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Review article

Systematic review of respiratory viral pathogens identified in adults with community-acquired pneumonia in Europe

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Abstract

Community-acquired pneumonia (CAP) is an important respiratory disease and the fifth leading cause of mortality in Europe. The development of molecular diagnostic tests has highlighted the contributions of respiratory viruses to the aetiology of CAP, suggesting the incidence of viral pneumonia may have been previously underestimated. We performed a systematic review and meta-analysis to describe the overall identification of respiratory viruses in adult patients with CAP in Europe, following PRISMA guidelines (PROSPERO; CRD42016037233). We searched EMBASE, MEDLINE, CINAHL, WHOLIS, COCHRANE library and grey literature sources for relevant studies, and screened these against protocol eligibility criteria. Two researchers performed data extraction and risk of bias assessments, independently, using a piloted form. Results were synthesised narratively, and random effects meta-analyses performed to calculate pooled estimates of effect; heterogeneity was quantified using I². Twenty-eight studies met inclusion criteria of which 21 were included in the primary meta-analysis. The pooled proportion of patients with identified respiratory viruses was 22.0% (95% CI: 18.0%–27.0%), rising to 29.0% (25.0%–34.0%) in studies where polymerase chain reaction (PCR) diagnostics were performed. Influenza virus was the most frequently detected virus in 9% (7%–12%) of adults with CAP.

Respiratory viruses make a substantial contribution to the aetiology of CAP in adult patients in Europe; one or more respiratory viruses are detected in about one quarter of all cases.

1. Introduction

Community-acquired pneumonia (CAP) is a principal cause of excess hospitalisation and mortality worldwide [1–3]. Historically, the overriding clinical approach to the management of CAP has been to focus on bacterial aetiologies, with Streptococcus pneumoniae the dominant pathogen [4–8]. More recently, coupled to the increasing availability of polymerase chain reaction (PCR) tests, the identification of viral pathogens in the aetiology of CAP has increased. Contemporary studies identify that viruses may be implicated in 15%–30% of all CAP [9–11]; in turn this heightens the possibility that empirical antibiotic treatment of CAP in the absence of adequate testing for viral pathogens may contribute to inappropriate antibiotic usage [12,13].

Given the considerable variation across individual studies in estimating the contribution of respiratory viruses to CAP aetiology, reliable summaries of relevant data are necessary to inform future research and policy initiatives, particularly as new respiratory virus vaccines and antiviral drugs are anticipated in the short to medium term [11,14–17].

Two recent systematic reviews of studies investigating the proportions of viral pathogens in patients with CAP focussed on studies that only used polymerase chain reaction (PCR)-based assays to detect viral pathogens and pooled results from studies conducted across the world. [18,19] We report an additional systematic review of studies conducted within the World Health Organization European Region, which offers additional granularity according to setting, timing of study, viral diagnostic techniques and study quality.

2. Methods

The study protocol was registered on the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO; CRD42016037233; available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037233) and conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20].

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## 2.1. Eligibility criteria

We identified studies which investigated the aetiology of CAP in adults in Europe (defined as those countries covered by the WHO Regional Office for Europe [http://www.euro.who.int/en/countries](http://www.euro.who.int/en/countries)) and reported quantitative data on the identification of respiratory viruses. We searched for original articles describing longitudinal studies or case series, in English, which investigated adults aged ≥16 years diagnosed with CAP. All other study designs were excluded. We included studies that performed either PCR or non-PCR detection techniques.

We excluded studies of paediatric populations and patients residing in nursing homes, residential care homes or rehabilitation facilities. Studies of adults diagnosed with CAP based on clinical signs but without radiologic confirmation, and studies focused on CAP in adults with severe immunosuppression through disease and/or drug treatment were also excluded.

## 2.2. Search strategy and screening

The following electronic databases were systematically searched: EMBASE, MEDLINE, CINAHL, WHOLIS, and Web of Science from January 1999 to April 2016. A comprehensive search strategy was developed for EMBASE (Supplementary Appendix A) and subsequently adjusted as required to suit other databases. The reference lists of all eligible articles were manually searched to identify other eligible studies.

All identified articles were imported to ENDNOTE software X4 (Thomson Reuters, Toronto, CA, USA) and duplicates removed. Two review authors (YA and JSN-V-T) independently screened the retained articles against protocol eligibility criteria, in three stages: by title, abstract and full text. Any disagreements were resolved through discussion between YA and JSN-V-T; and a third author (WSL) adjudicated in evaluable CAP patients. Sixteen studies (57.1%) [26,29,30,32,34,36,39,41–44,46,49,50] had used PCR techniques for the detection of respiratory viruses, alone or in combination with other diagnostic methods. 14 studies (50%) obtained upper respiratory samples [26,28,30,35,38,39,41–44,46,49,50], 16 (57.1%) lower respiratory [25,31,32,33,34,38,42,43,45,46,47,48,49,50,51] in mixed populations (n = 2738 patients). Details of the characteristics of the included studies are summarised in Table 1. Sixteen studies (57.1%) [26,29,30,32,34–36,39,41–45,47,49,50] had used PCR techniques for the detection of respiratory viruses, alone or in combination with other diagnostic methods. 14 studies (50%) obtained upper respiratory samples [26,28,30,35,38,39,41–44,46,49,50], 16 (57.1%) lower respiratory [25,31,32,33,34,38,42,43,45,46,47,48,49,50,51], and six (21.4%) both [38,42,43,46,49,50,51]. In 10 (35.7%) studies (9 publications) respiratory tract sampling was combined with assessment of paired serology [25,31,32,33,45,46,49,50,51]; and in four (14.3%) studies, serology alone was performed [27,29,37,40].

