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ORIGINAL ARTICLE

Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults

E. Hak[1,2*], D.E. Grobbee[1], E.A.M. Sanders[2], T.J.M. Verheij[1], M. Bolkenbaas[1], S.M. Huijts[1], W.C. Gruber[3], S. Tansey[3], A. McDonough[3], B. Thoma[3], S. Patterson[3], A.J. van Alphen[4], M.J.M. Bonten[1,5]

[1]Julius Center for Health Sciences and Primary Care, Departments of [2]Pediatric Immunology and Infectious Diseases, and [5]Medical Microbiology, University Medical Center Utrecht, the Netherlands, [3]Wyeth Vaccines Research, Wyeth, Pearl River New York, USA, [4]Netherlands Vaccine Institute, Bilthoven, the Netherlands, [*]corresponding author: tel.: +31 (0)88-756 82 14, fax: +31 (0)88-76 80 99, e-mail: e.hak@umcutrecht.nl

ABSTRACT

The burden of community-acquired pneumonia (CAP) among the elderly is high and has increased over the last decades. *Streptococcus pneumoniae* is the most common cause of CAP and in 10% the infection may be fatal. Although the 23-valent polysaccharide pneumococcal vaccine (23vPS) is considered effective in the prevention of invasive pneumococcal disease in the elderly population, the evidence is mainly from nonrandomised observational studies and effects on the occurrence of pneumonia have not been demonstrated. Conjugated pneumococcal vaccines which also stimulate T-cell dependent immune responses induced antibody responses in elderly persons which are similar to those induced by a primary series of 7-valent conjugated pneumococcal vaccine (7vPnC) in infants, and the response appeared similar or superior for all vaccine serotypes to that induced by 23vPS. The primary objective of the planned trial entitled CAPITA (Community Acquired Pneumonia Immunization Trial in Adults) is to establish the efficacy of a 13-valent PnC vaccine in the prevention of a first episode of vaccine-serotype specific pneumococcal CAP in 85,000 community-dwelling adult persons aged 65 years and older. This is a parallel group, randomised, placebo-controlled trial, with a 1:1 random allocation to vaccine or placebo vaccine. The occurrence of the primary outcome of vaccine-serotype specific (VT)-CAP will be established in hospitals on the basis of three sets of criteria: (1) a clinical definition of CAP; (2) independent interpretation of chest radiograph consistent with pneumonia; and (3) determination of *S. pneumonia* serotype. The trial will be critical to determine the position of conjugate pneumococcal vaccines in the prevention of pneumococcal disease.

PNEUMOCOCCAL INFECTIONS AMONG OLDER ADULTS

The burden of community-acquired pneumonia (CAP) among the elderly is high with an estimated million cases and between 350,000 and 620,000 hospitalisations in the United States alone, whereas CAP ranks among the top-5 causes of death.[1] Of note, hospitalisations and death rates for CAP have increased over the last years partly due to ageing and efficient chronic disease management. Annual CAP rates are estimated to be from approximately 20 per 1000 among those aged 65 to 69 years up to 50 per 1000 among those aged over 85 years of age.[2] In a Finnish trial among adults aged ≥60 years, the incidence of pneumococcal CAP was 9 per 1000 person-years ranging from 4 to 19 per 1000 person-years in low and high-risk individuals, respectively.[3] *Streptococcus pneumoniae* is the most common cause of CAP in adults, accounting for 25% to more than 40% of cases depending on the diagnostic tests used, geographic regions and setting.[4] However, the causative micro-organism of CAP cannot be demonstrated in the majority of patients and it is possible that the true proportion of cases caused by *S. pneumoniae* is higher than has been found so far. In persons aged ≥65, CAP infections may result in hospital admission in more than 25 to 40% of episodes and in 10% the infection may be fatal.[2] For all these reasons, effective prevention of pneumococcal CAP and invasive pneumococcal disease (IPD), for instance through influenza or pneumococcal vaccination, has been a high-priority issue for health policy makers worldwide.

