of PCV13 in elderly was modified by the presence of DM at the moment of vaccination, with a higher VE for subjects with DM than those without. This finding was consistently found by classification of DM based on detailed medical information for 139 subjects developing VT-CAP and ICPC coding in 40,427 study participants. Statistically significant effect modification was not apparent for respiratory disease, heart disease, smoking, or the presence of any comorbidity.

Pneumococcal polysaccharide vaccines (PPV) have been studied in subjects with comorbidities, however these cohorts were small (maximum number of participants 2345) and efficacy, let alone effect modification, could not be demonstrated [16–18]. There are no other studies evaluating PCV vaccination in adults with sufficient statistical power to determine differences in VE in subjects with and without comorbidities. Yet, an immunogenicity study of PCV vaccination in adults with and without medical conditions,

including DM, yielded comparable geometric mean titers of serotype-specific opsonophagocytic activity (OPA) assays (poster presentation Infectious Disease-week conference 2012, abstract 514) [19]. And subjects with COPD had superior immune response to two doses of PCV7 compared to PPV23 [20].

The effect modification by DM was highly statistically significant and consistent in two subgroups differing in size and possibilities for misclassification. Also analyses in the full cohort, using the self-reported co-morbidity status, demonstrated consistent results (Table S9).

The epidemiological nature of our study precludes elucidation of a biological mechanism explaining our findings. DM is associated with a higher risk of acquiring infections, including CAP [9,21], and various diabetes-specific in vitro defects in innate and adaptive immunity have been observed. Their clinical relevance, however, remains to be established [21,22]. Furthermore, DM has been associated with colonization with *S. aureus* [23], but whether this association also holds for *S. pneumoniae* is unknown.

Although the difference in VE among subjects with and without respiratory disease did not reach statistical significance, our findings suggest lower VE for those with respiratory disease, with VE point estimates ranging from 13.5% to 27.2% in the two analyses performed. Analyses using self-reported respiratory disease yielded similar results (Table S9) and the results were consistent in most sensitivity analyses. Yet, since respiratory disease is one of the strongest risk factor for pneumonia [6], even a lower VE among those patients would yield a higher absolute benefit from vaccination than in patients without respiratory disease.

Strengths of this study include the randomized allocation of PCV13 and placebo, study setting in a country with no regular PPV23 vaccination, verification of the comorbidity status of subjects developing VT-CAP in the per protocol population against medical records and performance of a sensitivity analysis in 40,427 subjects using ICPC coding in GP-based medical records.

Our findings are sensitive to misclassification of comorbidity status in the 139 subjects developing VT-CAP, and classification was, therefore, performed independently by two investigators, unaware of a subjects' vaccination status, using all medical information available. Still, incompleteness of medical information may have caused misclassification. However, as this incompleteness is not related to vaccine status it would lead to bias towards zero (i.e. we may have underestimated the interaction effect).

In the Netherlands the ICPC classification is used by the large majority of GPs, and the Dutch GP Association (Dutch: NHG) requires that all GP-consultations are coded by ICPC [24]. Accurate ICPC coding has become one of the quality targets imposed on GP practices by Dutch healthcare insurance companies [25]. Moreover, selection of subjects eligible for annual influenza vaccination is based on ICPC codes [26] and these codes are used to allocate extra reimbursement of healthcare costs for patients registered with ICPC defined DM and respiratory diseases under some conditions [27]. Nevertheless, the use of ICPC has not been validated and misclassification might occur. However, if pneumococcal vaccination for certain risk groups would be introduced in the Netherlands and if this would become the GP's responsibility, patient selection would most probably be based on ICPC codes, reflecting the comorbidity assignment as used in the current study.

In the CAPiTA study 84,496 subjects were randomly assigned to receive either PCV13 or placebo, assuring random distribution of all known and unknown confounders. Yet, stratification on the presence or absence of comorbidities may jeopardize this random assignment of confounders. Therefore, the results should be interpreted with caution. However, results were consistent in the adjusted and stratified analyses, ensuring that age, gender, smoking status and other available comorbidities were not the cause of the interaction effect observed for DM. Moreover, the observed

effect modification of DM was highly significant and consistent in both analyses (i.e. the VT-CAP and the GP-dataset).

In conclusion, among immunocompetent elderly, VE of PCV13 was significantly higher among subjects with DM compared to subjects without DM. Significant effect modification was not observed for subjects with heart disease, respiratory disease, smoking, or presence of any of these risk factors. The higher VE of PCV13 observed for those with DM merits further studies elucidating the underlying biological mechanism of this observation.

Authors' contributions

S.M. Huijts participated in conducting the CAPITA trial, she performed the data analysis, data interpretation and wrote the draft manuscript. M. Bolkenbaas participated in conducting the CAPITA trial, collected the data for the Etio CAP in the primary care and critically reviewed the data interpretation and the draft manuscript. C.H. van Werkhoven participated in conducting the CAPITA trial, assisted in and monitored the data analysis and critically reviewed the data interpretation and the draft manuscript. D.E. Grobbee was involved in the design and execution of the CAPITA trial and critically reviewed the draft manuscript. M.J.M. Bonten was the principle investigator of the CAPITA trial and critically reviewed the data interpretation and the draft manuscript.

Conflict of interest

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2017.01.071>.

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