Prevention and Management of Community-Acquired Pneumonia in Adults

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Prevention and Management of Community-Acquired Pneumonia in Adults

Preventie en behandeling van in de gemeenschap opgelopen pneumonie bij volwassenen
(met een samenvatting in het Nederlands)

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Voor Myrthe en Roos, mijn lieve dochters

Later zullen jullie er meer van begrijpen

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General introduction

Adapted from:

New trends in the prevention and management of community-acquired pneumonia

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Community-acquired pneumonia (CAP) is an important cause of morbidity and mortality worldwide.[1–3] Reported annual incidences differ between countries, probably reflecting heterogeneity of diagnostics, reporting and socio-economic factors.[4] A universal finding, however, is that *Streptococcus pneumoniae* is the most commonly identified bacterial pathogen for CAP in all age groups. The 30-day mortality of patients hospitalized with CAP is approximately 10%.[5,6] For those surviving the acute phase of the CAP episode, the long term prognosis is still poor with 45-50% not surviving five years.[7] It is however difficult (if at all possible) to determine which of these deaths are due to (sequelae of) the CAP episode and in which patients CAP is merely a marker of poor prognosis. In this thesis, the role of pneumococcal vaccination in the prevention of CAP in elderly and the effectiveness of different empirical antibiotic treatment strategies for adults hospitalized with CAP are discussed. First, current state of the art in the field of prevention and management of CAP is summarized, after which an introduction to the following chapters is provided.

MICROBIOLOGICAL AETIOLOGY OF CAP

Although many micro-organisms can cause CAP, most episodes are caused by a few pathogens only. Table 1 displays proportions of pathogens documented in patients hospitalised with CAP in European countries, in which the diagnostic workup included blood cultures together with at least one other test, such as serology, polymerase chain reaction (PCR) for respiratory pathogens or urinary pneumococcal antigen testing.

In most studies *S. pneumoniae* is the most frequently detected pathogen, accounting for 20-40% of CAP episodes. This proportion seems to be higher in studies from northern and western European countries compared to those from southern Europe. This may result from lower diagnostic sensitivity of blood and sputum cultures due to antibiotic use prior to hospital admission in southern countries.[44] Other common pathogens causing CAP include *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella pneumophila* and respiratory viruses. *Chlamydophila pneumoniae* and *Coxiella burnetii* are relatively rare causes of CAP, but may cause epidemics, as recently witnessed in the Netherlands during a Q-fever outbreak.[45–47]

In 30-60% of CAP episodes the aetiology remains unknown, and this proportion has remained unchanged in time, despite the introduction of antigen testing and PCR-based testing. This has been attributed to less microbiological testing in clinical care or increased use of antibiotics prior to diagnostic testing.[48] Therefore, although there are no discernible signs of major changes in the microbial aetiology of CAP in time, it is unknown whether such changes could have been masked by the suggested changes in clinical practice.

In addition, the patient population affected is changing, with increasing numbers of severely immuneocompromised patients, both due to more frequent use of immune modulating treatment modalities as well as to better survival of patients with serious illnesses.[49–51] These patients are prone to developing CAP with both common respiratory pathogens and opportunistic pathogens. Since these immunocompromised patients have been excluded in most studies, the contribution of opportunistic pathogens such as *Pneumocystis jirovecii*, atypical mycobacteria and fungi may have been underestimated. Among HIV-infected patients hospitalised with CAP, the reported proportion caused by *P. jirovecii* has

ranged from 9-31% and of *Mycobacterium species* from 1-17% of cases, which occurred in addition to pathogens common in immunocompetent populations.[52–56] Few data are available on CAP aetiology in patients with other types of immunosuppression, although higher rates of Gram-negative bacteria and fungal infections have been

reported in small case series.[57–60] Summarizing, the aetiology of CAP in immunocompetent patients seems unchanged with *S. pneumonia* remaining most prevalent, but less is known about pathogen distribution in the growing population of immunocompromised patients.

Table 1 - Aetiology of CAP in hospitalised patients

	The Netherlands 5 studies[5,6,8–10] N=1,047	**Germany 1 study[11] N=237**	**Switzerland 1 study[12] N=318**	**United Kingdom 3 studies[13–15] N=439**	**Southern Europe 19 studies[16–34] N=9,143**	**Slovenia 2 studies[35,36] N=320**	**Nordic countries 7 studies[37–43] N=1,582**
Streptococcus pneumoniae	31% (25-37)	13% (9-18)	13% (9-17)	35% (21-51)	23% (20-26)	9% (4-20)	30% (23-37)
Haemophilus influenzae	5% (3-10)	6% (4-10)	6% (4-9)	7% (5-10)	3% (2-4)	2% (1-7)	5% (4-8)
Staphylococcus aureus	1% (1-2)	4% (2-7)	4% (3-7)	2% (1-4)	1% (1-2)	1% (0-2)	1% (1-2)
Moraxella catarrhalis	1% (0-3)	-	2% (1-4)	2% (1-3)	0% (0-1)	1% (0-11)	1% (0-2)
Pseudomonas spp.	1% (0-3)	-	-	1% (0-3)	1% (0-2)	-	0% (0-1)
Klebsiella pneumoniae	0% (0-1)	-	1% (0-3)	1% (0-2)	0% (0-1)	-	1% (0-1)
Escherichia coli	1% (0-2)	-	-	1% (0-2)	1% (0-1)	2% (1-4)	1% (0-1)
Other gram-negatives	4% (1-12)	8% (6-13)	-	-	1% (1-2)	1% (0-3)	1% (1-3)
Mycoplasma pneumoniae	9% (4-16)	9% (6-14)	8% (5-11)	3% (2-6)	4% (3-7)	13% (3-43)	7% (5-10)
Chlamydophila pneumoniae	1% (0-3)	11% (8-16)	3% (1-5)	2% (0-24)	2% (1-5)	19% (15-24)	1% (0-3)
Chlamydophila psittaci	1% (0-4)	1% (0-3)	-	1% (0-4)	1% (0-1)	1% (0-3)	1% (0-2)
Coxiella burnetii	1% (0-1)	2% (1-5)	-	1% (0-2)	1% (1-2)	1% (0-2)	0% (0-1)
Legionella pneumophila	4% (3-7)	2% (1-4)	5% (3-8)	3% (2-5)	5% (4-7)	3% (1-5)	2% (1-3)
Virusses	9% (3-21)	10% (7-15)	-	16% (8-28)	4% (3-7)	5% (0-75)	10% (6-18)
Other agents	4% (2-8)	1% (0-3)	1% (0-3)	3% (0-6)	3% (2-5)	2% (0-8)	2% (1-5)
Unknown	36% (25-49)	33% (27-39)	61% (56-66)	40% (23-60%)	44% (40-49)	43% (34-52)	38% (27-49)

* a few studies included both general ward and ICU patients

PREVENTION OF CAP BY PNEUMOCOCCAL IMMUNIZATION

Based on differences in polysaccharide capsules over 90 different serotypes of *S. pneumonia* have been identified. Capsule polysaccharides have antiphagocytic activity, and are therefore relevant in the pathogenesis of CAP and invasive pneumococcal diseases (IPD).[61] As a result, incidence of IPD, clinical outcome after infection and age distribution differ between serotypes.[62–65]

The first human experiment of pneumococcal vaccination, based on administration of a mixture of polysaccharides, was conducted in 1911, and the first hexavalent-vaccine was registered in 1946. However, these vaccines were soon withdrawn because of the discovery of penicillin.[66] In the late 1970's a 14-valent pneumococcal polysaccharide vaccine (PPV) was registered in the United States, which was – in 1983 - replaced by a 23-valent PPV (Pneumovax/ Pneumo 23), containing purified capsular antigens from 23 serotypes, that cover approximately 87% of the isolates causing IPD in adults in the Netherlands.[63] The vaccine induces T-cell independent B-cell responses, yielding antibodies in adults but not in young children. As immunologic memory is not induced, revaccination needs to be repeated every five years. In the Netherlands, this vaccine is only recommended for patients with high risks for IPD, such as those with (functional) asplenia, sickle cell anemia and with liquor leakage or prior pneumococcal meningitis after skull trauma.[67] For patients with immune suppression due to (non)-Hodgkin's disease, HIV or organ transplantation immunisation is not strictly recommended, but can be applied.

Despite its use in many countries worldwide, the efficacy of the 23-PPV remains debated. Based on a recent meta-analysis quantifying combined risk ratios (based on random-effects model) of (quasi-)randomised studies PPV did not prevent infection (presumptive pneumococcal pneumonia, all cause pneumonia and death from all causes) in trials with a double-blind design and with adequate allocation of treatment.[68] Also the risk ratio of pneumococcal bacteraemia was close to one (RR 0.90 (0.46-1.77)), even without trial quality taken into account. These findings differ markedly from the reported effect of PPV on the occurrence of IPD (OR 0.26, 95% CI 0.15-0.46) based on ten studies in the most recent Cochrane review.[69] Yet, only five trials were included in both analyses. The different outcomes result from differences in study selection, illustrating the large variety in study populations and outcome definitions. Large randomized controlled trials are lacking and interpretation of observational studies suffers from the 'healthy vaccinee'-effect, which implies that subjects that have access to vaccination are usually in a better health condition than those who do not receive vaccination. Furthermore, there is no evidence that PPV prevents IPD in patients with chronic underlying medical illnesses. Therefore, we concur with the conclusion reached

by the Dutch Health Council in 2003 that there is no convincing evidence that PPV prevents pneumonia or IPD in adults and that PPV vaccination, as an adjunct to annual influenza vaccination, is not recommended.[67]

Since the turn of the century, pneumococcal conjugate vaccines (PCV) are available, with either seven (serotypes 4,6B, 9V, 14, 18C, 19F, 23F), ten (additional serotypes 1,5, 7F) or 13 (additional serotypes 3, 19A, 6A) polysaccharide capsular antigens conjugated to a protein. The latter induces T-cell dependent immune responses, yielding adequate antibody responses in adults and young children, and immunological memory. The efficacy of conjugated pneumococcal vaccines in preventing pneumococcal disease in young children has been well established, with estimated vaccine efficacies of 80% (95% CI 58-90%) and 27% (95% CI 15-36%) for vaccine type IPD and X-ray confirmed pneumonia, respectively.[70] Moreover, in the United States introduction of 7-valent PCV (PCV7) vaccination among children was associated with declines in IPD rates in elderly, presumably because of vaccine-induced herd immunity.[71] Conjugated vaccines have now been implemented in national immunization programs for children across the world.[72–76]

In the Netherlands PCV7 was introduced in the national immunization program ("Rijks Vaccinatie Programma") in 2006, and has been replaced by a 10-valent vaccine in 2011. Incidences of vaccine-serotype IPD in children <2 years had declined by 67% in 2008 (from 24.3 in 2005 to 8.0 cases/ 100.000 persons), but at that time, vaccine-serotype specific as well as overall IPD-rates had not declined significantly among elderly.[77]

In adults, a single dose of PCV7 yields higher or at least equal immune responses as a single dose of 23-PPV, both in immune-competent as in immune-compromised adults.[78–82] Since October 2011 PCV13 has been licensed for prevention of IPD in adults aged >50 years in Europe. A model-based cost-effectiveness analysis suggests that in the United States replacement of 23-PPV vaccination with PCV13, either at the age of >65 years – as currently recommended in the US - or routinely at the age of 50 and 65 years might reduce pneumococcal disease burden in an economic acceptable way, but model estimates were critically sensitive to vaccine efficacy (VE) in prevention of non-bacteraemic pneumococcal CAP and the magnitude of herd immunity created by childrens' vaccination.[83] Up till now, effectiveness of PCV7 vaccination in adults has only been determined in HIV-infected patients that had recovered from IPD in Blantyre, Malawi.[84] After a median follow-up of 1.2 years unadjusted VE to prevent a new episode of vaccine serotype IPD (PCV7 serotypes + serotype 6A) was 74% (95%CI 30-90%), but there were no significant beneficial effects on all-cause IPD (adjusted HR0.80 (95%CI 0.45-1.44)) or mortality (adjusted HR 1.24 (95% CI 0.88-1.75)). The effectiveness of PCV in preventing bacteraemic and non-bacteraemic CAP in immune-competent elderly is

unknown. This is addressed in an ongoing placebo-controlled double-blind trial evaluating the efficacy of PCV13 in 84.496 elderly (>65 years) in the Netherlands.[85] (http://clinicaltrials.gov/ct2/show/NCT00744263) The results of this study are expected in 2013.

MANAGEMENT OF CAP IN SECONDARY CARE

As the microbiological cause of CAP cannot be predicted reliably on clinical symptoms, guidelines recommend to base initial treatment choices on the severity of disease presentation.[86–88] Patients with mild diseases can be treated with narrow-spectrum antibiotics (always covering *S. pneumonia*e) with careful monitoring of treatment response within 48 hours. On the other hand, in those with severe CAP a broader spectrum is recommended that includes at least *S. pneumonia* and Legionella. In those with moderate severe CAP, empirical coverage of *S. pneumonia* is always needed, but coverage of Legionella can be based on the results of urinary antigen testing in most patients. Dutch guidelines recommend to use either of three severity classification systems; the CURB-65-score, the Pneumonia Severity Index score (PSI) or the pragmatic classification (Box 1).[89,90]. According to the guideline, one of these classification systems should be adopted in each hospital and be followed for all patients with CAP. However,

Box 1 - Current guideline recommendations for treatment of CAP

Mild CAP

- CURB-65: 0-1
- PSI: 1-2
- Pragmatic: Ambulatory treatment

Recommendation for empirical treatment: Amoxicillin, second choice doxycycline

Moderately severe CAP

- CURB-65: 2
- PSI: 3-4
- Pragmatic: Treatment on hospital ward (non-ICU wards)

Recommendation for empirical treatment: Amoxicillin (if no risk factors for Legionella infection and with a urinary Legionella antigen test to be done within 12 hours).

Severe CAP

- CURB-65: >2
- PSI: 5
- Pragmatic: Treatment in ICU ward

Recommendation for empirical treatment: Moxifloxacin or levofloxacin, penicillin/ amoxicillin with ciprofloxacin, or 2nd or 3rd generation cephalosporin with a macrolide

concordance of the classification systems is poor: patients will be classified as severe CAP in 22% of cases using the CURB-65-score, 13% with the PSI-score, and only 3% according to the pragmatic score, leading to high heterogeneity in the treatment of CAP.[91]

Current guideline recommendations are mainly based on non-experimental cohort studies and have, therefore, been criticized.[92–94] Some studies suggest that combined treatment with a betalactam antibiotic and macrolide improves outcome as compared to monotherapy with a betalactam antibiotic,[95–101] and some suggest that such combination therapy improves survival in pneumococcal pneumonia.[102–105] On the contrary, other studies failed to demonstrate beneficial effects of combination therapy (versus betalactam monotherapy) on patient outcome.[106–112] Better results of regimens that combine a macrolide and betalactam antibiotic or in which fluoroquinolones are used as monotherapy might result from coverage of atypical pathogens, less resistance, synergy between betalactams and macrolides, and anti-inflammatory effects of macrolides.[113]

A major pitfall for observational studies is *confounding by indication,* which arises when factors contributing to the endpoint differ between treatment groups because of the physician's treatment decision.[114] For instance, patients that received combination therapy might have had a higher suspicion of atypical pathogens because they were younger, and therefore, had a better prognosis. In several of the aforementioned cohort studies, either with or without beneficial effects for combination therapy, there is clear evidence of such confounding bias.[95,97,98,101,102,106,107] This was elegantly demonstrated in one study by using a propensity analysis to predict treatment on the basis of clinical variables. These propensity scores differed significantly between treatment groups and the benefit of combination therapy in the crude analysis disappeared after adjustment for the propensity score in multivariate analysis.[111]

As a result the relative effectiveness of empirical treatment of CAP with betalactam monotherapy, combination therapy with a betalactam and macrolide, or fluoroquinolone monotherapy is unknown. This was addressed in a multi-centre cluster randomised cross-over trial in 7 Dutch hospitals (CAP-START study, ClinicalTrials.gov number, NCT01660204). In each hospital one of the three treatment regimens was used as standard empirical therapy during a period of four consecutive months, after which preferred treatment changed to one of the other two regimens. The order of regimens was randomised per hospital to control for inter-hospital variables and seasonal effects.

THESIS AIM AND OUTLINE

In spite of recent developments in the management of CAP, the morbidity and mortality remain high, particularly in elderly. In the Netherlands, two randomized trials have been performed that aimed to provide insight into the prevention (through elderly vaccination with PCV13) and management (empirical antibiotic treatment) of CAP. In this thesis, results of these trials are described and implications for clinical practice and future research are discussed.

The first part will focus on the prevention of pneumococcal CAP and IPD in elderly through vaccination with PCV13. In Chapter 1 the main results of the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) are described. The next chapters are on differences in VE based on the risk of acquiring CAP, using a comprehensive risk score (Chapter 2) or based on one of the most important risk predictors: age (Chapter 3). The effects of child immunisation with PCV7 on the distribution of serotypes causing IPD and non-invasive pneumococcal CAP in elderly are an important determinant of the utility of pneumococcal vaccination in elderly and are described in Chapter 4. Finally, Chapter 5 provides data on the accurateness of endpoint detection in the CAPiTA study and how this has impacted absolute effect estimates derived from the trial.

The second part of the thesis is about the management of CAP patients admitted to non-ICU wards. Chapter 6 describes the rationale and design of the CAP-START study and discusses different advantages, challenges, and risks of the cluster-randomized cross-over design. In Chapters 7 and 8 the effects of the three antibiotic strategies on clinical endpoints and costs are presented. In Chapter 9 the role of treatment restrictions in the management and prognosis of CAP in elderly is explored. Finally, the added value of blood cultures in the management of CAP, and the potential to identify patients with a probable positive blood culture, are discussed in Chapter 10.

A summary of the results, recommendations for current clinical practice, and future research directions are provided in the General Discussion.

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Part I

Prevention of Community-Acquired Pneumonia in elderly

Chapter 1 The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA)

Part of:

The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA): what is the future of pneumococcal conjugate vaccination in elderly?

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ABSTRACT

Pneumococcal community-acquired pneumonia (PCAP) and invasive pneumococcal disease (IPD) are important causes of morbidity and mortality in elderly. In the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), a randomized double-blind placebo-controlled trial of 84,496 community-dwelling immunocompetent adults over 65 years of age, the 13-valent pneumococcal conjugate vaccine (PCV13) reduced the incidence of a first episode of vaccine-type (VT) PCAP with 38% and of VT-IPD with 76% in the modified intention-to-treat population.

INTRODUCTION

Pneumococcal community-acquired pneumonia (PCAP) and invasive pneumococcal disease (IPD, defined as infection with a positive culture for *Streptococcus pneumoniae* from a sterile body site) are an important cause of morbidity and mortality worldwide.[1,2] The incidence is highest in children under 2 years of age and rises again after the age of 50, with a steep increase per year of age particularly after the age of 65.[3] Mortality and morbidity following PCAP and IPD is highest in elderly.[2] With the introduction of antibiotics, mortality due to pneumococcal infections was largely reduced.[4] Subsequent improvements of medical care such as mechanical ventilation and vasopressor support in intensive care units, have further changed the prognosis of those with severe CAP, but the burden of disease remains high.[5] Prevention of pneumococcal infections through immunization, therefore, remains an important public health goal.

Pneumococcal polysaccharide vaccines (PPSV) have been available for over a century, but their effectiveness in reducing PCAP and IPD is controversial with different meta-analyses reaching different conclusions.[6,7] These vaccines are not immunogenic in children and fail to induce an immunologic memory in elderly due to the T-cell independent nature of the immune response. The introduction of pneumococcal conjugated vaccines (PCVs) in national childhood immunization programs yielded substantial reductions of IPD and all-cause CAP in children.[8] These vaccines contain pneumococcal capsular polysaccharides conjugated to a protein and thereby induce T-cell dependent immune responses. As a consequence, PCVs are also immunogenic in children and can induce T-cell dependent immunologic memory. Three different PCVs are currently available. Seven-valent PCV (PCV7, containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), PCV10 (containing additional serotypes 1, 5, and 7F), and PCV13 (containing additional serotypes 3, 6A, and 19A).

In the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA, http://clinicaltrials.gov/ct2/show/NCT00744263) efficacy and safety of PCV13 was assessed in immunocompetent community-dwelling individuals of age 65 and above living in the Netherlands.[9] Here we summarize the main results of the trial and discuss implications for current clinical practice and directions for future research.

BACKGROUND & RATIONALE

In the trial PCV13 was compared to placebo. This comparator was chosen because in the Netherlands vaccination of healthy elderly with 23-valent PPSV was not recommended based on the 2003 Dutch Health Council advise.[10] Moreover, uncertainty about the efficacy of PPSV in preventing vaccine-type PCAP hampered the design of a comparative study. The main objectives of the trial were to demonstrate efficacy of

PCV13 in the prevention of a first episode of confirmed vaccine-type (VT) CAP, non-bacteraemic/non-invasive (NB/NI) VT-CAP, and VT-IPD. Other objectives were to explore efficacy against all pneumococcal CAP and IPD, irrespective of serotype, and against all-cause CAP. The safety profile was assessed by comparing serious adverse events (SAEs), adverse events (AEs) and all-cause mortality.

Table 1 - Eligibility criteria

Inclusion criteria	Exclusion criteria
• Aged 65 years or older on the date of vaccination • Registered with a GP who was referring subjects to the trial • Able to fulfill study requirements	• Previous vaccination with any licensed or experimental pneumococcal vaccine • Residence in a nursing home, long-term care facility, or other institution, or requirement of semiskilled nursing care ǂ • Contraindication for vaccination with PCV13 • Contraindication for vaccination with influenza vaccine, if influenza vaccine was to be administered • Use of investigational vaccine or medication within 30 days before study vaccine administration • History of severe adverse reaction associated with a vaccine or vaccine component • Immune deficiency or suppression, defined as presence of 1 or more of the following conditions: o Human immunodeficiency virus (HIV) infection o Hematologic or solid organ malignancy § o Chronic renal failure or nephrotic syndrome ɬ o Receipt of immunosuppressive therapy within 3 months of study vaccine administration * o Receipt of an organ or bone marrow transplant

ǂ An ambulatory subject who was a resident of a retirement home or village was eligible for the trial.
§ Treated by, or been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years.
ɬ Chronic renal failure was defined as receipt of renal dialysis or transplant.
* For corticosteroids, this meant prednisone or equivalent, 0.5 mg/kg/day for 14 days. Inhaled, intra-articular, and topical steroids were not considered immunosuppressive.

DESIGN

All Dutch residents are registered in a single general practitioner (GP) practice, where all relevant medical information is contained. The GP pre-selected eligible individuals for study participation. These subjects received study information and were invited to one of the vaccination locations near to their home if interested in study participation. The most important eligibility criteria were age of 65 years or above, not living in a nursing home or long term care facility, and being immunocompetent (see Table 1 for all in- and exclusion criteria). After providing informed consent, subjects were randomized in a 1:1 ratio to receive PCV13 or placebo. Subjects were enrolled between September 15, 2008 and January 30, 2010.

Surveillance for suspected pneumonia and IPD was conducted at 59 sentinel centers, 58 hospitals and one regional primary care diagnostic center, all located in the regions

where participants were enrolled. In these centers dedicated research staff screened admission lists for trial participants suspected of pneumonia on a daily basis. In subjects presenting with a clinical suspicion of pneumonia urine was collected within 48 hours of admission for the serotype-specific urinary antigen detection (UAD) assay, which permits the detection of the 13 serotypes contained in the vaccine,[11] and for the BinaxNOW® pneumococcal urinary antigen test assay. Chest x-rays were adjudicated by independent radiologists blinded to treatment allocation and clinical symptoms.

SAEs were recorded up to a period of 28 days after vaccination (and up to six months in the safety subset of approximately 2,000 participants) and all-cause mortality was recorded for the total study duration. Death certificates were reviewed by physicians to determine the cause of death and if death was due to CAP or IPD. AEs up to 28 days after enrolment were recorded in the safety subset.

The study was designed as an endpoint driven trial, meaning that the collection of clinical endpoints continued up to a total of 130 primary endpoints. This number was reached at August 28, 2013, after which accrual of CAP and IPD cases was stopped.

Data analysis

The mITT population included participants who had developed a CAP or IPD with symptom onset at least 14 days after vaccination. The per-protocol population included those that satisfied the mITT criteria, were still compliant with the eligibility criteria at the time of symptom onset, and had no other major protocol deviations. The primary efficacy endpoint was first episode of VT-CAP in the per protocol population. An interim analysis was performed after accrual of half the required number of primary endpoints. Vaccine efficacy (VE) was calculated as [events in placebo group] minus [events in PCV13 group] divided by [events in placebo group]. Two-sided confidence intervals (CIs) were derived using the Clopper-Pearson method with alpha adjustment for interim analysis.[12]

RESULTS

A total of 84,946 participants were included and randomized to PCV13 (n=42,240) or placebo (n=42,256) and were followed up for a mean time of four years. All-cause mortality was 7.1% in both groups and 4.8% and 5.1% of participants were lost to follow-up in the PCV13 and placebo group, respectively.

Statistically significant VE was seen for VT-CAP, NB/NI VT-CAP, VT-IPD, all-serotype CAP and all-serotype IPD (Table 2). VE against all-cause CAP was 5% but not statistically significant. The VE against VT-CAP and VT-IPD remained constant throughout the study

period. Of the first episodes of all-cause CAP in the placebo population, 13% was caused by *S. pneumoniae* serotypes contained in PCV13.

Participants in the PCV13 group had more local and systemic reactions, particularly injection site reactions and muscular pain, which mostly were mild or moderate in severity. Frequencies of SAE's or deaths were not different.

Table 2 - Vaccine efficacy

Efficacy Endpoint	Analysis Population	Events PCV13 group (N)	Events placebo group (N)	Percent VE (95% CI)
First episode of VT-CAP	Per-protocol	49	90	45.6 (21.8 to 62.5) ǂ
	mITT	66	106	37.7 (14.3 to 55.1)
First episode of NB/NI VT-CAP	Per-protocol	33	60	45.0 (14.2 to 65.3) ǂ
	mITT	43	73	41.1 (12.7 to 60.7)
First episode of VT-IPD	Per-protocol	7	28	75.0 (41.4 to 90.8)
	mITT	8	33	75.8 (46.5 to 90.3)
First episode of PCAP	Per-protocol	100	144	30.6 (9.8 to 46.7)
	mITT	135	174	22.4 (2.3 to 38.5)
First episode of NB/NI PCAP	Per-protocol	66	87	24.1 (−5.7 to 45.8)
	mITT	90	109	17.4 (−10.2 to 38.2)
First episode of IPD	Per-protocol	27	56	51.8 (22.4 to 70.7)
	mITT	34	66	48.5 (20.9 to 67.0)
First episode of all-cause CAP	mITT	747	787	5.1 (−5.1 to 14.2)

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ǂ The confidence intervals for the end points of confirmed VT-CAP and confirmed NB/NI VT-CAP were adjusted to 95.2% to account for the assessment of these two endpoints at the interim and final analyses.
Abbreviations: VE: vaccine efficacy, CI: confidence interval, VT: vaccine-type, CAP: community-acquired pneumonia, PCAP: pneumococcal CAP, NB/NI: non-bacteraemic/non-invasive, IPD: invasive pneumococcal disease, mITT: modified intention-to-treat.

CONCLUSION

PCV13 is safe and effective in reducing first episode of VT-CAP (46% reduction in per protocol analysis and 38% in the mITT population) and first episode of VT-IPD (75% reduction in per protocol analysis and 76% in the mITT population) in immunocompetent elderly. Policy decisions on how to use an effective vaccine, however, depend not only on safety and efficacy, but also on the cost-effectiveness of the intervention. The actual burden of vaccine-preventable disease, the potential to identify patients at risk, and VE in these risk groups play an important role. These aspects will be discussed in the following chapters and in the General Discussion.

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Conflicts of interest

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Chapter 2 The prevention paradox of pneumococcal conjugate vaccination: highest efficacy in elderly at lowest risk of community-acquired pneumonia

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ABSTRACT

Objective

To evaluate the effectiveness of risk-based pneumococcal vaccination strategies based upon a prediction model for the occurrence of community-acquired pneumonia (CAP) in immunocompetent elderly.

Methods

Data were used from the Community-Acquired Pneumonia immunization Trial in Adults (CAPITA), a randomized placebo-controlled trial of 13-valent pneumococcal conjugate vaccine (PCV13) in immunocompetent adults ≥65 years. The placebo group was geographically divided in a derivation and validation cohort. Cox regression analysis was used to identify risk factors for all-cause CAP and the model was validated for all-cause CAP, and for pneumococcal CAP or invasive pneumococcal disease (pnCAP/IPD). PCV13 vaccine efficacy (VE) and absolute risk differences (ARD's) were assessed in participants with minimal, low, and moderate risk of CAP.

Results

The derivation and validation cohorts contained 20,861 and 21,394 participants, respectively. Median follow-up was four years. A model with age, male gender, smoking, education level, lung disease, heart disease, diabetes mellitus, and splenectomy was moderately predictive of all-cause CAP (area under the receiver operating characteristic curve (AUC) 0.73, 95% CI 0.71-0.76) and pnCAP/IPD (AUC 0.69, 95% CI 0.63-0.75). In the minimal, low, and moderate risk groups VE was 95% (95% CI 59%-99%), 45% (95% CI 17%-74%), and 10% (95% CI -66%-52%), and ARD's per 1,000 participants were 1.66 (0.80 to 2.52), 1.21 (-0.31 to 2.73), and 0.64 (-3.06 to 4.33), respectively.

Conclusion

In immunocompetent elderly, occurrence of CAP can be moderately predicted. VE was highest in the minimal risk patients, but ARD's were comparable in the three risk strata. These findings can assist in optimizing population-based implementation of PCV13 vaccination in elderly.

INTRODUCTION

Community acquired pneumonia (CAP) is a common disease among older adults, with an incidence of 3.2-47.4 per 1000 per year.[1,2] *Streptococcus pneumoniae* is the most commonly identified pathogen in CAP.[3] In developed countries, CAP ranks 6th in causes of death,[4] and 90% of deaths due to CAP occur in elderly.[5] The incidence increases with age, with an up to fivefold increase for those over 90 years old as compared to people aged 65-69 years.[6] This sharp increase may result from a higher prevalence of comorbidities and medication use, deterioration of pulmonary function, and age-related deficits in the innate and adaptive immune system.[7–10]

Despite causing the highest morbidity and mortality in elderly, most prognostic studies in CAP focused on adult populations of all ages. In four studies among adults over 65 years, age, male gender, previous hospitalization for CAP, chronic lung disease, and chronic heart disease were associated with an increased risk of pneumonia.[11–14] These studies suffered from potential misclassification by using ICD-9 or ICD-10 codes, which have a limited sensitivity for CAP,[15] without radiologic confirmation for CAP diagnosis in two of the studies, and predictor status determination at the time event in one study. Moreover, relative risk may have been biased in one study using controls from a hospitalized population, and the reported prognostic accuracy of the prediction model was not determined in any of these studies.

Due to ageing of the population, the burden of CAP is likely to further increase in the Western world.[16] Measures to prevent CAP, such as vaccination programs and optimal management of comorbidities, are necessary to control disease burden and health care costs due to CAP. Therefore, the aim of this study was to develop and validate a prediction model for the occurrence of CAP in elderly persons, and to evaluate the effectiveness of pneumococcal vaccination in different risk strata in a post-hoc analysis of the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA).[17] In this study, in which 84,496 immunocompetent elderly (65 years and older) were randomized to 13-valent pneumococcal conjugate vaccine (PCV13) or placebo, the efficacy of PCV13 in preventing a first episode of vaccine-type pneumococcal CAP was 46%. The study population included subjects considered to be at low and moderate risk of pneumococcal CAP.

METHODS

Study design

This is a post-hoc analysis of data from the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), a double-blind randomized placebo-controlled trial on the efficacy of PCV13 in immunocompetent individuals aged 65 years

and older. Patient enrollment was conducted between September 2008 and January 2010 and follow-up for CAP episodes ended on August 28th 2013.[17]

Study population

Participants were community-dwelling adults aged ≥ 65 years, living in the Netherlands. Exclusion criteria were residence in a nursing home or long-term care facility, previous vaccination with pneumococcal vaccine, a contraindication for PCV13, and immunodeficiency or immune suppression (see Supplementary Appendix Table S1 for full inclusion and exclusion criteria). A total of 84,496 participants were included, of which 84,492 were in the safety population and form the basis for this analysis. For the current analysis, participants in the placebo group (n=42,255) were geographically divided: those living in the west of the Netherlands (i.e. postal code starting with 52 or less) were allocated to the derivation cohort, and those living in the east of the Netherlands (i.e. postal code starting with 53 or more) were allocated to the validation cohort (Supplementary Appendix Figure S1).

Risk factor identification

A literature search in PubMed was performed by one of the authors (BSD) to identify potential predictors for CAP in people of all ages. A potential risk factor was selected if there was epidemiological evidence or a plausible pathophysiological mechanism to support an association with CAP and if this factor was collected at baseline or could be reconstructed from baseline data.

Derivation and validation of the model was performed using all-cause CAP referred to the hospital. Validation was additionally performed for the combined endpoint of pneumococcal CAP and invasive pneumococcal disease (pnCAP/IPD) and for general practitioner (GP) diagnosed CAP (see Supplementary Appendix Table S2 for definitions).

Data collection

Baseline characteristics, including self-reported comorbidities, were collected by the research staff at the day of enrollment. Additionally, participants were invited to participate in the cost-health-outcome of CAP (CHO-CAP) study, a piggyback study collecting data on outcomes, quality-of-life and costs.[18] The CHO-CAP baseline questionnaire included the EuroQol questionnaire with five dimensions and three severity levels (EQ-5D-3L),[19] from which we derived dependency in activities of daily living (ADL), education level, living situation, and history of stroke. As the CHO-CAP study started later than the CAPiTA study, the first 15% of CAPiTA participants were not approached for these data. Another 27% declined participation in the CHO-CAP study or did not return the informed consent or questionnaire. Dependency in ADL was defined as being bedridden (i.e. dimension mobility level 3), needing help with daily

activities such as washing or dressing (i.e. dimension self-care level 3), or residing in a retirement home. Education level was classified as high in participants with a Bachelor's or Master degree, medium in participants with a High School diploma, Associate's degree or comparable grade, and as low otherwise. Information about air pollution was based on data about particulate matter 2,5 (PM2,5) in the year 2010 and was obtained from the National Institute for Public Health and the Environment.[20] A high level of air pollution was defined as an average PM2,5 of ≥ 16 microgram/m^3/year, based on the participants' postal code at time of enrolment.

Statistical analysis

Missing data were handled by multiple imputation, consisting of 50 imputations. Because the CHO-CAP data was missing in 42% of the CAPiTA participants, we included data from Statistics Netherlands on average income and housing values, based on the participants' postal code, in order to improve the imputation of education level.[21]

The prediction model was derived using multivariate Cox regression analysis, taking time to first episode of all-cause CAP as the dependent variable. Patients that were lost to follow-up were censored. In order to account for competing events, the follow-up time of participants that had died during the study, was extended up to the last study day.[22,23] Starting from a model with all candidate predictors using stepwise backward selection, variables with a p-value below 0.10 were retained in the model.

Discrimination was tested using the time-dependent area under the receiver operating characteristic curve (AUC).[24] Calibration was tested by means of calibration plots, using bootstrapping to constitute confidence intervals. Patients were grouped in three risk strata using the 50th and 84th percentiles of the linear predictor in the derivation cohort (i.e. the median and the median plus one standard deviation in a normal distribution) as recommended.[25] Patients with a risk score up to the 50th percentile, between the 50th and 84th percentile, and above the 84th percentile were classified as minimal risk, low risk, and moderate risk, respectively. These terms were adopted since immunocompromised patients, who are generally classified as high risk, were not included in this study. Incidences were calculated in each risk stratum and compared across the derivation and validation cohorts. Since data on education level and air pollution are not routinely available in medical practice, we repeated the model derivation procedure omitting these variables. To assess the performance of the model in a PCV13 immunized population, discrimination was also tested in the subjects randomized to PCV13.

PCV13 vaccine efficacy (VE) and absolute risk differences (ARD) were assessed in the three risk strata. It was expected that in the derivation cohort VE would be biased

upward in the moderate risk group and downward in the minimal risk group, because the model was created in the placebo group of the derivation cohort. To avoid this bias, VE per risk group was primarily assessed in the validation cohort. To increase precision, VE per risk group was also calculated for the total population. To test the robustness of this analysis, we repeated the model derivation in the eastern part of the Netherlands, defined risk groups using the same percentiles, and estimated vaccine efficacy per risk group in the western part of the Netherlands and in the total study population. Differences in VE per risk stratum were tested using Poisson regression, using an interaction term of `risk group` and `study arm` to determine statistical significance. P-values <0.05 were considered statistically significant. R for Windows version 3.0.2 was used for the statistical analysis.[26]

RESULTS

Baseline characteristics

The derivation cohort contained 20,861 participants. The median follow-up was 4.0 years (interquartile range, IQR 3.8-4.8), median age was 71 years (IQR 68-76 years), and 11,669 (56%) were male (Table 1). 1,526 (7.3%) participants died within the study period and 1,344 (6.4%) were lost to follow-up. The validation cohort contained 21,394

Table 1 - Baseline characteristics

		Derivation cohort (N=20,861)	Validation cohort (N=21,394)
Median follow-up in years (IQR)		4.02 (3.84 to 4.79)	3.89 (3.82 to 4.14)
Median Age (IQR)		71.6 (68.2 to 76.5)	71.6 (68.2 to 76.3)
Male gender		11,669 (55.9%)	12,132 (56.7%)
Education level #	Low	8,733 (41.9%)	9,510 (44.5%)
	Medium	7,250 (34.8%)	7,256 (33.9%)
	High	4,879 (23.4%)	4,628 (21.6%)
Current smoking		2,642 (12.7%)	2,533 (11.8%)
ADL dependency #		250 (1.2%)	288 (1.3%)
Lung disease		2,967 (14.2%)	3,117 (14.6%)
Heart disease		5,352 (25.7%)	5,406 (25.3%)
Diabetes mellitus		2,549 (12.2%)	2,782 (13.0%)
Liver disease		119 (0.6%)	82 (0.4%)
History of stroke #		753 (3.6%)	851 (4.0%)
Splenectomy		18 (0.1%)	14 (0.1%)
High air pollution level		12,607 (60.4%)	11,695 (54.7%)
CHO-CAP questionnaire completed		11,887 (57.0%)	12,478 (58.3%)

Data are numbers and percentages unless otherwise indicated. Variable summaries are averaged over the imputations. For crude baseline characteristics and proportions of missing data, see Supplementary Appendix Table S3.
Abbreviations: IQR: inter quartile range. ADL: activities of daily living.
Data from CHO-CAP study baseline questionnaire.

persons. The median follow-up was 3.9 years (IQR 3.8-4.1), median age was 71 years (IQR 68-76 years), and 12,132 (57%) were male (Table 1). 1,479 (6.9%) participants died within the study period and 989 (4.6%) were lost to follow-up.

Outcome events

In the derivation cohort 495 episodes of all-cause CAP were reported in 396 participants (4.7 first episodes per 1,000 person years). In the validation cohort 465 episodes of all-cause CAP were reported in 370 participants (incidence of 4.5 first episodes per 1,000 person years). In all, 636 (83%) had one episode, 91 (12%) had 2 episodes and 40 (5%) had >2 episodes during the study. First episodes of pnCAP/IPD were reported in 99 and 97 participants (with in total 107 and 105 episodes) in the derivation and validation cohort, respectively (incidence of 1.2 per 1000 person years), of which 12 (6%) participants had two and 2 (1%) had three episodes. GP records were screened in 9,748 and 10,486 subjects in the derivation and validation cohorts, respectively, with 700 and 711 participants having at least one episode of GP-diagnosed CAP (incidence of 17 per 1000 patient years). A total of 779 and 814 episodes occurred in these cohorts, of which 115 (8%) had two and 25 (2%) had more than 2 episodes.

Risk factors

Independent risk factors for the occurrence of all-cause CAP were: age, male gender, smoking, lung disease, splenectomy, heart disease, education level (medium and high education were protective), and diabetes mellitus (Table 2). The strongest risk factors were lung disease and splenectomy. The risk of CAP increased with 5.7% per year of age. Compared to people aged 65 years, this corresponds to a HR of 1.74 at the age of 75 years and of 3.03 at the age of 85 years. History of stroke, liver disease, dependency in ADL, and air pollution were not significantly associated with occurrence of CAP.

Table 2 - Independent predictors of all-cause CAP

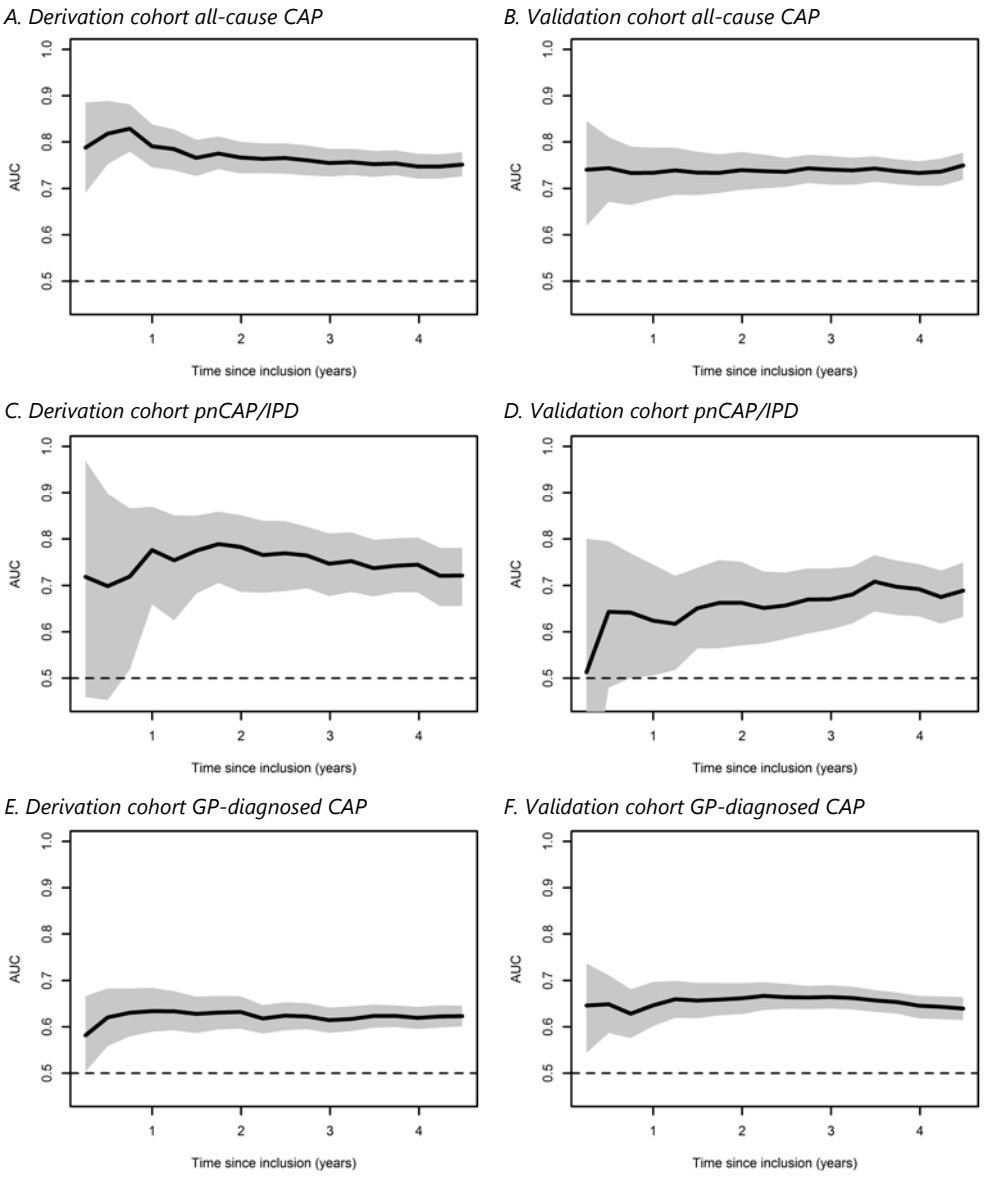
Variable	Beta	SE	HR	95% CI
Age at inclusion	0.056	0.008	1.057	1.041 - 1.074
Male gender	0.653	0.114	1.920	1.537 - 2.399
Lung disease	1.576	0.102	4.837	3.962 - 5.906
Heart disease	0.354	0.105	1.424	1.159 - 1.751
Diabetes mellitus	0.250	0.135	1.284	0.987 - 1.672
Splenectomy	1.593	0.711	4.917	1.220 - 19.826
Current smoking	0.592	0.125	1.808	1.416 - 2.307
Medium education level	-0.271	0.138	0.763	0.582 - 1.000
High education level	-0.308	0.156	0.735	0.541 - 0.999

Beta: regression coefficient for linear predictor. SE: standard error of beta. HR: hazard ratio. CI: confidence interval.

Validation

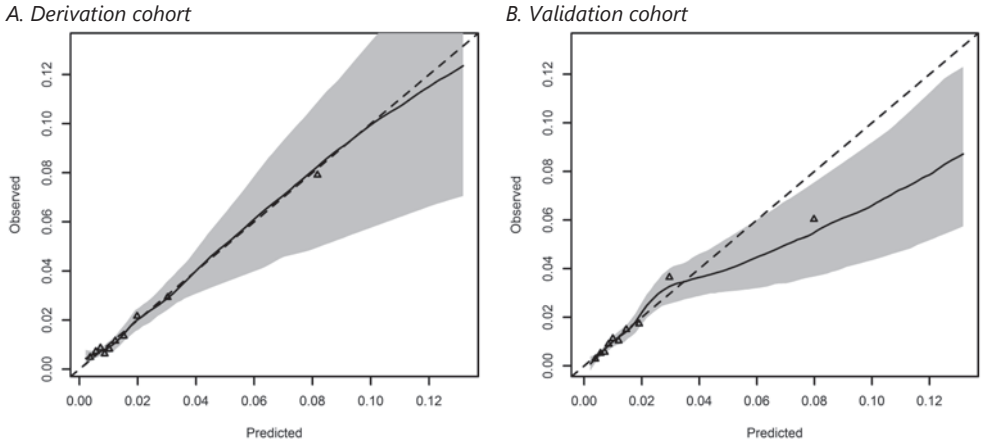
In the validation cohort, the model had an AUC after four years (i.e. the median follow-up duration) of 0.73 (95% CI 0.71-0.76) for all-cause CAP, 0.69 (95% CI 0.63-0.75) for pnCAP/IPD, and 0.65 (95% CI 0.62-0.67) for GP-diagnosed CAP, with constant discrimination over time for all outcome events (Figure 1). Model calibration against observed incidence

Figure 1 - Time-dependent area under the receiver operating characteristic curve



At different time points, the model AUC is calculated for cases observed up to that time point.
Abbreviations: AUC: area under the receiver operating characteristics curve. CAP: community-acquired pneumonia; pnCAP: pneumococcal CAP; IPD: invasive pneumococcal disease; GP: general practitioner.

Figure 2 - Calibration plot of model prediction on incidence of all-cause community-acquired pneumonia

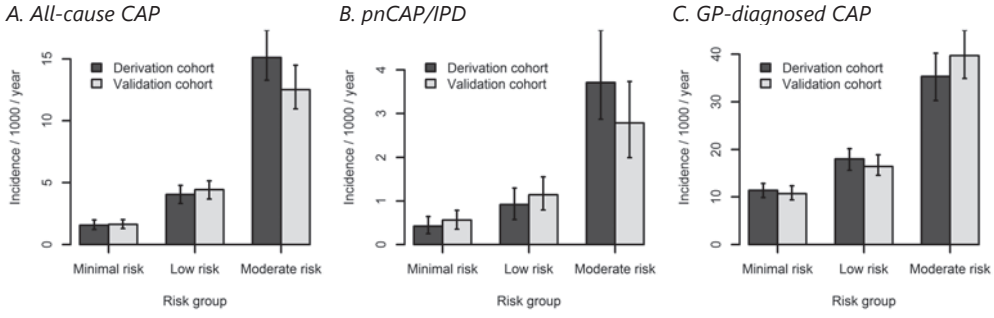


of all-cause CAP was adequate in 90% of participants, but the predicted risk was overestimated in the participants at highest risk (Supplementary Appendix Figure S2). Removing education level from the model did not change the AUC in the derivation cohort (Supplementary Appendix Figure S3). In the 42,237 participants randomized to PCV13, the model AUC was comparable for all-cause CAP and GP-diagnosed CAP, while for pnCAP/IPD the AUC was 0.78 (95% CI 0.74-0.83; Supplementary Appendix Figure S4).

Risk of CAP and vaccine efficacy

Participants with a risk score >5.43 were considered at moderate risk, those between 4.53 and 5.43 at low risk and those below 4.53 at minimal risk. Distribution of predictors in these risk strata are given in Supplementary Appendix Table S4 and incidence of endpoints per risk group is given in Figure 3. In the validation, cohort 172 (46%) of the

Figure 3 - Incidence per risk group in derivation and validation cohort



Abbreviations: CAP: community-acquired pneumonia; pnCAP: pneumococcal CAP; IPD: invasive pneumococcal disease; GP: general practitioner.

first episodes of all-cause CAP, 39 (41%) of the first pnCAP/IPD episodes, and 252 (35%) of the GP-CAP episodes occurred in the moderate risk group. The low risk group contained 128 (35%) of the CAP episodes, 33 (34%) of the pnCAP/IPD episodes, and 230 (32%) of the GP-CAP episodes.

PCV13 VE was significantly higher in the minimal risk group compared to the low risk and moderate risk groups (Table 3). The ARD was not significantly different between the groups. PCV13 reduced the number of VT-episodes in the validation cohort by 29 (48%). In the moderate risk group of the validation cohort PCV13 reduced the number of VT-episodes with 3 (11% of VT-episodes in the moderate risk group and 5% of VT-episodes in the derivation cohort). The higher VE in the minimal risk group and comparability of the ARD between the risk groups was confirmed when analyzing the total study population (Table 3) and in the sensitivity analysis (i.e. when the prediction model was derived in the validation cohort and VE per risk group was assessed in the derivation cohort), despite differences in model specification (Supplementary Appendix Table S5).

Table 3 – VE and ARD for different risk strata in the validation cohort

	Events / subjects (PCV13 group) ǂ	Events / subjects (placebo group) ǂ	VE (95% CI)	Risk*	ARD*
Validation cohort					
All subjects	31/21,376	60/21,394	48.3% (20.3% to 66.5%)	2.80	1.35 (0.47 to 2.24)
Minimal risk	1/10,571	19/10,567	94.6% (59.3% to 99.3%)	1.75	1.66 (0.80 to 2.52)
Low risk	11/7,380	20/7,320	45.3% (-16.6% to 74.3%)	2.67	1.21 (-0.31 to 2.73)
Moderate risk	19/3,424	22/3,508	10.2% (-66.1% to 51.5%)	6.24	0.64 (-3.06 to 4.33)
Total population #					
All subjects	67/42,237	116/42,255	42.2% (22.0% to 57.2%)	2.75	1.16 (0.53 to 1.79)
Minimal risk	3/21,073	29/20,964	88.9% (63.5% to 96.6%)	1.36	1.21 (0.67 to 1.75)
Low risk	23/14,336	37/14,415	36.9% (-7.1% to 62.9%)	2.54	0.94 (-0.13 to 2.00)
Moderate risk	41/6,828	51/6,876	19.2% (-22.0% to 46.5%)	7.40	1.42 (-1.34 to 4.18)

ǂ Differences between group and total numbers are caused by rounding of the average from multiple imputation.
* Risk is calculated per 1,000 subjects in the validation cohort for the average follow-up duration of four years and ARD is given as the absolute reduction in risk. Risk and ARD should be interpreted with caution given that relatively healthy subjects were included and given the possibility to have missed episodes.
# This comparison would be biased in the derivation cohort as the model is fitted to the placebo group of the derivation cohort. However, to increase precision we also performed the analysis in the total study population.
Abbreviations: PCV13: 13-valent pneumococcal conjugate vaccine, VE: vaccine efficacy, CI:confidence interval, ARD: absolute risk difference, VT: vaccine type, CAP: community-acquired pneumonia, IPD: invasive pneumococcal disease.

DISCUSSION

In a cohort of 42,255 community-dwelling immunocompetent seniors in the Netherlands, receiving placebo in the CAPiTA study and followed for a period of 4 years, risk factors for CAP were self-reported lung disease and splenectomy, ageing, male gender, smoking, heart disease, low education level and diabetes mellitus. In a post-hoc analysis, vaccine efficacy of PCV13 was substantially higher in subjects with a minimal risk of CAP compared to the low and moderate risk groups. The absolute risk difference was not significantly different between the risk groups.

Lung disease was associated with a nearly fivefold increased risk of CAP. This is substantially higher than previous estimates, ranging from 2.4 to 2.9.[11–13] However, oxygen and corticosteroid use were included as independent predictors in these studies, possibly explaining the different findings. Also, since we used self-reported comorbidities, misclassification may have occurred.[27] Chronic respiratory disease also had the strongest association with recurrent CAP episodes (data not shown). Diabetes was associated with a 30% increased risk. There were not enough CAP events to reliably quantify risks for those with insulin dependent and non-insulin dependent diabetes, although point estimates suggested that the risk was slightly higher for patients with insulin dependent diabetes (data not shown). Heart disease, the most prevalent comorbidity in our cohort, was also associated with CAP, in agreement with previous findings.[12–14] The association of low education level with CAP probably reflects differences in socioeconomic status.[28,29] Air pollution was recently found to be associated with CAP in elderly people.[30] We could not confirm this association, possibly because of the relatively low amount of air pollution in the Netherlands, or from the use of a binary definition of air pollution.

