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.[1] 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).[2] 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*, *Chlamydophila 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.[3]

Conflicts of interest: authors report none.

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Mycoplasma pneumoniae infection is thought to vary cyclically,[4,5] and has been the cause of outbreaks of LRTI.[6] Not to be confused with *Chlamydia psittaci* (which also causes respiratory infections but is contracted from birds), *Chlamydophila 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,[7] while others have posited an association with development of asthma.[8,9] 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.[10] Recently, increased risk of infection with *L pneumophila* has also been linked to wet, humid weather.[11] *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.[3]

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.[12] 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.[13] 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.[14-16] 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

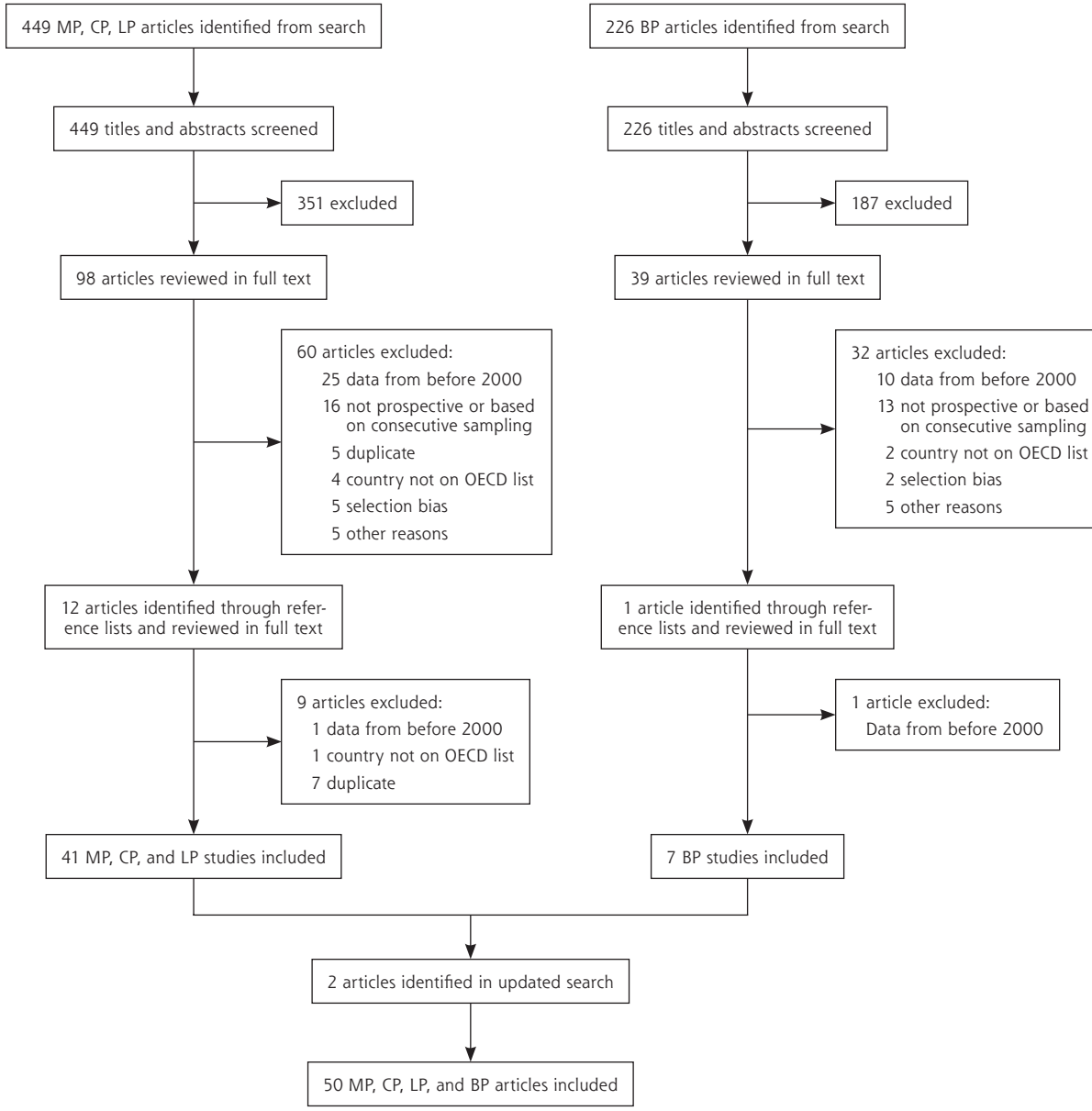
We identified 2 groups for the analysis: patients presenting with acute cough illness or lower respiratory tract symptoms and patients diagnosed with CAP. Where studies reported etiology separately for patients with CAP and those with non-pneumonia LRTI, we report these groups separately as well.

