Prevalence of Atypical Pathogens in Patients With Cough and Community-Acquired Pneumonia: A Meta-Analysis

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ABSTRACT

PURPOSE Community-acquired pneumonia (CAP), acute cough, bronchitis, and lower respiratory tract infections (LRTI) are often caused by infections with viruses or Streptococcus pneumoniae. The prevalence of atypical pathogens Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila, and Bordetella pertussis among patients with these illnesses in the ambulatory setting has not been previously summarized. We set out to derive prevalence information from the existing literature.

METHODS We performed a systematic review of MEDLINE for prospective, consecutive-series studies reporting the prevalence of M pneumoniae, C pneumoniae, L pneumophila and/or B pertussis in outpatients with cough, acute bronchitis, LRTI, or CAP. Articles were independently reviewed by 2 authors for inclusion and abstraction of data; discrepancies were resolved by consensus discussion. A meta-analysis was performed on each pathogen to calculate the pooled prevalence estimates using a random effects model of raw proportions.

RESULTS Fifty studies met our inclusion criteria. While calculated heterogeneity was high, most studies reported prevalence for each pathogen within a fairly narrow range. In patients with CAP, the overall prevalences of M pneumoniae and C pneumoniae were 10.1% (95% CI, 7.1%-13.1%) and 3.5% (95% CI, 2.2%-4.9%), respectively. Consistent with previous reports, M pneumoniae prevalence peaked in roughly 6-year intervals. Overall prevalence of L pneumophila was 2.7% (95% CI, 2.0%-3.4%), but the organism was rare in children, with only 1 case in 1,765. In patients with prolonged cough in primary care, the prevalence of B pertussis was 12.4% (95% CI, 4.9%-19.8%), although it was higher in studies that included only children (17.6%; 95% CI, 3.4%-31.8%).

CONCLUSIONS Atypical bacterial pathogens are relatively common causes of lower respiratory diseases, including cough, bronchitis, and CAP. Where surveillance data were available, we found higher prevalences in studies where all patients are tested for these pathogens. It is likely that these conditions are underreported, underdiagnosed, and undertreated in current clinical practice.

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INTRODUCTION

Cough is the 4th most common reason for an office visit to an ambulatory physician, accounting for 2.8% of all visits. In primary care, when cough is the patient’s primary complaint, it is most often caused by a virus, but approximately 5% of patients have community-acquired pneumonia (CAP). Although viruses and Streptococcus pneumoniae are the most common causes of CAP, some episodes are caused by an atypical bacterial infection such as Mycoplasma pneumoniae, Chlamydiaphila pneumoniae (also known as Chlamydia pneumoniae), and Legionella pneumophila. Some episodes of non-pneumonia lower respiratory tract infection (LRTI) are caused by the above pathogens as well as by Bordetella pertussis, and the incidence of the latter is increasing in the United States.
Mycoplasma pneumoniae infection is thought to vary cyclically, and has been the cause of outbreaks of LRTI. Not to be confused with Chlamydia psittaci (which also causes respiratory infections but is contracted from birds), Chlamydomphila pneumoniae is more common in children, but has been associated with subsequent serious adult disease as well. A meta-analysis reported an association with lung cancer in patients with previous C pneumoniae infections, while others have posited an association with development of asthma. Legionellosis, better known as Legionnaires’ disease, is caused by L pneumophila and is most commonly diagnosed as a cause of CAP in patients over 50 years of age, and more often in men than women. The organism is found naturally in the environment, and the infection is associated with inhalation of aerosolized water from sources such as hot tubs and cooling towers. Recently, increased risk of infection with L pneumophila has also been linked to wet, humid weather. Bordetella pertussis is highly communicable and is a source of significant morbidity in children and prolonged symptoms in all patients. Although B pertussis is the only atypical pathogen to have a widely available vaccine, the incidence of B pertussis in the United States is increasing, with more cases in 2012 than any year previously since 1955.

The prevalence of atypical pathogens, particularly in the outpatient primary care setting, has not been previously summarized. B pertussis and L pneumophila are reported by national surveillance systems in many countries, but they are laboratory-based systems that are subject to significant underreporting. The prevalence of C pneumoniae and M pneumoniae vary widely in previous studies of patients with CAP.

Because these atypical pathogens do not respond to beta-lactams, may carry a different prognosis, and can cause serious complications in some patients, it is important to understand their prevalence. Therefore, we performed a meta-analysis to describe the prevalence of atypical pathogens among 2 groups: patients with cough, acute bronchitis, or LRTI in the ambulatory setting and patients diagnosed with CAP. We also compared these “real world” prevalences with the prevalences reported by surveillance systems, where available.

METHODS
Literature Review
We searched MEDLINE for prospective studies that reported the results of testing for M pneumoniae, C pneumoniae, L pneumophila, or B pertussis in outpatients with cough, acute bronchitis, or LRTI, as well as among inpatients and outpatients diagnosed with CAP. In order to reflect contemporary prevalences and microbiology, searches were limited to articles where the majority of data was collected after January 1, 2000. We included articles with abstracts written in English and German (the primary languages of the investigators). Supplemental Appendix A (http://www.annfammed.org/content/14/6/552/suppl/DC1) includes detailed search terms used for each strategy. We also reviewed the reference lists for review articles identified by our search, and of any included studies.