The model showed moderate discrimination in the prediction of all-cause CAP and pnCAP/IPD and poor discrimination for GP-diagnosed CAP. Risk factors may have different effect sizes for the three endpoints, and model derivation using all-cause CAP explains the higher AUC for that endpoint. Also, GP-diagnosed CAP is generally not confirmed by chest radiograph and may represent a more heterogeneous group of suspected lower respiratory tract infections. It should be acknowledged that, using this model, about 50% of the all-cause CAP events still occur in the minimal and low risk groups. Indeed, their risk was 4.5 times lower compared to the moderate risk group, yet this group is five times larger. Still, a strategy in which only moderate risk people receive a preventive treatment may be preferred over treatment of the entire population, depending on the cost-benefit ratio of the intervention in the two populations.

By evaluating the effect of PCV13 in different risk strata, an approach that has been advocated as superior to single variable subgroup analyses,31 we were able to assess the benefit of risk-based vaccination compared to universal vaccination in terms of prevented episodes. Using the western part of the Netherlands for model derivation is an arbitrary choice, therefore, we reversed the cohorts and repeated the analysis to test the robustness of the findings. In the primary analysis and in all sensitivity analyses, VE was substantially higher in the minimal risk group, but ARD's were not different between the risk groups. Due to the combined effect of moderate model discrimination and the lower VE in the moderate risk group, a strategy in which only this group would have been immunized would have prevented substantially less VT-episodes compared to vaccination of the entire cohort, as was shown by the number of prevented episodes. The first phenomenon has been referred to as the 'prevention paradox': most of the incident cases occur in those classified as low risk because this group is largest.[32] This inverse relation between incidence and VE does not support a high-risk prevention approach, and VE based on the risk of CAP should be considered in cost-effectiveness analyses of PCV13 in adults.

The following limitations of our data need to be considered. First, we have studied a relatively healthy population, since immunocompromised people and nursing home residents were excluded, and trial participants are generally healthier compared to non-participating eligible people. Consequently, model accuracy may be less in the total population. Proportions of comorbidities in other Dutch cohorts vary considerably, therefore, the representativeness of the current study is difficult to determine.[33,34] Participants who had developed immunodeficiency during follow-up were however included in the analyses. Second, not all potential predictors that are reported in the literature could be investigated, either because they were not collected at baseline, or because these patients were excluded from the study. These include medication use (inhaled corticosteroids, gastric acid-suppressive drugs and antidepressants), alcohol abuse, chronic renal disease, malignancies, and other immune compromising conditions. Third, reported comorbidities and smoking status were not verified in medical records, therefore misclassification of comorbidities may have occurred, despite the use of trained staff to interview the patients. Fourth, in screening for CAP admissions, some episodes will have been missed, leading to overall underestimation of the risk and potentially to biased estimates of the predictors. For the same reason, ARD's are expected to be underestimated and these should only be used to compare the risk strata within the current study.

Several strengths of the study can be mentioned. First, predictors were collected at baseline, precluding the possibility of recall bias as in retrospective studies. Second, all-cause CAP and IPD episodes were identified prospectively based on predefined clinical criteria, including the presence of compatible abnormalities on chest X-rays as adjudicated by independent radiologists blinded for clinical symptoms. Third, there was

a median follow-up of four years, which is a relevant period to observe health effects in an elderly population. Fourth, we performed a Cox regression analysis, taking length of follow-up per patient into account and accounting for death as a competing event. Competing events analysis confines the risk of overestimation of the effect size of factors that are also associated with all-cause mortality.[22,23] Fifth, we have derived and validated the model in geographically distinct populations. This is preferred over using a random split sample validation method because the latter creates populations that are only different by chance, and, hence, differences will be very limited in a large study population. Still, our derivation and validation cohorts were rather similar with respect to baseline characteristics, and therefore external validation of the model is still desired. Last, we have validated the model on different clinically relevant endpoints and have evaluated PCV13 VE in the risk groups, which consistently showed higher VE estimates in the minimal risk group.

In conclusion, age, male gender, smoking, education level, chronic respiratory disease, asplenia, chronic heart disease and diabetes mellitus are independent predictors of the occurrence of CAP and a model containing these variables has moderately predictive capacity. A risk-based post hoc analysis of the CAPiTA study identified an inverse relation between risk of all-cause CAP and VE of PCV13 in preventing vaccine-type pneumococcal disease with no statistically significant differences in ARD. These findings can assist in optimizing population-based implementation of PCV13 vaccination in elderly.

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Potential conflicts of Interest

C.H.v.W. served in a Pfizer Advisory Committee. M.B. received presentation fees from Pfizer. C.W., and S.P. are employees of Pfizer, Inc., and hold company stock. M.J.M.B. received research funding and an unrestricted education grant from Pfizer and served on the CAPiTA European Expert Meeting (all fees paid to the institution). Other authors report no conflicts of interest.

SUPPLEMENTARY APPENDIX

Table S1 - Study eligibility criteria

Inclusion criteria	Exclusion criteria
• Age >= 65 years. • Registered with a participating general practitioner. • Able to visit the vaccination location.	• Residence in a nursing home or long term care facility • Previous vaccination with a pneumococcal vaccine • Contraindication for vaccination with PCV13 • History of severe adverse reaction associated with a vaccine or vaccine component. • Use of investigational vaccine or medication within 30 days before study entry • Immunodeficiency or immune suppression • Malignancy[1] • Human immunodeficiency virus infection • Chronic renal failure[2] or nephrotic syndrome • Organ or bone marrow transplant • Immunosuppressive therapy[3]

1. Any hematologic or solid organ malignancy which had been treated by, or had been eligible for treatment by radiotherapy and/or chemotherapy within the last 5 years
2. Chronic renal failure with receipt of transplantation or dialysis
3. High dosage steroids (prednisone >= 0.5 mg/kg/day, or an equivalent, for 14 days) within 3 months before enrolment

Table S2 - Endpoint definitions

All-cause CAP ł	All of the following: • Presentation to one of the participating hospitals • Presence of 2 or more clinical criteria (cough, production of purulent sputum or a change in the character of sputum, temperature >38.0° C or <36.1° C, auscultatory findings consistent with pneumonia including rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony), leukocyte count >= $10*10^9$/L, hypoxemia (oxygen saturation < 8 kPa), and elevated C-reactive protein (>30 mmol/L) • Abnormalities on chest X-ray within 48 hours of admission as adjudicated by independent radiologists • No hospitalization or residence in a long-term care facility at the time of symptom onset
pnCAP/IPD ł	Either of: • Meeting the criteria for all-cause CAP + detection of *S. pneumoniae* in blood culture or other cultures from sterile sites, or detection of pneumococcal antigen in urine collected within 48 hours of admission • IPD (i.e. culture of *S. pneumoniae* in normally sterile body fluid, independent of the source of infection)
GP-diagnosed CAP §	Record in the GP patient file of ICPC code R81 (pneumonia) followed by antibiotic treatment.

ł Participants who were referred to one of 58 participating hospitals with a suspicion of CAP, were screened by trained research nurses. Blood cultures and other microbiological tests were taken as part of routine clinical care. Urine for pneumococcal antigen testing was collected as part of the study protocol. Chest radiographs were independently interpreted by two radiologists (and by a third radiologist in case of disagreement), blinded for clinical symptoms and study arm allocation.
§ In a subset of 40,434 participants, GP records were screened for a diagnosis of CAP (ICPC code R81). Patient consultations with this ICPC code within 30 days of each other were considered to represent one episode. The first start dates of each episode were recorded in an electronic case record form.
Abbreviations: CAP: community-acquired pneumonia, pnCAP/IPD: combined endpoint of pneumococcal CAP or invasive pneumococcal disease, GP: general practitioner, ICPC: International Classification of Primary Care.

Table S3 - Baseline characteristics before multiple imputation

		Derivation cohort (N=20,861)	Validation cohort (N=21,394)
Median follow-up in years (IQR)		4.0 (3.8 to 4.8)	3.9 (3.8 to 4.1)
Median age (IQR)		71.6 (68.2 to 76.5)	71.6 (68.2 to 76.3)
Male gender		11,669 (55.9%)	12,132 (56.7%)
Education level	Low	4,880 / 11,753 (41.5%)	5,281 / 12,313 (42.9%)
	Medium	4,109 / 11,753 (35.0%)	4,201 / 12,313 (34.1%)
	High	2,764 / 11,753 (23.5%)	2,831 / 12,313 (23.0%)
Current smoking		2,642 / 20,858 (12.7%)	2,533 / 21,390 (11.8%)
ADL dependency		122 / 11,619 (1.1%)	146 / 12,196 (1.2%)
Lung disease		2,958 / 20,801 (14.2%)	3,111 / 21,356 (14.6%)
Heart disease		5,337 / 20,803 (25.7%)	5,390 / 21,334 (25.3%)
Diabetes mellitus		2,545 / 20,831 (12.2%)	2,779 / 21,374 (13.0%)
Liver disease		119 / 20,826 (0.6%)	82 / 21,379 (0.4%)
History of stroke		370 / 11,336 (3.3%)	467 / 11,868 (3.9%)
Splenectomy		18 / 20,851 (0.1%)	14 / 21,388 (0.1%)
High air pollution level		12,607 (60.4%) 11,887	11,695 (54.7%) 12,478
CHO-CAP questionnaire completed		(57.0%)	(58.3%)

Data are number (/ number with complete data) and percentages unless otherwise indicated.
Abbreviations: IQR: inter quartile range. ADL: activities of daily living.

Table S4 - Distribution of risk factors in the different risk strata

All subjects		**Minimal risk (N=10,567)**	**Low risk (N=7,320)**	**Moderate risk (N=3,508)**
Median age (IQR)		69.4 (67.3 to 73.0)	74.5 (70.3 to 78.7)	74.7 (70.2 to 80.1)
Male gender		3,905 (37.0%)	5,679 (77.6%)	2,549 (72.7%)
Education level	Medium	4,291 (40.6%)	2,066 (28.2%)	899 (25.6%)
	High	2,483 (23.5%)	1,548 (21.1%)	597 (17.0%)
Smoking		420 (4.0%)	1,292 (17.6%)	821 (23.4%)
Lung disease		0 (0.0%)	412 (5.6%)	2,705 (77.1%)
Heart disease		1,133 (10.7%)	2,736 (37.4%)	1,538 (43.8%)
Diabetes mellitus		803 (7.6%)	1,315 (18.0%)	664 (18.9%)
Splenectomy		0 (0.0%)	0 (0.0%)	14 (0.4%)
Subjects with VT-episode		**Minimal risk (N=19)**	**Low risk (N=20)**	**Moderate risk (N=22)**
Median age (IQR)		68.8 (66.8 to 70.6)	76.1 (72.1 to 79.7)	76.4 (72.6 to 80.9)
Male gender		7 (39.4%)	11 (55.1%)	19 (86.3%)
Education level	Medium	7 (36.6%)	6 (31.8%)	6 (25.8%)
	High	4 (19.2%)	2 (9.8%)	4 (17.9%)
Smoking		4 (21.7%)	5 (25.6%)	5 (22.9%)
Lung disease		0 (0.0%)	2 (10.2%)	18 (82.3%)
Heart disease		3 (18.6%)	7 (33.8%)	11 (49.7%)
Diabetes mellitus		4 (18.7%)	8 (38.3%)	9 (41.1%)
Splenectomy		0 (0.0%)	0 (0.0%)	0 (0.0%)

Minimal risk group: risk score <= 4.8. Low risk group: risk score between 4.8 and 5.7. Moderate risk group: risk score > 5.7. Data are given as N (%) unless otherwise indicated.
Abbreviations: IQR: inter quartile range, VT: vaccine-type, CAP: community-acquired pneumonia, IPD: invasive pneumococcal disease.

Table S5 - Sensitivity analysis for robustness of vaccine efficacy in risk groups

	Events / subjects (PCV13 group) ł	Events / subjects (placebo group) ł	VE (95% CI)	Risk*	ARD (95% CI)*
Derivation cohort					
All subjects	36/20,861	56/20,861	35.7% (2.3% – 57.7%)	2.68	0.96 (0.05 – 1.87)
Minimal risk	3/10,663	12/10,494	77.0% (4.0% – 94.5%)	1.14	0.87 (0.11 – 1.64)
Low risk	12/6,870	16/7,032	26.6% (-62.4% – 66.8%)	2.28	0.60 (-0.93 – 2.12)
Moderate risk	22/3,328	28/3,335	22.9% (-36.0% – 56.2%)	8.40	1.91 (-2.29 – 6.12)
Total population #					
All subjects	67/42,237	116/42,255	42.2% (22.0% – 57.2%)	2.75	1.16 (0.53 – 1.79)
Minimal risk	6/21,423	30/21,201	81.2% (52.6% – 92.6%)	1.43	1.16 (0.59 – 1.73)
Low risk	22/14,151	33/14,277	31.9% (-18.3% – 60.8%)	2.29	0.73 (-0.31 – 1.77)
Moderate risk	39/6,663	53/6,776	24.9% (-13.6% – 50.4%)	7.83	1.95 (-0.87 – 4.77)

For this analysis, the model was derived in the eastern part of the Netherlands (originally the validation cohort, i.e. postal code >= 5300) using all candidate predictors; variables with a p-value <0.1 were retained in the model, similar to the main analysis. Cardiovascular disease and asplenia were not retained in the model and air pollution and ADL dependency were added to the model. The 50th and 84th percentile of the linear predictor was 6.32 and 7.23, respectively. VE and ARD in the risk groups were determined using the first episode of VT-CAP or VT-IPD and were estimated in the western part of the Netherlands (originally the derivation cohort) and in the total study population.

ł Differences between group and total numbers are caused by rounding of the average from multiple imputation.

* Risk is calculated per 1,000 subjects in the validation cohort for the average follow-up duration of four years and ARD is given as the absolute reduction in risk. Risk and ARD should be interpreted with caution given that relatively healthy subjects were included and given the possibility to have missed episodes.

This comparison would be biased in the derivation cohort as the model is fitted to the placebo group of the derivation cohort. However, to increase precision we also performed the analysis in the total study population.

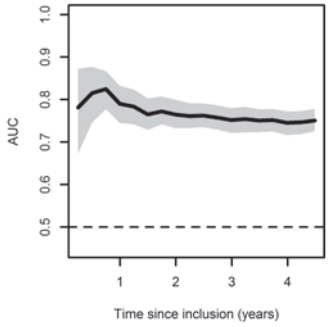
Abbreviations: PCV13: 13-valent pneumococcal conjugate vaccine, VE: vaccine efficacy, CI:confidence interval, ARD: absolute risk difference, VT: vaccine type, CAP: community-acquired pneumonia, IPD: invasive pneumococcal disease.

Figure S1 - Geographical division of derivation and validation cohort

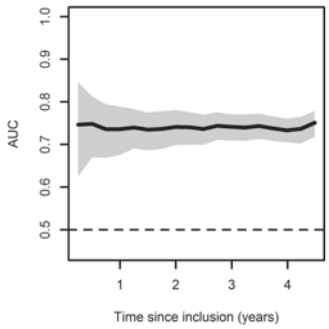
Participants living west of the black line (postal codes < 53) were assigned to the derivation cohort, while those living east of the black line (postal codes >= 53) were assigned to the validation cohort.

Figure S2 - Time-dependent AUC without education level

A. Derivation cohort



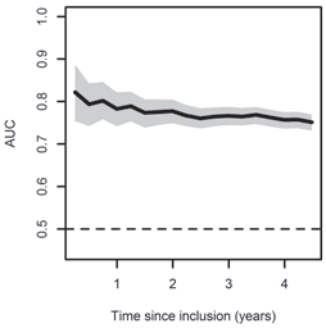
B. Validation cohort



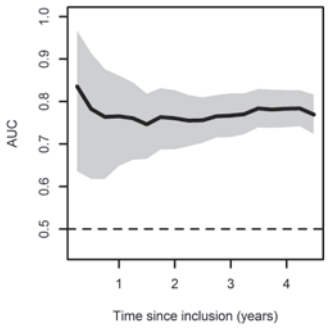
AUC: area under the receiver operating characteristic curve. Calculated for all-cause community-acquired pneumonia.

Figure S3 - Time-dependent AUC in the PCV13 arm

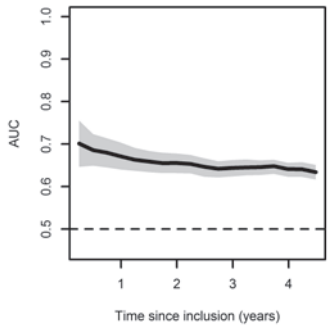
A. All-cause CAP



B. pnCAP/IPD



C. GP-diagnosed CAP



AUC: area under the receiver operating characteristic curve. PCV13: 13-valent pneumococcal conjugate vaccine. CAP: community-acquired pneumonia. pnCAP/IPD: pneumococcal CAP or invasive pneumococcal disease. GP: general practitioner.

Chapter 3 The impact of age on the efficacy of 13-valent pneumococcal conjugate vaccine in elderly

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ABSTRACT

In a post-hoc analysis of the Community-Acquired Pneumonia (CAP) immunization Trial in Adults the model-predicted 13-valent pneumococcal conjugate vaccine efficacy for preventing vaccine-type specific CAP and Invasive Pneumococcal Disease declined from 65% to 40% for subjects being 65 and 75 year olds at the time of vaccination, respectively.

INTRODUCTION

The humoral, cell-mediated and innate immune system are affected by increasing age, independent of comorbidities, which may impair immunogenicity of vaccines.[1–4] Indeed, antibody concentrations and opsonophagocytic activity after receipt of 23-valent pneumococcal polysaccharide vaccine were lower in elderly compared to young adults.[5] In contrast to polysaccharide vaccines, conjugate vaccines induce a T-cell dependent immune response and, therefore, enable B-cell memory. In elderly, immunogenicity of pneumococcal conjugate vaccines was higher than of polysaccharide vaccines,[6] although OPA levels after 12 months were not significantly different in adults receiving PCV13 compared to PPSV23.[7] The effect of increasing age on the efficacy of pneumococcal conjugate vaccines has not been established. We, therefore, analyzed the impact of age on the observed vaccine efficacy (VE) of 13-valent pneumococcal conjugate vaccine (PCV13) in the prevention of vaccine-type community-acquired pneumonia (VT-CAP) and invasive pneumococcal disease (VT-IPD) in immunocompetent subjects aged 65 years and older.

METHODS

This is a post-hoc analysis of the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), a randomized, double blind, placebo controlled study, in which 84,496 immunocompetent subjects aged 65 and over were randomized to receive either PCV13 or placebo.[8] The primary endpoint of this trial, CAP caused by any of the 13 vaccine-serotypes (VT-CAP), was determined in 84,492 subjects (the safety population, excluding four patients with missing safety information) through identifying hospitalizations for CAP in 58 participating hospitals and one diagnostic center. Within 24-48 hours after presentation, urine was collected for serotype-specific urinary antigen detection (UAD).[9] Blood cultures were collected as part of routine clinical care and isolated *Streptococcus pneumoniae* strains were serotyped. CAP was defined as the presence of at least 2 clinical criteria (cough, production of sputum or change in character of sputum, temperature >38°C or <36.1°C, auscultatory findings consistent with pneumonia, leucocyte count $>10*10^9$ / L, CRP > 30 mmol/L and arterial pO2 < 8 kPa) and abnormalities on chest X-ray consistent with pneumonia. VT-CAP was defined as CAP with detection of vaccine-serotype *S. pneumoniae* in blood culture, other sterile cultures, or serotype specific UAD and subjects were classified as having vaccine-type invasive pneumococcal disease (VT-IPD) when a vaccine-serotype *S. pneumoniae* strain was isolated from normally sterile body fluids, independent of CAP criteria (see Supplementary Material for more detailed definition). Urine samples collected more than 48 hours after the admission were not used, and the serotype-specific UAD was considered false-positive if another pulmonary pathogen or another pneumococcal

serotype was isolated from a sterile body fluid. Events occurring within 42 days of a previous episode were considered the same episode, unless a different pathogen or different serotype was detected. The modified intention-to-treat (mITT) population consisted of CAP and IPD episodes occurring more than 14 days after vaccination. In the per protocol population subjects who had become immunocompromised, had received another pneumococcal vaccine before event onset, or were hospitalized or resided in a long-term care facility at the time of symptom onset, were excluded.

Proportions of patients with blood cultures and serotype specific UAD tests were compared over age groups and between the vaccine and placebo group. The interaction effect of age at enrolment was assessed using a Cox proportional hazard model, with the first episode of either VT-CAP or VT-IPD as the outcome variable. This combined endpoint, although not protocol specified, was chosen to increase statistical power and because both are relevant vaccine preventable diseases. Subjects that had died were censored at time of death. Because subjects that were lost to follow-up could still be identified as CAP or IPD case if they presented in a participating hospital, loss to follow-up was ignored. Vaccination status, age, and an interaction term of vaccination status and age were included as independent variables. For example, a hazard ratio (HR) for the interaction of 1.05 means that the HR for vaccination increases with 5% for each year of age. Vaccine efficacy (VE), defined as 1-HR, than declines with increasing age. The analysis was repeated using VT-CAP and VT-IPD separately and using the per protocol population. Adjustment was performed for gender, and self-reported presence of chronic pulmonary disease, chronic cardiac disease, diabetes, and smoking at the time of vaccination. All models were checked for the proportional hazards assumption and for non-linearity. Graphical representation of model-predicted vaccine efficacy with 95% confidence intervals as a function of age was generated using 2,000 bootstrap samples. The analyses were performed in R version 3.0.2.[10]

RESULTS

Age was similarly distributed in the vaccine and placebo group with a median of 71.6 years (IQR 68.2-76.4). A total of 32,933 (39.0%) subjects were <70 years old, 25,145 (29.8%) were 70-74 years old, 15,758 (18.7%) were 75-79 years old, 7,715 (9.1%) were 80-84 years old, and 2,941 (3.5%) were 85+. The mean follow-up duration was 3.9 years (IQR 3.8-4.8 years). During follow-up 6,011 subjects (7.1%) died and 4,571 subjects (5.4%) were lost to follow-up.

Urine for serotype specific UAD was collected slightly more often in CAP episodes of subjects below 70 years (93%) compared to those over 85 years (90%, p-value for trend 0.03). Blood culture collection was performed in 78% of cases, with no effect of age

(p-value: 0.62). There were no differences in microbiological tests between the vaccine and placebo group.

There were 184 first episodes of VT-CAP or VT-IPD in the mITT population. A statistically significant vaccine-age interaction effect was observed (HR for interaction 1.057, 95% CI 1.008-1.109, p=0.023). The model-predicted that VE declined from 65% (95% CI 38% to 81%) in 65 year old subjects to 40% (95% CI 17%; 56%) in 75 year old subjects (Figure 1). Point estimates of the vaccine-age interaction effect were similar for VT-CAP and VT-IPD separately, for the per protocol analyses and after adjustment for covariates (Supplementary Figure S1). In all models, the proportional hazards assumptions were met, except for the direct effect of age in the models with IPD (Supplementary Figure S2A). The regression model may be not optimally fitted for subjects above 85 years of age, as shown by the residuals plot (Supplementary Figure S2B). However, they were not improved with different transformations of age.

Numbers of events per serotype and per age group in the primary analysis are displayed in Supplementary Appendix Figure S3. Of the most common serotypes, serotypes 3 and 7F were most associated with lower age groups and VE against these serotypes was higher than the average vaccine efficacy. Yet, within these serotypes, vaccine efficacy also tended to decrease with increasing age.

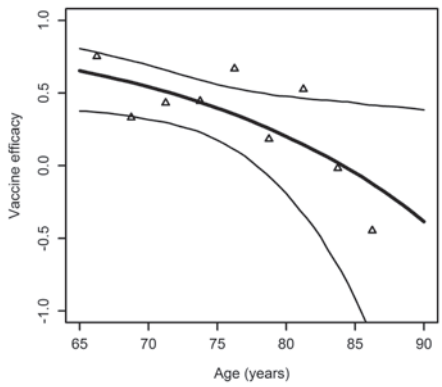

Figure 1 - Model derived vaccine efficacy by age

For first episode of vaccine-type community-acquired pneumonia or vaccine-type invasive pneumococcal disease in modified intention-to-treat population using a Cox proportional hazards model. Triangles represent crude estimates of age groups of 2.5 years each. The solid bold line represents the model derived vaccine efficacy. The 95% confidence interval (thin lines) was derived using 2,000 bootstrap samples.

DISCUSSION

In this study of immunocompetent elderly subjects, aged 65 years and older, efficacy of PCV13 in preventing VT-CAP or VT-IPD, was highest among those subjects aged 65 at the time of randomization, and VE declined with increasing age. A similar finding was obtained in the per protocol analysis, which was limited to subjects that were immunocompetent at the time of their first CAP or IPD episode. Although we used data

from a randomized controlled trial, the vaccine-age interaction could have been biased by other baseline characteristics, such as comorbidities associated with age and with different vaccine efficacy. However, after adjustment for gender and self-reported baseline comorbidities, effect estimates remained unchanged, minimizing the risk of this form of bias in the present study.

The differences in VE may be caused by age-related decreases in antibody avidity. Reduced antibody responses in subjects above 75 years of age, compared to subjects between 60 and 75 years have been reported for the 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 7-valent pneumococcal conjugate vaccine.[11] Antibodies following immunization with PPSV23 had lower avidity and opsonophagocytic activity in elderly compared to young adults, and these low avidity sera were less protective in mice.[5] However, immunogenicity data in a subset of the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) collected at 1, 12, and 24 months post vaccination showed only small differences in IgG antibody levels and opsonophagocytosis assay (OPA) titers in the very old, compared to younger subjects, which could not fully explain the observed effects (A.M.M. van Deursen et al, manuscript in preparation, see also https://idsa.confex.com/idsa/2014/webprogram/Paper47279.html). Other age-related changes in the immune system, such as reduced phagocytic function of macrophages, may also explain the observed decline in VE despite the absence of age-related differences in antibody and OPA titer levels.[3] Similar age-vaccine interactions on clinical outcomes have been observed in conjugate and polysaccharide meningococcal vaccines and hepatitis B vaccine.[12,13] Two of the most prevalent PCV13 serotypes (3 and 7F) were less common in the highest age group and had a higher overall VE. Yet, VE also tended to decrease with age for these serotypes. Due to the low numbers, it is not possible to determine whether the observed higher vaccine efficacy against these serotypes is causing the age effect, or rather that it is the result of it.

Several aspects of the study need to be considered. Measurement of the outcome events relied on identification of CAP and IPD episodes requiring hospitalizations and on timely collection of blood cultures and urine samples in any of the 58 participating hospitals. Therefore, episodes will have been missed. Since this is a randomized trial and subjects and investigators were blinded for vaccination status, missing outcome events can be considered as independent of vaccination status. However, identification of episodes and collection of urine samples and blood cultures might be associated with age, potentially inducing bias. Indeed, serotype specific UAD testing was performed less frequently in older age groups. Age effects were accounted for by adjusting for age at baseline.

Naturally, the trial was not designed to study vaccine-age interaction and the study contained 2,941 subjects over 85 years of age, with only 12 endpoints in this subgroup. Although the VE point estimate suggests no efficacy of PCV13 in this age group, a relevant effect could not be excluded. Also, there was a poor model fit in this age group in four of the models. The estimate of decreasing VE should therefore not be interpreted as an averaged decrease and should not be used for per age prediction of the VE. Nevertheless, overall there was a statistically significant decline in VE by increasing age.

In conclusion, in immunocompetent subjects aged 65 years and older, VE of PCV13 in the prevention of clinical outcomes decreased with increasing age.

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Potential conflicts of Interest

C.H.v.W. served in a Phizer advisory board. M.B. received a presentation fee from Pfizer. D.E.G. received speaker and consultancy fees from Pfizer, honoraria from Pfizer, served as an investigator for Pfizer, and received research funding from Roche Pharmaceuticals, Novartis, and Pfizer. M.J.M.B. received research funding from Pfizer and served on the CAPiTA European Expert Meeting. Other authors report no conflicts of interest.

SUPPLEMENTARY APPENDIX

Box S1 - Case definitions

Vaccine-type Community-Acquired Pneumonia (VT-CAP)

- Two or more the following clinical criteria: (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 (>109 white blood cells/liter or >15% bands); (6) C-reactive protein >3 times the upper limit of normal; (7) Hypoxemia with a partial oxygen pressure (PO2) <60 mm Hg while the patient is breathing room air
- Abnormalities on chest X-ray consistent with CAP
- Detection of vaccine-type S. pneumoniae in blood culture, other sterile cultures, and/or serotype specific UAD

Vaccine-type Invasive Pneumococcal Disease (VT-IPD)

- Vaccine-type S. pneumoniae strain isolated from sterile site
- Or: non-typable S. pneumoniae strain isolated from sterile site and detection of vaccine-type S. pneumoniae by serotype specific UAD
- Sterile site: blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, or joint fluid

Table S1 - Vaccine efficacy against first episode of VT-CAP or VT-IPD in mITT population for protocol defined age cohorts

	Total number of episodes	Number of episodes in PCV13 group	Number of episodes in Placebo group	VE (95% CI)	P-value
All subjects	184	68	116	41.4% (21.4;57.4)	<0.001
Age <75	113	38	75	49.3% (26.2;67.1)	<0.001
Age >=75	71	30	41	26.8% (-15.2;55.1)	0.094
Age >=75 & <85	59	22	37	40.5% (3.3;65.9)	0.023
Age >=85	12	8	4	-100% (-1000;28.6)	0.824

Abbreviations: VT: vaccine-type, CAP: community-acquired pneumonia, IPD: invasive pneumococcal disease, mITT: modified intention-to-treat.

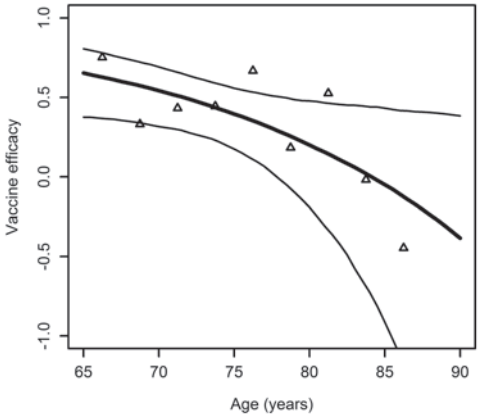
Table S2 - Vaccine-age interaction effects

	Events	Crude HR (95%CI)	P-value	Adjusted HR *	P-value
Modified intention-to-treat analysis					
VT-CAP or VT-IPD	184	1.057 (1.008-1.109)	0.023	1.058 (1.008-1.111)	0.023
VT-CAP	172	1.049 (0.999-1.102)	0.053	1.050 (0.999-1.104)	0.053
VT-IPD	41	1.086 (0.964-1.223)	0.173	1.078 (0.950-1.224)	0.243
Per protocol analysis					
VT-CAP or VT-IPD	149	1.067 (1.010-1.126)	0.019	1.067 (1.010-1.127)	0.021
VT-CAP	139	1.061 (1.004-1.121)	0.036	1.062 (1.003-1.123)	0.037
VT-IPD	35	1.090 (0.962-1.234)	0.176	1.085 (0.949-1.240)	0.231

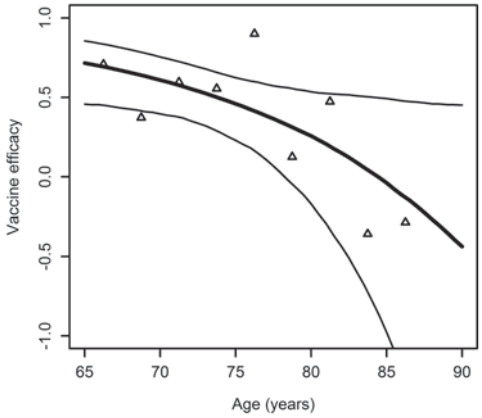
Abbreviations: HR: hazard ratio; CI: confidence interval. The HR represents increase of HR for the outcome of vaccinated subjects, for every year increase of age. HR above 1 means decreasing VE by increasing age.
* Adjusted for gender, pulmonary disease, cardiac disease, diabetes and smoking.

Figure S1 - Model derived vaccine efficacy by age in secondary analyses

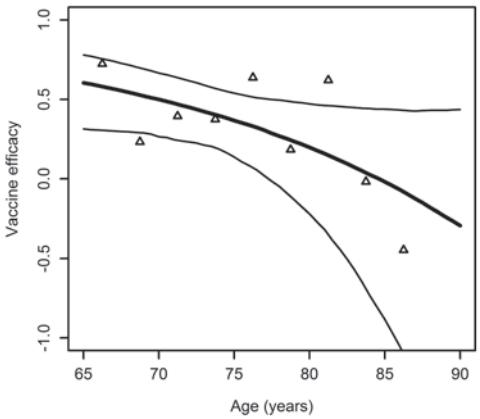
A. VT-CAP/IPD, mITT population



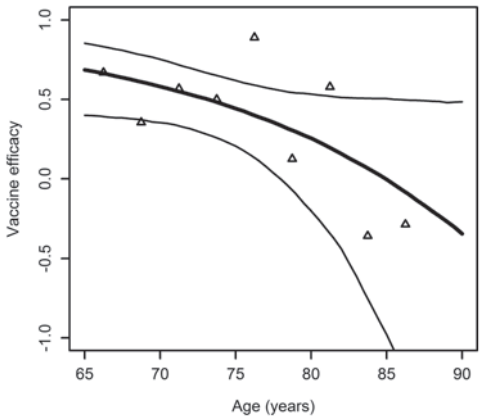
B. VT-CAP/IPD, per protocol population



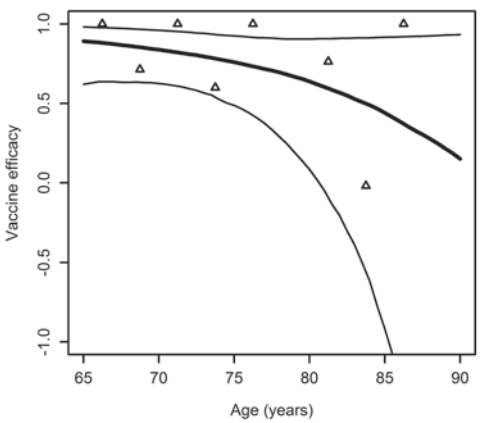
C. VT-CAP, mITT population



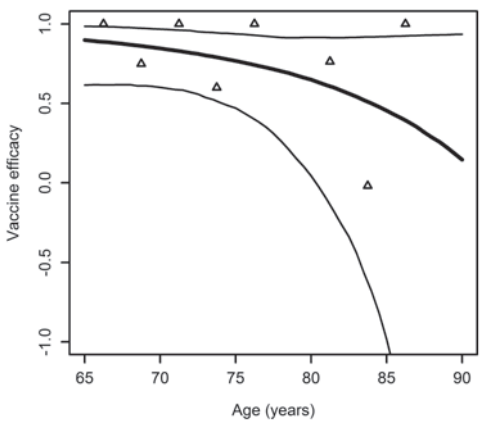
D. VT-CAP, per protocol population



E. VT-IPD, mITT population



F. VT-IPD, per protocol population

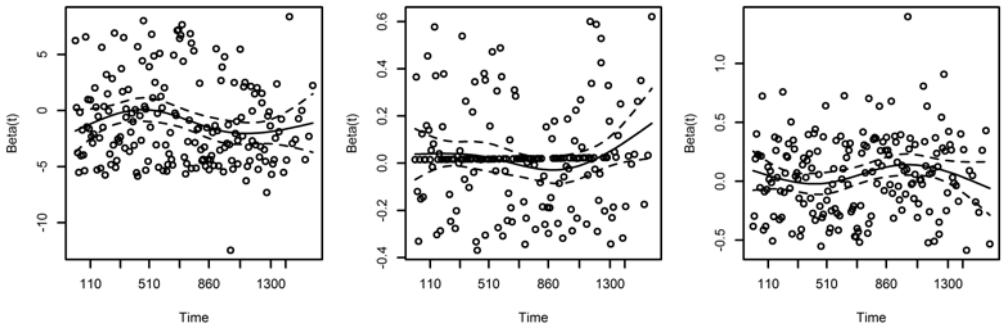


Confidence intervals were derived by bootstrapping. Abbreviations: mITT: modified intention-to-treat; VT-CAP: vaccine-type community-acquired pneumonia; VT-IPD: vaccine-type invasive pneumococcal disease.

Figure S2 - Model diagnostics for the primary analysis

A. Proportionality of hazards

Beta for vaccine (p=0.102) *Beta for age (p=0.967)* *Beta for vaccine * age (p=0.283)*



B. Residuals relative to age

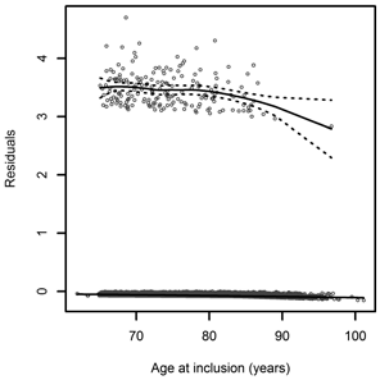
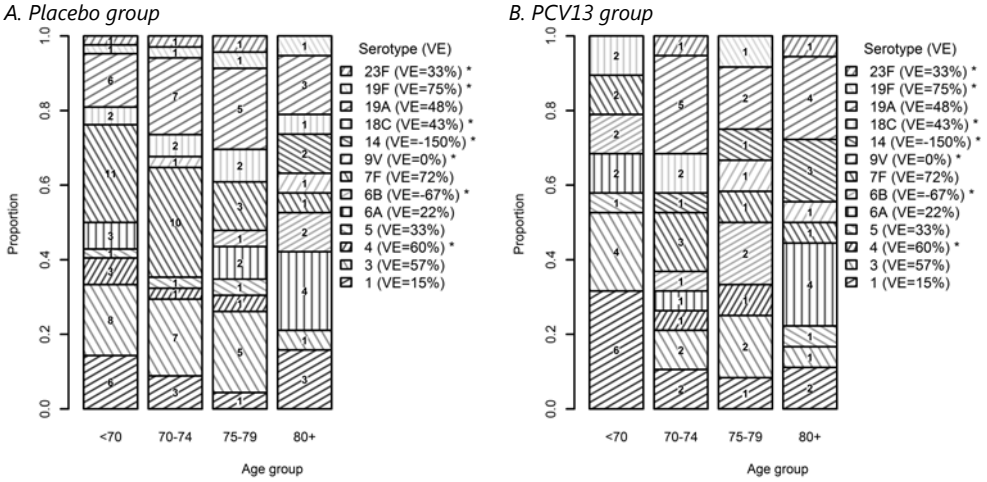


Figure S3: Serotype distribution in age groups and vaccine efficacy per serotype for the combined endpoint of first episode of VT-CAP or VT-IPD

A. Placebo group *B. PCV13 group*



Chapter 4 Herd effects of infant immunisation with pneumococcal conjugate vaccines on non-invasive pneumococcal pneumonia in elderly: a post-hoc analysis

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Submitted manuscript

ABSTRACT

Introduction

Herd protection following pneumococcal conjugate vaccines (PCVs) implementation in infants is well established for invasive pneumococcal disease (IPD) but not for non-IPD pneumococcal community-acquired pneumonia (PCAP). In the Netherlands, 7-valent PCV (PCV7) was introduced in 2006 and replaced by PCV10 in 2011. We assessed the contribution of vaccine-serotypes in non-IPD PCAP in adults 65 years and older in the period 2008-2013.

Methods

This is a post-hoc analysis of two prospective studies from the Netherlands. Serotype specific urinary antigen detection and routine microbiological testing were used to categorize episodes as IPD or non-IPD PCAP caused by PCV7, PCV10-7 (3 additional PCV10 serotypes), PCV13-10 (3 additional PCV13 serotypes), and non-PCV13 serotypes. Time trends in the contribution of vaccine-serotype groups were compared to national IPD surveillance data.

Results

117 and 270 patients had IPD and non-IPD PCAP, respectively, with known serotype. For non-IPD PCAP, PCV7 serotypes decreased from 29% in 2008 to 8% between 2012 and 2013 (p-value for trend <0.001). No change in PCV10-7 (19% overall) and PCV13-10 (29% overall) serotypes was observed. Non-PCV13 serotypes increased from 29% in 2008 to 43% between 2012 and 2013 (p-value for trend 0.048). Trends corresponded with national IPD data.

Conclusion

There was an ongoing reduction in PCV7 serotypes in non-IPD PCAP among elderly between 2008 and 2011, comparable to IPD data. No reduction in the additional PCV10 serotypes could be demonstrated within the first two years after PCV10 introduction.

INTRODUCTION

Invasive pneumococcal disease (IPD) and non-IPD pneumococcal community-acquired pneumonia (PCAP) remain leading causes of death worldwide.[1] The incidence is highest in children under 2 years of age and in older adults, while the case fatality rate increases with age.[2] Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the USA infant immunization program in 2000 in a 3+1 schedule, including recommendation for a catch-up program in children under five years of age.[3] For the 2000 to 2002 birth cohorts the uptake of at least one dosage of PCV7 at age 24 months was between 80-90%.[4] PCV7 was replaced by PCV13 in 2010, again with a catch-up program.[5] Shortly after introduction of PCV7, substantial reductions of IPD incidence were observed in children, and also decreased in adults, which is attributed to herd protection resulting from reduced carriage and transmission of vaccine serotypes by vaccinated children.[6] Similar effects have been reported after the introduction of PCV13.[7–11]

Although herd effects are well documented for IPD, the indirect effects on non-IPD PCAP are less well established. As IPD represents only about 25% of all pneumococcal infections in adults, evaluation of herd protection based on IPD may not accurately reflect herd protection for non-IPD PCAP.[12] Assumptions regarding herd protection for non-IPD PCAP are essential in cost-effectiveness analyses,[13] yet, these are mainly derived from herd effects observed for IPD. Studies from the USA after implementation of PCV7 show conflicting results for all-cause and pneumococcal CAP.[14,15] These studies were limited by the use of ICD9 codes and the inability to distinguish between invasive and non-invasive disease, or to study effects on vaccine-serotype non-IPD PCAP specifically. In the UK, adults with CAP that had regular contact with PCV7-vaccinated children were less likely to have CAP caused by PCV7 serotype *S. pneumoniae* than those with regular contact with unvaccinated children.[16] The vast majority of PCAP patients in this cohort had negative blood cultures, and the observed herd protection could not be fully explained by herd protection effect on IPD only. However, the design of this UK study did not allow for comparison of herd protection between non-IPD PCAP and IPD. In a USA-based study comparable incidence reductions of non-invasive and invasive pneumococcal pneumonia in the post-PCV13 period were found in all age groups.[17] However, this study also relied on ICD9 codes without stratification for vaccine-type and non-vaccine-type non-IPD PCAP. Two recent studies assessed serotype distribution changes after PCV13 introduction, one using a serotype specific urinary antigen test and the other using *S. pneumoniae* isolates from non-sterile cultures.[18,19] Both studies showed reductions of vaccine-serotypes, but quantitative comparisons of herd effects seen in non-IPD PCAP to those in IPD were not

performed. Finally, different PCV's are available which use different conjugation techniques, and while herd protection following implementation of PCV7 and PCV13 for IPD are well documented, to date there are only few reports on herd effects in adults following PCV10 introduction in children, with contradictory results.[20–23]

In the Netherlands, PCV7 was introduced into the infant immunization program in 2006 using a 3+1 schedule, and was replaced by PCV10 in 2011, in each case without a catch-up program. Vaccine uptake was approximately 95% among eligible children (all newborns, born after March 31, 2006) from the start of the PCV7 program.[24] Delayed herd effects were noted following PCV7 introduction which is likely due to the absence of a catch-up program, delaying vaccine serotype carriage reduction and transmission by all young children under five years of age with the highest pneumococcal carriage rates.[25] As these herd effects were only assessed for IPD, we determined the relative contribution of PCV7, PCV10, PCV13, and non-PCV13 serotypes in IPD and non-IPD PCAP in adults of 65 years and older in the period 2008-2013.

METHODS

This is a post-hoc analysis of two studies that were performed in The Netherlands. The CAP-pilot was a prospective study of 1,095 patients hospitalised with CAP between January 2008 and April 2009 and was designed as a preparatory observational study to optimize diagnostic procedures for PCAP.[26] From this study, patients aged 65 years or older were selected for the current analysis. The Community-Acquired Pneumonia immunisation Trial in Adults (CAPiTA) was a double-blind randomised placebo-controlled trial evaluating the efficacy of PCV13 in 84,496 community-dwelling immunocompetent adults aged 65 years and older. Subjects were included in this trial between September 2008 and January 2010 and follow-up was continued up to August 2013.[27] As PCV13 reduced the number of vaccine-type infections, only the 42,256 subjects allocated to the placebo group were included in the current analysis. In both studies, urine was collected for BinaxNOW pneumococcal urinary antigen testing (PUAT) and for the PCV13 serotype specific urinary antigen detection (UAD) assay.[26] The serotype-specific UAD assay was performed by Pfizer and the PUAT was performed by both the hospitals' laboratories and by Pfizer. Cultures of sterile and non-sterile body fluids were performed at the participating hospitals' laboratories as part of routine care. Isolates from cultures positive for *S. pneumoniae* were serotyped at the Netherlands Reference Laboratory for Bacterial Meningitis by co-agglutination and subtyping with the capsular swelling method (Quellung reaction) using antisera (Statens Serum Institut, Copenhagen, Denmark) according to the manufacturer's protocol. Patients with documented non-IPD PCAP or IPD were eligible for the current analysis.

Definitions

IPD was defined as an infection confirmed by the isolation of *S. pneumoniae* from a normally sterile site (with or without pneumonia) and non-IPD PCAP was defined by clinical, radiologic and microbiological criteria, in the absence of criteria for IPD (Table 1). Episodes were categorised in four vaccine-serotype groups as non-IPD PCAP or IPD caused by PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), PCV10-7 serotypes (1, 5, and 7F, the three additional serotypes in PCV10), PCV13-10 serotypes (3, 6A, and 19A, the three additional serotypes in PCV13), and non-PCV13 serotypes.

A pneumococcal isolate by culture, a positive PUAT, or UAD was considered proof of *S. pneumoniae* infection, except if another pathogen was confirmed as the cause of CAP by culture of a normally sterile site. In determining the serotype, results from serotyping of *S. pneumoniae* isolates cultured from sterile sites was given priority. In case of negative or non-typeable cultures, the combined results from the PUAT and serotype specific UAD were used. A positive PUAT with a negative serotype specific UAD was classified as non-PCV13 serotype, based on the high sensitivity of the serotype specific UAD.[26] A positive PUAT in the absence of serotype specific UAD testing was classified as

Table 1 - Definitions

Invasive Pneumococcal Disease (IPD)

- Isolation of *S. pneumoniae* from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, and joint fluid)

Non-IPD pneumococcal Community-Acquired Pneumonia (PCAP)

- At least 2 clinical criteria (cough, production of purulent sputum or a change in the character of sputum, temperature >38.0°C or <36.1°C, auscultatory findings consistent with pneumonia, including rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony), leukocytosis (>10 x 109 white blood cells/liter or >15% bands), C-reactive protein >3 times the upper limit of normal, or hypoxemia with a partial oxygen pressure <60 mmHg while the patient was breathing room air)
- Radiologic evidence of pneumonia
  - In the CAP-pilot study, chest X-rays obtained within 48 hours of admission were classified as compatible with CAP if the local radiologist described signs of an infiltrate, pleural fluid, or interstitial infiltrates.
  - In the CAPiTA study, chest X-rays obtained within 48 hours of admission were adjudicated by two independent readers answered the following question: "Is/are the image(s) consistent with community-acquired pneumonia?" If the answers differed, a third member reviewed the images, and the answer from 2 readers was accepted.
- Microbiological evidence of pneumococcal etiology:
  - Culture of S. pneumoniae from normally sterile isolates from the respiratory tract, such as transthoracic biopsies and direct puncture samples
  - Positive BinaxNOW Streptococcus pneumoniae urinary antigen test in the absence of a causative pathogen identified by culture of a normally sterile site
  - Positive serotype specific urinary antigen detection in the absence of a causative pathogen identified by culture of a normally sterile site
- Not residing in a long term care facility or being hospitalized at the time of symptom onset.
- Not fulfilling the criteria for IPD (see above)

unknown serotype. If the serotype specific UAD yielded more than one serotype in different PCV groups, the vaccine-serotype group was considered unknown.

External data sources

Yearly numbers of adults 65 years of age and above with IPD in the Netherlands, and distribution of vaccine-serotype group, were provided by the National Institute for Public Health and the Environment, from the Invasive Pneumococcal Disease Sentinel Surveillance Laboratory Group. The surveillance covers approximately 25% of the Dutch population. Details of the national IPD surveillance program are described elsewhere.[28]

Statistical analysis

Trends over time in the proportions of non-IPD PCAP caused by each vaccine-serotype group were assessed using LOWESS curves and estimates and confidence intervals of these proportions were calculated for each seasonal year starting at June 1st. Significance of time trends was tested using logistic regression, taking vaccine-serotype group as the dependent variable and time as the independent variable. Trends of non-IPD PCAP and IPD vaccine-serotype groups were compared to the national IPD surveillance data. All analyses were performed in R version 3.0.2.[29]

RESULTS

Of 409 patients, 288 (70%) were categorized as non-IPD PCAP (242 with a negative blood culture and 46 with no blood culture obtained) and 121 (30%) had IPD (of which 97 (80%) also had radiologically confirmed CAP). The proportion of blood cultures obtained from patients with radiologically confirmed CAP decreased from 87% before June 2008 to 77% during the 2012-2013 season (Supplementary Appendix Figure S1A). Urine collection for serotype specific UAD was performed in 74% of these episodes before June 2008 and in 90% during the 2009-2010 season, after which proportions remained stable (Supplementary Appendix Figure S1B). Urine for PUAT was collected in 93% of patients throughout the study (range 92%-95%), and, except in one patient, PUAT was performed in all confirmed CAP patients in whom a serotype specific UAD was performed (Supplementary Appendix Figure S1C-D).

Yearly numbers of episodes per vaccine-serotype group are given in Table 2. A vaccine-serotype group could not be determined in 18 patients with non-IPD PCAP (with positive PUAT results but missing serotype specific UAD test in 13 and a serotype specific UAD result positive for two different vaccine-serotype groups in 5 patients), leaving 275 non-IPD PCAP patients with serotype data of which 270 could be used for the vaccine-serotype group analysis. In two other non-IPD PCAP patients, serotypes from the same vaccine-serotype group were identified and these were included in the

Table 2 - number of non-IPD PCAP/IPD cases per year and study

	PCV7 serotypes	PCV10-7 serotypes	PCV13-10 serotypes	non-vaccine serotypes	Unknown
2008 (non-IPD PCAP)	34	22	28	34	10
2008 (IPD)	13	5	10	16	1
2009 (non-IPD PCAP)	11	4	15	7	3
2009 (IPD)	5	4	2	3	2
2010 (non-IPD PCAP)	3	5	9	6	1
2010 (IPD)	1	2	2	8	0
2011 (non-IPD PCAP)	5	6	11	10	0
2011 (IPD)	1	5	2	11	1
2012 (non-IPD PCAP)	1	10	9	17	3
2012 (IPD)	3	4	2	5	0
2013 (non-IPD PCAP)	3	5	6	9	1
2013 (IPD)	1	1	3	8	0

In 5 patients with non-IPD PCAP the serotype specific urinary antigen detection assay yielded positive results for serotypes from two serotype groups (see Supplementary Appendix Table S1 and S2). These are given as unknown in the table: PCV10-7+PCV13-10 (2008); PCV7+PCV10-7 (2009); PCV7+PCV10-7 (2009); PCV10-7+PCV13-10 (2010); PCV7+PCV10-7 (2012). Abbreviations: IPD: invasive pneumococcal disease; non-IPD PCAP: non-invasive pneumococcal community-acquired pneumonia; PCV7: 7-valent pneumococcal conjugate vaccine; PCV10-7: 3 additional serotypes in PCV10; PCV13-10: 3 additional serotypes in PCV13.

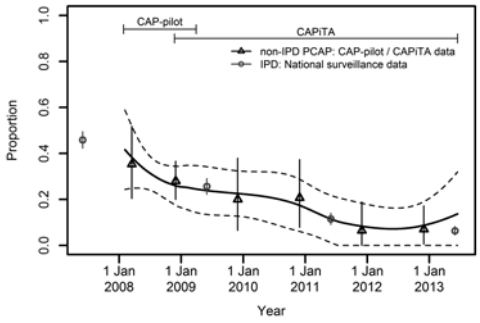
analysis. Of eight patients with IPD and non-typeable strains, the serotype was classified as non-VT in four patients based on a negative serotype specific UAD and as unknown in the other four as serotype specific UAD testing was not available, leaving 117 IPD-cases for analysis.

For non-IPD PCAP, the proportions of PCV7 serotypes decreased linearly from 29% in 2008 to 8% in the 2011-2012 season, and remained stable over the 2012-2013 season (p-value for trend <0·001). There was no statistically significant change in the proportion of PCV10-7 (overall 19%; p-value for trend 0·181) and PCV13-10 (overall 29%; p-value for trend 0·873), and the proportion of non-PCV13 serotypes increased during the observed period from 29% in 2008 to 43% between 2012 and 2013 (p-value for trend 0·048). Time trends were similar to data from the national IPD surveillance program, except that, compared to the national IPD data, proportions of non-IPD PCAP cases with PCV13-10 were higher and proportions with non-PCV13 were lower over the duration of the study (Figure 1).

