



A public health evaluation of 13-valent pneumococcal conjugate vaccine impact on adult disease outcomes from a randomized clinical trial in the Netherlands



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ABSTRACT

Background: We conducted a post-hoc analysis of a double blind, randomized, placebo-controlled trial of 13-valent pneumococcal conjugate vaccine (PCV13) among adults aged 65 years or older to assess public health impact.

Methods: For all outcomes, we included all randomized subjects, using a modified intention-to-treat (mITT) approach to determine vaccine efficacy (VE), vaccine preventable disease incidence (VPDI) defined as control minus vaccinated group incidence, and numbers needed to vaccinate (NNV) (based on a five-year duration of protection).

Results: Results are reported for, in order, clinical, adjudicated (clinical plus radiologic infiltrate determined by committee), pneumococcal, and vaccine-type pneumococcal (VT-Sp) community-acquired pneumonia; invasive pneumococcal disease (IPD) and VT-IPD. VEs (95% CI) for all hospital episodes were 8.1% (−0.6%, 16.1%), 6.7% (−4.1%, 16.3%), 22.2% (2.0%, 38.3%), 37.5% (14.3%, 54.5%), 49.3% (23.2%, 66.5%), and 75.8% (47.6%, 88.8%). VPDI per 100,000 person-years of observation (PYOs) were 72, 37, 25, 25, 20, and 15 with NNVs of 277, 535, 816, 798, 1016, and 1342. For clinical CAP, PCV13 was associated with a reduction of 909 (−115, 2013) hospital days per 100,000 PYOs translating to a reduction over 5 years of one hospital day for every 22 people vaccinated. When comparing at-risk persons (defined by self-report of diabetes, chronic lung disease, or other underlying conditions) to not at-risk persons, VEs were similar or lower, but because baseline incidences were higher the VPDI were approximately 2–10 times higher and NNVs 50–90% lower.

Conclusion: A public health analysis of pneumonia and IPD outcomes in a randomized controlled trial found substantial burden reduction following adult PCV13 immunization implemented in a setting with an ongoing infant PCV7-PCV10 program. VPDI were higher among at-risk adults.

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1. Introduction

The Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA) was a parallel-group double-blind placebo-

controlled randomized clinical trial (RCT) of 13-valent pneumococcal conjugate vaccine (PCV13) in over 80,000 adults aged 65 years and older living in the Netherlands [1]. The trial was conducted from September 2008 through August 2013 with study enrollment from 2008 to 2010. The Netherlands included 7-valent PCV (PCV7) in the infant immunization program from 2006, and a 10-valent PCV (PCV10) from 2011. Influenza vaccine coverage among persons

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age 65 years and older was reported as 77–83% during the course of the study [1].

The RCT found that PCV13 was safe and efficacious in the per-protocol and modified intention-to-treat (mITT) analyses against a first episode of vaccine-type (VT) community-acquired pneumonia (CAP) (vaccine efficacy [VE] 45.6%; 95.2% CI, 21.8–62.5%), non-bacteremic, non-invasive VT-CAP (VE 45.0%; 95.2% CI, 14.2–65.3%), and VT invasive pneumococcal disease (VT-IPD) (VE 75.0%; 95% CI, 41.4–90.8%). Measurement of VT-CAP was possible due to the development of a sensitive and specific serotype-specific urine antigen detection (SSUAD) assay able to detect the 13 vaccine serotypes [2]. Although the study protocol included sensitive but non-specific clinical outcome measures, the only reported non-etiological defined outcome in the primary manuscript was a first-event analysis of all-cause CAP that met both clinical and radiologic protocol-specified criteria (VE, 5.1%; 95% CI, –5.1% to 14.2%), referred to as adjudicated CAP.

While use of strict diagnostic criteria to evaluate etiologically-confirmed endpoints with a per-protocol approach are essential for the design and conduct of well-controlled clinical studies for vaccine licensure to assess if the product has the intended biological effect, this approach does not quantify the full public health impact afforded by a vaccine. To address this gap, recent publications have presented a public health framework for analysis of clinical trial data [3–6]. In addition to VE – a relative measure of impact – these publications recommend use of an all events, ITT analysis of vaccine impact on more sensitive clinical outcomes (e.g., all-cause pneumonia or all-cause gastroenteritis) including use of vaccine preventable disease incidence (VPDI) and number needed to vaccinate (NNV) for events and healthcare utilization. Numerous studies have illustrated the utility of this approach including those for vaccines against *Haemophilus influenzae* type b (Hib) [7], *Streptococcus pneumoniae* [6,7], rotavirus [9], and more recently dengue [10] and malaria [4,11]. To complement already published data on VE [1,12] and cost-effectiveness [13] and to describe the potential broader health impact of vaccinating adults with PCV13, here we now report PCV13 impact on the relatively sensitive outcome of clinically defined CAP as well as infection-related mortality; VPDIs and NNVs for all pneumonia and IPD outcomes; and PCV13-associated reductions in hospitalization and intensive care unit (ICU) days.

2. Methods

2.1. Design and intervention

This was a parallel-group, double-blind, placebo controlled clinical trial that enrolled 84,496 individuals aged 65 years and older at 101 community-based sites across The Netherlands as described previously [1,14]. Each enrolled participant was randomly assigned in a 1:1 ratio to receive a single dose of PCV13 or placebo.

2.2. Study enrollment

Over 2200 general practitioners working in strategically selected geographic regions – where patients would be representative of the country as a whole and where a limited number of sentinel hospitals existed for patients with CAP or IPD – agreed to refer potentially eligible patients to the study. During the initial stage of study recruitment, which occurred during the influenza season, persons aged 65 years and older were selected to receive both influenza and study vaccines. During the subsequent recruitment period, persons received only study vaccine. Participants were excluded if they had previously received any 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 including human immunodeficiency virus infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, receipt of immunosuppressive therapy, or an organ or bone marrow transplant. Details on participant recruitment and selection as well as key inclusion and exclusion criteria have been described elsewhere [1,14].

2.3. Surveillance

Participant evaluation and surveillance for suspected CAP and IPD were performed at 59 sentinel sites (58 hospitals and one outpatient center) located in the regions in which participants were enrolled. All patients who presented to a sentinel site with suspected lower respiratory tract infection underwent a diagnostic assessment based on standard of care that included medical history, physical examination, chest radiograph, laboratory tests, urinary pneumococcal antigen testing by BinaxNOW®, sputum culture, and blood culture based on the patient's presenting medical status. If a patient was suspected by the treating physician of having pneumonia based on this evaluation, the staff at the sentinel center searched a database to determine if the patient was a study participant. If so, a research nurse collected a 5-ml urine aliquot within 24 h for SSUAD and a commercially available BinaxNOW® *S. pneumoniae* assay, both performed by Pfizer. Results of chest radiography were read centrally to provide consistent interpretation and a study related clinical report form (CRF) was completed. Urine was collected and tested by SSUAD for 93% of all patients referred to a sentinel center for CAP. However, the SSUAD is validated, and thus interpretable, only in the presence of a radiological infiltrate consistent with CAP. Consequently, VT-CAP and pneumococcal CAP were subsets of adjudicated CAP.