We excluded studies of only or predominantly immunocompromised patients, studies of hospital-acquired infections, studies of special or unusual populations (eg, military recruits), studies of acute exacerbations of chronic obstructive pulmonary disease or asthma, and studies of the etiology of bronchiolitis. Further, we excluded studies set in low- or medium-income countries based on Organisation for Economic Cooperation and Development (OECD) criteria; (Supplemental Appendix B, http://www.annfammed.org/content/14/6/552/suppl/DC1) since we felt that they would not reflect the current practice and epidemiology of the United States. We also excluded case-control studies, case reports, case series and retrospective studies, outbreak investigations, and studies that did not use culture, polymerase chain reaction (PCR), serology, or urine antigen testing (for L pneumophila) to identify pathogens.

Data Abstraction
Two investigators reviewed each abstract to identify articles that should be reviewed in full. Any article selected for full review was examined by both investigators. For each included article, study characteristics and data regarding prevalence were abstracted by both authors. For prevalence data, definite and probable cases were included and possible cases were excluded. Any discrepancies were resolved by consensus discussion.

Surveillance Systems
We used surveillance data reported by high-income members of the OECD. The most recent complete data available, from 2012, were abstracted by 2 investigators, with any discrepancies resolved by consensus discussion. For each report, we documented the type of surveillance used, number of cases reported, and total population.

Study Quality
A meta-analysis usually uses a standardized tool to assess the risk of bias. Unfortunately, there are currently no published tools for assessing bias in studies of disease prevalence. To ensure that the studies included in our meta-analysis were of consistent high quality, we only included studies that met the following criteria: they enrolled consecutive patients, did not gather data from a specialized or unusual population, gathered data...
prospectively, and used diagnostic tests likely to classify patients accurately as having the pathogen in question.

**Analysis**

We identified 2 groups for the analysis: patients presenting with acute cough illness or lower respiratory tract symptoms and patients diagnosed with CAP. Where studies reported etiology separately for patients with CAP and those with non-pneumonia LRTI, we report these groups separately as well.

Pooled prevalence estimates were calculated with random effects model of raw proportions. Statistical analysis was performed in R (version 3.2.2, R Studio Version 0.99.441), including plots of proportions with each pathogen using the metafor procedure.

**RESULTS**

The search for *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila* yielded 449 abstracts. A separate search for
B. pertussis returned 226. After screening titles and abstracts, 98 articles for M. pneumoniae, C. pneumoniae, and L. pneumophila and 39 for B. pertussis remained for full-text review. Thirteen articles were additionally identified through a review of the reference lists (12 for M. pneumoniae, C. pneumoniae, and L. pneumophila, and 1 for B. pertussis). Full-text review excluded 102 articles. The most common reasons for exclusion were that the majority of data was collected before 2000 or that the study did not use a cohort design with prospective data collection. An updated search before writing yielded 2 additional studies and 10 studies reported the prevalence of these pathogens in children (Table 2). Only 2 studies were set in the United States.

Patients With Community-Acquired Pneumonia

Figures 2-4 show the forest plots for M. pneumoniae, C. pneumoniae, and L. pneumophila respectively in patients with CAP. The overall prevalence of M. pneumoniae was 10.1% (95% CI, 7.1%-13.1%). The prevalence was higher in children (17.6%; 95% CI, 8.7%-26.4%) than in adults (7.2%; 95% CI, 5.2%-9.3%). There was significant heterogeneity, though, especially in studies of children. This is likely because outbreaks of M. pneumoniae are thought to occur every 4 to 6 years, and inspection of the forest plot, which is sorted chronologically, does reveal peaks around 2004 and 2010.

The overall prevalence of C. pneumoniae in patients with CAP was 3.5% (95% CI, 2.2%-4.9%). Infection with C. pneumoniae was more common in adults (4.3%, 95% CI, 2.4%-6.2%) than in children (1.0%, 95% CI, 0.6%-1.5%). There was significant heterogeneity, although only 4 of 25 studies in adults had a prevalence greater than 10%, while the remainder had a prevalence between 0.3% and 7.7%. In children, only 2 of 10 studies had prevalences greater than 5%, while the remaining 8 had prevalences ranging from 0.5% to 2.7%. We reviewed the 6 identified outliers, but were...
**Table 2. Characteristics of Studies of the Prevalence of Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila in Patients With Community-Acquired Pneumonia or Lower Respiratory Tract Infection**

