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Original article

The impact of 13-valent pneumococcal conjugate vaccination on virus-associated community-acquired pneumonia in elderly Exploratory analysis of the CAPiTA trial

S.M. Huijts [1, 2, *], F.E.J. Coenjaerts [3], M. Bolkenbaas [2], C.H. van Werkhoven [2], D.E. Grobbee [2, 4], M.J.M. Bonten [2, 3], on behalf of the CAPiTA study team

[1)] Department of Respiratory Medicine, UMC Utrecht, Utrecht, The Netherlands
[2)] Julius Centre for Health Sciences and Primary Care, UMC Utrecht, Utrecht, The Netherlands
[3)] Department of Medical Microbiology, UMC Utrecht, Utrecht, The Netherlands
[4)] Julius Clinical, Zeist, The Netherlands

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ABSTRACT

Objectives: Our objective was to evaluate whether vaccination with the 13-valent pneumococcal conjugate vaccine (PCV13) prevents the incidence of community-acquired pneumonia (CAP) caused by influenza (influenza-associated CAP, IA-CAP) or other respiratory viruses in the elderly.
Methods: This analysis was part of the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA); a double blind, randomized, placebo-controlled trial in 84 496 immunocompetent individuals aged ≥65 years. CAP was defined by clinical and radiological criteria, and oropharyngeal swabs were collected from all individuals referred to a sentinel centre with a clinical suspicion of pneumonia. Presence of influenza A and B, parainfluenza 1, 2, 3 and 4, human adeno-, boca-, corona-, metapneumo-, rhino- and respiratory syncytial viruses was determined by real-time PCR.
Results: Of 3209 episodes of suspected pneumonia, viral aetiology was tested in 2917 and proportions with influenza virus, human metapneumovirus and respiratory syncytial virus were 4.6%, 2.5% and 3.1%, respectively. There were 1653 oropharyngeal swabs for PCR testing available from 1814 episodes that fulfilled criteria for CAP, yielding 23 first episodes of IA-CAP in the PCV13 and 35 in the in placebo group—vaccine efficacy for IA-CAP of 34.4% (95% CI −11.1% to 61.2%; p 0.117). Annual influenza vaccination was received by 672 (87.2%) in the PCV13 group and 719 (87.7%) in the placebo group of the confirmed CAP cases.
Conclusion: In a randomized study of 84 496 elderly individuals with a high uptake of influenza vaccination, PCV13 was not associated with a statistically significant reduction of influenza or virus-associated CAP. Overall incidence of non-influenza viral pneumonia was low. **S.M. Huijts, Clin Microbiol Infect 2018;24:764**

Introduction

Associations between infections with influenza virus and *Streptococcus pneumoniae* were described for the first time after the 1918 influenza pandemic [1], and subsequent studies have confirmed the relation between incidences of invasive pneumococcal disease and respiratory virus infections [2–4]. Moreover, animal studies have demonstrated pathogenic synergy between influenza virus and *S. pneumoniae* [5] and transmission and acquisition of *S. pneumoniae* was enhanced by influenza virus infection [6]. However, the exact mechanisms underlying these observations remain to be elucidated.

Pneumococcal conjugates vaccines (PCV) are effective in prevention of invasive pneumococcal disease, community-acquired pneumonia (CAP) and otitis media in children [7] and of vaccine type pneumococcal CAP and invasive pneumococcal disease in the

* Corresponding author. S.M. Huijts, Department of Respiratory Medicine, University Medical Centre Utrecht, 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).

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elderly [8]. In African children—with and without human immunodeficiency virus infection—the nine-valent PCV reduced the occurrence of pneumonia hospitalization associated with influenza A virus or any other of the investigated viruses (influenza B virus, parainfluenza virus 1, 2, 3, adenovirus, or respiratory syncytial virus) by 45% (95% CI 14%–64%) and 31% (95% CI 15%–43%), respectively [9]. This illustrates the importance of an *S. pneumoniae* superinfection in virus-associated pneumonias in children. Whether PCV has similar effects on virus-associated CAP in adults is unknown.

