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Prevalence of atypical pathogens in patients with severe pneumonia: a systematic review and meta-analysis

Sidan Wang ,[1] Jiaoqi Tang,[2] Yurong Tan,[3] Zhi Song,[1] Ling Qin[4]

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SW and JT contributed equally.

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[1]The Second Department of Gastrointestinal Surgery, Third Xiangya Hospital, Central South University, Changsha, Hunan, China
[2]Emergency Department, Zhuzhou Central Hospital, Zhuzhou, Hunan, China
[3]Department of Medical Microbiology, School of Basic Medical Sciences, Central South University, Changsha, Hunan, China
[4]Department of Respiratory Medicine, Xiangya Hospital, Central South University, Changsha, Hunan, China

Correspondence to
Dr Zhi Song;
13069778@qq.com

ABSTRACT

Objectives We aimed to summarise the prevalence of atypical pathogens in patients with severe pneumonia to understand the prevalence of severe pneumonia caused by atypical pathogens, improve clinical decision-making and guide antibiotic use.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase, Web of Science and Cochrane Library were searched through November 2022.

Eligibility criteria English language studies enrolled consecutive cases of patients diagnosed with severe pneumonia, with complete aetiological analysis.

Data extraction and synthesis We conducted literature retrieval on PubMed, Embase, Web of Science and The Cochrane Library to estimate the prevalence of *Chlamydia*, *Mycoplasma* and *Legionella* in patients with severe pneumonia. After double arcsine transformation of the data, a random-effects model was used for meta-analyses to calculate the pooled prevalence of each pathogen. Meta-regression analysis was also used to explore whether the region, different diagnostic method, study population, pneumonia categories or sample size were potential sources of heterogeneity.

Results We included 75 eligible studies with 18 379 cases of severe pneumonia. The overall prevalence of atypical pneumonia is 8.1% (95% CI 6.3% to 10.1%) In patients with severe pneumonia, the pooled estimated prevalence of *Chlamydia*, *Mycoplasma* and *Legionella* was 1.8% (95% CI 1.0% to 2.9%), 2.8% (95% CI 1.7% to 4.3%) and 4.0% (95% CI 2.8% to 5.3%), respectively. We noted significant heterogeneity in all pooled assessments. Meta-regression showed that the pneumonia category potentially influenced the prevalence rate of *Chlamydia*. The mean age and the diagnostic method of pathogens were likely moderators for the prevalence of *Mycoplasma* and *Legionella*, and contribute to the heterogeneity of their prevalence.

Conclusions In severe pneumonia, atypical pathogens are notable causes, especially *Legionella*. The diagnostic method, regional difference, sample size and other factors contribute to the heterogeneity of prevalence. The estimated prevalence and relative heterogeneity factors can help with microbiological screening, clinical treatment and future research planning.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first systematic review and meta-analysis to provide a comprehensive estimate of the prevalence of atypical pathogens in patients with severe pneumonia.
⇒ Unlike previous global reports, included data in this study is not limited to studies conducted in developed countries and the data from developing countries are also included.
⇒ We used subgroup analysis and meta-regression analysis to assess the potential cause of heterogeneity.
⇒ The lack of a widely and internationally adopted criteria for the diagnosis of severe pneumonia is likely to affect the inclusion and exclusion of eligible studies.
⇒ The substantial heterogeneity was not fully explained by the variables examined.

INTRODUCTION

Severe pneumonia is associated with high mortality, as well as pulmonary and extrapulmonary complications.[1] Despite the rapid development of critical care medicine, severe pneumonia continues to pose a serious threat to human health. According to a US report, more than 1.5 million patients have been hospitalised annually due to community-acquired pneumonia (CAP); 17.1% of these are admitted to the intensive care unit (ICU), 60.4% are scored as Pneumonia Severity Index risk class IV or V and CAP is thought to be the primary cause of one out of every three in-hospital deaths.[2] The incidence of atypical pathogens in CAP patients worldwide (including inpatients and outpatients) is about 22%.[3] Population-based surveillance for CAP requiring hospitalisation from 2010 to 2012 in the USA revealed that approximately 21% of adults[4] and children[5] required intensive care. The most common pathogens in hospitalised adults with CAP are viruses (15%) and *Streptococcus pneumoniae* (5%), but atypical pathogens (*Mycoplasma pneumoniae, Legionella pneumophila* and *Chlamydophila pneumoniae*) also account for 4%.[4] Among children aged 5 or older, *M. pneumoniae* is the most commonly detected (19%).[5] Although

the infection of atypical pathogens in severe pneumonia is not the most common, it can nonetheless cause serious complications, not only in the elderly but also in healthy adults.[6 7]

Chlamydia pneumoniae, *Chlamydia psittaci* and *Chlamydia trachomatis* are the most common species in the *Chlamydiaceae* family that are pathogenic to humans; these species can infect the respiratory tract and reproductive tract, cause trachoma, pneumonia and digestive disorders.[8] Children may have a higher frequency of infection with *C. pneumoniae*.[9 10] However, recent studies suggest that the prevalence of *Chlamydia* infection is probably underestimated due to a lack of awareness[11–13] or testing limitations.[14] In addition, some studies suggest that *Chlamydia* infection is a risk factor for asthma,[15] Alzheimer's disease[16] and cardiovascular disease.[17] *M. pneumoniae* infections are relatively more common than *Chlamydia* infections, with seasonal epidemic characteristics, and they exhibit a higher proportion of infections in young people (5–20 years of age).[3 5] However, in some countries, patients over the age of 25 also show a high prevalence.[18]

Legionnaires' disease, caused by *Legionella* bacteria, always manifests as severe atypical pneumonia and systemic infections, with a high percentage of patients requiring ICU admission.[19] The mortality rate of *Legionella* pneumonia is about 10%,[20] and higher in patients admitted to ICU at 20%.[21] The prevalence of Legionnaires' disease is seasonal, mostly occurring in the summer and early autumn.[22] Data from the US indicates that the incidence of Legionnaires' disease increased by 192% between 2000 and 2009.[23] Compared with 0.48 cases/100 000 population during 1992–2002, its average incidence soared to 2.71 cases/100 000 in 2018.[24]

Previous studies indicated variations in the prevalence of atypical pathogens in severe pneumonia in different groups, but mostly restricted to certain regions or only focused on a single pathogen, like *Legionella*. Prior reviews or meta-analysis about the prevalence of atypical pathogens in severe pneumonia is lacking. Understanding of the prevalence of infected pathogen is necessary when applying empirical antibiotic treatment in severe pneumonia.