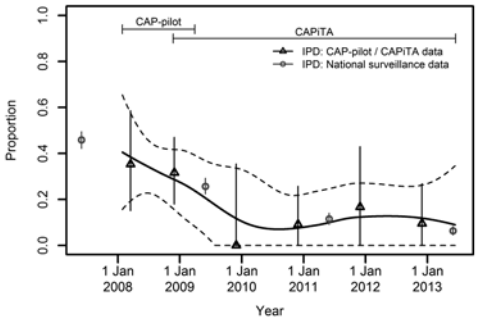
Among the 117 serotyped isolates associated with IPD, serotypes 8 (n=14, 12%), 7F (n=12, 10%), and 22F (n= 11, 9%) were most prevalent. From June 2011 onward, the most frequent IPD-serotypes (total n=32) were 8 (n=7, 22%) and 7F (n=5, 16%). Of 275 non-IPD PCAP episodes (including seven with two serotypes identified), the most

Figure 1 - Time trends for serotype groups in non-IPD PCAP and IPD and comparison to NIS data

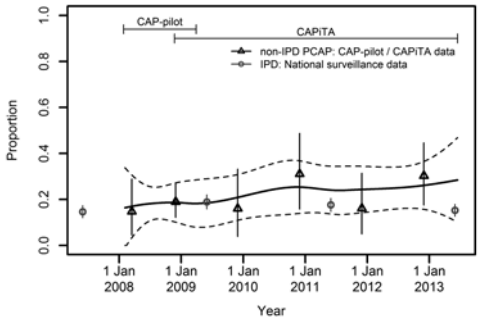
A. PCV7 serotypes (non-IPD PCAP)



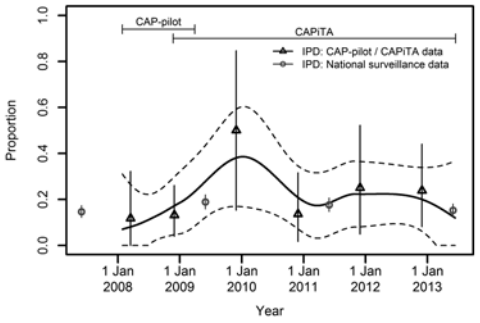
E: PCV7 serotypes (IPD)



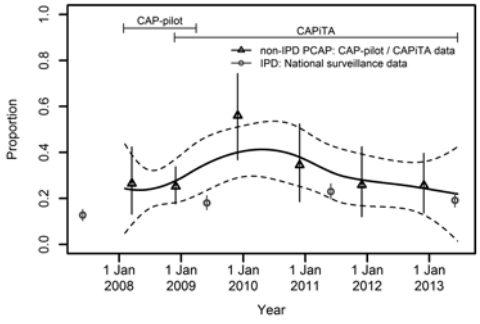
B. PCV10-7 serotypes (non-IPD PCAP)



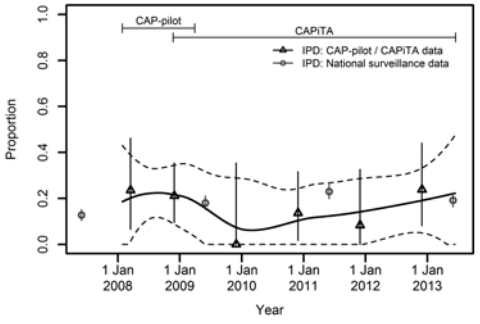
F: PCV10-7 serotypes (IPD)



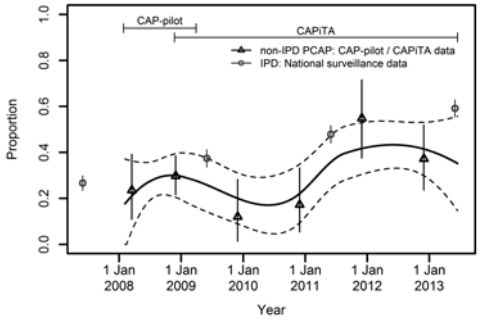
C. PCV13-10 serotypes (non-IPD PCAP)



G: PCV13-10 serotypes (IPD)



D: non-PCV13 serotypes (non-IPD PCAP)



H: Non-PCV13 serotypes

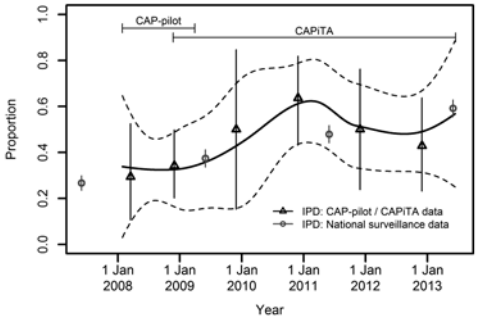


Figure 1 legend (facing page): Relative contribution of PCV7, PCV10-7, and non-PCV10 serotypes to non-IPD PCAP and IPD and comparison to national IPD surveillance data. Black line and triangle: LOWESS curve and yearly estimates of contribution per serotype groups from current studies. Gray circle: two-yearly estimates from national IPD surveillance.
Abbreviations: PCV: pneumococcal conjugate vaccine, PCAP: pneumococcal community-acquired pneumonia, IPD: invasive pneumococcal disease, NIS: national IPD surveillance, PCV7: serotypes contained in 7-valent PCV, PCV10-7: serotypes contained in PCV10 but not in PCV7, non-PCV10: serotypes not contained in PCV10.

frequent serotypes detectable by the serotype specific UAD were the PCV13-10 serotypes 3 (n=38, 14%, of which two had mixed results), and 19A (n=28, 10%, of which one had mixed results) and the PCV10-7 serotype 7F (n=32, 12%, of which three had mixed results). 83 cases (30·2%) were caused by non-PCV13 serotypes. From June 2011 onwards, of 76 non-IPD PCAP episodes the most prevalent serotypes detectable by serotype specific UAD were 1 (n=9, 12%), 7F (n=8, 11%), 19A (n=7, 9%), and 3 (n=7, 9%), and 34 (44·7%) were caused by non-PCV13 serotypes (see Supplementary Appendix Tables 1 and 2).

DISCUSSION

The findings of the current study demonstrate a clear, close to linear, decrease in the relative contribution of PCV7 serotypes in pneumococcal CAP and IPD in adults 65 years of age and older between 2008 and 2012 that coincides with the gradual increase in children vaccinated with PCV7 since 2006. In agreement with previous findings, 70% of the pneumococcal infections represented non-IPD PCAP, underlining the importance of studying herd protection effects for these infections in addition to the established effects for IPD.[12] As the time trends of PCV7, PCV10-7, PCV13-10, and non-PCV13 serotypes in non-IPD PCAP closely resembled those seen in IPD surveillance data, our results suggest that national IPD data can be used to extrapolate absolute changes seen in the IPD data to non-IPD PCAP, using the relative changes observed here.

With 95% of children receiving PCV7 during their first 2 years in life since 2006, maximum herd protection appeared to be established five to six years after the start of PCV7 vaccinations. This time period is in agreement with previous findings for IPD.[30] No reduction in the additional PCV10 serotypes could be demonstrated within the first two years after PCV10 introduction. Similarly, after introduction of PCV7 in the Netherlands, herd protection effects in adults were also not observed within two years.[25] Moreover, the additional serotypes 1, 5 and 7F were rarely observed in carriage studies in Dutch infants under two years of age in the years 2008-2010, therefore, herd effects for these serotypes may be less likely to occur or be less impactful.[31,32]

Our results are in line with findings in the Nottingham region in the UK after implementation of PCV7 in 2006 and PCV13 in 2010 in paediatric immunisation programs. Based on 653 adults with pneumococcal CAP, of which 13% had IPD, the incidence of PCV7 serotypes and additional PCV13 serotypes sharply declined after

vaccine introduction.[18] As in the current study, a serotype specific UAD assay was used. Yet, as the estimated sensitivity of the test used in that study was 79%, CAP episodes with negative serotype specific UAD and positive PUAT were considered of undetermined serotype. Consequently, one third of pneumococcal CAP patients were excluded from their assessment. Also, trends of serotypes seen in non-IPD PCAP were not compared to IPD.

In the Netherlands, PCV7 serotypes still caused 8% of the non-IPD PCAP cases in the 2011-2012 and 2012-2013 seasons, and 6% in the two last seasons of the national IPD surveillance (June 2012 to May 2014). Taking non-IPD PCAP and IPD together, though at a substantially reduced level, most PCV7 serotypes were still detected in older adults six to seven years after implementation of the infant vaccination program. Therefore, herd effects alone may be insufficient to fully address the public health impact of pneumococcal disease in adults.

This post-hoc analysis of two studies has several limitations. First, we could not determine incidence rates of non-IPD PCAP or IPD. In one study no denominator data (i.e. the number of individuals in the population) were collected, and the other study was a closed cohort with changing age and comorbidities over time, with no possibility for adjustment as presence of comorbidities was only obtained at baseline. We, therefore, could only use relative contribution of vaccine-serotype groups to the total number of non-IPD PCAP or IPD cases. However, the advantage of using relative measures is that it implicitly adjusts for seasonal and yearly variation in total incidence. Second, urine samples for the serotype specific UAD assay were collected less frequently at the start of the study and proportions of blood culture collection slowly decreased over time. Overall, 84% of patients with non-IPD PCAP had a blood culture obtained; therefore, some misclassification of non-IPD PCAP may have occurred. Yet, the remaining 16%, as well as patients with invasive infection with a false-negative blood culture, all represent pneumococcal CAP episodes undetectable by the IPD surveillance system, justifying classification of these episodes as non-IPD PCAP in order to assess herd effects beyond IPD surveillance. Because of the lower proportion of urine collection for the serotype-specific UAD assay at the start of the study, we may have missed a higher proportion of non-IPD PCAP episodes early in the study. Patients with a positive PUAT but missing serotype specific UAD were classified as unknown serotype. Therefore, assuming there is no correlation between sample collection and the pneumococcal serotype, the relative estimates should be unbiased. Bias could have resulted from patients in whom the serotype specific UAD but no PUAT was collected, as these patients could only be positive for PCV13 serotypes. However, this only occurred once. Third, the serotype specific UAD is more sensitive compared to the PUAT and this may have led to an overestimation of the proportion of non-IPD PCAP

episodes due to PCV13 serotypes. Indeed, the proportion of non-IPD PCAP caused by PCV13-10 serotypes was slightly higher and the proportion caused by non-PCV13 serotypes was slightly lower compared to that in IPD. Still, this difference was present over the total study period, enabling the unbiased interpretation of time trends. Fourth, because of the inclusion and exclusion criteria of the two studies, we probably had a lower proportion of immunocompromised CAP patients compared to the general over 65 population hospitalized with CAP. In the CAP-pilot study, patients with known bronchial obstruction, pulmonary malignancies or metastases, AIDS, a history of *Pneumocystis jirovecii* pneumonia, or active tuberculosis were excluded. In the Community-Acquired Pneumonia immunisation Trial in Adults (CAPiTA), participants had to be immunocompetent at baseline to be included, although patients who developed immunocompromising conditions during follow-up remained in the study. Additionally, subjects participating in this trial were probably healthier compared to the general over 65 population. If herd effects are modulated by being immunocompromised or by the general health status, this may limit generalizability of the time trends seen in our study. The strongly restricted use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) in the Netherlands for only limited high risk groups such as patients with (functional) asplenia may also limit generalizability of our results to countries where this is universally recommended to elderly, as effects of PPSV23 seem to be present for IPD but are not clear for non-IPD PCAP.[33,34] Finally, the number of episodes in our study precluded a meaningful analysis of individual serotypes for non-IPD PCAP.

Strengths of our study include the protocol-defined identification and confirmation of pneumonia by clinical suspicion, presence of at least two clinical criteria, and compatible chest X-ray abnormalities. Also, we used a standardized microbiological work-up for the detection of pneumococcal aetiology and we assessed changes in the contribution of vaccine-serotype groups in non-IPD PCAP and IPD within the same study cohort and compared this to national IPD surveillance data in the same age group.

In conclusion, the results of our analysis indicate that herd protection effects for non-IPD PCAP are very similar to those seen in IPD. PCV7 serotypes showed a relative decrease up to 5 to 6 years after introduction of the vaccine. Although at low rates, PCV7 serotypes were still observed after this period.

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Potential conflicts of Interest

C.H.v.W. served in a Pfizer Advisory Committee. R.H. is former employee of Pfizer, Inc. and holds company stock. C.W., and S.P. are employees of Pfizer, Inc., and hold company stock. E.A.M.S. received research funding from Pfizer and GlaxoSmithKline plc, consultancy for Pfizer and GlaxoSmithKline plc, and participation in independent data monitoring committees for Pfizer and GlaxoSmithKline plc (all fees paid to the institution). M.J.M.B. received research funding and an unrestricted education grant from Pfizer and served on the CAPiTA European Expert Meeting (all fees paid to the institution). Other authors report no conflicts of interest.

SUPPLEMENTARY APPENDIX

Table S1 - ranking of serotypes during the study

IPD (n = 117)			Non-IPD PCAP (n = 275)		
Serotype	**Frequency**	**Percentage**	**Serotype**	**Frequency**	**Percentage**
PCV13 serotypes					
7F [@]	12	10·3%	3	36	13.1%
3	9	7·7%	7F [@]	29	10.5%
19A	7	6·0%	19A	27	9.8%
1 [@]	7	6·0%	1 [@]	21	7.6%
14 [#]	6	5·1%	18C [#]	15	5.5%
23F [#]	5	4·3%	23F [#]	14	5.1%
6A	5	4·3%	6A	14	5.1%
4 [#]	4	3·4%	4 [#]	9	3.3%
18C [#]	3	2·6%	14 [#]	5	1.8%
9V [#]	3	2·6%	9V [#]	5	1.8%
6B [#]	2	1·7%	19F [#]	5	1.8%
5 [@]	2	1·7%	6B [#]	3	1.1%
19F [#]	1	0·9%	5 [@]	2	0.7%
			mixed*	7	1.8%
Non-PCV13 serotypes					
Total	51	43·6%	Total	83	30.2%
8	14	12·0%			
22F	11	9·4%			
16F	4	3·4%			
12F	3	2·6%			
33F	3	2·6%			
6C	2	1·7%			
9N	2	1·7%			
11A	2	1·7%			
24F	2	1·7%			
20	1	0.9%			
23B	1	0.9%			
33A	1	0.9%			
35F	1	0.9%			
Unknown ǂ	4	3·4%			

* mixed serotype results were positive for serotypes 18C + 23F, 18C + 7F, 19A + 5, 3 + 6A, 3+7F, 4+5, and 7F+23F.
[#] serotypes in PCV7. [@] additional serotypes in PCV10
ǂ Four patients with untypeable pneumococcal isolates were classified as non-PCV13 based on a negative serotype specific urinary antigen detection assay.
Abbreviations: IPD: invasive pneumococcal disease, PCAP: pneumococcal community-acquired pneumonia, PCV: pneumococcal conjugate vaccine (number indicating valency).

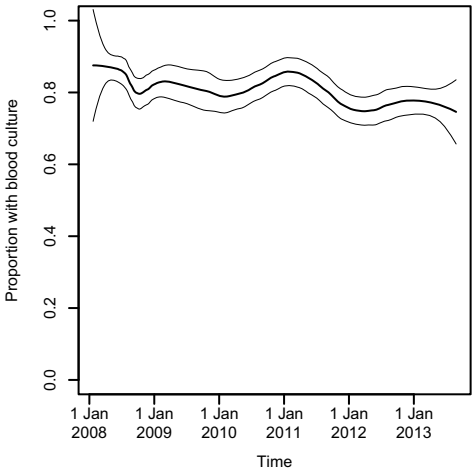
Table S2 - ranking of serotypes during 2011-2012 and 2012-2013 seasons ‡

IPD (n = 32)			Non-IPD PCAP (n = 76)		
Serotype	**Frequency**	**Percentage**	**Serotype**	**Frequency**	**Percentage**
PCV13 serotypes					
7F [@]	5	15.6%	1 [@]	9	11.8%
1 [@]	2	6.2%	7F [@]	8	10.5%
19A	2	6.2%	19A	7	9.2%
3	2	6.2%	3	7	9.2%
6A	2	6.2%	6A	5	6.6%
4 [#]	2	6.2%	14 [#]	2	2.6%
19F [#]	1	3.1%	4 [#]	1	1.3%
5 [@]	1	3.1%	19F [#]	1	1.3%
18C [#]	1	3.1%	6B [#]	1	1.3%
			mixed*	1	1.3%
Non-PCV13 serotypes					
Total	14	43.8%	non-VT	34	44.7%
8	7	21.9%			
22F	2	6.2%			
33F	2	6.2%			
16F	1	3.1%			
24F	1	3.1%			
33A	1	3.1%			

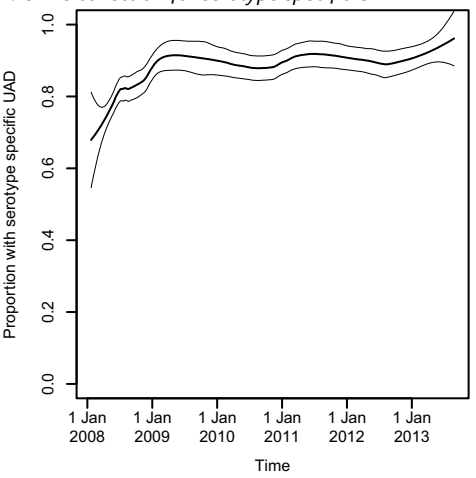
‡ includes episodes with hospital admission date on or after June 1, 2011.
* mixed serotype result was positive for serotype 4 + 5.
[#] serotypes in PCV7. [@] additional serotypes in PCV10.
Abbreviations: IPD: invasive pneumococcal disease, PCAP: pneumococcal community-acquired pneumonia, PCV: pneumococcal conjugate vaccine (number indicating valency).

Figure S1 - Trends in diagnostics in patients with radiologically confirmed CAP

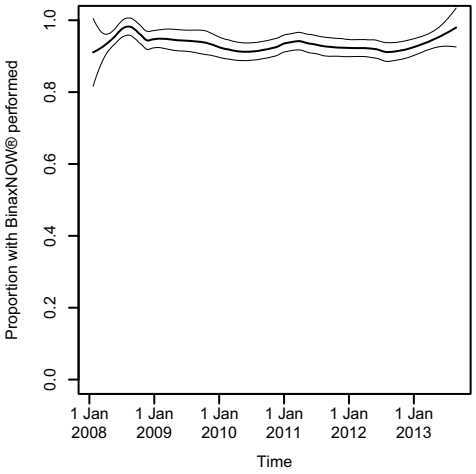
A. Blood culture collection



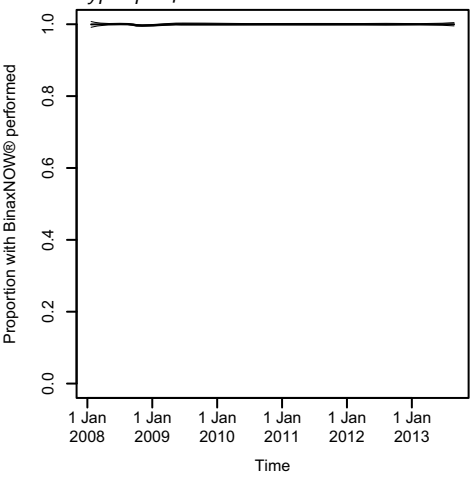
B. Urine collection for serotype specific UAD



C. Urine collection for BinaxNOW PUAT



D. Urine collection for BinaxNow PUAT in patients with serotype specific UAD collected



Abbreviations: CAP: community-acquired pneumonia, UAD: urinary antigen detection, PUAT: pneumococcal urinary antigen test.

Chapter 5 The scrutiny of identifying Community Acquired Pneumonia episodes quantified bias in absolute effect estimation in a population based pneumococcal vaccination trial

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ABSTRACT

Objective

To determine the accurateness of detecting community-acquired pneumonia (CAP) in the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), a community-based double-blind randomized placebo-controlled trial in which the NNT for prevention of vaccine-type pneumococcal CAP was 1,007 (95% CI 613-2,646).

Study design and setting

Study participants developing pneumonia were identified in 58 participating hospitals by research nurses using local-adapted protocols. In addition, general practitioner records were screened for hospital referrals for suspected pneumonia. Two independent reviewers determined reasons for not identifying pneumonia episodes, and the NNT adjusted for missed episodes was estimated.

Results

Of 2,183 hospital referrals with suspected pneumonia detected in general practitioner records, 232 (11%) were admitted outside established screening routes and 102 (5%) were not suspected of pneumonia on admission. Of the remaining 1,849 episodes, 1,374 (63% of all episodes and 74% of identifiable episodes) were identified by research nurses. Several causes of missing episodes were identified. After adjustment for missed episodes, the NNT reduced to 634 (95% CI 386-1,675).

Conclusion

With the screening procedure 63% of suspected pneumonia episodes were identified, and the estimated NNT reduced from 1,007 to 634. Root cause analysis of unidentified episodes provides guidance for improving pneumonia detection in future trials.

INTRODUCTION

Reliable measurement of outcome events in clinical intervention studies is of major importance.[1] Biased observations may lead to over- or underestimation of relative effects of interventions, which can be prevented by random treatment assignment, blinding of patients and investigators and using intention-to-treat analysis. These measures ensure that, on average, measurement errors will be the same for all study groups, provided that interventions do not influence measurement accuracy, ensuring a valid relative risk estimate.[2] However, missing outcome events, even if equally distributed among study groups, will reduce absolute effect estimates, such as risk differences, number needed to treat (NNT) or number needed to harm (NNH). As such, missing event data may severely compromise health outcome analyses leading to unjustified acceptance or rejection of interventions. For instance, harmful interventions may be implemented if serious adverse events are missed and the NNH is overestimated, and beneficial interventions may be rejected if outcome events are missed and hence the NNT is overestimated. Missed outcome events in clinical trials can be taken into account by describing reasons for withdrawal and loss to follow-up,[3–6] but this is not possible if outcome events are missed while subjects remain under study.

Community-acquired pneumonia (CAP) is an infection with a high incidence and high mortality rate, and *Streptococcus pneumoniae* is recognized as the most important pathogen for CAP.[7,8] In the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) the 13-valent pneumococcal conjugate vaccine (PCV13) reduced the incidence of a first episode of vaccine-type (VT) CAP in immunocompetent elderly by 46%.[9] In this randomized placebo-controlled double-blind study 84,496 immunocompetent community-dwelling subjects, aged 65 years and older, were recruited between September 2008 and January 2010 and endpoint detection was materialized through identifying study subjects with a clinical suspicion of pneumonia in 59 sentinel centers (58 hospitals and 1 outpatient clinic) between September 2008 and August 2013. The median follow-up duration for study participants was 4 years. Based on the detected primary endpoints the NNT to prevent one episode of VT-CAP was 1,007.

In the current analysis we aimed to determine the number of missed primary endpoints, estimated the effect of missed episodes on the NNT, and categorized the reasons for missing episodes, thus demonstrating the limitations of absolute effect estimation from clinical trials without proper adjustment for the accurateness of endpoint identification, and providing guidance for improved outcome detection in future studies.

METHODS

Data collection

Details of the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) have been described elsewhere.[9] Two data sources were used in the current study: the study database of identified episodes in the 58 participating hospitals and the GP records of participating subjects. In the original study 59 centers were used for identification of pneumonia episodes, of which one was a diagnostic center;[9] patients referred to this center were not included in the current analysis unless the patient was subsequently referred to one of the hospitals. Study subjects presenting to one of the hospitals with suspected pneumonia were identified by research nurses (RNs), who were trained to perform daily screening of emergency room (ER) registries of internal

Box 1: Definition of categories

Case not missed	Subject was already identified by the research nurse (RN).
Not Per Protocol	No (suspicion of) pneumonia <48 hours after admission. This also includes exacerbation COPD, even when possibly provoked by a respiratory tract infection. In case of exacerbation COPD, only when the possibility of pneumonia, lower respiratory tract infection, consolidation, or infiltrate is mentioned, the cases should be considered as a suspicion of pneumonia <48hours after admission.
Hospital not participating	Admitted to a hospital that is not participating in the study. Or when a patient presented in the participating hospital before the study was officially initiated in that hospital.
Other admission route	Admitted via another admission route than the ones that are to be screened by the RN, for example the outpatient department. The RN should screen all patients that are admitted for internal medicine (including sub-specializations), pulmonary medicine and cardiology.
No cooperation department	Admission department should be screened according to the general working instruction (i.e. ER admissions for internal medicine, pulmonology and cardiology), but screening of the department's admission list is not possible in this hospital.
Not admitted / deceased before identification	Presented at the ER and discharged after its visit and subject is not identified by the ER department and not identified by the RN. Or subject was deceased within 48 hours and RN identification of the subject occurred after the subject died.
Pneumonia not suspected at presentation	(Suspicion of) pneumonia was present within 48 hours of the admission, but this was not known or not recorded in the (differential) diagnosis of the ER physician.
Overlooked by RN	(Suspicion of) pneumonia present at the time the RN was screening this patient, and the patient was in the screening list of the RN, but the RN did not recognize the (suspicion of) pneumonia.
Technical / Logistical Failure	Technical problems caused missing the subject, for example failure of the hospital information system, failure of the study identification database or administrative problems.
Patient and/or relative refused/ withdrawn	Subject was identified, but does not want to cooperate with the study procedures or wants to withdraw from the study.

medicine, pulmonology and cardiology. For each hospital, screening procedures were implemented according to local circumstances. Among patients with a suspicion of pneumonia, trial participation was cross-checked with a study identification database. Primary endpoint determination required presence of at least two clinical criteria, chest X-ray abnormalities compatible with pneumonia, and detection of vaccine serotype *S. pneumoniae* in a blood culture, other sterile culture, or serotype specific urinary antigen detection (UAD) assay. A positive UAD test was needed in most (i.e. blood culture negative) pneumococcal CAP cases, for which urine had to be collected within 48 hours of admission. For this reason, pneumonia admissions identified by the RN more than 48 hours after admission were considered as missed. Pneumonia admissions that were identified within the time window but where the urine sample was not available for another reason (e.g. in case of anuria), were categorized as identified for the purpose of this analysis.

In the Netherlands, every inhabitant is registered with a single GP, who is routinely informed about important medical affairs and, therefore, should receive all discharge letters from hospital admissions or ER visits. As part of the study, dedicated study monitors checked GP records twice yearly for new information of participants indicating hospital referral for (suspected) pneumonia. This information was linked to the study database of episodes detected in the hospitals and if the GP-detected episode was not present in the study database, additional information was collected in the related hospital. This information included all medical letters and medical records from the ER, laboratory data at admission, radiology data within 48 hours after admission, discharge letters and information from RN for reasons of missed identification.

During the study, potentially missed episodes were independently reviewed by two of four investigators (CHvW, SMH, FPP [authors] and AN [see acknowledgements]), and reasons for missing were allocated according to a predefined protocol (Supplementary Appendix Figure S1 and S2, see Box 1 for definitions). Discrepant classifications were discussed until consensus was reached. If consensus could not be reached, a third investigator was asked to decide between the two categories. Episodes that were identified by the RN but where the urine sample was not collected or was collected more than 48 hours after admission, were independently reviewed by two of the investigators (CHvW and FPP) using the same classification approach.

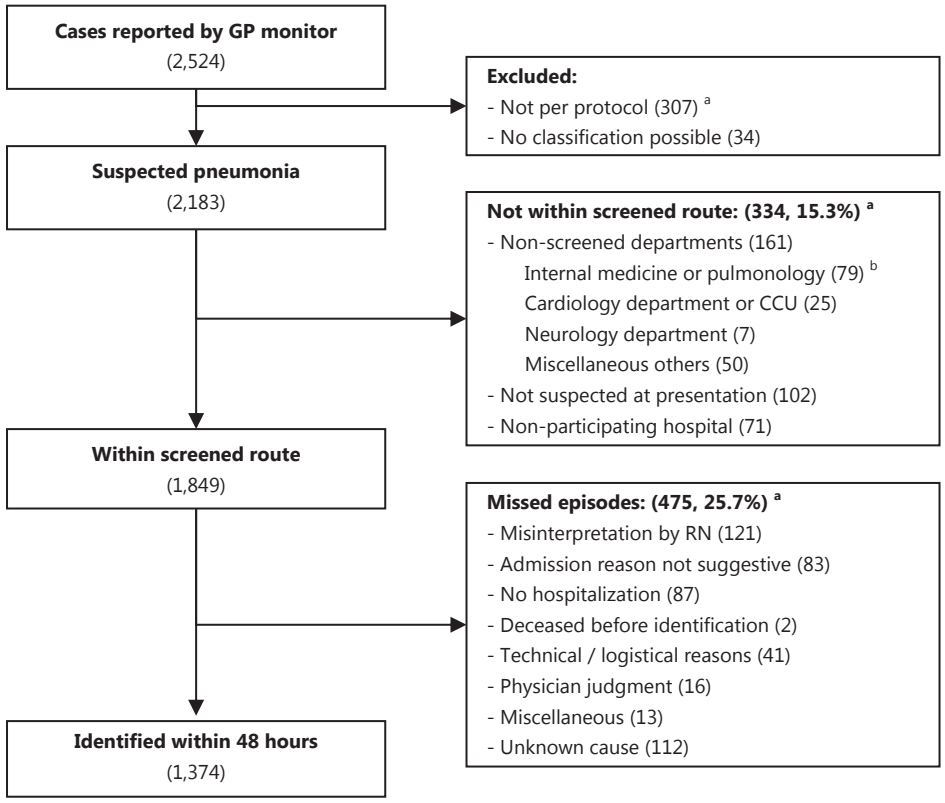
Data analysis

Root causes (i.e. the initial cause in the chain of events) for missing pneumonia episodes were determined from cases identified by GP monitors, assuming these will best represent the total of pneumonia episodes. Proportions of missed cases were related to hospital-based differences in screening methods. Trends in time of proportions of

episodes identified by RN and of probabilities of detecting episodes in GP records were assessed using Lowess curves. The differences in screening practice per hospital concerned identification of participants (i.e. checking all ER visits against the study database vs. checking only patients with suspected pneumonia); the screening team (same team every day of the week vs. other team in the weekend); screening frequency (once vs. twice a day); screening the cardiology department (yes/ no); and applying an electronic filter (yes/ no). Local differences in screening methods were compared to the proportions of missed episodes per hospital using Poisson regression analysis, with log('number of eligible cases') per hospital as the offset and number of missed episodes as the outcome variable.

As hospitalization and ER reports from hospitals to GPs cannot be considered 100% complete and GP monitors may overlook relevant episodes, clinical factors associated

Figure 1 - Flowchart of episodes reported by GP monitor



Abbreviations: GP: general practitioner; CCU: coronary care unit; RN: research nurse.
a. See box 1 for definitions.
b. Not admitted via ER or initially presenting to other (non-screened) medical specialism

with identification of pneumonia episodes in the GP-records were determined by logistic regression analysis, using hospital data of cases identified by the RN.

The NNT based on the detected primary endpoints (1st episode of VT-CAP) in the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), calculated as 1 divided by the risk difference of the primary outcome, was compared to the NNT based on the estimated frequency of both missed and identified episodes. For this analysis, we assumed that the proportions of missed episodes of suspected pneumonia were independent of the detected pathogen and that the proportion of missed episodes - as determined from the GP-monitor identified cases - represented the overall proportion of missed episodes. Hence we applied the proportion of missed episodes of all-cause pneumonia to the effect estimate of VT-CAP. As both the proportion of missed cases and the number of observed episodes of VT-CAP are estimates with uncertainty, bootstrapping was used to constitute the 95% confidence interval of the corrected NNT. Bootstrapping is a technique that uses sampling with replacement and can be used to make inferences of data with unknown distribution, for which standard statistical methods are not applicable.[10] We drew 10,000 bootstrap samples and used the percentile method, i.e. the 2.5th and 97.5th percentile, for the confidence interval. The analyses were performed in R for Windows version 3.0.2[11] and IBM SPSS for Windows version 21 (IBM corp., Armonk, NY, USA).

RESULTS

Root causes of missed episodes

During the study period, there were 3,260 episodes of clinical suspicion of pneumonia identified by the RN in the 58 hospitals. Of these, three were classified as "Not per protocol" in the current assessment and in 60 subjects it was uncertain whether the subject was identified within the 48 hours window, as the urine sample was – for unknown reasons - collected outside the 48 hours window; these were not included in the analysis of root causes, leaving a total of 3,197 episodes in the RN dataset (Table 1).

Table 1 - Numbers of episodes of clinically suspected pneumonia identified by RN and in GP-records

	Identified in GP records	Not identified in GP records	Total
Identified by RN < 48 hours	1,374	1,598	2,992
Identified by RN > 48 hours *	104 $	121	225
Not identified by RN *	705 $	*Unknown*	
Total	2,183		

Abbreviations: GP: general practitioner, RN: research nurse. * These episodes are considered missed. $ These 809 episodes are used for the root causes analysis of missed episodes.

A total of 2,524 hospital referrals were identified in the GP records. Of these, 307 did not meet the criteria for suspicion of pneumonia and were categorized as "Not per protocol". In 34 subjects it was uncertain whether the subject was identified within the 48 hours window, as the urine sample was – for unknown reasons - collected outside the 48 hours window. These episodes were removed, leaving a total of 2,183 episodes in the GP dataset (Table 1). Of these, 334 (15%) were not admitted via one of the screened routes, 475 (22%) were missed for different reasons and 1,408 (63% of all episodes and 74% of episodes within the screened route) were identified (Figure 1).

Among the 3,260 episodes identified by RN, urine samples were missing or were collected outside the 48 hours window in 391 episodes. Of these 60 (of which 34 in the GP dataset) had no reason provided, 103 (of which 34 in the GP dataset) were classified as not missed because there was a reason beyond identification for the delayed urine collection, 3 (of which 1 in the GP dataset) were not per protocol, and 225 (of which 104 in the GP dataset) were classified as 'identified by the RN >48 hours after admission' (Table 1). Reasons for delayed identification were comparable for episodes identified or not by GP monitors; only subjects "being deceased before identification" were less often identified by GP monitors (Supplementary Appendix Table S1). For the analysis of root causes, only the 2,183 episodes that were identified by the GP monitor were considered.

RNs misinterpreted the admission reason of 121 episodes, i.e. there was a documented suspicion of pneumonia and the referral indication or principal diagnosis should have led to case identification. Of these, 22 were due to misinterpretation of chest X-rays by study physicians and 14 were incorrectly rejected because they were considered hospital-acquired pneumonia, recurrent pneumonia, obstruction pneumonia, or pneumonia after chemotherapy, even though these cases met study criteria of suspected pneumonia. In the other episodes, referral indications or primary diagnoses should have alerted RNs. These included exacerbation of asthma or COPD (n=27), fever (n=13), suspicion of pulmonary embolism (n=11), pleural fluid or empyema (n=7), dyspnea (n=6), (nonspecific) interstitial pneumonia (n=3), sepsis (n=3), hemoptysis (n=3), and miscellaneous others (n=12).

The admission reason was considered not suggestive of pneumonia in 83 episodes, and these included a primary cardiac diagnosis (n=29), gastro-intestinal symptoms (n=17), collapse (n=6), neurological symptoms (n=6), urinary tract infection (n=5), dysglycemia (n=3), anemia (n=2), and miscellaneous others (n=15).

Using an electronic filter on admission diagnosis as part of the screening method was associated with a 1.7 fold increase in missed episodes (Table 2). There were minor fluctuations over time in proportions of suspected pneumonia episodes identified by RNs without a discernable temporal trend (Figure 2).

Table 2 - Proportion of episodes missed by RN's according to differences in screening methods

Screening method	Number of hospitals	Number of eligible cases	Number missed (%)	RR (95% CI) (crude)	P-value	RR (95% CI) (adjusted*)	P-value
Identification as study participant first	17	839	269 (32.1%)	-	-	-	-
Identification as suspected pneumonia case first	35	1,273	469 (36.8%)	1.149 (0.989-1.335)	0.069	1.095 (0.921-1.303)	0.303
One team performs screening	37	1,519	527 (34.7%)	-	-	-	-
Different team in weekend	13	567	200 (35.3%)	1.017 (0.864-1.196)	0.842	0.945 (0.794-1.124)	0.523
Unknown	2	26	11 (42.3%)	1.219 (0.671-2.216)	0.515	1.818 (0.554-5.972)	0.324
Screening twice a day	46	1,856	641 (34.5%)	-	-	-	-
Screening once a day	5	234	89 (38.0%)	1.101 (0.882-1.375)	0.394	1.241 (0.938-1.643)	0.131
Unknown	1	22	8 (36.4%)	1.053 (0.524-2.115)	0.885	0.635 (0.160-2.514)	0.518
Screening cardiology dpt.	32	1,191	413 (34.7%)	-	-	-	-
Not screening cardiology dpt.	9	284	99 (34.9%)	1.005 (0.807-1.252)	0.963	1.056 (0.838-1.329)	0.645
Unknown	11	637	226 (35.5%)	1.023 (0.870-1.203)	0.782	0.940 (0.756-1.170)	0.581
No electronic filter on diagnosis	49	1,966	658 (33.5%)	-	-	-	-
Electronic filter on diagnosis	3	146	80 (54.8%)	1.637 (1.298-2.065)	0.000	1.698 (1.304-2.211)	0.000

Abbreviations: RN: research nurse, RR: risk ratio estimated using Poisson regression, CI: confidence interval.
Six hospitals with two locations in which the same research team performed screening were taken as one unit in this analysis, leading to 52 hospitals. Missed episodes due to presentation in a non-participating hospital are not included. RR >1 indicates a higher probability of missing episodes.
* adjusted for differences in screening method.

Table 3: Factors associated with identification of episodes by GP monitor

Variable		Identified in GP-records (N=1,511)[a]	Missed in GP records (N=1,749)	OR (crude)	OR (adjusted)	p-value
Case definition	*Presence of infiltrate on chest X-ray* [b]	989 (66%)	1,024 (59%)	1.33 (1.16-1.54)	1,21 (1,02-1,42)	0.025
	2 or more clinical symptoms	1,489 (99%)	1,670 (96%)	3.21 (1.98-5.16)	2.25 (1.36-3.72)	0.002
Admission department	internal medicine or pulmonology	1,137 (75%)	1,237 (71%)	*Reference*	*Reference*	<0.001
	emergency admission department [c]	166 (11%)	136 (8%)	1.33 (1.04-1.69)	1.51 (1.17-1.96)	
	cardiology or CCU	57 (4%)	115 (7%)	0.54 (0.39-0.758)	0.70 (0.48-1.01)	
	ICU	64 (4%)	85 (5%)	0.82 (0.59-1.14)	1.27 (0.86-1.86)	
	geriatrics	8 (1%)	19 (1%)	0.46 (0.20-1.05)	0.64 (0.27-1.51)	
	surgical wards	10 (1%)	18 (1%)	0.60 (0.28-1.32)	0.81 (0.36-1.85)	
	transfer to other hospital	7 (1%)	19 (1%)	0.40 (0.17-0.96)	0.45 (0.18-1.11)	
	not admitted	47 (3%)	89 (5%)	0.58 (0.40-0.83)	0.55 (0.38-0.80)	
	other/ unknown	15 (1%)	31 (2%)	0.53 (0.28-0.98)	0.65 (0.34-1.27)	
PSI-class	2	167 (11%)	163 (9%)	*Reference*	*Reference*	0.044
	3	466 (31%)	450 (26%)	1.01 (0.79-1.30)	1.03 (0.79-1.34)	
	4	707 (47%)	814 (47%)	0.85 (0.67-1.08)	0.94 (0.73-1.21)	
	5	171 (11%)	322 (18%)	0.52 (0.39-0.69)	0.71 (0.52-0.98)	
Working diagnosis	pneumonia [d]	1,117 (74%)	961 (55%)	*Reference*	*Reference*	<0.001
	exacerbation COPD	169 (11%)	282 (16%)	0.52 (0.42-0.64)	0.47 (0.37-0.59)	
	other respiratory tract infection [d]	60 (4%)	107 (6%)	0.48 (0.35-0.67)	0.50 (0.35-0.71)	

	sepsis/ fever/ infection (unknown focus)	31 (2%)	72 (4%)	0.37 (0.24-0.57)	0.38 (0.24-0.60)	
	acute decompensated heart failure	18 (1%)	65 (4%)	0.24 (0.14-0.40)	0.30 (0.17-0.54)	
	pulmonary embolism	8 (1%)	17 (1%)	0.41 (0.17-0.94)	0.42 (0.18-1.00)	
	infection (non-pulmonary focus)	20 (1%)	52 (3%)	0.33 (0.20-0.56)	0.34 (0.20-0.58)	
	neutropenic fever/ malignancy related	7 (1%)	33 (2%)	0.18 (0.08-0.41)	0.16 (0.07-0.38)	
	other pulmonary diagnosis	32 (2%)	56 (3%)	0.49 (0.32-0.77)	0.55 (0.34-0.87)	
	other diagnosis and/ or combination	35 (2%)	79 (5%)	0.38 (0.25-0.57)	0.49 (0.32-0.75)	
	unknown	14 (1%)	25 (1%)	0.48 (0.25-0.93)	0.54 (0.27-1.08)	
Outcome after admission	Discharged home	1,323 (88%)	1,266 (72%)	*Reference*	*Reference*	<0.001
	Transferred to nursing home/ rehabilitation/ other hospital	124 (8%)	211 (12%)	0.56 (0.45-0.71)	0.61 (0.47-0.78)	
	Deceased in hospital	33 (2%)	238 (14%)	0.13 (0.09-0.19)	0.12 (0.08-0.18)	
	Unknown	31 (2%)	34 (2%)	0.87 (0.53-1.43)	1.07 (0.63-1.80)	
CAP pathogen [e]	No bacterial pathogen identified	1,036 (69%)	1,336 (76%)	*Reference*	*Reference*	0.004
	S. pneumoniae	283 (19%)	227 (13%)	1.61 (1.33-1.95)	1.27 (1.04-1.56)	
	Other bacterial pathogen	192 (13%)	186 (11%)	1.33 (1.07-1.66)	1.39 (1.10-1.76)	

Abbreviations: OR: odds ratio; GP: general practitioner; CRF: case record form; RN: research nurse; COPD: chronic obstructive pulmonary disease; CAP: community-acquired pneumonia; PSI: pneumonia severity index; CCU: coronary care unit; ICU: intensive care unit.
OR > 1 indicates that the factor increased the probability of being identified by the GP monitor. In **bold**: indicators significantly decreasing the probability of being identified by the GP monitor. In *italic*: indicators significantly increasing the probability of being identified by the GP monitor.
[a.] These Include 26 cases that were initially missed by the research nurse (RN), but a CRF was completed upon a second admission of these subjects. The total of 3260 episodes in the RN dataset includes 58 episodes that were registered by the RN but were excluded for the main trial analysis, mainly based on absence of pneumonia suspicion on admission.
[b.] 21 X-ray results were missing, these cases were excluded from multivariate analysis.
[c.] This department is not present in every hospital
[d.] Also considered the working diagnosis if exacerbation COPD was caused by pneumonia or respiratory tract infection.
[e.] Etiology was categorized and based on available cultures in the first two days after admission and results from urinary antigen testing.

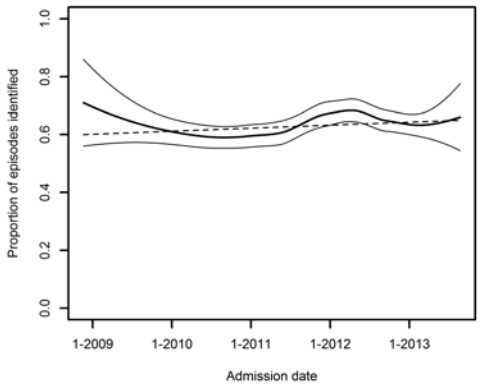


Figure 2 - Proportion of missed cases over time

Trends in percentage of suspected pneumonia episodes identified by the research nurse among 2,183 suspected pneumonia episodes found in the general practitioner records. The solid line represents a smoothed Lowess curve with 95% confidence interval. The dashed line represents a logistic regression analysis. P-value for overall trend: 0.27.

GP monitoring

In total 3,260 hospital visits for suspected pneumonia were identified by the RN, of which 46% was also found in the GP records (sensitivity of GP monitors). Factors positively associated with identifying episodes by GP monitors were the presence of an infiltrate on the chest X-ray, having more than two protocol defined clinical symptoms of pneumonia (cough, sputum production, fever or hypothermia, auscultatory findings of pneumonia, elevated CRP, leukocytosis, and hypoxemia), having an ER working diagnosis of pneumonia, low PSI score, being hospitalized, being admitted to an emergency admission department, identification of a bacterial pathogen, and being discharged home (Table 3). Not being admitted (i.e. receiving ambulatory treatment) was negatively associated with identification by GP monitors (Table 3).

Classification accuracy

Inter observer agreement was assessed for the main categories (Box 1). Cases with urine collected within 48 hours or with delayed urine collection for unknown reasons were not included, as these did not require subjective interpretation. Therefore, 1,342 episodes were assessed by the reviewers and discrepancy on the category between two reviewers occurred in 301 (22%) cases (kappa of 0.73, 95%CI 0.70-0.76, indicating substantial agreement).[12]

Inference on NNT

In the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) the NNT to prevent one episode of VT-CAP was 1,007 (95% confidence interval (CI) 613-2,646). After accounting for the proportion of missed episodes of 37% (95% CI 35-39%), and assuming that the proportion of missed cases was independent of the microbiological etiology, the NNT decreased to 634 (95% CI 386-1,675).

DISCUSSION

This root cause analysis of missed episodes of pneumonia in a population-based intervention study identified several possibilities for improvement from which future studies could benefit. In our study, the most frequent reasons for missing episodes were hospitalization occurring through other routes that were not screened, pneumonia not being suspected at presentation, and misinterpretation of the referral indication or diagnosis by the screening RN. As admission routes may differ substantially between countries and even between hospitals, for future studies, we recommend to carefully map these routes in each participating hospital in a pilot study. In our situation this might have resulted in inclusion of internal medicine and pulmonology wards admission lists into the screening, instead of only screening patients that present to the ER for these specialties as was done in many hospitals in our study. In this way, patients admitted via outpatient clinics and patients initially being presented to other specialties will be included in the screening. Also, the complete differential diagnosis should be screened, rather than the principal diagnosis, or worse, the referral indication. The latter was accepted in some hospitals for feasibility reasons but should be discouraged based on our findings. Furthermore, RNs should receive appropriate training to recognize medical terms that do not exclude pneumonia, such as exacerbation of COPD or asthma, suspicion of a pulmonary embolism, and symptoms like dyspnea, hemoptysis, and empyema. A clinical suspicion of a cardiac disease was also associated with missing pneumonia episodes. However, as this is such a frequent reason for hospital admission, including such patients in the screening route would considerably increase the number of patients needed to screen to detect one pneumonia. Finally, we recommend not to use an electronic filter for case selection if based on referral indication or admission diagnosis, as such filters, as used in our study, appear to increase the probability to miss pneumonia cases.

Based on this assessment and after adjustment for missed episodes, the estimated NNT decreased from 1,007 to 634. Still, the adjusted estimate of 634 should be interpreted with caution, as we assumed that the likelihood of missing episodes was pathogen independent. In fact, there was a higher likelihood of identifying pneumococcal than non-pneumococcal CAP in GP databases. Although the GP monitors screened in retrospect when all microbiological information was available, results of pneumococcal urinary antigen tests at the time of screening may have alerted RN. If so, the proportion of missed pneumococcal CAP episodes would be lower compared to all-cause pneumonia, which would reduce the adjusted NNT to a lesser degree.

In our inference of the percentage of missed episodes, we also assumed independency of GP monitor and RN sensitivity to detect pneumonia episodes. However, episodes of

X-ray confirmed pneumonia were more frequently identified by GP monitors. Moreover, identification of pneumonia episodes in GP records depends on the availability of discharge letters, which were more often missing from patients that deceased during admission or were transferred to other settings. Naturally, we could not quantify episodes that were missed by both RN and GP monitor and the 37% missing episodes is therefore the best estimate possible with the data available.

Assessment of reasons for missing episodes is subjective, which resulted in discrepancies in 22% of cases, despite the use of a standardized categorization approach. In part, this results from the amount of information available, which varied considerably from case to case. Most discrepant cases, however, could be solved by discussion. The relatively high proportion of discrepancies emphasizes the need of adjudication by two independent investigators, as was done in our study.

In our estimation of the adjusted NNT, we did not take into account the sensitivity of pneumococcal serotype detection. The sensitivity of the blood culture is known to be limited, and although the sensitivity of the serotype specific UAD is known to be nearly 100% for bacteraemic VT-CAP, the sensitivity remains unknown for non-bacteraemic patients.[13] Yet, the estimated vaccine efficacy for all-cause CAP was 5.1%, and approximately 13% of the first CAP episodes were VT pneumococcal CAP, which is consistent with the vaccine efficacy of 46% for VT-CAP.[9] Whether this indicates that there are no undetected VT-CAP episodes or that the number of undetected (and prevented) VT-CAP episodes equals the number of CAP episodes caused by other pathogens (i.e. replacement), remains a matter of speculation.

To the best of our knowledge, a scrutiny of identification of pneumonia admissions in population-based studies has not been published before. In an evaluation on accurateness of cardiovascular events detection in a Scottish trial, rigorously collected clinical trial data correlated well to routinely collected electronic patient records, with 97% correlation for cardiovascular death and 81% for non-fatal cardiovascular events.[14] Yet, in that study cardiovascular events were identified retrospectively at 3-monthly follow-up visits, including annual electrocardiography, while in our study the pneumonia episode had to be detected within 48 hours of admission to allow for additional testing, and identification was based on the differential diagnosis on admission.

In conclusion, based on a detailed analysis of all available sources we estimated that, by the screening system as outlined, 63% of suspected pneumonia episodes requiring hospitalization were identified within the required time window, and the estimated NNT changed from 1,007 to 634 after adjustment for missed episodes. Several causes of

missing episodes were identified, some of which appear preventable by adaptation of study procedures and training of study personnel. Our findings emphasize that population based studies that rely on real-time identification of endpoints cannot be used to determine absolute effect estimates of interventions, unless in parallel an accurate estimation of the proportion of missed episodes is performed.

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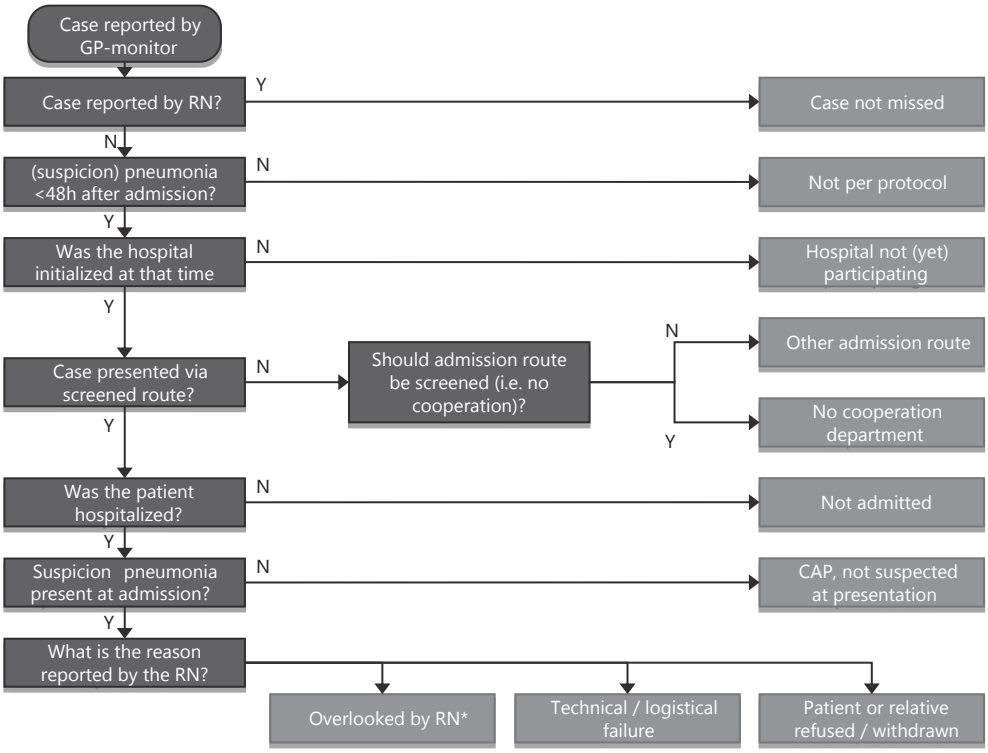
Supplementary Appendix

Figure S1 - Classification flowchart of non-identified cases



* If "Overlooked by RN" was the reason for missing the case, it was sub-categorized according to the reason provided by the RN (See Supplementary Appendix Figure S2). Abbreviations: GP: general practitioner; RN: research nurse.

Figure S2 - Review forms

Review form missed CAP cases

Reviewer SH / HW / FP / AN

Subject number ☐☐☐☐☐☐

Date hospitalization ☐☐-☐☐-20☐☐

Hospital ----------

Category

- ○ Case not missed
- ○ Not per protocol
- ○ Hospital not participating
- ○ Other admission route
- ○ No cooperation department
- ○ Not admitted
- ○ CAP, not suspected at presentation
- ○ Overlooked by RN (p.t.o.)
- ○ Technical / logistical failure
- ○ Patient or relative refused

Discharge diagnosis of Community Acquired Pneumonia?

○ **YES** ○ **NO**

Date __-__-20__

Signature:

Overlooked by RN - Categories

- ○ Discussed with physician: no CAP.
  (Case is identified, but after discussion with treating physician it was decided it is no CAP. However, according to the source documents the (suspicion of) CAP was present at admission and still at discharge.)
- ○ No infiltrate.
  (Admission chest X-ray doesn't show infiltrate. However, clinical diagnosis is CAP.)
- ○ Screening method out of office hours.
  (Different screening team in weekend or evening (e.g. physicians or ER nurses or phone contact))
- ○ Unknown reason.
  (Not screened by RN, no reason for missing.)
- ○ Misinterpretation of RN.
  (Screened by RN: clinical diagnosis or referral indication suggestive of CAP, however RN didn't consider it.)
  Clinical diagnosis/ referral:.....
- ○ Presentation/admission reason not suggestive.
  (The screened referral indication or diagnosis is such that RN cannot be expected to consider CAP. However pneumonia was (one of the) (differential) diagnoses of admission.)
  Admission reason:.....
- ○ Discussed with nurse on ward: no CAP.
  (Case is identified, but after discussion with nurse on the ward it was decided it is no CAP. However, according to the source documents the (suspicion of) CAP was present at admission and still at discharge.)