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

Figure 1. PRISMA diagram.



BP = *Bordetella pertussis*; CP = *Chlamydophila pneumoniae*; LP = *Legionella pneumophila*; MP = *Mycoplasma pneumonia;* OECD = Organization for Economic Cooperation and Development.

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[17,18] for a final of 50 included studies (Figure 1).

To compare the prevalences given in the identified studies with the prevalences from surveillance systems, we abstracted surveillance data for reported cases of *B pertussis* and *L pneumophila* in 2012. Data, which were available for 31 of the 32 high-income member countries of the OECD, are summarized in Table 1 (Israel did not provide any publicly accessible data.)

Table 1. Reported *Bordetella pertussis* and *Legionella pneumophila* Prevalence in 2012 by Case-Based Surveillance Systems of High-Income Countries Belonging to the OECD

Country[a]	BP Cases	LP Cases	Population[b]	BP Rate per 100,000	LP Rate per 100,000
Australia	24,069	382	22,918,688	105.0	1.67
Austria	425	101	8,428,915	5.0	1.20
Belgium	ND	106	10,787,788	ND	0.98
Canada	4,540	483	34,674,708	13.1	1.39
Chile	4,237	ND	17,423,214	24.3	ND
Czech Republic	707	56	10,565,678	6.7	0.53
Denmark	1,136	127	5,592,738	20.3	2.27
Estonia	149	3	1,339,762	11.1	0.22
Finland	541	10	5,402,627	10.0	0.19
France	ND	1,298	63,457,777	ND	2.05
Germany	ND	628	81,990,837	ND	0.33
Greece	40	27	11,418,878	0.35	0.77
Hungary	5	33	9,949,589	0.05	0.24
Iceland	36	2	328,290	11.0	0.61
Ireland	264	15	4,579,498	5.8	0.33
Italy	262	1,332	60,964,145	0.43	2.18
Japan	ND	903	126,434,653	ND	0.71
Korea, Rep.	126	25	48,588,326	0.26	0.05
Luxembourg	11	5	523,362	2.1	0.96
Netherlands	12,868	304	16,714,228	77.0	1.82
New Zealand	2,320	152	4,461,257	52.0	3.41
Norway	4,243	25	4,960,482	85.5	0.50
Poland[c]	1,824	8	38,317,090	4.8	0.02
Portugal	230	140	10,699,333	2.1	1.31
Slovak Republic	917	4	5,480,332	16.7	0.07
Slovenia	153	82	2,040,057	7.5	4.02
Spain	1,565	972	46,771,596	3.3	2.08
Sweden	279	12	9,495,392	2.9	0.13
Switzerland	ND	91	7,733,709	ND	1.18
United Kingdom	11,993	401	62,798,099	19.1	0.64
United States	48,277	3,688	315,791,284	15.3	1.17

BP = *Bordetella pertussis*; LP = *Legionella pneumophila*; ND = no data; OECD = Organisation for Economic Cooperation and Development.

[a] No data available for Israel.

[b] Population based on Gapminder 2012.[19]

[c] Poland used aggregated instead of case-based data.