| Author, Year (Country) | Population | Total / Confirmed Cases<sup>a</sup> | Setting | Age | Pathogen | Data Collection Period | Diagnostic Method |
|------------------------|------------|-------------------------------------|---------|-----|----------|------------------------|-------------------|
| Jain et al.,<sup>18</sup> 2015<sup>b</sup> (United States) | Adults ≥18 y with CAP | 2,320/853 | Inpatient | Median 57 y, range 18 y-100 y | MP, CP, LP | 2010-2012 | PCR, Culture, UA |
| Angeles et al.,<sup>20</sup> 2006 (Spain) | Adults ≥15 y with CAP | 198/112 | Inpatient | Median 70 y | MP, CP, LP | 2003-2006 | Serology, UA |
| Beovic´ et al.,<sup>21</sup> 2003 (Slovenia) | Adults ≥15 y with CAP (PSI I or II) | 113/68 | NR | Mean 44.9 y | MP, CP, LP | 1999-2001 | Serology |
| Charles et al.,<sup>22</sup> 2008 (Spain) | Adults ≥18 y with CAP | 885/404 | Inpatient | Mean 65.1 y, range 18 y-100 y | MP, CP, LP | 2004-2006 | Serology, UA |
| Cilloniz et al.,<sup>23</sup> 2012 (Spain) | Adults ≥16 y with CAP | 568/188 | Outpatient | Mean 47.2 y | MP, CP, LP | 2000-2010 | Serology, UA |
| Diaz et al.,<sup>24</sup> 2007 (Chile) | Adults ≥16 y with CAP | 176/98 | Inpatient | Mean 65.8 y, range 17 y-101 y | MP, CP, LP | 2003-2005 | Serology, UA |
| Espana et al.,<sup>25</sup> 2012 (Spain) | Adults ≥18 y with CAP | 344/153 | 73 Inpatient, 271 outpatient | Mean 53.5 y | MP, CP, LP | 2006-2007 | Serology, UA |
| Falguera et al.,<sup>26</sup> 2010 (Spain) | Adults ≥18 y or older with CAP (PSI IV or V) | 88/25 | Inpatient | Mean 64 y | LP | 2006-2008 | Serology, UA |
| Gutierrez et al.,<sup>27</sup> 2006 (Spain) | Adults ≥15 y with CAP | 493/250 | 361 Inpatient, 132 outpatient | Mean 56.6 y, range 15 y-94 y | MP, CP, LP | 2006-2009 | Serology, UA |
| Herrera-Lara et al.,<sup>28</sup> 2013 (Spain) | Adults ≥18 y with CAP | 243/139 | Inpatient | Mean 63.9 y | MP, CP, LP | 1999-2001 | Serology, UA |
| Holm et al.,<sup>29</sup> 2007<sup>b</sup> (Denmark) | Adults ≥20 y with CAP | 48/21 | 9 Inpatient, 39 outpatient | Mean 61 y, range 22 y-88 y | MP, CP, LP | 2002-2003 | PCR |
| Huiskens et al.,<sup>30</sup> 2013 (Netherlands) | Adults ≥20 y with CAP | 408/263 | NR | Mean 65 y, range 20 y-94 y | MP, CP, LP | 2008-2009 | Serology, PCR, UA |
| Johannson et al.,<sup>31</sup> 2010 (Sweden) | Adults ≥18 y with CAP | 184/124 | Inpatient | Mean 61.3 y, range 18 y-93 y | MP, CP, LP | 2004-2005 | Serology, PCR, UA |
| Lee et al.,<sup>32</sup> 2002 (South Korea) | Adults ≥16 y with CAP | 81/15 | Inpatient | Mean 66.3 y, range 17 y-92 y | MP, CP, LP | 1999-2000 | Serology |
| Luchsinger et al.,<sup>33</sup> 2013 (Chile) | Adults ≥18 y with CAP | 356/232 | 330 Inpatient, 26 outpatient | Mean 59.3 y | MP, CP, LP | 2005-2007 | Serology, PCR, UA |
| Marrie et al.,<sup>34</sup> 2005 (Canada) | Adults ≥18 y with CAP | 507/245 | Outpatient | Mean 47.8 y | MP, CP | 2003 | Serology |
| Miyashita et al.,<sup>35</sup> 2005 (Japan) | Adults ≥16 y with CAP | 506/318 | 400 Inpatient, 106 outpatient | Mean 58.3 y, range 16 y-97 y | MP, CP, LP | 1998-2003 | Serology, UA |
| Molinos et al.,<sup>36</sup> 2009 (Spain) | Adults with CAP<sup>3</sup> | 710/274 | Inpatient | Mean 67.1 y | MP, CP, LP | 2003-2004 | Serology, UA |
| Prat et al.,<sup>37</sup> 2006 (Spain) | Adults with CAP<sup>3</sup> | 217/116 | Inpatient | Mean 56.6 y | LP | 2005-2005 | UA |
| Saito et al.,<sup>38</sup> 2006 (Japan) | Adults ≥17 y with CAP | 232/170 | 200 Inpatient, 32 outpatient | Mean 60.2 y, range 17 y-99 y | MP, CP, LP | 1999-2000 | Serology, PCR, UA, Culture |
| Sangil et al.,<sup>39</sup> 2012 (Spain) | Adults ≥18 y with CAP | 131/92 | Inpatient | Mean 64.4 y, range 48 y-80 y | MP, CP, LP | 2009-2010 | Serology, PCR, UA |
| Shibbi et al.,<sup>40</sup> 2010 (Israel) | Adults ≥18 y with CAP | 126/84 | Inpatient | Mean 58.3, range 18 y-93 y | MP, CP, LP | 2006-2007 | Serology, PCR, UA |
| Stralin et al.,<sup>41</sup> 2010 (Sweden) | Adults ≥18 y with CAP | 235/133 | Inpatient | Median 71 y, range 18 y-96 y | MP, CP, LP | 1999-2002 | Serology, PCR, UA |
| Templeton et al.,<sup>42</sup> 2005 (Netherlands) | Adults ≥18 y with CAP | 105/80 | 92 Inpatient, 13 outpatient | Mean 63 y | MP, LP | 2004-2006 | PCR |
| van de Garde et al.,<sup>43</sup> 2008 (Netherlands) | Adults with CAP<sup>3</sup> | 201/128 | Inpatient | Mean 63 y | MP, LP | 2004-2006 | PCR |
| von Baum et al.,<sup>44</sup> 2008 (Germany [CAPNETZ]) | Adults ≥18 y with CAP | 2,503/877 | 1,727 Inpatient, 776 outpatient | Mean 61 y | LP | 2002-2005 | PCR, UA, Culture |
| von Baum et al.,<sup>45</sup> 2009 (Germany [CAPNETZ]) | Adults ≥18 y with CAP | 4,532/928 | 2,922 Inpatient, 1,610 outpatient | Mean 60 y | MP | 2002-2005 | Serology, PCR, UA |

CAP = community-acquired pneumonia; CP = Chlamydia pneumoniae; LP = Legionella pneumophila; LRTI = lower respiratory tract infection; MP = Mycoplasma pneumoniae; NR = not reported; PCR = polymerase chain reaction; PSI = pneumonia severity index; UA = urine antigen testing.