For detection of IPD, research nurses regularly reviewed laboratory culture data from sentinel sites. If a positive culture for *S. pneumoniae* was identified from a sterile site, and the patient was enrolled in this RCT, a CRF was completed and the pneumococcal isolate was sent to a reference laboratory for serotyping.

For all participants who presented to a sentinel center with suspected CAP or a diagnosis of IPD, information was collected about the hospital admission, ICU days, and readmission to a hospital for CAP or IPD within 1 month after discharge. A physician committee assigned cause of death including death due specifically to CAP or IPD.

As the study was designed not to interfere with standard of care, no specific follow-up visits were planned. Therefore, to assess person-years of follow-up, study staff contacted each participant's physician at least every month for the first 2.5 years and at least every 2 months thereafter; a list of study subjects was provided and the physician asked to indicate which subjects were still in their practice and which were lost to follow-up or had died. In addition, study staff visited each participating physician every 6 months to collect the same information directly from medical records. Loss to follow-up for each participant was defined as the earliest date among the following: death, leaving the physician's practice or the catchment area of any sentinel center, actively withdrawing from the study, or the participant's physician refusing further follow-up at his or her practice. In summary for each subject, the follow-up period began at the administration of vaccine (PCV13 or placebo) and ended at loss to follow-up, death, or study stop (28 August 2013), whichever occurred earlier.

2.4. Outcome definitions, outcome measures, and outcomes included

The current analysis compliments previously published data by including additional outcome definitions and outcome measures,

Table 1
Naming conventions for included outcomes.

Current Name	Definition	Name during original trial publication (2,3)
1. Clinical CAP	A subset of suspected CAP for patients with at least 2 of the following symptoms: (1) Cough (2) Production of purulent sputum or a change in the character of sputum (3) Temperature >38.0 °C or <36.1 °C (4) Auscultatory findings consistent with pneumonia including rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony) (5) Leukocytosis (>10 × 10 ⁹ white blood cells/liter or >15% bands) (6) C-reactive protein value >3 times the upper limit of normal (7) Hypoxemia with a partial oxygen pressure <60 mm Hg while breathing room air	Not included in the primary paper but was prespecified in the protocol as a criteria for CAP
2. Adjudicated CAP	A subset of clinical CAP that included patients who met the following radiological criteria. Within 48 h of presentation, the patient had a lateral and posterior-anterior chest radiograph if the clinical condition permitted and otherwise an anterior-posterior image; the image was subsequently adjudicated by a four-person committee whereby two of three blinded, independent readers had to agree that the radiograph was consistent with CAP	CAP
3. Sp-CAP	A subset of confirmed CAP that included patients with a positive result from sterile site culture, BinaxNOW®, or the sponsor's SSUAD assay. If a discrepancy existed between culture and SSUAD for serotype or presence of pneumococcus, the culture result was accepted regardless of urine antigen detection results	Confirmed Pneumococcal CAP
4. VT-CAP	A subset of Sp-CAP that included patients with a PCV13 vaccine-type identified by sterile site culture or SSUAD	Confirmed VT CAP
5. IPD	The identification of pneumococcus from a sterile site. A sterile site was defined as blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, or joint fluid (2,3)	IPD
6. VT-IPD	A subset of IPD, this included patients with the identification of PCV13 vaccine-type pneumococcus from a sterile site	VT IPD
7. Infection and infestation mortality	Any death assigned to a diagnosis in the system organ class of infection or infestation	Not included in the primary paper but defined in the method for categorizing deaths
8. All cause mortality	Same as previous publication	Death (included as a safety outcome)
9. Acute respiratory infection death	Any death with the following MedDRA preferred term: bronchitis; bronchitis bacterial; bronchopneumonia; lower respiratory tract infection; lower respiratory tract infection bacterial; lung abscess; pneumonia; pneumonia bacterial; pneumonia pneumococcal; respiratory tract infection	Not included in the primary paper but included as individual categories within the category of infection and infestation mortality

as well as an evaluation of public health impact. We assessed six clinical outcomes and three mortality outcomes (Table 1). Among the former, all but clinical CAP were pre-specified outcomes. While not a pre-specified outcome for analysis, clinical CAP was defined in the study protocol, and was the pre-requisite for adjudicated CAP. We also evaluated referral for CAP, as this was usually the pre-requisite for clinical CAP (rarely, patients were referred for diagnoses such as chest pain and possibly myocardial infarction); however, 97% of patients referred for CAP met the definition of clinical CAP (Fig. 1) giving almost identical results. Additionally, referral for CAP is not grounded in objective findings such as signs and symptoms. For these two reasons, we do not present these data.

For mortality, the primary study paper [1] reported no impact against VT-CAP associated deaths (an outcome with high specificity but low sensitivity) or all-cause mortality (an outcome with high sensitivity but low specificity). Consequently, we also included an analysis against “infection and infestation” mortality (Ref. [1] [Table S9]) (based on MedDRA coding, website: <https://www.meddra.org/>, last accessed 13 January 2018), an outcome with intermediate sensitivity and specificity. Within the category of infection and infestation mortality, we aggregated all sub-categories reflective of an acute respiratory infection death including the following preferred terms per MedDRA: bronchitis; bronchitis bacterial; bronchopneumonia; lower respiratory tract infection; lower respiratory tract infection bacterial; lung abscess; pneumonia; pneumonia bacterial; pneumonia pneumococcal; respiratory tract infection. In addition, for each non-fatal clinical outcome, we calculated PCV13 impact on healthcare utilization outcomes, including days of hospital admission and the sub-category of days admitted to an ICU.

Consistent with the pre-specified primary analysis [1] and a subsequent post-hoc analysis [12], here, we report first- and

all-episode results for the outcomes reported in Table 1. As specified in the analytic plan, separate CAP and IPD episodes were distinguished by onset ≥ 42 days after resolution of symptoms of a previous episode or by identification of a different pneumococcal serotype or a different organism from a sterile site culture. Episodes occurring within 14 days of vaccination were excluded, also consistent with the analytic plan.