## 3. Results

We identified a total of 1106 articles from database searches, reducing to 1083 after the removal of duplicates. Eleven additional papers were identified via citation tracking. After screening, 27 articles remained within protocol eligibility criteria (Fig. 1); one of the included articles [25] presented two separate studies and data from both were extracted and presented separately. Thus, 28 studies from 27 articles were included in the systematic review [25–51], and 21 from 20 in the primary meta-analysis [25–44]. When examined as full-text articles, seven studies did not present sufficient quantitative data for inclusion in the primary meta-analysis [45–51] (Fig. 1).

### 3.1. Study characteristics

All 28 studies included in the systematic review were prospective or retrospective longitudinal studies or case-series. The patient population size in each ranged from 71 to 1356 (total = 8777). The earliest publications were in 2001 [37,40], and the most recent article was published in October 2015 [26].

Studies from 11 different European countries were included of which Spain was most frequently represented (9 studies; 32.1%) [27,28,31,33,41,44,47,50,51]. Nineteen studies (67.9%) [25–26,29–32,33,35,36,39,41–44,46,49,50] were carried out among inpatient populations (n = 5515 patients), three [34,38,46] (10.7%) in outpatient/community populations (n = 524 patients) and six (21.4%) [27,28,33,37,45,51] in mixed populations (n = 2738 patients). Details of the characteristics of the included studies are summarised in Table 1. Sixteen studies (57.1%) [26,29,30,32,34–36,39,41–45,47,49,50] had used PCR techniques for the detection of respiratory viruses, alone or in combination with other diagnostic methods. In 10 (35.7%) studies (9 publications) respiratory tract sampling was combined with assessment of paired serology [25,31,32,33,45,46,49,50,51]; and in four (14.3%) studies, serology alone was performed [27,29,37,40].

### 3.2. Risk of bias assessment

Study population representativeness, diagnostic accuracy of CAP and ascertainment of virus aetiology were assessed with a maximum of three stars per study. Eleven studies [26,30,32,34–36,39,41–43,45] (39.3%) were assessed as being at low risk of bias (three stars; one star per domain), 14 studies [25,26,29,33,37,38,40,44,46,47,49,50,51] (53.6%) at moderate risk of bias (2 out of 3 stars), and three [28,31,48] (7.1%) at high risk of bias (one or zero stars). Six studies [1] (21.4%) were computed for outcomes. The primary outcome was the overall contribution of respiratory viruses in the aetiology of CAP, calculated as the total number of patients with respiratory viruses identified (numerator) as a proportion of the total number of evaluable patients (denominator). We report, as secondary outcomes, the contribution of individual viruses calculated as the total number of patients with individual respiratory viruses identified as a proportion of all evaluable patients for each specific pathogen.

Heterogeneity between studies was quantified using the I2 statistic [24]. We investigated potential sources of heterogeneity by performing subgroup analyses; by study setting (inpatient vs. outpatient), study quality, viral diagnostic methods used (PCR diagnostic techniques vs non-PCR methods) and mixed infections (bacterial and viral infections). All analyses were conducted using the metaprop commands within Stata (V.13, Stata Corp, College Station, Texas, USA).

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1. One article presented data on two separate studies [25].
2. Citation #25 describes two studies.
3. Citation #25 describes two studies.
reported difficulty in obtaining adequate samples for microbiological testing [25,27,32,37,41]. Within-study variation in viral diagnostic methods across different study years was reported in ten studies (35.7%) [26,29,30,35,36,39–44].

3.3. Overall identification of respiratory viruses

The percentage of respiratory viruses detected in CAP patients ranged from 6% in a Spanish study comprising both inpatients and outpatients [33], to 45% in a study of hospitalised patients in Israel [42]. By meta-analysis, the pooled proportion of respiratory viruses detected in CAP patients was 22.0% (95% CI 17.0%-27.0%; I² = 94.7%) (Fig. 2).

There was a significant trend for the identification of respiratory virus pathogens to be lower in studies (n = 8) published from 2001 to 2009 [25,31–34,37,40], (pooled estimate = 14.0% (95%CI 9.0%-21.0%)) compared with more recent studies (n = 13) published after 2010 [26–30,35,36,38,41–44] (pooled estimate = 27.0% (95%CI 20.0%-33.0%)), test for subgroup differences, p = 0.007 (Supplementary Appendix B).

3.4. Sub-group analyses

The pooled proportion of respiratory viruses identified among patients with CAP in inpatient studies (n = 15) [25,26,29–32,35,36,39–44] was 27.0% (95% CI 23.0%-31.0%; I² = 85.1%); compared with 19.0% (95% CI 14.0%-24.0%; I² = 95.3%) for outpatient studies (n = 2) [34,38], and 9.0% (95% CI 6.0%-12.0%; I² = 85.8%) in studies with mixed populations (n = 4) [27,28,33,37] (Fig. 3). Each of these populations revealed results that were statistically significantly different from each other (test for subgroup differences, p < 0.01). Studies with mixed populations [27,28,33,37], relied exclusively on non-PCR diagnostic methods and were of lower quality compared to other studies.

The pooled proportion of respiratory viral pathogens identified in 12 studies [26,29,30,32,34–38,41–44] using PCR (with or without additional testing methods) was 29.0% (95% CI 25.0%-34.0%, I² = 83.5%) compared with 13.0% (95% CI 9.0%-18.0%, I² = 90.7%) in nine studies using other non-PCR methods [25,27,28,31,33,37,38,40], with a significant difference between the two groups, p < 0.001 (Fig. 4).

In lower risk of bias studies (NOS score = 3 stars) [26,30,32,34–38,41–43] the pooled proportion for total respiratory viral pathogens was 30% (95% CI 25.0%-34.0%, I² = 77.4%), compared with 11% (95% CI 9%-13%, I² = 99.3%) in higher risk of bias studies (NOS score = 1 star) [28,31], explaining the observed overall heterogeneity between studies, p < 0.001 (Fig. 5).