Within the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) [8] we evaluated the efficacy of 13-valuent PCV (PCV13) vaccination in prevention of a first episode of influenza-associated CAP (IA-CAP) and the prevalence of other human viruses (parainfluenza viruses, adenovirus, coronavirus, bocavirus, metapneumovirus, respiratory syncytial virus and rhinovirus) in elderly patients with CAP. Furthermore the proportion of IA-CAP was evaluated by year and season and the coverage of influenza vaccination among patients with CAP was determined.

Materials and methods

Study design

The current study was a pre-specified exploratory objective of the CAPiTA-trial in which 84 496 community-dwelling, immunocompetent individuals of 65 years and older were randomly assigned to receive PCV13 or placebo vaccination. The design of the study and main results were described in earlier publications [8,10]. Informed consent was obtained for all participants and the study was approved by the local human investigations committees in the participating hospitals.

After receiving PCV13 or placebo, study participants presenting with a clinical suspicion of pneumonia to any of the 59 participating sentinel centres (58 hospitals and one outpatient clinic) underwent a standardized clinical evaluation, including physical, radiological and microbiological evaluation, as well as an oropharyngeal swab and a urine sample for urinary antigen detection.

Sample processing

Oropharyngeal swabs were analysed in a single laboratory (University Medical Centre, Utrecht, the Netherlands) for the presence of 12 human viruses: influenza virus A and B, respiratory syncytial virus, parainfluenza virus 1, 2, 3 and 4, human rhinovirus, metapneumovirus, coronavirus, bocavirus and adenovirus, using the TaqMan® quantitative real-time PCR (Roche Molecular Systems, Inc., Pleasanton, CA, USA). Nucleic acid isolation, cDNA synthesis and PCR were performed as described by Loens et al. [11]. Influenza virus A and B, parainfluenza virus 1 and 3, and parainfluenza virus 2 and 4 were tested in a stepwise manner: first by testing positivity to any of the two viruses, followed by subtyping. If subtyping failed, episodes were considered non-typeable influenza or parainfluenza.

Urine samples were centrally processed (Pfizer Vaccines, New York, NY, USA) for detecting pneumococcal urinary antigens using BinaxNOW® (Alere, Waltham, MA, USA) and the serotype specific urinary antigen detection (UAD) assay for identifying the 13 pneumococcal serotypes included in PCV13 [12,13]. Cultures— from either sterile or non-sterile sites—and the UAD assay for *Legionella pneumophilia* were collected and processed according to local practice.

End-point definition

In these analyses two different end-point definitions were used: 'confirmed CAP' and 'suspected pneumonia'. 'Confirmed CAP' was defined as an episode with a chest X-ray consistent with pneumonia (see Supplementary material, Appendix S1 for details) together with the presence of two or more of the following clinical criteria: cough, purulent sputum, temperature >38.0°C or <36.1°C, auscultatory findings consistent with pneumonia, leucocytosis (>10 × 10^9 white blood cells/litre or >15% bands), C-reactive protein more than three times the upper limit of normal or hypoxaemia (oxygen pressure <60 mmHg while the patient was breathing room air). Patients with 'suspected pneumonia' were all individuals presenting with a clinical suspicion of pneumonia at a participating sentinel centre, which also included those with 'confirmed CAP'. Only individuals with symptom onset at least 14 days after vaccination were included in the efficacy analyses.

IA-CAP was defined as a 'confirmed CAP' episode with influenza virus A or B detected in the oropharyngeal swab (regardless of presence of a bacterial pathogen or another viral pathogen). 'Viral associated CAP' was defined as 'confirmed CAP' with any of the viruses (including influenza virus) detected in the oropharyngeal swab (also regardless of other bacterial pathogens). The same definitions were applied for 'suspected pneumonia'.

Microbiological aetiology was based on samples obtained within the first 2 days of hospital admission or those obtained at presentation in the emergency room, in case an individual was not admitted. A pathogen was considered as causative if cultured from blood or any other sterile site, or in case of UAD assay positivity in the absence of a cultured microorganism from blood or any other sterile site. UAD for *Legionella* was performed according to standard care practices. For the purpose of this exploratory analysis we considered microorganisms cultured from sputum as causative, when microbiological cultures and UAD assays did not yield a causative pathogen (or had not been performed).