Reviewer: SH / HW / FP / AN Date: __-__-20__

Signature:

Table S1 - Classification of 228 episodes identified by RN >48 hours after admission

	Found by GP-monitor (N=105)	Not found by GP-monitor (N=123)	Total (N=228)	P-value*
Not per protocol	1 (1%)	2 (2%)	3 (1%)	1.000
Non-screened department	9 (9%)	22 (18%)	31 (14%)	0.064
Not suspected at presentation	11 (10%)	7 (6%)	18 (8%)	0.276
Misinterpretation	13 (12%)	10 (8%)	23 (10%)	0.400
Admission reason not suggestive	9 (9%)	6 (5%)	15 (7%)	0.394
No hospitalization	25 (24%)	39 (32%)	64 (28%)	0.240
Deceased before identification	2 (2%)	12 (10%)	14 (6%)	0.029
Technical / logistical failure	10 (10%)	4 (3%)	14 (6%)	0.091
Physician judgment	1 (1%)	2 (2%)	3 (1%)	1.000
Miscellaneous	4 (4%)	5 (4%)	9 (4%)	1.000
Unknown cause	20 (19%)	14 (11%)	34 (15%)	0.152

* Differences in proportions were tested using Chi-square test or Fisher's exact test, as appropriate. Abbreviations: RN: research nurse; GP: general practitioner.

Part II

Management of Community-Acquired Pneumonia in adults

Chapter 6 Antibiotic treatment of moderate-severe community-acquired pneumonia: design and rationale of a multi-centre cluster-randomized cross-over trial

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ABSTRACT

Background

For the empirical treatment of community-acquired pneumonia requiring admission to a non-ICU ward, the Dutch guidelines recommend either beta-lactam monotherapy, beta-lactam and macrolide combination therapy, or fluoroquinolone monotherapy. The lack of convincing evidence to preferentially recommend any of the three empiric regimens results from intrinsic limitations of current studies, such as bias by indication and residual confounding in observational studies, and the unknown effects of pre-randomisation antibiotic use in randomized controlled trials. In this paper we discuss the methodological drawbacks of observational cohorts and randomized controlled trials in antibiotic therapy. Next, we explain why we designed a multi-centre cluster-randomized cross-over study to evaluate the effectiveness of three antibiotic treatment strategies, consisting of a preferred treatment regimen of beta-lactam monotherapy, beta-lactam and macrolide combination therapy or fluoroquinolone monotherapy, in adult patients admitted to a non-ICU ward with a clinical diagnosis of community-acquired pneumonia. Furthermore we outline different aspects of this design that deserve thorough consideration.

Conclusion

We discuss different aspects of a cluster-randomized cross-over trial that is designed to determine the effects of three recommended regimens of antibiotic treatment of CAP.

Community-acquired pneumonia (CAP) has an incidence ranging from 3.3 to 46 per 1,000 per year in the elderly population.[1-4] Reported case fatality rates are usually less than 5% in outpatients, but hospital-mortality rates have ranged from 5 to 48%, depending on age, comorbidities, pneumonia severity and presence of bacteraemia.[2]

With the introduction of sulphonamides and penicillins in the 1930's, the estimated absolute risk of dying from CAP has decreased by 10%-25% for all CAP patients, and even by 48-65% in bacteraemic CAP patients. Yet exact estimates are difficult to derive since randomized placebo-controlled trials (RCT's) were not yet performed.[5] Advances in medical care, such as mechanical ventilation and vasopressor support, have most certainly improved survival in patients with high severity CAP, but for the majority of CAP patients, major improvements in the management of CAP are less obvious.[6] Adjunctive treatment with immunomodulators, e.g. corticosteroids, have not demonstrated clear improvements in survival.[7] Therefore, antimicrobial therapy remains the mainstay of CAP treatment.

Initial antibiotic therapy for CAP is usually empirical, covering the most frequent pathogens. Yet, patient and disease characteristics are not specific enough to guide antibiotic therapy in most patients.[8,9] Therefore, CAP severity, as determined by prognostic scores or site of admission, is widely recommended for guiding empiric antibiotic therapy.[8-11] In the Netherlands, it is recommended to treat patients with mild CAP empirically with doxycycline or amoxicillin, and those with severe CAP with combined treatment of a beta-lactam (such as 2nd or 3rd generation cephalosporins) and a macrolide, or a beta-lactam (such as penicillin or amoxicillin) and ciprofloxacin, or monotherapy with one of the newer fluoroquinolones (moxifloxacin or levofloxacin). The mid-range severity group, labelled moderate-severe CAP, should be treated either as mild CAP or as severe CAP, based on the perceived risks of Legionella infection. Three different classification tools are recommended to categorize CAP severity, with the recommendation to consistently use one of them: CURB-65 (0-1 is mild, 2 is moderate-severe and >2 is severe), PSI (1-2 is mild, 3-4 is moderate severe and 5 is severe), or a pragmatic score based on the level of care needed (ambulant is mild, non-ICU ward is moderate-severe, ICU admission is severe).[9] Because of the multiple options for severity classification and the subjectivity of clinical parameters, the use of these scoring systems promotes categorization of patients as severe CAP, with corresponding treatment choices. This becomes apparent in different studies of moderate-severe CAP, in which 20-40% of patients were treated with quinolones or combination therapy with a macrolide.[12-15] Recently, our group has investigated guideline adherence in hospitalized CAP patients in the Netherlands, and reported very heterogeneous empirical treatments.[16] In the Netherlands the three recommended empirical regimens

are considered equivalent for moderate-severe CAP. In the international literature, the discussion concerning the need for atypical coverage in non-ICU hospitalized CAP is still ongoing.[17-20]

Each strategy comes with different advantages and drawbacks. Beta-lactam antibiotics have less adverse events than macrolides, are less expensive than fluoroquinolones and the prevalence of antibiotic resistance in *Streptococcus pneumonia* is not clinically relevant in the Netherlands.[21,22] Yet, atypical pathogens are not covered. Macrolides are active against most atypical pathogens and they might offer anti-inflammatory effects, possibly leading to faster clinical responses.[23] On the other hand, rapid development of resistance of *S. pneumoniae* against macrolides during treatment, has been observed in vivo.[24] In the Netherlands proportions of *S. pneumoniae* isolates from hospitalized patients being resistant to macrolides were 2% - 3% in 1996, 7% - 10% in 2002 and 4.5% in 2011.[21,22] The newer fluoroquinolones, such as levofloxacin and moxifloxacin, are active against all common causes of CAP, can be used intravenously and orally, and might also have anti-inflammatory effects.[25] The major disadvantage, similar to macrolides, is a potentially higher risk of development of antibiotic resistance, as observed among *S. pneumoniae* after introduction of fluoroquinolones in Canada and Hong Kong.[26,27] In contrast, a study from Germany showed a low prevalence of quinolone resistance, while usage of moxifloxacin was high.[28]

The lack of well-designed randomized comparisons between beta-lactam monotherapy, beta-lactam and macrolide combination therapy and any of the newer fluoroquinolones is a serious limitation for interpreting the relative effectiveness of these strategies in patients hospitalized with CAP. Fluoroquinolones have been compared to beta-lactams and macrolides in randomized studies, but none yielded superiority of either treatment. Large meta-analyses failed to demonstrate an advantage of atypical coverage in the empirical antibiotic treatment of mild to moderately severe CAP patients not caused by Legionella.[29-31] Some observational studies showed beneficial effects of atypical coverage on clinical outcome,[32-40] but in a similar number of studies such effects could not be demonstrated.[41-49]

However, there are serious limitations in the design of observational studies and RCT's. To overcome some of the pitfalls of these classical study designs, we designed the "**C**ommunity-**A**cquired **P**neumonia - **S**tudy on the initial **T**reatment with **A**ntibiotics of lower **R**espiratory **T**ract infections" (CAP-START, http://clinicaltrials.gov/show/NCT01660204), a cluster-randomized cross-over study to evaluate the (cost-)effectiveness of three empirical antibiotic strategies in patients hospitalized with CAP in non-ICU wards. The first aim of this paper is to discuss pros and cons of observational studies and RCT's. Next, we discuss different aspects of designing a cluster-randomized

cross-over study, which we consider beneficial for the development of future trials for the comparison of intervention strategies.

DRAWBACKS OF OBSERVATIONAL STUDIES FOR ANTIBIOTIC TREATMENT OF CAP

In observational studies, the decision for the empirical antibiotic treatment has been made by treating physicians. Consequently, these studies suffer from bias by indication, as the choice of therapy will be influenced by e.g. severity of disease or the patients' overall prognosis. Thus, if patients receiving atypical coverage have a better outcome, this may in part result from the better prognosis at baseline, and not necessarily from better coverage of atypical pathogens. The magnitude of this form of bias was demonstrated by using a propensity score to predict treatment allocation based on clinical variables. The propensity was used in a multivariate analysis to adjust for confounding variables. The apparent beneficial effect of combination therapy (adjusted OR 0.39, 95% CI 0.19–0.79) was diminished after additional correction for the propensity score (OR 0.69, 95% CI 0.32–1.48).[50] Although analytical control in multivariable analysis is usually attempted, many determinants may be unknown or measured with error, resulting in so-called residual confounding. For example, (hidden) treatment restrictions may play a role in a substantial proportion of fatal CAP cases, especially in elderly patients with severe comorbidities,[51] which may also influence treatment decisions and, thus, confound observations. It is difficult, if at all possible, to predict the direction and quantity of residual confounding.

DRAWBACKS OF RANDOMIZED CLINICAL TRIALS FOR ANTIBIOTIC TREATMENT OF CAP

Randomization prevents bias by indication and residual confounding because treatment allocation is not influenced by patient or disease characteristics, but determined by chance. However, a consequence of an RCT is that the time-frame for initiation of the study medication is generally longer than in clinical practice, because the informed consent procedure and randomization need to be realized. International guidelines for clinical trials demand that eligible subjects are given sufficient time to consider participation in the trial. At the other end, current CAP guidelines emphasize the importance of early antibiotic administration, and recommend to initiate treatment within four to eight hours of hospital admission.[8,9,52] As a result, many patients have already received in-hospital antibiotic treatment before study enrolment. Since the adequacy of the first dose of antibiotics is considered crucial for patient outcome,[53-55] this may severely compromise accurate evaluation of effectiveness of the randomized antibiotics. In fact, it might even be dangerous to accept non-inferiority if a large proportion of patients has received similar pre-randomisation antibiotics. Any difference in effectiveness will, to some extent, be diluted by the therapeutic effect of

the antibiotics received prior to randomisation, leading to a reduced power to detect superiority of one of the antibiotics under study.

Another limitation of current RCT's is that their generalizability to daily clinical care is questionable. Prior antibiotic use, contra-indications, and exclusion criteria can lead to a very restricted study population. A comparison of empirical antibiotic strategies, in which the aforementioned exclusion criteria are not applied, would lead to more generalizable results.

CLUSTER-RANDOMIZED CROSS-OVER DESIGN

In an ideal comparison of empirical antibiotic therapies, the allocation of treatment would be unrelated to patient and disease characteristics, to ensure comparability of the treatment groups in terms of prognosis. Additionally, the timing of treatment and of concomitant therapy should be comparable to clinical practice. As pointed out, when studying empirical antibiotic treatment of CAP, the first requirement is not satisfied in observational studies, while RCT's don't comply with the second. Also, patients should be included on an intention-to-treat basis; treating physicians should be able to start another antibiotic because of prior use or contra-indications. To overcome these limitations, we have designed a multi-centre cluster-randomized cross-over study, comparing empirical antibiotic strategies. Participating centres are randomized to three consecutive periods of four months, in which one of the three empirical antibiotic strategies applies. All CAP patients admitted to a non-ICU ward, irrespective of the PSI or CURB-65 classification, are eligible for the study. The empirical strategies consist of beta-lactam monotherapy, fluoroquinolone monotherapy and beta-lactam macrolide combination therapy.

In this way, allocation of empirical strategy is determined by the date of admission and cannot be biased by patient characteristics. In each hospital the local antibiotics committee has been asked to adopt this empirical strategy as the standard treatment for CAP during that period. Because of this, the medical ethics review board judged that this cluster-randomized study is not liable to the same regulations as an individually randomized trial. Consequently, written informed consent is not needed prior to start of the preferred treatment of the study, but only for collection of individual patient data. Importantly, this is only legitimate for interventions that are registered for the disease under study and are considered equally effective.

Treating physicians will sometimes deviate from this strategy for a medical reason. These patients will also be included in the intention to treat analysis, which will be the primary analysis of our study. Thus, the strength of a cluster-randomized trial design is

that it enables a comparison of treatment strategies, rather than the individual treatments. Since patients from one hospital may not be comparable to those from another hospital, the cross-over design is used, enabling adjustment for hospital-specific confounding factors.

The most important challenges considering this design include adherence to the treatment strategy by the treating physicians, prevention of selection bias, and differences in number and severity of eligible CAP patients due to seasonality. These will be discussed in the next section.

CHALLENGES IN CLUSTER-RANDOMIZED CROSS-OVER DESIGNED STUDIES FOR ANTIBIOTIC TREATMENT OF CAP

Protocol adherence and route of administration

Naturally, treating physicians sometimes deviate from study protocols. This may compromise the intention-to-treat analysis if the alternative antibiotic therapy is different in effectiveness. If, however, the rationale for deviation from protocol is valid, i.e. in line with common practice, the intention-to-treat analysis will show the effect of implementation of either protocol in real life. Therefore, reasons for such deviations will be recorded to investigate their validity. Valid reasons include failure of prior antibiotic treatment with the same class of antibiotics, clinical suspicion of a pathogen that is not covered by the preferred regimen, targeted treatment because of previous microbiological results or a contra-indication for the treatment of choice. Episodes of non-protocol adherent treatment without a valid medical reason are considered protocol violations. All CAP patients, including those with protocol deviations and protocol violations, will be included in the intention-to-treat analysis. Hence, in this analysis we compare hospital-wide strategies of empirical treatment rather than antibiotics in individual patients. For instance, patients receiving non-preferred antibiotics for medical reasons, are still treated according to best medical practice during that study period. Rates of protocol deviations will provide insight in the implementation potential of each treatment strategy. In a classical RCT, such patients would be excluded because of a contra-indication for one of the treatment options. On the other hand, the per-protocol analysis will only include patients treated according to the preferred antibiotic regimen. Reasons for non-adherence will probably differ between treatment arms, and protocol deviations may therefore confound the per-protocol analysis if the protocol adherent patients in one period have a different prognosis compared to those in another. This will be dealt with in the statistical analysis.

The specific choice of agents within the treatment category is left to the treating physician, e.g. amoxicillin, co-amoxiclav or ceftriaxone are all acceptable as beta-lactam

monotherapy. All changes in therapy are monitored and deviations from protocol will be motivated by the treating physician. Although this approach will lead to a heterogeneously treated study population, and the antimicrobial activity of different agents within one class may differ, we have assumed that, in the empirical treatment of CAP, such differences are negligible compared to the additional coverage of atypical agents (by macrolides or fluoroquinolones) or the immunomodulatory effects of macrolides. Furthermore, the primary goal of this study is to compare treatment strategies rather than individual antibiotics. Decisions on the route of administration (intravenous or oral), the duration of antibiotic treatment, and the start of pathogen-directed therapy when a causative agent has been identified, will be taken according to the Dutch CAP guidelines.[9]

Improving compliance to the protocol

Sub-optimal adherence to study protocol is a threat to any study. As most CAP patients receive their first antibiotic dose on the emergency room (ER), all pulmonary, internal and ER physicians, and especially the residents, need to be informed about the study. In some hospitals this comprises a group of over 50 people with multiple changes due to rotations, career choices, holidays and leaves. We designed a three-step approach to optimize study protocol adherence. First, all physicians were informed through presentations at the start of the study, and presentations are repeated regularly. Second, study progress was communicated through monthly (and later two-monthly) newsletters. Third, adherence to study protocol was continuously monitored and proportions of patients classified as "adherent", "deviation with clinical reason" and "protocol violation" are regularly fed back to participating sites.

The intensity of information provided to physicians working "in the field" is challenging, as in our experience there is a subtle balance between the level of knowledge required for such a trial and the risk of information fatigue. The return of investment of informative group sessions was considered limited as the awareness of the study seemed to decrease rapidly after such meetings. They are necessary at the start of the study, after which individual contacts, both through key-persons in each hospital and directly with the care-providing physicians, are more essential for optimizing protocol compliance.[56,57] We, therefore, monitor compliance case by case directly after study inclusion, and ask the physician that initiated the treatment for the rationale of any deviation from study protocol that is not motivated in the patient records. Initially, we experienced some resistance to this approach, as it was perceived as criticism on treatment decisions by some. However, after explaining the reason, all understood and accepted this procedure. Along the way, an increasing number of physicians explicitly reported the rationale for deviations in the medical records.

Naturally, providing adequate information to caregivers is very important around the four-monthly switches of the preferred regimen to another antibiotic class. In our experience it takes one to two weeks to facilitate a change to the new standard treatment. As a consequence there are more protocol violations at the beginning of each cluster. In future studies using a similar design, investigators might consider the use of a run-in period, in which subjects are not included in the study while the interventional change is effectuated.

Figure 1 provides an example of how we reported the protocol compliance to the participating centres. Treatment according to protocol was highest during the fluoroquinolone period, and lowest during the periods of beta-lactam plus macrolide therapy.

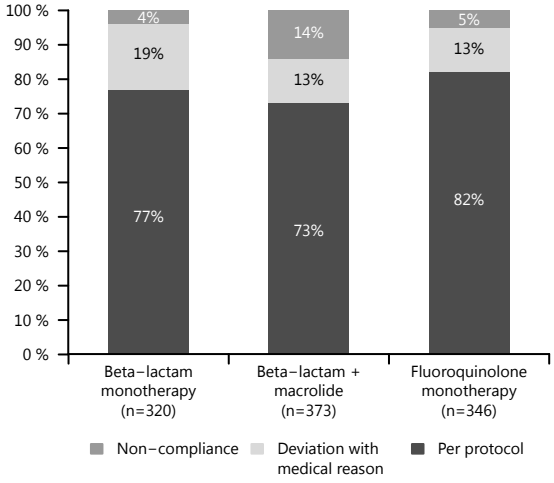

Figure 1 - Compliance to the protocol for the first 1,039 patients

Subject recruitment

A potential pitfall of a cluster-randomized study is patient inclusion with knowledge of treatment allocation. This may induce bias if inclusion criteria are not applied uniformly across different treatment arms.[58] Therefore, it is important to have clear inclusion criteria that are easily applicable. In CAP research the presence of an infiltrate on the chest X-ray is often used as one of the inclusion criteria. However, interpretation of the chest X-ray is not unambiguous and inter-observer agreement is therefore moderate.[59-61] Also, appearance of an infiltrated is delayed in a proportion of CAP patients.[62] Subsequent chest X-rays are performed mostly because of treatment failure, and will reveal an infiltrate in a proportion of the patients with initially negative chest radiographs. Therefore, if patients would be included based on presence of an infiltrate, this could lead to selection bias. In addition to that, the domain of interest of this study

does not consist of patients with proven CAP, but of patients who are treated for CAP, regardless of the presence of an infiltrate. Hence, inclusion in our study is based on a working diagnosis of CAP. We intend to perform a sensitivity analysis of patients with proven CAP. Definitions of CAP are very diverse in the literature.(for example [13,15,44]) We used a combination of several clinical parameters and a working diagnosis of CAP documented by the treating physician, as detailed in box 1. Screening for eligible patients is performed daily by research nurses not involved in the treatment of patients and is based on the admission diagnosis in the medical charts. Written informed consent, for the purpose of individual patient data collection, is requested by the research nurse or the treating physician. Of all eligible patients that are not included, the admission date and reason for non-inclusion is recorded, so that inclusion practice can be compared between hospitals and between treatment arms. We expect that the most important reason for non-inclusion will be patient refusal. Logistical reasons, such as discharge before the patient has been approached for inclusion, and ethical reasons, such as a presumed undue burden to the patient, should be closely monitored to ensure that these are not different between treatment arms. Selective recruitment, if present, will become apparent in differences in the inclusion rate or in differences in CAP severity between treatment arms. The magnitude of this will be assessed analytically, which is discussed in the section on data analysis.

Box 1 - Study definitions

Community-acquired:

Defined as an infection occurring in patients that were not recently hospitalized (>48 hours in the past two weeks) and not residing in long term care facilities.

Working diagnosis of CAP:

Defined as presence of at least 2 of the following clinical criteria* and treated with antibiotics for a clinical suspicion of CAP as documented by the treating physician. Patients with 2 or more criteria and an obvious non-respiratory source of the infection are not considered a working diagnosis of CAP.

Proven CAP:

Defined as a working diagnosis of CAP, with presence of a new or increased infiltrate on chest X-ray or CT-scan and at least 2 other clinical criteria*.

* *Clinical criteria:*

- Cough
- Production of purulent sputum or a change in the character of sputum
- Temperature > 38°C or < 36.1°C
- Auscultatory findings consistent with pneumonia including rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)
- Leucocytosis (>10.10^9 white blood cells/litre or > 15% bands),
- C reactive protein more than three times the upper limit of normal
- Dyspnea/ tachypnea/ hypoxia
- New or increased infiltrate on chest X-ray or CT-scan

Measurement of outcomes

As optimal treatment may require protocol deviation, blinding for treatment is not feasible. Therefore, it is pivotal to have an unambiguous study endpoint, preventing any bias in this aspect.[63,64] The primary endpoint is all-cause mortality up to 90 days after hospital admission with CAP, which can be obtained even if a patient's status at day 90 is not available in the hospital records (i.e. no death recorded and patient is not seen alive after day 90) from the Municipal Personal Records Database. Secondary outcomes include the length of intravenous treatment, length of hospital stay, complications relating to pneumonia or treatment, time to return to work and usual activities and (non-) health-care costs. Length of stay and length of intravenous treatment can be measured accurately, but may be more prone to bias because of the open label design. Self-reported time to return to usual activities and non-health care costs will probably not be influenced by knowledge of the type of antibiotic received, as most patients will not be aware of the pharmacological properties of their antibiotics.

Seasonality

Because of the seasonality of CAP, numbers of eligible patients will change over the year, which may also be the case for the average severity of CAP and spectrum of pathogens. In RCT's, this does not have consequences, since patients are randomized individually, and treatment arms will consist of comparable patients. However, in cluster-randomized cross-over trials, seasonality poses a challenge, because, by design, patients in one cluster are in a different season compared to those in another cluster. This may lead to an unequal number of inclusions between arms, which is less efficient for the analysis. More important, if the severity of CAP differs between seasons, this would lead to a biased evaluation. Although no evidence exists that CAP severity differs between seasons, aetiology is known to show variation.[65] Therefore, we aimed for a wedged start of periods to ensure continuous inclusion of patients across the year in all treatment arms.

Unfortunately, as the trial was initiated at different time points due to logistical reasons in some of the participating hospitals, the wedged start of periods was suboptimal. As a result, there are several months in the course of the study in which a substantial proportion of inclusions is made in one specific treatment arm. We are therefore planning to confirm analytically whether seasonality is of influence for the relative treatment effect. Furthermore we aim to compare proportions of pathogens between the treatment arms. For future studies with a cluster-randomized cross-over design, in which seasonality may play a role, we recommend to randomize based on calendar month. For example, assuming three periods of each four months, if the randomisation scheme of all centres would start in January, and one centre, randomized to treatment

order A-C-B, is initiated in July, it will start with two months of C, next have 4 months of B and 4 of A, and finish with two other months of C. Alternatively, if feasible, periods of one year could be chosen to avoid seasonality effects.

Sample size calculation

The study is designed to demonstrate non-inferiority of beta-lactam monotherapy on 90-day mortality. Based on an expected mortality rate of 5%,[14] 650 patients per study arm are needed to demonstrate non-inferiority of either strategy with a non-inferiority margin of 3% (alpha of 0.05 and power of 0.80). Accounting for possible drop-outs, 700 patients need to be included in each study-arm. Based on expected numbers of patients in each centre, a total study period of 24 months (6 periods of preferred antibiotic regimens) in seven participating centres was deemed necessary. In classical cluster randomized studies, the statistical power is generally reduced because of the intra-cluster correlation and because cluster sizes are unequal. The cross-over design limits these cluster level effects.[66] Furthermore, the effects of intra-cluster and inter-period correlation are considered limited, since treatment of one patient does not affect outcome of other patients, and clinical outcomes are associated with a low inter-cluster and intra-cluster correlation in general.[67] We performed a power simulation, comparing a classical RCT design to the cluster-randomized cross-over design, and estimated that statistical power is reduced in the latter by only 0.5% (95% confidence interval: 0.2 to 0.8%; simulation script is available on request to the authors).

Data analysis

Analysis will be performed according to the CONSORT statement recommendations for cluster randomized trials.[68] Since complexity and disease severity of patients might differ between hospitals, multilevel analysis will be used. The effect on the primary endpoint, 90-day all-cause mortality, will be determined by a random-effects logistic regression model. Both intention-to-treat and per-protocol analyses are planned, and stratified analyses are planned for severe CAP and non-severe CAP according to CURB-65 and PSI scores. The effect on length of hospitalization and length of intravenous treatment will be determined by a random-effects linear regression model. Alternative approaches to the analysis of cluster-randomized trials have been proposed, including cluster-level analysis and hierarchical models, which are discussed elsewhere.[69]

Another consideration in cluster-randomized cross-over trials, like in individual patient cross-over trials, is the so-called carry-over effect: the effect of treatment in one period may continue to have an effect in the next period. If so, a wash-out period should be implemented, which should be sufficiently long to eliminate the carry-over effect. Further testing for and analytical control of carry-over effects is debatable, since the power to find a carry-over effect is often limited.[70] Since in our trial the treatment of

one patient does not affect the outcome of others, carry-over effects will not be present. Therefore, no wash-out period is used and the analysis will not take carry-over effects into account.

As mentioned before, different mechanisms may lead to incomparability of the treatment groups. Therefore, analytical control of potential confounders is deemed necessary in cluster-randomized trials. Unlike in observational studies, selection of potential confounders is not based on an expected association with treatment allocation, because this association, if present, will be the result of mere chance in a cluster-randomized trial. For this reason, all analyses will be adjusted for known prognostic factors of the outcome. E.g. for mortality, these include age, gender, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment, PSI score, prior admissions in the past year and receipt of immunosuppressive therapy.

POTENTIAL APPLICATIONS OF THIS STUDY DESIGN

A cluster-randomized cross-over trial could be suitable in other areas of acute care medicine. When study treatment has to be started within a short period of time, and cannot be delayed by study procedures, this design may be superior to an RCT. Examples would include any severe infection requiring antimicrobial therapy, comparisons of biomarker guided treatment decisions on the ER, treatment of acute myocardial infarction or stroke, and others. Importantly, the study treatments should be considered equally effective, and they should therefore be registered treatments options.

SUMMARY

This study aims to determine the (cost)-effectiveness of three recommended strategies for empirical treatment of patients with a working diagnosis of CAP admitted to a non-ICU ward. The three strategies are beta-lactam monotherapy, fluoroquinolone monotherapy and combination therapy of a beta-lactam and a macrolide.

The cluster-randomized design of the study overcomes potential effects of confounding by indication and of pre-randomisation antibiotic use. Moreover, since the present study will compare empirical antibiotic strategies and patient inclusion is based on a working diagnosis of CAP, the study results will be generalizable to the patients that are eligible for treatment in clinical practice.

Naturally, deviations from protocol are possible (and will be needed) for medical reasons. All patients will be included in the intention-to-treat analysis, allowing the comparison of the different treatment strategies as they would be implemented in

clinical practice. However, true protocol violations (non-adherence without medical reason) are a threat to the study validity, and will, therefore, be monitored closely. Reasons for deviation will be recorded in the final study results and it is aimed to have less than 10% protocol deviations without medical reason.

Another important hazard for the validity of a cluster-randomized trial is differences in inclusion rates across study arms. We minimized this risk by using the clinical diagnosis as inclusion criterion, independent of compliance to the study protocol. Still, any differences in inclusion may lead to bias, which has to be dealt with analytically.

In conclusion, a properly executed cluster-randomized cross-over trial will provide a valid evaluation of empirical antibiotic strategies for patients hospitalized with CAP.

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Chapter 7 Antibiotic treatment strategies for community-acquired pneumonia in adults

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ABSTRACT

Background

The choice of empirical antibiotic treatment for patients with clinically suspected community-acquired pneumonia (CAP) who are admitted to non–intensive care unit (ICU) hospital wards is complicated by the limited availability of evidence. We compared strategies of empirical treatment (allowing deviations for medical reasons) with beta-lactam monotherapy, beta-lactam–macrolide combination therapy, or fluoroquinolone monotherapy.

Methods

In a cluster-randomized, crossover trial with strategies rotated in 4-month periods, we tested the noninferiority of the beta-lactam strategy to the beta-lactam–macrolide and fluoroquinolone strategies with respect to 90-day mortality, in an intention- to-treat analysis, using a noninferiority margin of 3 percentage points and a two-sided 90% confidence interval.

Results

A total of 656 patients were included during the beta-lactam strategy periods, 739 during the beta-lactam–macrolide strategy periods, and 888 during the fluoroquinolone strategy periods, with rates of adherence to the strategy of 93.0%, 88.0%, and 92.7%, respectively. The median age of the patients was 70 years. The crude 90-day mortality was 9.0% (59 patients), 11.1% (82 patients), and 8.8% (78 patients), respectively, during these strategy periods. In the intention-to-treat analysis, the risk of death was higher by 1.9 percentage points (90% confidence interval [CI], −0.6 to 4.4) with the betalactam– macrolide strategy than with the beta-lactam strategy and lower by 0.6 percentage points (90% CI, −2.8 to 1.9) with the fluoroquinolone strategy than with the beta-lactam strategy. These results indicated noninferiority of the beta-lactam strategy. The median length of hospital stay was 6 days for all strategies, and the median time to starting oral treatment was 3 days (interquartile range, 0 to 4) with the fluoroquinolone strategy and 4 days (interquartile range, 3 to 5) with the other strategies.

Conclusions

Among patients with clinically suspected CAP admitted to non-ICU wards, a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies with a beta-lactam–macrolide combination or fluoroquinolone monotherapy with regard to 90-day mortality. (Funded by the Netherlands Organization for Health Research and Development; CAP-START ClinicalTrials.gov number, NCT01660204.)

Community-acquired pneumonia (CAP) is a leading cause of hospitalization and death worldwide.[1-3] Most guidelines recommend that antibiotic treatment be based on the severity of disease at presentation, assessed either on the basis of the level of care needed or on the basis of a prognostic risk score.[4-6] For patients with clinically suspected CAP who are admitted to a non–intensive-care-unit (ICU) ward, guidelines recommend either combination therapy with a beta-lactam plus a macrolide or plus ciprofloxacin or monotherapy with moxifloxacin or levofloxacin for empirical treatment. These guidelines have increased the use of macrolides and fluoroquinolones, although these antibiotic classes have been associated with increased development of resistance.[7,8] The evidence in support of these recommendations is limited.[9-13] The recommendation to add a macrolide to a beta-lactam is based on observational studies, which are prone to confounding by indication.[14] Although fluoroquinolones have been evaluated in randomized, controlled trials, their superiority over betalactam monotherapy has not been shown.[15,16] Moreover, the results of randomized, controlled trials may be affected by in-hospital antibiotic exposure that occurs before randomization[17,18] and often have restrictive inclusion criteria, which limit the generalizability of their results to daily practice.

We therefore assessed whether a strategy of preferred empirical treatment with beta-lactam monotherapy is noninferior to either preferred beta-lactam–macrolide combination therapy or preferred fluoroquinolone monotherapy, with regard to 90-day all-cause mortality among adults with clinically suspected CAP who are admitted to non-ICU wards. These strategies allowed for deviation from the assigned antibiotic therapy for medical reasons, so as not to compromise care. We performed a pragmatic, cluster-randomized, crossover trial to overcome confounding by indication and the effects of prerandomization antibiotic therapy.

METHODS

Study Design and Oversight

The Community-Acquired Pneumonia — Study on the Initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START) was performed in seven hospitals in the Netherlands, from February 2011 through August 2013 (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The design and rationale of the study have been described elsewhere,[18] and the data are reported in accordance with Consolidated Standards of Reporting Trials (CONSORT) statements for cluster-randomized and noninferiority studies.[19,20] Additional study details are provided in the study protocol and statistical analysis plan, which are available at NEJM.org. The study protocol was approved by the ethics review board at the University Medical

Center Utrecht (reference number 10/148), by the local institutional review boards, and by the antibiotic committee at each participating hospital.

Eligibility and Recruitment of Patients

Patients 18 years of age or older with clinically suspected CAP who required antibiotic treatment and hospitalization in a non-ICU ward were eligible for the study (Table 1). Patients with cystic fibrosis were not eligible. Hospital G (see the Supplementary Appendix) included only patients with a CURB-65 score greater than 2 (the CURB-65 score is calculated by assigning 1 point each for confusion, uremia [blood urea nitrogen ≥20 mg per deciliter], high respiratory rate [≥30 breaths per minute], low systolic blood pressure [<90 mm Hg] or diastolic blood pressure [≤60 mm Hg], and an age of 65 years or older, with a higher score indicating a higher risk of death within 30 days).[21] We used on-site training of research nurses throughout the study to ensure the standardization of case definitions.

Table 1 - Definitions

Case definitions

Community-acquired pneumonia (CAP) (working diagnosis): The presence of at least two of the diagnostic clinical criteria and in-hospital treatment with antibiotics for clinically suspected CAP as documented by the treating physician. Patients with two or more criteria and an obvious nonrespiratory source of infection were not considered to have a working diagnosis of CAP, nor were patients who had recently been hospitalized (for >48 hours in the previous 2 weeks) or who resided in long-term care facilities.

Radiologically confirmed CAP: A working diagnosis of CAP plus the presence of a new or increased infiltrate on chest radiography or computed tomography (CT) and at least two other clinical criteria.

Diagnostic clinical criteria

- Cough
- Production of purulent sputum or a change in the character of sputum
- Temperature >38°C or <36.1°C
- Auscultatory findings consistent with pneumonia, including rales, evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony), or both
- Leukocytosis (>10×109 white cells per liter or >15% bands)
- C-reactive protein level more than 3 times the upper limit of the normal range
- Dyspnea, tachypnea, or hypoxemia
- New or increased infiltrate on chest radiography or CT scan

Intervention strategies*

Beta-lactam strategy: Preferred empirical treatment with amoxicillin, amoxicillin plus clavulanate, or a third-generation cephalosporin. Penicillin was not allowed as empirical beta-lactam monotherapy.

Beta-lactam–macrolide strategy: Preferred empirical treatment with penicillin, amoxicillin, amoxicillin plus clavulanate, or a third-generation cephalosporin in combination with azithromycin, erythromycin, or clarithromycin

Fluoroquinolone strategy: Preferred empirical treatment with moxifloxacin or levofloxacin

* Strategies were based on the recommendations in the Dutch guideline on treatment of CAP that was available before the start of the study.[23]

Emergency department registries were screened daily for eligible patients by research nurses or physicians. Obtaining informed consent before intervention was deemed unnecessary, because patients did not undergo randomization individually, and all the antibiotics we studied are used in current practice.[22] Written informed consent obtained within 72 hours after admission was required for data collection.

Intervention

During consecutive periods of 4 months, beta-lactam monotherapy, beta-lactam with a macrolide, or fluoroquinolone monotherapy was used as the preferred empirical treatment for eligible patients. The order of strategies was randomized separately in each hospital, without washout periods. Patients were treated and assessed in accordance with the strategy that was applicable on the admission date. Clinicians were repeatedly informed of the current antibiotic strategy by local investigators and with the use of newsletters and presentations.

The antibiotics allowed during each treatment strategy period (Table 1) were based on the 2005 Dutch guideline.[23] Physicians were encouraged to apply the assigned treatment strategies for the full treatment of patients with suspected CAP, unless there were medical reasons not to, such as adverse events or de-escalation of antibiotic treatment (e.g., because of a switch to targeted treatment when a causative pathogen had been identified). Adherence to the strategy was defined as treatment in accordance with the assigned strategy or deviation from the strategy for medical reasons (i.e., motivated deviation), irrespective of subsequent switches of antibiotic treatment to a nonassigned antibiotic. Adherence to the antibiotic was defined as initial treatment with the assigned antibiotic, irrespective of subsequent switches of antibiotic treatment to a nonassigned antibiotic.

Randomization

Computer-generated randomization was performed in blocks of six, each containing a sequence of the three antibiotic strategies. Hospitals were assigned to their sequence after approval of the study by the hospital antibiotic committee. Two hospitals that had closely collaborating medical staff were randomized as one cluster. All the hospitals planned to participate until the calculated sample size was met or for a maximum of 2 years (Supplementary Appendix Figure S1).

Outcomes

The primary outcome was all-cause mortality within 90 days after admission. The secondary outcomes were the time to starting oral treatment, length of hospital stay, and occurrence of minor or major complications during the hospital stay. All outcomes were measured at the individual patient level.

Data Collection

Data on clinical presentation, laboratory and microbiologic test results, the antibiotic agents used, complications, and clinical outcome were retrieved from medical records. Nonroutine data were recorded by research nurses directly after the patient's inclusion. When the reasons for deviations from the assigned empirical treatment were not clear in the medical chart, research nurses requested information from responsible physicians. The 90-day mortality was determined from the patient record database of each participating hospital or from the municipal personal records database (see the Supplementary Appendix).

Statistical Analysis

Details about the calculation of sample size are provided in the Supplementary Appendix. Analyses were performed in accordance with the intention-to-treat principle, with adjustment for clustering. Differences among the groups in 90-day mortality were assessed with the use of a mixed-effects logistic-regression analysis, including hospitals as a fixed effect and each strategy period per hospital as a random intercept.[24] We estimated absolute risk differences among strategies by averaging the computed individual risks for each treatment group, and confidence intervals were calculated with the use of 2000 bootstrapping samples.[25] Noninferiority was assessed in a one-sided test at a significance level of 0.05 with the use of two-sided 90% confidence intervals.

Differences in the length of hospital stay and the time to starting oral administration of antibiotics were tested with mixed-effects Cox proportional-hazards models.[26] The frequencies of major and minor complications were compared by means of mixed-effects multinomial regression. Post hoc analyses of the strategy-adherent and antibiotic-adherent populations were performed for all outcomes. We performed sensitivity analyses that included only patients with radiologically confirmed CAP (Table 1) and that assessed 30-day mortality instead of 90-day mortality, and we calculated two-sided 95% confidence intervals. Missing data were imputed by multiple imputation,[27] with the exception of data on respiratory rate, heart rate, and confusion at admission; the values for these variables were assumed to be normal when data were missing. The analyses were performed with the use of R software, version 3.0.2 (R Project for Statistical Computing).[28]

RESULTS

Enrollment

A total of 3325 patients were eligible for inclusion in the study, and 2283 (69%) gave consent. The median age of the patients was 70 years (interquartile range, 59 to 79). Among the patients who were not included, the median age was 74 years (interquartile range, 63 to 83) during the betalactam strategy periods, 74 years (interquartile range,

61 to 82) during the beta-lactam–macrolide strategy periods, and 74 years (interquartile range, 61 to 83) during the fluoroquinolone strategy periods, and the reasons for noninclusion were similar across strategies (Figure 1). The baseline characteristics of included patients were similar among strategy periods, and blood and sputum cultures and urinary antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed with similar frequency (Table 2). The microbial causes of CAP were similar in the three treatment groups. *S. pneumoniae* was the pathogen detected most frequently (in 15.9% of patients), followed by *Haemophilus influenzae* (in 6.8%); atypical pathogens were found in 2.1% of the patients (Supplementary Appendix Table S1). Resistance to the initiated antibiotic treatment was highest with the beta-lactam strategy (Supplementary Appendix Table S2).

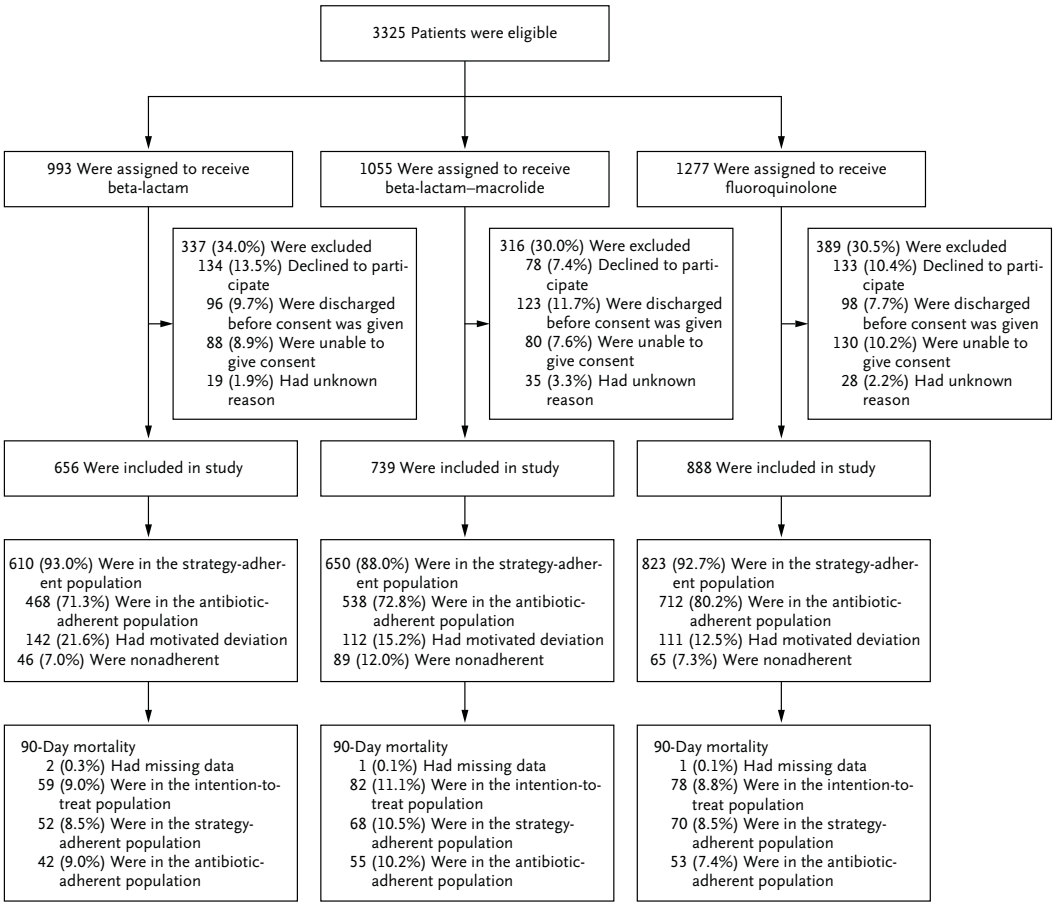

Figure 1 - Inclusion of Patients, Rates of Adherence, and Mortality.

The strategy-adherent population was the population that underwent treatment in accordance with the assigned strategy or had deviation from the strategy for medical reasons (i.e., motivated deviation), irrespective of subsequent switches of antibiotic treatment to a nonassigned antibiotic; the antibiotic-adherent population was the population that underwent initial treatment with the assigned antibiotic, irrespective of subsequent switches of antibiotic treatment to a nonassigned antibiotic.

Table 2 - Baseline Characteristics of Patients in the Intention-to-Treat Population

	Antibiotic treatment strategy		
Characteristic	**Beta-lactam (N=656)**	**Beta-lactam–macrolide (N=739)**	**Fluoroquinolone (N=888)**
Median age (IQR) — yr *	70 (60–79)	70 (59–80)	71 (59–79)
Male sex — no. (%)	381 (58.1%)	431 (58.3%)	505 (56.9%)
Median duration of symptoms (IQR) — days	3 (1-7)	3 (1-7)	3 (1-7)
Received antibiotics before admission — no./total no. (%)	219/637 (34.4%)	227/721 (31.5%)	303/873 (34.7%)
Current smoker — no./total no. (%)	109/627 (17.4%)	154/723 (21.3%)	196/872 (22.5%)
Past smoker — no./total no. (%)	379/627 (60.4%)	398/723 (55.0%)	490/872 (56.2%)
Received influenza vaccination — no./total no. (%)	453/624 (72.6%)	466/700 (66.6%)	572/847 (67.5%)
Received Pneumococcal vaccination			
PPSV23 — no./total no. (%)	16/594 (2.7%)	18/671 (2.7%)	13/822 (1.6%)
PCV13 — no./total no. (%)	19/656 (2.9%)	7/739 (0.9%)	10/888 (1.1%)
Dependency in ADL — no./total no. (%)	199/637 (31.2%)	200/714 (28.0%)	257/870 (29.5%)
Had one or more hospital stays in the previous year — no./total no. (%)	271/653 (41.5%)	298/722 (41.3%)	351/881 (39.8%)
Had coexisting condition — no. (%)			
Cardiovascular disease	153 (23.3%)	154 (20.8%)	172 (19.4%)
COPD or Asthma	260 (39.6%)	281 (38.0%)	377 (42.5%)
Other chronic pulmonary diseases	64 (9.8%)	97 (13.1%)	61 (6.9%)
Diabetes mellitus	118 (18.0%)	101 (13.7%)	161 (18.1%)
Cancer ‡	106 (16.2%)	124 (16.8%)	151 (17.0%)
HIV/AIDS	3 (0.5%)	6 (0.8%)	6 (0.7%)
Chronic renal failure or nephrotic syndrome	10 (1.5%)	14 (1.9%)	7 (0.8%)
Receiving immunosuppressive therapy — no. (%)	59 (9.0%)	57 (7.7%)	93 (10.5%)
Underwent organ or bone marrow transplantation — no. (%)	19 (2.9%)	24 (3.2%)	29 (3.3%)
PSI score §¶	84.6 ± 29.0	84.8 ± 27.8	85.4 ± 28.5
Median CURB-65 score (interquartile range) §‖	1 (1-2)	1 (1-2)	1 (1-2)
Proven CAP	506 (77.1%)	566 (76.6%)	665 (74.9%)
Blood culture taken	508 (77.4%)	559 (75.6%)	670 (75.5%)
Sputum culture taken	306 (46.6%)	347 (47.0%)	390 (43.9%)
PUAT performed	504 (76.8%)	582 (78.8%)	711 (80.1%)
LUAT performed	492 (75.0%)	574 (77.7%)	668 (75.2%)

Table 2 legend (facing page) - Plus–minus values are means ±SD. ADL denotes activities of daily living, COPD chronic obstructive pulmonary disease, LUAT legionella urinary antigen test, PCV13 13-valent pneumococcal conjugate vaccine (received in the Community Acquired Pneumonia Immunization Trial in Adults [CAPITA]), PPSV23 23-valent pneumococcal polysaccharide vaccine, PSI Pneumonia Severity Index, and PUAT pneumococcal urinary antigen test.
‡ Active cancer was defined as a solid or hematologic cancer treated with radiotherapy or chemotherapy within the previ- ous 5 years.
§ When data were missing, values were assumed to be normal. A total of 6.3% of data points used to calculate the PSI score had missing values, and 11.3% of data points used to calculate the CURB-65 score had missing values.
¶ The PSI score uses 20 clinical measures to predict risk of death within 30 days, with results ranging from 0.1% (in pa- tients with a score of 0–50) to 27.0% (in patients with a score >131).
‖ The CURB-65 score is calculated by assigning 1 point each for confusion, uremia (blood urea nitrogen ≥20 mg per deci- liter), high respiratory rate (≥30 breaths per minute), low systolic blood pressure (<90 mm Hg) or diastolic blood pres- sure (≤60 mm Hg), and an age of 65 years or older, with a higher score indicating a higher risk of death within 30 days.

Six hospitals completed 6 randomized strategy periods each; enrollment was discontinued in one hospital after 4.5 periods, when the intended number of patients per treatment group had been reached. Changeovers from one treatment strategy period to the next occurred as planned except in one hospital: because of unforeseen fluoroquinolone supply problems, 4 weeks of the first fluoroquinolone period were exchanged with the subsequent beta-lactam–macrolide period (Supplementary Appendix Figure S1).

Strategy Adherence and Antibiotic Use

Rates of adherence to the strategies and to antibiotic treatment are shown in Figure 1. Antibiotic use during each strategy period is summarized in Supplementary Appendix Table S3, and antibiotic adherence is summarized in Supplementary Appendix Figure S3. The number of patients empirically treated with antibiotic coverage for atypical pathogens (i.e., macrolides, fluoroquinolones, and doxycycline) during the betalactam strategy periods was 67% less than the number treated with atypical coverage during the beta-lactam–macrolide strategy periods and 69% less than the number during the fluoroquinolone strategy periods, and the cumulative number of days with atypical coverage was 57% and 62% less, respectively.

Deviations were made for 565 patients (24.8%); a total of 200 of these deviations had no documented medical reason. The most frequent medical reasons for deviation from the beta-lactam strategy were the perceived need to cover atypical pathogens (53 patients, 8.1%), a contraindication to beta-lactams (21 patients, 3.2%), and a recent start of treatment with another antibiotic class or a lack of response to preadmission treatment with beta-lactams (27 patients, 4.1%) (Supplementary Appendix Table S4). Among patients receiving the assigned therapy, switches to other antibiotic classes because of perceived insufficient clinical recovery were made for 41 patients (8.8%) during the beta-lactam strategy periods, for 33 patients (6.1%) during the betalactam–macrolide strategy periods, and for 26 patients (3.7%) during the fluoroquinolone

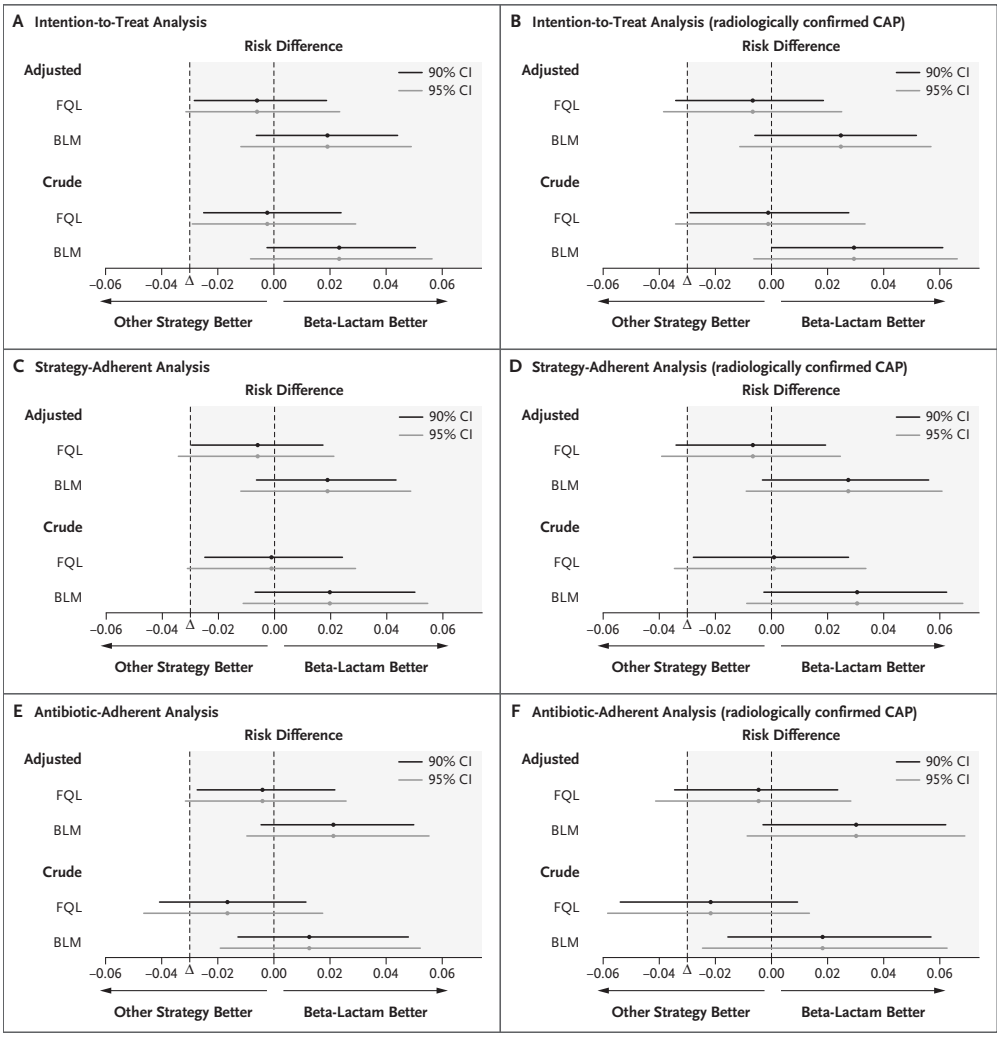

Figure 2 – Noninferiority Plots

The noninferiority plots show crude and adjusted absolute risk differences for 90-day mortality associated with the beta-lactam–macrolide combination and fluoroquinolone monotherapy strategies, as compared with the beta-lactam monotherapy strategy, in analysis of the intention-to-treat population, the strategy-adherent population, and the antibiotic-adherent population, as well as for the sensitivity analysis including only patients with radiologically confirmed community-acquired pneumonia (CAP). To allow for one-sided testing of noninferiority, 90% confidence intervals were calculated (shown in black); 95% confidence intervals are also provided (shown in grey). Confidence intervals within the gray-shaded area are noninferior. The crude analyses take into account cluster-period effects and center effects. The adjusted analyses are additionally corrected for Pneumonia Severity Index score (a score that uses 20 clinical measures, including age and sex, to predict the risk of death within 30 days, with results ranging from 0.1% [in patients with a score of 0–50] to 27.0% [in patients with a score >131]); smoking status; presence of chronic pulmonary diseases, chronic cardiovascular diseases, diabetes mellitus, or immunosuppression; previous treatment with antibiotics; and number of hospitalizations during the previous year. The analysis of the antibioticadherent population is further adjusted for duration of symptoms; dependency in activities of daily living; presence or absence of hematologic cancer, nonhematologic cancer, or immunosuppression; C-reactive protein level; whole-blood leukocyte count; and temperature at hospital admission. The noninferiority margin is −3 percentage points (shown as Δ). The intracluster correlation for cluster-period effects in the primary analysis was 4.5×10−7. Exact numbers are provided in Supplementary Appendix Table S6, and survival curves are shown in Supplementary Appendix Figure S4. BLM denotes beta-lactam–macrolide combination therapy and FQL fluoroquinolone monotherapy.

strategy periods. Other reasons for switching antibiotic classes are provided in Supplementary Appendix Table S5.

