

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

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4 Y. Alimi¹, W.S. Lim², L. Lansbury¹, J. Leonardi-Bee¹, J.S. Nguyen-Van-Tam¹

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6 *1. Health Protection and Influenza Research Group, Division of Epidemiology*
7 *and Public Health, University of Nottingham School of Medicine, Nottingham,*
8 *UK.*

9 *2. University Hospitals NHS Trust, Nottingham, UK.*

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11 Corresponding author: JS Nguyen-Van-Tam; jvt@nottingham.ac.uk

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15 Abstract

16 Community-acquired pneumonia (CAP) is an important respiratory disease and the fifth
17 leading cause of mortality in Europe. The development of molecular diagnostic tests has
18 highlighted the contributions of respiratory viruses to the aetiology of CAP, suggesting
19 the incidence of viral pneumonia may have been previously underestimated. We
20 performed a systematic review and meta-analysis to describe the overall identification
21 of respiratory viruses in adult patients with CAP in Europe, following PRISMA guidelines
22 (PROSPERO; CRD42016037233). We searched EMBASE, MEDLINE, CINAHL, WHOLIS,
23 COCHRANE library and grey literature sources for relevant studies, and screened these
24 against protocol eligibility criteria. Two researchers performed data extraction and risk of
25 bias assessments, independently, using a piloted form. Results were synthesised
26 narratively, and random effects meta-analyses performed to calculate pooled
27 estimates of effect; heterogeneity was quantified using I^2 . Twenty-eight studies met
28 inclusion criteria of which 21 were included in the primary meta-analysis. The pooled
29 proportion of patients with identified respiratory viruses was 22.0% (95% CI: 18.0%-27.0%),
30 rising to 29.0% (25.0%–34.0%) in studies where polymerase chain reaction (PCR)
31 diagnostics were performed. Influenza virus was the most frequently detected virus in 9%
32 (7%-12%) of adults with CAP. Respiratory viruses make a substantial contribution to the
33 aetiology of CAP in adult patients in Europe; one or more respiratory viruses are
34 detected in about one quarter of all cases.

35

36 Introduction

37 Community-acquired pneumonia (CAP) is a principal cause of excess hospitalisation
38 and mortality worldwide¹⁻³. Historically, the overriding clinical approach to the
39 management of CAP has been to focus on bacterial aetiologies, with *Streptococcus*
40 *pneumoniae* the dominant pathogen⁴⁻⁸. More recently, coupled to the increasing
41 availability of polymerase chain reaction (PCR) tests, the identification of viral pathogens
42 in the aetiology of CAP has increased. Contemporary studies identify that viruses may
43 be implicated in 15%-30% of all CAP⁹⁻¹¹; in turn this heightens the possibility that empirical
44 antibiotic treatment of CAP in the absence of adequate testing for viral pathogens may
45 contribute to inappropriate antibiotic usage^{12,13}.

46

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

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

58

59

60 **Methods**

61 The study protocol was registered on the National Institute for Health Research
62 International Prospective Register of Systematic Reviews (PROSPERO; CRD42016037233;
63 available at:
64 http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037233) and
65 conducted according to Preferred Reporting Items for Systematic Reviews and Meta-
66 Analyses (PRISMA) guidelines²⁰

67

68 **Eligibility criteria**

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

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

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85 Search strategy and screening

86 The following electronic databases were systematically searched: EMBASE, MEDLINE,
87 CINAHL, WHOLIS, and Web of Science from January 1999 to April 2016. A
88 comprehensive search strategy was developed for EMBASE (**Supplementary Appendix**
89 **1**) and subsequently adjusted as required to suit other databases. The reference lists of
90 all eligible articles were manually searched to identify other eligible studies.

91 All identified articles were imported to ENDNOTE software X4 (Thomson Reuters, Toronto,
92 CA, USA) and duplicates removed. Two review authors (YA and JSN-V-T) independently
93 screened the retained articles against protocol eligibility criteria, in three stages: by title,
94 abstract and full text. Any disagreements were resolved through discussion between YA
95 and JSN-V-T; and a third author (WSL) adjudicated over any outstanding discrepancies.

96

97 Data extraction and Risk of Bias assessment

98 Data extraction for each eligible study was also performed independently by YA and
99 JSN-V-T using a pre-piloted data extraction form using Microsoft® Office Excel® 2010
100 (Microsoft Corporation, Richmond, VA, USA). For all included studies, information was
101 extracted on: author(s); year of publication; country; healthcare setting; number of
102 evaluable patients; viral diagnostic techniques employed; samples collected for virus
103 detection; number of respiratory virus pathogens tested for; and number and proportion
104 of respiratory viruses detected. YA and JSN-V-T independently assessed the quality of all
105 included studies, using criteria adapted from the Newcastle – Ottawa scale for
106 observational studies²¹, focusing on three key domains: representativeness of patient
107 population; ascertainment of CAP diagnosis; and ascertainment of virus aetiology. We
108 awarded zero or one star in each domain; for representativeness, one star was awarded
109 for studies sampling from the general community (as opposed to more specialised

110 patient subgroups); for ascertainment of CAP diagnosis we awarded one star for
111 independent radiographic confirmation of diagnosis; and for virus aetiology, one star for
112 use of 'gold standard' PCR diagnostic techniques.

113

114

115 Summary measures, and analysis

116 The proportion of respiratory viruses identified in evaluable CAP patients was pooled
117 using the generic inverse variance approach, based on a random effects model
118 (DerSimonian- Laird weights method)²², stabilising the variances using the Freeman-
119 Tukey double arcsine transformation so that studies with proportions close to 0% or
120 100% were appropriately estimated²³. Exact binomial confidence intervals were
121 computed for outcomes. The primary outcome was the overall contribution of
122 respiratory viruses in the aetiology of CAP, calculated as the total number of patients
123 with respiratory viruses identified (numerator) as a proportion of the total number of
124 evaluable patients (denominator). We report, as secondary outcomes, the contribution
125 of individual viruses calculated as the total number of patients with individual respiratory
126 viruses identified as a proportion of all evaluable patients for each specific pathogen.

127 Heterogeneity between studies was quantified using the I^2 statistic²³. We investigated
128 potential sources of heterogeneity by performing subgroup analyses; by study setting
129 (inpatient vs. outpatient), study quality, viral diagnostic methods used (PCR diagnostic
130 techniques vs non-PCR methods) and mixed infections (bacterial and viral infections). All
131 analyses were conducted with the *metaprop* commands within Stata (V.13, Stata Corp,
132 College Station, Texas, USA).

133 Results

134 We identified a total of 1106 articles from database searches, reducing to 1083 after the
135 removal of duplicates. Eleven additional papers were identified via citation tracking.
136 After screening, 27 articles remained within protocol eligibility criteria (Figure 1); one of
137 the included articles²⁵ presented two separate studies and data from both were
138 extracted and presented separately. Thus, 28 studies from 27 articles were included in
139 the systematic review²⁵⁻⁵¹, and 21 from 20 in the primary meta-analysis²⁵⁻⁴⁴. When
140 examined as full-text articles, seven studies did not present sufficient quantitative data
141 for inclusion in the primary meta-analysis⁴⁵⁻⁵¹ (Figure 1).