Prevalence of *Mycoplasma pneumoniae*, *Chlamydophila pneumonia*, and *Legionella pneumophila*

A total of 30 studies reported the prevalence of *M pneumoniae*, *C pneumoniae*, or *L pneumophila* in adults,[18,20-48] and 10 studies reported the prevalence of these pathogens in children[49-58] (Table 2). Only 2 studies were set in the United States.[18,53]

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.[62,63]

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[a]	Setting	Age	Pathogen	Data Collection Period	Diagnostic Method
CAP in Adults							
Jain et al,[18] 2015[b] (United States)	Adults ≥18 y with CAP	2,320/853	Inpatient	Median 57 y,	MP, CP, LP	2010-2012	PCR, Culture, UA
Angeles et al,[20] 2006 (Spain)	Adults ≥15 y with CAP	198/112	Inpatient	Median 70 y	MP, CP, LP	2003-2004	Serology, UA
Beović et al,[21] 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,[22] 2008 (Australia)	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,[23] 2012 (Spain)	Adults ≥16 y with CAP	568/188	Outpatient	Mean 47.2 y	MP, CP, LP	2000-2010	Serology, UA
Diaz et al,[24] 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,[25] 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,[26] 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,[27] 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	1999-2001	Serology, UA
Herrera-Lara et al,[28] 2013 (Spain)	Adults ≥18 y with CAP	243/139	Inpatient	Mean 63.9 y	MP, CP, LP	2006-2009	Serology, UA
Holm et al,[29] 2007[b] (Denmark)	Adults ≥18 y with CAP	48/21	9 Inpatient, 39 outpatient	Mean 61 y, range 22 y-88 y	MP, CP, LP	2002-2003	PCR
Huijskens et al,[30] 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
Johansson et al,[31] 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,[32] 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,[33] 2013 (Chile)	Adults ≥18 y with CAP	356/232	330 Inpatient, 26 outpatient	Mean 59.3 y[c]	MP, CP, LP	2005-2007	Serology, PCR, UA
Marrie et al,[34] 2005 (Canada)	Adults ≥18 y with CAP	507/245	Outpatient	Mean 47.8 y	MP, CP	2003	Serology
Miyashita et al,[35] 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,[36] 2009 (Spain)	Patients with CAP[d]	710/274	Inpatient	Mean 67.1 y	MP, CP, LP	2003-2004	Serology, UA
Prat et al,[37] 2006 (Spain)	Patients with CAP[d]	217/116	Inpatient	Mean 56.6 y	LP	2005-2005	UA
Saito et al,[38] 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,[39] 2012 (Spain)	Adults ≥18 y with CAP	131/92	Inpatient	Mean 64.4 y, range 48 y-80	MP, CP, LP	2009-2010	Serology, PCR, UA
Shibli et al,[40] 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
Stralin et al,[41] 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,[42] 2005 (Netherlands)	Adults ≥18 y with CAP	105/80	92 inpatient, 13 outpatient	NR	MP, CP, LP	2000-2002	PCR
van de Garde et al,[43] 2008 (Netherlands)	Patients with CAP[d]	201/128	Inpatient	Mean 63 y	MP, LP	2004-2006	PCR
von Baum et al,[44] 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,[45] 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

continues

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.

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

[b] Study findings reported separately for patients with CAP and those with non-pneumonic LRTI.

[c] Estimated from median using method of Hozo.[61]

[d] 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 (Country)	Population	Total / Confirmed Cases[a]	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[a] (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] 2013 (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[e] (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[b] (Japan)	Children <15 y with CAP	398/383	362 Inpatient, 36 outpatient	NR	MP, CP	2000-2001	Serology, PCR
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[f] (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[b] (Japan)	Children <15 y with non-pneumonia LRTI	523/470	436 Inpatient, 87 outpatient	NR	MP, CP	2000-2001	Serology, PCR
Holm et al,[29] 2007[b] (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,[60] 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.

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

[b] Study findings reported separately for patients with CAP and those with non-pneumonic LRTI.

[c] Estimated from median using method of Hozo.[61]

[d] Age not reported but presumably adult based on hospital and mean age.