Reasons for not collecting urine samples were systematically collected, but this was not the case for reasons for not collecting oropharyngeal swabs. Therefore, if both the urine sample and the oropharyngeal swab were not collected in the same patient we assumed that the reason would be similar for both samples, except if the reason was 'urine-specific', e.g. anuria. If no reason was reported and individuals were directly admitted to the intensive care unit or were not hospitalized we assumed 'severe illness' or 'not admitted' as reason for missing, respectively. The pneumonia severity index (not part of the pre-specified analysis) was calculated for all individuals [14]. These data were prospectively collected outside the CAPiTA study protocol in a separate Case Record Form, as part of the Etio-CAP study [15].

Seasonal influenza vaccination in the previous year—as reported by individual—was recorded. For determination of the proportion of 'confirmed CAP' cases who had received seasonal influenza vaccination in the previous year, only the first CAP episodes between 1 September and 31 August were used. To evaluate the contribution of IA-CAP to the total aetiology of CAP per year and per season, the proportion IA-CAP among all 'confirmed CAP' episodes with a swab available was stratified by year (between 1 September and 31 August) based on day of admission.

Statistical analysis

For evaluation of the vaccine efficacy only the first episode of IA-CAP or any other virus-associated CAP was evaluated. If two or more viruses were detected, of which one was influenza virus, this CAP episode was included in both efficacy analyses. A Cox-regression model with time to the first viral episode (e.g. IA-CAP) was used to determine vaccine efficacy by (1 − HR) × 100%. To correct for multiple testing a confidence interval of 99.3% was used. Analyses were performed according to intention-to-treat principles. The overall proportions, also including following episodes, were also presented.

For calculation of the pneumonia severity index it was assumed that missing variables were within the normal range (e.g. normal pH and normal p_{O_2} if no arterial blood gas test was performed).

In descriptive analyses, Pearson's chi-square test was used to calculate the p-value for categorical variables. The Mann–Whitney *U* test was used for continuous variables with a non-normal distribution. The statistical program IBM SPSS statistics (version 21.0, IBM Corp.; Armonk, NY, USA) was used for all analyses.

Results

Study population

There were 42 240 individuals receiving PCV13 and 42 256 receiving placebo vaccination. The mean duration of follow up was 3.97 years, in which 3209 episodes with 'suspected pneumonia' were identified in the participating sentinel centres. Of them 1814 had an episode fulfilling the criteria for 'confirmed CAP' (Fig. 1a) and from 1653 (91.1%) of these individuals an oropharyngeal swab was available. Fig. 2 displays the combination of available diagnostic methods in these individuals. In 1388 (84%) either all diagnostic methods (i.e. any culture, legionella UAD and any pneumococcal UAD) or a culture and a pneumococcal UAD were available. There were 3179 individuals meeting the criteria for 'suspected pneumonia' with 2917 (91.7%) having an oropharyngeal swab available (Fig. 1b).

Virus-associated CAP

Oropharyngeal swabs were missing in 161 confirmed CAP episodes, equally distributed among the treatment arms. Reasons for