3.5. Mixed infections

The pooled proportion of mixed respiratory viruses and bacterial co-infections detected in CAP patients was 10% (95% CI 6%-14%,
| First author | Study setting | Study design | Patient characteristics | Total number of patients with CAP | Number of viruses tested for | Male% Diagnostic methods | Principal study focus | Specimen sites* |
|-------------|---------------|--------------|-------------------------|----------------------------------|-----------------------------|--------------------------|------------------------|------------------|
| Le Bel [26] | France, inpatients | Prospective cohort | Patients aged > 18 years presented to Emergency dept. | 319 | PCR | 81 (31.7%) | Blood culture, viral antigen tests, direct immunofluorescence antibody | Acute respiratory distress syndrome in CAP patients |
| Capelastegui [27] | Spain, inpatients and outpatients | Prospective cohort | Patients aged > 18 years in the community and hospital | 700 | PCR, ELISA | 101 (31.7%) | Blood and Sputum culture, PCR | Aetiology of CAP |
| Cilloniz [28] | Spain, inpatients and outpatients | Prospective cohort | Patients aged > 16 years admitted to the Emergency wards and outpatients. | 568 | PCR | 301 (53.0%) | Serology, blood culture, antigen tests. | Aetiology of CAP |
| Clark [29] | UK, inpatients | Prospective cohort | Patients aged > 18 years admitted to hospital with acute respiratory infection but subset with CAP patients | 166 | PCR | 87 (52.4%) | Blood and Sputum culture, PCR | Aetiology of CAP |
| Das [30] | France, inpatients | Prospective cohort | Patients aged > 18 years admitted to the Emergency dept. | 125 | PCR | Not reported | PCR | Aetiology of CAP |
| de Roux [31] | Spain, inpatients | Prospective cohort | Patients aged > 18 years admitted to hospital | 1356 | PCR, ELISA | 893 (65.8%) | Serology, complement fixation kit, PCR | Viral CAP in non-immunocompromised adults |
| Diederen [32] | Netherlands, Inpatients | Prospective cohort | Patients aged > 18 years admitted to the hospital | 242 | PCR, ELISA | 79 (32.9%) | PCR, serology | Detection of respiratory pathogens using PCR |
| Guiterrez [33] | Spain, inpatients and outpatients | Prospective cohort | Patients aged > 15 years admitted to the hospital | 493 | PCR | 301 (62.5%) | Blood and Sputum culture, PCR | Investigating the influence of age and gender on the incidence of CAP |
| Holm [34] | Denmark, outpatients | Prospective cohort | Patients aged > 18 years admitted to the GP | 267 | PCR | 135 (50.6%) | Culture, serology, PCR | Aetiology of CAP in Norway |
| Holter [35] | Norway, inpatients | Prospective cohort | Patients aged > 18 years admitted to the hospital | 267 | PCR | 135 (50.6%) | Culture, serology, PCR | Aetiology of CAP |
| Howard-a [36] | UK, inpatients | Prospective cohort | Patients aged > 15 years | 69 | PCR | Uncertain | PCR, serology | Aetiology of CAP |
| Howard-b [37] | UK, inpatients | Prospective cohort | Patients aged > 16 years admitted to the hospital | 99 | PCR | Uncertain | PCR, serology | Aetiology of CAP |
| Johansson [38] | Sweden, inpatients and outpatients | Prospective cohort | Patients aged > 18 years admitted to the hospital | 184 | PCR | 99 (51.1%) | Culture, PCR, Serology | Aetiology of CAP |
| Joikinen [39] | Finland, inpatients and outpatients | Prospective cohort | Patients aged > 15 years admitted to the hospital and patients in the community | 345 | PCR | 176 (51.0%) | Culture, Serology | Aetiology of CAP in adults in Eastern Finland |
| Koksal [40] | Turkey, outpatients | Cross-sectional | Patients aged > 17 years with CAP in outpatient settings | 292 | PCR, ELISA | 147 (50.3%) | Culture, direct immunofluorescence, serology | Aetiology of CAP in adults in Turkey |
| Lim [41] | UK, inpatients | Prospective cohort | Patients aged > 16 years admitted to the hospital | 267 | PCR | 135 (50.6%) | Culture, serology | Aetiology of CAP |
| Sangil [42] | Spain, inpatients | Prospective cohort | Patients aged > 18 years admitted to the hospital | 169 | PCR | Not reported | PCR, DNA & RNA extraction, Serology | Aetiology of CAP in adults in Spain |
| Shibli [43] | Israel, inpatients | Prospective cohort | Patients aged > 18 years admitted to the hospital | 127 | PCR | 73 (57.5%) | PCR, DNA & RNA extraction, Serology | Investigate the aetiology of CAP in hospitalised patients |
| Templeton [44] | Netherlands, inpatients and outpatients | Prospective cohort | Patients aged > 18 years admitted to the hospital | 136 | PCR | 75 (55.1%) | Culture, serology, PCR | Aetiology of CAP |

(continued on next page)
Table 1 (continued)

| Study design | Study setting | First author | Total number of patients with CAP | Number of viruses tested | Mol/\% | Principal study focus | Diagnostic methods | Study outcomes |
|--------------|---------------|--------------|----------------------------------|--------------------------|--------|-----------------------|------------------|---------------|
| Prospective cohort | Switzerland, outpatient | Bochud [46] | 184 | 4 | 82/44.6\% | Aetiology of CAP in outpatients | Serology | Aetiology of CAP LR, S |
| Prospective cohort | Spain, inpatients | Marcos [47] | 198 | 7 | 115/58.1\% | PCR, immunofluorescence and culture | Immunoassay/PCR | Aetiology of CAP LR |
| Prospective cohort | Finland, inpatients | Hohenthal [48] | 71 | 7 | 48/67.6\% | Culture and serology | Culture and serology | Differences in aetiology of CAP LR, S |
| Prospective cohort | Spain, inpatients | Huijskens [49] | 408 | 11 | 259/61.3\% | PCR, Culture and serology | Culture and serology | Differences in aetiology of CAP LR, S |
| Prospective cohort | Spain, inpatients | Almirall [50] | 496 | 7 | 302/60.9\% | Culture and serology | Culture and serology | Differences in aetiology of CAP LR, S |

Specimen sites: UR = upper respiratory tract; LR = lower respiratory tract; S = serological assessment (using paired sera). *In studies which sampled from > 1 site, not all patients will have undergone sampling at all sites.

\[ \chi^2 = 94.7\% \] reported across 14 studies [26–29,32,33,35–37,40–44] (Fig. 6).