Recommendations about the antibiotic treatment in severe pneumonia should be based on the best available evidence. To improve clinical decision-making and guide empirical antibiotic use, we systematically reviewed the prevalence of atypical pathogens, mainly *Chlamydia, Mycoplasma* and *Legionella*, in patients with severe pneumonia. We also explored the potential causes for differences between the original studies through meta-regression analysis, and investigated whether the prevalence was associated with the year of publication, study regions, mean age, study population, sample size, pneumonia categories and diagnostic methods.

METHODS

Search strategies and screening criteria

We searched PubMed, Embase, Web of Science and The Cochrane Library for publications to identify studies that contain information on the prevalence of the atypical pathogen in severe pneumonia. All the studies were published before 13 November 2022. The search strategy is described in online supplemental material 1. We also manually screened the reference lists of review articles identified through previous searches. Our analysis process complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[25]

Two reviewers (SW and JT) independently screened the titles and abstracts of all potentially eligible studies with support from a third reviewer (LQ). After the exclusion of studies according to the eligibility criteria, full-text articles were assessed by the same reviewers. The inclusion criteria are as follows: studies enrolled consecutive cases of patients diagnosed with severe pneumonia, conducted a complete aetiological analysis and provided information on the prevalence of *Chlamydia*, *Mycoplasma* or *Legionella*. We also confirmed that the studies definitively tested for at least one atypical pathogen. The pathogen detection methods in all the literature are all recognised as meeting the testing guidelines. We excluded studies if they targeted specific populations, such as elderly individuals, post-transplant populations and patients requiring mechanical ventilation, or if atypical pathogenic infections were grouped and prevalence was not available separately for *Chlamydia*, *Mycoplasma* and *Legionella*. We also excluded non-English reports when reviewing the full texts. The protocol of this meta-analysis was published in PROSPERO (International Prospective Register for Systematic Reviews).

Data extraction and quality assessment

Data extraction was a multistep process based on the eligibility criteria. Two investigators (SW and JT) were responsible for the main research, and they independently extracted data onto a standardised form that included data related to study characteristics, including published year, mean age, geographical region, study population, diagnostic criteria, classification of severe pneumonia and diagnostic methods of *Chlamydia, Mycoplasma* and *Legionella* spp. Extracted data were compared, whereas disagreements between the two investigators were resolved through consensus discussion.

A modified version of an 11-item checklist recommended by the Agency for Healthcare Research and Quality (AHRQ) was used to evaluate the risk of bias in non-randomised studies.[26–28] All studies that met the inclusion criteria for analyses were assessed for risk of bias by the AHRQ checklist. An item would be scored '1' if it was answered 'Yes'; if it was answered 'No' or 'Unclear', then the item scored '0'. Article quality was assessed as follows: low quality=0–3; moderate quality=4–7; high quality=8–11 (online supplemental material 2 and table 1). All studies were independently rated by SW and JT, and checked

Table 1 Univariate meta-regression for prevalence of *Chlamydia, Mycoplasma* and *Legionella* in patients with severe pneumonia

Covariate	Estimate (%)	Lower 95% CI	Upper 95% CI	P value	R^2 (%)
Chlamydia (n=49)					
Year of publication	−0.12	−0.43	0.18	0.42	4.55
Sample size (continuous)	−0.01	−0.02	0.00	0.03	2.35
Sample size (≥100 vs <100)	−6.02	−12.71	0.67	0.08	3.19
Mean age	−0.06	−0.26	0.14	0.58	0.43
Population (adults vs children)	−3.05	−10.29	4.19	0.41	24.03
Region (Asia vs others)	12.08	0.15	24.02	0.05	42.22
Category (others vs CAP)	−9.85	−17.06	2.64	0.01	13.14
Diagnostic method (others vs culture)	3.09	−3.39	9.57	0.35	0.00
Diagnostic method (PCR vs others)	−11.30	−17.59	−5.01	0.004	9.66
Mycoplasma (n=62)					
Year of publication	0.21	−0.14	0.55	0.24	1.35
Sample size (continuous)	−0.00	−0.01	0.01	0.79	0.00
Sample size (≥100 vs <100)	−0.88	−8.38	6.62	0.82	0.00
Mean age	−0.18	−0.34	−0.03	0.01	26.91
Population (adults vs children)	6.50	−1.73	14.90	0.12	8.95
Region (Asia vs others)	0.15	−0.47	30.98	0.06	39.58
Category (others vs CAP)	−5.43	−14.27	3.41	0.23	4.08
Diagnostic method (others vs culture)	2.84	−4.62	10.31	0.46	0.00
Diagnostic method (PCR vs others)	0.96	−6.60	8.51	0.80	0.00
Legionella (n=57)					
Year of publication	−0.49	−0.76	−0.21	0.0001	6.01
Sample size (continuous)	−0.01	−0.02	0.00	0.04	0.46
Sample size (≥100 vs <100)	−7.58	−13.58	−1.59	0.01	8.89
Mean age	−0.42	−0.70	0.13	0.004	7.73
Population (adults vs children)	−9.10	−19.11	0.92	0.08	9.51
Region (Asia vs others)	5.66	−14.39	25.71	0.58	13.09
Category (others vs CAP)	−1.09	−8.35	6.17	0.77	0.00
Diagnostic method (others vs culture)	1.24	−4.88	7.36	0.69	4.50
Diagnostic method (PCR vs others)	−10.53	−16.66	−4.40	0.008	21.22

CAP, community-acquired pneumonia; PCR, polymerase chain reaction.

by LQ to resolve any disagreements. We extracted the prevalence of each pathogen or the pool prevalence of atypical pathogens in the category of severe pneumonia, and calculated the rate by the number of cases and total participants in those without exact prevalence.

Statistical analysis

The pooled and separate prevalence of atypical pathogens (*Chlamydia, Mycoplasma* and *Legionella*) in severe pneumonia were estimated using the 'meta' package in R software (V.4.1.3), with double arcsine transformation to convert data, calculating 95% CIs using the Wilson method. We quantified heterogeneity estimates for the pooled estimates of prevalence using the I^2 statistic. Since considerable heterogeneity was expected (I^2 >50%), we used random effects models in our analyses.