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POLYSACCHARIDE PNEUMOCOCCAL VACCINES

Approximately 90 different immunogenic carbohydrates have been identified in the capsule of *Streptococcus pneumoniae*. The first polysaccharide pneumococcal vaccine, including 14 serotypes, was introduced in 1977 and replaced by a 23-valent vaccine (23vPS) in 1983. These 23 serotypes account for more than 90% of all prevalent serotypes in Western countries.[5] For infants and elderly people, though, these polysaccharide vaccines provide little protection against pneumococcal disease because these individuals respond poorly to T-cell independent antigens such as pure polysaccharide antigens. Although 23vPS is considered effective in the prevention of IPD in the elderly population in the developed world, because of the low incidence rates of IPD, the evidence is mainly from nonrandomised observational studies. Randomised trials were inadequately powered to establish effects on IPD. In meta-analyses, pooled results indicate an effectiveness varying from 30 to 45%, but the confidence intervals were wide.[5] Observational studies have generally shown significant efficacy, although estimates range from 40 to 80%[6-12] and one study did not observe reductions in IPD.[13] There is growing evidence that 23vPS has no effect on the occurrence of pneumonia in the elderly population. In the only adequately sized trial, the efficacy of the vaccine against pneumonia was -20% (95% CI -50%, 10%) and against pneumococcal pneumonia -20% (95% CI -90%, 20%).[14] Again, to increase the power of multiple small studies, a number of meta-analyses have been conducted, but these also could not disclose efficacy against pneumonia.[2] In a recent observational study in the United States, the relative risk of hospitalisation for CAP was 1.21 (95% CI 1.08, 1.35) in vaccinated compared with unvaccinated subjects, but there was a significant reduction in pneumococcal bacteraemia (RR 0.58, 95% CI 0.35, 0.96).[12] However, there may have been inadequate control of confounding in these nonrandomised studies.[2,15] These results imply that 23vPS is unlikely to have a significant effect on reduction of CAP in persons ≥65 years. Nevertheless, the current recommendation in most countries is to vaccinate people aged ≥65 years and people in certain high-risk groups aged 2 to 64 years with 23vPS. One of the few countries in which widespread vaccination of the elderly with this vaccine is not recommended is the Netherlands.[16]

CONJUGATED PNEUMOCOCCAL VACCINES

In infants and elderly people a protective immune response against polysaccharide antigens can be induced if these antigens are conjugated with proteins that induce a T-cell dependent response. A single dose of a 7-valent conjugated pneumococcal (7vnC) vaccine, for instance, induced antibody responses in the elderly which are similar to those induced by a primary series of 7vPnC vaccine in infants and the response appeared similar or superior for all vaccine serotypes to that induced by 23vPS.[17] Therefore, the efficacy of 7vPnC against IPD in elderly people is predicted to be at least similar to 23vPS. In children, conjugate pneumococcal vaccines appeared highly efficacious against vaccine serotype IPD (more than 90% reduction), total radiological confirmed CAP (25 to 37% reduction) and total otitis media episodes (6 to 7% reduction) in large vaccination trials in children.[18-21] Importantly, conjugate pneumococcal vaccines also reduce nasopharyngeal carriage and indirect protective effects on IPD of approximately 50% have been observed in other, nonvaccinated, adult age groups in the United States and other countries after the start of widespread infant immunisation.[22-24] Apart from herd-immunity effects, modulation of colonisation through vaccination is also associated with marked replacement of serotypes. For instance, infections with serotypes 1, 3 and 19A, not covered by the 7vPnC, have increased many-fold.[25] Singleton *et al*. reported even a 140% increase in invasive pneumococcal disease caused by nonvaccine serotypes in Alaskan children after introduction of 7vPnC.[26] Therefore, new conjugate vaccines with a broader coverage are warranted for children and the effects of conjugate vaccines should be evaluated in the elderly. Two new conjugate vaccines are now in the process of clinical evaluation: a 10-valent (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 23F) and a 13-valent (containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) vaccine.