3.6. Individual viruses

Data on the seven most common respiratory viruses identified are presented in Table 2. Influenza viruses were most frequently detected (9%), followed by rhinoviruses (5%) and coronavirus (4%); together accounting for the majority of respiratory viruses detected (Table 2).

4. Discussion

This review updates evidence on the microbiological identification of respiratory viral pathogens in adult patients with radiographically confirmed CAP in Europe. Overall our data suggest that respiratory viruses are detectable in at least 22% of radiologically confirmed CAP cases, mostly hospitalised cases. However significantly higher proportions of respiratory viruses were evident in studies conducted after 2010 (27%), studies that included viral PCR techniques (29%), and studies assessed to be at lower risk of bias (29%), suggesting that the true proportion of CAP associated with respiratory viruses is at least one quarter (25%). Our findings accord with recent major studies or reviews conducted in Asia and North America [11,14,52,53]. In the CDC EPIC study [11], viruses were detected in 27.0% of adult patients with CAP, while Qu et al. detected viruses in 27.5% of Asian patients with CAP [51].

Our review suggests that in Europe, as in other parts of the world, a relatively large burden of CAP disease may be attributable to viral infections. However, the clinico-pathological significance of virus detection in patients with CAP remains uncertain. A clear limitation of our approach (and of each of the included studies) is that no proof is offered that the virus or viruses identified were of pathological significance in all cases. There was also heterogeneity between studies in terms of the respiratory sites sampled and/or use of serology. Viruses recovered from upper respiratory tract (URT) sites might have less pathological significance than those recovered from lower respiratory tract (LRT) sites; nevertheless, in the absence of concomitant sampling from URT and LRT it is not possible to disregard viruses identified from URT sites which may have been replicated in the LRT if it had also been sampled. Whilst respiratory viruses are undoubtedly implicated in the aetiology of a substantial proportion of the cases in which they are detected, asymptomatic illness associated with virus shedding is well recognised, especially in children who experience longer periods of shedding than adults [54]. In addition, modern PCR diagnostic techniques are comparatively more sensitive than methods for the detection of bacteria, and capable of detecting small quantities of nucleic acid which may not in all cases represent cultivable virus; therefore, some patients with ‘viral-only’ pathogens identified may also have a microbiologically unrecognised bacterial infection; and some detections of viral pathogens may represent previous or resolved virus infection. In a recent study, Gadsby et al. employed PCR techniques to identify bacteria as well as viruses from lower respiratory tract samples, viruses were detected in 30% of 323 adults admitted to hospital with CAP and a co-bacterial pathogen was detected in 82% of these [55]. In contrast, we noted only 10% of cases with a bacterial co-pathogen; this might reflect the use of PCR testing for bacteria by Gadsby and colleagues, whereas the studies we included used standard approaches for the identification of bacteria. The detection of respiratory viruses in healthy asymptomatic individuals is not as extensively described as in symptomatic patients; nevertheless Jartti and colleagues summarised data from 51 studies, noting maximum baseline prevalences of respiratory viruses in asymptomatic subjects as follows: rhinoviruses, 15%; adenoviruses, 5.3%; influenza, 4.3%; RSV, 2.6%; coronaviruses, 2.5%; enteroviruses 1.2%; human bocavirus, 1.1%; parainfluenza, 0.9%; and hMPV, 0.6% [54]. Jansen and colleagues have observed that rhinovirus is extremely common in asymptomatic children (28%), but that if other viruses are
Fig. 2. Forest plot: overall identification of respiratory viruses in European adult patients with CAP.
ES = effect size for pooled identification of respiratory viruses.

| Study                  | ES (95% CI)    |
|------------------------|----------------|
| Lim (2001)             | 0.23 (0.18, 0.29) |
| Jokinen (2001)         | 0.09 (0.06, 0.13) |
| Howard (2004)          | 0.14 (0.08, 0.23) |
| Howard (2004)          | 0.15 (0.07, 0.26) |
| de Rieux (2004)        | 0.17 (0.13, 0.22) |
| Gutierrez (2005)       | 0.06 (0.04, 0.08) |
| Holm (2007)            | 0.12 (0.05, 0.25) |
| Diederen (2009)        | 0.24 (0.18, 0.29) |
| Koivt (2010)           | 0.21 (0.15, 0.27) |
| Johansen (2010)        | 0.29 (0.23, 0.36) |
| Lerman (2010)          | 0.32 (0.25, 0.39) |
| Shih (2010)            | 0.45 (0.36, 0.54) |
| Capetlandegui (2011)   | 0.13 (0.11, 0.16) |
| Sangi (2012)           | 0.36 (0.28, 0.45) |
| Citron (2012)          | 0.07 (0.05, 0.10) |
| van Gageldonk-Lafeber (2012) | 0.23 (0.18, 0.28) |
| Clark (2014)           | 0.39 (0.31, 0.46) |
| Viesca (2014)          | 0.22 (0.19, 0.25) |
| Dei (2015)             | 0.30 (0.22, 0.39) |
| Holm (2015)            | 0.34 (0.29, 0.40) |
| Le Bel (2015)          | 0.30 (0.21, 0.40) |
| Overall ($\chi^2 = 0.45$, $p = 0.18$) | 0.22 (0.17, 0.27) |

Fig. 3. Forest plot: overall identification of respiratory viruses in European patients with CAP, stratified by study setting.
ES = effect size for pooled identification of respiratory viruses.

