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REVIEW

The role of *Streptococcus pneumoniae* in community-acquired pneumonia among adults in Europe: a meta-analysis

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Abstract The primary objective of this meta-analysis was to estimate the prevalence of adult community-acquired pneumonia (CAP) caused by *Streptococcus pneumoniae* in Europe, adjusted for possible independent covariates. Two reviewers conducted a systematic literature search using PubMed on English-language articles that involved human subjects with CAP during the period from January 1990 to November 2011 across European countries. A mixed-effects meta-regression model was developed and populated with 24,410 patients obtained from 77 articles that met the inclusion criteria. The model showed that the observed prevalence of *S. pneumoniae* in CAP significantly varies between European regions, even after adjusting for explanatory covariates, including patient characteristics, diagnostic tests, antibiotic resistance, and health-care setting. The probability of detecting *S. pneumoniae* was substantially higher in studies that performed more frequently a diagnostic polymerase chain reaction assay compared to all the other diagnostic tests included. Furthermore, *S. pneumoniae* was more likely to be confirmed as the cause of a CAP in studies with intensive care unit patients as compared to those with hospital- or community-treated patients. This study provides estimates of the average observed prevalence of *S. pneumoniae*, which could be used for projecting the health and economic benefits of pneumococcal immunization.

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Introduction

Community-acquired pneumonia (CAP) is a common disease, with an annual incidence of 5 to 11 cases per thousand adults in Europe and Northern America [1]. *Streptococcus pneumoniae* is generally accepted to be the most common cause of CAP [2–4]. There is, however, no consensus regarding the prevalence of *S. pneumoniae* in CAP, and estimates vary from 5 to 60 % between different studies [2–4]. This may either reflect a true difference or, rather, a difference in confirmation rates.

Two earlier reviews, which focused on the causative agents of CAP, suggested that the frequency of *S. pneumoniae* differs between countries [3] and health-care settings [4]. However, large variations between studies within the same setting and country were observed, suggesting that these differences could be more related to the study methodology than to real differences [4]. Another factor which might have impacted the findings of the previous reviews is that the investigators also included studies in which radiographic confirmation of

pneumonia was not an inclusion criterion. As a consequence, part of the study patients can be expected to have had respiratory tract infections other than pneumonia, or entirely other conditions, and the respiratory pathogens detected in those cases might not be relevant to describe the relative contribution of *S. pneumoniae* in CAP [5].

It is important to have a reliable estimate of the share of *S. pneumoniae* in the total burden of CAP, especially now that the results of a clinical trial estimating the efficacy of the 13-valent conjugated pneumococcal vaccine (PCV13) in the elderly are pending and the country-specific health and economic impact of this vaccine will largely depend on the share of *S. pneumoniae* in CAP [6, 7].

The primary objective of this meta-analysis is to estimate the average etiological fraction of *S. pneumoniae* in CAP while controlling for potential sources of heterogeneity attributed to regional, health-care settings, and other differences.

Methods

Search strategy and selection criteria

We used PubMed (http://www.pubmed.com) to search for original study reports during the period between January 1990 and November 2011 on the etiology of CAP among adults using the following search terms: *"Pneumonia" [MAJR] AND ("etiology" [Subheading] OR "epidemiology" [Subheading]) AND ("Pneumonia, Bacterial" [MH] OR "Pneumonia, Viral" [MH] OR "microbiology" [Subheading] OR "virology" [Subheading] OR "Streptococcus pneumoniae" [MH]) AND ("Adult" [MH] OR "aged" [MH]) AND ("Journal article" [PT] NOT "meta-analysis" [PT] NOT "review" [PT] NOT "guideline" [PT])*. We limited the articles to the English language. To ensure that articles actually dealt with the most accurate diagnostic definition of CAP, studies in which the CAP diagnosis was not confirmed with a new or increased infiltrate on a chest radiograph were excluded. Furthermore, we excluded: (1) case reports, editorials, reviews, and letters without original data; (2) studies which focused primarily on pneumonia related to sources other than the community; (3) articles that included only specific patient groups, such as patients with chronic obstructive pulmonary disease (COPD); (4) studies performed during the 2009 influenza pandemic; (5) clinical trials; and (6) studies which did not report the fraction of CAP being caused by *S. pneumoniae*.

After applying these inclusion and exclusion criteria, the titles of all potentially eligible articles were independently reviewed by two investigators (M.H.R. and E.H.). Articles were excluded from further review only if both investigators agreed on one or more reasons for exclusion. If a study was not excluded on the basis of the title, the study abstract was reviewed independently by both investigators. Subsequently, all articles judged to meet the inclusion criteria based on the reviewed abstract were retrieved for further evaluations. After reviewing the entire text of the retrieved papers, only those that met all inclusion criteria were included in the analysis and the relevant data were extracted (see below).