We assessed the possible sources of heterogeneity by performing subgroup and meta-regression analyses. In subgroup analysis, we divided the population into adults, children and mixed groups. Mixed groups were defined as when the studies did not distinguish between adults or children and only reported the overall prevalence of atypical pathogenic infections. We also calculated the prevalence of atypical pathogens in patients with severe pneumonia by different continents. To investigate the prevalence of atypical pathogens for different categories of severe pneumonia, we performed the following analysis: since the classification of severe pneumonia was not

reported in most paediatric studies, for *Chlamydia* and *Mycoplasma*, we conducted a subgroup analysis of non-paediatric studies by pneumonia category. We divided the sample into adults and children in one study,[29] as it presents different prevalence in two groups, respectively, and we also divided a study[30] into the severe community-acquired pneumonia (SCAP) group and severe hospital-acquired pneumonia (SHAP) group for the same reason.

In meta-regression, factors included in the univariate and multivariate analyses were the year of publication, sample size (by treating sample size as a continuous variable, and by comparing sample size greater than or equal to 100 with less than 100), mean age, study population (by comparing adults samples with children samples), region of the study (by comparing studies from Asia with those from other continents), pneumonia categories (by comparing SCAP with other types of pneumonia) and diagnostic methods of the pathogens (by comparing the traditional method of culture and PCR with others). To promote model stability, we only included factors that exhibited significant differences (p<0.05) in the univariate analysis into the multivariate meta-regression model. Sensitivity analyses were conducted on *Chlamydia, Mycoplasma* and *Legionella* groups, respectively, to test the robustness of our statistical model. Publication bias of the studies was examined using the Egger's test.[31] All statistical analyses were conducted using R software (V.4.1.3). A p value of <0.05 was considered statistically significant.

Patient and public involvement

No patients were involved in setting the research question, in developing plans for design, interpretation, reporting or implementation of the study. No patients were asked to advise on interpretation or reporting of results.

RESULTS

A total of 6795 articles were identified from the database searches. After removing duplicates and preliminary screening, 376 studies with full text available were assessed. Through strict screening criteria, we finally included 75 studies (n=18 379) published between 1985 and 2022 in our meta-analysis (figure 1). Among the studies included, 53 studies reported data for adults (n=10 404),[4 29 30 32–81] 17 studies for children (n=6652)[29 35 82–96] and 7 studies for mixed groups (n=1323)[97–103] (online supplemental material 2 and table 1). Forty-eight reported data for *Chlamydia* (n=12 087)[4 30 32–34 39–42 44 46 48–50 53 56 58 60–65 67–70 72 74 75 78–82 84–88 90 91 93 97–99 101 102], 61 for *Mycoplasma* (n=15 101)[4 30 32–34 36 37 39–50 53–58 60–70 72 74 79–91 93–102] and 56 for *Legionella* (n=11 144).[4 30 32–34 36–50 52 55 56 58–65 67–70 72–81 84 86 87 92 93 97–101 103] The most frequent reason for excluding literature was the lack of a complete aetiological analysis. It should be noted that there were four studies[29 52 80 98] that considered the prevalence of *Mycoplasma* and *Chlamydia* as a whole, and we could not obtain more detailed information on their respective prevalence rate; we then excluded this

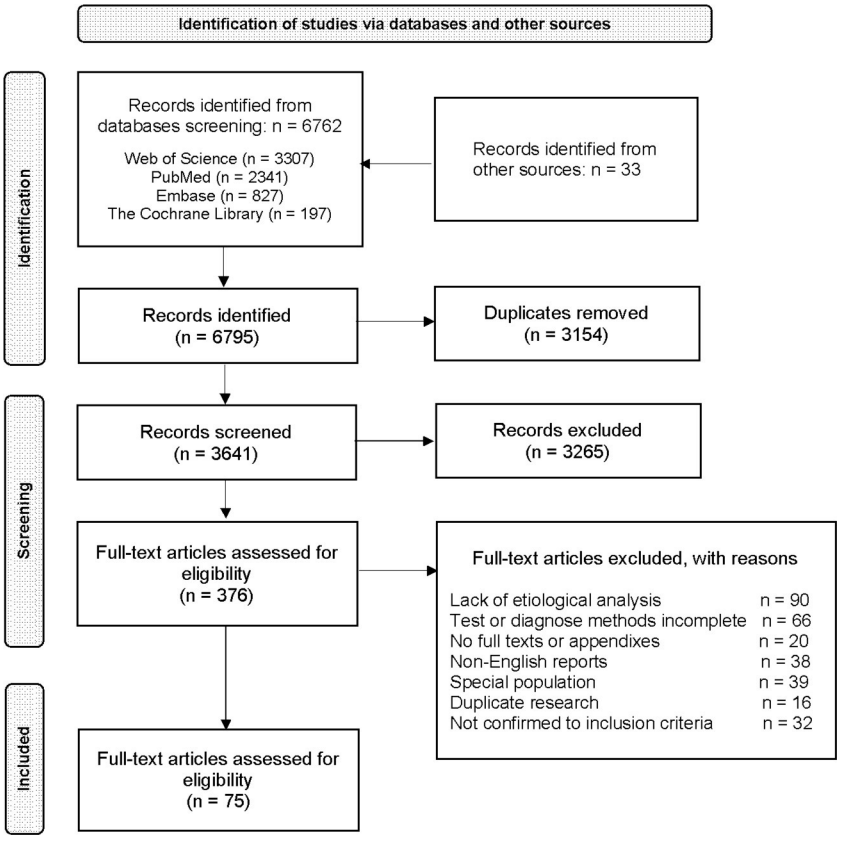

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

study when calculating the pooled prevalence of either *Chlamydia* or *Mycoplasma*. Moreover, 27 of the 75 studies were from Asia,[29 43 53 54 59 63 64 67 68 70 75–78 81–83 89 92–96 99–102] 28 from Europe,[30 32–34 37–42 44–47 50–52 56 57 60 61 65 66 71 72 74 97 98] 9 from Africa,[35 36 62 73 84–87 91] 4 from South America,[48 55 69 88] 3 from North America,[4 49 79] 2 from Australia[58 103] and 2 studies[80 90] did not present the exact continents.

All of the included studies were assessed for risk of bias. The quality score of each study was presented in online supplemental material 2 and table 1. Of all the 75 included studies, 56 studies were of high quality and 19 studies were of moderate quality. There were no studies with low quality ratings. The quality scores ranged from 5 to 10 (moderate-to-high quality), indicating satisfactory quality in the meta-analysed literature.