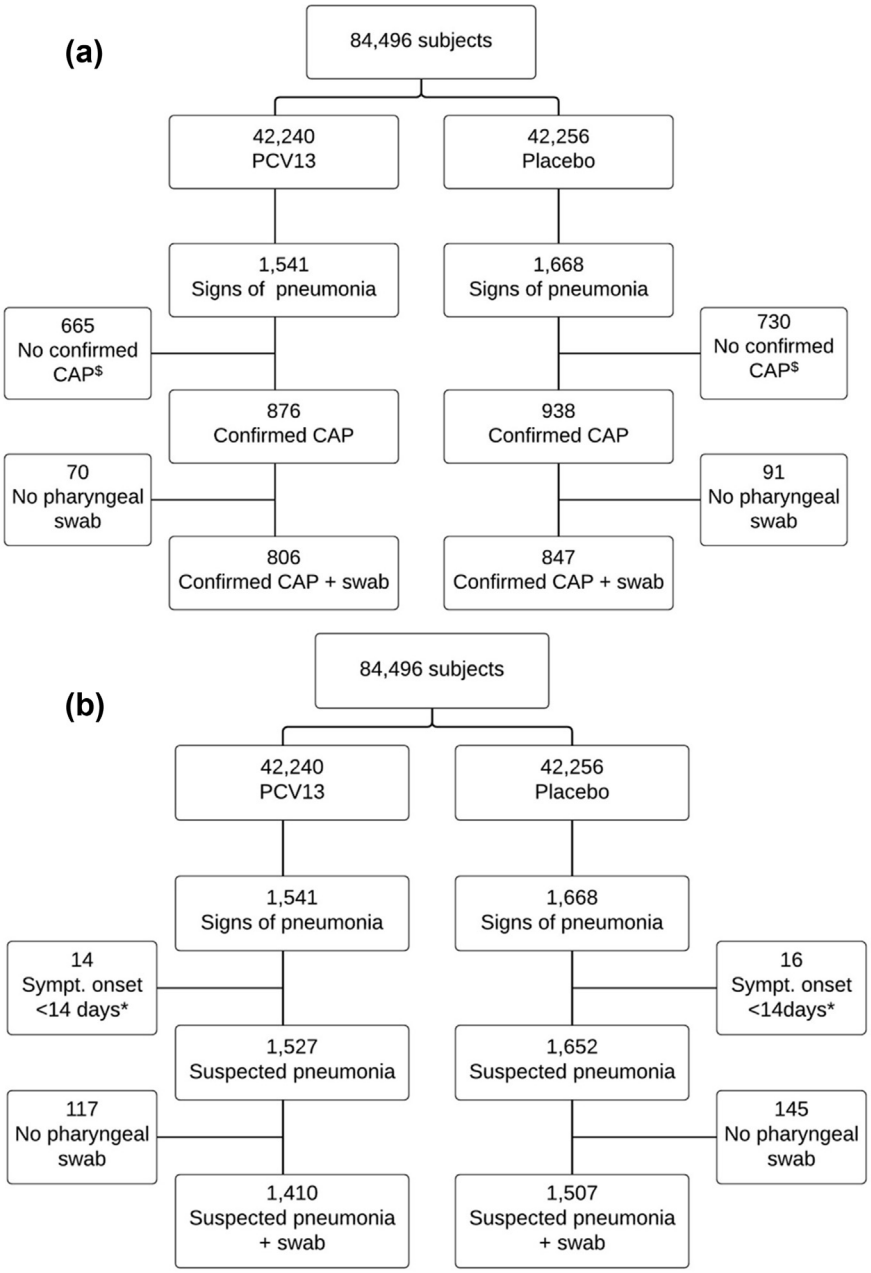

Fig. 1. (a) Flow-chart of 'confirmed CAP' study population ($n = 1653$). $ No confirmed CAP = episodes not fulfilling the definition 'confirmed CAP', i.e. chest X-ray not consistent with pneumonia and/or less than two clinical symptoms. (b) Flow-chart of 'suspected pneumonia' study population ($n = 2917$). *Symptom onset <14 days after vaccination. Abbreviations used: PCV13, 13-valent pneumococcal conjugate vaccine; CAP, community-acquired pneumonia; UAD, urinary antigen detection assay.