Data extraction

Two reviewers independently extracted the total number of CAP episodes and the number of CAP episodes in which *S. pneumoniae* could be detected. A CAP episode was assumed to be caused by *S. pneumoniae* if it was detected in a normally sterile site, in the nasopharynx, or in sputum. We also recorded the type of diagnostic tools applied and distinguished them between culture, serological, or polymerase chain reaction (PCR) tests, or more invasive sampling methods. Culture tests were sub-divided into those performed on either sputum or blood. Serological tests were separated into tests performed on urine and those performed on blood and sputum. More invasive sampling methods included transthoracic needle aspirations and bronchoscopic techniques.

Further, the following study-specific data were extracted: health-care setting, country and time period, age (mean or median if the mean is not reported), gender distribution, percentage of included patients with COPD and patients with severe immunosuppression (including patients with organ transplants, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), chemotherapy, and chronic corticosteroids use of >20 mg/day). The health-care setting was divided into three distinctive groups: (1) cases managed in primary care; (2) cases admitted to hospital; and (3) cases admitted to the intensive care unit (ICU). Four different geographical regions were defined based on the United Nations geoscheme (North, East, South, and West) [8].

Also, country-specific antibiotic use and resistance of *S. pneumoniae* to antibiotics might have an impact on the observed prevalence of the respiratory agents [9].

To take antibiotic use into account, we used the defined daily dose of outpatient antibiotics (antimicrobials for systemic use, ATC Group J01) per 1,000 inhabitants as reported by Muller et al. for the year 2002 [10]. Since only reimbursement data were available for Spain, we corrected the number of doses upwards to correct for the fact that over-the-counter antibiotic use in Spain stands at around 30 % [9].

The *S. pneumoniae*-specific level of antibiotic resistance was based on the percentage of penicillin non-susceptibility using 2010 data of the antimicrobial resistance surveillance

in Europe [11] and other sources for Switzerland [12] and Greece [13]. Although shifts in the use of antibiotics and related resistance might occur, it has been shown that antibiotic use and resistance in the selected countries remained quite stable over time [9–11, 14].

Statistical methods

In order to synthesize the collected evidence, we used a meta-regression model framework for binomial outcomes [15]. Given the large expected true variation of prevalence between studies, we decided to use a mixed-effects instead of a fixed-effects meta-regression framework [16]. In this specification, we assumed that the covariate-adjusted log odds of an *S. pneumoniae*-induced CAP is not constant but varies randomly across studies. We further assumed that the additional, study-specific random effects follow a normal distribution with zero mean and variance σ^2_{Study}. It was also assumed that the measure of association between the log odds of an *S. pneumoniae*-induced CAP and countries is random and normally distributed with mean zero and variance $\sigma^2_{\text{Country}}$. Additionally to these random effects, the model was corrected for a number of study- and country-specific covariates which were incorporated as fixed effects. From the full set of covariates, we subselected those that significantly improved the fit of the model. We fitted a variety of models with different covariates included and compared their goodness of fit using the Akaike information criterion (AIC) in order to arrive at the final set of covariates [17, 18].

Missing values in the covariates used were handled through multiple imputation [19, 20]. We created 25 imputed datasets, in each of which every missing value was replaced with a plausible value estimated through a regression model. Next, the meta-regression framework described above was applied for every dataset. The results were subsequently synthesized for statistical inference. All statistical analyses were implemented using the statistical software R (version 2.13.2) [21]. We additionally used the "mi", "lme4", and "meta" R packages for the implementation of multiple imputation, the estimation of the mixed-effects meta-regressions, and the visualization of the results, respectively [20, 22].

Results

Search results

Of the 3,738 original citations, we excluded 3,290 (88 %) based on a review of the titles (Fig. 1). Of the remaining 448 selected studies, 277 were excluded after reviewing the abstract. After reviewing the entire text of the remaining 171 studies, 73 met eligibility criteria. In addition to the 73 studies included by the initial search term, four more were identified by the scanning of references and subsequently added, resulting in a total of 77 included studies [5, 23–98]. Several studies reported data separately for health-care settings. These studies were, therefore, split into setting-specific "sub-studies" in this analysis.

Study characteristics

The characteristics of the 77 selected studies are presented in Table 1. Of all (sub-)studies included, the majority reported cases admitted to hospital (n=60), 17 were available for cases admitted to the ICU, and 14 for cases managed in the primary care. A total of 24,410 patients were included, with an average age of 62.1 years, with 62.3 % being male. Most of the studies originated from Southern Europe, with Spain being the most frequently represented country. No studies were found for Eastern Europe. In Fig. 2, the crude proportion of *S. pneumonia* per country is presented.

S. pneumoniae

We identified 24,423 CAP episodes in 24,410 patients (patients could have more than one episode), of which 4,714 (19.3 %) were attributed to *S. pneumoniae*. Figure 3 presents the unadjusted, study-specific proportions of *S. pneumoniae* as the causative agent for CAP, together with the proportions' confidence intervals (CIs).