142

143 Study characteristics

144 All 28 studies included in the systematic review were prospective or retrospective
145 longitudinal studies or case-series. The patient population size in each ranged from 71 to
146 1356 (total=8,777). The earliest publications were in 2001^{37,40}, and the most recent article
147 was published in October 2015²⁶.

148 Studies from 11 different European countries were included of which Spain was most
149 frequently represented (9 studies; 32.1%)^{27,28,31,33,41,44,47,50,51}. Nineteen studies* (67.9%)<sup>25,26,29-
150 32,35,36,39-44,47-50</sup> were carried out among inpatient populations (n=5,515 patients),
151 three^{34,38,46} (10.7%) in outpatient/community populations (n=524 patients) and six
152 (21.4%)^{27,28,33,37,45,51} in mixed populations (n=2,738 patients). Details of the characteristics
153 of the included studies are summarised in Table 1. Sixteen studies (57.1%)<sup>26,29,30,32,34-36,39,41-
154 45,47,49,50</sup> had used PCR techniques for the detection of respiratory viruses, alone or in
155 combination with other diagnostic methods. 14 studies (50%) obtained upper respiratory
156 samples^{26,28,30,35,36,38,39,41-44,46,49,50}, 16 (57.1%) lower respiratory^{25,31-34,38,42,43,45-51} (nine
157 publications), and six (21.4%) both^{38,42,43,46,49,50}. In 10 (35.7%) studies (9 publications)
158 respiratory tract sampling was combined with assessment of paired serology<sup>25,31-33,45,46,49-
159 51</sup>; and in four (14.3%) studies, serology alone was performed^{27,29,37,40}.

* Citation #25 describes two studies

160

161 Risk of bias assessment

162 Study population representativeness, diagnostic accuracy of CAP and ascertainment of
163 virus aetiology were assessed with a maximum of three stars per study. Eleven
164 studies^{26,30,32,34-36,39,41-43,45} (39.3%) were assessed as being at low risk of bias (three stars;
165 one star per domain), 14[†] studies^{25,26,29,33,37,38,40,44,46,47,49-51} (53.6%) at moderate risk of bias
166 (2 out of 3 stars), and three^{28,31,48} (7.1%) were at high risk of bias (one or zero stars). Six
167 studies^a (21.4%) reported difficulty in obtaining adequate samples for microbiological
168 testing^{25,27,32,37,41}. Within-study variation in viral diagnostic methods across different study
169 years was reported in ten studies (35.7%)^{26,29,30,35,36,39,41-44}.

170

171 Overall identification of respiratory viruses

172 The percentage of respiratory viruses detected in CAP patients ranged from 6% in a
173 Spanish study comprising both inpatients and outpatients³³, to 45% in a study of
174 hospitalised patients in Israel⁴². By meta-analysis, the pooled proportion of respiratory
175 viruses detected in CAP patients was 22.0% (95% CI 17.0%-27.0%; I²=94.7%) (Figure 2).

176

177 There was a significant trend for the identification of respiratory virus pathogens to be
178 lower in studies (n=8)^a published from 2001 to 2009^{25,31-34,37,40}, (pooled estimate=14.0%
179 (95%CI 9.0%-21.0%)) compared with more recent studies (n=13) published after 2010<sup>26-
180 30,35,36,38,39,41-44</sup> (pooled estimate=27.0% (95%CI 20.0%-33.0%)), test for subgroup differences,
181 p=0.007 (Supplementary Appendix 2).

182

183 Sub-group analyses

184 The pooled proportion of respiratory viruses identified among inpatient studies (n=15)
185 ^{25,26,29-32,35,36,39-44} with CAP was 27.0% (95% CI 23.0%-31.0%; I²=85.1%); compared with 19.0%

[†] Citation #25 describes two studies

186 (95% CI 14.0%-24.0%; $I^2=95.3\%$) for outpatient studies ($n=2$)^{34,38}, and 9.0% (95% CI 6.0%-
187 12.0%; $I^2 =85.8\%$) in two studies with mixed populations ($n=4$)^{27,28,33,37} (Figure 3). Each of
188 these populations revealed results that were statistically significantly different from each
189 other (test for subgroup differences, $p<0.01$). Studies with mixed populations^{27,28,33,37}, relied
190 exclusively on non-PCR diagnostic methods and were of lower quality compared to other
191 studies.

192

193 The pooled proportion of respiratory viral pathogens identified in 12 studies^{26,29,30,32,34-36,38,41-}
194 ⁴⁴ using PCR (with or without additional testing methods) was 29.0% (95% CI 25.0%–34.0%,
195 $I^2=83.5\%$) compared with 13.0% (95% CI 9.0%–18.0%, $I^2=90.7\%$) in nine studies using other
196 non-PCR methods^{25,27,28,31,33,37,38,40}, with a significant difference between the two groups,
197 $p<0.001$ (Figure 4).

198

199 In lower risk of bias studies (NOS score=3 stars)^{26,30,32,34-36,39,41-43}the pooled proportion for
200 total respiratory viral pathogens was 30%, (95% CI 25%–34%, $I^2=77.4\%$), compared with 11%
201 (95% CI 9%-13%, $I^2=99.3\%$) in higher risk of bias studies (NOS score=1 star)^{28,31}, explaining the
202 observed heterogeneity between studies, $p<0.001$ (Figure 5).

203

204 Mixed Infections

205 The pooled proportion of mixed respiratory viruses and bacterial co-infections detected
206 in CAP patients was 10% (95% CI 6%-14%, $I^2=94.7\%$) reported across 14 studies ^{26-29,32,33,35-}
207 ^{37,40-44} (Figure 6).

208

209 Individual viruses

210 Data on the seven most common respiratory viruses identified are presented in Table 2.
211 Influenza viruses were most frequently detected (9%), followed by rhinoviruses (5%) and

212 coronaviruses (4%); together accounting for the majority of respiratory viruses detected
213 (Table 2).

214

215 Discussion

216 This review updates evidence on the microbiological identification of respiratory viral
217 pathogens in adult patients with radiographically confirmed CAP in Europe. Overall our
218 data suggest that respiratory viruses are detectable in at least 22% of radiologically
219 confirmed CAP cases, mostly hospitalised cases. However significantly higher proportions
220 of respiratory viruses were evident in studies conducted after 2010 (27%), studies that
221 included viral PCR techniques (29%), and studies assessed to be at lower risk of bias (29%),
222 suggesting that the true proportion of CAP associated with respiratory viruses is at least
223 one quarter (25%). Our findings accord with recent major studies or reviews conducted in
224 Asia and North America ^{11,14,52,53}. In the CDC EPIC study¹¹, viruses were detected in 27.0%
225 of adult patients with CAP, while Qu et al. detected viruses in 27.5% of Asian patients with
226 CAP⁵¹.