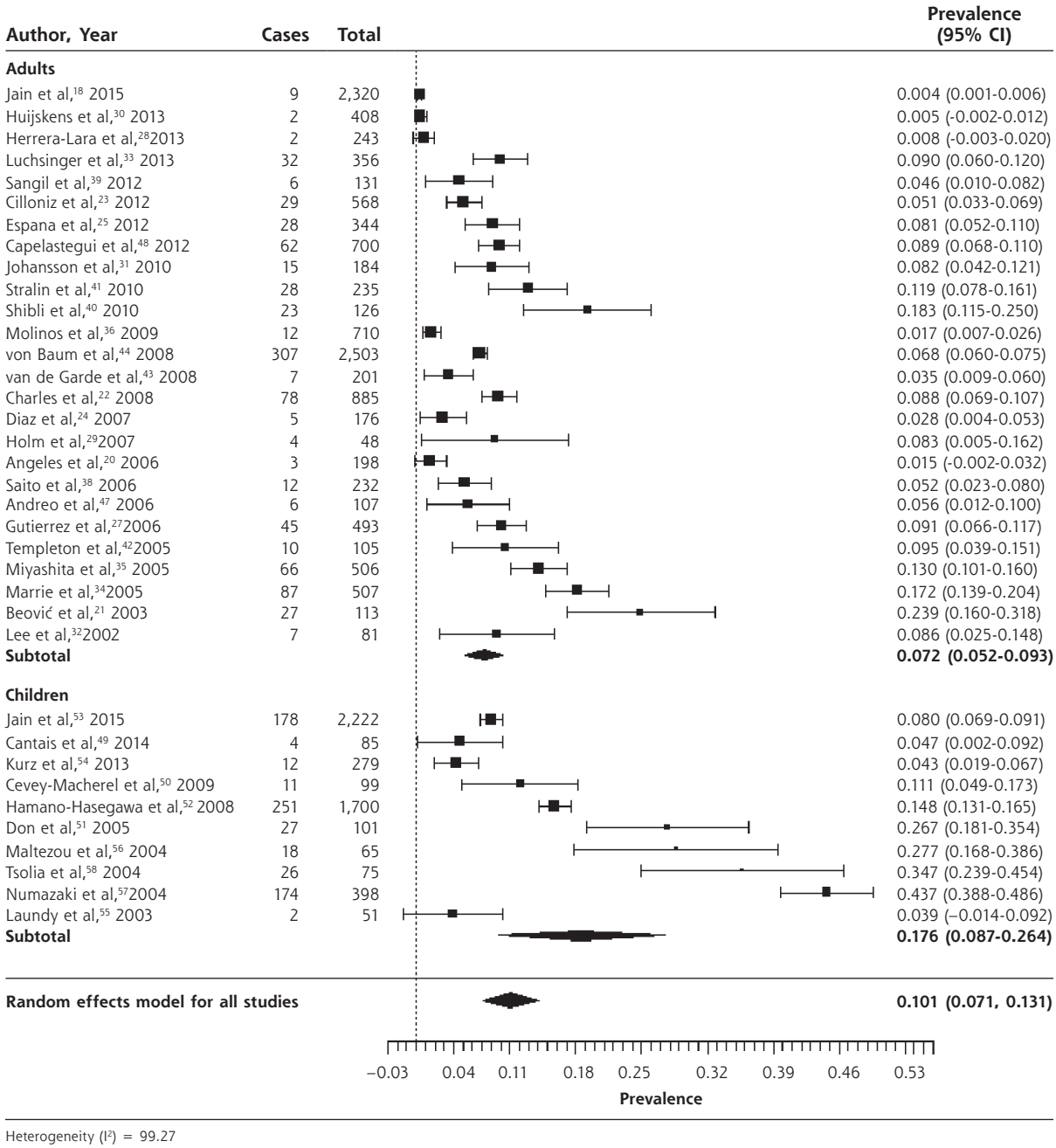
[e] Classified as study of CAP if at least 85% of patients in the series were diagnosed with CAP.

[f] 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.[52,56] 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,[27,28,36,37] and a fifth, a study that also reported the highest prevalence of *C pneumoniae*, was set in another Mediterranean country, Israel.[40] The largest series, set in Germany, found *L pneumophila* in 3.7% of patients treated in ambulatory care and 3.8% of inpatients.[44] Clearly, it is not only found in severely ill patients.