2.5. Analysis

All enrolled participants who received PCV13 or placebo were included in the analysis. Cases were based on the modified intention-to-treat (mITT) analysis as described previously, which assumed an equivalent follow-up period between the PCV13 and placebo groups [1]. The only stratification applied was whether or not study participants had a condition that put them at recognized risk for pneumococcal disease (i.e., at-risk), which was chosen because many countries target PCVs to adults with at-risk conditions. At-risk conditions were based on self-report at the baseline screening visit of heart disease, lung disease, asthma, liver disease, diabetes with and without insulin use, or current cigarette smoking. Self-reported medical conditions were not verified by medical record review. As this study was not intended to recruit subjects with immunodeficiency, such as self-identification of splenectomy, participants not meeting eligibility criteria or who did not respond to any of the screening questions were not stratified by risk status.

VE for each of the clinical outcomes and death was estimated as 1 minus the ratio of incidence rates (per 100,000 person-years of observation [PYO]) in the PCV13 and placebo groups (this is different from the primary manuscript where the total PYO were assumed to be equal in the two vaccine groups [1] leading to minor differences in point estimates for some outcomes). We conducted

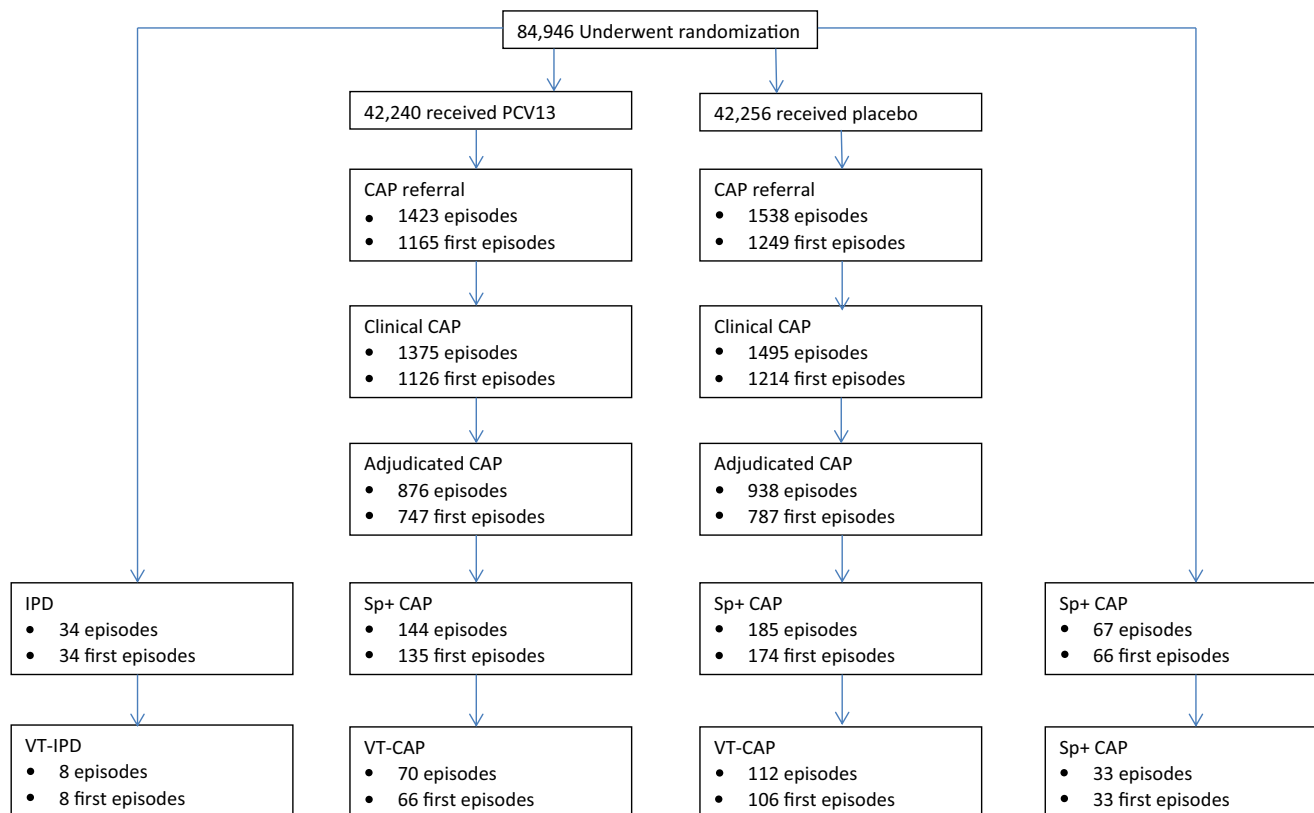


Fig. 1. Flow diagram of outcomes evaluated in the current analysis including clinical community acquired pneumonia (CAP), adjudicated CAP, pneumococcal CAP (Sp + CAP), vaccine type pneumococcal CAP (VT-CAP), invasive pneumococcal disease (IPD), and vaccine type IPD (VT-IPD).

three analyses of statistical variation to allow for comparison with previous studies. To account for sampling variability and individual subject variability, we chose a Poisson regression model with mixed effect (i.e., random subject variability with a fixed effect of the vaccine group) as the primary analysis method for estimation of VE and 95% CIs for both all and first episode analyses. As a secondary analysis, and consistent with the original report [1] (including two all-episode analyses) we also constructed nominal two-sided 95% CIs for VE using the exact method based on the conditional binomial distribution of the number of episodes in the PCV13 group given the total episodes in both groups [15]. Consistent with a previous PCV clinical trial that reported all and first episode analyses for pneumonia outcomes [16], Cox regression models were added as an additional sensitivity analysis for the first episode endpoints, with VE calculated as $(1 - \text{hazard ratio})$. We report nominal one-sided p-values consistent with other published individual and cluster randomized vaccine efficacy trials [17,18], based on the assumption that incidence rates should be higher in control than PCV13 groups and given that the VE was calculated as $1 - (\text{incidence rate ratio})$.

In addition to VE, we report VPDI and NNV for each outcome [3]. VPDI was defined as the control group incidence minus the intervention group incidence (VPDI has also been referred to as the incidence rate reduction or absolute rate reduction and is equivalent to the attributable risk). VPDI was calculated per 100,000 PYO. NNV was defined as one divided by the product of the VPDI and duration of protection with the latter estimated as 5 years $(=1/(\text{VPDI} \times 5))$ [19]; this formulation assumes that risk over the duration of immunity does not change. For VPDI, nominal 95% CIs were based on the Poisson regression model with mixed effect. Incidence rates were calculated using total PYO as the denominator by aggregating individual follow-up years for each study participant, which was calculated as the duration from vaccination to the earliest of study end, withdrawal from the study (e.g., moving out of the catchment area), or death.