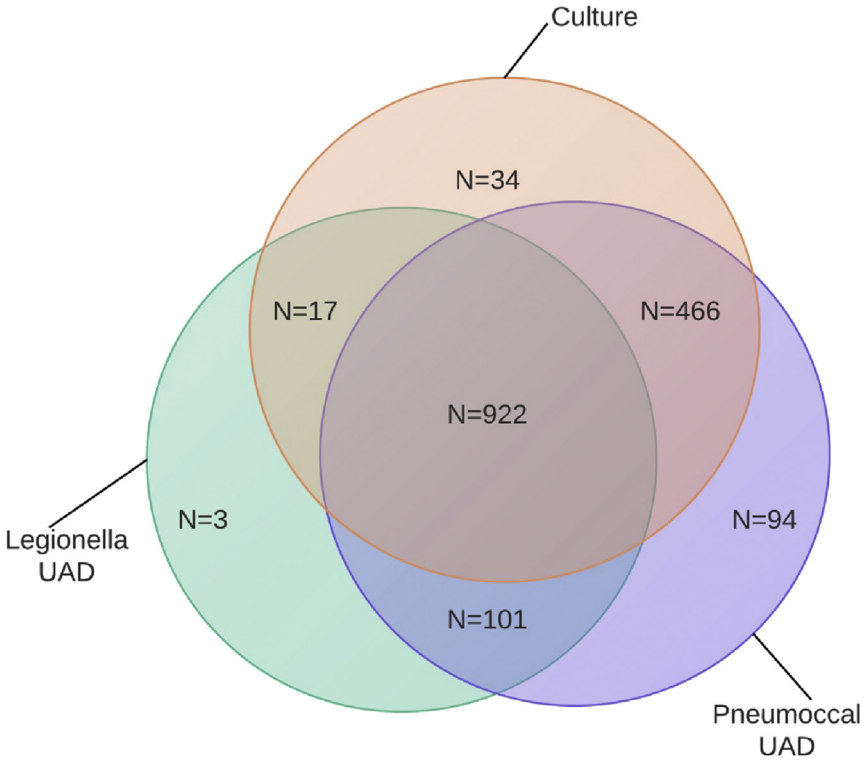

Fig. 2. Diagram of available diagnostic methods for individuals with confirmed CAP and a oropharyngeal swab available (n = 1653). Abbreviations used: CAP, community-acquired pneumonia; UAD, urinary antigen detection assay; Culture, either a sterile (e.g. blood) or non-sterile (e.g. sputum) sample available for culture; pneumococcal UAD, either conventional pneumococcal urinary antigen detection assay (i.e. Binax) or serotype-specific urinary antigen detection assay. Please note that this diagram excludes 16 patients who did not have any of these diagnostic methods available (i.e. only an oropharyngeal swab for viral analyses).

missing swabs are presented in the Supplementary material (Table S1). Subjects without a swab had a higher pneumonia severity index (p 0.010) and were less frequently hospitalized (p <0.001).

A virus was detected in 342 (20.7%) of the 1653 individuals with 'confirmed CAP', and in ten of them two viruses were detected (see Supplementary material, Table S2). Among the 'confirmed CAP' episodes with a swab available, 221 (13.4%) had only a viral pathogen detected, 121 (7.3%) had a viral–bacterial co-infection and 399 (23.8%) had a bacterial cause only. In 912 episodes no causative pathogen was detected (Table 1). Table 1 presents the most frequent pathogens in patients with confirmed CAP stratified by aetiological category and treatment arm. Among the episodes with the influenza virus or one of the parainfluenza viruses detected, there were five and nine non-typeable swabs, respectively.

Overall numbers of virus detected in patients with 'confirmed CAP' and 'suspected pneumonia' (including confirmed CAP) were 58 (3.5%) and 134 (4.6%) for influenza, 36 (2.2%) and 74 (2.5%) for human metapneumovirus, 35 (2.1%) and 91 (3.1%) for respiratory syncytial virus and 127 (7.7%) and 213 (7.3%) for rhinovirus (see Supplementary material, Table S3).

There were 58 first episodes of IA-CAP among the confirmed CAP episodes, 23 in the PCV13 arm and 35 in the placebo arm, which resulted in a vaccine efficacy of 34.4% (95%CI −11.1% to 61.2%; p 0.117). A total of 332 first episodes of virus-associated CAP occurred, and vaccine efficacy was 3.6% (95% CI −19.5% to 22.2%; p 0.736) (Table 2). Among the 'suspected pneumonia' episodes no significant reduction in IA-CAP or virus-associated CAP could be demonstrated either (Table 2).