227

228 Our review suggests that in Europe, as in other parts of the world, a relatively large burden
229 of CAP disease may be attributable to viral infections. However, the clinico-pathological
230 significance of virus detection in patients with CAP remains uncertain. A clear limitation of
231 our approach (and of each of the included studies) is that no proof is offered that the
232 virus or viruses identified were of pathological significance in all cases. There was also
233 heterogeneity between studies in terms of the respiratory sites sampled and/or use of
234 serology. Viruses recovered from upper respiratory tract (URT) sites might have less
235 pathological significance than those recovered from lower respiratory tract (LRT) sites;
236 nevertheless, in the absence of concomitant sampling from URT and LRT it is not possible
237 to disregard viruses identified from URT sites which may have been replicated in the LRT if

238 it had also been sampled. Whilst respiratory viruses are undoubtedly implicated in the
239 aetiology of a substantial proportion of the cases in which they are detected,
240 asymptomatic illness associated with virus shedding is well recognised, especially in
241 children who experience longer periods of shedding than adults⁵⁴. In addition, modern
242 PCR diagnostic techniques are comparatively more sensitive than methods for the
243 detection of bacteria and capable of detecting small quantities of nucleic acid which
244 may not in all cases represent culturable virus; therefore, some patients with 'viral-only'
245 pathogens identified may also have a microbiologically unrecognised bacterial infection;
246 and some detections of viral pathogens may represent previous or resolved virus infection.
247 In a recent study, Gadsby et al. employed PCR techniques to identify bacteria as well as
248 viruses from lower respiratory tract samples, viruses were detected in 30% of 323 adults
249 admitted to hospital with CAP and a co-bacterial pathogen was detected in 82% of
250 these⁵⁵. In contrast we noted only 10% of cases with a bacterial co-pathogen; this might
251 reflect the use of PCR testing for bacteria by Gadsby and colleagues, whereas the studies
252 we included used standard approaches for the identification of bacteria. The detection
253 of respiratory viruses in healthy asymptomatic individuals is not as extensively described as
254 in symptomatic patients; nevertheless Jartti and colleagues summarised data from 51
255 studies, noting maximum baseline prevalences of respiratory viruses as follows:
256 rhinoviruses, 15%; adenoviruses, 5.3%; influenza, 4.3%; RSV, 2.6%; coronaviruses, 2.5%;
257 enteroviruses 1.2%; human bocavirus, 1.1%; parainfluenza, 0.9%; and hMPV, 0.6%⁵⁴.
258 Jansen and colleagues have observed that rhinovirus is extremely common in
259 asymptomatic children (28%), but that if other viruses are identified, notably RSV,
260 adenoviruses and hMPV, these are much more likely to be clinically relevant⁵⁶; this may
261 be different in adults. We lacked direct comparison with any such 'asymptomatic control'
262 group in the included studies, nor did we have access to data on the host response to
263 viruses in individual subjects. However separate studies in asymptomatic patients^{54,56} offer

264 important contextualization for our findings; and inclusion of an asymptomatic
265 comparator group would be likely to add granularity in future studies.

266

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

275

276 Influenza (9%) viruses, rhinoviruses (5%) and coronaviruses (4%) accounted for the majority
277 of virus detections; these proportions are similar to the estimates reported previously by
278 Burk et al and Wu et al^{18,19}. However, RSV was identified in only 2% of adult CAP which
279 may be relevant to the potential role of future RSV vaccines targeted at the elderly.

280

281 These findings highlight the importance of respiratory viruses in the aetiology of adult CAP,
282 and the potential relevance of our findings towards improving clinical outcomes, and
283 reducing inappropriate antibiotic use. Influenza appears to be the most significant virus
284 pathogen, followed by rhinoviruses and coronaviruses. Notwithstanding, different
285 included studies looked for between 4-11 separate respiratory viruses (Table 1); if all
286 included studies had tested for all 11 viruses the overall proportion of virus detection may
287 well have been considerably higher, although, as discussed above, not all detections
288 necessarily have clinical relevance to CAP. This potential source of bias will not have
289 affected the estimates for individual viruses (Table 2) because these analyses were
290 organism-specific and based on all available data by organism. Viral diagnostic

291 evaluation of CAP facilitates greater precision in the assessment of illness severity, and the
292 tailoring of therapy, in particular the rapid use of neuraminidase inhibitors for cases of
293 influenza and more judicious use of antibiotics. Since there are realistic near-term
294 prospects for novel antiviral treatments for several respiratory virus infections and RSV
295 vaccines⁵⁹⁻⁶¹, there is a need to establish baseline data on the incidence of viral CAP and
296 develop a wider culture of testing for respiratory virus pathogens without which it will be
297 difficult to assess the impact of advances in therapy.

298

299 We included only articles reported in English. An analysis including country-specific data
300 reported in other languages may reveal regional variations in the contribution of
301 respiratory viruses to the microbiology of CAP. Although, the effect of age was
302 considered as an important source of heterogeneity, a sub-analysis by age could not be
303 performed due to the lack of detailed reporting of study results by age groups; this may
304 have influenced our results. Similarly, subgroup analyses could not be performed
305 according to patient illness severity, patient comorbidities, type of respiratory sample or
306 the presence of specific bacterial co-pathogens due to lack of data. Publication bias
307 applies when studies reporting 'positive' findings are more likely to be published than
308 those reporting 'negative' findings and is an important consideration in meta-analyses
309 evaluating treatment effects. However, in the context of studies examining the
310 proportion of CAP patients in whom viruses were detected, well-conducted 'negative'
311 studies are as 'surprising' as 'positive' studies and both would be expected to be
312 published. The first study to examine the use of standard publication bias tests for
313 proportional meta-analyses (such as this one) found that funnel plots and statistical tests
314 potentially yield misleading results, especially where the proportions within the studies
315 are either very high or very low⁶². These researchers describe an alternative method that
316 can be used to explore the potential for publication bias, where the sample size is used
317 instead of the standard error for each study; however, the reliability and accuracy of this

318 method has yet to be fully explored and independently validated. Therefore, we
319 elected not to analyses publication bias.