<sup>a</sup> Total = number of patients included in study. Confirmed = number of patients with a pathogen identified.

<sup>b</sup> Study findings reported separately for patients with CAP and those with non-pneumonic LRTI.

<sup>c</sup> Estimated from median using method of Hozo.<sup>46</sup>

<sup>d</sup> Age not reported but presumably adult based on hospital and mean age.
Table 2. Characteristics of Studies of the Prevalence of *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* in Patients With Community-Acquired Pneumonia or Lower Respiratory Tract Infection (continued)

| Author, Year | Population | Total/Confirmed Cases | Setting | Age | Pathogen | Data Collection Period | Diagnostic Method |
|--------------|------------|-----------------------|---------|-----|----------|------------------------|-------------------|
| CAP in Adults (continued) | | | | | | | |
| Wellinghausen et al,46 2006 (Germany [CAPNETZ]) | Adults ≥18 y with CAP | 546/NR | 364 Inpatient, 182 outpatient | Median 62 y; | CP | 2002-2004 | PCR |
| Andreo et al,47 2006 (Spain) | Adults ≥16 y with CAP | 107/39 | Inpatient | Mean 58.6 y, range 16 y-86 y | MP, CP, LP | 2000-2001 | Serology |
| Capelastegui et al,48 2012 (Spain) | Adults ≥18 y with CAP | 700/390 | 276 Inpatient, 424 outpatient | Mean 59.7 y | MP, CP, LP | 2006-2007 | Serology, UA |
| CAP in Children | | | | | | | |
| Cantais et al,49 2014 (France) | Children age 1 mo to 16.5 y with CAP | 85/81 | Inpatient | Median 2.8 y, range 1 mo to 16.5 y | MP, CP | 2012-2013 | PCR |
| Cevey-Macherel et al,50 2009 (Switzerland) | Children 2 mo to 5 y with CAP | 99/85 | Inpatient | Mean 29 mo, range 2 mo to 5 y | MP, CP | 2003-2005 | Serology, PCR |
| Don et al,51 2005 (Italy) | Children 4 mo to 16 y with CAP | 101/66 | Inpatient | Mean 4.7 y, range 0.3 y-16 y | MP, CP | 2001-2002 | Serology |
| Hamano-Hasegawa et al,52 2008 (Japan) | Children <19 y with CAP | 1,700/1,316 | NR | Median 6.1 y for MP; Median 5.4 y for CP; Range 0 y-19 y | MP, CP, LP | 2005-2006 | PCR |
| Jain et al,53 2015* (United States) | Children <18 y with CAP | 2,222/1,802 | Inpatient | Median 2 y, range 0 y-17 y | MP, CP | 2010-2012 | PCR |
| Kurz et al,54 2005 (Austria) | Children 2 mo to 17 y with CAP | 279/190 | Inpatient | Median 36 mo, range 2 mo to 17 y | MP, CP | 2005-2008 | PCR |
| Laundy et al,55 2003 (England) | Children <5 y with CAP | 51/25 | 42 Inpatient, 9 outpatient | Median 1.3 y, range 2 wk to 4.8 y | MP, CP | 2001-2002 | PCR |
| Maltezou et al,56 2004* (Greece) | Children 6 mo to 14 y with CAP (n = 60), cough >3 weeks (n = 1) or infectious asthma exacerbation (n = 4) | 65/19 | Inpatient | Mean 6 y, range 10 mo to 13 y | MP, CP, LP | 2001 | Serology |
| Numazaki et al,57 2004* (Japan) | Children <15 y with CAP | 398/383 | 362 Inpatient, 36 outpatient | NR | MP, CP | 2000-2001 | Serology, PCR, Culture |
| Tsolia et al,58 2004 (Greece) | Children 5y-14 y with CAP | 75/58 | Inpatient | Median 86.5 mo, range 5 y-14 y | MP, CP | 2003 | Serology, PCR |
| Nonpneumonia LRTI | | | | | | | |
| Graffelman et al,59 2008* (Netherlands) | Adults ≥18 y consulting GP with LRTI; 26 of 129 had CAP | 129/84 | Outpatient | Mean 50 y | MP | 1998-2001 | Serology, PCR, Culture |
| Numazaki et al,57 2004* (Japan) | Children <15 y with non-pneumonia LRTI | 523/470 | 436 Inpatient, 87 outpatient | NR | MP, CP | 2000-2001 | Serology, PCR |
| Holm et al,50 2007* (Denmark) | Adults ≥18 y with non-pneumonia LRTI | 316/124 | 10 Inpatient, 306 outpatient | Median 48 y, range 18 y-94 y | MP, CP, LP | 2002-2003 | PCR |
| Various | | | | | | | |
| Defilippi et al,50 2008 (Italy) | Children with LRTI (acute bronchitis, wheezy bronchitis, pneumonia, or bronchiolitis) admitted to the hospital | 886/NR | Mean 6.2 y, range 1 mo to 13.5 y | MP | 2005-2006 | PCR |

CAP = community-acquired pneumonia; CP = *Chlamydia pneumoniae*; LP = *Legionella pneumophila*; LRTI = lower respiratory tract infection; MP = *Mycoplasma pneumoniae*; NR = not reported; PCR = polymerase chain reaction; PSI = pneumonia severity index; UA = urine antigen testing.