The overall prevalence of atypical pathogens including *Chlamydia*, *Mycoplasma* and *Legionella* in patients with severe pneumonia was 8.1% (95% CI 6.3% to 10.1%; I^2=95%), ranging from 0% to 48.1%, of which the prevalence in adults (7.6%; 95% CI 5.8% to 9.6%; I^2=91%) was slightly lower than that in children (7.8%; 95% CI 3.6% to 13.2%; I^2=98%). The mixed group that did not distinguish adults and children presented a prevalence of 12.1%, which contributed a lot to the overall prevalence (figure 2). SCAP has a greater overall prevalence of 8.96% (95% CI 6.85% to 11.29%, I^2=94.5%) than other types of pneumonia (5.57%, 95% CI 2.91% to 8.96%, I^2=94.4%). In different regions, the prevalence in Europe is highest (10.12%, 95% CI 7.79% to 12.69%, I^2=83.4%), followed by Asia (9.23%, 95% CI 6.00% to 13.04%, I^2=96.0%) and other continents (4.08%, 95% CI 2.11% to 6.59%, I^2=90.9%).

Chlamydia

In the meta-analysis of the prevalence for each pathogen, the pooled prevalence of *Chlamydia* in patients with severe pneumonia was 1.8% (95% CI 1.0% to 2.9%; I^2=91%), ranging from 0% to 23.1% and the prevalence in children (1.1%; 95% CI 0.06% to 3.0%; I^2=92%) was slightly lower than that in adults (1.8%; 95% CI 0.1% to 2.8%; I^2=85%) (figure 3). Geographically, patients with severe pneumonia had the highest prevalence of *Chlamydia* in Asia at 4.0% (95% CI 1.6% to 7.1%; I^2=91%), followed by Europe at 1.3% (95% CI 0.6% to 2.1%; I^2=56%) and other continents at 0.7% (95% CI 0% to 1.9%; I^2=85%) (online supplemental figure S1). As many studies focused on children did not identify the pneumonia categories, we performed a subgroup analysis of all adults' studies and we found only one *Chlamydia* infection in patients with pneumonia categories other than SCAP.

After we excluded two large studies[82 101] based on sensitivity analysis, the pooled prevalence rate dropped slightly to 1.44% (95% CI 0.77% to 2.26%), but it displayed high heterogeneity (I^2=86.4%). In the meta-regression analysis, the region (Asia or others) of the study that exhibited the highest statistical difference in the univariate analysis (p=0.05) accounted for 42.2% of the sources of overall heterogeneity (table 1). The univariate regression also shows that the prevalence in SCAP is higher than in other pneumonia categories, which also takes 13.14% of the heterogeneity. The diagnostic method of pathogens (PCR vs others) also contributes to the heterogeneity with statistical significance (p=0.004). And sample size (continuous), pneumonia categories and diagnostic methods remained statistically significant in the multivariate analysis, indicating that these factors account for a great part of the heterogeneity (R^2=41.5%). The Egger's test indicated that there was no significant publication bias for analysis evaluating the prevalence of *Chlamydia* (p=0.052).

Mycoplasma

The pooled estimated prevalence of *Mycoplasma* in patients with severe pneumonia was 2.8% (95% CI 1.7% to 4.3%; I^2=95%), ranging from 0% to 32.7% and it was more common in children (4.8%; 95% CI 1.3% to 10.1%; I^2=98%) than in adults (1.9%; 95% CI 1.2% to 2.8%; I^2=77%) (figure 4). In terms of regional distribution, the prevalence of *Mycoplasma* in patients with severe pneumonia was highest in Asia (6.1%; 95% CI 3.0% to 10.1%; I^2=96%), followed by Europe (2.1%; 95% CI 1.1% to 3.3%; I^2=70%) and other continents (0.8%; 95% CI 0.1% to 1.7%; I^2=75%) (online supplemental figure S2). In the subgroup analysis of adults, we found that SCAP (2.0%; 95% CI 1.2% to 3.0%; I^2=79%) was more common than hospital-acquired pneumonia (HAP) (1.1%, 95% CI 0.03% to 2.3%, I^2=21%).

Based on the results of the sensitivity analysis, we excluded four studies in children,[82 86 94 95] three of which had the highest prevalence and one with the lowest prevalence; after the exclusion, the prevalence of *Mycoplasma* in patients with severe pneumonia was slightly reduced to 2.24% (95% CI 1.50% to 3.08%), with a heterogeneity of I^2=84.4% (95% CI 80.5% to 87.5%). In the univariate meta-regression analysis, the prevalence of *Mycoplasma* was lower in studies with higher mean age (p=0.01), accounting for 26.9% of overall heterogeneity; and the diagnostic methods (PCR vs other) also show statistical significance. Region of the studies was also a possible source of heterogeneity accounting for 39.6%, but with weak statistical significance (p=0.06) (table 1). As other factors had no obvious relationships with heterogeneity, we did not perform further multivariate meta-regression analysis. The Egger's test did not show evidence of publication bias for analysis evaluating the prevalence of *Mycoplasma* (p=0.87).

Legionella

The prevalence rate of *Legionella* in severe pneumonia was 4.0% (95% CI 2.8% to 5.3%; I^2=90%), ranging from 0% to 30% and adults (4.2%; 95% CI 2.9% to 5.6%; I^2=87%) had a higher prevalence than children (1.4%, 95% CI 0% to 6.4%; I^2=94%) (figure 5). Compared with other regions, Europe (6.3%; 95% CI 3.9% to 9.2%; I^2=89%) had the highest prevalence of *Legionella* in patients with severe pneumonia, followed by Asia (3.6%; 95% CI 2.0% to 5.7%; I^2=84%)