320

321 **Conclusion**

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

328

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332

333 **Contributorship**

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

338

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351

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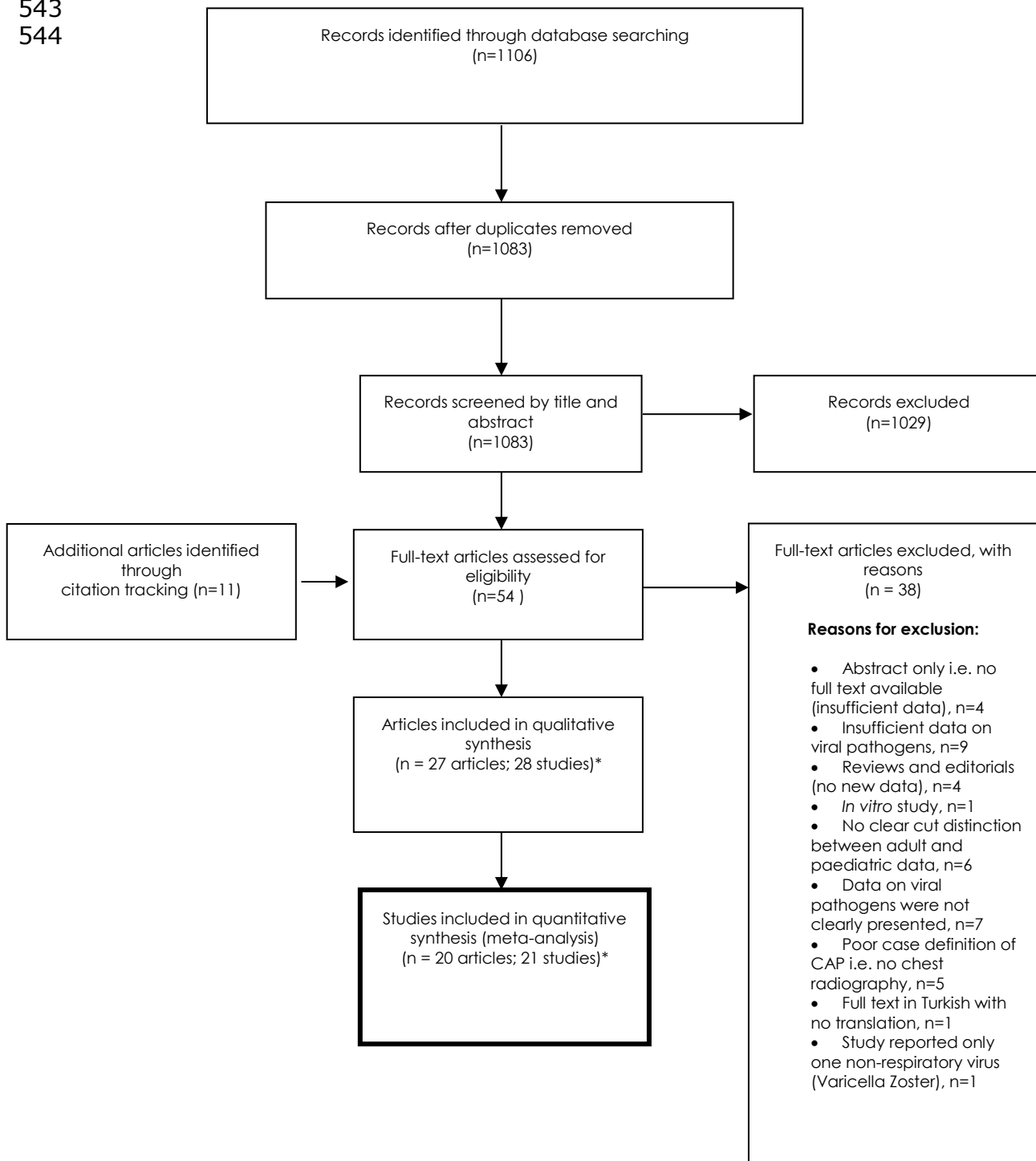
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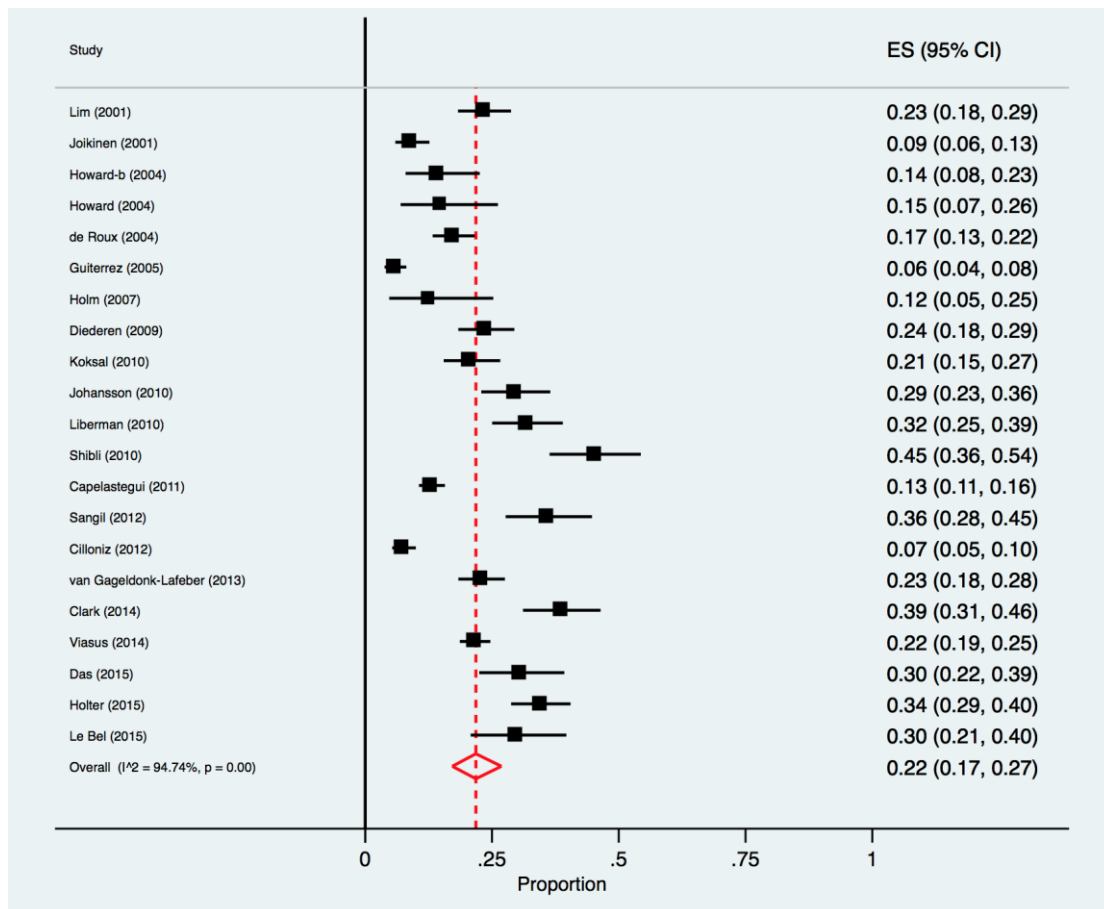
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542 Figure 1: PRISMA flowchart.‡