Mixed-effects meta-regression

The results of the final model, in which country and study were estimated as random-effects parameters and the rest of the covariates as fixed-effects parameters, are presented in Table 2. This model assumes as baseline a study with average proportions of blood cultures, urine serology, blood or sputum serology, and PCR tests. Additionally, this baseline study is assumed to originate from a Northern European country with average antibiotic resistance and with CAP episodes that were managed in primary care. Hence, the estimated odds of an *S. pneumoniae*-caused CAP for a study with baseline characteristics was 0.176, which corresponds to a probability of 0.15. The model also showed that, in studies in which the percentage of blood cultures, urine serology, blood or sputum serology, or PCR tests increased, the likelihood of detecting *S. pneumoniae* also significantly increased, with the highest increase observed for PCR tests (odds ratio 2.49; 95 % CI: 1.39–4.46).

Compared to studies with CAP episodes managed in primary care, the odds of *S. pneumoniae* being the cause of a CAP was 1.45 (95 % CI: 1.19–1.77) times higher in

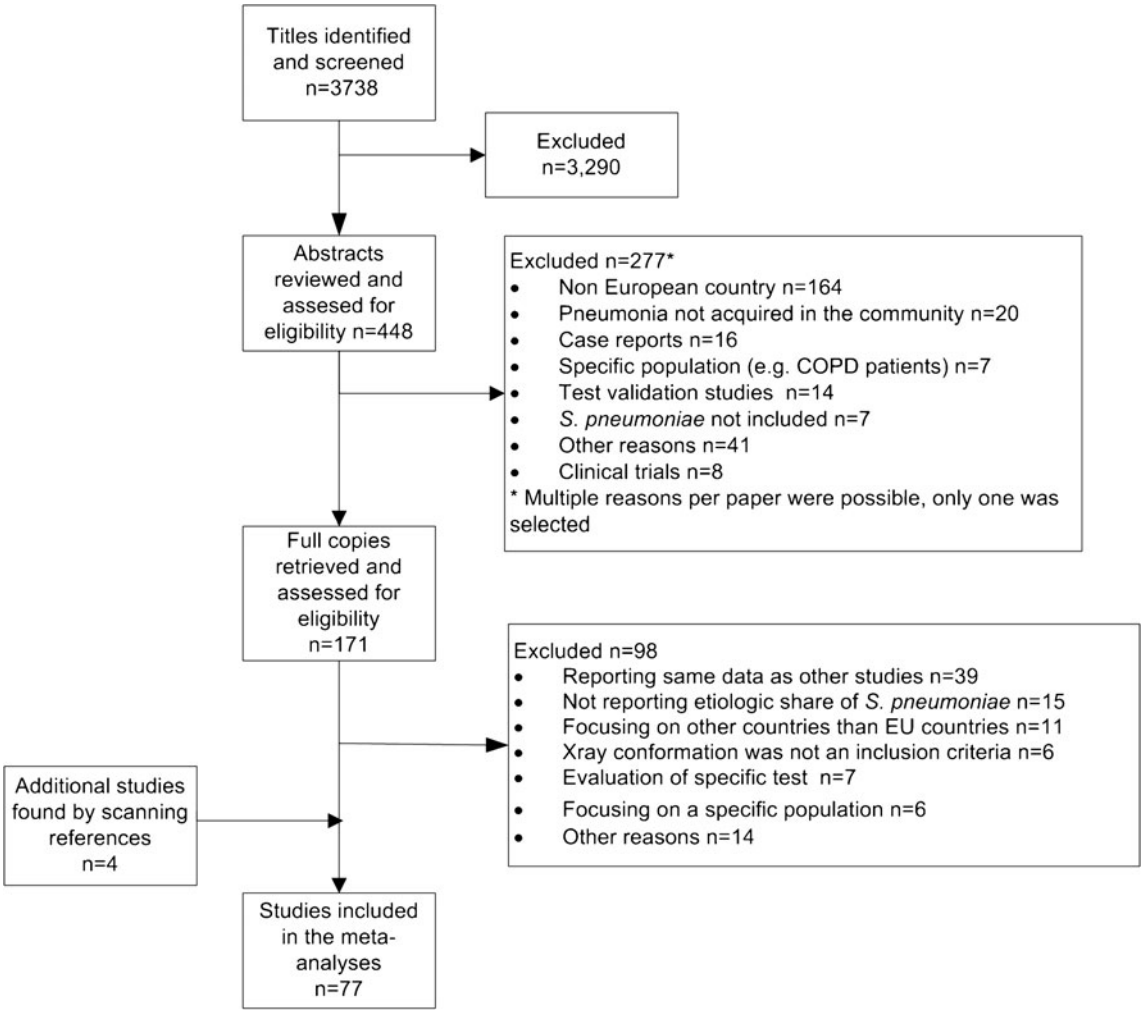


Fig. 1 Flow diagram for the selection of studies

studies with episodes treated in the hospital and 2.33 (95 % CI: 1.80–3.02) times higher in the ICU. The odds of detecting *S. pneumoniae* as the cause of CAP in studies from Western and Southern Europe were almost two and three times smaller, respectively, compared to studies conducted in Northern Europe, where *S. pneumoniae* was the most frequently observed, independently of the percentage of diagnostic testing [Western Europe: 0.57 (95 % CI: 0.32–1.00); Southern Europe: 0.40 (95 % CI: 0.2–0.80)]. Illustratively, a study with baseline characteristics but originating from Southern Europe is expected to identify *S. pneumoniae* as the causative agent in 6.5 % of the CAP episodes (since $(0.176 * 0.397)/(1 + 0.176 * 0.397) = 0.065$).