Primary Outcome

All-cause mortality at 90 days could not be assessed for four patients; these patients were included only in secondary analyses (Figure 1). The absolute difference in the adjusted risk of death between the beta-lactam strategy and the betalactam–macrolide strategy was 1.9 percentage points (90% confidence interval [CI], −0.6 to 4.4) in favor of the beta-lactam strategy, and the absolute difference between the beta-lactam strategy and the fluoroquinolone strategy was −0.6 percentage points (90% CI, −2.8 to 1.9) in favour of the fluoroquinolone strategy. These confidence intervals do not include the prespecified margin of a 3–percentage-point higher 90-day mortality, thus demonstrating the noninferiority of the beta-lactam strategy to the beta-lactam–macrolide and fluoroquinolone strategies (Figure 2).

In the strategy-adherent and antibiotic-adherent populations, the absolute adjusted risk differences were similar to those in the intention-to-treat population. Similar estimates were obtained in sensitivity analyses of patients with radiologically confirmed CAP and in analyses of 30-day mortality. The two-sided 95% confidence interval for the comparison of the beta-lactam strategy with the fluoroquinolone strategy crossed the noninferiority margin (Figure 2, and Supplementary Appendix Table S6, S7, and S8).

Secondary Outcomes

The median length of hospital stay was 6 days for all strategies, but the upper quartile was higher during the beta-lactam–macrolide strategy periods (Table 3). The median duration of intravenous treatment was 3 days during the fluoroquinolone strategy periods and 4 days during the other strategy periods (Table 3). The proportions of patients whose treatment started with oral antibiotics were 27% during the fluoroquinolone strategy periods, as compared with 13% and 10% during the beta-lactam and beta-lactam–macrolide strategy periods, respectively. There were no significant differences among the three strategies in the incidence of major or minor complications (Table 3).

DISCUSSION

In this pragmatic, cluster-randomized, crossover trial, a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies of treatment with beta-lactam–macrolide combination therapy and with fluoroquinolone monotherapy among patients with suspected CAP who were admitted to non-ICU wards. Moreover, there were no clinically relevant differences among treatment

Table 3 - Effects of antibiotic treatment strategies on secondary outcomes.

Outcome	Antibiotic Treatment Strategy		
	Beta-lactam (N=656)	**Beta-lactam–Macrolide (N=739)**	**Fluoroquinolone (N=888)**
Median length of stay (IQR) — days†	6 (4-8)	6 (4-10)	6 (4-8)
Hazard ratio for discharge alive (95% CI)‡			
Intention-to-treat population			
Crude	*reference*	0.86 (0.77 to 0.96)	1.03 (0.93 to 1.15)
Adjusted	*reference*	0.87 (0.78 to 0.97)	1.04 (0.94 to 1.16)
Strategy adherent population			
Crude	*reference*	0.86 (0.77 to 0.96)	1.03 (0.93 to 1.15)
Adjusted	*reference*	0.86 (0.77 to 0.97)	1.04 (0.93 to 1.16)
Antibiotic adherent population			
Crude	*reference*	0.84 (0.74 to 0.96)	1.04 (0.92 to 1.17)
Adjusted	*reference*	0.84 (0.74 to 0.95)	1.03 (0.92 to 1.17)
Time to starting oral treatment§			
Receipt of oral antibiotics as initial in-hospital therapy — no. (%)	87 (13.3%)	73 (9.9%)	241 (27.1%)
Median time receiving IV antibiotic treatment (IQR) — days	4 (3-5)	4 (3-5)	3 (0-4)
Hazard ratio for starting oral treatment (95% CI)¶			
Intention-to-treat population			
Crude	*reference*	0.95 (0.84 to 1.08)	1.28 (1.13 to 1.44)
Adjusted	*reference*	0.97 (0.86 to 1.09)	1.29 (1.15 to 1.46)
Strategy adherent population			
Crude	*reference*	0.94 (0.82 to 1.07)	1.30 (1.15 to 1.48)
Adjusted	*reference*	0.94 (0.83 to 1.08)	1.33 (1.17 to 1.51)
Antibiotic adherent population			
Crude	*reference*	0.93 (0.78 to 1.10)	1.47 (1.24 to 1.73)
Adjusted	*reference*	0.93 (0.79 to 1.11)	1.52 (1.28 to 1.80)
Complications‖			
None — no. (%)	550 (83.8%)	608 (82.3%)	725 (81.6%)
Minor — no. (%)	72 (11.0%)	97 (13.1%)	109 (12.3%)
Major — no. (%)	32 (4.9%)	42 (5.7%)	47 (5.3%)
Unknown — no. (%)	8 (1.2%)	12 (1.6%)	26 (2.9%)
Odds ratio (95% CI)**			
Intention-to-treat population	*reference*	1.06 (0.76 to 1.48)	1.02 (0.73 to 1.41)
Strategy adherent population	*reference*	1.06 (0.74 to 1.52)	1.03 (0.73 to 1.46)
Antibiotic adherent population	*reference*	1.20 (0.82 to 1.77)	1.03 (0.71 to 1.51)

Table 3 legend (facing page) - Crude analyses take into account cluster-period effects and center effects. Adjusted analyses are additionally corrected for PSI score (including age and sex); smoking status; presence of chronic pulmonary disease, chronic cardiovascular disease, diabetes mellitus, or immunosuppression; previous receipt of antibiotics; and number of hospitalizations in the previous year. IQR denotes interquartile range, and IV intravenous.

† The length of stay was unknown for 5 patients in the beta-lactam strategy group (0.8%), 2 patients in the beta-lactam–macrolide strategy group (0.3%), and 5 patients in the fluoroquinolone strategy group (0.6%), who were transferred to other hospitals.

‡ Hazard ratios are from a Cox proportional-hazards model predicting the day of discharge as the event of interest. A hazard ratio below 1 indicates a longer length of stay. The survival curve is shown in Supplementary Appendix Figure S5.

§ The duration of intravenous treatment was unknown for 1 patient in the fluoroquinolone strategy group (0.1%) who was transferred to another hospital while receiving intravenous treatment.

¶ Hazard ratios are from a Cox proportional-hazards model predicting the end of intravenous treatment or the start of oral treatment as the event of interest. A hazard ratio below 1 indicates a longer duration of intravenous treatment. The survival curve is shown in Supplementary Appendix Figure S6.

‖ Major complications include in-hospital death, respiratory insufficiency, ICU admission, organ failure, and septic shock. A detailed description of complications is provided in Supplementary Appendix Table S9.

** Odds ratios (all crude analyses) are from a mixed-effects ordinal logistic-regression model with no, minor, or major complications as the dependent variable.

strategies in the length of hospital stay or in reported complications. The median time to starting oral treatment was shorter with the fluoroquinolone strategy, mainly because more patients during those strategy periods started with oral empirical treatment at admission, but this did not result in a decreased length of hospital stay.

Our approach differs from those of previous studies in four aspects. First, this study addressed treatment strategies, rather than individual antibiotics, in the treatment of patients hospitalized with a clinical suspicion of CAP. To reflect daily medical practice, we allowed for deviations from the assigned therapy for medical reasons. To minimize confounding, all the patients were included in the intention-to-treat analysis. Although deviations and switches reduced the differences among treatment strategies, empirical atypical coverage was reduced by 67% during the beta-lactam strategy periods as compared with the beta-lactam–macrolide strategy periods and by 69% during the beta-lactam strategy periods as compared with the fluoroquinolone strategy periods. The number of in-hospital days with atypical coverage was also reduced during the beta-lactam strategy periods, by 57% and 62%, respectively. In the post hoc analysis of the strategy-adherent and antibiotic-adherent populations, the beta-lactam strategy remained noninferior to the beta-lactam–macrolide strategy. In the crude analysis of the antibiotic-adherent population, the lower limit of the confidence interval crossed −3 percentage points for the comparison between beta-lactam and fluoroquinolone monotherapy; however, after adjustment for confounders, the lower limit of the confidence interval fell within the defined margins of noninferiority.

Second, we used a cluster-randomized design that allowed for an immediate start of the assigned empirical treatment strategy. The crossover component increased the efficiency of the trial by allowing comparisons of the effect of the strategies within each cluster and ensuring that all hospitals used all three strategies, a design that minimized

the possibility of confounding. Despite the risk of selection bias that is inherent to cluster-randomized studies, the baseline characteristics of the patients were similar among strategies, and statistical adjustment for potential confounders changed the findings only minimally. Differential inclusion of patients across treatment groups was unlikely, given the similar age patterns for nonincluded patients and similar enrollment rates. We were not allowed to collect data on other characteristics of the patients who were not included. The pathogens found were similar among strategy groups, but the resistance of pathogens to the actual treatment was highest during the beta-lactam strategy periods. This did not appear to lead to a worse outcome, possibly because not all were proven causative pathogens and because of antibiotic switches.

Third, all patients for whom the antibiotic strategy might have been used in daily practice were eligible for enrollment, which increases the generalizability of the results. Although this could increase the heterogeneity of the population and the potential for bias toward noninferiority, the effect estimates were similar in the sensitivity analysis that included only patients with radiologically confirmed CAP.

Finally, the primary end point was 90-day all-cause mortality, because CAP is associated with high long-term mortality and this is a patient-relevant outcome that is not susceptible to observation bias.[17,29,30] An unplanned sensitivity analysis with 30-day mortality as the outcome yielded similar results. Among the secondary outcomes, complications, which were extracted from the medical records, might have been misclassified and subject to observation bias.

The noninferiority of the beta-lactam strategy to the beta-lactam–macrolide strategy was apparent in all analyses. These findings, together with the slightly longer length of hospital stay with the latter strategy, reported associations with the development of resistance,[7,8] and possible increased risks of cardiac events,[31,32] indicate that the addition of macrolides for empirical treatment of CAP should be reconsidered. In a recent randomized, controlled trial, the noninferiority of beta-lactam monotherapy to beta-lactam–macrolide combination therapy with respect to clinical stability at day 7 could not be shown, although superiority of the beta-lactam–macrolide combination therapy was not shown, either. Moreover, 30-day and 90-day all-cause mortality and length of hospital stay were similar with the two therapies.[33] Differences between that study and the current study include the strict criteria for eligibility and for switching therapy in cases of clinical deterioration in that study.

Some aspects of our study require explanation. In the noninferiority design, we used one-sided testing with an alpha significance level of 0.05. With 95% confidence intervals — that is, an alpha level of 0.025 — the noninferiority of beta-lactams to

fluoroquinolones was not shown (Figure 2); however, there was no clear trend toward superiority for fluoroquinolones in any of the other adjusted analyses.

Differences in the numbers of eligible patients per strategy resulted from cluster randomization. The beta-lactam and fluoroquinolone strategies were assigned more frequently during the 2011–2012 and 2012–2013 winter seasons, respectively, and more patients were hospitalized during 2012–2013 winter months. However, the proportions of patients included were similar throughout the seasons and among strategies (Figure 1, and Supplementary Appendix Figure S2). Although a low incidence of atypical infections during the 2011–2012 winter season could have favored the beta-lactam strategy, national surveillance data showed a higher incidence of *Mycoplasma pneumoniae* infections, mostly CAP, during that period,[34] for which the beta-lactam strategy might have been less effective. The outbreak of Q fever in the Netherlands ended before the start of the current study,[35] and the distribution of pathogens was similar to those in other studies that have relied on routine microbiologic testing.[36-38]

Regional differences in microbial causes could reduce the generalizability of our findings. However, resistance of S. pneumoniae to penicillin,[39] which rarely occurs in the Netherlands, is unlikely to influence the outcome in patients with pneumonia treated with beta-lactam antibiotics.[40] The prevalence of S. pneumoniae resistance to macrolides was 4.2% in the Netherlands in 2011.[39] The incidence of legionella in this study was less than 1%. A higher incidence could influence the effectiveness of empirical treatment with beta-lactam monotherapy, which stresses the importance of rapid testing in patients with risk factors for Legionnaires' disease. In the current study, rapid urinary antigen testing for legionella was performed in 492 patients (75%) during the beta-lactam strategy periods; 5 of the patients (1%) tested positive, 2 of whom received ciprofloxacin empirically because of a high clinical suspicion. For the other 3 patients, antibiotic therapy was adjusted after test results became available. All 5 patients had a good clinical outcome. Higher incidences of community-acquired *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* infections would require the adaptation of all three treatment strategies.

In conclusion, among patients with suspected CAP who were admitted to non-ICU wards, we found that a strategy of preferred empirical treatment with beta-lactam monotherapy that allowed for deviations for medical reasons was noninferior to strategies with beta-lactam–macrolide combination therapy or fluoroquinolone monotherapy in terms of 90-day all-cause mortality. In addition, beta-lactam monotherapy was not associated with a longer length of hospital stay or a higher incidence of complications.

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This article is dedicated to the memory of Reinier Veenhoven, an investigator for this study in Spaarne Hospital and Kennemer Gasthuis, who died in October 2013.

SUPPLEMENTARY APPENDIX

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Supplementary methods

Setting

Of 24 hospitals in the Netherlands that were screened for the trial, seven hospitals agreed to participate. These were two university and five non-university teaching hospitals: University Medical Center Utrecht (hospital A), Spaarne Hospital Hoofddorp (B), Kennemer Gasthuis Haarlem (C), Medical Center Alkmaar (D), Amphia Hospital Breda (E), Diakonessenhuis Utrecht (F) and Amsterdam Medical Center (G). Starting dates of each hospital can be found in Figure S1.

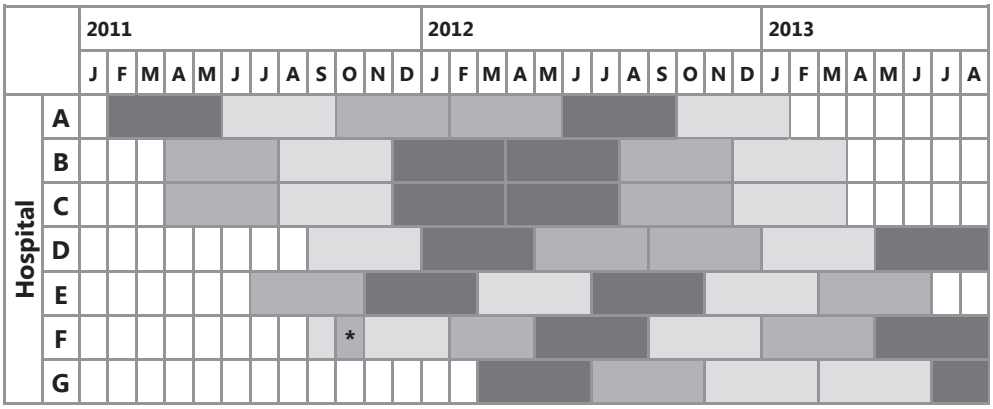
Sample size calculation

The study was designed to demonstrate non-inferiority of beta-lactam monotherapy on day-90 mortality in intention to treat. Based on an expected mortality rate of 5%,(19) with an absolute non-inferiority margin of 3%, one-sided alpha of 0.05 and power of 0.80, 650 patients were needed per study arm. Accounting for possible drop-outs, we aimed to include 700 patients in each study arm. Since we used a cross-over design and we did not expect large differences in care-practices between hospitals, the intra-cluster correlation for cluster-period effects was expected to be negligible, but was planned to be determined during the analysis.(20)

Primary outcome assessment

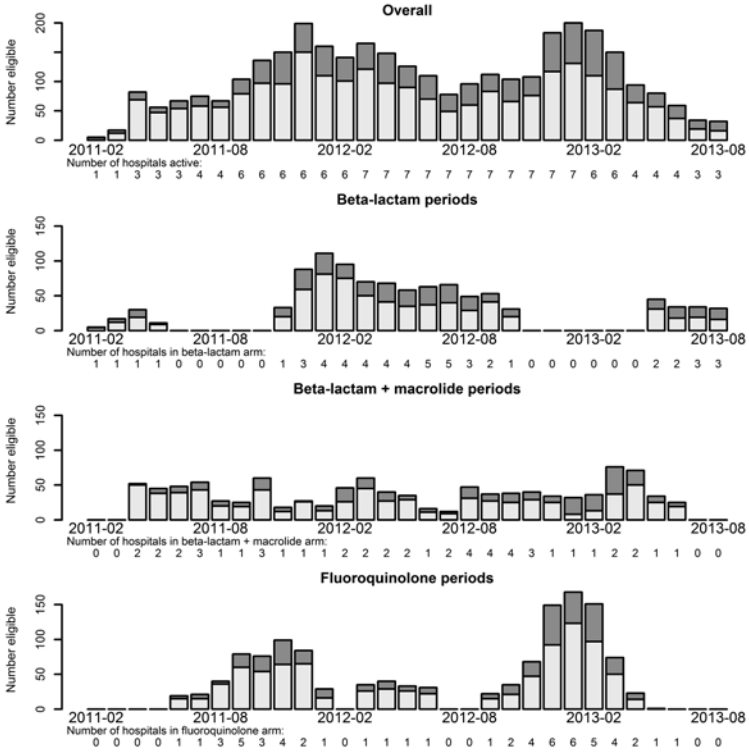
Mortality status at day 90 was recorded from the medical charts in patients that died in-hospital, and patients that had visited the hospital after day 90 (e.g. in an out-patient clinic). The status of all other patients, except in one hospital, were checked electronically in the municipal personal records database, which is based on the citizen service number, date of birth and name. In the one hospital without electronic access to this database, research nurses contacted the general practitioner of each patient with an unknown status. In the Netherlands, every inhabitant is registered with a single general practitioner, who is routinely informed about important medical affairs. We were unable to assess mortality status in 4 patients because they were not Dutch residents.

Figure S1 - Randomization chart



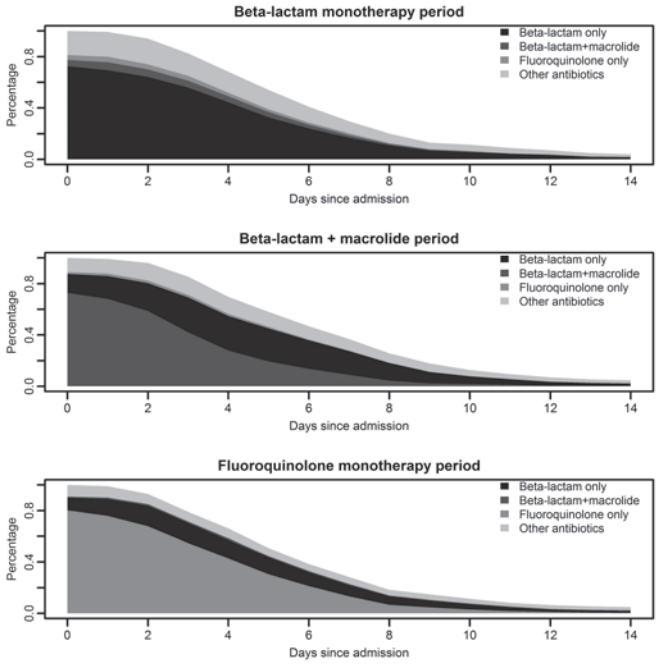
* due to supply problems of fluoroquinolones in hospital F, four weeks of the first fluoroquinolone monotherapy period were exchanged with the subsequent beta-lactam/ macrolide combination period

Figure S2 - Eligible and included patients per month per treatment arm.



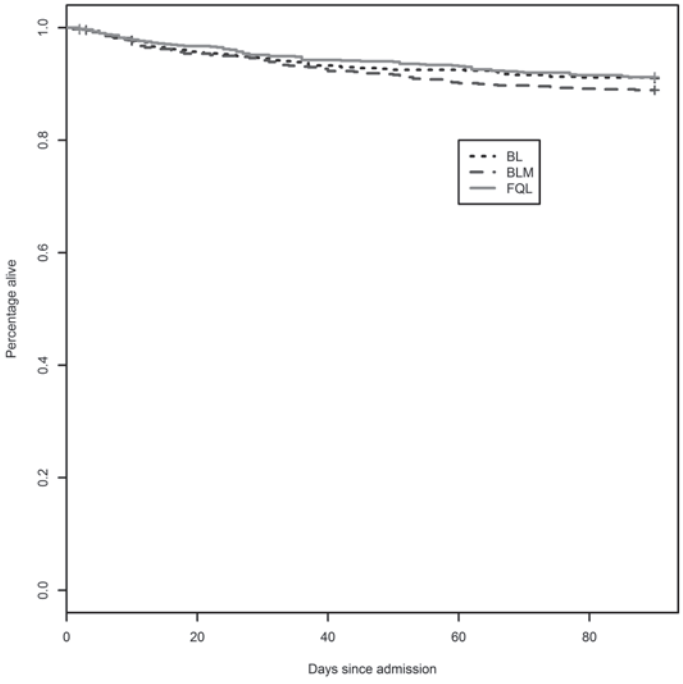
Light gray bars represent number of included patients. Dark gray bars represent number of eligible non-included patients.

Figure S3 - Antibiotic pattern during admission



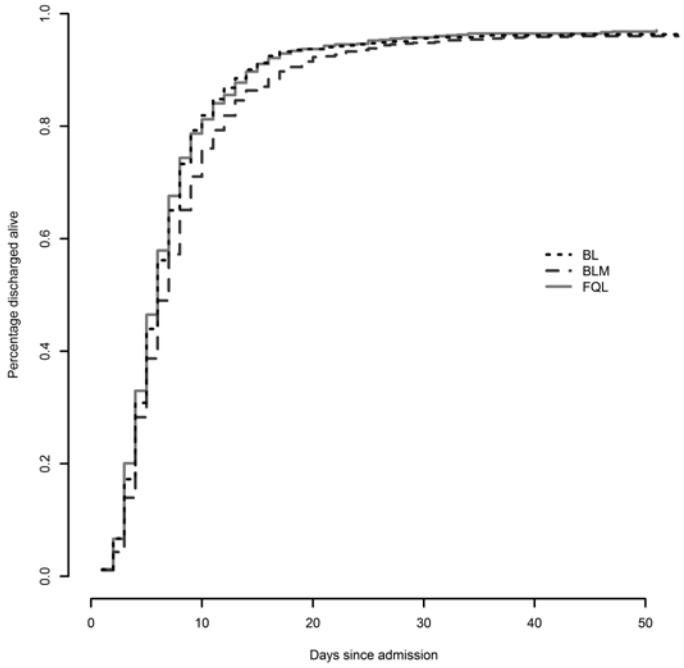
The daily proportion of patients receiving in-hospital treatment with a certain class or combination of antibiotics is plotted for the three treatment strategies.

Figure S4 - Survival curve



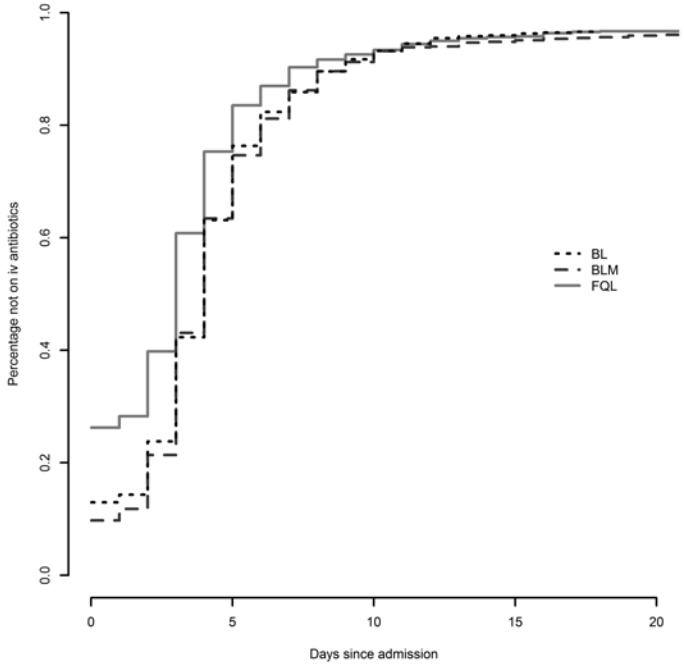
Survival curve for the three treatment strategies. Four patients (2 in the beta-lactam, 1 in the beta-lactam macrolide and 1 in the fluoroquinolone strategy) that were discharge alive, but for whom no day 90 mortality status is known, are censored at time of discharge. BL: beta-lactam monotherapy; BLM: beta-lactam / macrolide combination therapy; FQL: fluoroquinolone monotherapy.

Figure S5 - Time to discharge alive



Cumulative percentage of patients discharge alive per treatment strategy. BL: beta-lactam monotherapy; BLM: beta-lactam / macrolide combination therapy; FQL: fluoroquinolone monotherapy.

Figure S6 - Time to oral treatment



Cumulative percentage of patients that either started with oral treatment, or switched from iv treatment to oral treatment, or stopped iv treatment for reason other than death. BL: beta-lactam monotherapy; BLM: beta-lactam / macrolide combination therapy; FQL: fluoroquinolone monotherapy.

Table S1 - Causative pathogens in patients with radiologically confirmed CAP

	Beta-lactam strategy		Beta-lactam / macrolide strategy		Fluoroquinolone strategy	
	Proven	**Possible**	**Proven**	**Possible**	**Proven**	**Possible**
Streptococcus pneumoniae	60 (11.9%)	15 (3.0%)	76 (13.4%)	16 (2.8%)	93 (14.0%)	17 (2.6%)
Staphylococcus aureus	2 (0.4%)	16 (3.2%)	2 (0.4%)	17 (3.0%)	4 (0.6%)	16 (2.4%)
Other gram-positives	1 (0.2%)	4 (0.8%)	2 (0.4%)	4 (0.7%)	6 (0.9%)	3 (0.5%)
Haemophilus influenzae	1 (0.2%)	33 (6.5%)	3 (0.5%)	40 (7.1%)	2 (0.3%)	39 (5.9%)
Moraxella catarrhalis	-	6 (1.2%)	-	11 (1.9%)	-	7 (1.1%)
Escherichia coli	1 (0.2%)	15 (3.0%)	5 (0.9%)	17 (3.0%)	3 (0.5%)	8 (1.2%)
Klebsiella pneumoniae	-	4 (0.8%)	1 (0.2%)	5 (0.9%)	-	5 (0.8%)
Pseudomonas aeruginosa	-	11 (2.2%)	-	19 (3.4%)	-	7 (1.1%)
Other gram-negatives	2 (0.4%)	26 (5.1%)	2 (0.4%)	35 (6.2%)	4 (0.6%)	16 (2.4%)
Legionella pneumophila	6 (1.2%)	-	7 (1.2%)	-	2 (0.3%)	1 (0.2%)
Mycoplasma pneumoniae	-	7 (1.4%)	-	2 (0.4%)	-	12 (1.8%)
Coxiella burnetti	-	-	-	1 (0.2%)	-	-
Mycobacteria	-	1 (0.2%)	-	1 (0.2%)	-	-
Virusses	-	10 (2.0%)	-	15 (2.7%)	-	19 (2.9%)
Fungi / yeast	1 (0.2%)	9 (1.8%)	-	11 (1.9%)	-	12 (1.8%)
No Pathogen	-	323 (63.8%)	-	343 (60.6%)	-	437 (65.7%)

Proven pathogens: based on pathogens detected in blood cultures, pleural fluid cultures, and urinary antigen tests (BINAX Now for S. pneumoniae and L. pneumophila). Possible pathogens: based on pathogens detected in sputum cultures, bronchoalveolar lavage fluid cultures, and serology.
Candida species cultured from sputum and common skin contaminants from blood cultures where antibiotic treatment was not changed, were considered as contamination. BL: beta-lactam monotherapy; BLM: beta-lactam / macrolide combination therapy; FQL: fluoroquinolone monotherapy.

Table S2 - Antimicrobial resistance patterns of most common proven and probable pathogens

Pathogen	Number of isolates	Penicillins	Amoxicillin	Amoxicillin / clavulanate	2nd/3rd gen. cephalosporins	Macrolides	Levofloxacin or moxifloxacin
Streptococcus pneumoniae	168	2/157 (1.3%) 11 unk	2/118 (1.7%) 50 unk	0/99 (0.0%) 69 unk	0/71 (0.0%) 97 unk	7/145 (4.8%) 23 unk	0/31 (0.0%) 137 unk
Staphylococcus aureus	62	37/52 (71.2%) 10 unk	8/9 (88.9%) 53 unk	0/13 (0.0%) 49 unk	0/14 (0.0%) 48 unk	6/57 (10.5%) 5 unk	3/34 (8.8%) 28 unk
Haemophilus influenzae	122	37/39 (94.9%) 83 unk	13/87 (14.9%) 35 unk	6/117 (5.1%) 5 unk	1/104 (1.0%) 18 unk	47/92 (51.1%) 30 unk	0/2 (0.0%) 120 unk
Moraxella catarrhalis	24	14/15 (93.3%) 9 unk	15/21 (71.4%) 3 unk	2/24 (8.3%) 0 unk	3/18 (16.7%) 6 unk	10/24 (41.7%) 0 unk	0/1 (0.0%) 23 unk
Klebsiella pneumoniae / Escherichia coli	64	-	50/63 (79.4%) 1 unk	23/64 (35.9%) 0 unk	6/64 (9.4%) 0 unk	-	6/20 (30.0%) 44 unk
Pseudomonas aeruginosa	37	-	5/5 (100.0%) 32 unk	15/16 (93.8%) 21 unk	16/22 (72.7%) 15 unk	-	1/6 (16.7%)* 31 unk

* P. aeruginosa is intrinsically resistant to moxifloxacin and was tested only for levofloxacin

Table S3 - Antibiotics received as initial treatment and during hospitalization

	As initial therapy			During hospitalization		
	BL (n=656)	**BLM (n=739)**	**FQL (n=888)**	**BL (n=656)**	**BLM (n=739)**	**FQL (n=888)**
Beta-lactams						
Amoxicillin	201 (30.6%)	113 (15.3%)	40 (4.5%)	229 (34.9%)	221 (29.9%)	105 (11.8%)
Amoxicillin/clavulanate	280 (42.7%)	246 (33.3%)	84 (9.5%)	330 (50.3%)	354 (47.9%)	127 (14.3%)
Ceftriaxone	109 (16.6%)	118 (16.0%)	41 (4.6%)	120 (18.3%)	142 (19.2%)	63 (7.1%)
Cefuroxime	23 (3.5%)	115 (15.6%)	7 (0.8%)	27 (4.1%)	121 (16.4%)	15 (1.7%)
Cefotaxime	2 (0.3%)	3 (0.4%)	1 (0.1%)	3 (0.5%)	5 (0.7%)	4 (0.5%)
Ceftazidime	7 (1.1%)	15 (2.0%)	12 (1.4%)	13 (2.0%)	21 (2.8%)	15 (1.7%)
Penicillin *	14 (2.1%)	166 (22.5%)	22 (2.5%)	20 (3.0%)	175 (23.7%)	39 (4.4%)
Macrolides						
Azithromycin	13 (2.0%)	140 (18.9%)	7 (0.8%)	26 (4.0%)	176 (23.8%)	17 (1.9%)
Clarithromycin	34 (5.2%)	199 (26.9%)	7 (0.8%)	43 (6.6%)	212 (28.7%)	11 (1.2%)
Erythromycin	21 (3.2%)	261 (35.3%)	5 (0.6%)	25 (3.8%)	263 (35.6%)	10 (1.1%)
Fluoroquinolones						
Moxifloxacin	30 (4.6%)	15 (2.0%)	528 (59.5%)	40 (6.1%)	26 (3.5%)	541 (60.9%)
Levofloxacin	2 (0.3%)	3 (0.4%)	204 (23.0%)	4 (0.6%)	3 (0.4%)	206 (23.2%)
Ciprofloxacin *	85 (13.0%)	44 (6.0%)	25 (2.8%)	129 (19.7%)	79 (10.7%)	47 (5.3%)
Others	48 (7.3%)	43 (5.8%)	51 (5.7%)	89 (13.6%)	93 (12.6%)	98 (11.0%)
Atypical coverage#						
Any atypical coverage	176 (26.8%)	601 (81.3%)	770 (86.7%)	254 (38.7%)	618 (83.6%)	796 (89.6%)
Total in-hospital days	-	-	-	1,131	2,958	3,991
Average in-hospital days (any atypical coverage)	-	-	-	4.5	4.8	5.0
Average in-hospital days (total cohort)	-	-	-	1.7	4.0	4.5

Data given as number (percentage) per study arm. * Penicillin and ciprofloxacin were not allowed as preferred initial treatment in beta-lactam and fluoroquinolone monotherapy periods respectively. # Atypical coverage includes macrolides, fluoroquinolones and doxycycline. In hospital days represent number of days during hospitalization with at least one atypical antibiotic prescribed. BL: beta-lactam strategy; BLM: beta-lactam / macrolide strategy; FQL: fluoroquinolone strategy. Antibiotic adherence throughout the admission is visualized in Figure S3.

Table S4 - Strategy adherence and reasons for deviation

	BL (n=656)	BLM (n=739)	FQL (n=888)
Non-adherence	46 (7.0%)	89 (12.0%)	65 (7.3%)
Strategy adherence	610 (93.0%)	650 (88.0%)	823 (92.7%)
Received preferred strategy	468 (71.3%)	538 (72.8%)	712 (80.2%)
Strategy adherent deviations			
Suspected pathogen	56 (8.5%)	11 (1.5%)	11 (1.2%)
Suspected atypical CAP	53 (8.1%)	2 (0.3%)	0 (0.0%)
Other pathogen	3 (0.5%)	9 (1.2%)	11 (1.2%)
Relating to pre-hospital antibiotics	27 (4.1%)	27 (3.7%)	23 (2.6%)
Continuation pre-hospital antibiotics	6 (0.9%)	13 (1.8%)	21 (2.4%)
Failure pre-hospital antibiotics	21 (3.2%)	14 (1.9%)	2 (0.2%)
Contraindication	21 (3.2%)	29 (3.9%)	25 (2.8%)
Known colonization	17 (2.6%)	26 (3.5%)	23 (2.6%)
Other reasons*	22 (3.4%)	22 (3.0%)	31 (3.5%)

* Other reasons include: concomitant infection, aspiration, diagnostic uncertainty, recent pneumonia, recent admission, based on medical history, possible ICU indication. BL: beta-lactam strategy; BLM: beta-lactam / macrolide strategy; FQL: fluoroquinolone strategy.

Table S5 - Reasons for switch to a different antibiotic class in the antibiotic adherent population

	BL (n=468)	BLM (n=538)	FQL (n=712)
Proven pathogen	19 (4.1%)	72 (13.4%)	86 (12.1%)
De-escalation to BL	NA	40 (7.4%)	65 (9.1%)
Insufficient clinical	41 (8.8%)	33 (6.1%)	26 (3.7%)
recovery Adverse effect	8 (1.7%)	39 (7.2%)	21 (2.9%)
Other infection	7 (1.5%)	10 (1.9%)	10 (1.4%)
Unknown	12 (2.6%)	16 (3.0%)	13 (1.8%)

Only switches to other antibiotic classes were defined as treatment switches. De-escalation of beta-lactam/macrolide combination to beta-lactam monotherapy based on clinical recovery after at least 2 treatment days, was not considered as a treatment switch since macrolides are often given as short course treatment. BL: beta-lactam strategy; BLM: beta-lactam / macrolide strategy; FQL: fluoroquinolone strategy.

Table S6 - Risk differences and 90% confidence intervals of 90-day mortality as compared to the beta-lactam strategy

	N	Beta-lactam/macrolide strategy	Fluoroquinolone strategy
All cases			
Intention-to-treat (crude)	2,279	2.3% (-0.2%;5.0%)	-0.2% (-2.5%;2.4%)
Intention-to-treat (adjusted)	2,279	1.9% (-0.6%;4.4%)	-0.6% (-2.8%;1.9%)
Strategy adherent (crude)	2,083	2.0% (-0.7%;5.0%)	-0.1% (-2.5%;2.4%)
Strategy adherent (adjusted)	2,083	1.9% (-0.6%;4.3%)	-0.6% (-3.0%;1.7%)
Antibiotic adherent (crude)	1,717	1.3% (-1.3%;4.8%)	-1.7% (-4.1%;1.1%)
Antibiotic adherent (adjusted)	1,717	2.1% (-0.5%;5.0%)	-0.4% (-2.7%;2.2%)
Radiologically confirmed CAP			
Intention-to-treat (crude)	1,733	2.9% (0.0%;6.1%)	-0.1% (-2.9%;2.8%)
Intention-to-treat (adjusted)	1,733	2.5% (-0.6%;5.2%)	-0.7% (-3.4%;1.8%)
Strategy adherent (crude)	1,591	3.1% (-0.3%;6.2%)	0.1% (-2.7%;2.7%)
Strategy adherent (adjusted)	1,591	2.7% (-0.3%;5.6%)	-0.7% (-3.4%;1.9%)
Antibiotic adherent (crude)	1,309	1.8% (-1.6%;5.7%)	-2.2% (-5.4%;0.9%)
Antibiotic adherent (adjusted)	1,309	3.0% (-0.3%;6.2%)	-0.5% (-3.5%;2.4%)

Positive numbers indicate higher mortality in the comparative strategy, compared to the beta-lactam monotherapy strategy. Crude analyses take into account cluster-period effects and center effects. Adjusted analyses are additionally corrected for PSI (including age and gender), smoking, chronic pulmonary diseases, chronic cardiovascular diseases, diabetes mellitus, immunosuppression, previous antibiotics and number of hospitalizations in the previous year. The antibiotic adherent analysis is further adjusted for duration of symptoms, dependency in activities of daily living, hematologic malignancy, generalized malignancy, immunosuppression, c-reactive protein level, blood leucocyte count and temperature on admission.

Table S7 - Odds ratios and 95% confidence intervals of 90-day mortality as compared to the beta-lactam strategy

Analysis	N	Beta-lactam/macrolide strategy	Fluoroquinolone strategy
All cases			
Intention-to-treat (crude)	2,279	1.30 (0.91;1.85)	0.97 (0.68;1.39)
Intention-to-treat (adjusted)	2,279	1.28 (0.87;1.88)	0.92 (0.62;1.35)
Strategy adherent (crude)	2,083	1.26 (0.86;1.85)	0.99 (0.68;1.44)
Strategy adherent (adjusted)	2,083	1.29 (0.85;1.95)	0.91 (0.60;1.38)
Antibiotic adherent (crude)	1,717	1.16 (0.76;1.77)	0.80 (0.52;1.23)
Antibiotic adherent (adjusted)	1,717	1.38 (0.84;2.26)	0.93 (0.57;1.52)
Radiologically confirmed CAP			
Intention-to-treat (crude)	1,733	1.37 (0.92;2.05)	0.99 (0.66;1.48)
Intention-to-treat (adjusted)	1,733	1.37 (0.88;2.13)	0.91 (0.58;1.42)
Strategy adherent (crude)	1,591	1.42 (0.92;2.18)	1.01 (0.65;1.57)
Strategy adherent (adjusted)	1,591	1.44 (0.89;2.33)	0.90 (0.55;1.47)
Antibiotic adherent (crude)	1,309	1.22 (0.76;1.96)	0.75 (0.46;1.23)
Antibiotic adherent (adjusted)	1,309	1.58 (0.89;2.79)	0.92 (0.51;1.66)

Crude analyses take into account cluster-period effects and center effects. Adjusted analyses are additionally corrected for PSI (including age and gender), smoking, chronic pulmonary diseases, chronic cardiovascular diseases, diabetes mellitus, immunosuppression, previous antibiotics and number of hospitalizations in previous year. The antibiotic adherent analysis is further adjusted for duration of symptoms, dependency in activities of daily living, hematologic malignancy, generalized malignancy, immunosuppression, c-reactive protein level, blood leucocyte count and temperature on admission. BL: beta-lactam monotherapy. BLM: beta-lactam/macrolide combination therapy. FQL: fluoroquinolone monotherapy. Intra-cluster correlation for cluster-period effects in primary analysis: 4.5×10^{-7}.

Table S8 - Risk differences and 90% confidence intervals of 30-day mortality according to treatment arm

Analysis	N	BLM	FQL
All cases			
Intention-to-treat (crude)	2,279	0.4% (-1.5%;2.3%)	-0.4% (-2.2%;1.6%)
Intention-to-treat (adjusted)	2,279	0.3% (-1.7%;2.1%)	-0.5% (-2.3%;1.5%)
Strategy adherent (crude)	2,083	-0.1% (-2.0%;2.1%)	-0.5% (-2.4%;1.4%)
Strategy adherent (adjusted)	2,083	0.0% (-2.0%;2.0%)	-0.7% (-2.5%;1.1%)
Antibiotic adherent (crude)	1,717	-0.2% (-2.6%;2.3%)	-1.6% (-3.6%;0.6%)
Antibiotic adherent (adjusted)	1,717	-0.1% (-0.5%;5.0%)	-1.2% (-2.8%;2.1%)

Positive numbers indicate higher mortality in the comparative strategy, compared to the beta-lactam monotherapy strategy. Crude analyses take into account cluster-period effects and center effects. Adjusted analyses are additionally corrected for PSI (including age and gender), smoking, chronic pulmonary diseases, chronic cardiovascular diseases, diabetes mellitus, immunosuppression, previous antibiotics and number of hospitalizations in the previous year. The antibiotic adherent analysis is further adjusted for duration of symptoms, dependency in activities of daily living, hematologic malignancy, generalized malignancy, immunosuppression, c-reactive protein level, blood leucocyte count and temperature on admission.

Table S9 - Complications

	BL (n=656)	BLM (n=739)	FQL (n=888)
Major complications	32 (4.9%)	42 (5.7%)	47 (5.3%)
In-hospital mortality	21 (3.2%)	28 (3.8%)	26 (2.9%)
Respiratory insufficiency	18 (2.7%)	11 (1.5%)	18 (2.0%)
ICU admission	18 (2.7%)	12 (1.6%)	14 (1.6%)
Organ failure	5 (0.8%)	2 (0.3%)	9 (1.0%)
Septic shock	4 (0.6%)	3 (0.4%)	3 (0.3%)
Minor complications	72 (11.0%)	97 (13.1%)	109 (12.3%)
Cardiovascular complications	24 (3.7%)	35 (4.7%)	37 (4.2%)
Pleural fluid	13 (2.0%)	18 (2.4%)	22 (2.5%)
Delirium or confusion	15 (2.3%)	12 (1.6%)	24 (2.7%)
Secondary infection	4 (0.6%)	9 (1.2%)	16 (1.8%)
Renal impairment	11 (1.7%)	12 (1.6%)	5 (0.6%)
Empyema	3 (0.5%)	12 (1.6%)	12 (1.4%)
Dysglycaemia	6 (0.9%)	11 (1.5%)	7 (0.8%)
Other complications	6 (0.9%)	9 (1.2%)	4 (0.5%)
No complications	550 (83.8%)	608 (82.3%)	725 (81.6%)
Unknown	8 (1.2%)	12 (1.6%)	26 (2.9%)

Other complications include: splenic infarction, urine retention, psychiatric disorder decompensation, hydronephrosis, seizures, ileus, collapse, icu-acquired weakness / critical illness polyneuropathy, other pulmonary complications. BL: beta-lactam monotherapy; BLM: beta-lactam / macrolide combination therapy; FQL: fluoroquinolone monotherapy.

Table S10 - baseline characteristics of antibiotic adherent populations

	BL (n=468)	BLM (n=538)	FQL (n=712)
Age *	68.8 (14.7)	67.4 (15.7)	66.9 (16.1)
Male gender	275 (58.8%)	316 (58.7%)	396 (55.6%)
Duration of symptoms ^	3 (1;7)	4 (2;7)	4 (2;7)
Antibiotics before admission	122 (27.1%)	144 (27.5%)	232 (33.0%)
Current smoking	86 (19.2%)	118 (22.3%)	164 (23.5%)
Past smoking	274 (61.2%)	288 (54.4%)	382 (54.7%)
Influenza vaccination	328 (74.4%)	341 (66.0%)	453 (66.6%)
Pneumococcal vaccination (PPSV23)	13 (3.1%)	13 (2.6%)	8 (1.2%)
Pneumococcal vaccination (PCV13)	14 (3.0%)	4 (0.7%)	9 (1.3%)
ADL dependency	151 (33.3%)	129 (24.8%)	197 (28.2%)
One or more hospitalizations last year	189 (40.5%)	193 (36.6%)	258 (36.6%)
Cardiovascular disease	117 (25.0%)	105 (19.5%)	139 (19.5%)
COPD or Asthma	188 (40.2%)	206 (38.3%)	292 (41.0%)
Other chronic pulmonary diseases	46 (9.8%)	61 (11.3%)	49 (6.9%)
Diabetes	84 (17.9%)	71 (13.2%)	135 (19.0%)
Malignancy $	83 (17.7%)	81 (15.1%)	111 (15.6%)
HIV/AIDS	2 (0.4%)	4 (0.7%)	6 (0.8%)
Chronic renal failure or nephrotic syndrome	7 (1.5%)	5 (0.9%)	5 (0.7%)
Immunosuppressive therapy	41 (8.8%)	38 (7.1%)	63 (8.8%)
Organ or bone marrow transplantation	10 (2.1%)	15 (2.8%)	18 (2.5%)
PSI score *	85.7 (27.7)	83.5 (27.3)	84.4 (28.6)
CURB-65 score ^	1 (1;2)	1 (0;2)	1 (1;2)
Proven CAP	351 (75.0%)	423 (78.6%)	536 (75.3%)

Data given as N (%), unless otherwise indicated. * normally distributed variable reported as mean (standard deviation). ^ non-normally distributed variable reported as median (inter quartile range). BL: beta-lactam strategy. BLM: beta-lactam/macrolide strategy. FQL: fluoroquinolone strategy. PPSV23: 23-valent pneumococcal polysaccharide vaccine. PCV13: 13-valent pneumococcal conjugate vaccine received in CAPiTA trial. ADL: activities of daily living. $ Active malignancy: treated with radio and/or chemotherapy for solid or hematologic malignancy within the last five years.

Chapter 8 Cost-effectiveness of antibiotic treatment strategies for community-acquired pneumonia

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Manuscript in preparation

ABSTRACT

Objective

To determine the cost-effectiveness of strategies of preferred antibiotic treatment with beta-lactam/macrolide combination or fluoroquinolone monotherapy compared to beta-lactam monotherapy.

Methods

Costs were estimated using resources utilization data from a cluster-randomized cross-over trial of antibiotic treatment strategies, primarily from the reduced third payer perspective (i.e. hospital admission costs). Cost-minimization analysis (CMA) and cost-effectiveness analysis (CEA) were performed using linear mixed models. CMA results were expressed as difference in costs per patient. CEA results were expressed as cost-effectiveness ratios (CER) showing additional costs per prevented death.

Results

A total of 2,283 patients were included. Crude average costs within 90 days from the reduced third payer perspective were €4,294, €4,392, and €4,002 per patient for the beta-lactam monotherapy, beta-lactam/macrolide combination, and fluoroquinolone monotherapy strategy, respectively. CMA results were €106 (95% CI €-697 to €754) for the beta-lactam/macrolide combination strategy and €-278 (95%CI €-991 to €396) for the fluoroquinolone monotherapy strategy, both compared to the beta-lactam monotherapy strategy. The CER was not statistically significantly different between the strategies. Other perspectives yielded similar results.

Conclusion

There were no significant differences in cost-effectiveness of strategies of preferred antibiotic treatment of CAP on non-ICU wards with either beta-lactam monotherapy, beta-lactam/macrolide combination therapy, or fluoroquinolone monotherapy.

INTRODUCTION

Community-acquired pneumonia (CAP) is an important reason for hospitalization worldwide.[1–3] It has been estimated that the total costs associated with CAP amount to approximately 11 billion euros annually in Europe, with approx. 5 billion euros accounting for in-hospital CAP costs.[1] In the Netherlands there are an estimated 25,000-36,000 hospital admissions for CAP each year,[4] with an estimated total costs of about 100 to 144 million euro annually.[5] The intramural costs are mainly determined by the length of hospitalization.[5]

In choosing the optimal antibiotic treatment strategy for CAP, effectiveness, cost-effectiveness and ecological effects of antibiotics should be taken into account. Optimally, this would consist of a strategy associated with the best patient outcome at the lowest price and with least selective pressure for antibiotic resistance. The three treatment strategies most widely used are beta-lactam monotherapy, beta-lactam/macrolide combination therapy, and fluoroquinolone monotherapy. From an ecological perspective beta-lactam monotherapy is preferred over beta-lactam/macrolide combination therapy, and fluoroquinolone monotherapy.[6,7]

In a cluster-randomized cross-over trial of patients hospitalized with CAP to non-ICU wards, a strategy of beta-lactam monotherapy was non-inferior to beta-lactam/macrolide combination therapy, and fluoroquinolone monotherapy in terms of all-cause day-90 mortality (CAP-START study).[8] The quinolone monotherapy strategy was associated with a shorter length of intravenous treatment, but this was not reflected in a statistically significant shorter length of stay. In the current study, we set out to investigate the cost-effectiveness of these different antibiotic strategies by conducting a cost-minimization and a cost-effectiveness analysis from a third payer as well as a social perspective.

METHODS

Intervention

The Community-Acquired Pneumonia Study on the initial Treatment with Antibiotics of Lower Respiratory Tract Infections (CAP-START, http://clinicaltrials.gov/show/NCT01660204) was a cluster-randomized cross-over trial that was performed in seven hospitals in the Netherlands between February 2011 and August 2013. Details of the study design, enrolment, and clinical outcomes have been published previously.[8,9] In short, three strategies were compared in which one class or combination of antibiotics (beta-lactam monotherapy, beta-lactam/macrolide combination therapy or fluoroquinolone monotherapy) was the preferred empirical treatment for adult patients hospitalized to non-intensive care unit (ICU) wards with a clinical diagnosis of CAP.

Hospitals were randomized to a sequence of consecutive periods of four months, in each of which one of the strategies were applied. Deviations from the preferred empirical treatment for medical reasons were allowed, e.g. because of contra-indications, allergy to the preferred regimen, or a suspected pathogen not covered by the preferred regimen. Physicians were encouraged to complete the preferred empirical treatment unless for a medical reason, e.g. insufficient recovery or deterioration of the patient, or detection of a pathogen for which targeted antibiotic treatment was initiated. Based on an intention-to-treat principle, inclusion of patients was independent of compliance with the strategy, which allowed us to assess the effect of the strategy as a whole.

Effects

For health outcome we used 30- and 90-day all-cause mortality, which have been reported previously.[8] Mortality status at day 90 was recorded from the medical charts in patients that died during hospitalization, and patients that had visited the hospital after day 90 (e.g. in an out-patient clinic). The status of all other patients, except in one hospital, were checked electronically in the municipal personal records database, which is based on the citizen service number, date of birth and name. In the one hospital without electronic access to this database, research nurses contacted the general practitioner of each patient with an unknown status. In the Netherlands, every inhabitant is registered with a single general practitioner, who is routinely informed about important medical affairs. We were unable to assess mortality status in 4 patients because they were not Dutch residents.

Cost of illness

Data on healthcare resource utilization during hospitalization were derived from the medical records by trained research nurses using a predefined clinical record form. For other resources, patients were asked to complete a questionnaire on the 28th day after admission. This questionnaire included post-discharge healthcare use including nursing home admission and general practitioner and specialist consultations, patient costs (e.g. travel costs), and the number of days absent from paid and unpaid work for both patients and their caregivers.

Direct healthcare costs (DHC), direct non-healthcare costs (DNHC) - also referred to as patient costs -, and productivity losses (i.e. indirect non-healthcare costs – INHC) were considered in the current study. In accordance with the current Dutch guidelines for health economic evaluations, this study did not consider indirect healthcare costs.[10,11] Indirect healthcare costs would comprise the future savings in healthcare costs in the life years lost due to premature death. DHC were composed of healthcare costs related to hospitalization, e.g. days admitted to non-ICU wards, ICU days with and without

mechanical ventilation, medical interventions, antibiotic use, other medication use, and post-discharge healthcare consumption. In the DNHC category, travel costs to GP and hospital and over-the-counter medication were considered. Productivity losses were estimated for non-fatal CAP cases by multiplying self-reported sick leave from paid and unpaid work with the corresponding age and gender specific unit prices as reported in Table S1. For fatal cases younger than 65 years, two approaches were used: the friction approach, according to Dutch guidelines, in which productivity loss from paid work due to case fatality was taken into account for a period of 23 weeks,[10,11] and the human capital approach in which productivity losses up to the age of retirement would be considered. Costs were estimated by multiplying resources used with their corresponding unit cost prices presented in Tables S1 and S2. All costs are expressed in 2012 euros and, if necessary, updated using Dutch consumer price indexes.[4]

Two time horizons of 30 and 90 days were used for the economic evaluation, in accordance with the time horizons used for the effects under study, i.e. 30-day and 90-day mortality.[8] Hospital and nursing home admission costs were calculated until discharge or until the time horizon, whichever came first. For productivity losses from case-fatality, death falling within the defined time horizon were used, but costs were extended to 23 weeks using the friction approach,[10,11] and retirement age using the human capital approach, respectively. Discounting was only applied for productivity losses longer than 1 year (i.e. the human capital approach), using a 3% annual discount rate.[12] As in the primary analysis of clinical outcomes, the 90-day time horizon was considered for the primary analysis.