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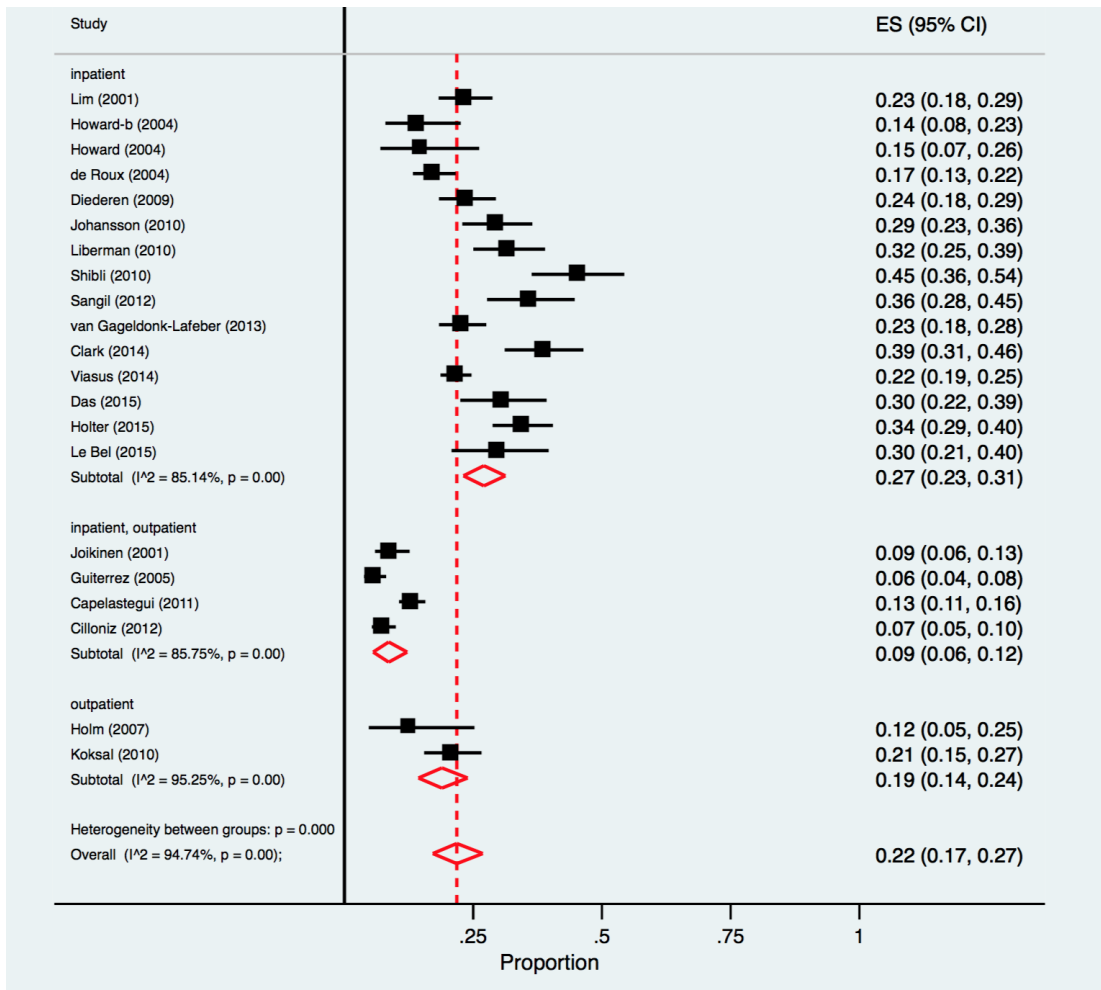


‡ One article presented data on two separate studies²⁵



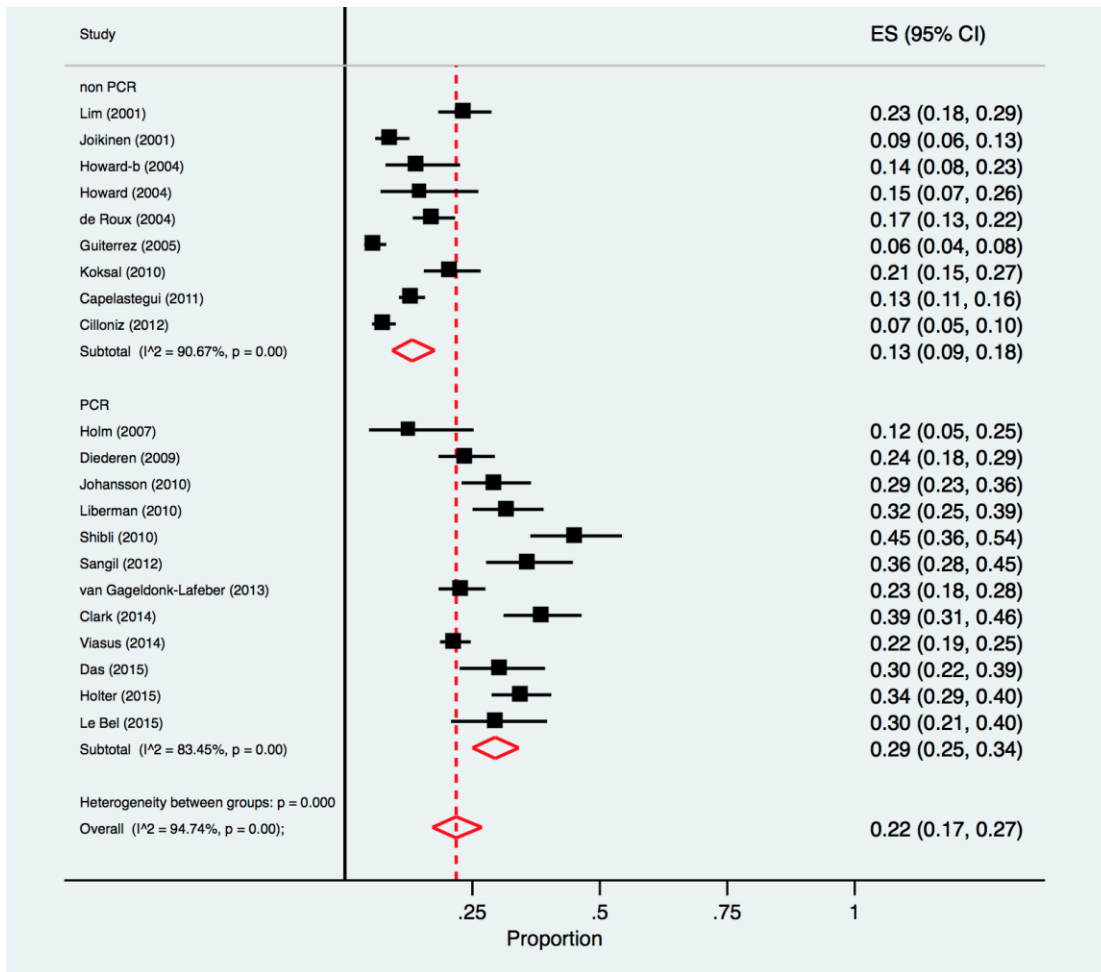
ES = effect size for pooled identification of respiratory viruses

Figure 2: Forest plot: overall identification of respiratory viruses in European adult patients with CAP.