* Total = number of patients included in study. Confirmed = number of patients with a pathogen identified.

† Study findings reported separately for patients with CAP and those with non-pneumonic LRTI.

‡ Estimated from median using method of Hozo.61

§ Age not reported but presumably adult based on hospital and mean age.

‖ Classified as study of CAP if at least 85% of patients in the series were diagnosed with CAP.

¶ In this study, LRTI was defined as abnormal lung sounds plus 2 of 3 of: (1) fever; (2) dyspnea or cough; (3) tachypnea, malaise or confusion.
unable to determine a reason for their high prevalence. There was also no clear pattern of variation by year of study.

*Legionella pneumophila* was exceedingly rare in children, with only 1 case in 1,765 patients with CAP. The overall prevalence in adults was 2.8% (95% CI, 2.1%-3.6%), although in most studies it was between 1% and 3%. Again, there was significant heterogeneity.

Of the studies reporting a prevalence of 5% or higher, 4 of 6 were in Spain, and a fifth, a study that also reported the highest prevalence of *C. pneumoniae*, was set in another Mediterranean country, Israel. The largest series, set in Germany, found *L. pneumophila* in 3.7% of patients treated in ambulatory care and 3.8% of inpatients. Clearly, it is not only found in severely ill patients.

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Patients With Non-Pneumonia LRTI
Two studies reported the prevalence of atypical pathogens in patients with LRTI in whom pneumonia had been excluded by normal chest radiography, and a third enrolled predominantly patients with non-pneumonia LRTI. The prevalence of *M pneumoniae* was 7/316 (2.2%), 13/129 (10.0%), and 78/523 (14.9%) in these 3 studies, while the prevalence of *C pneumoniae* was 2/316 (0.6%) in 1 study and 3/523 (0.6%) in a second. A single study found no cases of *L pneumophila* in a primary care series of 316 adults with non-pneumonia LRTI. A fourth study did not provide adequate information to differentiate the number of children with acute bronchitis, pneumonia, or bronchiolitis.

Prevalence of *Bordetella pertussis* in Outpatients
Table 3 summarizes data from 8 studies of the prevalence of *B pertussis* in outpatients with prolonged or bothersome cough, largely in primary care. Three studies enrolled adults and children, 4, children only, and 2, only adults. The prevalence ranged from 0.003 (95% CI: 0.000-0.005) to 0.079 (95% CI: 0.070-0.089), with a pooled estimate of 0.035 (95% CI: 0.022-0.049). The forest plot in Figure 3 illustrates the distribution of prevalence estimates across studies.
and 1, adults only. Data were collected between 2001 and 2012. One study assessed children referred from primary care due to suspicion for *B. pertussis*, based on the duration of cough. The prevalence of *B. pertussis* is summarized in the forest plot in Figure 5. While there was significant heterogeneity when including all studies, this was primarily due to heterogeneity in the 4 studies of children only.

**Figure 4. Forest plot of the prevalence of Legionella pneumophila in adults and children with community-acquired pneumonia, sorted by prevalence.**

| Author, Year          | Cases | Total | Prevalence (95% CI) |
|-----------------------|-------|-------|---------------------|
| **Adults**            |       |       |                     |
| Holm et al,²⁹ 2007    | 0     | 48    | 0.010 (-0.018-0.038) |
| Lee et al,³¹ 2002     | 0     | 81    | 0.006 (-0.011-0.023) |
| Sangil et al,³⁸ 2012  | 1     | 131   | 0.008 (-0.007-0.023) |
| Andreo et al,²⁷ 2006  | 1     | 107   | 0.009 (-0.009-0.028) |
| Miyashita et al,³³ 2005 | 6   | 506   | 0.012 (0.002-0.021) |
| Stralin et al,³⁵ 2010 | 3     | 235   | 0.013 (-0.002-0.027) |
| Jain et al,³⁶ 2015    | 32    | 2,320 | 0.014 (0.009-0.019) |
| Espana et al,²⁵ 2012  | 5     | 344   | 0.015 (0.002-0.027) |
| Johansson et al,³² 2010 | 3 | 184 | 0.016 (-0.002-0.035) |
| Beović et al,²¹ 2003  | 2     | 113   | 0.018 (-0.007-0.042) |
| Diaz et al,³⁸ 2007    | 4     | 176   | 0.023 (0.001-0.045) |
| Cillozzi et al,²¹ 2012 | 13   | 568   | 0.023 (0.011-0.035) |
| Capelastegui et al,³⁹ 2012 | 17 | 700   | 0.024 (0.013-0.036) |
| van de Garde et al,⁴⁰ 2008 | 5  | 201   | 0.025 (0.003-0.046) |
| Charles et al,²¹ 2008 | 25    | 885   | 0.028 (0.017-0.039) |
| Angeles et al,²⁰ 2006 | 6     | 198   | 0.030 (0.006-0.054) |
| Falguera et al,³⁶ 2010 | 3    | 88    | 0.034 (-0.004-0.072) |
| Luchsinger et al,³¹ 2013 | 13 | 356   | 0.037 (0.017-0.056) |
| Huijksens et al,³⁰ 2013 | 15  | 408   | 0.037 (0.019-0.055) |
| von Baum et al,⁴⁰ 2008 | 94  | 2,503 | 0.038 (0.030-0.045) |
| Saito et al,²⁶ 2006   | 9     | 232   | 0.039 (0.014-0.064) |
| Gutierrez et al,²² 2006 | 27  | 493   | 0.055 (0.035-0.075) |
| Molinos et al,²⁶ 2009 | 40    | 710   | 0.056 (0.039-0.073) |
| Templeton et al,³⁴ 2005 | 6   | 105   | 0.057 (0.013-0.102) |
| Shibli et al,⁴⁰ 2010  | 9     | 126   | 0.071 (0.026-0.116) |
| Herrera-Lara et al,³⁸ 2013 | 21 | 243   | 0.086 (0.051-0.122) |
| Prat et al,³¹ 2006    | 21    | 217   | 0.097 (0.057-0.136) |
| **Subtotal**          |       |       | 0.028 (0.021-0.036)  |
| **Children**          |       |       |                     |
| Hamano-Hasegawa et al,²¹ 2008 | 0 | 1,700 | 0.000 (-0.001-0.001) |
| Maltezou et al,³⁶ 2004 | 1     | 65    | 0.015 (-0.015-0.045) |
| **Subtotal**          |       |       | 0.000 (-0.001-0.001)  |