Figure 2. Forest plot of the prevalence of *Mycoplasma pneumoniae* in adults and children with community-acquired pneumonia, sorted in reverse chronological order.



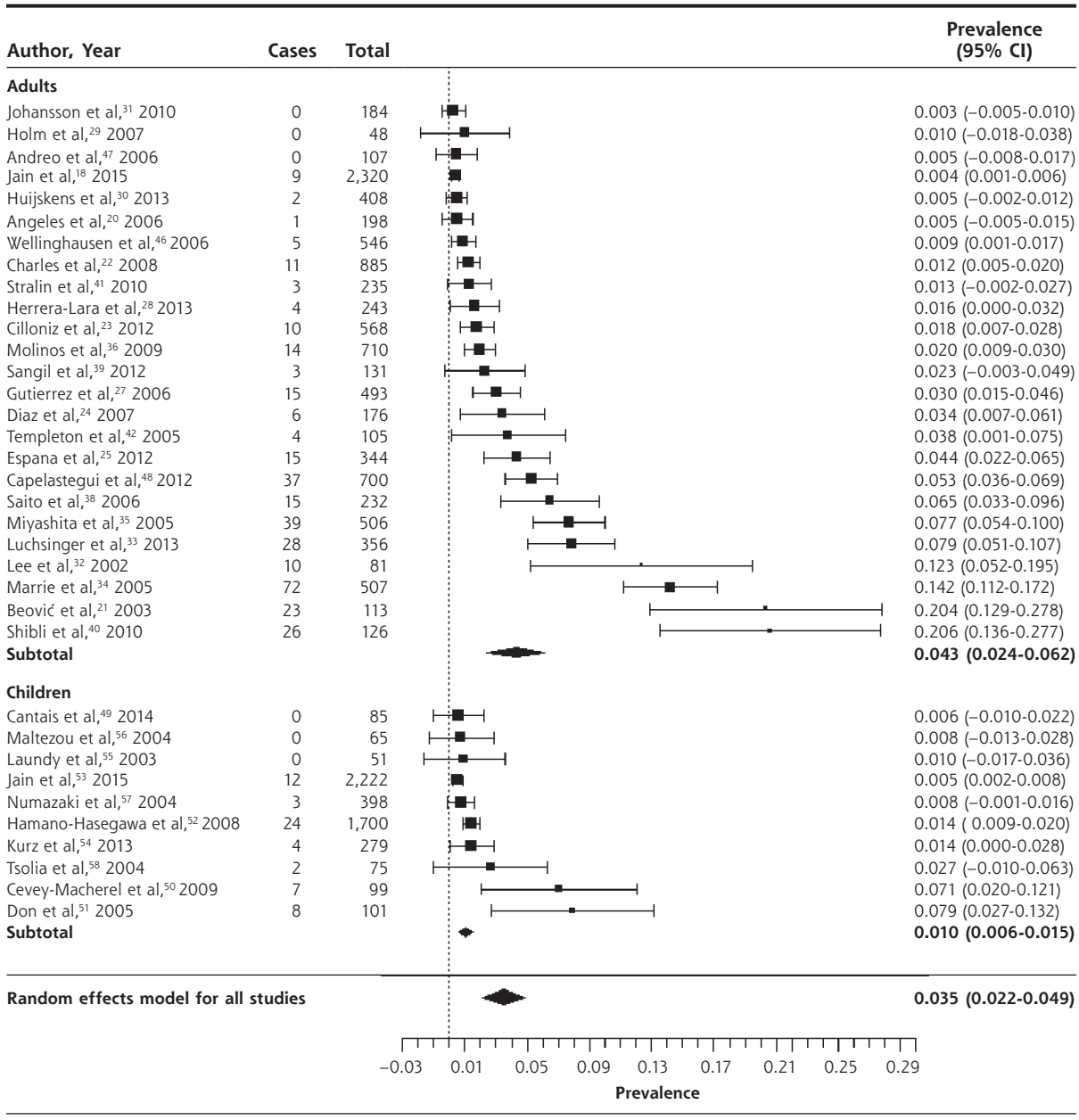
Patients With Non-Pneumonia LRTI

Two studies reported the prevalence of atypical pathogens in patients with LRTI in whom pneumonia had been excluded by normal chest radiography,[29,57] and a third enrolled predominantly patients with non-pneumonia LRTI.[59] The prevalence of *M pneumoniae* was 7/316 (2.2%), 13/129 (10.0%),and 78/523 (14.9%) in these 3 studies,[29,57,59] while the prevalence of *C pneumoniae* was 2/316 (0.6%) in 1 study[29] and 3/523 (0.6%) in a second.