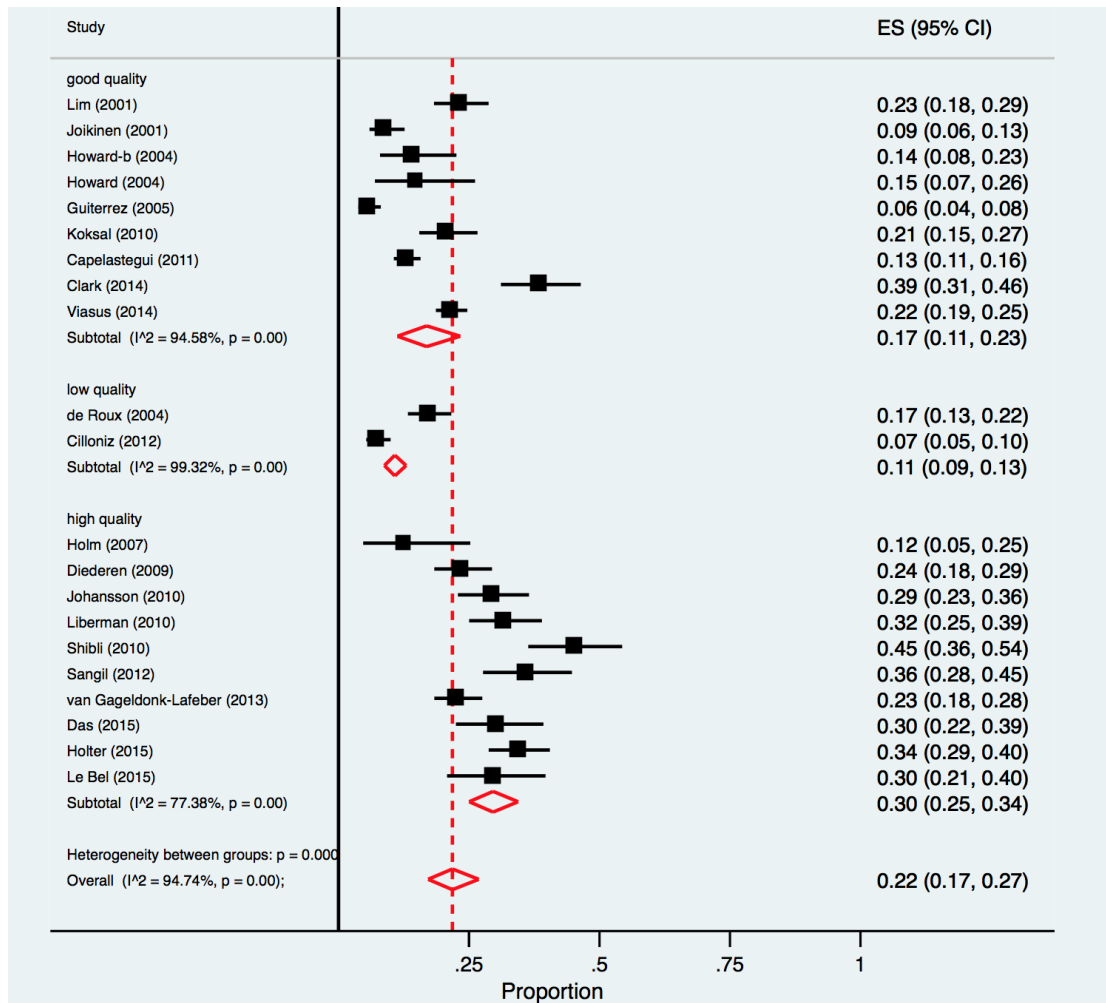
ES = effect size for pooled identification of respiratory viruses

Figure 3: Forest plot: overall identification of respiratory viruses in European patients with CAP, stratified by study setting.



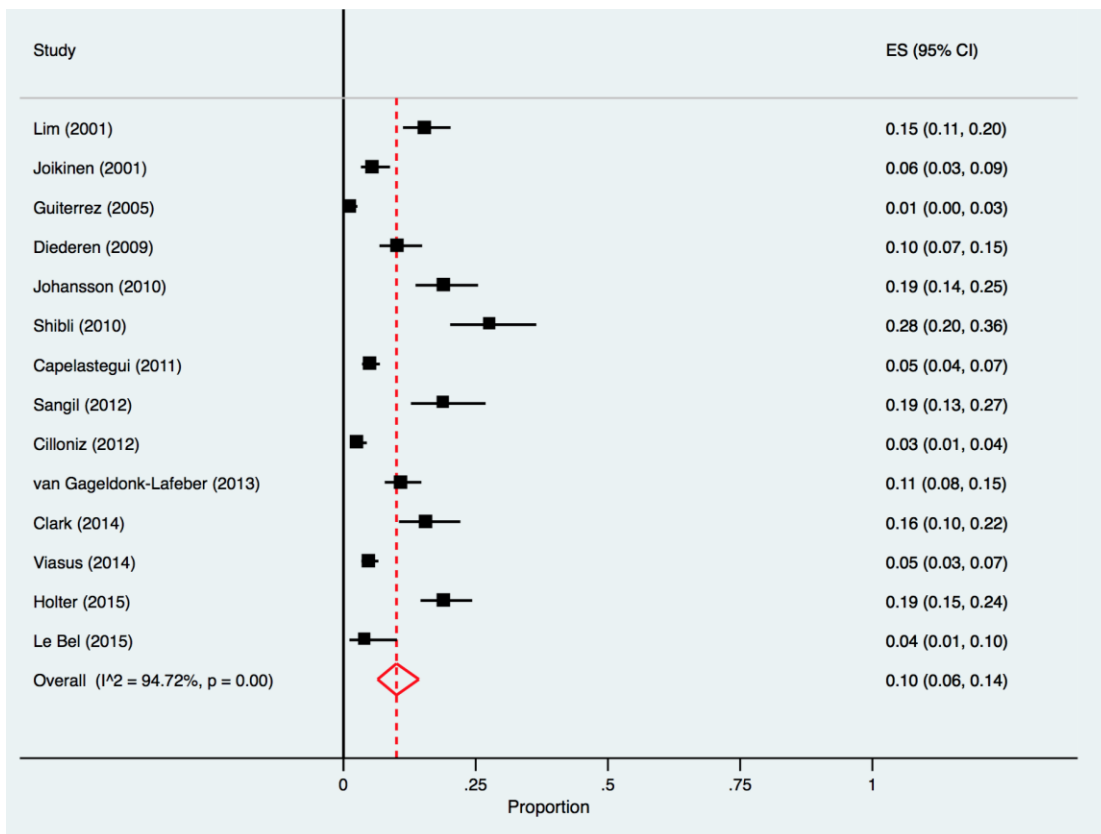
ES = effect size for pooled identification of respiratory viruses

Figure 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

Figure 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

Figure 6: Forest plot: mixed respiratory virus and bacterial co-infections in European patients with CAP.