PNEUMOCOCCAL VACCINE TRIAL IN THE NETHERLANDS

Recommendations for immunisation with the 23vPS of all elderly people in the United States and many other developed countries have been a barrier to the design of a large-scale efficacy trial with conjugated vaccines due to the finding that a prior dose of 23vPS severely restricts the subsequent immunogenicity of a conjugate vaccine.[27] Also, such a recommendation surmounts practical and ethical problems of studying a population naive to 23vPS. Finally, if 23vPS has minimal efficacy against CAP, this may compromise the power of a clinical trial with conjugated pneumococcal vaccines. As mentioned, the Netherlands Health Council decided on the basis of a detailed review that 23vPS is recommended (and is actually used) for only a small number of very high-risk individuals.[16] In contrast, the Health Council has evaluated the evidence for

influenza vaccination and has been recommending its use for this high-risk population over more than a decade. Since then, more than 74% of adults aged ≥65 years receive such vaccine through the Netherlands primary care preventive programme.[28] Thus, in the Netherlands a large group of adults ≥65 years, naive to 23vPS, is available which makes it possible to conduct a large placebo-controlled efficacy study in this age group by linking study vaccine administration to routine influenza vaccination. Importantly, all health care for both acute and chronic diseases in the Netherlands is delivered through a unified and highly computerised healthcare system with a strong tradition of academic research.[29] Medical drugs such as antibiotics in case of bacterial infections can only be obtained by patients after prescription by a medical doctor. This allows identification of almost all cases of hospitalised CAP and IPD occurring in defined geographical areas by basing case ascertainment within hospitals serving that vaccine research area.

OBJECTIVES OF THE CAPITA TRIAL

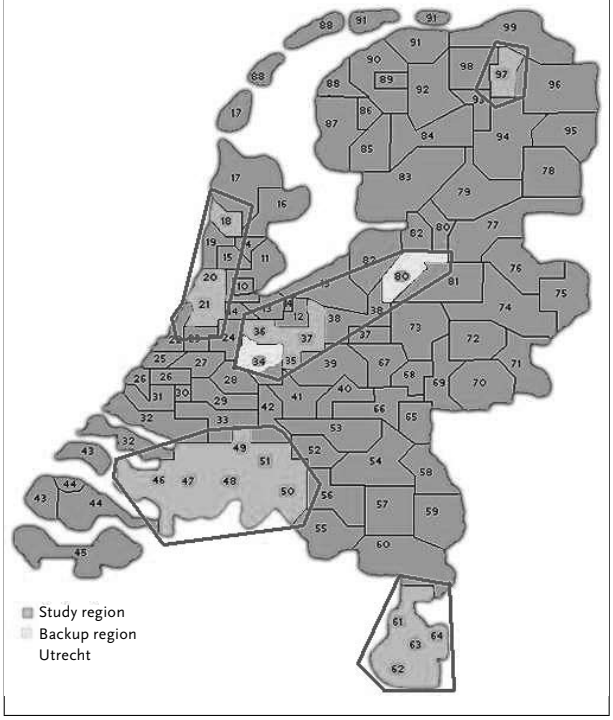
The primary clinical objective of the planned trial entitled CAPITA (Community Acquired Pneumonia Immunization Trial in Adults) is to establish the efficacy of 13vPnC vaccine in the prevention of a first episode of vaccine-serotype specific (VT) pneumococcal CAP in community-dwelling adult persons aged ≥65 years. Secondarily, we aim to establish the efficacy of the 13vPnC vaccine in the prevention of a first episode of non-bacteraemic VT pneumococcal CAP and a first episode of VT-IPD. Additional objectives include evaluation of efficacy against all pneumococcal CAP and evaluation of outcomes, also including death. Further, the study will evaluate the safety profile of 13vPnC as measured by the incidence rates of serious adverse events (SAEs) for predefined intervals after study vaccine administration. In addition to these efficacy and safety objectives, immunogenicity and nasopharyngeal carriage will be evaluated in a subset of 2000 participants. Furthermore, a detailed analysis of health care outcomes and quality of life will be performed to allow for subsequent health economic analyses.

