Journal of Clinical Virology 95 (2017) 26–35

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Review article

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

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ARTICLE INFO

Keywords:
Community
Acquired
Pneumonia
Virus
Aetiology
Pathogen

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 I^2. 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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http://dx.doi.org/10.1016/j.jcv.2017.07.019
Received 13 March 2017; Received in revised form 7 July 2017; Accepted 31 July 2017

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) 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 over any outstanding discrepancies.

2.3. Data extraction and risk of bias assessment

Data extraction for each eligible study was also performed independently by YA and JSN-V-T using a pre-piloted data extraction form using Microsoft® Office Excel® 2010 (Microsoft Corporation, Richmond, VA, USA). For all included studies, information was extracted on: author(s); year of publication; country; healthcare setting; number of evaluable patients; viral diagnostic techniques employed; samples collected for virus detection; number of respiratory virus pathogens tested for; and number and proportion of respiratory viruses detected. YA and JSN-V-T independently assessed the quality of all included studies, using criteria adapted from the Newcastle − Ottawa scale for observational studies [21], focusing on three key domains: representativeness of patient population; ascertainment of CAP diagnosis; and ascertainment of virus aetiology. We awarded zero or one star in each domain; for representativeness, one star was awarded for studies sampling from the general community (as opposed to more specialised patient subgroups); for ascertainment of CAP diagnosis we awarded one star for independent radiographic confirmation of diagnosis; and for virus aetiology, one star for use of 'gold standard' PCR diagnostic techniques.

2.4. Summary measures, and analysis

The proportion of respiratory viruses identified in evaluable CAP patients was pooled using the generic inverse variance approach, based on a random effects model (DerSimonian- Laird weights method) [22], stabilising the variances using the Freeman-Tukey double arcsine transformation so that studies with proportions close to 0% or 100% were appropriately estimated [23]. Exact binomial confidence intervals 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 I^2 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).

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[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[2] (67.9%) [25,26,29–32,35,36,39–44,47–50] 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. 14 studies (50%) obtained upper respiratory samples [26,28,30,35,36,38,39,41–44,46,49,50], 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]. 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[3] 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%) were at high risk of bias (one or zero stars). Six studies[3] (21.4%)

[1] One article presented data on two separate studies [25].
[2] Citation #25 describes two studies.
[3] Citation #25 describes two studies.