To calculate incidence rates for hospital or ICU days, the numerator was the total days across all episodes for each relevant clinical outcome measure, while the denominator was PYO. The few patients that were not hospitalized were assigned zero days of hospitalization. NNV was calculated as for clinical outcomes. As with disease outcomes, for hospital and ICU days, we provide VPDIs and their 95% CI with the latter based on a bootstrap random sampling method. While 95% CI are provided, differences in incidence rates of hospital or ICU days between intervention and control groups were determined not only by the effect of differences in the rate of hospitalization but also by the length of hospital stay per episode, which depends on local standard of care. Because standard of care varies widely even with small differences in time or place, the 95% CI should not be taken to imply that the bounds of these results can be extrapolated outside the current setting.

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

3.1. Study population

A total of 42,240 persons received PCV13 and 42,256 placebo with a corresponding 167,874 and 167,748 PYO, respectively. The mean and median years of follow-up per subject varied from 3.9 to 4.0 for PCV13 and placebo groups, including when stratified

by at-risk status. While one outpatient center was included in the study, all but 40 clinical CAP episodes among vaccinees and 51 among controls of the total 2870 episodes involved hospitalization; these patients were assigned a hospital duration of zero days.

For clinical CAP, 1375 and 1495 clinical CAP episodes occurred among vaccine and placebo recipients, respectively, of which 1126 and 1214 were first episodes (Fig. 1, Table 2a, and Supplemental Table 2). These values were 50–60% higher than corresponding values for adjudicated CAP. Background disease incidence rates (i.e., among placebo recipients) for all episodes of clinical CAP, adjudicated CAP, Sp-CAP, and VT-CAP as well as IPD and VT-IPD were, respectively 891, 559, 110, 67, 40, and 20 per 100,000 PYO (Table 2a). The most common PCV13 serotypes among IPD cases were 7F and 1 while the most common PCV13 serotypes among non-bacteremic pneumonia cases were 19A, 3, and 7F (Supplemental Table 1).

3.2. All episode analyses

When evaluating all episodes, the adjusted VEs for clinical CAP, adjudicated CAP, Sp-CAP, VT-CAP, IPD, and VT-IPD were, respectively, 8.1%, 6.7%, 22.2%, 37.5%, 49.3%, and 75.8% (Table 2a). The all episode analyses included impact on health care utilization. We found that the control group experienced 9698 hospital days – of which 678 were ICU days – per 100,000 PYO (Table 2b) due to clinical CAP. PCV13 led to VPDIs for hospital and ICU days, respectively, due to clinical CAP of 909 and 138 per 100,000 PYO, with NNVs to prevent one hospital or ICU day of 22 and 145, respectively.

Persons not at-risk tended to have higher VEs for CAP outcomes than at-risk persons and similar VEs for IPD outcomes (Table 3a). However, because background incidence rates were higher for the former than the latter, VPDIs were higher and NNVs for prevention of disease episodes were lower for at-risk than not at-risk persons. The fold-increase in VPDI (and reduction in NNV for prevention of hospital episodes) for at-risk compared to not at-risk persons for the six outcomes varied from 1.9 for VT-CAP to 9.9 for adjudicated CAP. For all outcomes, PCV13 was associated with a greater reduction in hospital days for at-risk compared to not at-risk persons (Table 3b) with a fold-increase in VPDI varying from 2.2 for clinical CAP to 11.2 for IPD.

3.3. First episode analyses

While not the primary goal of this public health analysis, to provide context we present results for first events as well. The VEs for clinical CAP, adjudicated CAP, Sp-CAP, VT-CAP, IPD, and VT-IPD were, respectively, 7.3%, 5.2%, 22.5%, 37.8%, 48.5%, and 75.8% (Supplemental Table 2). Respective VPDIs were 53, 24, 23, 24, 19, and 15. While VEs were approximately the same for the first and all episode analyses, VPDIs were substantially higher for the latter, reflecting the greater background disease incidence for all episodes. When stratifying by risk status, the number of numerator events was correspondingly smaller, and particularly for the not at-risk population (Supplemental Table 3). Consequently CIs around point estimates of VE were wide.

3.4. Mortality analyses

As reported previously [1], the VE against all-cause mortality was 0 (Supplemental Table 4). Among the 5–6% of deaths associated with infection, PCV13 VE was 14.7% (95% CI, –5.5% to 31.1%), while among the 2–3% of deaths associated with ARI, PCV13 VE was 22.9% (95% CI, –5.1% to 43.4%). While ARI mortality had a slightly higher VE than infectious disease mortality, VPDI was lower.

Table 2a

Impact of 13-valent pneumococcal conjugate vaccine (PCV13) on number of all disease episodes (primarily hospitalizations) by outcome category. Number of persons = 42,240 for the PCV13 and 42,256 for the control groups; person-years of observation (PYO) were 167,874 for the PCV13 and 167,748 for the control groups. CAP = community acquired pneumonia, Sp-CAP = pneumococcal CAP, VT = serotypes included in PCV13, IPD = invasive pneumococcal disease, VPDI = vaccine preventable disease incidence, NNV = number needed to vaccinate to prevent one episode (assuming 5 years duration of PCV13 immunity). Some of the data on vaccine efficacy for adjudicated CAP, Sp-CAP, VT-CAP, IPD, and VT-IPD have been presented previously [1,12].

Outcome [*]	Episodes		Vaccine efficacy		Incidence per 100,000 PYO			NNV
	PCV13	PLACEBO	Random poisson (95% CI) [†] (1-SIDED P-VALUE)	Exact method (95% CI) [‡] (1-SIDED P-VALUE)	PCV13	PLACEBO	VPDI (95% CI) [§]	
Clinical CAP	1375	1495	8.1% (−0.6%, 16.1%) (0.034)	8.1% (1.0%, 14.6%) (0.013)	819.1	891.2	72.2 (−5.3, 149.6)	277
Adjudicated CAP	876	938	6.7% (−4.1%, 16.3%) (0.11)	6.7% (−2.4%, 15.0%) (0.076)	521.8	559.2	37.4 (−21.5, 96.2)	535
Sp-CAP	144	185	22.2% (2.0%, 38.3%) (0.016)	22.2% [§] (2.8%, 37.9%) (0.014)	85.8	110.3	24.5 (2.0, 47.0)	816
VT-CAP	70	112	37.5% (14.3%, 54.5%) (0.0018)	37.5% [§] (15.1%, 54.3%) (0.0011)	41.7	66.8	25.1 (8.4, 41.8)	798
IPD	34	67	49.3% (23.2%, 66.5%) (0.0007)	49.3% [§] (22.3%, 67.5%) (0.0007)	20.3	39.9	19.7 (7.9, 31.5)	1016
VT-IPD	8	33	75.8% (47.6%, 88.8%) (0.0002)	75.8% [§] (46.5%, 90.3%) (<0.0001)	4.8	19.7	14.9 (7.4, 22.4)	1342

^{*} All outcomes were defined in the protocol and all except clinical CAP were pre-specified in the study analysis plan.

[†] Poisson regression model with mixed effects.