Random effects model for all studies: 0.027 (0.020-0.034)

Heterogeneity (I²) = 91.18
The overall prevalence was 12.4% (95% CI, 4.9%-19.8%). In a large, multi-country, European prospective study of adults presenting to primary care with cough of up to 28 days duration,\textsuperscript{17} prevalence was 3% (95% CI, 2.4%-3.6%). The prevalence was higher in studies of children (17.6%; 95% CI, 3.4%-31.8%) than in those of adults and children (8.9%; 95% CI, 6.7%-11.2%), but there was significant heterogeneity in the studies of children, with a range from 4.6% to 37.2%.\textsuperscript{67-70}

**Surveillance Data for *Bordetella pertussis* and *Legionella pneumophila***

Of the 26 countries to report data on *B pertussis*, Australia had the highest incidence rate of 105.0 cases per 100,000 persons per year. Hungary reported the lowest incidence rate of 0.05 cases per 100,000 persons per year. With 48,277 cases, the United States had the most reported cases of all countries, twice as many as the next country. Of the 26 countries reporting *L pneumophila*, the United States had the most cases at 3,688. Poland reported the lowest incidence of *L pneumophila* (0.02 per 100,000 persons per year) and Slovenia the highest (4.02 per 100,000 persons per year). It is likely that differences in surveillance systems and reporting account for much of this variability.

**DISCUSSION**

Among adults with CAP, 14% had an atypical pathogen: 7% had *Mycoplasma pneumoniae*, 4% had *Chlamydia pneumoniae*, and 3% had *Legionella pneumophila*. Among children with CAP, 18% had *Mycoplasma pneumoniae*, only 1% had *Chlamydia pneumoniae*, and *Legionella pneumophila* was extremely rare (1 case in 1,765 patients). Among patients with prolonged cough, 9% of adults and 18% of children had *Bordetella pertussis*.

**Evidence for Underdiagnosis**

CAP is diagnosed in an estimated 5.6 million patients annually in the United States, and 1.1 million hospitalizations result.\textsuperscript{71,72} Laboratory-based surveillance, however, identifies only 3,700 infections caused by *L pneumophila* each year, or 0.06% of all community-acquired pneumonias. Our systematic review found that when a consecutive series of patients with CAP are all tested for *L pneumophila*, it is detected in 3% of patients, with a range of 1% to 10%. This is consistent with the most recent US study,\textsuperscript{18} which found that 1.9% of episodes of CAP in a consecutive series of hospitalized adults were caused by *L pneumophila*. If 2% of all episodes of CAP are caused by *L pneumophila*, this would be 112,000 cases per year. Thus, the vast majority of cases of *L pneumophila* in the United States, approximately 100,000, may be undiagnosed. It is therefore important that physicians consider this pathogen when diagnosing CAP, and consider ordering urine antigen tests for *L pneumophila* more routinely, particularly when patients are non-responsive or slowly responsive to therapy with a beta-lactam. The recommended antibiotic for *L pneumophila* is a respiratory fluoroquinolone.\textsuperscript{73,74}

### Table 3. Characteristics of Studies of the Prevalence of *Bordetella pertussis* in Outpatients With Prolonged Cough or Non-Pneumonia Lower Respiratory Tract Infection

| Author, Year | Population | Age | Year of Data Collection | Diagnostic Method |
|--------------|------------|-----|-------------------------|-------------------|
| Adults and children | Adolescents and adults age 11 y and older presenting to GP with bothersome cough up to 30 days duration | Mean 44.3 y | 2011-2012 | PCR |
| Philipson et al,\textsuperscript{65} 2013 (New Zealand) | Children and adults age 5 to 49 y with cough for 2 weeks or longer | Range 5-49 y | 2011 | Serology |
| Riffelmann et al,\textsuperscript{66} 2006 (Germany) | Patients presenting to GP with at least 7 days cough | Not reported (all ages) | 2001-2004 | Serology or PCR |
| Children | Children with cough of 2-8 weeks duration presenting to GP | Mean 9.6 y | 2010-2012 | Serology |
| van den Brink et al,\textsuperscript{68} 2014 (Netherlands) | Children age 12 y and under with RTI referred for evaluation of suspected BP | Mean age 9.4 y, range 5-17 | 2001-2005 | PCR |
| Harnden et al,\textsuperscript{69} 2006 (England, United Kingdom) | Children age 5-16 y presenting to their GP with cough for at least 2 weeks | Mean age 6.2 y, range 0-15 y | 2001-2002 | Serology |
| Diez Domingo et al,\textsuperscript{70} 2004 (Spain) | Children age 15 y and under presenting with cough for at least 2 weeks | Mean age 44.3 y | 2011-2012 | Serology |
| Adults | Adults with acute cough <28 days duration presenting to GP | Mean age 50 y | 2007-2010 | Serology or PCR |