SETTING AND STUDY DESIGN

This is a parallel group, randomised, placebo-controlled trial, with a 1:1 random allocation to vaccine or placebo vaccine. Study participants will receive the vaccine or placebo through trained investigator vaccination teams and endpoints will be captured within all selected and participating hospitals in the catchment areas of the participating GPs, which will guarantee the detection of most of all possible cases. Approximately 85,000 study subjects (42,500 in each group) will be recruited from community-dwelling adult persons aged over 65 years enlisted at about 75 primary care centres in each of the five study areas in the Netherlands (*figure 1*). In the Netherlands, primary care physicians are the porte d'entree for secondary and tertiary care and all citizens are registered in one centre. Inclusion criteria include:

- male or female adults aged 65 years or older as of 1 September 2008;
- registered with a GP who are participating in the study;
- ability to fulfil study requirements.

Figure 1. *Research areas in the Netherlands*



Exclusion criteria include:

- previous vaccination with any pneumococcal vaccine;
- residence in long-term care facility;
- contraindication for 13vPnC;
- contraindication for influenza vaccines;
- use of investigational products in 30 days prior to study vaccine administration;
- history of severe adverse reaction associated with any vaccine component;
- immunodeficiency or immune suppression.

Subjects will be identified from primary care centre information systems and the physicians will refer eligible subjects for enrolment. Subjects will then be invited to

attend study vaccination clinics, at which the informed consent process, enrolment, administration of study vaccine and administration of routine influenza vaccine will be performed. Subjects are expected to be enrolled and immunised during the period of routine influenza vaccination in the Netherlands.

Vaccine and placebo

The 13vPnC vaccine contains saccharides from pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to cross-reactive material 197 (CRM_{197}), a nontoxic variant of diphtheria toxin. Placebo vaccine is formulated similarly to the study vaccine, except for its active components.

Capturing the primary and secondary outcomes

The occurrence of the primary outcome of VT-CAP will be established on the basis of three sets of criteria: (1) a clinical definition of CAP; (2) independent interpretation of chest radiograph consistent with pneumonia; and (3) determination of *S. pneumonia* serotype (see also *table 1*). If all three criteria are met, the participant will be defined as having VT or non-VT pneumococcal pneumonia. Because of the size of the study, active follow-up of study participants is not feasible. Instead, all hospitals providing daily care to the inhabitants living in the selected vaccination research areas will apply a standard diagnostic checklist for all elderly people presenting with a clinical suspicion of lower respiratory infection. This protocol will be used for those admitted as inpatients or those seen in the emergency room and treated as outpatients. Patient characteristics, which include age, sex, comorbidity, vaccination status, previous antibiotic treatment, symptoms and duration of symptoms, will be collected and the Pneumonia Severity Index (PSI) will be determined.[30] In addition, detection of C-polysaccharide in urine (Binax test) and blood and sputum cultures (if available) will be part of the routine diagnostic work up. Identification of *S. pneumoniae* as the definite causative agent of CAP currently relies on blood cultures and positive urinary antigen detection. The specificities of both tests are considered to be close to 100%. Identification of the serotype is only possible with cultured isolates. Serotype-specific detection of *S. pneumoniae* in blood and urine could markedly enhance the aetiological fraction of CAP caused by *S. pneumoniae*. To this aim, we are currently evaluating two diagnostic techniques, a qPCR blood test and a urine test for detection of pneumococcal antigens. Whether these tests will be included in the diagnostic workup depends on their sensitivity and specificity. This will be determined by evaluation of these assays in patients with CAP and control populations. IPD will be defined as presence of *S. pneumoniae* in a normally sterile site defined as blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, or joint fluid.[31] For all deaths, the cause and date will be recorded.