[‡] Presented previously with identical point estimates [1].

[§] Exact methods based on conditional binomial distribution.

[§] Presented previously with identical point estimates [12].

Table 2b

Impact of 13-valent pneumococcal conjugate vaccine (PCV13) on number of hospital and intensive care unit (ICU) days by outcome category for all hospitalizations. PYO = person-years of observation, CAP = community acquired pneumonia, Sp-CAP = pneumococcal CAP, VT = serotypes included in PCV13, IPD = invasive pneumococcal disease, VPDI = vaccine preventable disease incidence, NNV = number needed to vaccinate to prevent one hospital day (assuming 5 years duration of PCV13 immunity).

Outcome	Episodes		Average days per hospitalization		Total hospital days		Days hospitalization per 100,000 PYO			NNV
	PCV13	PLACEBO	PCV13	PLACEBO	PCV13	PLACEBO	PCV13	PLACEBO	VPDI (95% CI) [*]	
ALL HOSPITAL DAYS										
Clinical CAP	1375	1495	10.7	10.9	14,755	16,268	8789	9698	909 (−115, 2013)	22
Adjudicated CAP	876	938	11.5	11.5	10,046	10,782	5984	6428	443 (−374, 1357)	45
Sp-CAP	144	185	10.7	11.5	1538	2133	916	1272	355 (42, 700)	56
VT-CAP	70	112	10.0	11.6	702	1299	418	774	356 (134, 602)	56
IPD	34	67	14.6	14.7	495	986	295	588	293 (61, 546)	68
VT-IPD	8	33	19.5	15.6	156	513	93	306	213 (72, 371)	94
INTENSIVE CARE UNIT DAYS										
Clinical CAP	1375	1495	0.7	0.8	907	1137	540	678	138 (−94, 407)	145
Adjudicated CAP	876	938	0.9	1.0	804	920	479	548	70 (−146, 315)	288
Sp-CAP	144	185	1.1	1.1	163	206	97	123	26 (−78, 129)	778
VT-CAP	70	112	1.3	1.2	93	135	55	80	25 (−64, 113)	797
IPD	34	67	2.7	2.0	91	133	54	79	25 (−55, 106)	797
VT-IPD	8	33	6.5	2.6	52	87	31	52	21 (−41, 83)	957

^{*} Based on 2000 runs of bootstrap resampling with replacement.

Table 3a

Impact of 13-valent pneumococcal conjugate vaccine (PCV13) on number of all disease episodes (primarily hospitalizations) by outcome category, stratified by risk category. Number of persons in the PCV13 group for at-risk and not at-risk populations = 20,680 (81,676 person-years of observation [PYOs]) and 21,339 (85,408 PYOs), respectively; number of persons in the placebo group for at-risk and not at-risk populations = 20,705 (81,668 PYOs) and 21,340 (85,318 PYOs), respectively. CAP = community acquired pneumonia, Sp-CAP = pneumococcal CAP, VT = serotypes included in PCV13, IPD = invasive pneumococcal disease, VPDI = vaccine preventable disease incidence, NNV = number needed to vaccinate to prevent one episode (assuming 5 years duration of PCV13 immunity).

Outcome [*]	Risk group	Episodes		Vaccine efficacy		Incidence per 100,000 PYO			NNV
		PCV13	PLACEBO	Random poisson (95% CI) [†] (1-SIDED P-VALUE)	Exact method (95% CI) [‡] (1-SIDED P-VALUE)	PCV13	PLACEBO	VPDI (95% CI) [†]	
Clinical CAP	At-risk	1078	1177	8.4% (−1.6%, 17.5%) 0.049	8.4% (0.4%, 15.8%) (0.02)	1319.9	1441.2	121.4 (−22.3, 265.0)	165
	Not at-risk	270	300	10.1% (−7.9%, 25.1%) 0.13	10.1% (−6.3%, 24.0%) (0.11)	316.1	351.6	35.5 (−25.3, 96.3)	563
Adjudicated CAP	At-risk	678	737	8.0% (−4.2%, 18.8%) 0.094	8.0% (−2.2%, 17.2%) (0.062)	830.1	902.4	72.3 (−35.4, 180.1)	277
	Not at-risk	179	185	3.3% (−21.8%, 23.3%) 0.39	3.3% (−19.4%, 21.7%) (0.40)	209.6	216.8	7.3 (−42.0, 56.5)	2757
Sp-CAP	At-risk	114	147	22.5% (−0.7%, 40.3%) 0.028	22.5% (0.3%, 39.8%) (0.024)	139.6	180.0	40.4 (−1.0, 81.8)	495
	Not at-risk	25	36	30.6% (−16.3%, 58.6%) 0.083	30.6% (−18.8%, 60.1%) (0.10)	29.3	42.2	12.9 (−5.2, 31.1)	1547
VT-CAP	At-risk	60	88	31.8% (3.3%, 52.0%) 0.016	31.8% (4.3%, 51.7%) (0.013)	73.5	107.8	34.3 (3.2, 65.4)	583
	Not at-risk	8	23	65.3% (21.0%, 84.7%) 0.0058	65.3% (19.5%, 86.6%) (0.0053)	9.4	27.0	17.6 (4.5, 30.6)	1137
IPD	At-risk	25	51	51.0% (20.6%, 69.8%) 0.0019	51.0% (19.4%, 70.9%) (0.0019)	30.6	62.5	31.8 (10.7, 52.9)	628
	Not at-risk	8	15	46.7% (−25.6%, 77.4%) 0.075	46.7% (−33.9%, 80.4%) (0.11)	9.4	17.6	8.2 (−2.8, 19.2)	2435
VT-IPD	At-risk	6	26	76.9% (43.9%, 90.5%) 0.0006	76.9% (42.7%, 92.2%) (0.0003)	7.4	31.8	24.5 (10.9, 38.1)	817
	Not at-risk	2	7	71.5% (−37.4%, 94.1%) 0.059	71.5% (−49.9%, 97.1%) (0.090)	2.3	8.2	5.9 (−1.0, 12.8)	3411

^{*} All outcomes were defined in the protocol and all except clinical CAP were pre-specified in the study analysis plan.

[†] Poisson regression model with mixed effects.

[‡] Exact methods based on conditional binomial distribution.

Table 3b

Impact of 13-valent pneumococcal conjugate vaccine (PCV13) on number of hospital and intensive care unit (ICU) days by outcome category for all hospitalizations, stratified by risk status. PYO = person-years of observation, CAP = community acquired pneumonia, Sp-CAP = pneumococcal CAP, VT = serotypes included in PCV13, IPD = invasive pneumococcal disease, VPDI = vaccine preventable disease incidence, NNV = number needed to vaccinate to prevent one hospital day assuming 5 years duration of PCV13 immunity.