| Study                  | ES (95% CI)    |
|------------------------|----------------|
| Inpatient              |                |
| Lim (2001)             | 0.23 (0.18, 0.29) |
| Howard (2004)          | 0.14 (0.08, 0.23) |
| Howard (2004)          | 0.15 (0.07, 0.26) |
| de Rieux (2004)        | 0.17 (0.13, 0.22) |
| Diederen (2009)        | 0.24 (0.18, 0.29) |
| Johansen (2010)        | 0.29 (0.23, 0.36) |
| Lerman (2010)          | 0.32 (0.25, 0.39) |
| Shih (2010)            | 0.45 (0.36, 0.54) |
| Sangi (2012)           | 0.36 (0.28, 0.45) |
| van Gageldonk-Lafeber (2012) | 0.23 (0.18, 0.28) |
| Clark (2014)           | 0.39 (0.31, 0.46) |
| Viesca (2014)          | 0.22 (0.19, 0.25) |
| Dei (2015)             | 0.30 (0.22, 0.39) |
| Holm (2015)            | 0.34 (0.29, 0.40) |
| Le Bel (2015)          | 0.30 (0.21, 0.40) |
| Subtotal ($\chi^2 = 0.2$, $p = 0.00$) | 0.27 (0.23, 0.31) |

| Outpatient             |                |
| Jokinen (2001)         | 0.09 (0.06, 0.13) |
| Gutierrez (2005)       | 0.06 (0.04, 0.08) |
| Capetlandegui (2011)   | 0.13 (0.11, 0.16) |
| Citron (2012)          | 0.07 (0.05, 0.10) |
| Subtotal ($\chi^2 = 0.2$, $p = 0.00$) | 0.09 (0.06, 0.12) |

| Heterogeneity between groups: $p = 0.00$ |
| Overall ($\chi^2 = 0.45$, $p = 0.18$) | 0.22 (0.17, 0.27) |
Fig. 4. Forest Plot: overall identification of respiratory viruses in European patients with CAP, by diagnostic method employed.
ES = effect size for pooled identification of respiratory viruses.

Fig. 5. Forest plot: overall identification of respiratory viruses in European patients with CAP, according to study quality.
ES = effect size for pooled identification of respiratory viruses.
bocavirus and herpes simplex virus were detected in < 1% of adult patients with CAP. Enterovirus, poliovirus, cytomegalovirus, coxsackie virus, varicella-zoster virus, human bocavirus and herpes simplex virus were detected in < 1% of adult patients with CAP. Influenza (9%) viruses, rhinoviruses (5%) and coronaviruses (4%) accounted for the majority of virus detections; these proportions are similar to the estimates reported previously by Burk et al. and Wu et al [18,19]. However, RSV was identified in only 2% of adult CAP which may be relevant to the potential role of future RSV vaccines targeted at the elderly.

These findings highlight the importance of respiratory viruses in the aetiology of adult CAP, and the potential relevance of our findings towards improving clinical outcomes, and reducing inappropriate antibiotic use. Influenza appears to be the most significant virus pathogen, followed by rhinoviruses and coronaviruses. Notwithstanding, different included studies tested for between 4 and 11 separate respiratory viruses (Table 1); if all included studies had tested for all 11 viruses the overall proportion of virus detection may well have been considerably higher, although, as discussed above, not all detections necessarily have clinical relevance to CAP. This potential source of bias will not have affected the estimates for individual viruses (Table 2) because these analyses were organism-specific and based on all available data by organism. Viral diagnostic evaluation of CAP facilitates greater precision in the assessment of illness severity, and the tailoring of therapy, in particular the rapid use of neuraminidase inhibitors for cases of influenza and more judicious use of antibiotics. Since there are realistic near-term prospects for novel antiviral treatments for several respiratory virus infections and RSV vaccines [59–61], there is a need to establish baseline data on the incidence of viral CAP and develop a wider culture of testing for respiratory virus pathogens without which it will be difficult to assess the impact of advances in therapy.

We included only articles reported in English. An analysis including country-specific data reported in other languages may reveal regional variations in the contribution of respiratory viruses to the microbiology of CAP. Although, the effect of age was considered as an important source of heterogeneity, a sub-analysis by age could not be performed due to the lack of detailed reporting of study results by age groups; this may have influenced our results. Similarly, subgroup analyses could not be performed according to patient illness severity, patient comorbidities, type of respiratory sample or the presence of specific bacterial co-pathogens due to lack of data. Publication bias applies when studies reporting ‘positive’ findings are more likely to be published than those identically, notably RSV, adenoviruses and hMPV, these are much more likely to be clinically relevant; this may be different in adults. We lacked direct comparison with any such ‘asymptomatic control’ group in the included studies, nor did we have access to data on the host response to viruses in individual subjects. However separate studies in asymptomatic patients [54,56] offer important contextualization for our findings; and inclusion of an asymptomatic comparator group would be likely to add granularity in future studies.

Since previous work identified high heterogeneity in the extant literature from other parts of the world, [18,19] we expected this and decided, a priori, that high heterogeneity would not preclude meta-analysis. We were unable to identify a single clear reason for the observed high heterogeneity which we attribute to multiple factors including study quality (Fig. 5), variable settings, patient populations, sampling sites, and diagnostic methods (Fig. 4); disease severity and co-infections with other pathogens. Since rhinovirus and Respiratory syncytial virus (RSV) RSV infections have a predilection for asthmatic patients [57,58], underlying comorbidities may also have influenced our findings.

| Virus type                | Pooled% | 95% CI | No. of studies (and patients) included in pathogen-specific meta-analysis | I²(%) |
|--------------------------|---------|--------|-------------------------------------------------------------------------|-------|
| Influenza (A or B)       | 9       | 7–12   | 17 (6487)                                                               | 93.45 |
| Rhinovirus               | 5       | 4–7    | 12 (3324)                                                               | 88.22 |
| Coronavirus              | 4       | 2–7    | 7 (1343)                                                                | 80.37 |
| Parainfluenza            | 3       | 2–5    | 14 (5600)                                                               | 88.35 |
| Human metapneumovirus    | 2       | 1–2    | 10 (1779)                                                               | 7.49  |
| (hMPV)                   |         |        |                                                                         |       |
| Respiratory syncytial virus (RSV) | 2.3   | 1–3    | 17 (5968)                                                               | 82.42 |
| Adenovirus               | 1       | 0–1    | 13 (3166)                                                               | 32.88 |

Enterovirus, poliovirus, cytomegalovirus, coxsackie virus, varicella-zoster virus, human bocavirus and herpes simplex virus were detected in < 1% of adult patients with CAP.