Economic evaluation

Cost-minimization analysis (CMA) and cost-effectiveness analysis (CEA) were conducted using four different perspectives. The "reduced third payer" perspective included only DHC of the CAP hospitalization. This perspective was considered the primary analysis because data needed for this perspective was available for all patients. The full "third payer" perspective included both DHC during admission and post-discharge. The societal perspective considered all three categories (i.e. DHC, DNHC and INHC). Two approaches were used here, the friction and the human capital approach, as explained previously.

The beta-lactam monotherapy strategy was considered the reference arm, as this is considered the first choice treatment for patients hospitalized with CAP to non-ICU wards in the Netherlands.[13] As the primary outcome, i.e. prevented deaths per treated person, was not statistically significantly different between the strategies,[8] we conducted a CMA, assessing the difference in costs per treated case. Additionally, a CEA

Table 1 - Baseline characteristics

	Beta-lactam monotherapy (N=656)	Beta-lactam / macrolide (N=739)	Fluoroquinolone monotherapy (N=888)
Median age (IQR)	70.6 (60.6 - 79.4)	70.7 (59.1 - 80.3)	71.0 (59.6 - 79.4)
Male gender	381 (58.1%)	431 (58.3%)	505 (56.9%)
Elderly home	32/644 (5.0%)	38/727 (5.2%)	41/878 (4.7%)
Hospitalization past 12 months	271/653 (41.5%)	298/722 (41.3%)	351/881 (39.8%)
Median number of comorbidities (IQR) *	1 (0 - 2)	1 (0 - 2)	1 (1 - 2)
Immunocompromised ^	147 (22.4%)	173 (23.4%)	213 (24.0%)
Day-28 questionnaire received	276 (42.1%)	253 (34.2%)	376 (42.3%)
Reports paid work	51/246 (20.7%)	45/233 (19.3%)	78/342 (22.8%)
Reports volunteer work	23/245 (9.4%)	32/234 (13.7%)	35/340 (10.3%)

Data are reported as N (%) unless otherwise indicated. IQR: inter quartile range.
* Reported comorbidities include chronic cardiovascular disease, heart failure, cerebrovascular disease, asthma, COPD, other chronic pulmonary disease, HIV/AIDS, diabetes mellitus, haematological malignancies#, solid organ malignancies#, chronic renal failure requiring dialysis, nephrotic syndrome, organ or bone marrow transplantation, alcoholism, chronic liver disease and functional or anatomic asplenia.
^Patients were categorized as immunocompromised if any of the following conditions applied: HIV/AIDS, haematological malignancies#, solid organ malignancies#, chronic renal failure requiring dialysis, nephrotic syndrome, organ or bone marrow transplantation, or receipt of immunosuppressive therapy (for corticosteroids this required at least 0.5 mg/kg/day prednisolone or equivalent dosage for a minimum of 14 days).
having received or been eligible for chemotherapy or radiotherapy in the past 5 years.

was conducted showing the additional costs (or savings) of the net effect, expressed as cost-effectiveness ratio (CER) showing costs per prevented death.

Data analysis

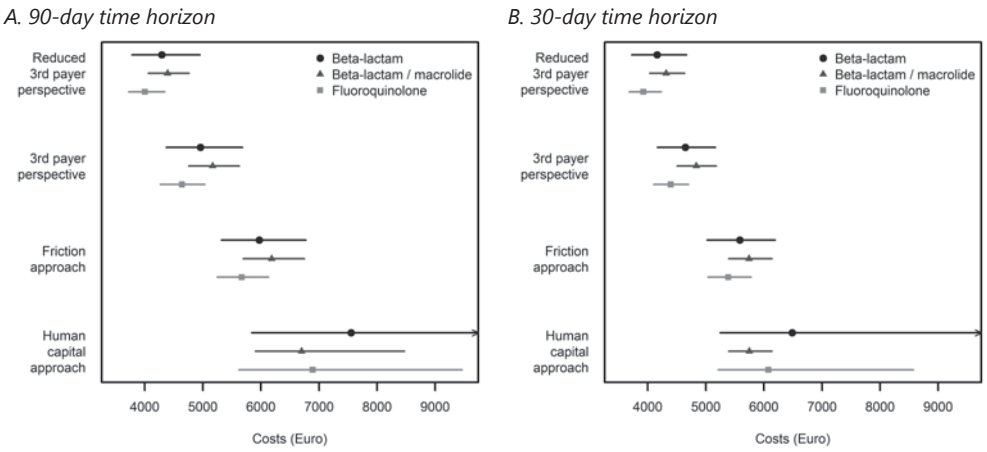
From the crude data, 2,000 bootstrapping samples were taken, and in each bootstrapped dataset five imputations were performed. Costs were calculated in each imputed dataset. To account for the cluster-randomized design of the study, differences in costs were assessed using a mixed-effects linear regression analysis, with a random intercept for each cluster-period of 4 months, and fixed effects for hospital and treatment arm.[14] Differences in mortality were similarly assessed using a mixed-effects logistic regression analysis. Effect estimates were averaged over the 5 imputations, resulting in 2,000 estimates for each perspective and time horizon, from which confidence intervals and cost-effectiveness plots were derived. Significance was tested using the 95% confidence intervals.

RESULTS

Patients

In total 656, 739, and 888 patients were included during the beta-lactam, beta-lactam/macrolide and fluoroquinolone strategies. Age, gender, and comorbidities had

Figure 1 - Average costs per treatment strategy for the different perspectives



Point estimates and confidence intervals are derived from the 50th, 2.5th and 97.5th quantiles of 2000 bootstrapping samples. Exact numbers are given in Supplementary Appendix Table S3.

similar distributions in the three treatment arms (Table 1). Inclusion rates, strategy adherence, and reasons for protocol deviations and switches have been described previously.[8]

Cost of illness and economic evaluation

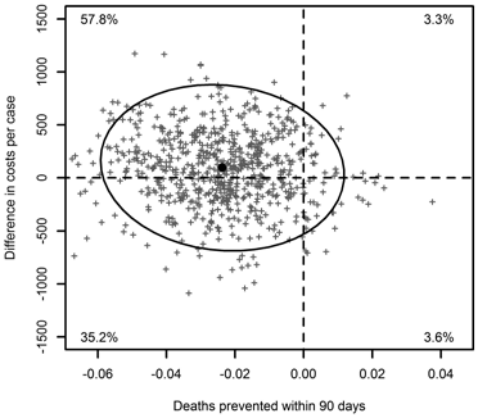
Crude (i.e. not adjusted for the cluster-randomized cross-over design) average costs within 90 days from the reduced third payer perspective (i.e. hospitalization costs) were €4,294 (95% confidence interval, CI €3,782 to €4,952) per patient for the beta-lactam monotherapy strategy, €4,392 (95% CI €4,062 to €4,760) per patient for the beta-lactam/macrolide combination strategy, and €4,002 (95% CI €3,725 to €4,341) per patient for the fluoroquinolone monotherapy strategy (Figure 1). For the CMA using the reduced third payer perspective within the 90-day time horizon, estimated differences in costs, adjusted for cluster and period effects, were €106 (95% CI -€697 to €754) per patient for the beta-lactam/macrolide combination strategy and -€278 (95%CI -€991 to €396) for the fluoroquinolone monotherapy strategy, a positive number indicating higher costs as compared to the beta-lactam monotherapy strategy.

For the beta-lactam/macrolide strategy compared to the beta-lactam strategy, using the reduced third payer perspective and the 90-day time horizon, 57.8% of the bootstrap results was in the north-west quadrant (i.e. dominated), 3.3% was in the north-east quadrant (i.e. higher costs with better health outcome), 35.2% was in the south-west quadrant (i.e. lower costs with worse health outcome), and 3.6% was in the south-east quadrant (i.e. cost-saving), with the point estimate in the north-west quadrant (Figure 2A). For the fluoroquinolone strategy compared to the beta-lactam

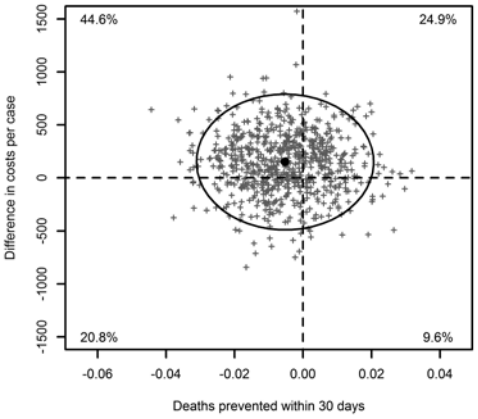
strategy, using the same perspective and time window, 11.6% was in the north-west quadrant, 10.2% in the north-east quadrant, 35.3% in the south-west quadrant, and 43.0% was in the south-east quadrant, with the point estimate in the south-east quadrant (Figure 2C). Thus, the 95% confidence interval of the CER was from being dominated to cost-saving for both comparisons.

Figure 2 - Cost-effectiveness plots from a reduced third payer perspective

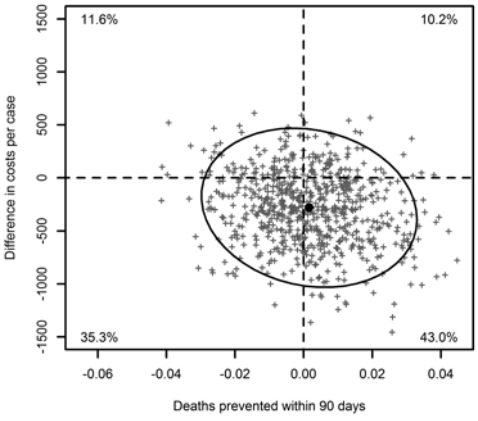
A. Beta-lactam/macrolide strategy vs. beta-lactam strategy – 90-day time horizon



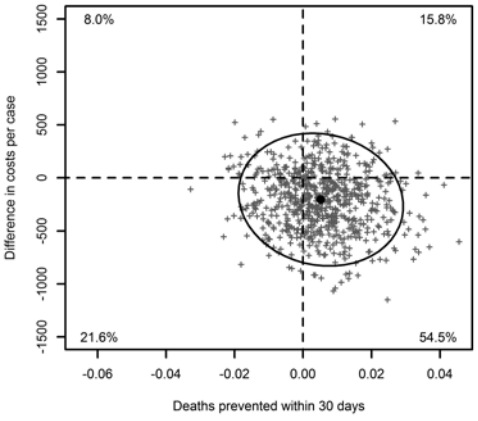
B. Beta-lactam/macrolide strategy vs. beta-lactam strategy – 30-day time horizon



C. Fluoroquinolone monotherapy strategy vs. beta-lactam strategy – 90-day time horizon



D. Fluoroquinolone monotherapy strategy vs. beta-lactam strategy – 30-day time horizon



Grey points represent incremental costs and incremental effects of 2,000 bootstrapping samples for the beta-lactam/macrolide combination strategy compared to the beta-lactam monotherapy strategy within 90 (A) and 30 (B) days of admission, and for the fluoroquinolone monotherapy strategy compared to the beta-lactam monotherapy strategy within 90 (C) and 30 (D) days of admission. The black points and curves represent the point estimates and the 95% confidence ellipses. Proportions in each quadrant indicate the proportion of bootstrap samples in that quadrant. Point estimates in the north-west quadrant are in favour of the beta-lactam monotherapy strategy; point estimates in the south-east quadrant are in favour of the other strategy. Exact point estimates and 95% confidence intervals for incremental costs and incremental effects are given in Supplementary Appendix Table S3.

Similar results for crude costs, CMA, and CEA were obtained for the 30-day time horizon, for the third payer perspective, and for the societal perspective with friction approach (Figure 2, Supplementary Appendix Figure S1, Figure S2, and Table S3). The societal perspective with human capital approach had large confidence intervals for costs, leading to uninterpretable results for both CMA and CEA (Supplementary Appendix Figure S3 and Table S3).

DISCUSSION

In this analyses, we have demonstrated that the differences in costs associated with the either of three preferred empirical antibiotic treatment strategies (i.e., beta-lactam monotherapy, beta-lactam/macrolide combination therapy, or fluoroquinolone monotherapy) for patients hospitalized with and treated for community-acquired pneumonia did not reach statistical significance. Together with non-inferiority of the beta-lactam monotherapy for day-90 mortality[8] and the perceived preference of beta-lactam monotherapy from an ecological perspective, these data support the use of beta-lactam monotherapy as preferred empirical treatment.

This is the first comparison of costs and cost-effectiveness for different preferred antibiotic treatment strategies in patients hospitalized with CAP. Our study has several strengths. First, because this was a pragmatic trial, where patients were included during strategy periods regardless of the actual antibiotics used, the intention-to-treat analysis of our study is well generalizable to daily clinical practice. All patients that received antibiotic treatment for a working diagnosis of CAP and who were hospitalized to a non-ICU medical ward, were eligible. Second, the cluster-randomized design allowed the immediate start of the allocated antibiotic treatment because individual randomization was not needed. This minimizes effects of other antibiotics prescribed in the Emergency Departments before study randomization. Third, because of the cross-over design, all hospitals applied all three strategies, thus minimizing confounding bias. As a result, baseline characteristics of the three strategies were very comparable. Fourth, we have collected comprehensive data on antibiotic treatment and medical procedures that allowed us to estimate hospitalization costs per patient. Using 2,000 bootstrapping samples and five imputations per sample, we were able to provide robust estimates and confidence intervals for the different cost categories. Our estimated costs per CAP admission are in line with previously published data from the Netherlands.[5,15] Fifth, different economic viewpoints were pursued in the current analysis. The (reduced) 3rd payer perspective and the societal perspective with friction approach all gave the same direction and magnitude of effect. The large confidence interval observed in the societal perspective with human capital approach was due to the low number of fatal cases in subjects under 65 years of age and that working status was unknown for patients that

had not returned a questionnaire, the proportion of which was larger for the patients that had died.

Our approach has some limitations. We had limited data on medication use other than antibiotics. Although it seems unlikely that one of the antibiotic treatment strategies would be associated with other patterns of non-antibiotic medication use, if so, we may have slightly underestimated the costs. For other than the direct hospitalization costs, questionnaires were returned by approximately 40% of the participants. We used multiple imputation to deal with the missing data because response to the questionnaire was obviously dependent on clinical outcome and was also related to baseline characteristics (e.g. dependency in activities of daily living and hospitalizations in the previous year). This may have increased uncertainty for the third payer and societal perspectives, and it certainly did for the societal perspective with human capital approach, as explained. For future studies it is recommended to collect data on paid and volunteer working status already during hospitalization in order to avoid missing data, as this is an important determinant for productivity loss.

The number of days on intravenous antibiotic treatment was significantly lower during the fluoroquinolone monotherapy strategy. This was fully explained by the larger proportion of patients starting with oral treatment from the day of admission, despite the similar baseline characteristics between the different strategies, and can, therefore, not be attributed to a faster clinical response. The known high bioavailability of oral fluoroquinolones[16] may have stimulated physicians to directly start with oral antibiotics and this may have contributed to the more favourable point estimate of difference in costs seen in the fluoroquinolone monotherapy period. Whether the same proportion of patients could start with oral beta-lactam monotherapy without compromising patient outcome remains to be elucidated.

In an open-label randomized controlled trial from Switzerland, beta-lactam monotherapy was not non-inferior to beta-lactam/macrolide combination therapy in establishing clinical stability after seven days of antibiotic treatment.[17] This study was not designed to determine non-inferiority for day-30 or day-90 mortality, and there were no statistically significant or clinically relevant differences in outcome between both study arms. Time to clinical stability was not determined in our study, however, length of stay was significantly longer for the beta-lactam/macrolide combination strategy, and consequently also the costs per patient were higher, although not statistically significant. The seemingly opposite findings of the two studies might in part be explained by the maximized adherence to the allocated antibiotic and the strict criteria for switching antibiotic treatment that were applied in the Swiss study. The

current analysis shows that any benefit of beta-lactam/macrolide combination treatment on time to clinical stability, if present, does not lead to cost reduction.

Generalizability of the estimated costs may depend on several factors, the most important of which are the duration of hospitalization, the length of intravenous and oral antibiotics, and post discharge patterns of healthcare use. Generalizability of effects may depend on the proportion of CAP caused by pathogens not covered by beta-lactam monotherapy, as discussed previously.[8]

In conclusion, there is no significant difference in cost-effectiveness of a strategy of preferred beta-lactam monotherapy compared to beta-lactam/macrolide combination therapy or fluoroquinolone monotherapy for the empirical antibiotic treatment of CAP in non-ICU wards. Together with the preference of narrow-spectrum antibiotics from an ecological perspective, these data support the use of beta-lactam monotherapy as preferred empirical treatment for patients hospitalized with community-acquired pneumonia.

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SUPPLEMENTARY APPENDIX

Table S1 - Costs assumptions, unit cost prices in 2012 €

Variable	Unit cost	Source
DIRECT HEALTHCARE COSTS (DHC)		
Pharmacy costs		
Pharmacy fee for delivery per prescription	5.80	a
Additional pharmacy fee for first delivery	3.23	a
Overhead costs per antibiotic dosage		
Nursery costs	0.90	b
Material costs	7.64	b
Antibiotics per antibiotic dosage		
penicillin iv (6 dd. 1 milj. IE)	0.88	c, [1]
amoxicillin iv (3 dd. 1000mg)	1.37	c, [1]
amoxicillin oral (3 dd. 500mg)	0.09	c, [1]
amoxicillin/clavulanic acid iv (3 dd. 1000/200mg)	3.25	c, [1]
amoxicillin/clavulanic acid oral (3 dd. 500/125mg)	0.39	c, [1]
cefuroxime iv (3 dd. 750mg)	2.9	c, [1]
cefuroxime-axetil oral (3 dd. 250mg)	0.59	c, [1]
ceftriaxone iv (1 dd. 2g)	17.625	c, [1]
cefotaxim iv (2 dd. 1g)	5.94	c, [1]
ceftazidim iv (3 dd. 1g)	8.91	c, [1]
cefazolin iv (2 dd. 1g)	2.88	c, [1]
azitromycin oral (1 dd. 500 mg)	0.565	c, [1]
erytromycin iv (4 dd. 500mg)	7.26	c, [1]
erytromycin oral (4 dd. 500mg)	1.35	c, [1]
claritromycin iv (2 dd. 500mg)	1.15	c, [1]
claritromycin oral (2 dd. 500 mg)	0.36	c, [1]
moxifloxacin iv (1 dd. 400mg)	63.6	c, [1]
moxifloxacin oral (1 dd. 400mg)	2.715	c, [1]
levofloxacin iv (1 dd. 500mg)	113.78	c, [1]
levofloxacin oral (1 dd. 500mg)	0.86	c, [1]
ciprofloxacin iv (2 dd. 400mg)	20.93	c, [1]
ciprofloxacin oral (2 dd. 500mg)	0.125	c, [1]
ofloxacin oral (2 dd. 400mg)	0.42	c, [1]
doxycyclin iv (1 dd. 100 mg (1e dag 200mg))	3.72	c, [1]
doxycyclin oral (1 dd. 100 mg (1e dag 200mg))	0.17	c, [1]
vancomycin iv (2 dd. 1g)	15.195	c, [1]
metronidazole iv (4 dd. 500mg)	3.59	c, [1]

Table S1 - Costs assumptions, unit cost prices in 2012 € (continued)

Variable	Unit cost	Source
metronidazole oral (3 dd. 500mg)	0.22	c, [1]
piperacilline-tazobactam iv (4 dd. 4g/500mg)	12.55	c, [1]
piperacillin iv (4 dd. 4g)	12.55	c, [1]
clindamycin iv (3 dd. 600mg)	4.89	c, [1]
clindamycin oral (4 dd. 300mg)	0.465	c, [1]
flucloxacillin iv (4 dd. 1g)	4.585	c, [1]
flucloxacillin oral (3 dd. 500mg)	0.14	c, [1]
imipenem-cilastatine iv (4 dd. 1g/1g)	21.535	c, [1]
meropenem iv (3 dd. 1g)	22.42	c, [1]
cotrimoxazole iv (2 dd. 960mg)	2.56	c, [1]
cotrimoxazole oral (2 dd. 960mg)	0.17	c, [1]
gentamycin iv (1 dd. 350-400mg)	9.35	c, [1]
tobramycin iv (1 dd. 350-400mg)	23.997	c, [1]
rifampicine iv (1 dd. 600mg)	6.69	c, [1]
rifampicine oral (1 dd. 600mg)	1.645	c, [1]
feniticilline oral (3 dd. 500mg)	0.3	c, [1]
nitrofurantoine oral (4 dd. 50mg)	0.105	c, [1]
trimethoprim oral (1 dd. 300mg)	0.2	c, [1]
pyrazinamide oral (1 dd. 2g)	0.66	c, [1]
colistin iv (3 dd. 0.5Milj IE)	5.06	c, [1]
minocycline oral (1 dd. 100mg)	0.37	c, [1]
ethambutol oral (1 dd. 1200mg)	1.15	c, [1]
linezolid iv (2 dd. 600mg)	59.16	c, [1]
Other medication costs per day		
Analgetics: paracetamol (4 dd. 1g)	0.40	c, [2]
Inhaled drugs: salbutamol/ipratropium (4 dd. 0.75/7.5 mg)	0.90	c, [2]
Non-inhaled corticosteroids: prednisolone (4 dd. 10mg)	0.26	c, [2]
vasopressors: noradrenaline (5mg / day)	4.03	c, [2]
Hospitalization		
Hospital admission (general ward) / day	410.24	a, [3]
Intensive care unit		
— with artificial ventilation/day	2699.47	d
— without artificial ventilation/day	1719.29	d
In-hospital medical procedures		[4]
Bronchoscopy / broncho-alveolar lavage	483.97	d
Non-invasive Positive Pressure Ventilation	291.78	d
Pleural puncture	146.07	d

Table S1 - Costs assumptions, unit cost prices in 2012 € (continued)

Variable	Unit cost	Source
Thorax drainage	969.08	d
Pleurodesis	1061.09	d
Abces drainage	424.21	d
Pacemaker implantation	8770.00	d
Thoracotomy	6597.07	d
Lumbar puncture	316.54	d
Transesophageal echocardiogram	247.00	d
Chest echography (including cardiac echography)	72.95	d
Abdominal echography	107.15	d
Chest CT-scan	208.60	d
Cranial CT-scan	192.40	d
CT pulmonary angiogram	244.42	d
Sinus CT-scan	192.40	d
Abdominal CT-scan	208.60	d
Ventilation/perfusion scan	502.67	d
Video Assisted Thoracoscopic Surgery	6761.80	d
Coronary angiography	296.96	d
Chest X-ray	96.87	d
General practitioner consultations post-discharge		
Telephone consultation	14.87	d
Consultation hour visit	29.73	d
Home visit	45.66	d
Medical specialist consultations post-discharge		
Telephone consultation	38.23	d
Outpatient clinic visit	76.45	a
Emergency department visit	160.34	a
Readmission to any hospital / day	485.28	a
Other direct healthcare costs post-discharge		
Ambulance costs to nursing home		
Nursing home / day	252.73	a
Home care / hour	37.17	a
DIRECT NON-HEALTHCARE COSTS (DNHC)		
Transport cost/specialist consultation or hospital visit	4.57	a, [5]
Transport cost/GP consultation	2.06	a, [5]
Transport cost/nursing home	3.16	a, [5]
Paid household help (not including home care)	13.27	a

Table S1 - Costs assumptions, unit cost prices in 2012 € (continued)

Variable	Unit cost	Source
INDIRECT NON-HEALTHCARE COSTS (INHC)		
Productivity loss due to absence from:		
— Unpaid work / hour	13.27	a, [6]
— Paid work (average working person) / hour	31.88	a, [6]
— Paid work (Males <20 years) / hour	10.25	a
— Paid work (Females <20 years) / hour	9.30	a
— Paid work (Males 20-24 years) / hour	18.85	a
— Paid work (Females 20-24 years) / hour	18.24	a
— Paid work (Males 25-29 years) / hour	25.69	a
— Paid work (Females 25-29 years) / hour	25.08	a
— Paid work (Males 30-34 years) / hour	31.48	a
— Paid work (Females 30-34 years) / hour	29.24	a
— Paid work (Males 35-39 years) / hour	36.14	a
— Paid work (Females 35-39 years) / hour	31.06	a
— Paid work (Males 40-44 years) / hour	38.94	a
— Paid work (Females 40-44 years) / hour	30.86	a
— Paid work (Males 45-49 years) / hour	40.69	a
— Paid work (Females 45-49 years) / hour	30.70	a
— Paid work (Males 50-54 years) / hour	41.48	a
— Paid work (Females 50-54 years) / hour	31.06	a
— Paid work (Males 55-59 years) / hour	41.82	a
— Paid work (Females 55-59 years) / hour	31.33	a
— Paid work (Males 60-64 years) / hour	41.55	a
— Paid work (Females 60-64 years) / hour	30.44	a
— Paid work (Males >=65 years) / hour	41.55	[7]
— Paid work (Females >=65 years) / hour	30.44	[7]

1. Prices are given per single standard dosage.
2. For non-antibiotic drugs data on group level were available (e.g. number of days with analgetics). Prices were calculated for the most prescribed drug in this group, based on authors' experience, and are given per standard daily dosage.
3. Medication costs were not included in the daily hospitalization costs of the CAP admission.
4. The following interventions were considered not CAP related and therefore no costs were attributed: liver abcess drainage, abdominal X-ray, PET-CT, dialysis except when patient was on the ICU, and tube feeding.
5. Using average distances as reported in Hakkart et al., assuming that 50% would use a car and 50% would use public transport.
6. Including productivity loss of a caregiver if reported.
7. No data available for subjects over 65 years of age. If these subjects reported paid work, the productivity loss of subjects 60-64 years of age was used.
8. Hakkaart - van Roijen L, Tan S, Bouwmans C. Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. 3 ed. Diemen: College van Zorgverzekeringen; 2010.
9. Oosterheert et al. J Clin Microbiol. 2003 Oct;41(10):4708-13.
10. Medication costs derived from http://www.medicijnkosten.nl/ (Dutch medication costs by "Zorginstituut Nederland" (Health Institute Nederlands)). Prices were looked up in December 2014 and adapted to 2012 euro. Prices are displayed per single standard dose.
11. Mangen et al. Eur Respir J. 2015 Jul 9. pii: ERJ-00325-2015.

Table S2 - Resources used

	Beta-lactam monotherapy strategy	Beta-lactam / macrolide strategy	Fluoroquinolone monotherapy strategy
ADMISSION DAYS			
Days in non-ICU ward	8.1 (7.7 to 8.5)	9.1 (8.7 to 9.4)	8.1 (7.8 to 8.5)
ICU (%)	2.7 (1.6 to 4.0)	1.6 (0.8 to 2.6)	1.6 (0.9 to 2.4)
— Days (not intubated)	2.4 (1.3 to 4.1)	5.1 (1.3 to 10.3)	2.0 (1.3 to 3.2)
— Days (intubated)	6.6 (2.4 to 11.1)	2.6 (1.0 to 4.7)	5.3 (2.8 to 8.3)
INTERVENTIONS			
Bronchoscopy (%)	7.3 (5.5 to 9.4)	7.6 (5.8 to 9.4)	6.6 (5.0 to 8.5)
Broncho-alveolar lavage (%)	0.0 (0.0 to 0.0)	0.1 (0.0 to 0.4)	0.1 (0.0 to 0.3)
Non-invasive ventilation (%)	1.1 (0.4 to 2.0)	0.6 (0.1 to 1.2)	1.0 (0.4 to 1.8)
Pleural puncture (%)	4.2 (2.6 to 6.5)	4.9 (3.3 to 6.9)	4.1 (2.6 to 5.6)
Thorax drainage (%)	1.2 (0.5 to 2.1)	2.2 (1.2 to 3.5)	2.1 (1.2 to 3.2)
Pleurodesis (%)	0.2 (0.0 to 0.5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Abces drainage (%)	0.0 (0.0 to 0.0)	0.8 (0.3 to 1.5)	0.3 (0.0 to 0.7)
Pacemaker implantation (%)	0.2 (0.0 to 0.5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Thoracotomy (%)	0.0 (0.0 to 0.0)	0.3 (0.0 to 0.7)	0.1 (0.0 to 0.3)
Lumbar puncture (%)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.4)	0.2 (0.0 to 0.6)
Trans esophageal echo (%)	0.2 (0.0 to 0.5)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Echo chest (%)	0.3 (0.0 to 0.8)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
Echo abdomen (%)	0.2 (0.0 to 0.5)	0.3 (0.0 to 0.7)	0.0 (0.0 to 0.0)
Echo heart (%)	0.3 (0.0 to 0.8)	0.3 (0.0 to 0.7)	0.6 (0.1 to 1.2)
CT thorax (%)	2.4 (1.3 to 3.8)	1.4 (0.6 to 2.4)	0.9 (0.3 to 1.5)
CT brain (%)	0.0 (0.0 to 0.0)	0.1 (0.0 to 0.4)	0.0 (0.0 to 0.0)
CT angiography (%)	0.5 (0.0 to 1.2)	0.1 (0.0 to 0.4)	0.0 (0.0 to 0.0)
CT sinus (%)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.4)	0.0 (0.0 to 0.0)
CT abdomen (%)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.4)	0.0 (0.0 to 0.0)
Ventilation Perfusion scan (%)	0.2 (0.0 to 0.5)	0.4 (0.0 to 0.9)	0.0 (0.0 to 0.0)
Video assisted thoracal surgery (%)	0.2 (0.0 to 0.5)	0.1 (0.0 to 0.4)	0.1 (0.0 to 0.4)
Coronary angiography (%)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.1 (0.0 to 0.3)
Chest X-ray during admission (%)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.5)	0.0 (0.0 to 0.0)
MEDICATION USE DURING ADMISSION			
Analgetics (%)	44.7 (40.9 to 48.5)	49.6 (45.8 to 53.4)	43.4 (39.9 to 47.0)
- Days on analgetics	6.8 (6.1 to 7.9)	7.1 (6.5 to 7.8)	6.7 (6.2 to 7.2)

Table S2 - Resources used (continued)

	Beta-lactam monotherapy strategy	Beta-lactam / macrolide strategy	Fluoroquinolone monotherapy strategy
Inhalation medication (%)	48.5 (44.7 to 52.4)	49.2 (45.7 to 52.5)	52.0 (49.3 to 55.4)
— Days	7.3 (6.5 to 8.4)	7.6 (7.0 to 8.4)	7.3 (6.9 to 7.8)
Sytemic corticosteroids (%)	42.9 (39.3 to 47.1)	40.5 (37.1 to 43.8)	45.0 (41.9 to 48.7)
— Days	7.5 (6.9 to 8.5)	7.7 (7.1 to 8.2)	7.7 (7.1 to 8.4)
Vasopressors (%)	0.2 (0.0 to 0.5)	0.1 (0.0 to 0.4)	0.6 (0.1 to 1.0)
— Days	4.0 (4.0 to 4.0)	1.0 (1.0 to 1.0)	4.2 (1.7 to 6.7)
ANTIBIOTIC USE DURING ADMISSION (DAYS)			
penicillin iv	0.1 (0.1 to 0.2)	0.8 (0.7 to 0.9)	0.3 (0.2 to 0.4)
amoxicillin iv	0.8 (0.7 to 0.9)	0.3 (0.3 to 0.4)	0.1 (0.1 to 0.2)
amoxicillin oral	0.9 (0.7 to 1.0)	0.9 (0.8 to 1.1)	0.3 (0.2 to 0.4)
amoxiclav iv	1.4 (1.2 to 1.5)	1.1 (0.9 to 1.2)	0.3 (0.2 to 0.4)
amoxiclav oral	1.3 (1.2 to 1.5)	1.3 (1.2 to 1.5)	0.4 (0.3 to 0.6)
cefuroxim iv	0.2 (0.1 to 0.3)	0.6 (0.5 to 0.7)	0.1 (0.0 to 0.1)
ceftriaxone iv	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)	0.3 (0.2 to 0.4)
cefotaxim iv	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
ceftazidim iv	0.1 (0.0 to 0.2)	0.2 (0.1 to 0.3)	0.1 (0.0 to 0.1)
azitromycin oral	0.2 (0.1 to 0.3)	0.9 (0.8 to 1.1)	0.1 (0.0 to 0.1)
erytromycin iv	0.1 (0.1 to 0.2)	0.9 (0.8 to 1.0)	0.1 (0.0 to 0.1)
erytromycin oral	0.0 (0.0 to 0.0)	0.1 (0.1 to 0.2)	0.0 (0.0 to 0.0)
claritromycin oral	0.3 (0.2 to 0.5)	1.4 (1.2 to 1.6)	0.1 (0.0 to 0.1)
moxifloxacin iv	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.1)	1.3 (1.2 to 1.4)
moxifloxacin oral	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	1.7 (1.6 to 1.9)
levofloxacin iv	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.4 (0.4 to 0.5)
levofloxacin oral	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.9 (0.8 to 1.1)
ciprofloxacin iv	0.2 (0.2 to 0.3)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)
ciprofloxacin oral	0.7 (0.6 to 0.9)	0.5 (0.3 to 0.6)	0.2 (0.1 to 0.2)
doxycyclin iv	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
doxycyclin oral	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)
piperacillin(-tazobactam) iv	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.1 (0.0 to 0.2)
meropenem iv	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)
metronidazol iv	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)
clindamycin iv	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)

Table S2 - Resources used (continued)

	Beta-lactam monotherapy strategy	Beta-lactam / macrolide strategy	Fluoroquinolone monotherapy strategy
flucloxacillin iv	0.0 (0.0 to 0.0)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.2)
imipenem iv	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)
cotrimoxazole oral	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)	0.1 (0.0 to 0.1)
gentamicin iv	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.1 (0.0 to 0.1)
tobramycin iv	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.1)
clindamycin oral	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.1)
flucloxacillin oral	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
rifampicin oral	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)
cefuroxim oral	0.0 (0.0 to 0.0)	0.1 (0.1 to 0.2)	0.0 (0.0 to 0.0)
ceftazidim oral	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)
nitrofurantoin oral	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)
POST DISCHARGE HEALTH CARE USE			
GP phone contact (%)	29.2 (24.5 to 34.0)	31.8 (26.5 to 37.3)	31.4 (26.5 to 37.1)
— N contacts	2.7 (2.1 to 3.5)	2.6 (2.1 to 3.4)	2.4 (2.0 to 3.0)
GP consultation (%)	24.8 (20.9 to 29.8)	22.2 (17.9 to 26.8)	21.5 (18.0 to 25.6)
— N consultations	1.6 (1.3 to 1.9)	1.7 (1.4 to 2.1)	1.7 (1.3 to 2.1)
GP home visits (%)	28.7 (24.2 to 33.1)	28.7 (23.9 to 34.2)	30.1 (25.1 to 34.3)
— N home visits	2.1 (1.7 to 2.5)	2.0 (1.7 to 2.5)	2.0 (1.7 to 2.4)
Outpatient clinic visit (%)	28.6 (24.5 to 33.0)	29.3 (24.2 to 34.2)	31.4 (27.1 to 35.9)
— N outpatient visits	1.7 (1.4 to 2.2)	1.7 (1.4 to 2.1)	1.7 (1.4 to 2.1)
Readmission (%)	7.6 (4.5 to 11.7)	8.4 (5.2 to 13.0)	7.8 (4.9 to 12.0)
— Days readmitted	9.0 (6.7 to 14.0)	10.1 (6.9 to 16.2)	8.9 (6.6 to 12.9)
Nursing home admission (%)	2.9 (1.0 to 5.3)	3.7 (1.5 to 7.4)	2.3 (0.8 to 4.6)
— Days nursing home	21.5 (7.8 to 42.3)	20.2 (8.5 to 39.3)	19.7 (7.6 to 40.4)
Professional home care (%)	14.8 (11.0 to 19.1)	15.5 (11.3 to 20.7)	15.5 (11.7 to 19.3)
— Hours home care	10.6 (8.0 to 15.4)	11.5 (8.3 to 16.1)	9.8 (7.4 to 13.3)
POST DISCHARGE ANTIBIOTIC USE			
amoxicillin oral pd	0.7 (0.6 to 0.9)	0.6 (0.5 to 0.7)	0.3 (0.2 to 0.3)
amoxiclav oral pd	1.2 (1.0 to 1.7)	1.3 (0.9 to 2.1)	0.4 (0.3 to 0.6)
cefuroxime oral pd	0.0 (0.0 to 0.1)	0.1 (0.1 to 0.2)	0.0 (0.0 to 0.0)
azitromycin oral pd	0.1 (0.0 to 0.3)	0.7 (0.2 to 1.8)	0.0 (0.0 to 0.1)
erytromycin oral pd	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)

Table S2 - Resources used (continued)

	Beta-lactam monotherapy strategy	Beta-lactam / macrolide strategy	Fluoroquinolone monotherapy strategy
claritromycin oral pd	0.2 (0.1 to 0.2)	0.4 (0.3 to 0.5)	0.0 (0.0 to 0.1)
moxifloxacin oral pd	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)	1.6 (1.3 to 2.3)
levofloxacin oral pd	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0.4 (0.3 to 0.5)
ciprofloxacin oral pd	0.3 (0.2 to 0.5)	0.1 (0.1 to 0.3)	0.6 (0.1 to 1.4)
doxycyclin oral pd	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.1)
cotrimoxazole oral pd	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.3)	0.0 (0.0 to 0.1)
clindamycin oral pd	0.1 (0.0 to 0.2)	0.2 (0.0 to 0.3)	0.2 (0.0 to 0.3)
flucloxacillin oral pd	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)
feniticilline oral pd linezolid	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)
iv pd	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.1)
PATIENT COSTS			
Patient declared costs	129 (96 to 175)	129 (100 to 168)	120 (92 to 161)
(Euro) **PRODUCTIVITY**			
LOSS Paid work patient (%)	21.6 (18.1 to 25.7)	22.8 (19.0 to 26.4)	22.7 (19.2 to 26.2)
— Weekly hours	31.7 (29.1 to 34.9)	31.6 (29.0 to 34.9)	31.1 (28.7 to 34.3)
— Work loss (hours)	22.2 (18.1 to 27.7)	23.3 (19.1 to 29.6)	22.8 (18.3 to 27.8)
— 90-day mortality (%)	6.1 (2.1 to 13.5)	5.6 (2.1 to 12.1)	4.9 (1.7 to 10.7)
— 30-day mortality (%)	3.8 (0.6 to 10.9)	2.8 (0.3 to 9.1)	3.0 (0.5 to 8.3)
Volunteer work patient (%)	12.4 (9.4 to 16.1)	14.9 (11.3 to 19.6)	13.6 (10.6 to 17.8)
— Weekly hours	10.0 (7.6 to 12.9)	9.6 (7.4 to 12.9)	10.6 (8.1 to 14.1)
— Work loss (hours)	5.2 (3.1 to 8.0)	6.2 (3.9 to 9.2)	6.0 (3.6 to 9.4)
Caregiver paid work loss (hours)	4.0 (3.0 to 5.4)	4.2 (2.9 to 5.9)	4.1 (3.0 to 5.7)
Caregiver volunteer work loss (hours)	1.1 (0.4 to 2.0)	1.0 (0.4 to 1.8)	1.1 (0.4 to 1.8)

Data represent the point estimate and 95% confidence interval of the mean or proportion, as indicated. These were derived from the 50th, 2.5th and 97.5th percentile of the 2000 bootstrapped datasets following 5 imputations in each dataset.

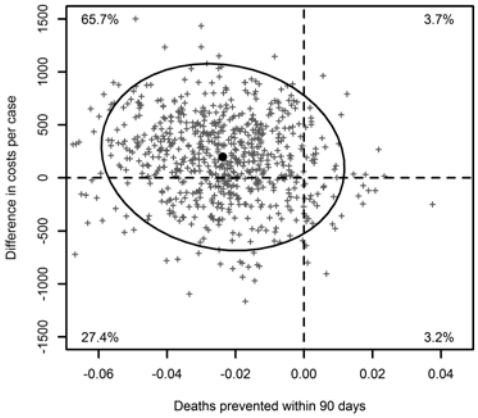
Table S3 - Cost and effect estimates and cost-effectiveness ratios

	Beta-lactam monotherapy strategy	Beta-lactam/ macrolide strategy	Fluoroquinolone monotherapy strategy
90-DAY TIME HORIZON			
All-cause mortality	9.1% (7.0% - 11.6%)	11.1% (8.9% - 13.5%)	8.8% (6.9% - 10.5%)
Costs (€/patient)			
Reduced third payer	4,294 (3,782 - 4,952)	4,392 (4,062 - 4,760)	4,002 (3,725 - 4,341)
Third payer	4,959 (4,372 - 5,682)	5,170 (4,759 - 5,627)	4,641 (4,270 - 5,033)
Societal (friction)	5,972 (5,322 - 6,772)	6,184 (5,697 - 6,747)	5,668 (5,249 - 6,128)
Societal (human capital)	7,554 (5,842 - 11,134)	6,700 (5,906 - 8,468)	6,891 (5,621 - 9,463)
Difference costs (Δ€/patient) ł			
Reduced third payer	*[reference]*	106 (-697 to 754)	-278 (-991 to 396)
Third payer	*[reference]*	210 (-722 to 911)	-279 (-1,094 to 464)
Societal (friction)	*[reference]*	216 (-725 to 1,032)	-277 (-1,246 to 539)
Societal (human capital)	*[reference]*	-964 (-4,967 to 1,614)	-865 (-4,806 to 2,247)
30-DAY TIME HORIZON			
All-cause mortality	5.5% (4.0% to 7.3%)	5.8% (4.3% to 7.5%)	4.9% (3.5% to 6.3%)
Costs (€/patient)			
Reduced third payer	4,161 (3,727 to 4,668)	4,316 (4,035 to 4,632)	3,925 (3,683 to 4,231)
Third payer	4,649 (4,169 to 5,164)	4,835 (4,508 to 5,179)	4,395 (4,105 to 4,700)
Societal (friction)	5,586 (5,023 to 6,193)	5,744 (5,395 to 6,136)	5,386 (5,039 to 5,779)
Societal (human capital)	6,487 (5,247 to 9,726)	5,748 (5,395 to 6,136)	6,077 (5,213 to 8,571)
Difference costs (Δ€/patient) ł			
Reduced third payer	*[reference]*	159 (-459 to 679)	-200 (-798 to 352)
Third payer	*[reference]*	184 (-447 to 724)	-197 (-820 to 365)
Societal (friction)	*[reference]*	175 (-598 to 799)	-133 (-926 to 548)
Societal (human capital)	*[reference]*	-842 (-4,522 to 499)	-362 (-4,084 to 2,122)

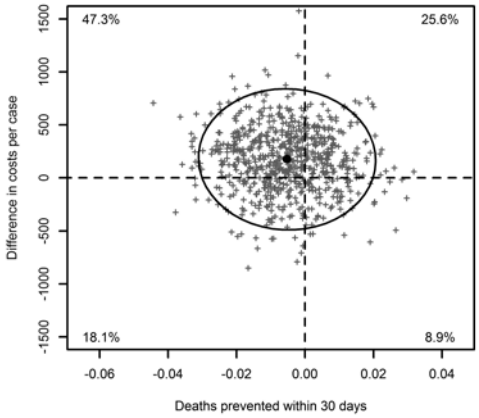
ł As the primary effect (i.e. case-fatality) was not significantly different,[8] a cost-minimization analysis was applied. CMA is expressed as the difference in costs using mixed-effects linear regression analysis with beta-lactam monotherapy as the reference strategy.

Figure S1 - Cost-effectiveness plots from a third payer perspective

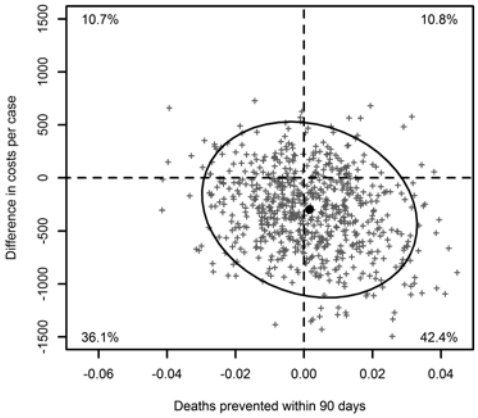
A. Beta-lactam/macrolide strategy vs. beta-lactam strategy – 90-day time horizon



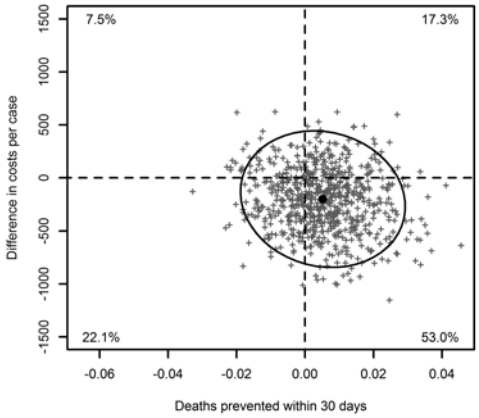
B. Beta-lactam/macrolide strategy vs. beta-lactam strategy – 30-day time horizon



C. Fluoroquinolone strategy vs. beta-lactam strategy – 90-day time horizon



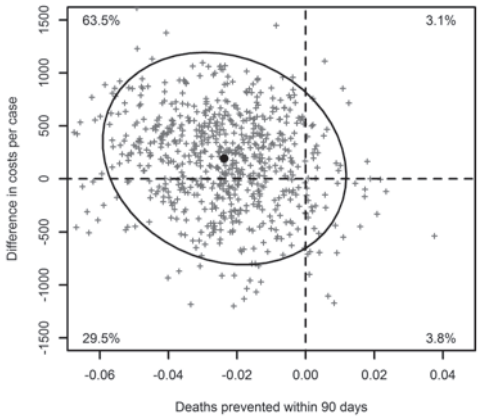
D. Fluoroquinolone strategy vs. beta-lactam strategy – 30-day time horizon



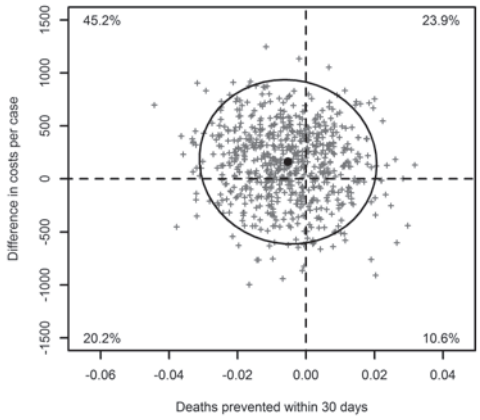
Grey points represent incremental costs and incremental effects of 2,000 bootstrapping samples for the beta-lactam/macrolide combination strategy compared to the beta-lactam monotherapy strategy within 90 (A) and 30 (B) days of admission, and for the fluoroquinolone monotherapy strategy compared to the beta-lactam monotherapy strategy within 90 (C) and 30 (D) days of admission. The black points and curves represent the point estimates and the 95% confidence ellipses. Proportions in each quadrant indicate the proportion of bootstrap samples in that quadrant. Point estimates in the north-west quadrant are in favour of the beta-lactam monotherapy strategy; point estimates in the south-east quadrant are in favour of the other strategy. Exact point estimates and 95% confidence intervals for incremental costs and incremental effects are given in Supplementary Appendix Table S3.

Figure S2 - Cost-effectiveness plots from a societal perspective, friction approach

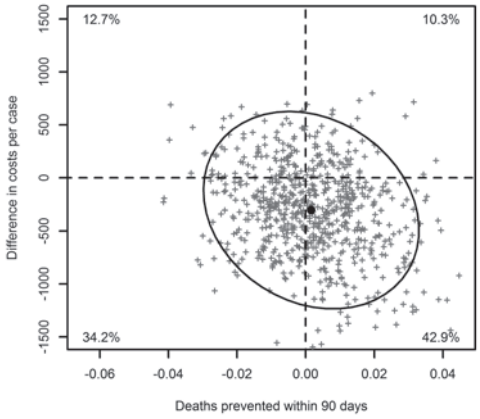
A. Beta-lactam/macrolide strategy vs. beta-lactam strategy – 90-day time horizon



B. Beta-lactam/macrolide strategy vs. beta-lactam strategy – 30-day time horizon



C. Fluoroquinolone strategy vs. beta-lactam strategy – 90-day time horizon



D. Fluoroquinolone strategy vs. beta-lactam strategy – 30-day time horizon

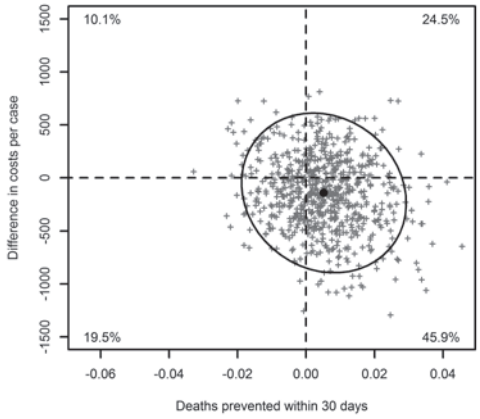


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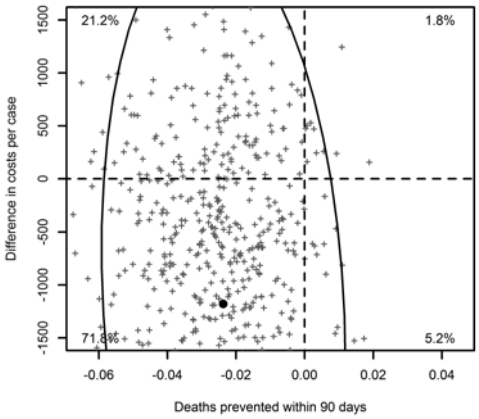
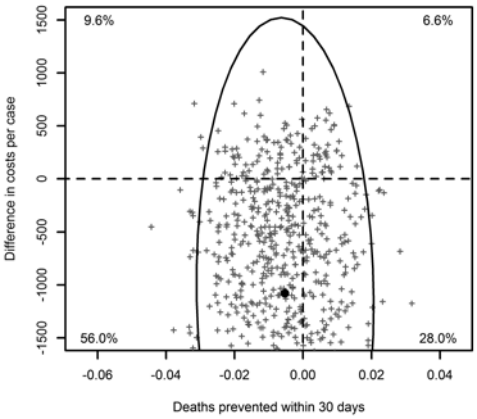
Figure S3 - Cost-effectiveness plots from a societal perspective, human capital approach

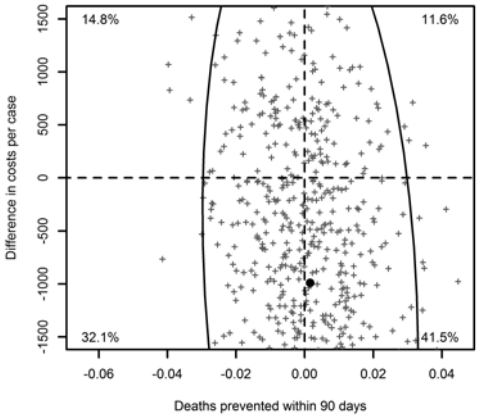
A. Beta-lactam/macrolide strategy vs. beta-lactam strategy – 90-day time horizon



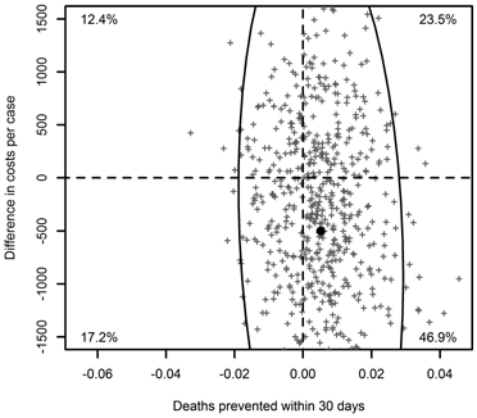
B. Beta-lactam/macrolide strategy vs. beta-lactam strategy – 30-day time horizon



C. Fluoroquinolone strategy vs. beta-lactam strategy – 90-day time horizon



D. Fluoroquinolone strategy vs. beta-lactam strategy – 30-day time horizon



Grey points represent incremental costs and incremental effects of 2,000 bootstrapping samples for the beta-lactam/macrolide combination strategy compared to the beta-lactam monotherapy strategy within 90 (A) and 30 (B) days of admission, and for the fluoroquinolone monotherapy strategy compared to the beta-lactam monotherapy strategy within 90 (C) and 30 (D) days of admission. The black points and curves represent the point estimates and the 95% confidence ellipses. Proportions in each quadrant indicate the proportion of bootstrap samples in that quadrant. Point estimates in the north-west quadrant are in favour of the beta-lactam monotherapy strategy; point estimates in the south-east quadrant are in favour of the other strategy. Exact point estimates and 95% confidence intervals for incremental costs and incremental effects are given in Supplementary Appendix Table S3.

Chapter 9 Do treatment restrictions influence empirical antibiotic therapy in elderly patients hospitalized with community-acquired pneumonia?

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Submitted manuscript

ABSTRACT

Background

Treatment restrictions are common in hospitalized elderly patients with community-acquired pneumonia (CAP). It is unknown if these are associated with antibiotic treatment decisions and thus confound the association between antibiotic treatment and mortality in observational studies. We aimed to determine variables associated with treatment restrictions and to determine whether treatment restrictions act as a confounder of the association between empirical antibiotic treatment (i.e. coverage of atypical pathogens) and clinical outcomes.

Methods

Prospective cohort study on hospitalized elderly CAP patients in the Netherlands.