In patients with an oropharyngeal swab available a viral mono-infection was more frequent in those with 'suspected pneumonia' excluding those with confirmed CAP (263 of 1264, 20.8%), than in patients with confirmed CAP (221 of 1653, 13.4%, p <0.001). In contrast, a bacterial cause more frequently occurred among confirmed CAP cases (n = 399, 24.1%) than among individuals with 'suspected pneumonia' excluding those with confirmed CAP (n = 226, 17.9%, p <0.001). Aetiological categories were equally spread among PCV13 and placebo (Table 1).

Influenza vaccination and seasonality

Accumulation of all first admissions between 1 September and 31 August of every study year resulted in 1711 episodes of 'confirmed CAP'. In 1591 individuals their influenza status in the previous year was known. Of these, 1391 (87.4%) received seasonal influenza vaccination, 672 (87.2%) of the 771 in the PCV13 arm and 719 (87.7%) of the 820 in the placebo arm. Seasonal Influenza vaccination was also reported for 49 of the 58 (84.5%) IA-CAP episodes. There was no significant difference in IA-CAP between individuals with and without seasonal influenza vaccination (p 0.378). The proportion of seasonal influenza vaccination per year gradually decreased from 91.8% in 2008/09 to 86.2% in 2012/13 (see Supplementary material, Fig. S1).

Annual rates of IA-CAP among the confirmed CAP episodes with swabs varied from 0.7% in the 2009/10 season to 8.1% in the 2012/13 season (Fig. 3).

Discussion

We were not able to detect a statistically significant reduction of first episodes of IA-CAP or other virus-associated CAP episodes among elderly vaccinated with PCV13 in a large, double-blind, randomized controlled trial with 84 496 participants and a high (but slightly decreasing) annual uptake of seasonal influenza

Table 1
Five most frequent pathogens in patients with confirmed CAP ($n = 1653$), stratified by aetiological category and treatment arm

Aetiological category	Pathogen	PCV13 (n)	Placebo (n)	Total (n)	% of total ($n = 1653$)
Bacterial	*Streptococcus pneumoniae*	107	137	244	14.8%
	Haemophilus (para)influenzae	25	24	49	3.3%
	Staphylococcus aureus	8	14	22	1.3%
	Pseudomonas aeruginosa and *Pseudomonas* spp.	6	14	20	1.2%
	Escherichia coli	4	7	11	0.7%
	Polymicrobial	8	3	11	0.7%
	Other	21	21	42	2.5%
	Total	179	220	399	24.1%
Viral	Human rhinovirus	43	35	78	4.7%
	Influenza virus A or B[a]	14	24	38	2.3%
	Human coronavirus	13	17	30	1.8%
	Human metapneumovirus	8	16	24	1.5%
	RSV	16	7	23	1.4%
	Two viral pathogens	3	5	8	4.8%
	Other	11	9	20	1.2%
	Total	108	113	221	13.4%
Bacterial–viral co-infection	*S. pneumoniae* & human rhinovirus	12	15	27	1.6%
	S. pneumoniae & human coronavirus	6	10	16	1.0%
	S. pneumoniae & influenza virus A or B[a]	5	7	12	0.7%
	S. pneumoniae & RSV	4	7	11	0.7%
	H. influenzae & human rhinovirus	3	8	11	0.7%
	Other bacteria & influenza virus A or B[a]	4	2	6	0.4%
	Other bacteria & other virus	27	11	38	2.3%
	Total	61	60	121	7.3%
No pathogen		458	454	912	55.2%
	Overall total	1154	1240	1653	100%

Abbreviations: CAP, community-acquired pneumonia; PCV13, 13-valent pneumococcal conjugate vaccine; RSV, respiratory syncytial virus.
[a] Note that 18 episodes of influenza virus A or B were diagnosed together with a bacterial pathogen and in two episodes two viral pathogens were detected (i.e. influenza virus could not be considered as the only causative pathogen).