Table 2 Summary of individual pathogen-specific meta-analyses for respiratory viruses most commonly identified in European adult patients with CAP.
reporting 'negative' findings and is an important consideration in meta-analyses evaluating treatment effects. However, in the context of studies examining the proportion of CAP patients in whom viruses were detected, well-conducted 'negative' studies are as 'surprising' as 'positive' studies and both would be expected to be published. The first study to examine the use of standard publication bias tests for proportional meta-analyses (such as this one) found that funnel plots and statistical tests potentially yield misleading results, especially where the proportions within the studies are either very high or very low [62]. These researchers describe an alternative method that can be used to explore the potential for publication bias, where the sample size is used instead of the standard error for each study; however, the reliability and accuracy of this method has yet to be fully explored and independently validated. Therefore, we elected not to analyses publication bias.

5. Conclusion

This systematic review suggests that, in Europe, respiratory viruses are identifiable in at about one quarter of all adults presenting with CAP. Of these, the most frequently identified pathogens are influenza viruses, rhinoviruses and coronaviruses, accounting for over one half of all identified viral pathogens. Further study to determine the importance of identifying viral pathogens in relation to treatment with antibiotics or antivirals is warranted.

Contributors

All of the authors designed and contributed to the systematic review. Y.A. and J.S. N-V-T. performed study selection independently. Y.A. and JS. N-V-T. performed paired data extraction, data synthesis and quantitative analyses. Y.A. and JS. N-V-T drafted the article, and all other authors critically reviewed the article before submission.

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Potential conflicts of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcv.2017.07.019.

References

[1] C.J.J. Murray, A. Lopez, C. Mathers, C. Stein, The Global Burden of Disease 2000 Project: Aims, Methods and Data Sources, Global Programme on Evidence for Policy, Discussion Paper No. 36, World Heal Organ, Geneva, 2001.

[2] T.P. Quan, N.J. Fawcett, J.M. Wrightson, J. Finney, D. Wylie, K. Jeffery, et al., Increasing burden of community-acquired pneumonia leading to hospitalisation, Thorax 17 (2016) 1998–2014.

[3] C.L. Trotter, J.M. Stuart, R. George, E. Miller, Increasing hospital admissions for pneumonia, England, Emerg. Infect. Dis. 14 (5) (2008) 727–733.

[4] H.M. Loele, Managing community-acquired pneumonia: a European perspective, Respir. Med. (2007) 1864–1873.

[5] A. Torres, W.E. Peetermans, G. Viegi, F. Blasi, Risk factors for community-acquired pneumonia in adults in Europe: a literature review, Thorax 68 (11) (2013) 1057–1065.

[6] T. Welte, A. Torres, D. Nathwani, Clinical and economic burden of community-acquired pneumonia among adults in Europe, Thorax 67 (1) (2012) 71–79.

[7] M.H. Rosénbaum, P. Peclhivanoglou, T.S. van der Werf, J.R. Lo-Ten-Foe, M.J. Postema, E. Hak, The role of Streptococcus pneumoniae in community-acquired pneumonia among adults in Europe: a meta-analysis, Eur. J. Clin. Microbiol. Infect. Dis. 32 (3) (2013) 303–316.

[8] W.S. Lim, S.V. Baudouin, R.C. George, A.T. Hill, C. Jamieson, I. Le Jeune, J.T. Macfarlane, R.C. Read, H.J. Roberts, M.L. Levy, M. Wani, BTS guidelines for the management of community acquired pneumonia in adults: update 2009, Thorax 64 (October (Suppl. 3)) (2009) iii1–55.

[9] J. Johnstone, S.R. Majumdar, J.D. Fox, T.J. Marrie, Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation, Chest 134 (6) (2008) 1141–1148.

[10] A.T. Pavia, What is the role of respiratory viruses in community-acquired pneumonia? What is the best therapy for influenza and other viral causes of community-acquired pneumonia? Infect. Dis. Clin. 27 (1) (2013) 157–175.

[11] S. Iain, W.H. Self, R.G. Whitcomb, S. Fabbrini, R.M. Bradley, et al., Community-acquired pneumonia requiring hospitalization among U.S. adults, N. Engl. J. Med. 373 (5) (2015) 415–427.

[12] E. Polverino, A. Torres Marti, Community-acquired Pneumonia. Minerva Anestesiol. 77 (2011) 196–211.

[13] M. Woodhead, Community-acquired pneumonia in Europe: causative pathogens and resistance patterns, Eur. Respir. J. 20 (July (36 Suppl.)) (2002) 20s–27s.

[14] W.H. Self, D.J. Williams, Y. Zhu, K. Ampollo, A.T. Pavia, J.D. Chappell, et al., Respiratory viral detection in children and adults: comparing asymptomatic controls and patients with community-acquired pneumonia, J. Infect. Dis. 213 (4) (2015) 584–591.

[15] M. von Itzstein, W.Y. Wu, G.B. Kok, M.S. Pegg, J.C. Dyason, B. Jin, et al., Rational design of potent sialidase-based inhibitors of influenza virus replication, Nature 363 (1993) 418–423.