Results

We studied 1,093 patients of whom 296 patients (27.1%) had treatment restrictions, 401 (36.7%) received atypical coverage, and 188 (17.2%) died within 90 days. Age, ADL dependency, cardiovascular disease, previous hospital admissions, smoking and pneumonia severity were independently associated with treatment restrictions. Treatment restrictions were associated with day 90 mortality (crude HR 4.035, 95% CI 2.905-5.606; adjusted HR 2.636, 95% CI 1.912-3.634), but not with empirical antibiotic treatment (crude OR 0.962, 95% CI 0.729-1.269; adjusted OR 1.002, 95% CI 0.732-1.372). The adjusted hazard ratio for atypical coverage as a predictor of 90-day mortality was 1.199 (95% CI 0.893-1.611) without treatment restrictions, and 1.195 (95% CI 0.888-1.610) with the inclusion of treatment restrictions in the multivariate model (relative change in HR 0.3%). Comparable results were obtained for day 30 mortality and length of hospital stay.

Conclusions

In this study 27.1% of elderly hospitalized with CAP had treatment restrictions. These were associated with mortality, but did not confound associations between empirical antibiotic treatment and clinical outcomes.

INTRODUCTION

Community-acquired pneumonia (CAP) is a major health problem in the elderly, causing an annual estimated 5,100 deaths in the Netherlands and over 59,000 deaths in the United States.[1,2] The incidence of CAP increases with age, varying from 18 per 1,000 person years in those aged 65-69 years to 52 per 1,000 person years in those 85 years or older.[3,4] Treatment of CAP in the very elderly poses several challenges. Preexisting comorbidities, quality of life, ethical dilemmas and end-of-life decisions are important determinants for therapeutic interventions in elderly patients.[5] Optimal care in some of these patients may involve not initiating treatment, withholding treatment escalation or even discontinuing therapy. Adjustments in treatment, based on prognosis and sometimes requested by patients, can vary from specific restrictions, such as a do-not-resuscitate (DNR) or do-not-ventilate (DNV) status, to providing palliative care only.

Treatment restrictions are associated with an increased in-hospital mortality, and may also lead to less aggressive or inadequate care compared to patients that do not receive a treatment restriction.[6,7] For instance, trauma patients with DNR orders were less likely to be hospitalized and the presence of DNR orders negatively affected physicians' willingness to order interventions unrelated to the treatment restriction, such as transmissions to intensive care units or blood transfusions.[8,9] Yet, the presence of treatment restrictions is usually not reported in therapeutic clinical studies, such as studies evaluating treatment strategies for CAP.[5,10,11] To the best of our knowledge, the effect of treatment restrictions on non-related treatment choices have not been studied in CAP patients and the epidemiology of treatment restrictions in CAP are known only for a limited number of countries.[8,12-15]

We, therefore, described the epidemiology of treatment restrictions in patients hospitalized with CAP in the Netherlands, and quantified associations between treatment restrictions, empirical antibiotic treatment and outcome of hospitalized CAP patients. Furthermore, we determined which factors are associated with imposing treatment restrictions, whether presence of treatment restrictions influences the choice of empirical antibiotic treatment and whether treatment restrictions confound the association between antibiotic treatment and outcome of CAP.

METHODS

Study setting

We performed an observational study nested within the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA), a double blind placebo-controlled randomized trial (RCT) evaluating the effectiveness of a 13-valent conjugated pneumococcal vaccine in the prevention of pneumococcal CAP in 84,496 community

dwelling individuals over 65 years of age in the Netherlands.[16] Participants were included in the trial between September 2008 and January 2010 and hospitalizations for suspected CAP were identified in 58 hospitals until August 2013. For the current study, data on treatment restrictions were only collected from hospitals that had identified at least 30 X-ray confirmed CAP cases (Figure 1).

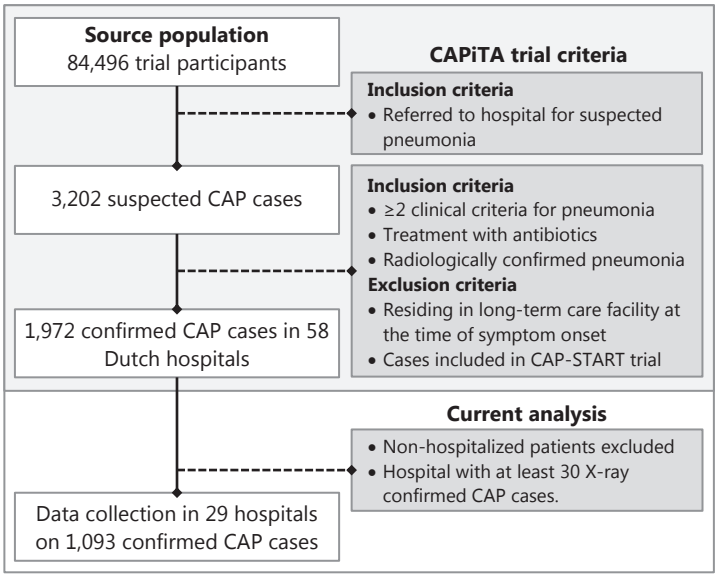


Figure 1 - Identification of cases.

Clinical criteria for pneumonia include: Cough, production of purulent sputum or a change in the character of sputum, temperature >38°C or < 36.1°C, auscultatory findings consistent with pneumonia, leukocytosis >10 * 109 or left shift, C reactive protein > 30 or hypoxia (arterial pO2 < 8 kPa or < 60 mmHg).

Data collection and definitions

For participants presenting to the emergency room with suspected CAP, data were collected by trained research nurses as part of the CAPiTA protocol, but also on demographics, comorbidities, frailty, 1,17 clinical parameters, antibiotic consumption and outcome. An episode of CAP was confirmed in case of the presence of two or more clinical criteria for CAP (i.e cough, production of purulent sputum, or a change in the character of sputum, temperature >38°C or < 36.1°C, auscultatory findings consistent with pneumonia, leukocytosis >10 * 109 or left shift, C-reactive protein > 30mg/L or hypoxia (arterial pO2 < 8 kPa). Patients who presented at the emergency room (ER), but were not admitted, and patients that did not receive antibiotic treatment during hospital admission were not included. During the study period the CAP-START study, a cluster-randomized cross-over trial on antibiotic treatment of CAP was performed in 7 hospitals.[18] As this impacted empirical antibiotic treatment choice, patients hospitalized during the trial period were excluded from the current analysis.

Data on treatment restrictions during hospitalization were retrospectively collected from the medical records by one author (TM); application of treatment restrictions

within 48 hours after hospital admission only were determined. This window of 48 hours was chosen to ensure that physicians and patients had sufficient time to make a balanced decision regarding a treatment restriction and for documentation, and because treatment restrictions applied after 48 hours might represent treatment failures. In case of alterations in treatment restrictions within the 48 hours window, e.g. due to change in prognosis or requested by the patient, the first documented treatment restriction status was recorded.

Patients were categorized in four groups based on their treatment restriction status. Patients receiving no treatment restrictions, or with no documentation of treatment restriction status, were considered to receive full treatment, classified as code A. Patients receiving a DNR status, defined as a physician's directive to limit resuscitative efforts, e.g. chest compression or defibrillation, in case of a cardiopulmonary arrest, were classified as code B.[19] Code C included patients who received a combination of restrictions, mostly a DNR status combined with another restriction, typically a DNV order or a restriction in ICU admission. Additional restrictions may include withholding hemodialysis, and surgical interventions. Patients who did not receive any treatment with curative intent were considered to be fully restricted or to receive palliative care only (code D). Documentation of treatment restriction status on admission was standard of care in all participating hospitals.

Smoking was defined as existent when patients were smokers at the time of presentation or quit smoking less than 2 years before admission. Pneumonia severity at the time of presentation was estimated with the pneumonia severity index (PSI).[20]

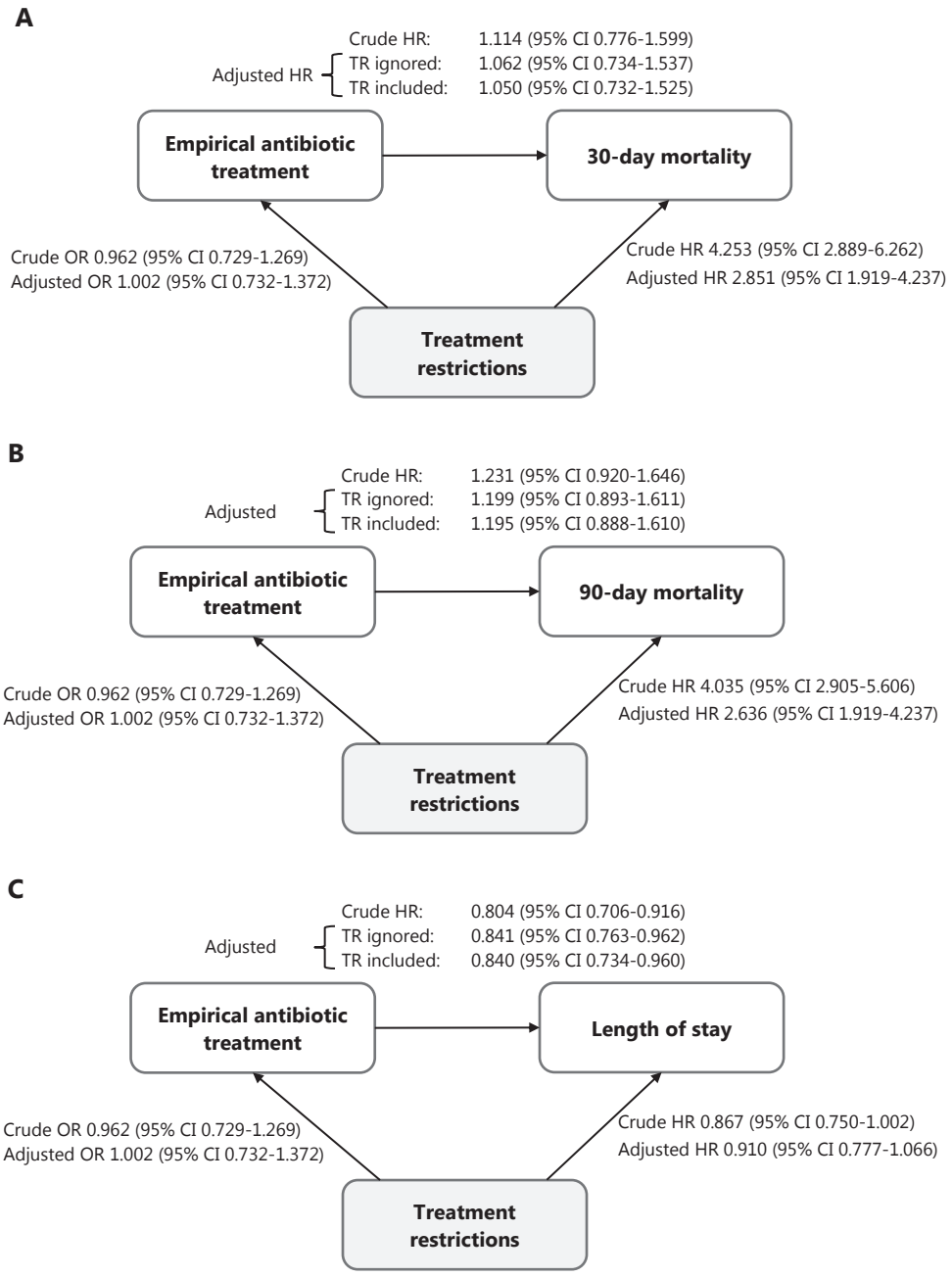
Empirical antibiotic therapy was specified as antibiotic treatment initiated within 24 hours of admission. Antibiotic therapy with atypical coverage was defined as receiving antibiotics active against Mycoplasma pneumonia, Legionella pneumophila and Chlamydia pneumoniae, including quinolones, macrolides and tetracyclins. [21,22]

The primary outcome was all-cause 90-day mortality after hospital admission. Secondary outcome variables included all-cause 30-day mortality and length of hospital stay.

Medical ethical aspects

The trial was approved by the Netherlands Ministry of Health, Welfare and Sport, the Ethics Review Board of the University Medical Center Utrecht, and Ethics Review Boards of all participating hospitals. Collection of data on treatment restrictions was covered by the trial's informed consent and additional approval by local trial investigators was acquired.

Figure 2 – Assessment of treatment restrictions as possible confounders



(A) The influence of treatment restrictions on the association between empirical antibiotic treatment and 30-day mortality, (B) The influence of treatment restrictions on the association with 90-day mortality, and (C) on length of stay. Abbreviations: CI: confidence interval; HR: hazard ratio; OR: odds ratio; TR: treatment restrictions

Statistical analysis

Data analysis software (IBM SPSS Statistics 20.0) was used for all statistical analyses. A p-value of <0.05 was considered statistically significant. Because of the small number of patients with treatment restrictions, we compared patients with code A (full treatment) with patients with code B, C, or D (receiving any treatment restriction).

Independent predictors of treatment restrictions were defined in multivariate logistic regression analysis, using the following candidate predictors: age, gender, use of antibiotics two weeks prior to hospital admission, hospital admissions in the past year, smoking, and an adapted PSI score (i.e. calculation of pneumonia severity without inclusion of age and gender). Comorbidities that are not included in the PSI score (i.e. diabetes, cardiovascular disease, chronic pulmonary disease and tuberculosis) were included as separate variables.

To investigate if the presence of treatment restrictions confounds the association between antibiotic treatment and clinical outcomes, we used a three-step approach (Figure 2). The first step was to evaluate the univariate association between treatment restrictions and empirical antibiotic treatment. Second, the univariate and multivariate association between treatment restrictions and the clinical outcomes (30-day mortality, 90-day mortality and length of stay) were investigated, using cox proportional hazards regression, using time to death and time to discharge alive as the outcomes, respectively. The third step was to evaluate whether addition of treatment restrictions in a multivariate model changed the hazard ratio of antibiotic treatment on outcome variables. Changes in the effect estimates of 10% or more were considered confirmation of a confounding effect.[23,24]

RESULTS

During the study, 3,202 episodes of suspected CAP were identified in the 58 participating hospitals, of which 1,833 had confirmed CAP. Data on treatment restrictions were collected from 29 of 58 hospitals that had identified 1,093 episodes of confirmed CAP (Figure 1).

In total, 797 (72.9%) episodes of CAP had no treatment restriction, of which 696 (63.7%) episodes had a documented code A and 101 (9.2%) episodes had no documentation of treatment restriction status within 48 hours of admission, which were also classified as code A (Table 1). In 88 (8.1%) episodes, a DNR order was documented (code B), 201 (18.4%) episodes received other restrictions in addition to a DNR order (code C), and 7 (0.6%) cases were on palliative care (code D). Nearly all treatment restrictions were

Table 1 - Baseline characteristics

Characteristic	Cohort (N=1,093)	Code A (N=797)	Code B (N=88)	Code C (N=201)	Code D (N=7)
Age ł	77 (72-83)	76 (72-81)	82 (76-87)	81 (75-86)	78 (75-87)
Male	806 (73.7%)	587 (73.7%)	62 (70.5%)	150 (74.3%)	7 (100%)
ADL dependent	352 (32.2%)	201 (25.2%)	43 (48.9%)	104 (51.7%)	4 (57.1%)
CSHA Clinical Frailty Scale					
Well (1-3)	487 (45.8%)	403 (50.6%)	41 (46.6%)	42 (20.8%)	1 (14.3%)
Apparent / mild (4-5)	403 (36.9%)	300 (37.7%)	32 (36.4%)	88 (43.6%)	2 (28.6%)
Moderate / severe (6-7)	184 (16.8%)	94 (11.8%)	15 (17%)	71 (35.3%)	4 (57.1%)
Smoking					
Not current smoker	656 (60%)	489 (61.4%)	48 (54.5%)	116 (57.7%)	3 (42.9%)
Current smoker	201 (18.4%)	137 (17.2%)	20 (22.7%)	43 (21.3%)	1 (14.3%)
Unknown	236 (21.6%)	171 (21.5%)	20 (22.7%)	42 (20.8%)	3 (42.9%)
Comorbidities					
Cardiovascular disease	572 (52.3%)	345 (43.3%)	41 (46.5%)	83 (41.3%)	3 (42.9%)
Heart failure	301 (27.5%)	203 (25.5%)	34 (38.6%)	66 (32.8%)	1 (14.3%)
Cerebrovascular disease	117 (10.7%)	77 (9.7%)	17 (19.3%)	23 (11.4%)	0
Chronic lung disease	676 (61.8%)	483 (60.6%)	56 (63.6%)	132 (65.7%)	5 (55.6%)
Diabetes mellitus [&]	254 (23.2%)	175 (22.0%)	21 (23.9%)	57 (28.2%)	1 (14.3%)
Chronic kidney disease [#]	9 (0.8%)	4 (0.5%)	0	5 (2.5%)	0
HIV/AIDS	0	0	0	0	0
Primary malignancy [§]	36 (3.3%)	22 (2.8%)	7 (8.0%)	35 (17.3%)	0
Generalized malignancy	129 (11.8%)	67 (8.4%)	15 (17.0%)	43 (21.3%)	4 (57.1%)
Chronic liver disease	12 (1%)	9 (1.1%)	1 (1.1%)	2 (0.9%)	0
Tuberculosis	1 (<0.1%)	0	1 (0.9%)	0	0
Asplenia	1 (<0.1%)	1 (0.1%)	0	0	0
Received prior antibiotics[^]	322 (29.5%)	230 (28.9%)	29 (33.0%)	62 (30.8%)	1 (14.3%)
Hospitalized in past year					
None	484 (44.8%)	393 (49.4%)	36 (40.9%)	54 (26.7%)	1 (14.3%)
1	234 (21.4%)	169 (21.2%)	14 (15.9%)	50 (24.8%)	1 (14.3%)
2 or more	322 (29.5%)	193 (24.2%)	31 (35.3%)	93 (46%)	5 (55.6%)
Unknown	49 (4.6%)	38 (4.8%)	6 (6.8%)	5 (2.5%)	0
Pneumonia severity index					
Class 2	62 (5.7%)	56 (7.0%)	1 (1.1%)	5 (2.5%)	0
Class 3	286 (26.2%)	242 (30.4%)	11 (12.5%)	32 (15.8%)	1 (14.3%)
Class 4	570 (51.2%)	406 (51%)	51 (58.0%)	111 (55.0%)	2 (28.6%)
Class 5	175 (16.0%)	93 (11.7%)	25 (28.4%)	53 (26.4%)	4 (57.1%)

Table 1 - Baseline characteristics (continued)

Characteristic	Cohort (N=1,093)	Code A (N=797)	Code B (N=88)	Code C (N=201)	Code D (N=7)
Ward of admission					
Internal medicine	168 (15.4%)	123 (15.4%)	16 (18.1%)	29 (14.4%)	0
Pulmonology	673 (61.6%)	488 (61.3%)	50 (56.8%)	130 (64.4%)	5 (55.6%)
Intensive care unit	61 (5.6%)	44 (5.5%)	7 (8.0%)	7 (3.5%)	1 (14.3%)
Other	191(17.5%)	140 (17.6%)	15 (17%)	34 (16.9%)	1 (14.3%)
Empirical treatment with atypical coverage	401 (36.7%)	294 (36.9%)	35 (39.8%)	69 (34.3%)	3 (42.9%)
Outcomes					
30-day mortality	123 (11.3%)	54 (6.8%)	18 (20.5%)	45 (22.3%)	6 (85.7%)
90-day mortality*	188 (17.2%)	89 (11.2%)	27 (30.7%)	66 (32.7%)	6 (85.7%)
Length of stay ł	8 (5-12)	8 (5-11)	8 (5-14)	9 (5-13)	2.5 (2-5)

Code A represents 696 episodes with documentation of full treatment within 48 hours and 101 episodes without documentation of treatment restrictions. Abbr.: ADL: activities of daily living; AIDS: acquired immune deficiency syndrome; CSHA: Canadian study of health and aging; HIV: human immunodeficiency virus; IQR: interquartile range
Chronic kidney disease is defined as chronic renal failure or nephrotic syndrome.
& Diabetes mellitus includes all insulin dependent and insulin independent variants.
§ Primary malignancy is defined as the presence of primary malignant tumors, lymphoma, multiple myeloma, leukemia or Hodgkin's disease, requiring treatment with chemotherapy or radiotherapy in the past five years.
^ Received antibiotic treatment in the 14 days prior to the current admission.
* 35 patients were lost to follow up before day 90.
ł Median (IQR).

documented in the first 24 hours (N=986, 90.2%), and in six episodes (0.5%) treatment restrictions were recorded on the second day of admission. Accuracy of documentation varied largely between hospitals, ranging from 100% documentation of treatment restriction status within 48 hours in 11 of 29 hospitals to 46% in one hospital. In 8 hospitals (27.6%) documentation accuracy was below 85%.

Patients with treatment restrictions were older, had more comorbidities, and had a higher PSI score compared to patients that received full treatment (Table 1). 401 CAP episodes (36.7%) were treated with empirical antibiotic treatment active against atypical pathogens within 24 hours of admission, ranging from 34.3% (n=69) for code C, to 39.8% (n=35) for code B episodes. All-cause mortality within 90 days of admission was 17.2% (n=288) and ranged from 11.2% (n=89) in patients with code A to 85.7% (n=6) in patients with code D. The median length of stay was 8 days (IQR 5-12) and ranged from 2.5 days (IQR 2-5) for code D to 9 (IQR 5-13) days for code C patients.

Predictors of treatment restrictions

In multivariate analysis, age, number of previous hospital admissions in the past 12 months, current smoking, PSI-score, cardiovascular disease, and ADL dependency were independently associated with presence of treatment restrictions (Table 2).

Table 2 Variables associated with treatment restrictions within 48 hours

Predictor		OR (95% CI)	P-value
Age *		1.114 (1.086-1.142)	< 0.001
ADL dependence		2.012 (1.480-2.73)	< 0.001
Cardiovascular disease		0.689 (0.508-0.934)	0.016
PSI-score *		1.017 (1.010-1.023)	< 0.001
Hospitalized in the past yr		2.237 (1.640-3.051)	< 0.001
Smoking	No current smoker	Reference	
	Current smoker	1.864 (1.253-2.771)	0.002
	Unknown status	1.100 (0.758-1.595)	0.617

PSI: Pneumonia Severity Index, calculated without inclusion of age and gender. CI: confidence interval. OR:odds ratio. Comorbidities that are not included in the PSI score were included as separate variables: i.e tuberculosis, diabetes, cardiovascular disease and chronic pulmonary disease.
* Per unit increase

Associations of treatment restrictions with atypical coverage and clinical outcomes

The crude odds ratio (OR) for patients with a treatment restriction to receive atypical antibiotic treatment was 0.962 (95% CI 0.729-1.269), the adjusted OR was 1.002 (95% CI 0.732-1.372) (Figure 2). The crude and adjusted hazard ratio (HR) for patients with a treatment restriction on 90 day mortality was 4.035 (95% CI 2.905-5.606) and 2.636 (95% CI 1.912-3.634), respectively. For 30-day mortality, the crude and adjusted HR was 4.253 (95% CI 2.889-6.262) and 2.851 (95% CI 1.919-4.237), respectively. For the association between treatment restrictions and length of stay, the crude and adjusted HR were 0.867 (95% CI 0.750-1.002) and 0.910 (95% CI 0.777-1.066), respectively, representing a (not statistically significant) longer length of stay for patients with a treatment restriction.

Confounding effect of treatment restrictions

The crude HR of the associations between atypical coverage and clinical outcomes were 1.114 (95% CI 0.776-1.599) for 30-day mortality, 1.231 (95% CI 0.920-1.646) for 90-day mortality and 0.804 (95% CI 0.706-0.916) for length of stay (Figure 2).

Multivariate survival analyses were performed with and without the inclusion of treatment restrictions as potential confounders. For 90-day mortality, the adjusted HR for atypical coverage was 1.199 (95% CI 0.893-1.611) without treatment restrictions and 1.195 (95% CI 0.888-1.610) with the inclusion of treatment restrictions in the multivariate model (relative change in HR 0.3%). For 30-day mortality the adjusted HR was 1.062 (95% CI 0.734-1.537) without treatment restrictions and 1.050 (95% CI 0.732-1.525) with treatment restrictions (relative change in HR 1.1%). For length of stay we found an adjusted hazard ratio of 0.841 (95% CI 0.736-0.962) for atypical coverage

when treatment restrictions are not included as confounder and 0.840 (95% CI 0.734-0.960) when we included treatment restrictions in the model (relative change 0.1%). All relative changes in effect estimate were below the predefined margin of 10%, indicating that treatment restriction was not a confounder in this study.

DISCUSSION

In this study, treatment restrictions were applied within the first 48 hours in 27.1% (n=296) of elderly patients hospitalized with CAP. This is in agreement to previous studies, reporting treatment restrictions in 16.4% to 28.5% of elderly CAP-patients.[12,15,25] Patients receiving treatment restrictions were older and had more comorbidities compared to those without treatment restrictions. We also identified several factors associated with treatment restrictions that contain information on patient well-being. Treatment restrictions were also associated with a more than twofold increased risk of mortality, independent of other factors, in agreement with previous findings. Our observations confirm that treatment restrictions could serve as a sensitive marker for multimorbidity and prognosis.[11,26]

The absence of a confounding effect due to treatment restrictions resulted from absence of difference in the proportion of patients receiving antibiotic therapy covering atypical pathogen. Although our findings suggest that treatment restrictions do not act as a confounder, and thus do not need to incorporated in the analyses of effects of empirical antibiotic therapy in observational studies, this may not apply to all settings. Effects of DNR orders on the willingness of physicians to perform diagnostic testing or start an intervention has been shown previously, although not in CAP patients.[27] Yet, treatment restrictions were also strongly associated with other confounders, such as age and comorbidities. Therefore, the effect of including treatment restrictions as a separate confounder may be negligible when other strongly associated confounders are already in the model.[28]

Our study also demonstrated that in Dutch hospitals 90.7% of the patients had a treatment restriction status reported within 48 hours of admission, and 90.2% within 24 hours. The 101 patients (9.2%) without appropriate recording indicate room for improvement in documenting treatment restrictions. Besides, there was variation in treatment restriction documentation between hospitals, which is probably representative for the Netherlands, but may not be generalizable to other countries.

The relatively large sample size and the collection of different types of treatment restrictions are the major strengths of the current study. DNR orders represented the majority of treatment restrictions given within 48 hours of admission; however, nine

patients received treatment restrictions without DNR order, which we would have missed if we had only collected DNR orders.

Several limitations of our study should be mentioned. We extracted routinely documented data from the medical records and used 48 hours as a cut-off point for recording treatment restrictions, therefore we may not have recorded all treatment restrictions because of inadequate or delayed documentation. Furthermore, we aimed to investigate the effect of different extents (code A to D) of restrictions. Unfortunately, the small number of patients with codes C and D precluded a separate analysis of these groups. Last, generalizability of the study results may be reduced by differences in attitudes towards treatment restrictions, which may lead to different patients receiving a treatment restriction or may have consequences for subsequent treatment choices.

In conclusion, in hospitalized CAP patients, treatment restrictions are a sensitive proxy for severity of comorbidity, frailty and prognosis. Treatment restrictions did not confound associations between empirical antibiotic treatment and clinical outcome of CAP. However, given the strong and independent association with clinical outcome, documentation of treatment restrictions in future studies is recommended.

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Chapter 10 Predictors of bacteraemia in patients with suspected community-acquired pneumonia

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ABSTRACT

The diagnostic yield of blood cultures is limited in patients with community-acquired pneumonia (CAP). Yet, positive blood culture results provide important information for antibiotic treatment and for monitoring epidemiologic trends. We investigated the potential of clinical predictors to improve the cost-benefit ratio of obtaining blood cultures.

Data from two prospective cohort studies of adults with suspected CAP, admitted to non-ICU wards, were combined. Two models were created, one using readily available parameters and one additionally including laboratory parameters.

3,786 patients were included (2,626 (69%) with X-ray confirmed CAP). Blood cultures were obtained from 2,977 (79%) patients (and from 2,107 (80%) with X-ray confirmed CAP). 266 (8.9%) of the patients with a blood culture had bacteraemia. Clinical predictors of bacteraemia were absence of pre-admission antibiotic treatment, pleuritic pain, gastro-intestinal symptoms, tachycardia, tachypnea, hypotension and absence of hypoxia. After including laboratory results in the model, younger age, C-reactive protein, leukocytosis or leukopenia, low thrombocyte count, low sodium level, elevated urea and elevated arterial pH were added, while gastro-intestinal symptoms and hypotension were no longer significant. The area under the receiver operating characteristics curve was 0.66 (95% confidence interval 0.63-0.70) for the first model and 0.76 (95% confidence interval 0.73-0.79) for the second model.

In conclusion, in patients hospitalized with CAP, bacteraemia was moderately predictable using clinical parameters only. We recommend against the use of a risk prediction model for the decision to obtain blood cultures.

INTRODUCTION

Community-acquired pneumonia (CAP) is an infectious disease with a high incidence, especially in elderly or immunocompromized adults, that requires hospitalization in 20-40% of cases.[1,2] Antibiotic treatment is usually empirical, since the causative pathogen is mostly unknown at presentation. Microbiological testing is recommended and positive results may allow pathogen-directed antibiotic treatment.[3–5] Blood cultures are relatively cheap and can be safely obtained. Positive results provide essential information for monitoring longitudinal trends in CAP aetiology and antibiotic susceptibility.[5] However, the advantages for individual patients are less clear. Blood cultures generally suffer from a considerable diagnostic delay, reducing the benefit of streamlining antibiotic treatment.[6] Moreover, reported blood culture positivity in patients hospitalized with CAP has ranged from 5-16%, with growth of common skin contaminants in almost equal proportions of episodes, possibly leading to unjustified changes in antibiotic treatment.[7–12] For these reasons, the recommendation of routinely obtaining blood cultures in all patients with CAP has been questioned. The latest IDSA/ATS guideline recommends to only obtain blood cultures in case of required intensive care unit (ICU) admission, leukopenia, alcohol abuse, severe chronic liver disease, severe obstructive or structural lung disease, asplenia, or if radiologic imaging reveals cavitary infiltrates or pleural effusion.[4] The disadvantage of this approach is that it compromises surveillance of CAP aetiology and antimicrobial resistance. Also, selectively obtaining blood cultures may prohibit pathogen directed therapy in some patients.

To increase efficiency, blood culture drawing could be restricted to patients with a high probability of bacteraemia. Different factors have been associated with bacteraemia in patients with sepsis, including age, previous antibiotic therapy, chills and rigor, vomiting, fever, hypotension, tachycardia, tachypnoea, leukocyte count, thrombocyte count, CRP, creatinine, blood urea nitrogen, and pro-calcitonin.[13–16] In patients hospitalized with X-ray confirmed CAP, absence of prior antibiotic use, chronic liver disease, pleuritic pain, tachycardia, tachypnea, systolic hypotension, temperature, blood urea levels, sodium, and white blood cell count were independent predictors of bacteraemia.[9,17] However, for patient management the domain should not be limited to X-ray confirmed CAP, but include all patients suspected of and treated for CAP and laboratory results (which are generally not available at the time of blood culture taking) should not be included in such models. Therefore, the objective of our study was to identify clinical parameters that predict bacteraemia in patients with clinically suspected CAP admitted to non-ICU wards, and to assess whether a strategy to withhold blood

cultures in low-risk patients would be possible without compromising patient management and surveillance of epidemiological trends.

METHODS

Study subjects

Data from two multi-centre Dutch cohort studies were combined. The CAP-pilot study was a prospective observational study, conducted in 23 hospitals between January 2008 and April 2009 and the CAP-START study was a cluster-randomized cross-over trial, conducted in 7 hospitals between February 2011 and August 2013. Further details about the design of these studies are described elsewhere.[18,19] From both studies, adult patients of 18 years and above, with clinically suspected CAP, initially admitted to a non-ICU ward, were eligible for this analysis. Demographic data, comorbidities, clinical parameters, laboratory data, X-ray results, and antibiotic use were collected from the medical records by trained research nurses and were anonymously recorded. Blood cultures were taken as part of routine clinical care. Blood cultures yielding coagulase-negative staphylococci and other skin contaminants were not considered to represent bacteraemia. Antibiotic susceptibility testing was performed as part of routine care; these were only available for the CAP-START study. Prior antibiotic use was defined as antibiotic use in the 14 days prior to the current admission.

Analysis

Candidate predictors of bacteraemia were selected from the literature and included age, immunocompromised state, chronic liver disease, receipt of pre-hospital antibiotics, gastro-intestinal symptoms, pleuritic pain, chills, confusion, hypotension (systolic blood pressure below 90 mmHg or diastolic blood pressure below 60 mmHg), tachycardia (heart rate above 125 / min), tachypnea (respiratory rate above 30 / min), hypoxia (oxygen saturation below 90% without oxygenation), C-reactive protein, body temperature, leukocyte count, thrombocyte count, sodium, urea, glucose, arterial pH, and presence of an infiltrate on chest X-ray.[9,13–17] Continuous predictors were assessed for linearity with the outcome by visual inspection of Lowess curves. Variables with no linear association were entered in the model using a piecewise linear function, which generates separate regression lines for the variable below and above a specified break point.[20] Missing data were handled using Multivariate Imputation by Chained Equations,[21] except for confusion, gastro-intestinal symptoms, and chills. These were assumed to be absent if not documented in the medical records. Fifty imputed datasets were created.

Prediction models were derived using multivariable logistic regression, starting from the model with all candidate predictors, with stepwise backward elimination to identify

independent predictors, using the likelihood ratio test statistic with a p-value below 0.1 for selection. Two models were created, one only including candidate predictors that are available at the time of blood culture collection, and one also including laboratory and radiology results. The models were internally validated using 200 bootstrap samples. Performance of the models was assessed using the Area Under the Curve (AUC) of the Receiver Operator Characteristic, sensitivity, specificity, and positive and negative predictive values at different risk scores. As a sensitivity analysis, the AUC was also determined in patients with confirmed CAP, defined as at least 2 clinical criteria (cough, production of sputum or change in sputum character, temperature >38.0 or <36.1 degrees Celcius, auscultatory findings consistent with pneumonia, leucocyte count > 10*10^9 / L, CRP > 30 mmol/L, and arterial oxygen pressure <8 kPa) and signs of an infiltrate on chest X-ray according to the local radiologist. Performance of previously published models[9,17] was assessed similarly. Since accepting a lower sensitivity in itself will already reduce the number of required blood cultures (e.g. one could randomly collect blood cultures in 50% of patients to achieve 50% sensitivity), we calculated the truly added value of the prediction model for different sensitivity targets as the sensitivity minus the proportion of patients scoring above the associated cut-off value.

Using the model with readily available data, the optimal cut-off value was chosen such that discrimination was largest. For patients with a risk score below the cut-off value, lost opportunities by omitting the blood cultures were described. This was defined as (1) missing *S. pneumoniae* bacteraemia together with a negative pneumococcal urinary antigen test (PUAT); (2) missing antibiotic resistant pathogens; (3) missing pathogens that are intrinsically resistant to usual empiric antibiotic treatment of CAP.

Patients in whom blood cultures had not been obtained were excluded from the analysis of predictors of bacteraemia. To assess which factors were associated with blood culture drawing, we used logistic regression, using the same candidate predictors. All analyses were performed in R version 3.0.2.[22]

RESULTS

Together, 3,786 patients were initially hospitalized to a non-ICU ward with clinically suspected CAP: 1,503 in the CAP-pilot study and 2,283 in the CAP-START study. Baseline characteristics were comparable between the studies, except for being immunocompromised, which was more frequent in the CAP-START study (Table 1). CAP was confirmed by X-ray in 2,626 patients (69%). Blood cultures were drawn in 2,977 patients (79%), of whom 2,107 (71%) had X-ray confirmed CAP. Bacteraemia was present in 266 (8.9%) of all patients with a blood culture obtained, mostly with

Streptococcus pneumoniae (Table 2), and an additional 91 (3.1%) patients had positive blood cultures with skin contaminants.

Prediction of bacteraemia

A piecewise linear function was needed for temperature (breakpoint at 38°C), leukocyte count (breakpoint at 9.5 * 10^9/L), glucose (breakpoint at 6.5 mmol/L) and urea (breakpoint at 7 mmol/L). Additionally, leukocyte count and urea level were right-truncated at 40 * 10^9/L and 15 mmol/L, respectively, since higher values were rare and not discriminative in univariate analysis.

Table 1 - Baseline characteristics of the study populations

	CAP-pilot (N=1,503)	CAP-START (N=2,283)	Combined (N=3,786)	Missing data (%)
Age	68.28 (15.09)	67.48 (15.71)	67.79 (15.47)	0%
Male gender	913 (60.8%)	1,317 (57.7%)	2,230 (58.9%)	0%
Immunocompromised	197 (13.1%)	533 (23.3%)	730 (19.3%)	0%
Previous antibiotics	495 (33.5%)	749 (33.6%)	1,244 (33.6%)	2.1%
Temperature (°C)	38.21 (1.15)	38.11 (1.07)	38.15 (1.10)	2.6%
Chills	197 (13.1%)	452 (19.8%)	649 (17.1%)	0%
Confusion	161 (10.7%)	204 (8.9%)	365 (9.6%)	0%
Gastrointestinal symptoms	131 (8.7%)	304 (13.3%)	435 (11.5%)	0%
Heart rate > = 125 / min	166 (11.8%)	287 (12.9%)	453 (12.5%)	4%
Respiratory rate > = 30 / min	136 (22.0%)	255 (17.4%)	391 (18.7%)	44.9%
Hypotension*	219 (15.3%)	311 (13.9%)	530 (14.4%)	2.8%
Hypoxia^	255 (18.5%)	369 (19.4%)	624 (19.0%)	13.2%
Leukocytes (10^9/L) #	13 (9.6 - 17.3)	13.1 (9.4 - 17.8)	13.1 (9.5 - 17.5)	0.3%
Thrombocytes (10^9/L) #	NA†	250 (191 - 326)	250 (191 - 326)	41.2%
CRP (mg/L) #	103 (38 - 219)	118 (54 - 222)	114 (46 - 221)	1.5%
Sodium (mmol/L)	136.31 (7.33)	136.43 (4.27)	136.38 (5.68)	0.8%
Urea (mmol/L)	6.9 (5 - 9.6)	6.6 (4.7 - 9.3)	6.7 (4.8 - 9.4)	4%
Glucose (mmol/L) #	7.1 (6.1 - 8.5)	7.1 (6.2 - 8.5)	7.1 (6.1 - 8.5)	6.8%
Arterial pH	7.43 (0.10)	7.45 (0.06)	7.44 (0.08)	18.2%
Presence of infiltrate	1,041 (69.3%)	1,585 (69.4%)	2,626 (69.4%)	0%
Blood cultures taken	1,240 (82.5%)	1,737 (76.1%)	2,977 (78.6%)	0%

Data given as mean (SD) or N (%), unless otherwise indicated. # median (inter-quartile range). NA: not available.
* Defined as systolic blood pressure < 90 mmHgor diastolic blood pressure < 60 mmHg.
^ Hypoxia was defined as oxygen saturation below 90% without oxygenation.
† Thrombocyte count was not recorded in the CAP-pilot study.

In the first model, only using data available at the time of blood culture collection, independent predictors of bacteraemia were: absence of pre-admission antibiotic treatment, pleuritic pain, gastro-intestinal symptoms, tachycardia, tachypnea, hypotension and absence of hypoxia (Table 3). Discrimination of the model was poor, with an AUC of 0.66 (95% CI 0.63-0.70) both in the full cohort and in the subset of patients with X-ray confirmed CAP (Supplementary Appendix Figure S1A and B). In internal validation, optimism of the model was 1.9%, yielding a bias-corrected AUC of 0.64 (95% CI 0.59-0.69).

After adding laboratory and radiology results to the candidate predictors, gastro-intestinal symptoms and hypotension were no longer statistically significant, while the following variables were added to the model: younger age, C-reactive protein, leukocyte count, thrombocyte count, sodium level, urea level and arterial pH. Discrimination of this model was moderate, with an AUC of 0.76 (95% CI 0.73-0.79) in the total population and 0.76 (95% CI 0.73-0.80) in patients with X-ray confirmed CAP (Supplementary Appendix Figure S1C and D). In internal validation, optimism of the model was 2.1%, yielding a bias-corrected AUC of 0.74 (95% CI 0.70-0.78).

Table 2 - pathogens isolated from blood cultures and numbers classified as low or high risk by the model without laboratory results (using 60% sensitivity target)

Pathogens	Total *	Risk < 0.09	Risk >= 0.09	% in low risk group
Streptococcus pneumoniae	167	62	105	37%
Other Streptococcus species	19	6	13	32%
Staphylococcus aureus	15	8	7	53%
Other gram-positives[1]	4	2	2	50%
Enterobacteriaceae[2]	47	21	26	45%
Haemophilus influenzae	7	2	5	29%
Pseudomonas aeruginosa	7	5	2	71%
Other gram-negatives[3]	6	3	3	50%

[1)] *Enterococcus faecalis* (3x), unspecified gram-positive coccus.
[2)] *Citrobacter diversus*, *Enterobacter cloacae*, *Escherichia coli* (31x), *Klebsiella oxytoca* (5x), *Klebsiella pneumoniae* (4x), *Morganella morganii*, *Proteus mirabilis* (3x), Salmonella enteritidis.
[3)] Acinetobacter species, *Capnocytophaga canimorsus, Fusobacterium necrophorum,* Moraxella species, *Porphyromonas asaccharolytica*, unspecified gram-negative rod.
* Six patients had two different pathogens, making the total number of patients with a pathogen 266: *E. coli + K. oxytoca*, *E. coli + K. pneumoniae* (2x), *E. cloacae + P. mirabilis*, *P. aeruginosa + P. mirabilis*, and *P. aeruginosa + S. aureus.*

Table 3 - Multivariable models of predictors independently associated with bacteraemia

	Model without laboratory results				Model including laboratory results			
	Beta	**SE**	**OR**	**95% CI**	**Beta**	**SE**	**OR**	**95% CI**
(Intercept)	-2.533	0.112			-13.957	8.232		
(+ intercept if leukocytes > 9.5) †	-				-0.884	-		
(+ intercept if urea > 7) †	-				1.754	-		
Age *	-				-0.009	0.005	0.991	(0.981 to 1.001)
Previous antibiotics within 14 days before admission	-0.786	0.171	0.456	(0.326 to 0.637)	-0.698	0.177	0.498	(0.352 to 0.703)
Pleuritic pain	0.565	0.163	1.760	(1.279 to 2.421)	0.596	0.178	1.815	(1.281 to 2.570)
Gastro-intestinal symptoms	0.547	0.170	1.727	(1.237 to 2.413)	-			
Heart rate > = 125/min	0.564	0.166	1.757	(1.269 to 2.433)	0.536	0.176	1.709	(1.211 to 2.413)
Respiratory rate > = 30/min	0.421	0.173	1.524	(1.085 to 2.139)	0.406	0.179	1.501	(1.056 to 2.133)
Hypotension §	0.486	0.164	1.627	(1.179 to 2.244)	-			
Hypoxia ǂ	-0.348	0.192	0.706	(0.484 to 1.029)	-0.384	0.202	0.681	(0.459 to 1.012)
C-reactive protein (mg/L) $	-				0.024	0.005	1.024	(1.013 to 1.034)

Leukocytes (values < = 9.5*10^9/L) * #	-	-0.052	0.045	0.949	(0.869 to 1.036)
Leukocytes (values > 9.5*10^9/L) * #	-	0.041	0.010	1.041	(1.021 to 1.062)
Trombocytes (10^9/L) $	-	-0.017	0.008	0.983	(0.968 to 0.998)
Sodium (mmol/L) *	-	-0.027	0.016	0.974	(0.944 to 1.005)
Urea (values < = 7 mmol/L) * ^	-	0.329	0.077	1.389	(1.195 to 1.615)
Urea (values > 7 mmol/L) * ^	-	0.078	0.028	1.081	(1.024 to 1.142)
Arterial pH @	-	0.186	0.103	1.204	(0.984 to 1.474)

OR: Odds ratio. CI: confidence interval. * per unit increase. $ per 10 units increase. @ per 0.1 units increase. # right truncated at a value of 40*10^9/L. ^ right truncated at a value of 15 mmol/L. † Leukocyte count and urea are modelled using piecewise linear transformation, therefore, an additional intercept has to be added to the regression line for patients with a value above the break point. § Hypotension was defined as diastolic blood pressure < 60 mmHg or systolic blood pressure <90 mmHg. ǂ Hypoxia was defined as oxygen saturation below 90% without oxygenation. Variables not in any of the models: being immunocompromised, history of chronic liver disease, chills, confusion, body temperature, glucose, and presence of an infiltrate on chest X-ray.

Performance of these models and of previously published models is given in Table 4. For different sensitivity targets, proportions of patients in whom blood culture collection can be prevented, using either of the two models, is given in Figure 1. The maximum proportion of blood cultures preventable by the model without laboratory results was 25%, using a risk cut-off of 0.09, yielding a sensitivity of 60%. For the model including laboratory results, the maximum reduction by the model was 36%, using a risk cut-off of 0.08, yielding a sensitivity of 73%.

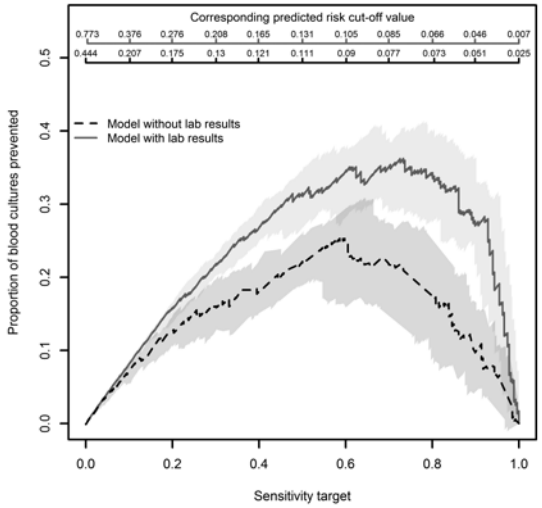

Figure 1 - Proportion of all patients in which obtaining a blood culture can be prevented by either of the two models.

For a given sensitivity target, the base scenario in which no model is used, assumes that a random selection equal to the sensitivity will have a blood culture obtained (e.g. 60% of patients need to be cultured to achieve 60% sensitivity). After applying the model, the proportion of prevented blood cultures is calculated as sensitivity minus proportion of patients scoring above the cut-off value associated with this sensitivity (e.g. in the model without lab results 35% of patients need to be cultured to achieve 60% sensitivity; the proportion of blood cultures prevented by the model equals 25%).

Implications for patient management

We, hypothetically, applied the model without laboratory results to the current patient population and assumed that blood cultures were omitted in patients with a risk score below 0.09 (low risk group, i.e. 65% of the total population). In that scenario, 109 (40%) of all pathogens would have been missed (Table 2). Among the 62 episodes of *S. pneumoniae* bacteraemia in the low-risk group, 30 (48%) were PUAT positive which would have allowed streamlining of therapy. Yet, 24 (39%) were PUAT negative (sensitivity 56%) and in 8 (13%) episodes PUAT was not performed. Comparable PUAT results were obtained in the 167 *S. pneumoniae* cases in the high-risk group: 45% were positive, 46% negative, and 10% not tested.

Of 157 patients with bacteraemia in the CAP-START study, data on antibiotic susceptibility were available for 126 (80%) pathogens, all in unique patients (47 patients in the low risk group and 79 in the high-risk group). Resistance to penicillin / amoxicillin, the recommended antibiotic treatment in this patient population according to Dutch guidelines,[5] was observed in ten patients in the low-risk group (4 *Escherichia coli*, 1 *Haemophilus influenzae*, 1 *Klebsiella oxytoca*, 3 *Staphylococcus aureus*, and

1 Moraxella species) and ten in the high-risk group (3 *E. coli*, 2 *H. influenzae*, 1 *K. oxytoca*, 1 *K. pneumoniae*, 1 *Morganella morganii*, and 2 *S. aureus*). Resistance to amoxicillin-clavulanic acid or cephalosporins was found in only one patient with *M. morganii* bacteraemia in the high-risk group.

Table 4 - Performance of prediction models at different cut-off values

Models without laboratory results						
Model	**Cut-off**	**% >= cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Current study AUC: 0.64 (95% CI 0.59-0.69)* *Cut-off values are predicted risks*	5.0%	80.1%	89.8%	20.8%	10.0%	95.4%
	7.5%	51.6%	72.9%	50.5%	12.6%	95.0%
	9.0%	34.7%	59.8%	67.8%	15.4%	94.5%
	11.0%	28.0%	50.0%	74.1%	15.9%	93.8%
	14.0%	10.0%	25.2%	91.5%	22.6%	92.6%
Falguera et al.[9] AUC: 0.64 (95% CI 0.61-0.68) *Cut-off values are number of points*	1	81.8%	91.4%	19.2%	10.0%	95.8%
	2	38.1%	58.6%	64.0%	13.8%	94.0%
	3	10.8%	25.6%	90.6%	21.1%	92.5%
	4	1.5%	5.3%	98.9%	31.8%	91.4%
	5	0.2%	0.8%	99.9%	40.0%	91.1%
Metersky et al.[17] AUC: 0.62 (95% CI 0.59-0.65) *Cut-off values are number of points*	1	76.7%	89.1%	24.6%	10.4%	95.8%
	2	23.5%	39.5%	78.1%	15.0%	92.9%
	3	3.2%	7.1%	97.2%	20.2%	91.4%
	4	0.2%	0.8%	99.8%	28.6%	91.1%
Models including laboratory results						
Model	**Cut-off**	**% >= cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Current study AUC: 0.74 (95% CI 0.69-0.78)* *Cut-off values are predicted risks*	5.0%	59.0%	88.0%	43.9%	13.3%	97.4%
	7.5%	40.0%	74.8%	63.4%	16.7%	96.2%
	10.0%	27.9%	62.4%	75.4%	20.0%	95.3%
	12.5%	20.2%	51.9%	82.9%	22.9%	94.6%
	17.5%	11.8%	37.2%	90.7%	28.2%	93.6%
	22.5%	6.8%	26.3%	95.1%	34.7%	92.9%
Metersky et al.[17] AUC: 0.69 (95% CI 0.66-0.73) *Cut-off values based on the linear predictor*	-0.106	82.3%	93.6%	18.8%	10.2%	96.8%
	0.000	76.3%	91.0%	25.2%	10.7%	96.6%
	0.095	47.3%	74.4%	55.4%	14.1%	95.7%
	0.641	29.3%	54.9%	73.3%	16.8%	94.3%
	1.229	11.0%	26.3%	90.6%	21.5%	92.6%

PPV: positive predictive value. NPV: negative predictive value. * For comparison with previously published models, the AUC of the current model is bias-corrected, since it was developed and validated in the same dataset.

Of seven patients with *Pseudomonas aeruginosa* isolated from the blood culture, five were in the low risk group, of which two were empirically treated with ciprofloxacin. In one other patient *P. aeruginosa* was isolated from sputum. The remaining two were empirically treated with amoxicillin-clavulanic acid and sputum culture was not performed in one and negative in the other patient.

Predictors of obtaining blood cultures

Blood cultures were not obtained from 809 (21%) patients. Presence of hypothermia or fever had a strong association with obtaining blood cultures, while younger age, confusion, presence of chills, tachypnea, elevated CRP level, leukopenia or leucocytosis, thrombocytopenia or thrombocytosis, and elevated blood glucose level were all weak predictors of obtaining blood cultures (Supplementary Appendix Table S1).

DISCUSSION

In patients hospitalized with clinically suspected CAP, seven readily available parameters and six parameters available after laboratory examination were independent predictors of bacteraemia. The model without laboratory results was marginally predictive with a bias-adjusted AUC of 64%, while the model with laboratory results had a bias-adjusted AUC of 74%.

The first model had similar discriminative power as two previously published models.[9,17] Apparently, accurate prediction of bacteraemia is not feasible without using laboratory results. The slightly better performance of our second model compared to a previously published model may result from using continuous variables and piecewise linear transformations for the laboratory results.

It has been argued that blood cultures should not be obtained in all CAP patients, but only in patients at high risk of bacteraemia.[7,9–11] However, such a policy would have led to several missed opportunities for optimizing antibiotic treatment in our population. By far the most frequently identified pathogen by blood culture is *S. pneumoniae*. Identification of this pathogen provides the opportunity to deescalate antibiotic treatment to penicillin or amoxicillin. This could also be achieved with urinary antigen testing, yet, the sensitivity of this test in bacteraemic patients appeared to be only 52% in our cohort. This is low compared to previously reported sensitivities that range from 65% to 92%.[5] Consequently, omitting blood cultures decreases the proportion of patients in which physicians feel comfortable to switch to narrow-spectrum antibiotics. Antibiotic resistance was present in only a few bacteraemia isolates and there was no obvious difference between patients at low or high risk of bacteraemia. Although a relatively low proportion of CAP patients had resistant pathogens isolated from blood,

these will obviously have important consequences for antibiotic treatment, in particular in the few cases of *P. aeruginosa* bacteraemia that were not covered by empirical treatment and in whom *P. aeruginosa* was not found in sputum cultures.

Pathogens obtained from blood cultures are also important for monitoring epidemiological trends in CAP aetiology and antibiotic resistance. Use of a model to omit blood cultures in low-risk patients will reduce the number of pathogens identified, which may be acceptable. For the model with readily available parameters, the optimal discrimination was reached at a risk score of 0.09, yielding a sensitivity of 60%. Compared to the current situation, blood cultures could be omitted in 65% of patients when using this cut-off value, of which 40% is due to setting the sensitivity target and 25% is due to selection of high-risk patients by the model. More importantly, use of the model may also affect the distribution of detected pathogens or resistance patterns, e.g. if the model is more sensitive to certain pathogens. In our study, there were no clear differences in distributions of pathogens or in proportions of resistance between the low and high risk patients, but the numbers are too small to draw firm conclusions.

Models including laboratory results predicted bacteraemia better. Yet, in patients presenting with CAP, blood cultures are usually collected at the same time as blood samples for laboratory results, and changing this practice to allow additional sampling for blood cultures in selected patients seems unrealistic. Models predicting the risk of bacteraemia could still be beneficial for research purposes. For example in trials with a minimum required proportion of bacteraemic patients, inclusion could be based on the risk of bacteraemia. Also, adjustment for risk of bacteraemia in observational studies can be achieved using the model.