Table 2
First episode of virus-associated 'confirmed CAP' and 'suspected pneumonia'

First episode	Confirmed CAP ($n = 1653$)						Suspected pneumonia ($n = 2917$)					
	PCV13	Placebo	VE	99.3%CI		p-value VE[a]	PCV13	Placebo	VE	99.3% CI		p-value VE[a]
Influenza virus (either A or B)	23	35	34.4%	−35.4%	68.2%	0.117	61[c]	71[c]	14.2%	−37.4%	46.4%	0.381
Influenza virus A	18[b]	28[b]	35.8%	−45.0%	71.6%	0.143	48[c]	57[c]	15.9%	−42.7%	50.4%	0.377
Influenza virus B	4[b]	3[b]	−33.2%	−100.0%	83.0%	0.707	10	9	−11.0%	−283.2%	67.9%	0.821
Detection of any virus	163	169	3.6%	−29.6%	28.3%	0.736	313	324	3.5%	−19.5%	22.0%	0.656
Para-influenza virus (1, 2, 3 or 4)	18	8	−124.8%	−607.2%	28.5%	0.057	34	22	−54.5%	−223.1%	26.1%	0.112
Human adenovirus	4	2	−99.9%	−1966%	80.7%	0.424	6	6	0.1%	−374.0%	78.9%	0.999
Human bocavirus	2	2	0.0%	−1383%	93.3%	1.000	2	3	33.4%	−681.6%	94.3%	0.657
Human coronavirus	26	34	23.6%	−54.3%	62.2%	0.302	50	72	30.6%	−14.0%	57.8%	0.047
Human metapneumovirus	17	19	10.6%	−120.0%	63.7%	0.737	37	36	−2.7%	−93.1%	45.4%	0.910
Respiratory syncytial virus	20	15	−33.2%	−234.6%	47.0%	0.401	51	40	−27.4%	−125.2%	27.9%	0.251
Human rhinovirus	63	62	−1.5%	−64.5%	37.3%	0.932	98	101	3.1%	−42.1%	33.9%	0.827

Abbreviations: CAP, community-acquired pneumonia; PCV13, 13-valent pneumococcal conjugate vaccine; VE, vaccine efficacy.
[a] Bonferroni cut-off level for multiple testing does apply for all parameters at a level of 0.00714. Resulting in non-significant differences for all values.
[b] Numbers do not sum to the total of influenza viruses, because in five cases the result for either influenza virus A or B was indeterminate.
[c] Numbers do not sum to the total of influenza viruses, because in eight cases the result for either influenza virus A or B was indeterminate.

vaccination and a low overall incidence of IA-CAP. The proportion of IA-CAP fluctuated by year and by season.

The impact of PCV13 vaccination on virus-associated CAP in adults has not been determined before. In children, vaccination with nine-valent PCV reduced the occurrence of IA-CAP [9]. Absence of a significant reduction in the current study may have resulted from the low incidence of detected influenza infections. Given the observed incidence in the placebo group, the minimal detectable effect size for IA-CAP and IA-'suspected pneumonia' (i.e. the effect size that would have been statistically significant) was a vaccine efficacy of 42% and 30%, respectively. Influenza virus and *S. pneumoniae* co-infection is more common among children than in adults [16] and there was a high uptake of seasonal influenza vaccination in the study population.

The observed prevalence of IA-CAP of 3.5% in the current study is similar to the reported 3.1% in a large study detecting viruses by PCR in adults hospitalized with CAP [17]. In other studies, prevalences of influenza virus among adult CAP patients varied between 0.4% [18] and 13% [19].

In the Netherlands, consultations for influenza-like illness at the general practitioner are monitored on a weekly basis during the influenza season and incidences fluctuate per year [20]. The observed Dutch influenza-like illness incidence patterns between 2008 and 2013, though, did not resemble the observed incidence patterns in our study cohort. On a national level influenza-like illness incidences were highest in 2012/13 and lowest in 2011/12. In our cohort the proportion of IA-CAP was highest in 2008/09 and lowest in 2009/10 (Fig. 3). This probably results from the different measures used (incidence versus proportion), also different patient populations are studied (individuals visiting their general practitioner versus patients hospitalized with CAP), and different severity and dominance of certain influenza strains might also play a role.