RATIONALE FOR NUMBER OF SUBJECTS

The annual incidence of CAP in the elderly population is estimated at approximately 10 per 1000 persons based

Table 1. *Definitions of community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD)*

CAP diagnosis category[1]	Episode of CAP plus ...
VT pneumococcal CAP	Culture of VT S. *pneumoniae* from blood and/or pleural fluid[2] or: positive urinary VT antigen[3] or: positive VT blood PCR[3]
NVT pneumococcal CAP	Culture of non-VT *S. pneumoniae* from blood and/or pleural fluid[2] or: positive urinary C-polysaccharide but negative urinary VT antigen[3] or: positive diagnostic PCR but negative VT blood PCR[3]
Pneumococcal CAP	Culture of *S. pneumoniae* from blood and/or pleural fluid[2] or: positive urinary C-polysaccharide[3] or: positive diagnostic PCR[3]
Culture confirmed VT pneumococcal CAP	Culture of VT *S. pneumoniae* from blood and/or pleural fluid[2]
Culture confirmed NVT pneumococcal CAP	Culture of non-VT *S. pneumoniae* from blood and/or pleural fluid[2]
Culture confirmed pneumococcal CAP	Culture of *S. pneumoniae* from blood and/or pleural fluid[2]
Probable pneumococcal VT CAP	Culture of VT *S. pneumoniae* from an evaluable sample of sputum[4]
Probable pneumococcal NVT CAP	Culture of non-VT *S. pneumoniae* from an evaluable sample of sputum[4]
Probable pneumococcal CAP	Culture of *S. pneumoniae* from an evaluable sample of sputum[4]
Possible pneumococcal CAP	Predominant gram-positive cocci in pairs and chains in evaluable sputum on microscopy[4]

[1]If there is a discrepancy between serotype results among the tests, the culture result will be considered definitive. [2]Also include normally sterile isolates from respiratory tract, such as transthoracic biopsies and direct puncture samples. [3]May be urinary antigen test alone, PCR alone, or both. This will be determined based on pilot study 6115A1-3012.[4] Also include normally non-sterile samples from respiratory tract, such as bronchoscopic brushings, transtracheal samples or washings, etc. For sputum an evaluable sample means < 10 epithelial cells and at least 20 neutrophils per low power field. VT = vaccine-serotype specific.

on data before the introduction of 7vPnC vaccination of children that started in 2006. With conventional diagnostic techniques 25 to 30% of CAP episodes can conclusively be linked to *S. pneumoniae*.[4] Prior to introduction of 7vPnc, 49% of IPD isolates in the Netherlands were due to the serotypes covered by the vaccine and 31% due to the six new types covered by the 13vPnC. The effects of herd immunity for the seven serotypes of 7vPnC are assumed to be similar to those observed in the USA, and this has been taken into account in forecasting the expected baseline incidence of pneumococcal disease in adults in the Netherlands, over the course of the trial. Accounting for age-adjusted mortality of elderly people ≥65 years and loss to follow-up, this study plans to enrol a total of 85,000 subjects to demonstrate the primary objective of efficacy against VT-CAP.

For the efficacy analyses, two main analysis populations will be defined: (modified) intent-to-treat (ITT) and per-protocol. The efficacy of 13vPnC in prevention of the primary outcome will be estimated from the difference in incidence rates for VT-CAP in each treatment group. The two-sided, O'Brien-Fleming adjusted, 95% confidence interval of efficacy (1 – relative risk) will be presented, where relative risk is defined as the incidence rate of VT-CAP in subjects receiving 13vPnC relative to subjects receiving placebo. The two-sided, adjusted confidence interval will be computed, the exact method conditional upon the total number of subjects diagnosed with VT-CAP.

It is planned to perform an interim analysis, at approximately one year after the last study vaccine based on accumulation of a predefined number of VT-CAP or IPD cases. An independent Data Monitoring Committee will review blinded and unblinded data to protect subject safety and evaluate efficacy and will make recommendations to a study steering committee.

CONCLUSION

This randomised, placebo-controlled double-blind trial for VT-CAP in adults aged over 65 years is one of the largest randomised trials ever conducted and will be critical to determine the position of conjugate pneumococcal vaccines in the prevention of pneumococcal disease. The trial has been conceived and designed in productive interaction between academic investigators and the producer of the vaccine. In addition to the primary objectives of the trial, several substudy objectives are currently under development to maximise opportunities to learn about the health conditions in this older adult population.

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