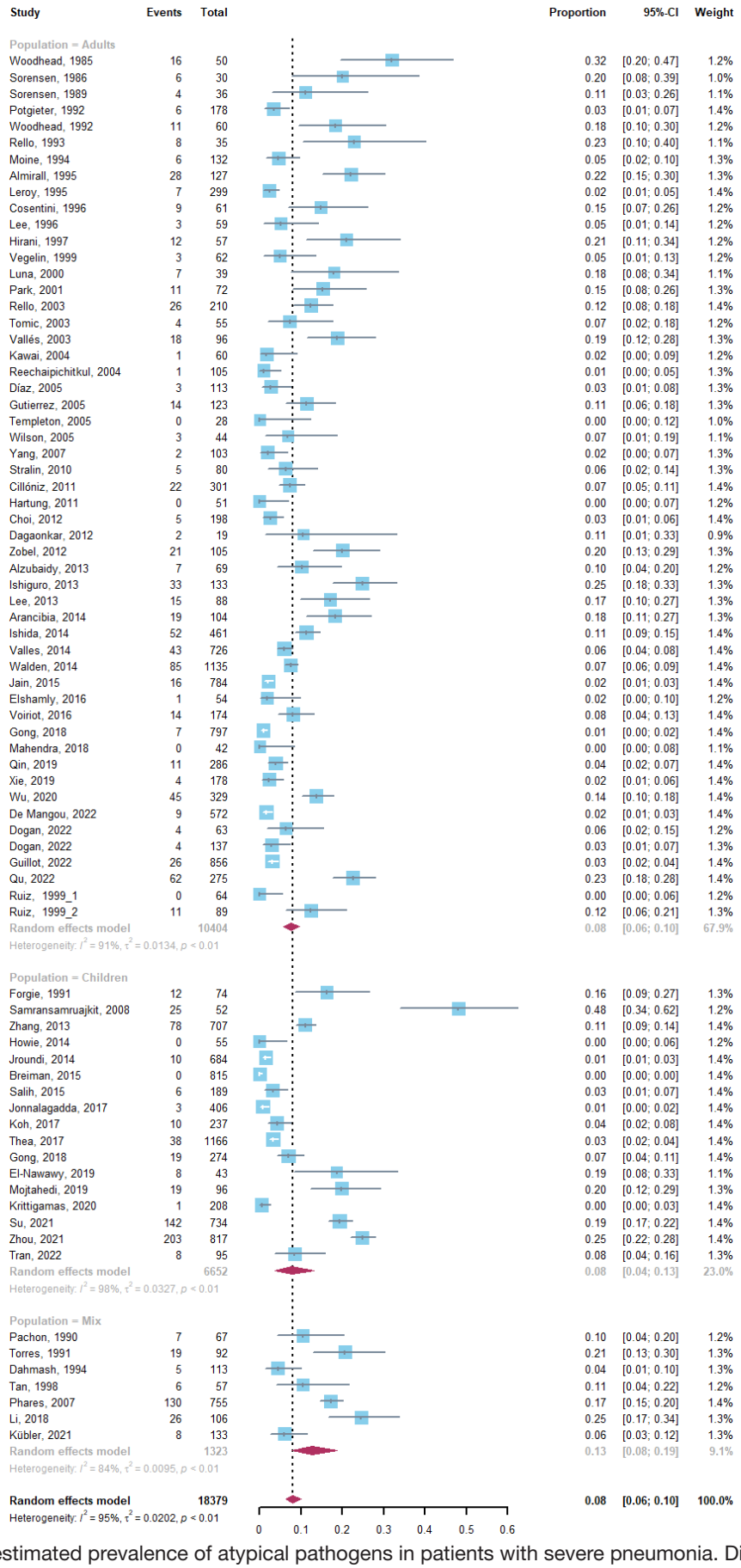

Figure 2 The pooled estimated prevalence of atypical pathogens in patients with severe pneumonia. Displayed values are mean and 95% CIs.

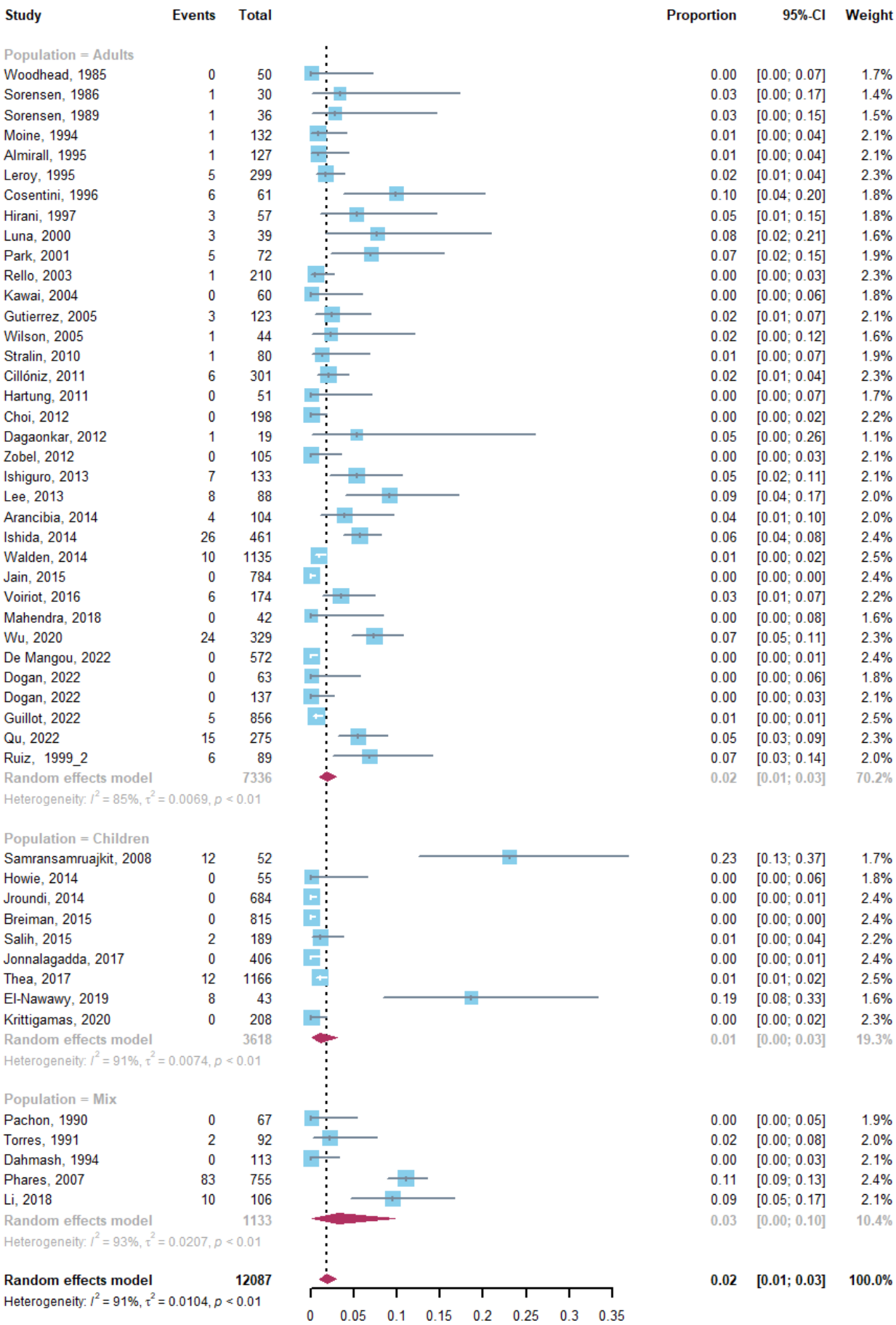

Figure 3 The estimated prevalence of *Chlamydia* in patients with severe pneumonia. Displayed values are mean and 95% CIs.