BP = *Bordetella pertussis*; GP = general practitioner; PCR = polymerase chain reaction.
Similarly, the annual incidence of acute bronchitis or non-pneumonia LRTI is approximately 440 episodes in 10,000 adults, and the annual incidence of *B. pertussis* based on surveillance is 1.5 of 10,000 persons. Our systematic review found that 18% of episodes of non-pneumonia LRTI in children and 9% of those in adults were caused by *B. pertussis*. Most of these studies limited inclusion to patients with a cough for at least 1 to 2 weeks, although 1 included adults and children with a shorter duration of cough and still found a prevalence of 7%. If one conservatively estimates based on these data that 3% of episodes of acute bronchitis or non-pneumonia LRTI are caused by *B. pertussis*, that corresponds to 13 episodes per 10,000. Again, these data suggest that there is widespread underdiagnosis of *B. pertussis* in the United States, with approximately 90% of episodes undiagnosed. This is important because family members and relatives are the source for 75% to 83% of pertussis cases in infants. Moreover, immunization with the pertussis vaccine wanes after five years. Current recommendations to vaccinate pregnant women with Tdap should be closely adhered to.

*C. pneumoniae* infection has traditionally been described as being more common in children. We found that the mean prevalence , however, was 4% in studies of adults with CAP compared with 1% in children.

Diagnosis of these infections could be improved in several ways. One is to make better use of the history

| Author, Year | Cough Duration | Cases | Total | Prevalence (95% CI) |
|--------------|----------------|-------|-------|---------------------|
| Adults       |                |       |       |                     |
| Teepe et al, 2015 | ≤28 days | 93    | 3,074 | 0.030 (0.024-0.036) |
| Subtotal     |               |       |       | 0.030 (0.024-0.036) |
| Adults and Children |           |       |       |                     |
| Park et al, 2014 | ≤30 days | 34    | 490   | 0.069 (0.047-0.092) |
| Riffelmann et al, 2006 | ≥7 days | 97    | 971   | 0.100 (0.081-0.119) |
| Philipson et al, 2013 | >14 days | 23    | 222   | 0.104 (0.064-0.144) |
| Subtotal     |               |       |       | 0.089 (0.067-0.112) |
| Children     |                |       |       |                     |
| van den Brink et al, 2014 | Not reported | 14    | 306   | 0.046 (0.022-0.069) |
| Diez Domingo et al, 2004 | >14 days | 5     | 57    | 0.088 (0.014-0.161) |
| Wang et al, 2014 | >14 days | 56    | 273   | 0.205 (0.157-0.253) |
| Harnden et al, 2006 | >14 days | 64    | 172   | 0.372 (0.300-0.444) |
| Subtotal     |               |       |       | 0.176 (0.034-0.318) |
| Random effects model for all studies |             |       |       | 0.124 (0.049-0.198) |

Heterogeneity (I²) = 98.83
and physical examination. The best evidence regarding diagnosis of each pathogen is summarized in Table 4. Data regarding diagnosis are quite limited, and only in the case of *L pneumophila* has an attempt been made to develop and validate a clinical decision rule that combines several signs and symptoms. In general, individual signs and symptoms are of little value in the diagnosis of these atypical pathogens. Another approach would be to integrate signs and symptoms with a point-of-care test such as c-reactive protein (CRP), as has been done for pneumonia and influenza diagnosis.

Greater use of urine antigen tests for *L pneumophila* should be encouraged for patients diagnosed with CAP, and the development of accurate, rapid point-of-care tests for *C pneumoniae* and *B pertussis* should be prioritized.

**Limitations**

As with any systematic review, our conclusions are limited by the quality of the published literature and the completeness and accuracy of reporting. We found considerable heterogeneity. For *M pneumoniae* this may be related to the cyclical nature of outbreaks, while for other pathogens the cause is less clear but may lie in the differences in the populations studied, varying laboratory techniques, and varying sample collection methods across countries. It is noteworthy that the majority of studies found similar prevalences, with the heterogeneity for *C pneumoniae* and *L pneumophila* introduced by a small number of outliers, and for *B pertussis* limited to studies in children only. We limited our analysis to studies that gathered data within the past 15 years in highly developed economies, so our findings may not be generalizable to low- or middle-income countries. Many patients with acute cough do not seek care.