The estimate of the variance for the study- and country-specific random effects indicated that there was significant heterogeneity among the estimates that was not captured through the fixed-effects covariates. The inclusion of both study- and country- specific random effects significantly improved the goodness-of-fit of the model.

Sputum culture and invasive detection techniques did not have a significant impact on the model or contributed to a better fit of the model to the study data, according to the AIC. Antibiotic resistance also did not significantly affect the probability to detect *S. pneumoniae* after inclusion of the random-effects term for per-country variations. However, antibiotic resistance was deemed as being useful for the fit of the model and was, therefore, included in the analysis.

Discussion

In this analysis, we showed that the observed prevalence of *S. pneumoniae* in adult CAP significantly varies between studies conducted in different European regions, even after correcting for effect modifiers, including diagnostic tests used, antibiotic resistance, and health-care setting. The probability of detecting *S. pneumoniae* was also substantially higher in studies that performed more frequently a diagnostic PCR assay compared to all the other diagnostic tests

Table 1 Basic study characteristics of the (sub-)studies included into the mixed-effects logistic regression

First author and reference	Study start and end (year)	Country	European region	Setting	Average age[a]	Sex[a] (% male)	Antibiotic resistance level (%)[b]
Ewig et al. [23]	1999–2000	Germany	Western	Hospital	68	62	3.7
Ewig et al. [70]	1985–1993	Germany	Western	Hospital	51	67	3.7
Krüger et al. [71]	2002–2007	Germany	Western	Community	62	55	3.7
Krüger et al. [71]	2002–2007	Germany	Western	Hospital	62	55	3.7
Steinhoff et al. [72]	1991–1992	Germany	Western	Hospital	57	62	3.7
Bella et al. [73]	NS–1991	Spain	Southern	Community	59	78	29.8
Blanquer et al. [74]	1985–1986	Spain	Southern	Community	41	70	29.8
Blanquer et al. [74]	1985–1986	Spain	Southern	Hospital	60	70	29.8
Briones et al. [75]	2000–2004	Spain	Southern	Hospital	66	64	29.8
Valencia et al. [76]	1996–2003	Spain	Southern	Hospital	79	69	29.8
Valencia et al. [76]	1996–2003	Spain	Southern	ICU	79	75	29.8
Cillóniz et al. [63]	1996–2008	Spain	Southern	Community	66	63	29.8
Cillóniz et al. [63]	1996–2008	Spain	Southern	Hospital	66	63	29.8
Cillóniz et al. [63]	1996–2008	Spain	Southern	ICU	66	63	29.8
Falcó et al. [64]	1988–1989	Spain	Southern	Hospital	56	100	29.8
Falguera et al. [65]	1997–2000	Spain	Southern	Community	51	57	29.8
García-Ordóñez et al. [66]	1996–1998	Spain	Southern	Hospital	76	58	29.8
García-Vázquez et al. [67]	2003–2003	Spain	Southern	Hospital	63	66	29.8
Garcia-Vidal et al. [68]	1995–2005	Spain	Southern	Hospital	65	68	29.8
Gómez et al. [69]	1991–1994	Spain	Southern	Hospital	58	67	29.8
Gutiérrez et al. [89]	1999–2001	Spain	Southern	Community	57	63	29.8
Gutiérrez et al. [89]	1999–2001	Spain	Southern	Hospital	57	63	29.8
Lorente et al. [90]	1996–1998	Spain	Southern	Hospital	62	61	29.8
Martínez-Moragón et al. [91]	2003–2003	Spain	Southern	Hospital	73	45	29.8
Menéndez et al. [92]	1996–1997	Spain	Southern	Hospital	62	63	29.8
Molinos et al. [93]	1991–1994	Spain	Southern	Hospital	58	79	29.8
Molinos et al. [94]	2003–2004	Spain	Southern	Hospital	67	68	29.8
Sopena et al. [95]	1994–1996	Spain	Southern	Hospital	54	73	29.8
Pachon et al. [96]	1985–1987	Spain	Southern	ICU	57	67	29.8
Pareja et al. [97]	1989–1991	Spain	Southern	Hospital	57	67	29.8
Querol-Ribelles et al. [98]	2000–2003	Spain	Southern	Hospital	71	71	29.8
Rello et al. [77]	1991–1992	Spain	Southern	ICU	72	65	29.8
Rello et al. [78]	1993–1999	Spain	Southern	ICU	61	79	29.8
Rello et al. [79]	1988–1990	Spain	Southern	ICU	45	76	29.8
Riquelme et al. [80]	1993–1994	Spain	Southern	Hospital	79	67	29.8
Ruiz-González et al. [81]	1993–1994	Spain	Southern	Hospital	51	62	29.8
Ruiz-González et al. [81]	1993–1994	Spain	Southern	Community	51	62	29.8
Sordé et al. [82]	2007–2008	Spain	Southern	Hospital	64	67	29.8
Torres et al. [83]	1984–1987	Spain	Southern	ICU	53	77	29.8
Zalacain et al. [84]	1997–1997	Spain	Southern	Hospital	76	63	29.8
Howard et al. [85]	1999–2000	UK	Northern	Hospital	NS	NS	3.1
Lim et al. [86]	1998–1999	UK	Northern	Hospital	65	51	3.1
[No authors listed] [87]	1987–1987	UK	Northern	ICU	54	57	3.1
Venkatesan et al. [88]	1987–1988	UK	Northern	Hospital	NS	52	3.1
Woodhead et al. [54]	1988–1989	UK	Northern	Hospital	NS	55	3.1
Boersma et al. [55]	1987–1989	Netherlands	Western	Hospital	59	64	2.0
Boersma et al. [56]	1988–1992	Netherlands	Western	Hospital	52	60	2.0
Bohte et al. [57]	1991–1993	Netherlands	Western	Hospital	NS	58	2.0
Endeman et al. [58]	2004–2006	Netherlands	Western	Hospital	63	62	2.0