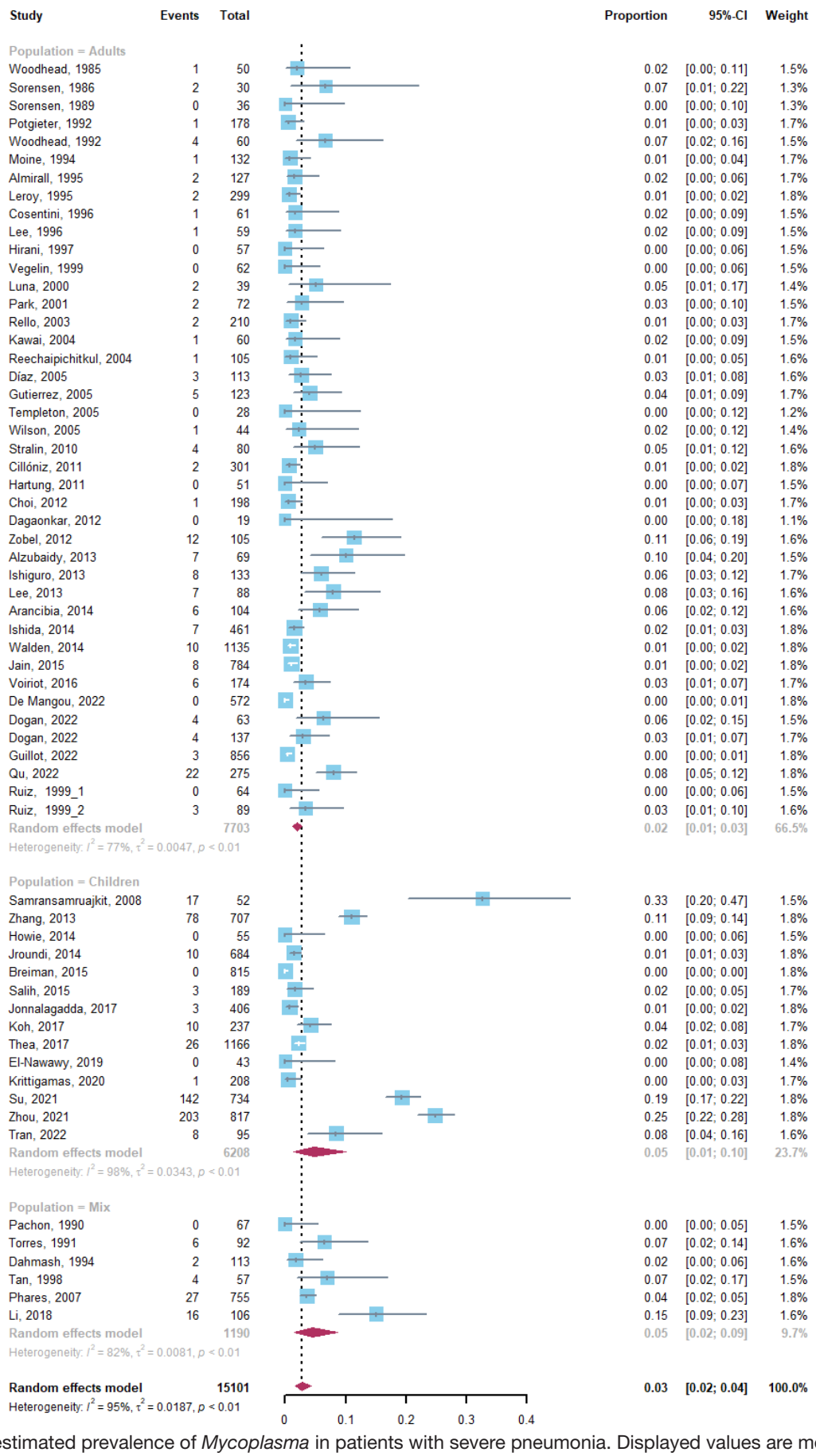

Figure 4 The estimated prevalence of *Mycoplasma* in patients with severe pneumonia. Displayed values are mean and 95% CIs.

