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

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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 CAPiTA 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: CAPiTA trial registration number: www.ClinicalTrials.gov; trial number NCT00744263.

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 (CAPiTA) 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].

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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 CAPiTA-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 Practioner (GP) coded by the International Classification of Primary Care (ICPC) of 40,427 CAPiTA participants (see below "GP-dataset").

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.

[a]Presence defined as having been treated by or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years.
[b]Receipt of renal dialysis or transplant.
[c]Including 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.

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 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