Evolving Understanding of the Causes of Pneumonia in Adults, With Special Attention to the Role of Pneumococcus

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Before 1945, *Streptococcus pneumoniae* caused more than 90% of cases of pneumonia in adults. After 1950, the proportion of pneumonia caused by pneumococcus began to decline. Pneumococcus has continued to decline; at present, this organism is identified in fewer than fewer10%–15% of cases. This proportion is higher in Europe, a finding likely related to differences in vaccination practices and smoking. Gram-negative bacilli, *Staphylococcus aureus*, *Chlamydia*, *Mycoplasma*, and *Legionella* are each identified in 2%–5% of patients with pneumonia who require hospitalization. Viruses are found in 25% of patients, up to one-third of these have bacterial coinfection. Recent studies fail to identify a causative organism in more than 50% of cases, which remains the most important challenge to understanding lower respiratory infection. Our findings have important implications for antibiotic stewardship and should be considered as new policies for empiric pneumonia management are developed.

    Keywords. community-acquired pneumonia; *Streptococcus pneumoniae*; pneumococcus; etiology; antibiotic stewardship.

Pneumonia, at first called "the special enemy of old age" [1] by Osler and later, by a more mature Osler, "the friend of the aged" [2], has long been with humankind and shows little likelihood of going away. In the preantibiotic era, *Streptococcus pneumoniae* was the overwhelmingly predominant cause of pneumonia, but this is clearly no longer the case. Despite its prevalence and importance—pneumonia affects about 2% of all elderly persons each year [3]—and despite newly available techniques for diagnosis, at the present time and in the majority of cases, the causative organism(s) remain(s) uncertain.

How does such an evolution occur? For recognized or unrecognized reasons, there may be changes in the actual incidence of a disease. Rheumatic fever began to decline in the late 1920s, well before the introduction of antibiotics, and auxotrophic strains of *Neisseria gonorrhoeae* that made acute arthritis an everyday occurrence in public hospitals in the early 1980s have largely disappeared. Newly discovered organisms may cause disease, and new diagnostic techniques may increase recognition of already-identified diseases. Raised awareness of a condition may lead to more diagnostic testing and increased documentation.

Here, we document the declining role of *S. pneumoniae* and the increasing recognition of other pathogens in the etiology of community acquired pneumonia (CAP) in adults.

LITERATURE ANALYSIS

A PubMed search of the English-language literature through December 2015 was performed using the following search term: (pneumonia[title]) AND (etiolog* OR aetiolog* OR cause OR microbiolog* OR "Streptococcus pneumoniae"[Mesh] OR bacteria OR culture*) NOT (children OR infant* OR pediatric* OR randomized OR nosocomial[title] OR organizing[title] OR interstitial[title] OR healthcare[title] OR ventilator[title] OR Case Reports[ptyp]). The references of included studies were also searched for candidate articles. We included studies that applied validated pneumococcal tests to ≥50% of patients. The following were considered evidence of pneumococcal infection: *S. pneumoniae* cultured from a sterile site or from a lower respiratory tract specimen (ie, not a nasopharyngeal specimen), including recovery after mouse intraperitoneal inoculation; pneumococcal antigen detection in urine; and polymerase chain reaction (PCR) testing of pleural fluid. Studies that focused on a specific population (eg, the elderly or immunocompromised) were excluded. See Supplementary Material for details. We identified 31 studies (21 120 patients) from the United States and Canada published between 1917 and 2015 and 37 studies (21 166 patients) from Europe. We included all publications that met our inclusion criteria [4–71] (Table 1).

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Table 1. Frequency of *Streptococcus pneumoniae* in Community-Acquired Pneumonia in Included Studies