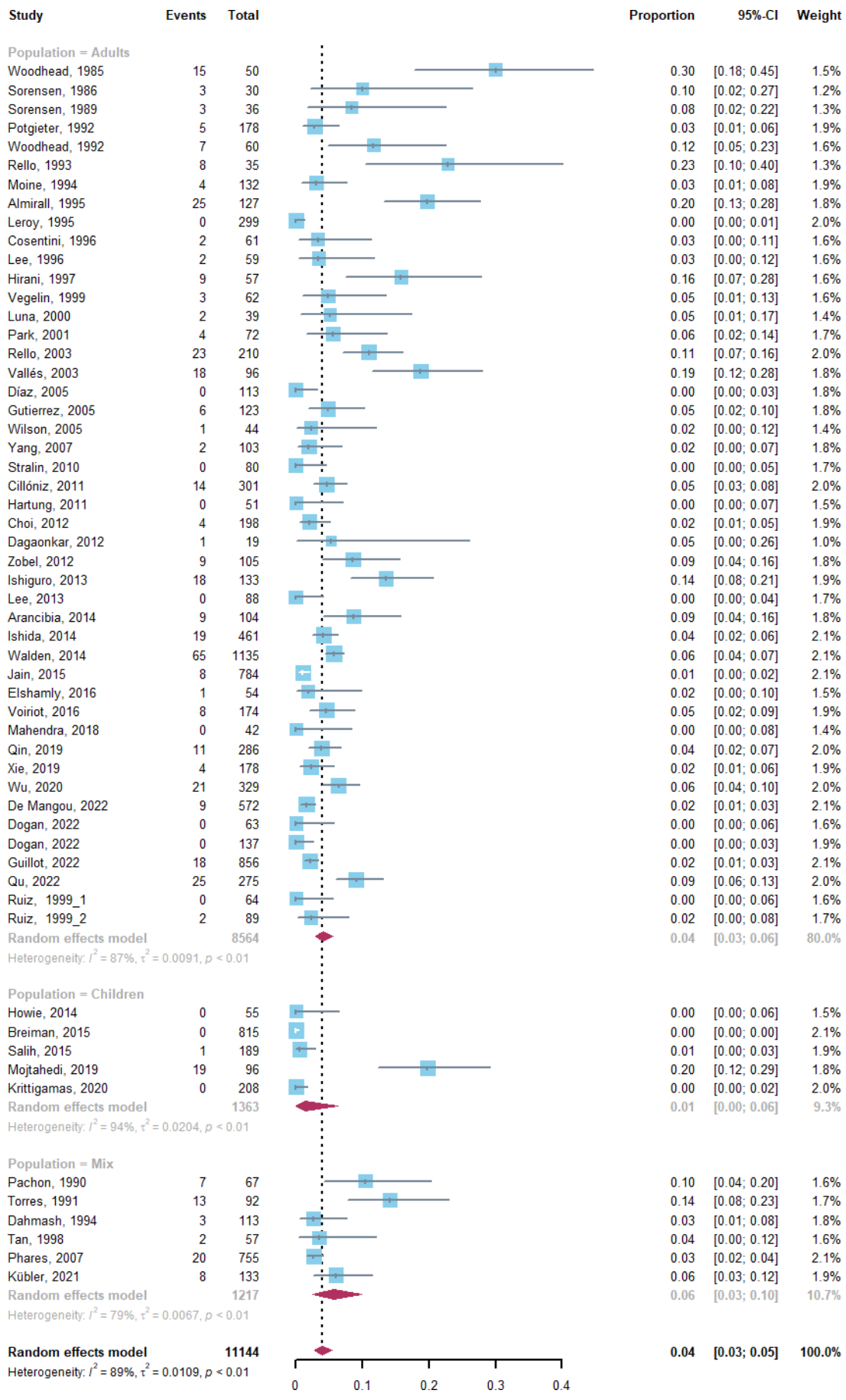

Figure 5 The estimated prevalence of *Legionella* in patients with severe pneumonia. Displayed values are mean and 95% CIs.

and other continents (1.5%; 95% CI 0% to 3.1%; I^2=82%) (online supplemental figure S3). Analysis of 46 adults studies showed that the overall *Legionella* prevalence in adults was 4.2% (95% CI 2.91% to 5.58%; I^2=87%). And detailed pneumonia categories analysis revealed that in 40 SCAP studies, the prevalence of *Legionella* in patients with SCAP was 4.0% (95% CI 2.73% to 5.41%; I^2=85%), which was slightly lower than the other pneumonia categories (5.28%; 95% CI 0.92% to 12.51%; I^2=93%), but there was no significant statistical difference between the two groups (p=0.72) and the small sample size of other pneumonia categories (n=6) may attribute to this difference.

After a sensitivity analysis, we excluded a large sample size study in children and three studies with the highest prevalence rates[32 40 92] after which the prevalence of *Legionella* in patients with severe pneumonia slightly fell to 3.49% (95% CI 2.5% to 4.6%), with a slightly lower but still significant heterogeneity (I^2=84.2%; 95% CI 80.1% to 87.5%). The individual variable meta-regression analysis revealed that year of publication (p<0.0001), sample size, mean age (p=0.004) and the diagnostic methods (PCR vs others) were likely related to heterogeneity, and notably, the diagnostic methods (PCR vs others) accounted for 21.22% of overall differences. It indicates the methods with higher accuracy and new diagnostic method may be the possible reason for the heterogeneity of the prevalence. The prevalence was remarkably higher in older reports and older adults. And after multivariate meta-regression analysis, only mean age was strongly associated with heterogeneity (p=0.002). Factors included in our multivariate regression explained 12.86% of the total heterogeneity (table 2). The Egger's test indicated the existence of publication bias in the prevalence of *Legionella* (p=0.02).

DISCUSSION

Our meta-analysis identified 75 studies of 18 379 individuals from 6 continents. The main finding is that the overall prevalence of the atypical pathogen in severe pneumonia is 8.1%, and children present a higher prevalence than adults. In patients with severe pneumonia, the prevalence of *Legionella* was the highest and *Chlamydia* was the lowest. The trend of the prevalence in adults was similar to the overall trend, while in children, *Mycoplasma* was the most common and *Legionella* was rare. Our study also suggests that in adults, atypical pathogens (including *Chlamydia* and *Mycoplasma*) had a higher prevalence in SCAP than that in other types of pneumonia.

Previous research of the prevalence of atypical pathogens in patients with CAP showed that the prevalence of *Mycoplasma* is highest in both adults and children, and *Legionella* had the lowest prevalence, with a rate of 2.7%.[104] Studies based on outpatients with CAP showed a similar conclusion.[105 106] Nevertheless, our study indicates that *Legionella* is the most common atypical pathogen, with a prevalence of 4.0% in both severe pneumonia and SCAP. This finding leads to the inference that *Legionella* is more likely to cause serious infections compared with the other two pathogens, especially in adults. Furthermore, *L. pneumophila* serotype 1 is previously the most-tested and widely-studied *Legionella* spp that causes human pneumonia, but other species have recently been reported, such as *Legionella bozemanii*[34] and *Legionella longbeachae*,[101 107] which are also responsible for severe infections. For *Mycoplasma* and *Chlamydia*, young people displayed a higher prevalence than elderly individuals did in both CAP and SCAP.[108] In our meta-analysis, the prevalence of *Mycoplasma* and *Chlamydia* in severe pneumonia was 2.8% and 1.8%; these rates are significantly lower than a previous study in which non-severe pneumonia had a prevalence of 10.1% and 3.5%, respectively.[104] Therefore, these two pathogens may cause severe lung conditions in only a small percentage of cases. Moreover, Gacouin *et al*[109] found that severe pneumonia due to *C. psittaci* shared similarities with various aspects of severe legionellosis.

In addition, the distribution of pathogens varied according to the geographical region: in Asia, the prevalence of *Mycoplasma* was the highest in patients with severe pneumonia, followed by *Chlamydia* and *Legionella*; however, in Europe,

Table 2 Multivariate meta-regression for prevalence of *Chlamydia,* and *Legionella* in patients with severe pneumonia

Covariate	Estimate (%)	Lower 95% CI	Upper 95% CI	P value
Chlamydia (n=49)				
Sample size (continuous)	−0.01	−0.02	0.00	0.01
Region (Asia vs others)	0.75	−6.88	21.85	0.30
Category (others vs CAP)	−8.52	−15.16	−1.87	0.01
Diagnostic method (PCR vs others)	−8.15	−14.18	−2.13	0.008
Legionella (n=57)				
Year of publication	−0.25	−0.60	−0.10	0.16
Sample size (continuous)	0.00	−0.01	0.02	0.85
Sample size (≥100 vs <100)	−1.90	−9.50	5.71	0.62
Mean age	−0.45	−0.74	−0.15	0.002
Diagnostic method (PCR vs others)	−7.67	−15.56	0.23	0.06

CAP, community-acquired pneumonia; PCR, polymerase chain reaction.