		Episodes		Average days per hospitalization		Total hospital days		Days hospitalization per 100,000 PYO			
Outcome	Risk group	PCV13	PLACEBO	PCV13	PLACEBO	PCV13	PLACEBO	PCV13	PLACEBO	VPDI (95% CI) [*]	NNV
<i>All hospital days</i>											
Clinical CAP	At-risk	1078	1177	11.0	11.0	11,855	12,953	14,515	15,861	1346 (–632, 3370)	15
	Not at-risk	270	300	9.7	10.4	2607	3110	3052	3645	593 (–191, 1418)	34
Adjudicated CAP	At-risk	678	737	11.7	11.5	7899	8504	9671	10,413	742 (–817, 2320)	27
	Not at-risk	179	185	10.8	11.2	1935	2079	2266	2437	171 (–525, 892)	117
Sp-CAP	At-risk	114	147	10.3	11.5	1175	1688	1439	2067	628 (59, 1272)	32
	Not at-risk	25	36	12.7	10.4	318	373	372	437	65 (–208, 334)	308
VT-CAP	At-risk	60	88	10.3	11.7	620	1029	759	1260	501 (80, 959)	40
	Not at-risk	8	23	8.9	10.5	71	242	83	284	201 (60, 370)	100
IPD	At-risk	25	51	12.2	14.2	304	724	372	887	514 (132, 960)	39
	Not at-risk	8	15	22.4	14.5	179	218	210	256	46 (–196, 287)	435
VT-IPD	At-risk	6	26	17.8	15.4	107	399	131	489	358 (115, 648)	56
	Not at-risk	2	7	24.5	16.3	49	114	57	134	76 (–66, 222)	262
<i>Intensive care unit days</i>											
Clinical CAP	At-risk	1078	1177	0.7	0.7	723	844	885	1033	148 (–288, 609)	135
	Not at-risk	270	300	0.7	1.0	184	288	215	338	122 (–88, 391)	164
Adjudicated CAP	At-risk	678	737	0.9	0.9	621	631	760	773	12 (–370, 406)	1623
	Not at-risk	179	185	1.0	1.5	183	284	214	333	119 (–93, 386)	169
Sp-CAP	At-risk	114	147	1.1	1.3	130	186	159	228	69 (–132, 277)	292
	Not at-risk	25	36	1.3	0.6	33	20	39	23	–15 (–73, 30)	NA
VT-CAP	At-risk	60	88	1.6	1.4	93	124	114	152	38 (–147, 218)	527
	Not at-risk	8	23	0	0.5	0	11	0	13	13 (0, 35)	1551
IPD	At-risk	25	51	2.5	2.3	62	119	76	146	70 (–76, 237)	287
	Not at-risk	8	15	3.6	0.9	29	14	34	16	–18 (–77, 27)	NA
VT-IPD	At-risk	6	26	6.8	3.1	41	80	50	98	48 (–75, 171)	419
	Not at-risk	2	7	5.5	1.0	11	7	13	8	–5 (–39, 25)	NA

NA: Not applicable to calculate NNV since VE was <0.

^{*} Based on 2000 runs of bootstrap resampling with replacement.

4. Discussion

Pneumococcus is considered one of the main causes of CAP in adults worldwide. The Community Acquired Pneumonia Immunization Trial in Adults was the first and, to date, only randomized double-blind placebo-controlled PCV efficacy trial in adults. Using a regulatory framework focused on VE for first episodes of etiologically defined outcomes, the primary study publication demonstrated the safety and efficacy of PCV13 against all VT-CAP, non-bacteremic/non-invasive VT-CAP, and VT-IPD [1]. Subsequent publications evaluated all episodes [12] and modelled cost-effectiveness [13]. The current analysis has further quantified the public health impact of PCV13 using a public health framework that included VPDIs and NNVs for clinically-defined pneumonia outcomes and hospital utilization outcomes.

While for some outcomes uncertainty (as measured by the CI) was relatively large, taken as a whole the data from this analysis were coherent with PCV13 protection against different pneumococcal infection syndromes. More sensitive, clinically defined outcomes had a lower VE but higher VPDIs than more specific etiologically confirmed outcomes. PCV13 prevented 8.1% of clinical CAP, i.e., CAP regardless of etiology or radiological confirmation. The IPD VPDIs indicated the potential for vaccine impact against this clinically severe outcome, yet it was a fraction of that for clinical CAP, particularly when considering all episodes. PCV13 worked similarly among at-risk and not-at-risk persons but VPDIs were higher among the former due to the higher background disease incidence. Within the specific context of health care delivery in The Netherlands during the trial, the reduction of disease episodes that primarily involved hospitalization translated to a reduction in hospitalization and ICU days, particularly among at-risk persons. Lastly, in an elderly population with high mortality, no impact on all-cause mortality was demonstrated. However, among the fraction of deaths associated with infection, PCV13 may have had an impact, entirely among at-risk persons who were at higher background risk of infectious disease, and possibly pneumococcal, mortality (although we recognize the study was not designed to detect mortality endpoints as reflected in the wide CIs and lack of statistical significance).

Comparable data from other randomized PCV trials in adults do not exist. However, these results are comparable to a VPDIs of 230 medically attended events per 100,000 PYO with 6% VE for all clinical pneumonia (outpatient, emergency room, inpatient) found for PCV7 in children <4 years of age in the United States [20] and 180 per 100,000 PYO with 12% VE found for PCV9 impact against all-cause severe clinical pneumonia among children age 6–104 weeks in The Gambia [8]. Both of these results were pivotal evidence for decisions to include PCV in pediatric national immunization programs globally. Additionally, the VPDIs was comparable to the 271 per 100,000 PYO seen for hospital-diagnosed pneumonia in Finnish children [6]. NNVs were even more similar between Dutch elderly and Finnish children because NNVs take into account duration of protection; duration of protection is less important for children because pneumonia risk drops precipitously after age 2 years but highly relevant for an elderly population whose pneumonia risk rises precipitously over time. Furthermore, the VPDIs shown in the current analysis are likely to be underestimates. Subsequent analysis of incidence rates in the Community Acquired Pneumonia Immunization Trial in Adults found that this study missed approximately 30–40% of pneumonia outcomes (depending on the definition) [21]. While this would not alter VE estimates, the VPDIs will be underestimated and corresponding NNVs overestimated.

PCV13 prevented approximately twice as many episodes of clinical CAP as adjudicated CAP. Since the latter was a subset of the former, this finding is expected and consistent with pediatric PCV studies [22]. Surprisingly, the VE for these two outcomes

was similar, suggesting that the addition of the adjudicated radiologic criterion for CAP did not increase specificity for PCV13-preventable pneumonia. This contrasts to the increased specificity seen with World Health Organization (WHO) criteria for radiological endpoints (an obvious alveolar infiltrate, lobar consolidation, or pleural effusion as judged by two of three readers) for PCV and *H. influenzae* type b conjugate vaccine trials in children [23]. The successful performance of the WHO pediatric definition, as judged by clinical trials [8,20], suggests a similar process, and possibly a similar definition, should be assessed for adults.