Table 1 (continued)

First author and reference	Study start and end (year)	Country	European region	Setting	Average age[a]	Sex[a] (% male)	Antibiotic resistance level (%)[b]
Holloway et al. [59]	NS–1991	Netherlands	Western	Hospital	58	60	2.0
Templeton et al. [60]	2000–2002	Netherlands	Western	Hospital	NS	71	2.0
Templeton et al. [60]	2000–2002	Netherlands	Western	ICU	NS	71	2.0
van der Eerden et al. [61]	1998–2000	Netherlands	Western	Hospital	64	54	2.0
Vegelin et al. [62]	1992–1996	Netherlands	Western	ICU	64	61	2.0
Fantin et al. [45]	1995–1997	France	Western	Community	52	50	27.6
Fantin et al. [45]	1995–1997	France	Western	Hospital	52	50	27.6
Georges et al. [46]	1987–1995	France	Western	ICU	63	66	27.6
Leroy et al. [47]	1987–1992	France	Western	ICU	63	63	27.6
Leroy et al. [47]	1993–1994	France	Western	ICU	61	68	27.6
Moine et al. [48]	1987–1989	France	Western	ICU	58	74	27.6
Paganin et al. [49]	1995–2000	France	Western	ICU	55	84	27.6
Renaud et al. [50]	2002–2003	France	Western	Community	71	64	27.6
Renaud et al. [50]	2002–2003	France	Western	Hospital	71	64	27.6
Laurichesse et al. [51]	1998–1999	France	Western	Hospital	67	53	27.6
Blasi et al. [52]	1991–1993	Italy	Southern	Community	42	52	9.2
Blasi et al. [52]	1991–1993	Italy	Southern	Hospital	42	52	24.4
Cosentini et al. [53]	1992–1993	Italy	Southern	ICU	68	64	9.2
Farina et al. [32]	1999–2000	Italy	Southern	Hospital	NS	NS	9.2
Guglielmo et al. [33]	NS–1995	Italy	Southern	Hospital	63	62	9.2
Michetti et al. [34]	1991–1992	Italy	Southern	Community	NS	43	9.2
Michetti et al. [34]	1991–1992	Italy	Southern	Hospital	NS	70	9.2
Burman et al. [35]	1982–1984	Sweden	Northern	Hospital	NS	52	3.8
Johansson et al. [36]	2004–2005	Sweden	Northern	Hospital	61	51	3.8
Ortqvist et al. [37]	NS–1987	Sweden	Northern	Hospital	62	43	3.8
Strålin et al. [38]	1999–2002	Sweden	Northern	Hospital	0	53	3.8
Hohenthal et al. [39]	1999–2004	Finland	Northern	Hospital	50	52	14.2
Jokinen et al. [40]	1981–1982	Finland	Northern	Community	49	58	14.2
Jokinen et al. [40]	1981–1982	Finland	Northern	Hospital	49	58	14.2
Beović et al. [41]	1999–2001	Slovenia	Southern	Community	45	62	15.5
Socan et al. [42]	1996–1997	Slovenia	Southern	Hospital	57	50	15.5
Melbye et al. [43]	1988–1989	Norway	Northern	Community	NS	46	15.5
Holm et al. [5]	2002–2003	Denmark	Northern	Community	NS	58	3.6
Kirk et al. [30]	1995–1996	Denmark	Northern	Hospital	NS	44	3.6
Ostergaard et al. [31]	1988–1993	Denmark	Northern	Hospital	65	46	3.6
Leesik et al. [44]	1996–1998	Estonia	Northern	Hospital	56	77	1.6
Genné et al. [29]	1999–2000	Switzerland	Western	Hospital	68	57	9.3
Janssens et al. [28]	1988–1989	Switzerland	Western	Hospital	85	36	9.3
Müller et al. [27]	2002–2005	Switzerland	Western	Hospital	67	63	9.3
Müller et al. [26]	2006–2008	Switzerland	Western	Hospital	73	59	9.3
Manali et al. [25]	1999–2002	Greece	Southern	Hospital	58	61	48.3
Marques et al. [24]	2004–2006	Portugal	Southern	ICU	63	74	14.7