Legionella was the most common pathogen with a high prevalence of 6.3%, while *Chlamydia* was the least prevalent. The different testing frequency of atypical pathogens is one reason for the inconsistent prevalence among regions. Compared with other countries, Europe had the highest frequency of patients that underwent testing for atypical pathogens, whereas Africa and South America had a lower frequency; moreover, patients with severe CAP have a lower testing frequency compared with that of non-severe patients.[110] In our study, we only included studies that reported testing for at least one atypical pathogen; these studies were primarily from Asia and Europe, even though we did not restrict the inclusion criteria regarding regions. As there is likely regional variation in the degree of recognition by clinicians and economic conditions, future studies in low-income countries are necessary.

In meta-regression analysis, we found several possible factors for heterogeneity. For *Chlamydia*, we found that *Chlamydia* infection almost exclusively occurred in SCAP, which is consistent with the conventional cognition that *C. pneumoniae* is one of the pathogens associated with CAP, rather than HAP.[105] Additionally, *C. psittaci*, another species of *Chlamydia*, can cause zoonotic disease, although this condition is often contracted outside the hospital because it necessitates a clear history of contact with birds.[8] A recent study inferred that *C. pneumoniae* and *M. pneumoniae* are not related to nosocomial respiratory tract infections in ICU patients.[111] For *Mycoplasma*, the mean age accounted for a part of the heterogeneity, with lower prevalence in older people. This is consistent with the traditional belief that *M. pneumoniae* is more common in children.[112] Although Legionnaires' disease is rare in children, Greenberg *et al*[113] suggested heightened vigilance to its non-specific clinical manifestations and high mortality rate (33%), especially when empirical antibiotic treatment is ineffective. *Legionella* was also a common microorganism in severe HAP, and previous studies revealed that both CAP[105 114] and HAP (whether or not mechanical ventilation is required)[115] account for a certain proportion of *Legionella* infections. However, other research[116] showed a lower prevalence rate in HAP, from which our results are different. The higher rate of HAP and other pneumonia types displayed in our results may be related to the small sample size of this group. Another factor may be the aquatic properties of *Legionella* spp.[22] Regional water pollution, including in hospitals, can lead to outbreaks of *Legionella* pneumonia. The significant heterogeneity in these analyses demonstrates the need for aetiology analysis to place special emphasis on a thorough description of pneumonia categories and samples.

Regarding the diagnostic method of pathogens detection, we identified several possible reasons to explain the heterogeneity. After we factored this variable into meta-regression analysis, we found the diagnostic method (PCR vs others) demonstrated statistical significance in the prevalence of *Chlamydia* and *Legionella*. However, many studies used multiple test methods and merged the results to calculate the overall prevalence, so the factor cannot be fully explained. The lack of uniform guidelines for the detection of atypical pathogen infections also led to statistical differences between studies. Furthermore, the latest detection methods used in the studies, like metagenomic next-generation sequencing and transmission electron microscope screening, only included a small sample size in severe pneumonia, which prevented us from further analysis. Some factors that we did not assess might also be related to heterogeneity, such as the diagnostic criteria of severe pneumonia, the distribution of infection throughout different seasons, or whether antibiotics were used prior to microbial testing. Accordingly, future studies should describe these aspects more specifically.

The outbreak of COVID-19 may influence the prevalence of atypical pathogens in severe pneumonia.[117] However, unlike the natural occurrence of CAP in the population, COVID-19 pneumonia is a manually-managed infectious disease with strict quarantine measures for a long period.[118] Therefore, we did not include the study about the atypical pathogen infections in COVID-19. But in the post-pandemic era, analysis of COVID-19 and its co-infection with atypical pathogens may present different insights.

The primary takeaway from our research is that the atypical pathogen is a common cause of severe pneumonia, and the identification of infections should be integral to the effective empirical treatment of severe cases. The high prevalence of the atypical pathogen implies when traditional antibiotic therapy fails to treat severe pneumonia, atypical pathogens infection should be considered. Or we can use antibiotics covering atypical pathogens once severe pneumonia is diagnosed. The empirical antibiotic coverage for CAP or other pneumonia mainly focuses on using penicillin and cephalosporins. But for patients with severe pneumonia, it is important to cover the atypical pathogen infection by using antibiotics such as quinolones, tetracyclines and sulfonamides.

The results of our systematic review should be explained within limited contexts. First, our results may be influenced by the quality of original studies and their reporting bias, and the exclusion of non-English publications likely contributed to the bias. However, based on the Egger's test, only *Legionella* presented publication bias with statistical significance. To reduce such effects, we strictly stipulated literature-screening criteria and excluded studies for special populations, which likely do not represent the prevalence in the whole population. Second, our analysis did not include infection due to *Coxiella burnetii*, one of the atypical pathogens commonly discussed,[119] because there were few relevant reports at the initial search, and only a small number of cases of *C. burnetii* infection exhibit mild-to-moderate pneumonia while severe pneumonia is infrequent.[120]Third, our analysis found substantial heterogeneity; although several factors were identified, there were still some characteristics that could not be assessed, such as the different diagnostic criteria for severe pneumonia. Although we found the diagnostic method (PCR vs others) contributes a lot to the heterogeneity, the detection of pathogens still varies greatly and is hard to be sorted. Additionally, the articles we included

cover a wide time span, and the definition of severe pneumonia has been gradually improved from scratch over time. As shown in online supplemental material 2 and table 2, many old studies only used ICU admission as the inclusion criteria, which prevented us from the further subgroup analysis. Furthermore, the impact of seasonal epidemics and regional outbreaks and different sensitivities and specificities of various laboratory testing methods may contribute to underdiagnosis.[104] Although PCR can provide rapid results,[14 121] a combination of multiple laboratory methods can be more reliable.[122 123]

CONCLUSIONS

This meta-analysis summarises the prevalence of atypical pathogens in patients with severe pneumonia. Our work demonstrates that atypical pathogens infections are common in severe pneumonia, and covering atypical pathogens in the empirical antibiotic treatment is necessary. Differences in estimated prevalence may be associated with the pneumonia category, the diagnostic method used for detection, the region of the studies and the sample size. These factors should be considered when performing microbiological screening for patients with severe pneumonia, especially when conventional empirical antibiotic therapy is ineffective. Additional studies with large sample sizes, rigorous designs and better testing methods are needed to provide further guidance regarding antibiotic treatment in severe pneumonia.

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ORCID iD

Sidan Wang http://orcid.org/0000-0002-6506-9848

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