We found relatively high VPDIs for clinical CAP compared to etiologically-confirmed CAP. Some of the additional VPDIs likely occurred because non-adjudicated CAP nevertheless had VT disease but was not included in VT-CAP because the SSUAD was validated only for CAP in the presence of a radiological infiltrate. Additionally, The SSUAD was validated against blood culture confirmed pneumonia with high sensitivity and specificity [2]. However, SSUAD sensitivity for non-bacteremic pneumonia remains undefined since no gold standard exists; if non-bacteremic pneumonia leads to less antigenuria than bacteremic pneumonia, SSUAD may have lower sensitivity for the former. Another theory is that some VT pneumococcal infections occur in the causal chain of disease but are absent at presentation, for example if prior pneumococcal pneumonia precipitated more pneumonia following subsequent infection from other pathogens (including non-VT pneumococcus). A similar theory has been suggested for pediatric otitis media: a first episode of VT-Sp acute otitis media can lead to recurrent otitis media caused by non-VT-Sp or non-typable *H. influenzae*, and thus PCV13 prevention of a first episode of VT acute otitis media can prevent subsequent recurrent episodes caused by other organisms [24]. Nevertheless, biologic mechanisms of CAP in the elderly likely differ from otitis media during childhood, so this theory would require further evaluation. Lastly vaccine may have prevented disease due to cross-reactive serotypes not included in the SSUAD test, although little biological evidence exists for this.

In addition to the impact on clinically-defined CAP episodes that mainly involved hospitalization, the current analysis provides the impact on overall hospital days and the subcategory of ICU days. Similar data on rate reductions for hospital duration have not been presented from other randomized PCV trials. The NNVs to prevent a single hospital day for clinical CAP, which was calculated as 16 and 22 for at-risk and all participants, respectively, can be put in perspective considering the cost of a hospital day for CAP in The Netherlands of €686 (in 2012 euros) [25]. These NNV values cannot be generalized outside the study setting given the extreme variability in healthcare utilization over time and place. For example, the total cost of a hospital day for CAP in the US is higher at approximately \$2300–2500 (in 2007 to 2009 US dollars) [26,27]; however, whether PCV represents a more efficient intervention in the US or the Netherlands also will depend on the threshold for hospitalization, differences in the average length of hospital stay and propensity for using ICU care.

The current analysis has several limitations. The pre-specified analytic plan did not include VPDIs or NNVs for any outcomes or VE for clinical CAP or infection and infestation mortality. Nevertheless, the additional outcome variables were pre-defined in the original study protocol (clinical CAP) or the determination method was pre-defined (infection-associated or ARI mortality). Additionally, this study used an individually randomized design, which prevented assessment of whether adult vaccination provided further indirect effects beyond those resulting from infant immunization; if this occurred, VPDIs would be underestimated and NNVs overestimated. NNVs also will be overestimated if the duration of immunity for PCV13 is longer than 5 years or if risk of illness increases for patients as they age over the duration of immunity.

The most substantial limitation is that results of this study may not apply directly to other epidemiological environments. First, the current results were from The Netherlands, a country with a long-standing routine infant pneumococcal immunization program, initially with PCV7 and subsequently with PCV10, with high coverage (approximately 96% for the third dose during the study period) [28]. Countries with no pneumococcal infant vaccination program, those with recent PCV introduction, or those with relatively low infant PCV coverage (either nationally or focally) may observe a larger public health impact from direct PCV13 vaccination in adults because of sub-optimal herd protection afforded by childhood vaccination. Second, this study was conducted in the context of high adult influenza vaccination coverage (>80% for 2008/9 and 2009/10, the highest in Europe) [29]. Because influenza infection may increase pneumococcal pneumonia risk [30], countries without strong adult influenza vaccination programs may have greater impact from adult PCV immunization than reported here. Moreover, influenza H3N2 may be more likely than H1N1 to precipitate pneumococcal pneumonia [30] and during our study pandemic A/H1N1 was common; consequently, adult PCV13 vaccination programs may have greater impact than reported here during years when H3N2 predominates. Third, childhood immunization programs may eventually reduce adult vaccine serotype disease to residual levels. This study took place during the use of PCV7 and then PCV10 among infants, and 1.5%, 4.3% and 7.6% of the total CAP episodes (mITT cases) were caused by PCV7, PCV10 and PCV13 serotypes, respectively. Residual disease from serotypes in PCV13 but not in either of the other products may be substantially reduced when infant programs with PCV13 are in longstanding use, which may imply less impact of adult PCV13 immunization in countries using PCV13. Current evidence, however, suggests that even in countries with many years of high coverage from PCV infant vaccination programs, vaccine serotypes continue to cause some burden of IPD – and thus probably non-bacteremic pneumonia – in adults [31]. To resolve this issue, continued monitoring will be required to determine the level of persistent disease and whether transmission of VT disease occurs among adults in the setting of high, long-term PCV use. Fourth, new, higher valent PCVs may be licensed in adults before licensure in infants. In this case, direct adult vaccination may have a higher impact than reported here, at least until childhood immunization programs have matured. Lastly, given the large global variations in hospital care, the PCV13 impact on hospital utilization outcomes we report cannot be extrapolated with certainty to other settings. Nevertheless, we hope our findings will encourage other jurisdictions to consider the potential for PCVs to reduce the number of days the elderly spend in the hospital, including the ICU. In summary, the total impact of adult PCV13 immunization will be influenced by several factors including pneumonia and IPD incidence, the proportion of these outcomes due to VTs, and the proportion of these outcomes that become hospitalized or admitted to the ICU; influenza vaccine coverage; infant PCV choice, schedule (e.g., if some schedules lead to less reduction in VT-Sp transmission), and coverage; and PCV13 VE against different outcomes, including possibly carriage.

Our results complement other analyses from the Community Acquired Pneumonia Immunization Trial in Adults [1,12,13] in providing an overall assessment of the public health benefit of directly immunizing elderly adults with PCV13. More generally, as has increasingly been done [4,17–19], the public health approach used here should be incorporated into future randomized double blind vaccine efficacy trials by including relevant outcomes in pre-specified analytic plans. Such an approach can assist with providing directly measured (rather than modeled) data on the public health impact of introducing a vaccine into a population. Specifically, data on VPDIs and NNVs for both clinically-defined and healthcare utilization outcomes could be used by decision-

makers as additional evidence when evaluating whether or not to include vaccines in their national immunization programs. Given their importance, such data also could be considered for inclusion into regulatory pathways for licensure of new vaccines, as has been advocated for recently [5].