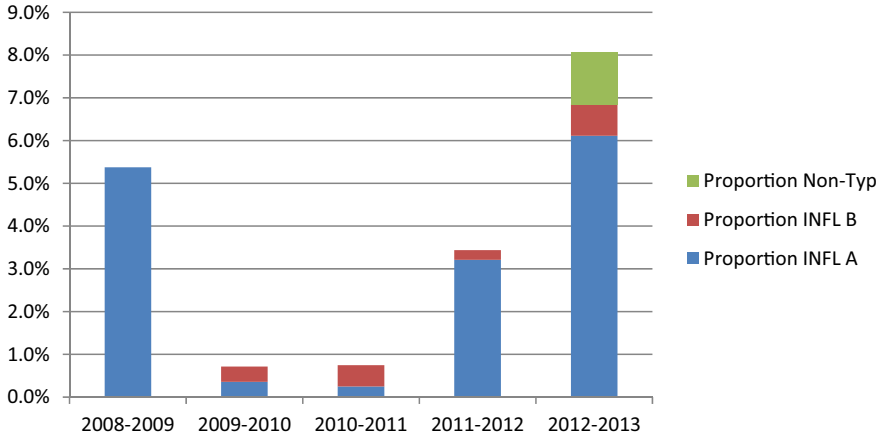

Fig. 3. Proportion of IA-CAP among confirmed CAP episodes with swab (n = 1653), stratified by year. Abbreviations used: IA-CAP, influenza associated community-acquired pneumonia; INFL A, influenza A; INFL B, influenza B; Non-typ, non-typeable influenza, i.e. subtyping failed. The proportion represents the part of IA-CAP cases among all confirmed CAP cases with oropharyngeal swab available, admitted in that period. Year 2008/9 starts at 1 September 2008 until 31 August 2009, this also applies to the following years.

Moreover, the incidences of influenza-like illness consultations cover all ages and are not defined by aetiology.

Our study also provides insight into the epidemiology of respiratory infections associated with non-influenza viruses in the elderly. For instance the proportion of episodes of confirmed and suspected CAP associated with respiratory syncytial virus detection in respiratory samples was 2.1% and 3.1%, respectively. These findings extend previous observations of low incidences of respiratory syncytial virus among severely ill patients admitted to intensive care units with respiratory infections [21,22].

The strengths of this study are its randomized, double-blind design, the sample size and standardized diagnostic methods to diagnose pneumonia and detect viruses. The PCR assay has been widely validated and is considered the reference standard for detection of respiratory viruses [11]. Weaknesses include missing oropharyngeal swabs in 161 confirmed episodes of CAP. Swabs were missing more frequently for individuals who were severely ill or in those who were not admitted, but due to the randomized and double-blind design it is unlikely that missed swabs have influenced the observed relative effects. Furthermore, our study cohort included relatively healthy adults, as immunodeficient individuals were excluded. Although study participants did have chronic comorbidities and some did develop immunodeficiencies during follow up, our findings may lack external validity for immunodeficient individuals. Generalizability of the results may also be limited for countries with other epidemiology of influenza and pneumococcal disease and with lower influenza vaccine uptake.

No statistically significant vaccine efficacy of PCV13 vaccination in the elderly on IA-CAP could be demonstrated in this study of 84 496 people with an average duration of follow up of 3.97 years. Yet, because of the low incidence of IA-CAP, a clinically relevant effect cannot be ruled out. PCV13 vaccination has been recommended for adults of 65 years and older in the USA since September 2014 [23] and observational studies after implementation may provide further evidence for the effects of pneumococcal conjugate vaccination on influenza infections.

Transparency declaration

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. MBon received a research grant from Pfizer. SH, FC, MBol, CW and MBon are employed by the University Medical Centre, Utrecht. CW participated in a Pfizer expert meeting. CW and SH report financial support from Pfizer for thesis printing.

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Contribution

SH was involved in the set up of the study, acquisition of data and drafting the manuscript. FC was involved in acquisition of data and critically revising the manuscript. MBol and CW were involved in set up of the study, acquisition of data and critically revising the manuscript. DG and MBon were involved in conception and design of the study and critically revising the manuscript. All authors approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2017.10.006.

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