NS not stated

When studies reported data separately for different health-care settings, they were split into different sub-studies

[a] When average age and sex was not provided across different health settings, the overall average corresponding estimates were used instead

[b] The level of *S. pneumoniae* antibiotic resistance was based on the percentage of penicillin non-susceptibility using the Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and national guidelines for clinical breakpoints [11]

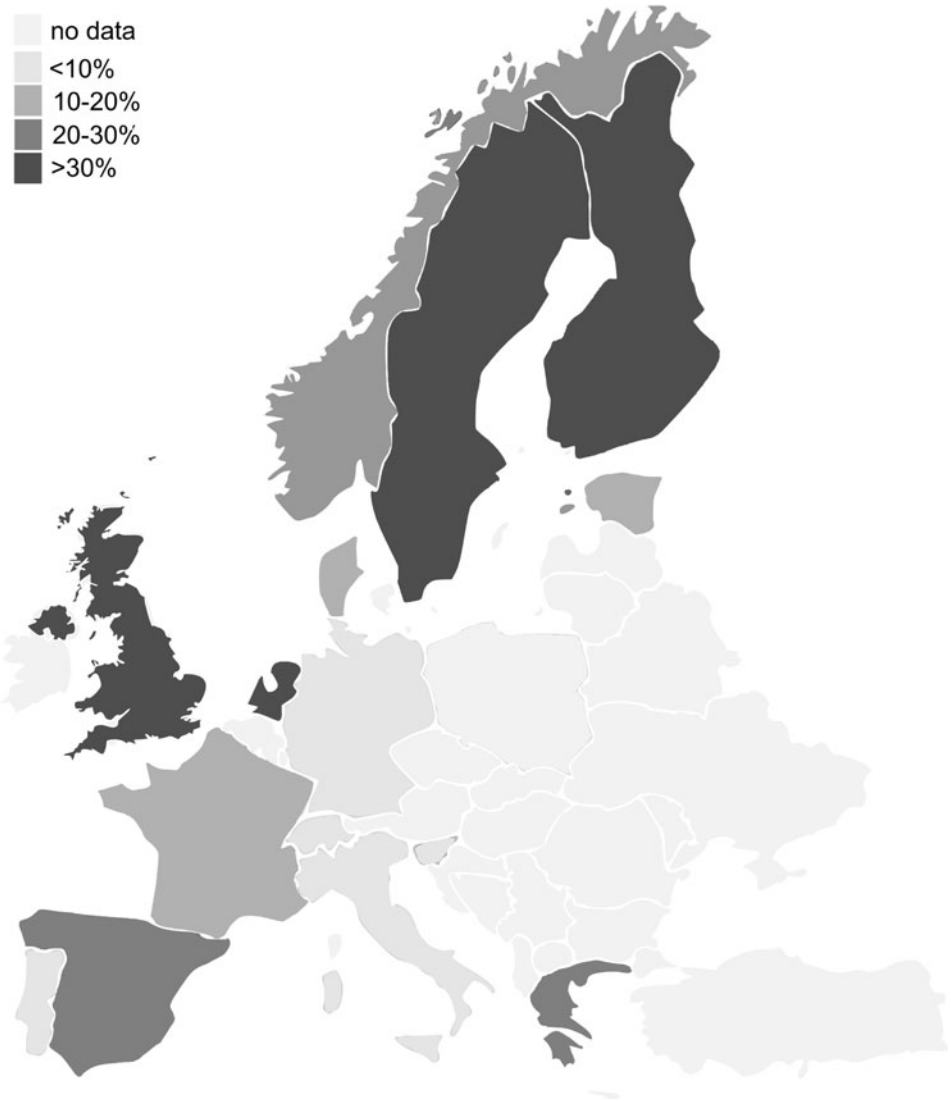


Fig. 2 The country-specific, crude proportion of *Streptococcus pneumoniae* as a causative agent for community-acquired pneumonia (CAP). Numbers of episodes per country: Germany (1,783), Spain (12,804), UK (605), Netherlands (1,318), France (2,480), Italy (897), Sweden (892), Finland (688), Slovenia (325), Norway (19), Denmark (545), Estonia (439), Switzerland (1,464), Greece (88), Portugal (76)