[16] S.G. Muthuri, S. Venkatesan, P.R. Myles, J. Leonard-Bee, W.S. Lim, A. Al Mamun, et al., Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an IPD meta-analysis, Influenza Other Respir. Viruses 10 (3) (2016) 192–204.

[17] L.J. Anderson, P.R. Dormitzz, D.J. Nokes, R. Rappuoli, A. Roca, B.S. Graham, Strategic priorities for respiratory syncytial virus (REV) vaccine development, Vaccine 2 (April (31 Suppl.)) (2013) B209–B215.

[18] M. Burck, R. El-Kersh, M. Saad, T. Wiemken, J. Ramirez, R. Cavallazzi, Viral infection in community-acquired pneumonia: a systematic review and meta-analysis, Eur. Respir. Rev. 25 (140) (2016) 178–188.

[19] X. Xu, Q. Wang, M. Wang, X. Su, Z. Wang, et al., Incidence of respiratory viral infections detected by PCR and real-time PCR in adult patients with community-acquired pneumonia: a meta-analysis, Respira 89 (4) (2015) 343–352.

[20] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement, BMJ 339 (2009) b2535.

[21] G.A. Wells, B. Shea, D. O’Connell, J. Peterson, V. Welch, et al., The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses, (2017) Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (last Accessed: 23 February 2017).

[22] R. DerSimonian, N. Laird, Meta-analysis in clinical trials, Control. Clin. Trials 7 (3) (1986) 177–188.

[23] M.F. Freeman, J.W. Tukey, Transformations related to the angular and the square root, Ann. Math Stat. 21 (1950) 607–611.

[24] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (7431) (2003) 557–560.

[25] L.S.G.E. Howard, M. Silvis, M.C. Pauter, A.V. Kamath, B.W.H. Harrison, Microbiological profile of community-acquired pneumonia in adults over the last 20 years, J. Infect. 50 (2) (2005) 107–113.

[26] J.L. Bell, P. Hausfater, C. Chennevier-Gobeaux, F.X. Blanc, M. Benjoar, C. Ficco, et al., Diagnostic accuracy of C-reactive protein and procalcitonin in suspecting community-acquired pneumonia adults visiting emergency department and having a systematic thoracic CT scan, Crit. Care 19 (2015) 1–12.

[27] A. Carpelastegui, P.P. Espana, A. Bilbao, J. Garmazo, F. Medei, J. Salgado, et al., Etiology of community-acquired pneumonia in a population-based study: link between etiology and patients characteristics, process-of-care, clinical evolution and outcomes, BMC Infect. Dis. 12 (2012) 134 (no pagination).

[28] C. Cilloniz, S. Ewig, E. Polverino, M. Angeles Marcos, E. Prina, J. Sellares, et al., Community-acquired pneumonia in outpatients: aetiology and outcomes, Eur. Respir. J. 40 (4) (2012) 931–938.

[29] T.W. Clark, M.J. Medina, S. Batham, M.D. Curran, S. Parmar, K.G. Nicholson, Adults hospitalised with acute respiratory illness rarely have detectable bacteria in the absence of COPD or pneumonia: viral infection predominates in a large prospective UK sample, J. Infect. 69 (5) (2014) 507–515.

[30] D. Das, Y.E. Claessens, M. Maynard, C. Leport, E. Bouver, N. Houhou, et al., Viruses detected by systematic multiplex polymerase chain reaction in adults with suspected community-acquired pneumonia attending emergency departments in
France. Clin. Microbiol. Infect. 21 (6) (2015) e1–e8 608.

[31] A. de Roux, M.A. Marcos, E. Garcia, J. Mensa, S. Ewig, H. Lode, et al., Viral community-acquired pneumonia in nonimmunocompromised adults, Chest 125 (4) (2004) 1345–1351.

[32] B.M. Diederon, M.M. Van Der Erden, E. Vlaspolder, W.G. Boersma, J.A. Klyuitmans, M.F. Peeters, Detection of respiratory viruses and Legionella spp. by real-time polymerase chain reaction in patients with community acquired pneumonia, Scand. J. Infect. Dis. 41 (11) (2009) 45–50.

[33] F. Gutierrez, M. Masia, C. Mirate, B. Soldan, J. Carlos Rodriguez, S. Padilla, et al., The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens, J. Infect. 53 (3) (2006) 166–174.

[34] A. Holm, J. Nexoø, L.A. Bistrup, S.S. Pedersen, N. Obel, L.P. Nielsen, Aetiologie and prediction of pneumonia in lower respiratory tract infection in primary care, Br. J. Gen. Pract. 57 (540) (2007) 547–554.

[35] J.C. Holfar, F. Muller, O. Bjorang, H.H. Smedal, J.B. Marti, P.C. Ene, et al., Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway, BMC Infect. Dis. 15 (1) (2015) 64 (no pagination).

[36] N. Johansson, M. Kalin, A. Tiveljung-Lindell, C.G. Giske, J. Hedlund, Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods, Clin. Infect. Dis. 50 (2) (2010) 202–209.

[37] C. Jokinen, L. Heiskanen, H. Juvonen, S. Kallinen, M. Kleemola, M. Koskela, et al., Microbial etiology of community-acquired pneumonia in the adult population of 4 municipalities in eastern Finland, Clin. Infect. Dis. 32 (8) (2001) 1141–1154.

[38] I. Koskala, T. Ozlu, O. Bayraktar, G. Yilmaz, Y. Bulbul, F. Ozuma, et al., Etiological agents of community-acquired pneumonia in adult patients in Turkey: a multicentric, cross-sectional study, Tuberkoz ve Toraks 58 (2) (2010) 119–127.

[39] D. Lieberman, A. Shimoeny, Y. Shemer-Avni, A. Keren-Naos, R. Shainberg, Respiratory viruses in adults with community-acquired pneumonia, Chest 138 (4) (2010) 811–816.

[40] W.S. Lim, J.T. Macfarlane, T.C.J. Boswell, T.G. Harrison, D. Rose, M. Leinonen, et al., Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines, Thorax 56 (4) (2001) 296–301.