[57] A single study found no cases of *L pneumophila* in a primary care series of 316 adults with non-pneumonia LRTI.[29] A fourth study did not provide adequate information to differentiate the number of children with acute bronchitis, pneumonia, or bronchiolitis.[60]

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.[17,64-70] Three studies enrolled adults and children; 4, children only;

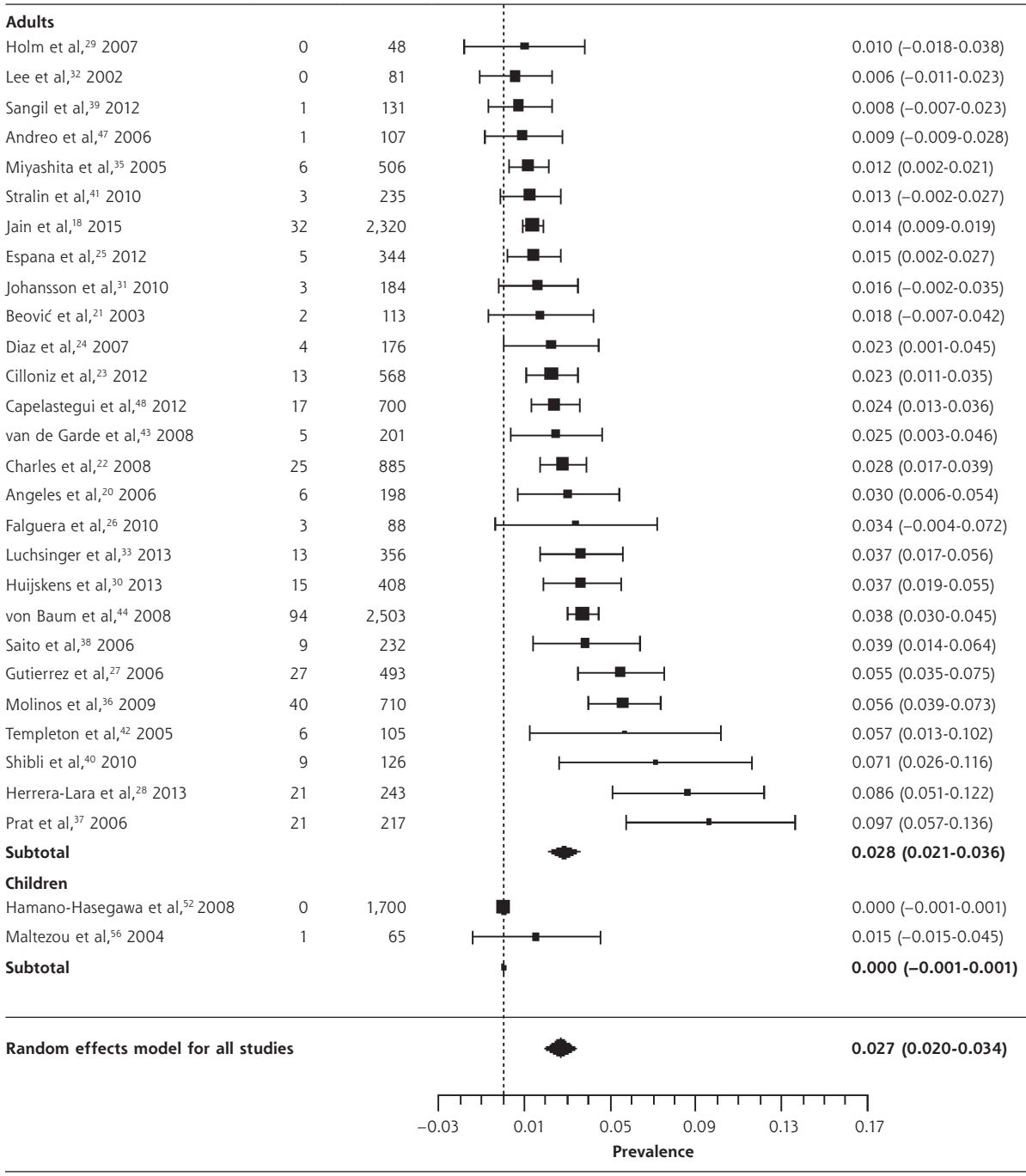
Figure 3. Forest plot of the prevalence of *Chlamydia pneumoniae* in adults and children with community-acquired pneumonia, sorted by prevalence.