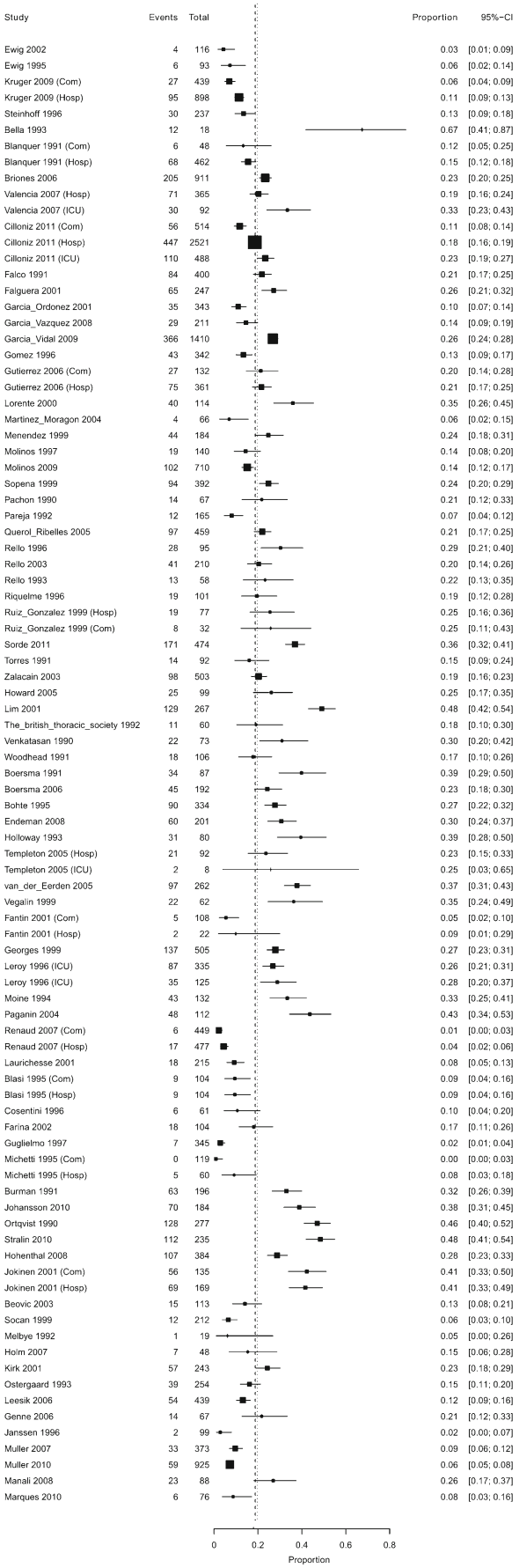
included. Furthermore, *S. pneumoniae* was observed less frequently in studies with CAP cases treated in the community as compared to those with cases treated in the hospital or in the ICU.

In contrast to earlier review studies on this topic, we approached the analysis of the observed frequency of *S. pneumoniae* among pneumonia cases through a mixed-effects meta-regression framework [3, 4]. In this respect, we not only accounted for the influence of various covariates on the observed prevalence of *S. pneumoniae*, such as the health-care setting, diagnostic tests used, and antibiotic resistance, but we also corrected for other study- and country-specific unobserved parameters that might also have an impact on this share. This correction revealed that significant unobserved variation exists among countries, as well as across studies, regarding the observed share of *S. pneumoniae* in CAP.

The finding that this share differs across health-care settings was also noted previously by Woodhead [4], although this was accompanied with the remark that individual studies showed a wide variety in the frequency of detecting *S. pneumoniae*. Our findings agreed with those observed by Woodhead, but through the use of a meta-regression model and the inclusion of more recent studies, we were able to confirm significant differences that were independent of other covariates.

One of the limitations of the previous reviews was that they did not exclude studies in which a radiographic confirmation of pneumonia was not an inclusion criterion. Without a chest radiograph, a CAP diagnosis cannot be made with certainty [5]. Similar clinical signs and symptoms can also be caused by non-infectious diseases, such as congestive heart failure or atelectasis [27]. Therefore, and because the interpretation of clinical assessments are prone to inter-observer variability, we only included those studies in which this was an inclusion criterion.

Our meta-analysis showed that, in studies in which the percentage of invasive techniques or sputum culture



◀ **Fig. 3** Forest plot showing the unadjusted proportion (with 95 % confidence intervals) of *Streptococcus pneumoniae* as the causative agent for community-acquired pneumonia (CAP). CAP cases reported for different health settings are reported separately across studies

increased, the likelihood of detecting *S. pneumoniae* did not significantly increase. This finding for invasive testing might be counterintuitive, but can be attributed to the under-reporting of the proportion of patients tested with this invasive method. In particular, almost all included studies report that invasive tests were performed, but the majority did not report the proportion of the patients tested. In most studies, the use of invasive techniques is likely to be limited to a few patients, as invasive sampling methods for lower respiratory secretions are impractical. This limited the accuracy of the estimate of the impact of invasive tests on detecting *S. pneumoniae*. A sub-analysis in the studies that reported the fraction of invasive testing revealed that the percentage of invasive tests performed had a significant positive impact on the study's detected fraction of *S. pneumoniae* in CAP (data not shown).