Some aspects of the study need to be addressed. First, in contrast to previous studies, our domain consisted of patients with clinically suspected CAP. Since these are the patients typically managed according to CAP guidelines, our study domain ensures generalizability of our findings to clinical practice. For example, for patients that turn out to have a different source of infection, obtaining blood cultures may still be beneficial, even though the clinical suspicion of CAP is not confirmed. On the other hand, the inclusion of patients with a different source of infection or non-infectious disease may have increased heterogeneity in clinical presentation, thereby hampering accurate prediction. For this reason, we performed a sensitivity analysis in patients with confirmed CAP, which yielded the same AUCs. Second, blood cultures were not obtained in 21% of patients and factors predicting bacteraemia and obtaining blood cultures partly overlapped, which may have attributed to the moderate discrimination. In particular, abnormal body temperature had a strong association with obtaining blood cultures, but was not a predictor of bacteraemia; the latter may have resulted from

selection bias due to the presence of fever or hypothermia. Third, although most candidate predictors were selected from previous publications, we used urea instead of creatinine, because creatinine was not available in our study data. Urea is also used in the CURB-65 score, widely used to predict 30-day mortality in CAP,[23] and appears to be a strong predictor of bacteraemia. Procalcitonin is a known predictor of bacteraemia in sepsis,[24] but is currently not obtained in routine clinical practice and is, therefore, not useful for clinical prediction. Prior antibiotic use was associated with a reduction of the yield of blood cultures by 50%. Unfortunately we had no data on the timing of in-hospital antibiotic use and blood culture collection. Obviously, collection of blood cultures before administration of antibiotic therapy should always be attempted. Fourth, data on respiratory rate, thrombocyte count, arterial pH, and hypoxia were frequently missing, which may have compromised our analysis. However, consistent parameter estimates were derived from individual imputed datasets (data not shown). Fifth, combining two study cohorts may compromise the study if different in- and exclusion criteria are used. In the CAP-pilot study, patients with known bronchial obstruction, pulmonary malignancies or metastases, AIDS, a history of *Pneumocystis jirovecii* pneumonia, and active tuberculosis were excluded. Although each of these conditions is relatively rare, the proportion of immunocompromised patients in this study was lower compared to the CAP-START study. Other baseline characteristics and the proportion of bacteraemic patients were comparable. Last, we did not split data into a derivation and validation cohort. Instead we used internal validation to assess model optimism, which turned out to be small. The use of a piecewise linear function for urea and leukocyte counts, with a break point based on our own data, might reduce generalizability of the model including laboratory data. If so, this would only further support our finding that prediction models of bacteraemia in CAP have moderate discrimination.

In conclusion, clinical parameters can only moderately predict the presence of bacteraemia. Given the limited added value of the model, the relatively low costs and non-invasiveness of the blood culture, and the potential benefits for patient management and surveillance of epidemiological trends, we recommend against the use of a risk prediction model for the decision to obtain blood cultures.

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Potential conflicts of interest.

All authors declare that there are no conflicts of interests

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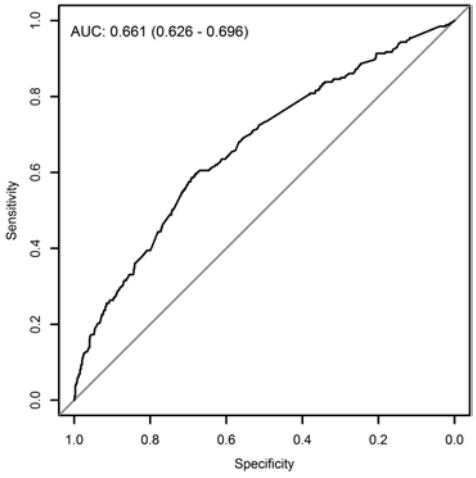
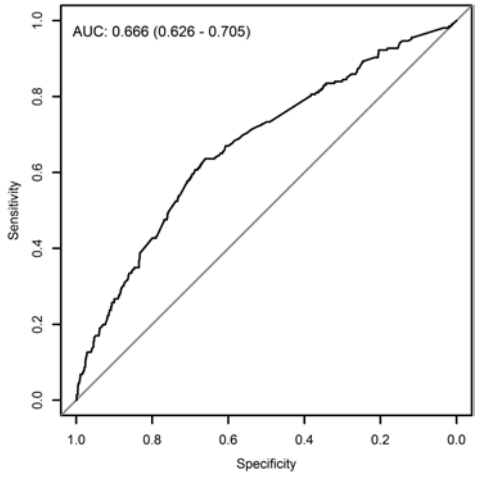
SUPPLEMENTARY APPENDIX

Figure S1 - ROC-curves of the two models in clinically suspected and confirmed CAP patients.

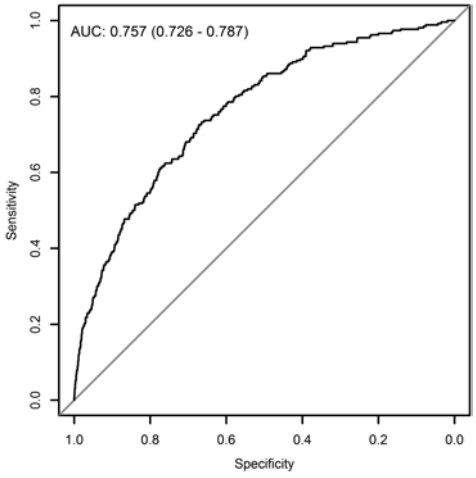
A. Model without lab parameters (all suspected CAP patients)



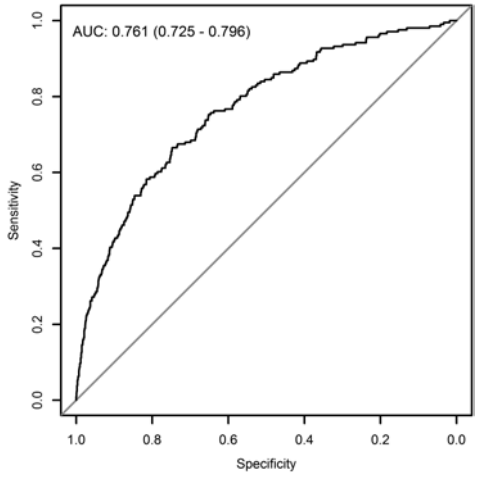
B. Model without lab parameters (X-ray confirmed CAP patients)



C. Model including lab parameters (all suspected CAP patients)



D. Model including lab parameters (X-ray confirmed CAP patients)



Abbreviations: ROC: receiver operating characteristic; AUC: area under the curve. A: ROC-curve of model without laboratory and radiology results in patients with clinically suspected CAP. B: ROC-curve of model without laboratory and radiology results in patients with confirmed CAP, defined as presence of at least 2 clinical criteria and signs of an infiltrate on chest X-ray. C: ROC-curve of full model in patients with clinically suspected CAP. D: ROC-curve of full model in patients with confirmed CAP.

Table S1 - Factors associated with obtaining blood cultures

Variable	OR	95% CI	Contribution to AUC #
Age *	0.990	(0.984 to 0.997)	0.2%
Chills	1.661	(1.252 to 2.204)	0.2%
Confusion	1.386	(0.992 to 1.936)	0.0%
Tachypnea	1.296	(0.955 to 1.758)	0.0%
Temperature			14.7%†
(values < 37° Celcius) *	0.670	(0.509 to 0.882)	
(values > 37° Celcius) *	4.131	(3.571 to 4.779)	
C-reactive protein (mg/L) $	1.010	(1.002 to 1.018)	0.1%
Leukocyte count			0.4%†
(values < 10*10^9/L) *	0.914	(0.859 to 0.972)	
(values > 10*10^9/L) *^	1.038	(1.020 to 1.055)	
Thrombocyte count			0.4%†
(values < 500*10^9/L) *	0.998	(0.997 to 0.999)	
(values > 500*10^9/L) *	1.001	(0.998 to 1.004)	
Blood glucose level (mmol/L)*	1.029	(0.998 to 1.061)	0.1%

OR: odds ratio. CI: confidence interval. AUC: Area Under the Received Operator Characteristic Curve.
Contribution to the AUC was calculated by comparing the full model to the model without each variable.
* OR per one unit increase.
$ OR per 10 units increase.
^ Right-truncated at 40*10^9/L.
† For these variables piecewise linear transformation was used, yielding two effect estimates, but they are considered one variable when calculating contribution to the AUC.

General Discussion

The section on pneumococcal vaccination in elderly is based on:

The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA): what is the future of pneumococcal conjugate vaccination in elderly?

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Future Microbiology 2015 (accepted manuscript)

Different aspects of the prevention and management of community-acquired pneumonia (CAP) in adults were addressed in this thesis. The following two sections summarize and discuss (a) the benefit of 13-valent pneumococcal conjugate vaccine (PCV13) in elderly over 65 years of age and (b) the choice of empirical antibiotic therapy for adults with CAP hospitalized to non-ICU wards. In each section, recommendations for clinical practice and future research directions are given.

PNEUMOCOCCAL VACCINATION IN ELDERLY

Cost benefit ratio

PCV13 is safe and effective in reducing first episode of VT-CAP (46% reduction in per protocol analysis and 38% in the mITT population) and first episode of VT-IPD (75% reduction in per protocol analysis and 76% in the mITT population) in immunocompetent elderly (Chapter 1). Policy decisions on how to use an effective vaccine, however, depend not only on safety and efficacy, but also on the cost-effectiveness of the intervention. In 42,240 subjects the number of prevented first episodes in the mITT population was 40 for VT-CAP and 8 for non-CAP VT-IPD (of 33 VT-IPD cases in the placebo group and 8 in the PCV13 group, 10 and 2 had no confirmed CAP, respectively; data not previously reported) during an average follow-up of 4 years. Consequently, one could calculate that the number needed to treat (NNT) in this trial was approximately 900. Yet, this will be inaccurate (and probably too conservative) for three reasons. First, the trial included a relatively healthy population with exclusion of immunocompromised elderly. The excluded population is more prone to develop PCAP and IPD, but may also benefit less from vaccination. Yet, the combined effect of both aspects is uncertain. It is also uncertain whether the included population is fully representative (with respect to the risks for pneumococcal infection) for the eligible population, as all-cause mortality of the study population was lower compared to the age and gender matched Dutch population (3.6% per year, 13.1% per four years).[1] As a consequence, incidences of PCAP and IPD were probably lower in the trial than they would have been in the general population, which increases the NNT. Second, due to the low sensitivity of blood cultures in PCAP, detection of the primary endpoint required collection of urine samples within 48 hours of hospital admission. This was not always achieved as CAP episodes or urine samples were missed. Based on recalculations of hospital-based and GP-based information we estimated that approximately one third of all-cause CAP was missed. If this proportion would reflect the number of missed primary endpoints, the NNT would also decline with 33% (Chapter 5). Third, the mean follow-up period was 4 years and the VE remained constant over this period. Therefore, a prolonged beneficial effect can be assumed, which will further reduce the NNT.

For several reasons we do not expect that adult immunization with PCV13 will induce additional benefit for unvaccinated elderly through herd protection, nor that it will induce replacement disease by non-VT pathogens, effects seen after introduction of PCVs in children. First, in children the herd protection and replacement effects coincides the replacement of colonizing VT *S. pneumoniae* strains by non-VT strains.[2,3] As the proportion of adults colonized with *S. pneumoniae* is much lower,[2] herd protection and replacement disease from immunization of elderly, if at all present, is expected to be

limited. Second, in the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) the numbers of patients with a first episode of non-VT-CAP was comparable between both study groups (69 in the PCV13 and 68 in the placebo group in the mITT population), suggesting that replacement with other *S. pneumoniae* serotypes had not occurred in the vaccinated individuals during the four years follow-up. Third, although VE against all-cause CAP was not statistically significant, the point estimate of 5% reduction in the mITT analysis is consistent with the reduction of VT-CAP episodes by 38%, given that 13% of the first episodes of all-cause CAP was caused by VT *S. pneumoniae* and that urine collection was omitted in approximately 7% of patients. This also suggests absence of replacement disease by other pathogens, although - in theory - replacement disease could have been counterbalanced by an unobserved protective effect of PCV13 for VT-CAP episodes with false-negative or missing urinary antigen test and culture results.

In a cost-effectiveness analysis that was based on data from the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) and other Dutch cohort studies, the incremental cost-effectiveness ratio of PCV13 vaccination in elderly was below the gross domestic product in 99% of simulations, indicating cost-effectiveness.[4] This analysis was based on the pneumococcal disease burden in 2012 in the Netherlands and several assumptions were needed, such as for vaccine efficacy in immunocompromised elderly. However, due to the relatively low proportion of immunocompromised elderly in the population, overall cost-effectiveness was not sensitive to this assumption.

In summary, for the Dutch situation the cost-benefit ratio of universal vaccination of elderly with PCV13 seems beneficial, under the assumption of VE among immunocompromised elderly and absence of replacement disease. The immunocompromised population though was excluded from the trial, creating considerable uncertainty. For other countries, the cost-benefit ratio will mostly depend on the actual burden of VT pneumococcal disease in elderly.

Decreasing burden of VT disease

Under the assumption that immunization of elderly with PCV13 will not cause replacement disease, the benefit of PCV13 will depend mainly on two parameters: VE and the absolute number of VT-CAP and VT-IPD events that can be prevented. Since the introduction of PCVs in child immunization programs, decreased incidences of VT-IPD have consistently been reported in all age groups, with reductions of over 80% among elderly in the UK.[5–7] These so-called herd effects are well established for invasive pneumococcal disease (IPD) but not for non-IPD pneumococcal community-acquired pneumonia (PCAP). Using the serotype specific urinary antigen detection (UAD) assay that was performed during the CAP-pilot (a preparatory study of the CAPiTA study) and

the CAPiTA study, we showed that trends of serotype distribution in non-IPD PCAP were comparable to those seen in the Dutch national IPD surveillance data between 2008 and 2013 (Chapter 4). These herd effects generally take five to seven years to be maximized, depending on whether a catch-up program among children was implemented.[5,8] Nasopharyngeal pneumococcal colonization in children is considered to be the most important reservoir of pneumococcal infection in adults, and it is assumed that herd protection for adults results from changes in the serotype distribution of pneumococci carried in children.[3] In the Netherlands, PCV7 was introduced in June 2006 with no catch-up program, and was replaced by PCV10 in 2011. PCV10 uses different proteins for the conjugate compared to PCV7 and PCV13.[9] While herd effects following use of PCV7 and PCV13 are well documented, to date only limited data is available on herd effects in adults following implementation of PCV10 in children.[10,11] In Finland PCV10 was evaluated in a cluster-randomized trial from February 2009 onward, with about half of that birth cohort receiving PCV10 and the other half receiving hepatitis A or B vaccine (depending on the age at first vaccination), before PCV10 was implemented universally in the pediatric national immunization program in September 2010. National surveillance data from Finland up to 2013 show evidence of herd effects in all age groups, albeit less impressive compared to previous reported experience with PCV7 and PCV13 in other countries.[12] In a systematic review of randomized-controlled trials comparing one of the PCV's to controls (receiving no vaccine, non-pneumococcal vaccine, or placebo) effects of immunization on pneumococcal carriage in children aged six to twelve months were less for 11-valent pneumococcal protein D conjugate vaccine (the precursor of PCV10) compared to studies of PCV7.[13] This review included only one trial comparing PCV11 to controls (receiving hepatitis A vaccine) which yielded no difference in pneumococcal nasopharyngeal carriage in the first year of life, but a 43% lower VT *S. pneumoniae* carriage rate in the PCV11 group (p=0.13) between 15 and 18 months of age, i.e. after the booster vaccine.[14] In contrast, there was no difference in VT colonization in a trial comparing PCV7 and PCV10 (although effects may have been masked by universal child immunization with PCV7 during this trial),[15] and PCV10 caused both direct and indirect (i.e. in unvaccinated siblings) reductions in VT *S. pneumoniae* carriage in the afore mentioned cluster-randomized trial,[16,17] and in a before-after analysis following implementation of PCV10 in Kenia.[18] Possible local differences, e.g. in contact patterns between elderly and children, hamper comparison of the observed herd effects. Yet, if PCV10 immunization of children (as compared to PCV7 or PCV13) would have less herd effects in adults this would have important consequences for policy making. Moreover, the three additional serotypes contained in PCV13 are among the most frequently observed replacing serotypes following PCV7 introduction.[8] Naturally, the amount of herd protection, will also be influenced by the coverage of child immunization

programs, although associations between proportions of children vaccinated and herd effects in elderly have not been quantified. Consequently, universal vaccination of elderly with PCV13 may be justified when there is sufficient disease burden caused by VT *S. pneumoniae*. This may be the case in an early stage of child immunization with PCV13, if lower-valency vaccines are used, or if PCV13 coverage in children is low. However, if PCV13 is used for child immunization the maximum herd protection effects among elderly seem, depending on the uptake level, to be expected within five to seven years from implementation. During this period the cost-benefit ratio for vaccination of adults may change considerably. Discontinuation of such a program among adults based on an updated cost-effectiveness analysis may arouse ethical discussions, as was seen following recommendations to reduce breast cancer screening intensity.[19] Therefore, it might be appropriate to define the criteria for future policy adaptations before implementing an adult immunization program if changes in herd protection are expected. In the meantime it would be worthwhile to develop a new PCV for adults containing the non-vaccine serotypes that cause most replacement disease in adults, provided that the incidence of CAP and IPD caused by these serotypes is high enough to reach cost-effectiveness. With this approach elderly would be protected against the serotypes included in the pediatric vaccine through herd protection and to additional serotypes through direct immunization.

Ethical considerations

One century ago pneumonia was named the old man's friend, as it frequently led to a relatively quick death in elderly, preventing the suffering of age-associated decay and chronic illnesses, or ending the suffering from terminal illness, and it is still frequently referred to by that name in the medical literature.[20] For such conditions prevention of pneumococcal pneumonia by vaccination would pose an ethical dilemma.[21] Nowadays, CAP and IPD still occur mostly in patients with comorbidities and high age, which is reflected in the high prevalence of treatment restrictions, with do-not-resuscitate policies in 29% of hospitalized elderly CAP patients in a study from Japan.[22] In the CAPiTA study we observed treatment restrictions at the time of admission in 27% of participants hospitalized for CAP and presence of treatment restrictions was a sensitive proxy for frailty and worse outcome (Chapter 9). The life expectancy in patients surviving CAP is also lower compared to the age and gender matched population, presumably because of existing comorbidities and the sequelae following CAP.[23] However, opposite to the pre-antibiotic era, most pneumonia episodes are treated with good outcome, and relatively few pneumonia cases remain life-terminating events nowadays.[24,25] Thus, in such patients preventing pneumonia cannot be considered as unnecessarily prolonging life. Life expectancy of elderly has also increased substantially over the past century. Today, the life expectancy of a 65 year old individual in the

Netherlands is 18 years in men and 21 in women, with a healthy life expectancy of 12 years for both sexes. Even in 80 year old people, life expectancy is still 8 years in men and 10 in women, and the healthy life expectancy is 4 years.[1] Still, pneumonia remains a frequent, sometimes welcomed, life-terminating event in patients with end-stage comorbidities such as malignancies, dementia, and Parkinson's disease, or in the very old nursing home resident. Therefore, one could argue that pneumonia should be called the "diseased man's friend" and prevention still poses an ethical dilemma in these patients. This plays less of a role when the vaccine is offered to relatively healthy 65 year old individuals, but the complicating factor is that the occurrence and course of progressive diseases are often difficult to predict and that the duration of protection from PCV13 is unknown as well.

Some epidemiological data from the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) may provide guidance. First, in the trial, there was no difference in all-cause mortality of subjects receiving PCV13 or placebo (7.1% in both groups) and there was a small, not statistically significant, difference in mortality due to all-cause CAP or IPD, for which outcomes the study was underpowered. An estimated 2.5% of deaths in the placebo group were caused by CAP or IPD, of which most are caused by other pathogens or non-VT *S. pneumoniae* and are, therefore, not preventable by PCV13. Therefore, if the vaccine is able to prevent death due to CAP or IPD, it will have minimal impact on population life expectancy. Still, it may be substantial for the individual patient in whom the CAP or IPD is prevented. Second, in a post-hoc analysis, VE was decreasing with increasing risk of CAP (Chapter 2) and with increasing age (Chapter 3), which may in part explain the lack of an effect on cause-specific mortality. Third, VE also seems to be lower in patients that become immunocompromised after vaccination (e.g. due to a malignancy) as suggested by the stratified analysis based on the immune status at the time of the CAP episode, although these numbers are too small to draw conclusions. Taken together, the vaccine seems more likely to prevent PCAP or IPD in relatively healthy young elderly than to prevent a "beneficial" life-terminating event in individuals at the end of their lives. If true, this would provide a solution for the ethical problem as delineated. It would be worthwhile to further investigate the association between an individual's risk profile and PCV13 VE. Obviously, the responsibility of public health authorities is to specify if and for whom the vaccine is recommended, and who will be reimbursed. Such decisions can be based on the presence of medical benefit and on cost-effectiveness analyses. It remains the autonomic decision of the individual patients, supported by information from his or her physician and taking the aforementioned aspects into account, whether or not to follow these recommendations.

Recommendations for current practice

The Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) has demonstrated that PCV13 offers protection against vaccine-type pneumococcal CAP and IPD in immunocompetent elderly. Although the individual's expected benefit is limited due to the low disease incidence per person per year, the public health benefit may be very relevant. Yet, in many countries the disease burden due to PCV13 serotypes has decreased substantially due to herd protection offered by pediatric immunization programs, majorly affecting the cost-benefit ratio of PCV13 vaccination in elderly. Little is known about VE of PCV13 in immunocompetent elderly with a high risk of CAP (i.e. the very elderly and patients with comorbidities associated with CAP) and in the immunocompromised patients. Of note, a lower VE in a population with a higher disease incidence may still result in similar (or even higher) absolute benefits compared to a large population with low disease incidence but higher vaccine efficacy. For patients with end-stage chronic illness (e.g. malignancies or dementia) or for people living in nursing homes, the benefits of PCV13 remain uncertain. First, vaccine efficacy has not been determined in these patients. Second, even if effective the health care gain of preventing PCAP/IPD, in terms of quality-adjusted life years, will be low in such patients. Third, as stated, beneficence of prevention may be inversed in terminally ill patients. For these reasons, a conservative approach towards life prolonging interventions may sometimes best benefit the patient.[27]

Conclusion

PCV13 is safe and effectively reduces the incidence of PCAP and IPD in elderly over 65 years of age. Yet, it is expected that in the years ahead indirect effects due to child immunization will also decrease the incidence of VT-CAP and VT-IPD in elderly, thereby reducing the benefit of PCV13 in elderly.

ANTIBIOTIC TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Empirical antibiotic treatment choice

The optimal empirical antibiotic treatment of community-acquired pneumonia in adults hospitalized to non-ICU wards is unknown. In observational studies, antibiotics active against atypical pathogens (*Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, and *Coxiella burnetii*) have been associated with improved outcomes compared to beta-lactams (Introduction and Chapter 6). This may result from the broader coverage of potential pathogens or, in the case of macrolides, from anti-inflammatory effects.[28] However, interpretation of these studies is hampered by the presence of indication bias (Chapter 6). In a meta-analysis of randomized controlled trials there was no difference in outcome between beta-lactams

and fluoroquinolones in patients hospitalized with CAP.[29] Yet, due to study procedures such as informed consent, a proportion of patients will have received non-study antibiotics before randomization. This may have diluted differences in the effects of randomized antibiotics and compromises non-inferiority testing (Chapter 6). Current consensus is that in patients hospitalized with *Legionella pneumoniae* pneumonia targeted treatment has to start as soon as possible, at least within 24 hours after admission.[30] This is, in part, based on an observational study of survival in patients with Legionnaires' disease in the outbreak of Bovenkarspel, the Netherlands, in 1999.[31] During this outbreak, patients with a positive Legionella urinary antigen test (LUAT) who had received active treatment against Legionella within 24 hours of admission had a better survival compared to patients with a positive LUAT in whom targeted treatment was initiated later. This study has raised worries to initially miss Legionella and empirical coverage of atypical pathogens is frequently given to hospitalized CAP patients,[32] even though Legionella is rare in a non-outbreak setting in the Netherlands.[33–36] Yet, the benefit of empirically covering Legionella in patients with CAP in the first 24 hours of admission is unknown. From an ecological perspective, prudent antibiotic use is to treat with the narrowest possible antibiotic spectrum without compromising patient outcome, thereby minimizing the effect of antibiotics on resistance development.[37]

The CAP-START study

The CAP-START study was a cluster-randomized cross-over study in which we investigated whether a strategy of preferred antibiotic treatment with a beta-lactam antibiotic is non-inferior to strategies of either a beta-lactam combined with a macrolide or fluoroquinolone monotherapy in the treatment of patients with CAP hospitalized to a non-ICU ward. This design was chosen to overcome the major limitations of observational studies (i.e. confounding bias) and of individually randomized studies (i.e. in-hospital pre-randomization antibiotics). In this study, the strategy in which beta-lactam monotherapy was the preferred empirical treatment had a 57% to 62% lower number of patient days with atypical coverage compared to strategies with beta-lactam/macrolide combination therapy or fluoroquinolone monotherapy, without leading to a worse patient outcome (Chapter 7). Moreover, there were no differences in costs (Chapter 8). Non-inferiority was particularly evident in the comparison with the beta-lactam/macrolide combination strategy. Given the high likelihood of resistance development associated with macrolide use, there seems to be no future for the general recommendation of macrolides in this patient population. For fluoroquinolones, the upper margin of the confidence interval was close to the non-inferiority margin of 3% absolute difference in mortality. Yet, the point estimate of the difference in all-cause 30 and 90-day mortality was close to zero and there were no differences in any of the secondary outcomes. The choice of an appropriate non-

inferiority margin in antibiotic treatment of CAP has been source of debate.[24] Yet, a smaller non-inferiority margin of e.g. 1.5% would have required about four times as many patients, which was not feasible with the available recourses.

The recently published randomized controlled trial by Garin et al. that compared beta-lactam monotherapy to beta-lactam/macrolide combination therapy failed to show non-inferiority for clinical stability on day seven, neither did this study show superiority of combination treatment.[38] The seemingly opposite findings of the two studies might in part be explained by the maximized adherence to the allocated antibiotic and the strict criteria for switching antibiotic treatment that were applied in the study by Garin et al., which are not representative for medical practice and may have negatively affected patient outcome. In contrast, in the CAP-START study physicians were allowed to deviate from the preferred treatment and switches to other antibiotic classes were allowed. In the beta-lactam strategy, 29% of patients were empirically treated with a non-beta-lactam antibiotic, and of the 468 patients initially treated with beta-lactam monotherapy, 19% switched to another class later on, the most frequent reason being insufficient clinical recovery. Despite this, overall length of stay was not prolonged during the beta-lactam strategy. Deviations and cross-overs have reduced the contrast between the study arms and may have led to bias towards no difference. Yet, the post-hoc analysis of the antibiotic adherent population gave similar results, which suggests that for those patients treated with beta-lactams in the beta-lactam period, the omission of atypical coverage in the initial treatment did not lead to a worse outcome.

The interpretation of these findings is that universal recommendation of atypical coverage does not advantage the patients. The reason for this finding could be either that empirical coverage of atypical pathogens can be safely withheld, as long as treatment is timely switched in case of lack of improvement or deterioration, or that physicians are well able to determine which patients will benefit from empirical atypical coverage, and maybe both interpretations are true. Unfortunately, with the current study it is not possible to determine which of the deviations that had occurred were really needed. Whether further reductions of macrolides and fluoroquinolones are possible without compromising patient outcome, is therefore unknown. In my opinion, there is currently no single or combination of antibiotics that is the best choice for all patients. The art of medicine is to determine which antibiotics are most appropriate for the individual patient, taking into account the benefits and risks of the different options, primarily for the patients but certainly also on the ecological level.

In the beta-lactam arm, many patients were treated with amoxicillin-clavulanic acid or cephalosporins. These antibiotics have the advantage that they provide better coverage of gram-negative pathogens, the importance of which is however unknown for the

empirical treatment of CAP. Yet, these agents have also been associated with the development of beta-lactam resistance[39] and – no less than for macrolides and fluoroquinolones – their use should be restricted to patients that really benefit from it. Whether this is the case for patients with CAP admitted to non-ICU wards is unknown and an unbiased assessment of this question is not possible using the CAP-START data because this is not a randomized comparison and because of the low numbers of patients in these subgroups. Future randomized studies are needed to compare the effectiveness of different subclasses of beta-lactams. One of these studies is the Protocol Adherence in Community-acquired pneumonia Treatment (PACT) study. This multi-centre stepped-wedge trial will investigate the impact of an antibiotic stewardship program aiming to reduce broad-spectrum antibiotic use, and will (among others) assess non-inferiority of this intervention for 30-day mortality.

Dutch guidelines already recommend small spectrum beta-lactams as initial treatment of patients with moderate-severe CAP.[30] Still, in practice, many patients are treated with antibiotics that cover atypical pathogens.[32] The results of the CAP-START study support the guideline recommendations and can be used to improve guideline adherence. Recommendations in international guidelines to cover atypical pathogens in all hospitalized CAP patients should be reconsidered.[40,41]

Determining microbiological aetiology

In clinical practice, the microbiological aetiology of CAP remains unknown for most patients.[42] Yet, an etiological diagnosis should be attempted as this allows for targeted antibiotic treatment.[30] Depending on the pathogen, targeted treatment can have the advantage of a narrower antibiotic spectrum (i.e. less selective pressure), less side effects, and/or higher effectiveness. Blood cultures are positive in only approx. 10% of hospitalized CAP patients and it has been discussed whether these should be collected in all patients.[43–45] We have shown that the positivity of blood cultures can be only moderately predicted by patient characteristics at the time of presentation (Chapter 10). As a result, many of the positive blood cultures, including pneumococci, occurred in the patients that were classified as having a low risk of bacteraemia, including not otherwise identified pneumococci, gram-negative bacteria, and not empirically covered rare pathogens. The predicted risk of bacteraemia should therefore not be used for the decision to obtain blood cultures. A positive PUAT is the best predictor of pneumococcal aetiology[35] and can be used to initiate targeted, narrow spectrum antibiotic treatment.[46] The Legionella urinary antigen test (LUAT) is useful to detect *L. pneumophila* within a short time window, and is recommended to enable a test-and-treat approach (i.e. starting with a beta-lactam and adapting therapy upon a positive test result) in patients with low to moderate CAP severity.[30] However, it should be

reminded that the sensitivity of this test is limited, especially in the earliest stage of Legionnaires' disease and for non-serogroup 1 Legionella, thus Legionella should still be considered if patients do not respond to beta-lactam antibiotics.[47] New developments include multiplex polymerase chain reaction (PCR) assays, which allow for the rapid detection of multiple bacterial and viral pathogens in respiratory samples.[48,49] For viruses, the fear of missing a bacterial co-infection may explain why a rapid diagnosis using PCR has no impact on antibiotic treatment.[50] Whether the detection of bacterial DNA in respiratory samples is specific enough to allow streamlining of antibiotic treatment is a challenging question that remains to be determined.

Conclusion

In conclusion, most CAP patients admitted to non-ICU wards can be safely treated with beta-lactam antibiotics alone. A strategy in which beta-lactam monotherapy is the preferred empirical treatment does not lead to a worse outcome or increased costs compared to preferred treatment strategies that cover atypical pathogens. Whether the proportion of patients treated with narrow spectrum beta-lactams can be safely further increased, and the role of rapid diagnostics to achieve this, is subject for future studies.

PREVENTION AND TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS: FINAL REMARKS

PCV13 can prevent approx. 5% of CAP episodes in elderly but did not lead to a lower all-cause mortality in the CAPiTA study. In fact, the vaccine appeared to have highest efficacy in patients with the lowest risk to acquire CAP. Prevention is better than cure. Yet, if patients develop a CAP, different strategies of preferred empirical antibiotic treatment for patients with CAP admitted to non-ICU wards do not show differences in patient outcome or costs.

The question arises whether pneumococcal vaccination in elderly will have consequences for the choice of empirical antibiotic treatment of CAP. This is – in my opinion – not the case. If 5% of the CAP episodes are prevented, the majority of CAP episodes will still be cause by pathogens sensitive to beta-lactams (a.o. non-VT *S. pneumoniae* and 54% of VT *S. pneumoniae*). If all prevented episodes would have responded well to beta-lactams, as can be expected, the proportion of non-response to initial treatment with beta-lactams, thus requiring switches of antibiotic treatment and probably a delayed clinical response, would increase with a factor 1.05. This does not justify a change of empirical treatment for all patients.

The absence of a mortality benefit of PCV13 may be disappointing. However, that something is not measurable does not mean it is not relevant. Prevention of an IPD episode with fulminant course in otherwise healthy elderly, although rare, is likely to substantially increase life expectancy for this patient. Apart from that, in my opinion life is more than just postponing death. The prevention of hospitalisations for CAP or IPD is a relevant achievement from the patient's perspective. Last, if every little bit helps, use of PCV13 in elderly will also reduce any antibiotic use for CAP hospitalisations by 5%.

In response to publication of the results of the CAP-START study someone blogged: "Unlike the pre-antibiotic era (when Sir William Osler called pneumonia 'the Captain of the Men of Death'), modern medicine has a panoply of effective antibiotics from which to choose when a patient is admitted with CAP. What is the take-home message from CAP-START? Perhaps beta-lactam monotherapy is an adequate first volley to fire at the Captain."[51] The results of the CAP-START study contribute to discussions about the need to empirically cover atypical pathogens in the treatment of CAP, are likely to influence evidence-based recommendations on the antibiotic treatment of CAP, and will hopefully lead to substantial reductions of macrolide and fluoroquinolone use worldwide.

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Nederlandse samenvatting (Dutch summary)

Longontsteking komt veel voor, met name bij jonge kinderen en bij ouderen, en het veroorzaakt veel ziektelast. Dit proefschrift gaat over de preventie en behandeling van in de gemeenschap opgelopen longontsteking (Engels: Community-Acquired Pneumonia, afgekort CAP) bij volwassenen. Het eerste deel van het proefschrift beschrijft de resultaten van de "**C**ommunity-**A**cquired **P**neumonia **i**mmunization **T**rial in **A**dults" (CAPiTA) waarin de beschermende werking van een nieuw pneumokokkenvaccin is onderzocht bij 65+'ers. In deel twee worden de resultaten van de "**C**ommunity-**A**cquired **P**neumonia - **S**tudy on the initial **T**reatment with **A**ntibiotics of lower **R**espiratory **T**ract infections" (CAP-START) beschreven, waarin verschillende antibiotica voor de behandeling van CAP met elkaar vergeleken worden.

PREVENTIE BIJ OUDEREN D.M.V. PNEUMOKOKKENVACCINATIE

Bij volwassenen die in Nederlandse ziekenhuizen met een longontsteking worden opgenomen, wordt bij ongeveer 30% een pneumokok gevonden. Terecht wordt de pneumokok dan ook gezien als de belangrijkste veroorzaker van CAP. Naast CAP kan de pneumokok ook andere ernstige infecties veroorzaken zoals hersenvliesontsteking. Een infectie waarbij de pneumokok wordt aangetoond op een normaal gesproken steriele plaats (meestal is dat in het bloed) wordt een invasieve pneumokokkeninfectie (Engels: invasive pneumococcal disease, afgekort IPD) genoemd. Patiënten met IPD hebben een hogere kans om aan de infectie te overlijden dan patiënten met een niet-invasieve pneumokokken-CAP.

De pneumokok heeft als buitenste laag een kapsel van suikerketens (polysachariden). Er zijn inmiddels meer dan 100 varianten gevonden in de opbouw van het polysacharidekapsel. Dit worden serotypen genoemd. Het serotype is een belangrijke bepaler van hoe ziekmakend de pneumokok is en het polysacharidekapsel is ook het belangrijkste aangrijpingspunt van ons immuunsysteem om de pneumokok uit te schakelen. De afweerreactie is serotype-specifiek.

Vaccins tegen pneumokokken bestaan al meer dan 100 jaar in de vorm van polysacharidevaccins. Hierbij worden enkel de polysachariden van verschillende serotypen ingespoten en ontstaat er een afweerreactie. Of dit vaccin daadwerkelijk leidt tot een afname van pneumokokken-CAP is onduidelijk doordat grootschalige, goed opgezette studies ontbreken. Een nadeel van dit vaccin is dat het bij kinderen geen afweerreactie veroorzaakt. Een nieuwe techniek is het binden (conjugeren) van de polysachariden aan een eiwit, het zogenaamde conjugaatvaccin, destijds met 7 verschillende serotypen (Engels: 7-valent pneumococcal conjugate vaccine, afgekort PCV7). Dit vaccin werd in 2000 met succes geïntroduceerd in het

kindervaccinatieprogramma in de Verenigde Staten. Niet alleen bij kinderen, ook bij volwassenen nam het aantal IPD's af. Dit wordt in het Engels *herd protection* genoemd (letterlijk: bescherming van de kudde). *Herd protection* is minder duidelijk voor niet-invasieve pneumokokken-CAP doordat dit lastiger te meten is. In Nederland is het vaccin in 2006 geïntroduceerd. Recent zijn twee nieuwe vaccins beschikbaar gekomen die 10 en 13 serotypen bevatten (PCV10 en PCV13). Gebaseerd op een afweging van kosten en gezondheidswinst is in Nederland gekozen voor vaccinatie van kinderen met PCV10. Of dit vaccin ook bij ouderen beschermt tegen pneumokokken-CAP of IPD was tot recent onbekend.

In **Hoofdstuk 1** worden de resultaten van de Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) samengevat. In deze studie werden 84.496 65+'ers gevaccineerd met PCV13 of een placebo. Wat ze kregen werd door toeval bepaald (gerandomiseerd). De belangrijkste criteria voor deelname waren het wonen in een thuissituatie (zelfstandig of in een bejaardentehuis) en een gezond afweersysteem. De studie laat zien dat het aantal ziekenhuisopnames voor CAP veroorzaakt door een van de serotypen in PCV13 afnam met 38%. Het aantal IPD's veroorzaakt door deze serotypen nam af met 76%.

De kans om een CAP te krijgen kan redelijk worden ingeschat aan de hand van patiëntkenmerken zoals leeftijd, geslacht, rookgedrag en onderliggende ziekten. Het is dan ook verleidelijk om over te gaan tot een hoog-risicostrategie, waarbij alleen personen met een hoog risico op een CAP gevaccineerd worden. In **Hoofdstuk 2** wordt beschreven wat het effect zou zijn geweest wanneer we dat in de CAPiTA-populatie zouden hebben toegepast. Uit deze analyse blijkt dat het percentage door PCV13 voorkomen ziekenhuisopnames voor pneumokokken-CAP of IPD afneemt naarmate het risico op een CAP toeneemt. De netto winst (het absolute aantal voorkomen episodes) is in de verschillende risicogroepen ongeveer gelijk. Deze resultaten pleiten tegen een hoog-risicostrategie voor pneumokokkenvaccinatie bij ouderen.

Hoofdstuk 3 gaat over het effect van leeftijd bij vaccinatie op de effectiviteit van het vaccin. Deze analyse laat zien dat bij 65+'ers de effectiviteit afneemt naarmate de leeftijd toeneemt. Het is niet duidelijk waardoor dit ontstaat. Aan de afweerreactie lijkt het in ieder geval niet te liggen, want die was niet verschillend tussen oudere en jongere 65+'ers. Een mogelijke verklaring is een afname van functionaliteit van de afweercellen die de pneumokokken op moeten ruimen, dit zou verder onderzocht moeten worden. Belangrijk om te vermelden is dat een lagere effectiviteit bij de zeer ouderen nog steeds tot een even grote afname van CAP-episodes kan leiden doordat in deze leeftijdsgroep CAP veel vaker voorkomt.

De beschreven *herd protection* is tot nu toe bijna alleen maar onderzocht met betrekking tot IPD. Dit komt doordat de bepaling van het serotype tot recent alleen kon met een levende pneumokok, bijv. uit een bloedkweek. Met een relatief nieuwe urine-antigeentest is het ook mogelijk het serotype van de pneumokok te bepalen. Deze test werd in de Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA) en in de voorbereidende CAP-pilot studie toegepast bij patiënten opgenomen met CAP. In **Hoofdstuk 4** wordt *herd protection* op IPD vergeleken met de niet-invasieve pneumokokken-CAP. Voor IPD hebben we gegevens van het RIVM gebruikt over de serotypeverdeling bij 65+'ers in Nederland. Deze analyse laat zien dat de verandering in serotypeverdeling die gezien wordt bij niet-invasieve pneumokokken-CAP hetzelfde is als bij IPD. Dit heeft belangrijke gevolgen voor de kosteneffectiviteit van pneumokokkenvaccinatie bij kinderen, maar ook heeft de *herd protection* belangrijke gevolgen voor de kosteneffectiviteit van pneumokokkenvaccinatie bij ouderen.

In **Hoofdstuk 5** bekijken we in detail hoe accuraat research nurses in de deelnemende ziekenhuizen in staat waren om deelnemers die met een CAP werden opgenomen te herkennen. Hieruit blijkt dat ongeveer 1/3 van de patiënten met een verdenking op een CAP niet als zodanig waren geregistreerd. Voor een deel ging het om patiënten die in een niet-deelnemend ziekenhuis opgenomen werden (in Nederland of in het buitenland) of die werden opgenomen op een niet-gebruikelijke afdeling zoals cardiologie of neurologie. Ook bleken research nurses zich soms te vergissen in de aanwezigheid van verdenking op longontsteking. Hieruit kunnen we lessen trekken die ons helpen om toekomstige studies beter uit te voeren. Omdat het een gerandomiseerd onderzoek betreft, heeft het missen van CAP-episodes geen invloed op de gemeten effectiviteit (in de groepen werd een gelijk percentage episodes gemist). Wel heeft het invloed op de gemeten *Number Needed to Treat*, hoeveel personen je zou moeten vaccineren om één episode te voorkomen. Dit getal hebben we overschat door het missen van episodes, waardoor het nut van het vaccin wordt onderschat. Het is daarom van belang om transparant te zijn over de kwaliteit van het identificatieproces.

In de ***General discussion*** wordt ingegaan op aspecten die een rol spelen bij de besluitvorming rondom pneumokokkenvaccinatie bij ouderen: de kosten-batenafweging, de afname van pneumokokkenpneumonieën veroorzaakt door de 13 serotypen waartegen het vaccin beschermt, en ethische aspecten. Ook wordt gepleit voor de ontwikkeling van een vaccin dat specifiek gericht is op de serotypen die bij ouderen voorkomen en die in de plaats van de 13 serotypen gekomen zijn. Ten slotte wordt een aanbeveling gedaan voor de praktijk.

ANTIBIOTICASTRATEGIEËN VOOR DE BEHANDELING VAN CAP BIJ VOLWASSENEN

Over wat de juiste antibioticabehandeling is van patiënten met CAP, en specifiek diegenen die in het ziekenhuis opgenomen moeten worden maar niet op een Intensive Care Unit, is veel discussie gaande in de medisch-wetenschappelijke literatuur. Hoe breder de antibiotische dekking hoe meer risico er is op toename van antibioticaresistentie. Een brede antibiotische dekking is daarom alleen te rechtvaardigen wanneer dit gepaard gaat met een betere uitkomst voor de patiënt. In **Hoofdstuk 6** wordt uitgelegd waarom de onderzoeken die tot nu toe zijn gedaan (observationele onderzoeken en gerandomiseerde studies) niet tot een helder antwoord hebben geleid. Een heel andere studieopzet, de *cluster-randomized cross-over trial*, werd toegepast bij de CAP-START-studie. Daarbij werd aan de zeven deelnemende ziekenhuizen willekeurig toegewezen welke antibioticastrategie ze moesten toepassen op de patiënten die met CAP op een niet-ICU verpleegafdeling werden opgenomen. Er werden drie antibioticastrategieën vergeleken: een beta-lactam, een beta-lactam in combinatie met een macrolide, of een van de nieuwe fluorchinolonen. De behandelend arts had de mogelijkheid om van het voorkeursmiddel af te wijken als daar een medische noodzaak toe was. Er werden dus voorkeursstrategieën vergeleken. De voor- en nadelen en de uitdagingen die horen bij een *cluster-randomized cross-over trial* worden in dit hoofdstuk besproken besproken.

In **Hoofdstuk 7** worden de resultaten op voor de patiënt relevante klinische eindpunten besproken. De uitkomst in sterfte tot 90 dagen na opname was niet slechter tijdens de strategie met beta-lactam-monotherapie in vergelijking met de andere strategieën. Ook was er geen langere opnameduur of hoger aantal complicaties tijdens de beta-lactam-periode. De gemiddelde duur van intraveneuze antibioticabehandeling was een dag korter tijdens de fluorchinolon-periode; dit werd veroorzaakt door een hoger percentage patiënten dat met orale antibiotica startte en heeft niet geleid tot een kortere opnameduur voor deze patiënten ten opzichte van vergelijkbare patiënten in de beta-lactam-periode. Zoals beschreven in **Hoofdstuk 8** werd er ook geen verschil gevonden in de gemiddelde kosten per opname tussen de drie strategieën.

In het onderzoek beschreven in **Hoofdstuk 9** werd gekeken naar de rol van behandelbeperkingen bij CAP. Behandelbeperkingen betreffen bijna altijd een niet-reanimeerbeleid, vaak aangevuld met een beperking voor ICU-opname en beademing. Dit komt bij CAP-patiënten boven de 65 jaar veel voor. Toch wordt dit in publicaties over de antibioticabehandeling van CAP bijna nooit beschreven. Wij vroegen ons af of de interpretatie van die onderzoeken daaronder lijdt. In ons onderzoek, waarbij gegevens van de CAPiTA-studie gebruikt werden, had meer dan een kwart van de patiënten een behandelbeperking. Patiënten met een behandelbeperking hadden,

onafhankelijk van andere factoren, een sterk verhoogde kans om te overlijden. Er werd echter geen verband gezien tussen de aanwezigheid van behandelbeperkingen en de keuze van het antibioticum. Als dit generaliseerbaar is naar andere landen (iets wat lastig te onderbouwen is) dan zou dat betekenen dat voorgaande publicaties geïnterpreteerd kunnen worden zonder kennis over de behandelbeperkingen. Vanwege de impact van behandelbeperkingen op de uitkomst is het wel aan te bevelen in toekomstige publicaties te rapporteren hoeveel behandelbeperkingen er in de geanalyseerde groepen waren ingesteld.

In de CAP-START-studie werden verschillende empirische antibioticastrategieën vergeleken. Microbiologische diagnostiek leidt in de praktijk tot identificatie van de verwekker bij ongeveer 25% van de opgenomen CAP-patiënten. Dit biedt de mogelijkheid om de antibioticabehandeling te versmallen, wat de kans op resistentieontwikkeling verkleint. De rol van de bloedkweek is hier echter omstreden. Bloedkweken zijn bij slechts 5-10% van de opgenomen CAP-patiënten positief en doordat de meeste verwekkers die in een bloedkweek gevonden worden al door de empirische antibioticabehandeling gedekt worden, en het een tot enkele dagen duurt voordat de bloedkweekuitslag bekend is, heeft de test in de praktijk vaak weinig consequenties voor de patiënt. Er wordt dan ook gesuggereerd dat bloedkweken alleen gedaan zouden moeten worden bij patiënten met een hoge vooraf-kans op een positieve bloedkweek. In **Hoofdstuk 10** wordt een studie beschreven waarin gezocht werd naar voorspellers van een positieve bloedkweek. De bloedkweekuitslag blijkt matig voorspelbaar op basis van patiëntkenmerken die bekend zijn op het moment dat de bloedkweek afgenomen wordt. Door deze voorspellers te gebruiken als beslisregel om al dan niet een bloedkweek af te nemen, zouden in onze studiepopulatie diverse kansen gemist zijn om gericht te gaan behandelen. Ons advies is dan ook om de beslisregel niet op die manier in te zetten in de kliniek.

CONCLUSIE

Met PCV13 kan ongeveer 5% van de opnames voor CAP voorkomen worden. Het vaccin lijkt het best te werken bij personen met een laag risicoprofiel. Hoe in de toekomst pneumokokkenvaccinatie bij ouderen vormgegeven moet worden is nog onduidelijk. Wanneer iemand (alsnog) een CAP ontwikkelt en daarvoor opgenomen moet worden op een niet-ICU afdeling, leiden verschillende antibioticastrategieën niet tot een verschil in herstel of in kosten. Daarom moet de voorkeursbehandeling van deze categorie patiënten een beta-lactam zijn. Of dit verder versmald kan worden naar smal-spectrum penicillinen is een vraag die in vervolgstudies moet worden beantwoord.

Samenvatting in jip-en-janneketaal (child summary)

De opa van Janneke is ziek. Hij moet zo hoesten, zo vreselijk hoesten. En hij heeft het benauwd ook. Jip en Janneke zijn op bezoek. Ze hebben een koekje gekregen. En limonade. Oma zegt dat ze de dokter gaat opbellen. Opa heeft daar helemaal geen zin in en hij moppert wat. Maar als oma het zegt, dan zal opa toch luisteren. En dan komt de dokter snel kijken. Opa moet zuchten en de dokter luistert met een slangetje op opa's rug. Jip vindt het erg mooi. “Ik word later ook dokter”, zegt hij. Dat vindt Janneke raar: Jip met een witte jas aan. En een slangetje in zijn oren. Maar Jip weet het echt zeker. En nu moet Janneke de patiënt zijn en Jip wil luisteren. Maar de echte dokter heeft lang genoeg geluisterd en hij zegt: “U bent erg ziek. U hebt een longontsteking. Ik stuur u naar het ziekenhuis.” Dan moeten Jip en Janneke naar huis. “Komen jullie opa snel opzoeken?” vraagt oma. Ja, ze zullen het dadelijk aan moeder vragen.

De volgende morgen gaat de moeder van Janneke naar het ziekenhuis. En Janneke mag mee. Jip ook? Ja, Jip mag ook mee, als hij zich tenminste rustig houdt. Jip heeft een trosje druiven meegenomen. Voor opa. En Janneke heeft een bosje bloemen. Ook voor opa. Dat zal opa fijn vinden. En daar is opa al. Maar wat ziet Janneke nu? Er zit een slangetje in opa’s arm. "Wat is dat?" vraagt Janneke geschrokken. "Daar gaat antibiotica in", legt opa uit, "dat zorgt ervoor dat de longontsteking snel over gaat." En kijk, opa heeft alweer praatjes. Maar hij is wel bijna de hele dag in bed. Want hij is nog erg moe.

Er komt een mevrouw aan. "Hallo, ik ben Lia." Ze gaat op de stoel naast het bed zitten en vraagt of opa aan een onderzoek mee wil doen. "Wat is onderzoek?" vraagt Jip. Lia vertelt dat ze alles opschrijven over mensen met een longontsteking. Daar willen ze iets van leren. “Wat dan?” vraagt opa. Lia zegt: “De dokters weten niet welke antibiotica het beste zijn voor longontsteking. Want er zijn zoveel verschillende. Ze weten daardoor vaak niet wat ze moeten kiezen.” Dat vindt opa ook een interessante vraag. Nu moet opa een formulier invullen en een boel vragen beantwoorden. Jip en Janneke vinden dat wel een beetje saai. Gelukkig is Lia snel klaar met het onderzoek. Nu kunnen Jip en Janneke fijn weer met opa praten. Opa vertelt dat hij een inenting van de dokter krijgt. Als hij weer beter is. Het is een prikje tegen pneumokokken. Jip en Janneke hebben nog nooit van pneumokokken gehoord, en ook niet van inenting. Maar ze begrijpen nu wel dat opa van pneumokokken zo ziek was geworden en dat de inenting de pneumokokken kan tegenhouden. “En voorkomen is beter dan genezen”, zegt moeder.

“Morgen gaan we weer op bezoek”, zegt Jip. “Hè ja,” zegt Janneke, “dan nemen we weer fruit mee.” “Morgen niet,” zegt moeder, “veel te druk. Maar als opa weer beter is, mogen jullie mee om hem op te halen.” “Over twee dagen?” vraagt Jip. “Wie weet”, zegt moeder. En daar wachten Jip en Janneke nu op.

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> "It's no use," he said. "I do not know enough about this place or its people to decide what would serve me best to learn." "Well spoken," said the old woman. "That is the first step toward knowledge. Come. I will guide you through the city, and we will find the answers you seek."
>
> *(Stephen R. Lawhead, In the hall of the Dragon King)*

Een proefschrift schrijven doe je niet alleen. Het zoeken naar de juiste vragen, het vinden van de antwoorden – velen hebben op verschillende manieren daaraan bijgedragen. Mijn dank gaat naar jullie allemaal uit.

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Henri van Werkhoven, juli 2015

About the author

Cornelis Hendrinus van Werkhoven (given name: Henri) was born on January 4, 1983 in Streefkerk, the Netherlands. After finishing secondary school at the Wartburg College in Rotterdam he studied Medicines at the University Medical Center Utrecht (UMCU) from 2001 to 2008. As of 2008, he worked as a research physician in the group of Marc Bonten on the CAP-pilot study, a preparatory study for the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA). Together with the CAPiTA study Henri moved his headquarters to Julius Clinical, where he acquired experience with the conduct of a large clinical trial. In 2010 he moved back to the UMCU to start his PhD track. In close collaboration with his colleague PhD student Douwe Postma he performed the CAP-START study under the inspiring supervision of Marc Bonten en Jan Jelrik Oosterheert. The CAP-pilot, CAPiTA, and CAP-START study together formed the basis of his thesis. During his PhD track Henri completed the postgraduate master in Clinical Epidemiology with a specialization in the epidemiology of infectious diseases. After acquiring his PhD he plans to work as post-doctoral researcher in the group of prof. Marc Bonten.

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