Heterogeneity (I^2) = 98.4

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.[68] 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.



Heterogeneity (I^2) = 91.18

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				
Park et al,[64] 2014 (South Korea)	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,[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,[66] 2006 (Germany)	Patients presenting to GP with at least 7 days cough	Not reported (all ages)	2001-2004	Serology or PCR
Children				
Wang et al,[67] 2014 (United Kingdom)	Children with cough of 2-8 weeks duration presenting to GP	Mean 9.6 y	2010-2012	Serology
van den Brink et al,[68] 2014 (Netherlands)	Children age 12 y and under with RTI referred for evaluation of suspected BP	<12 y	2007-2009	PCR
Harnden et al,[69] 2006 (England, United Kingdom)	Children 5-16 y presenting to their GP with cough for at least 2 weeks	Mean age 9.4 y, range 5-17	2001-2005	Serology
Diez Domingo et al,[70] 2004 (Spain)	Children age 15 y and under presenting with cough for at least 2 weeks	Mean 6.2 y, range 0-15 y	2001-2002	Serology
Adults				
Teepe et al,[17] 2015 (12 European countries)	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.

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,[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%.[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 30 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 *Chlamydophila pneumoniae*, and 3% had *Legionella pneumophila*. Among children with CAP, 18% had *Mycoplasma pneumoniae*, only 1% had *Chlamydophila 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