Of course, our study also has some limitations, which can be divided into those related to health-care setting, population, epidemiological, study methodological, and model-related factors [4]. Our model showed that *S. pneumoniae* was more likely to be prevalent in CAP cases treated in the ICU as compared to those treated in the hospital or in the community. We do, however, note that admission criteria for hospitalization or ICU admission might differ between hospitals and countries and may not always reflect severity. For example, in Spain, many patients seek medical care directly from the emergency service of the hospital rather than after a visit to a primary care physician [65]. Nevertheless, some of the country variation on the detection of *S. pneumoniae* is expected to have been captured through the country-specific random-effects parameter.

Secondly, factors related to the population, such as antibiotic therapy, vaccination status, immunosuppression, and comorbid conditions, might impact the share of *S. pneumoniae* detected. We tried to obtain as much information on the included studies as possible in order to be able to correct for these factors. For example, we obtained information on the proportion of immunosuppressed patients and patients suffering from COPD. However, the fit of the model was best when these factors were excluded. This might be explained by the fact that different definitions of 'immunocompromised' among studies were used or that specific data were just not reported. Additionally, the country-specific random-effects term used in the model might have corrected for enough across-country variation, constituting these variables as redundant. Furthermore, to minimize heterogeneity between studies, we decided to exclude clinical trials, as patients enrolled in these studies differ from those

Table 2 Mixed-effects meta regression model results

	Odds ratio	Lower CI bound	Upper CI bound	*p*-value
Fixed-effects estimates				
Intercept[a]	0.176	0.113	0.274	<0.001
Region				
Western Europe	0.565	0.32	0.998	0.048
Southern Europe	0.397	0.198	0.797	0.009
Health-care Setting				
Hospital	1.451	1.191	1.769	<0.001
ICU	2.334	1.804	3.021	<0.001
Blood culture (%)	1.782	1.002	3.17	0.048
Urine serology (%)	1.987	1.283	3.077	0.002
PCR (%)	2.491	1.39	4.464	0.002
Blood or sputum serology (%)	1.836	1.114	3.023	0.017
Antibiotic resistance (%)[b]	1.021	0.995	1.047	0.115
Random-effects estimates				
σ^2_{Study}	0.185			
$\sigma^2_{\text{Country}}$	0.094			

[a]Baseline study characteristics: region: Northern Europe; health-care setting: primary care; average proportions of blood culture, urine serology, blood and sputum serology, and PCR testing, as well as average antibiotic resistance

[b]The level of *S. pneumoniae* antibiotic resistance was based on the percentage of penicillin non-susceptibility using the Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and national guidelines for clinical breakpoints [11]

encountered in daily clinical practice. Considering the long time span of studies included into the model, we were unable to include PPV23 or influenza vaccination status, as country-specific vaccination coverage over time are not abundantly available. The impact of PPV23 vaccination is probably small, as the uptake, the efficacy, and the duration of protection of PPV23 are limited [99, 100]. Although the influenza vaccine does not protect directly against pneumococcal pneumonia, viral infections may pave the way for pneumococcal infections [101]. We based the level of antibiotic resistance on recent antimicrobial resistance surveillance data [11]. Resistance levels may change over time, but we note that the resistance patterns of the most recent EARSS report [11] are very similar to the earliest EARSS report using data from 1999 to 2001 [14].

Thirdly, epidemiological factors may change the share of *S. pneumoniae* cases. For example, the time of year might impact the frequency of *S. pneumoniae* detected. Most of the studies included in our analysis had a time span of over a year, which might have been long enough to capture the short-term seasonal effects.

Fourthly, methodological factors such as comprehensiveness of sample collection and microbiological investigation performed are important [4]. We explicitly took this into account by correcting for both the type of microbiological investigation performed, as well as for the frequency at which these tests were performed. As previously noted by Woodhead, some studies did not explicitly state the percentages of actually performed tests [4].

Finally, a limitation of our analysis is the inability to accurately estimate the true prevalence of *S. pneumoniae* among CAP cases. The main reason for this is that the applied tests cannot detect the true fraction of *S. pneumoniae* among the CAP cases, and, hence, the *S. pneumoniae* prevalence, due to their limited sensitivity and specificity. It is expected that there will be an undetected fraction of *S. pneumoniae* due to false-negative tests, i.e., low sensitivity. However, this undetected fraction might be partly compensated by the false-positive tests, i.e., low specificity.

Recently, the European Commission extended the indication of PCV13 to adults aged 50 years and older to prevent invasive pneumococcal disease caused by *S. pneumoniae*. While there is currently no indication for non-invasive pneumonia, clinical trial data will become available soon [6]. Recent cost-effectiveness studies have shown that, next to the vaccine efficacy, the proportion of non-bacteremic pneumonia due to *S. pneumoniae* is one of the key determinants of cost-effectiveness [7, 102]. Our current study might, therefore, support the decision-making process of the introduction of PCV13 [7, 102].

In conclusion, our study provides estimates of the average observed prevalence of *S. pneumoniae*, which could be used for projecting the health and economic benefits of pneumococcal immunization.

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