Table 1: Characteristics of included studies.

| 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 [2015] ²⁶ | France, inpatients | Prospective cohort | Patients aged >18 years presented to Emergency dept. | 319 | 8 | 101 (31.7%) | PCR | Inflammatory biomarkers in CAP patients | UR |
| Capelastegui [2011] ²⁷ | Spain, inpatients and outpatients | Prospective cohort | Patients aged >18 years in the community and hospital | 700 | 5 | Not reported | Blood cultures, urinary antigen tests, serology, direct immunofluorescence antibody assay | Aetiology of CAP | S |
| Cilloniz [2012] ²⁸ | Spain, inpatients and outpatients | Prospective cohort | Patients aged >16 years admitted to the Emergency wards and outpatients. | 568 | 5 | 301 (53.0%) | Serology, blood culture, antigen tests. | Aetiology of CAP | UR |
| Clark [2014] ²⁹ | UK, inpatients | Prospective cohort | Patients aged >18 years admitted to hospital with acute respiratory infection but | 166 | 9 | 87(52.4%) | Blood and Sputum culture, PCR | Aetiology of ARI in adults | S |

| | | | | | | | | | |
|--------------------------------|-----------------------------------|--------------------|---|------|---|--------------|---|---|-------|
| | | | subset with CAP patients | | | | | | |
| Das [2015] ³⁰ | France, inpatients | Prospective cohort | Patients aged >18 years admitted to the Emergency dept. | 125 | 7 | Not reported | PCR | Aetiology of CAP | UR |
| de Roux [2004] ³¹ | Spain, inpatients | Prospective cohort | Patients aged >18 years admitted to hospital | 1356 | 5 | 893(65.8%) | Serology, complement fixation kit tests for viruses. | Viral CAP in non-immunocompromised adults | LR, S |
| | | | | | | | | | |
| Diederens [2001] ³² | Netherlands, Inpatients | Prospective cohort | Patients aged >18 years admitted to the hospital | 242 | 8 | 7(2.9%) | PCR, serology, ELISA | Detection of respiratory pathogens using PCR | LR, S |
| Gutierrez [2005] ³³ | Spain, inpatients and outpatients | Prospective cohort | Patients aged >15 years admitted to the hospital | 493 | 5 | 308(62.5%) | Blood and sputum cultures, complement fixation tests. | Investigating the influence of age and gender on the incidence of CAP | LR, S |
| Holm [2007] ³⁴ | Denmark, outpatients | Prospective cohort | Patients aged >18 years with CAP presenting to the GP | 48 | 6 | 28(58.3%) | PCR | Aetiology of CAP | LR |
| Holter [2015] ³⁵ | Norway, inpatients | Prospective cohort | Patients aged >18 years admitted to the hospital | 267 | 8 | 140(52.4%) | Culture, serology, PCR | Aetiology of CAP in Norway | UR |

| | | | | | | | | | |
|--------------------------------|-------------------------------------|--------------------|--|-----|--------------|--------------|---|---|--------|
| Howard-a [2004] ²⁵ | UK, inpatients | Prospective cohort | Patients aged >15 years | 69 | Not reported | 6(8.7%) | Complement fixation tests, blood culture | Not reported | LR, S |
| Howard-b [2004] ²⁵ | UK, inpatients | Prospective cohort | Patients aged >16 years | 99 | Not reported | 6(6.1%) | Complement fixation tests, blood culture | Aetiology of CAP | LR,S |
| Johansson [2015] ³⁶ | Sweden, inpatients | Prospective cohort | Patients aged >18 years admitted to the hospital | 184 | 9 | 94(51.1%) | Culture, PCR, Serology | Aetiology of CAP | UR |
| Joikinen [2001] ³⁷ | Finland, inpatients and outpatients | Prospective cohort | Patients aged >15 years admitted to the hospital and patients in the community | 345 | 7 | 176(51.0%) | Serology | Aetiology of CAP in adults in Eastern Finland | S |
| Koksal [2010] ³⁸ | Turkey, outpatients | Cross – sectional | Patients aged >17 years with CAP in outpatient settings | 292 | 6 | 147(50.3%) | Culture, direct immunofluorescence , serology | Aetiology of CAP in adults in Turkey | UR, LR |
| Liberman [2010] ³⁹ | Israel, inpatients | Prospective cohort | Patients aged >18 years admitted to the hospital | 183 | 8 | 105(57.4%) | PCR | Evaluate the role of respiratory viruses in adult CAP | UR |
| Lim [2001] ⁴⁰ | UK, inpatients | Prospective cohort | Patients aged >16 years admitted to the hospital | 267 | 5 | 135(50.6%) | Other conventional methods | Investigate the aetiology of CAP and implication for CAP management | S |
| Sangil [2012] ⁴¹ | Spain, inpatients | Prospective cohort | Patients aged >18 years | 169 | 9 | Not reported | PCR, serology | Aetiology of CAP using PCR and other | UR |

| | | | | | | | | | |
|--|--|--------------------|--|-----|--------------|--------------|--|---|-----------|
| | | | admitted to the hospital | | | | | conventional methods. | |
| Shibli [2010] ⁴² | Israel, inpatients | Prospective cohort | Patients aged >18 years admitted to the hospital | 127 | 6 | 73(57.5%) | PCR, DNA & RNA extraction, Serology | Investigate the aetiology of CAP in hospitalised patients . | UR, LR |
| van Gageldonk-Lafeber [2013] ⁴³ | Netherland, inpatients | Prospective cohort | Patients aged >18 years presented to the Emergency dept. | 339 | 9 | 212(62.5%) | Culture , serology, antigen tests, PCR | Aetiology of CAP | UR, LR |
| Viasus [2014] ⁴⁴ | Spain, inpatients | Prospective cohort | Adult patients admitted to the hospital | 747 | 8 | | PCR, Serology | Aetiology of CAP | UR |
| Templeton [2005] ⁴⁵ | Netherlands , inpatients and outpatients | Prospective cohort | Patients aged >18 years admitted to the hospital | 136 | Not reported | 75(55.1%) | Culture, PCR, Serology | Aetiology of CAP | LR, S |
| Bochud [2001] ⁴⁶ | Switzerland, outpatients | Prospective cohort | Patients aged >15 years | 184 | 4 | 82(44.6%) | Serology | Aetiology of CAP in outpatients | UR, LR, S |
| Marcos [2006] ⁴⁷ | Spain, inpatients | Prospective cohort | Patients aged >14 years admitted to the hospital | 198 | 7 | Not reported | PCR, immunofluorescence and culture | Aetiology of CAP | LR |
| Hohenthal [2004] ⁴⁸ | Finland, inpatients | Prospective cohort | Patients aged >18 years admitted to the hospital | 71 | 7 | 48(67.6%) | Culture | Diagnostic value of BAL | LR |
| Huijskens [2013] ⁴⁹ | Netherland , inpatients | Prospective | Patients aged >18 years | 408 | 11 | 250(61.3%) | PCR , Culture and serology | to differentiate pure bacterial, pure viral | UR, LR, S |

| | | | | | | | | | |
|-------------------------------|-----------------------------------|--|--|-----|---|------------|---------------------------------------|---|-----------|
| | | | presented to the emergency dept. | | | | | and mixed viral and bacterial aetiologies based on clinical signs admission | |
| Cilloniz [2011] ⁵⁰ | Spain, Inpatients | | >18 years with CAP admitted to ICU within 24hrs | 362 | 5 | 232(64.1%) | Immunofluorescence, PCR | polymicrobial pneumonia | UR, LR, S |
| Almirall [2007] ⁵¹ | Spain, inpatients and outpatients | | >14 years, 216 patients were managed at home and 280 patients were admitted to hosp. | 496 | 7 | | Culture, serology, Immunofluorescence | 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

| 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 (6,487) | 93.45 |
| Rhinovirus | 5 | 4-7 | 12 (3,324) | 88.22 |
| Coronavirus | 4 | 2-7 | 7 (1,343) | 80.37 |
| Parainfluenza | 3 | 2-5 | 14 (5,600) | 88.35 |
| Human metapneumovirus (hMPV) | 2 | 1-2 | 10 (1,779) | 7.49 |
| Respiratory syncytial virus (RSV) | 2 | 1-3 | 17 (5,968) | 82.42 |
| Adenovirus | 1 | 0-1 | 13 (3,166) | 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