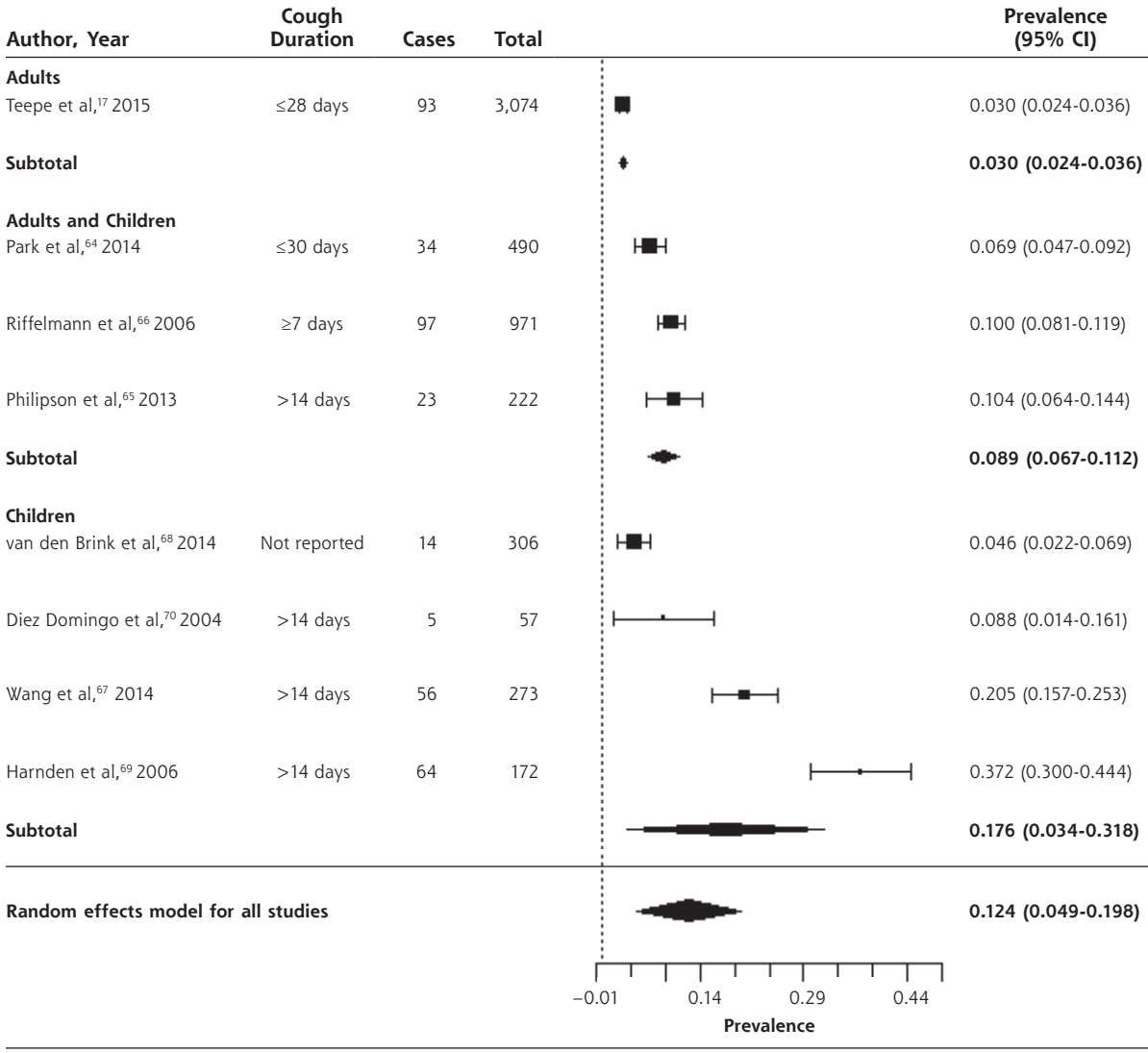
CAP is diagnosed in an estimated 5.6 million patients annually in the United States, and 1.1 million hospitalizations result.[71,72] Laboratory-based surveillance, however, identifies only 3,700 infections caused by *L pneumophila* each year, or 0.06% of all community-acquired pneumonias. Our systematic 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,[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.[73,74]

Similarly, the annual incidence of acute bronchitis or non-pneumonia LRTI is approximately 440 episodes in 10,000 adults,[75] 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%.[64] 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.[76,77] Moreover, immunization with the pertussis vaccine wanes after five years.[78-80] 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

Figure 5. Forest plot of the prevalence of *Bordetella pertussis* in outpatients with prolonged cough or non-pneumonia lower respiratory tract infection, sorted by prevalence.



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.[84] 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.[86,87] 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.

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[a]				
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		
Chlamydophila pneumoniae				
Adults[b]				
History of cough	0.81			
History of sore throat	0.52			
Abnormal breathing sounds	0.38			
History of fever	0.24			
Children[c]				
Rales	0.85			
Fever	0.80			
Cough	0.50			
Rhinitis	0.30			
Tachypnea	0.25			
Wheezes	0.20			
Rhonchi	0.15			
Legionella pneumophila[d]	aOR (95% CI)			
C-reactive 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[e]				
Paroxysmal cough			1.1 (1.1-1.2)	0.52 (0.27-.0)
Posttussive emesis			1.8 (1.4-2.2)	0.58 (0.44-0.77)
Inspiratory whoop			1.9 (1.4-2.6)	0.78 (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.[81]

[b] Data from a study of 21 adult primary care patients diagnosed with *Chlamydophila pneumoniae* infection (7 primary infections and 14 with reinfection based on the antibody pattern).[82]

[c] Data from a study of 20 children hospitalized for CAP and diagnosed with *Chlamydophila pneumoniae*.[83]

[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.[84]

[e] Systematic review of 3 studies with a total of 486 adults and children set in South Korea, United Kingdom, and United States.[85]

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 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.

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.[88] 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; Chlamydophila pneumoniae; Legionella pneumophila; Bordetella pertussis*

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