[41] A. Sangi, E. Calbo, A. Robles, S. Benet, M. Viladot, V. Pascual, et al., Etiology of community-acquired pneumonia among adults in an H1N1 pandemic year: the role of respiratory viruses, Eur. J. Clin. Microbiol. Infect. Dis. 31 (10) (2012) 2765–2772.

[42] F. Shihi, B. Chazan, O. Nitzan, E. Flatau, H. Edelstein, O. Blondheim, et al., Etiology of community-acquired pneumonia in hospitalized patients in Northern Israel, Isr. Med. Assoc. J. 12 (8) (2010) 477–482.

[43] A.B. Van Gageldonk-Lafeber, P.C. Wever, L.M. Van Der Lubben, C.P.C. De Jager, A. Meijer, M.C. De Vries, et al., The aetiology of community-acquired pneumonia and implications for patient management, Neth. J. Med. 71 (8) (2013) 418–425.

[44] D. Viazus, C. Martinezu, A. Villoisla, E. Cordero, J. Galvez-Acebal, M.C. Farinas, et al., Community-acquired pneumonia during the first post-pandemic influenza season: a prospective, multicentre cohort study, J. Infect. 67 (3) (2013) 185–193.

[45] K.E. Templeton, S.A. Schelpings, W.C. van den Eeden, W.A. Graffelman, P.J. van den Broek, E.C. Claas, Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction, Clin. Infect. Dis. 41 (3) (2005) 345–351.

[46] P.Y. Bouchard, F. Moser, P. Erard, F. Verdon, J.P. Studer, G. Villard, et al., Community-acquired pneumonia. A prospective outpatient study, Medicine 80 (2) (2001) 75–87.

[47] M.A. Marcos, M. Camps, T. Pumarola, J.A. Martinez, E. Martinez, J. Mensa, et al., The role of viruses in the aetiology of community-acquired pneumonia in adults, Antivir. Ther. 11 (3) (2006) 351–359.

[48] U. Hombntel, J. Sipila, P. Rannikou, O. Murnier, K. Rantakokko-Jalava, J. Nioke, K. Kallininen, et al., Diagnostic value of bronchoalveolar lavage in community-acquired pneumonia in a routine setting: a study on patients treated in a Finnish university hospital, Scand. J. Infect. Dis. 36 (3) (2004) 198–203.

[49] E.G. Huijksens, M. Koopmans, F.M. Palmen, A.J. van Elk, P.G. Mulder, J.W. Rossen, The value of signs and symptoms in differentiating between bacterial, viral and mixed aetiology in patients with community-acquired pneumonia, J. Med. Microbiol. 63 (3) (2014) 441–452.

[50] C. Gilli, S. Ewig, M. Ferrer, E. Polverino, A. Gabbri, J. Puig de la Bellacasa, et al., Community-acquired polymicrobial pneumonia in the intensive care unit: aetiology and prognosis, Crit. Care 15 (5) (2011) R209.

[51] J. Almirall, R. Boixeda, I. Bolibar, J. Bassa, G. Saura, J. Vidal, et al., Differences in the etiology of community-acquired pneumonia according to site of care: a population based study, Respi. Med. 101 (10) (2007) 2168–2175.

[52] H. Farida, M.H. Gasem, A. Suryanto, M. Keuter, N. Zulkarnain, B. Satoto, et al., Viruses and gram-negative bacilli dominate the etiology of community-acquired pneumonia in Indonesia, a cohort study, Int. J. Infect. Dis. 38 (2015) 101–107.

[53] J.-X. Qu, L. Gu, Z.-H. Pu, X.-M. Yu, Y.-M. Liu, R. Li, et al., Viral etiology of community-acquired pneumonia among adolescents and adults with mild or moderate severity and its relation to age and severity, BMC Infect. Dis. 15 (1) (2015) 89.

[54] T. Jarri, L. Jarri, R. Pelola, et al., Identity of respiratory viruses in asymptomatic subjects: asymptomatic respiratory viral infections, Pediatr. Infect. Dis. J. 27 (2008) 1103–1110.

[55] N.J. Gaddby, C.D. Russell, M.P. McHugh, H. Mark, A. Conway Morris, I.F. Lawson, et al., Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia, Clin. Infect. Dis. 62 (7) (2016) 817–823.

[56] R.R. Jansen, J. Wieringa, S.M. Koekkoek, C.E. Visser, D. Pajkrt, R. Molenkamp, et al., Frequent detection of respiratory viruses without symptoms: toward defining clinically relevant cutoff values, J. Clin. Microbiol. 49 (7) (2011) 2631–2636.

[57] S.F. Thomsen, S. v.d. Sluis, L.G. Stensballe, D. Posthuma, A. Skytthe, K.O. Kyvik, et al., The importance of gender and age region on the incidence of community-acquired pneumonia, Eur. J. Clin. Microbiol. Infect. Dis. 28 (2009) 1091–1097.

[58] J.E. Gern, W.W. Busse, Association of rhinovirus infections with asthma, Clin. Microbiol. Rev. 12 (1) (1999) 9–18.

[59] F.G. Hayden, Advances in antivirals for non-influenza respiratory virus infections, Influenza Other Respir. Viruses 7 (2013) 36–43 (45).

[60] F.G. Hayden, Newer influenza antivirals, biotherapeutics and combinations, Influenza Other Respir. Viruses 7 (2013) 63–75.

[61] N. Jaberalansor, I. Toth, F.R. Young, M. Skwarczynski, Recent advances in the development of subunit-based RVF vaccines, Expert Rev. Vaccines 15 (1) (2016) 53–68.

[62] J.P. Hunter, A. Saratzi, A.J. Sutton, R.H. Bouche, R.D. Sayers, M.J. Bown, In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias, J. Clin. Epidemiol. 67 (8) (2014) 897–903.