1 APPENDIX 1: EMBASE SEARCH STRATEGY
2

1. virus.mp. or virus/
2. exp virus pneumonia/et [Etiology]
3. exp Adenoviridae/
4. exp Coronavirus/ or exp SARS coronavirus/
5. exp Influenzavirus B/ or exp Influenzavirus A/ or exp Influenzavirus C/
6. exp influenza/ or exp influenza B/ or exp Influenza B virus/ or exp influenza C/ or exp Influenza C virus/ or exp influenza A/ or exp Influenza A virus/
7. exp Parainfluenza virus infection/
8. exp Human respiratory syncytial virus/
9. exp Rhinovirus/ or exp Human rhinovirus/ or exp Rhinovirus infection/
10. exp Human metapneumovirus/
11. exp Human metapneumovirus/ or exp Metapneumovirus infection/ or exp Metapneumovirus/ or exp Human metapneumovirus infection/
12. Nipah virus/ or exp Paramyxovirinae/
13. (virus* or viral or (influenza or flu) or (parainfluenza or paraflu) or (metapneumovirus or hmpv) or adenovirus or (respiratory and syn* and virus*) or rsv or rhinovirus or coronavirus).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp community acquired pneumonia/ep, et [Epidemiology, Etiology]
16. exp infectious pneumonia/ep, et [Epidemiology, Etiology]
17. (community and acquired and pneumonia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
18. (community-acquired and pneumonia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
19. 15 or 16 or 17 or 18
20. exp Europe/ or exp Eastern Europe/ or exp Western Europe/ or exp Southern Europe/
21. exp Spain/ or exp Eastern Europe/ or exp Europe/ or exp France/ or exp Italy/ or exp United Kingdom/ or exp Germany/

22. exp United Kingdom/ or exp France/ or exp Europe/ or exp Netherlands/ or exp European/ or exp Italy/ or exp Germany/

23. (albania or andorra or armenia or austria or azerbaijan or belarus or belgium or herzegovina or bulgaria or croatia or cyrus or czech or denmark or estonia or finland or france or georgia or germany or greece or hungary or iceland or ireland or israel or italy or kazakhstan or kyrgyzstan or latvia or lithuania or luxembourg or malta or monaco or montenegro or netherlands or norway or poland or portugal or moldova or romania or russia * or san marino or serbia or slovakia or spain or sweden or switzerland or tajikistan or macedonia or turkey or turkmenistan or ukraine or england or wchartales or scotland or united kingdom or Uk or uzbekistan).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

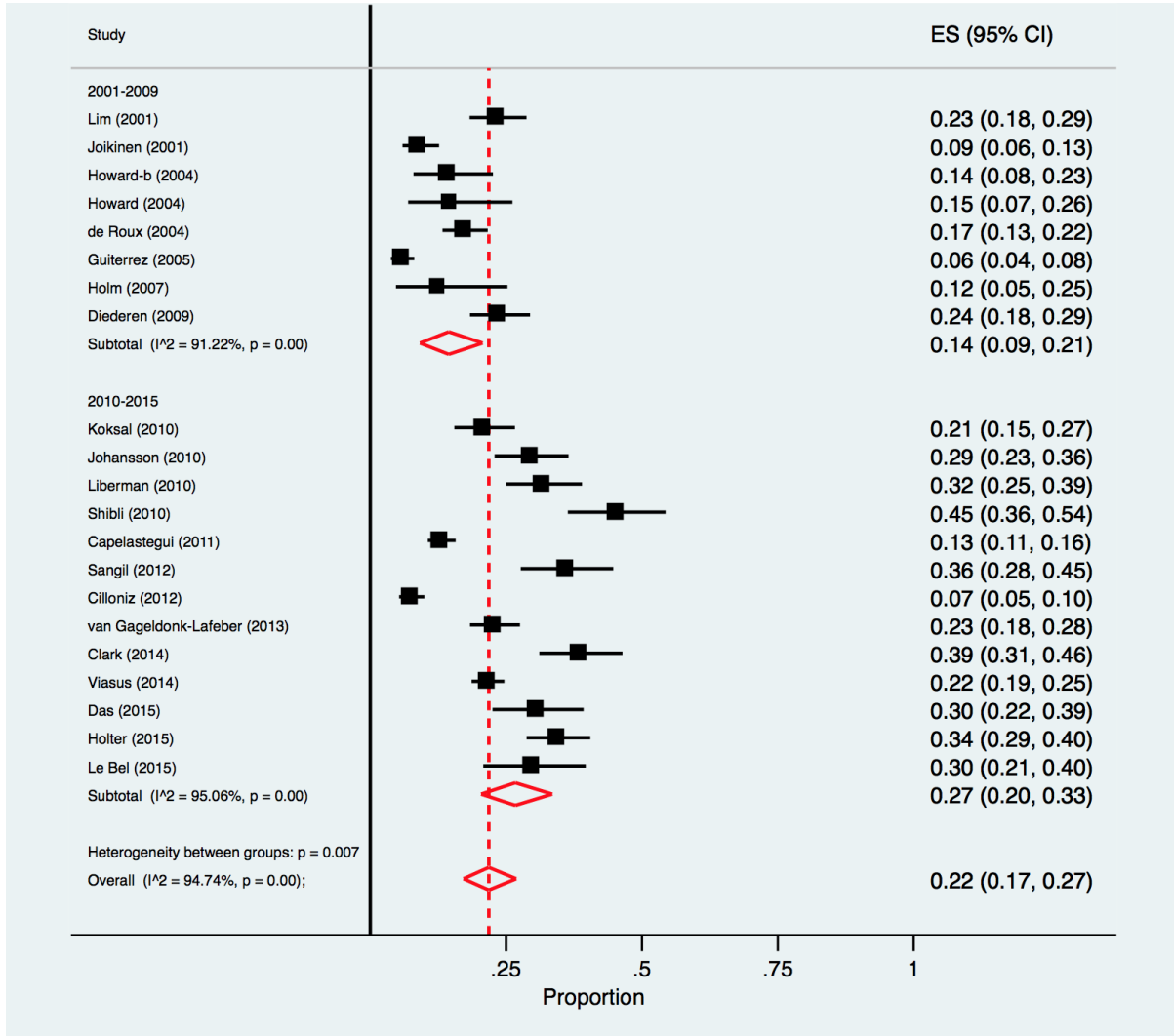
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5

6 APPENDIX 2

7



8

9 ES = effect size for pooled identification of respiratory viruses
10

11 Appendix 2: Forest plot: overall identification of respiratory viruses in European patients
12 with CAP, by study year