5. Author contributions

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

6. Declaration of interests

BDG, QJ, HLS, CW, DS, and LJ are employees of Pfizer Inc. KLOB reports research grant funding for pneumococcal vaccines from Pfizer, GSK, Gavi the Vaccine Alliance, the Bill & Melinda Gates Foundation, and the US National Institutes of Health and has served on pneumococcal advisory groups for Merck, Sanofi Pasteur, Affinivax, ClearPath, and PATH. RGW participates in a clinical evaluation committee for a Pfizer-sponsored antibiotic trial. 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.

7. 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.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.vaccine.2018.05.097>.

References

- [1] Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med* 2015;372(12):1114–25.
- [2] Huijts SM, Pride MW, Vos JM, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. *Eur Respir J* 2013;42(5):1283–90.
- [3] Feikin DR, Scott JA, Gessner BD. Use of vaccines as probes to define disease burden. *Lancet* 2014;383(9930):1762–70.
- [4] Gessner BD, Feikin DR. Vaccine preventable disease incidence as a complement to vaccine efficacy for setting vaccine policy. *Vaccine* 2014;32(26):3133–8.
- [5] Wilder-Smith A, Longini I, Zuber PL, et al. The public health value of vaccines beyond efficacy: methods, measures and outcomes. *BMC Med* 2017;15(1):138.
- [6] Palmu AA, Jokinen J, Nieminen H, et al. Vaccine-preventable disease incidence of pneumococcal conjugate vaccine in the Finnish invasive pneumococcal disease vaccine trial. *Vaccine* 2018;36(14):1816–22.
- [7] Gessner BD, Sutanto A, Linehan M, et al. Incidences of vaccine-preventable Haemophilus influenzae type b pneumonia and meningitis in Indonesian children: hamlet-randomised vaccine-probe trial. *Lancet* 2005;365(9453):43–52.
- [8] Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in

- The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005;365(9465):1139–46.
- [9] Feikin DR, Laserson KF, Ojwando J, et al. Efficacy of pentavalent rotavirus vaccine in a high HIV prevalence population in Kenya. *Vaccine* 2012;30(Suppl 1):A52–60.
 - [10] Gessner BD, Wilder-Smith A. Estimating the public health importance of the CYD-tetravalent dengue vaccine: Vaccine preventable disease incidence and numbers needed to vaccinate. *Vaccine* 2016;34(20):2397–401.
 - [11] Rts SCTP. Efficacy and safety of RTS, S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *Lancet* 2015;386(9988):31–45.
 - [12] Webber C, Patton M, Patterson S, Schmoele-Thoma B, Huijts SM, Bonetti MJM, et al. Exploratory efficacy endpoints in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA). *Vaccine* 2017;35:1266–72.
 - [13] Mangen MJJ, Rozenbaum MH, Huijts SM, van Werkhoven CH, Postma DF, Atwood M, et al. Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. *Eur Respir J* 2015;46:1407–16.
 - [14] Hak E, Grobbee DE, Sanders EA, et al. Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. *Neth J Med* 2008;66(9):378–83.
 - [15] Chan ISF, Bohidar NR. Exact power and sample size for vaccine efficacy studies. *Commun Statist - Theory and Methods* 1998;27(6):1305–22.
 - [16] Tregnaigh MW, Saez-Llorens X, Lopez P, et al. Efficacy of pneumococcal nontypable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in young Latin American children: A double-blind randomized controlled trial. *PLoS Med* 2014;11(6):e1001657.
 - [17] Sur D, Lopez AL, Kanungo S, et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2009;374(9702):1694–702.
 - [18] Qadri F, Ali M, Chowdhury F, et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. *Lancet* 2015;386(10001):1362–71.
 - [19] Patterson S, Webber C, Patton M, et al. A post hoc assessment of duration of protection in CAPiTA (Community Acquired Pneumonia immunization Trial in Adults). *Trials Vaccinol* 2016;5:92–6.
 - [20] Hansen J, Black S, Shinefield H, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia: updated analysis using World Health Organization standardized interpretation of chest radiographs. *Pediatr Infect Dis J* 2006;25(9):779–81.
 - [21] van Werkhoven CH, Huijts SM, Paling FP, Bonten MJ. The scrutiny of identifying community-acquired pneumonia episodes quantified bias in absolute effect estimation in a population-based pneumococcal vaccination trial. *J Clin Epidemiol* 2016;69:185–92.
 - [22] Madhi SA, Klugman KP. World Health Organisation definition of “radiologically-confirmed pneumonia” may under-estimate the true public health value of conjugate pneumococcal vaccines. *Vaccine* 2007;25(13):2413–9.
 - [23] Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. *Bull World Health Organ* 2005;83(5):353–9.
 - [24] Dagan R, Pelton S, Bakaletz L, Cohen R. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. *Lancet Infect Dis* 2016;16(4):480–92.
 - [25] Vissink CE, Huijts SM, de Wit GA, Bonten MJ, Mangen MJ. Hospitalization costs for community-acquired pneumonia in Dutch elderly: an observational study. *BMC Infect Dis* 2016;16:466.
 - [26] Kozma CM, Dickson M, Raut MK, et al. Economic benefit of a 1-day reduction in hospital stay for community-acquired pneumonia (CAP). *J Med Econ* 2010;13(4):719–27.
 - [27] Raut M, Schein J, Mody S, Grant R, Benson C, Olson W. Estimating the economic impact of a half-day reduction in length of hospital stay among patients with community-acquired pneumonia in the US. *Curr Med Res Opin* 2009;25(9):2151–7.
 - [28] WHO and UNICEF estimates of national immunization coverage, 2015 revision. http://www.who.int/immunization/monitoring_surveillance/data/nld.pdf [accessed 10 July 2017].
 - [29] Evaluation of seasonal influenza vaccination policies and coverage in the WHO European Region. http://www.euro.who.int/__data/assets/pdf_file/0003/241644/Evaluation-of-seasonal-influenza-vaccination-policies-and-coverage-in-the-WHO-European-Region.pdf [accessed 10 July 2017].
 - [30] Zhou H, Haber M, Ray S, Farley MM, Panozzo CA, Klugman KP. Invasive pneumococcal pneumonia and respiratory virus co-infections. *Emerg Infect Dis* 2012;18(2):294–7.
 - [31] Hanquet G. Indirect effect of infant PCV10/13 vaccination on IPD in the elderly: pooled analysis from 13 EU sites. https://www.slideshare.net/ECDC_EU/germaine-hanquet-indirect-effect-of-infant-pcv1013-vaccination-on-ipd-in-the-elderly-pooled-analysis-from-13-eu-sites [accessed June 2, 2017].