### Table 4. Accuracy of Signs and Symptoms for Respiratory Infections With Atypical Pathogens

| Symptom or Sign (number of studies) | Sensitivity (95% CI) | Specificity (95% CI) | Positive LR (95% CI) | Negative LR (95% CI) |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| **Mycoplasma pneumoniae** |                      |                      |                      |                      |
| Cough (5)                           | 0.89 (0.67-0.97)     | 0.15 (0.05-0.37)     | 1.04 (0.95-1.13)     | 0.78 (0.44-1.39)     |
| Wheeze (6)                          | 0.25 (0.17-0.36)     | 0.67 (0.56-0.76)     | 0.76 (0.60-0.97)     | 1.12 (1.02-1.23)     |
| Coryza (4)                          | 0.32 (0.08-0.72)     | 0.66 (0.28-0.91)     | 0.95 (0.71-1.26)     | 1.03 (0.90-1.17)     |
| Crepitations (5)                    | 0.84 (0.78-0.88)     | 0.22 (0.14-0.32)     | 1.06 (0.96-1.18)     | 0.77 (0.52-1.12)     |
| Fever (5)                           | 0.53-0.94            | 0.02-0.43            |                      |                      |
| Rhonchi (4)                         | 0.11-0.74            | 0.33-0.81            |                      |                      |
| Chest pain (2)                      | 0.08-0.19            | 0.93-0.97            |                      |                      |
| Diarrhea (2)                        | 0.14-0.21            | 0.79-0.85            |                      |                      |

**Chlamydia pneumoniae**

| Adults |                      |                      |                      |                      |
|--------|-----------------------|----------------------|----------------------|----------------------|
| History of cough                        | 0.81                 |                      |                      |                      |
| History of sore throat                  | 0.52                 |                      |                      |                      |
| Abnormal breathing sounds               | 0.38                 |                      |                      |                      |
| History of fever                        | 0.24                 |                      |                      |                      |

**Children**

|        |                      |                      |                      |                      |
|--------|-----------------------|----------------------|----------------------|----------------------|
| Rales  | 0.85                  |                      |                      |                      |
| Fever  | 0.80                  |                      |                      |                      |
| Cough  | 0.50                  |                      |                      |                      |
| Rhinitis | 0.30                |                      |                      |                      |
| Tachypnea | 0.25            |                      |                      |                      |
| Wheezes | 0.20                 |                      |                      |                      |
| Rhonchi | 0.15                 |                      |                      |                      |

**Legionella pneumophila**

| aOR (95% CI)                          |                      |                      |                      |                      |
|---------------------------------------|-----------------------|----------------------|----------------------|----------------------|
| Creactive protein >187 mg, L          | 4.4 (2.0-9.6)         |                      |                      |                      |
| Sodium <133 mmo/L                     | 4.5 (2.2-9.0)         |                      |                      |                      |
| Temperature >39.4°C                    | 4.3 (1.9-9.8)         |                      |                      |                      |
| Platelet count <171 x 10^3 /mL        | 1.2 (0.6-2.5)         |                      |                      |                      |
| Lactate dehydrogenase >225 mmol/L     | 1.7 (0.4-7.6)         |                      |                      |                      |
| Dry cough                             | 0.6 (0.3-1.4)         |                      |                      |                      |

**Bordetella pertussis**

| aOR (95% CI)                          |                      |                      |                      |                      |
|---------------------------------------|-----------------------|----------------------|----------------------|----------------------|
| Paroxysmal cough                       | 1.1 (1.1-1.2)         | 0.52 (0.27-0.9)      |                      |                      |
| Posttussive emesis                    | 1.6 (1.4-2.2)         | 0.58 (0.44-0.77)     |                      |                      |
| Inspiratory whoop                     | 1.9 (1.4-2.6)         | 0.76 (0.66-0.93)     |                      |                      |

aOR = adjusted odds ratio from multivariate analysis; CAP = community-acquired pneumonia; LR = likelihood ratio.

a Cochrane systematic review of 7 moderate quality studies with a total of 1,491 children, although each sign and symptom was only reported by a subset of studies. Pooled results from 4 to 6 studies are shown for cough, wheeze, coryza, and crepitations; for the other signs and symptoms, a range or the results of a single study are shown.

b Data from a study of 21 adult primary care patients diagnosed with *Chlamydia pneumoniae* infection (7 primary infections and 14 with reinfection based on the antibody pattern).

c Data from a study of 20 children hospitalized for CAP and diagnosed with *Chlamydia pneumoniae*.

d Data from 37 patients hospitalized with CAP due to *Legionella pneumophila*. A clinical rule that included 6 variables had an area under the receiver operating curve of 0.73.

e Systematic review of 3 studies with a total of 486 adults and children set in South Korea, United Kingdom, and United States.
It is possible that those seeking care have a different (and perhaps more severe) illness and a different prevalence of these pathogens. Finally, the literature regarding the prevalence of pathogens in patients with non-pneumonia lower respiratory tract infection is quite limited, with no studies in the United States or Canada.

We have demonstrated that atypical bacterial pathogens are relatively common causes of CAP in a range of populations including both adults and children, and that B pertussis is a common cause of prolonged cough. We do not feel that broader use of antibiotics for patients with acute cough is warranted. What is needed are studies to help clinicians more accurately diagnose these pathogens or to help them identify a large group of patients at low risk for such pathogens who do not require further testing or antibiotic therapy. Approaches that develop clinical decision rules integrating signs, symptoms, and point-of-care tests such as CRP are particularly promising. Finally, research is needed to determine if and when antibiotics are helpful, since data regarding treatment of B pertussis and M pneumoniae from well designed, adequately powered contemporary clinical trials are lacking.

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**Key words:** community acquired pneumonia; cough; respiratory tract infection; Mycoplasma pneumoniae; Chlamydia pneumoniae; Legionella pneumophila; Bordetella pertussis

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