Study	Location	Year(s) of Study	No. of Patients[a]	Pneumococcal Community-Acquired Pneumonia	
				n	%
United States/Canada					
Avery 1917 [4]	United States	NR	529	454	85.8
Cecil 1922 [5]	United States	1920	1000	834	83.4
Sutliff 1933 [6]	United States	NR	1067	996	93.3
Bullowa 1937 [7]	United States	1928–1936	4416	3591	81.3
Cecil 1938 [8]	United States	1928–1938	560	531	94.8
Warner 1945 [9]	United States	1943–1944	150	139	92.7
Warner 1948 [10]	United States	1944–1946	202	172	85.1
Dowling 1948 [11]	United States	NR	2500	2453	98.1
Tillotson 1969 [12]	United States	1967	149	84	56.4
Fiala 1969 [13]	United States	1966–1967	193	107	55.4
Fekety 1971 [14]	United States	1965–1966	100	62	62.0
Dorff 1973 [15]	United States	1969–1970	148	79	53.4
Moore 1977 [16]	United States	1971–1972	154	65	42.2
Oseasohn 1978 [17]	United States	1971–1972	187	171	91.4
		1972–1973			
Miller 1978 [18]	United States	1975	54	26	48.1
Ebright 1980 [19]	United States	1973	106	38	35.8
Boerner 1982 [20]	United States	NR	89	32	36.0
Dans 1984 [21]	United States	1979–1980	147	51	34.7
Marrie 1985 [22]	Canada	1981–1982	138	13	9.4
Larsen 1984 [23]	United States	1981–1982	217	52	24.0
Fang 1990 [24]	United States	1986–1987	359	55	15.3
Farr 1991 [25]	United States	1984–1986	245	45	18.4
Bates 1992 [26]	United States	1985	154	9	5.8
Mundy 1995 [27]	United States	1990	205	31	15.1
Marston 1997 [28]	United States	1991	2776	351	12.6
Fine 1999 [29]	United States, Canada	1991–1994	1551	158	10.2
Park 2001 [30]	United States	1994–1996	389	46	11.8
Yang 2005 [31]	United States	2001–2003	131	30	22.9
Restrepo 2008 [32]	United States	1999–2002	730	60	8.2
Musher 2013 [33]	United States	2011–2012	215	19	8.8
Jain 2015 [34]	United States	2010–2012	2259	115	5.1
Europe					
Hug 2001 [35]	Switzerland	1998–1998	293	30	10.2
Garbino 2002 [36]	Switzerland	1997–1999	318	40	12.6
Genne 2006 [37]	Switzerland	1999–2000	67	25	37.3
Piso 2012 [38]	Switzerland	2007–2008	139	39	28.1
Stralin 2010 [39]	Sweden	1999–2002	235	74	31.5
Johansson 2010 [40]	Sweden	2004–2005	184	53	28.8
Pareja 1992 [41]	Spain	NR	165	12	7.3
Almirall 1993 [42]	Spain	1990–1991	105	13	12.4
Lorente 2000 [43]	Spain	1996–1998	110	40	36.4
Almirall 2000 [44]	Spain	1993–1995	232	27	11.6
Gutierrez 2005 [45]	Spain	1999–2001	493	101	20.5
Andreo 2006 [46]	Spain	2000	107	35	32.7
Briones 2006 [47]	Spain	2000–2004	959	290	30.2
Fernandez Alvarez 2007 [48]	Spain	1995–1998	258	14	5.4
		2003–2006	229	17	7.4
		1999–2002	268	11	4.1
Falguera 2009 [49]	Spain	1995–2005	3272	972	29.7
Cilloniz 2011 [50]	Spain	1996–2008	3523	613	17.4
Sorde 2011 [51]	Spain	2007–2008	474	177	37.3
Capelastegui 2012 [52]	Spain	2006–2007	700	170	24.3
Viasus 2013 [53]	Spain	2010–2011	747	118	15.8
Tudose 2010 [54]	Romania	2008–2010	120	11	9.2
Roysted 2016 [55]	Norway	2007–2008	374	75	20.1
Boersma 1991 [56]	Netherlands	1987–1989	87	34	39.1
Bohte 1995 [57]	Netherlands	1991–1993	334	90	26.9
Endeman 2008 [58]	Netherlands	2004–2006	201	60	29.9
Huijts 2014 [59]	Netherlands	2008–2009	1057	332	31.4
Ruf 1989 [60]	Germany	1984–1985	442	68	15.4
Kothe 2008 [61]	Germany	2003–2005	2647	130	4.9
Levy 1988 [62]	France	1983–1984	116	30	25.9
Lehtomaki 1988 [63]	Finland	1983–1984	106	26	24.5
Hohenthal 2008 [64]	Finland	1999–2004	384	107	27.9
Leesik 2006 [65]	Estonia	1996–1998	439	54	12.3
White 1981 [66]	England	1974–1980	210	24	11.4
Bewick 2012 [67]	England	2008–2010	920	366	39.8
Ostergaard 1993 [68]	Denmark	NR	254	39	15.4
Marekovic 2008 [69]	Croatia	NR	80	23	28.8
Blasi 1993 [70]	Italy	1991–1992	108	10	9.3
Logroscino 1999 [71]	Italy	1994–1996	409	36	8.8

Abbreviation: NR, not reported.

[a]See Supplementary Material for details on inclusion criteria.

PREANTIBIOTIC ERA

In the preantibiotic era, *S. pneumoniae* caused approximately 90% of all cases of pneumonia [4, 72–74] (Figure 1A). *Streptococcus pyogenes, Klebsiella, Haemophilus influenzae*, and *Staphylococcus aureus* were identified in the remaining cases; in fewer than 5%, no bacterial cause could be found. In the preantibiotic era, no antibiotic would have interfered with a bacteriologic diagnosis, and, compared to current practice, clinicians made greater efforts to obtain sputum samples for culture. Of course, pneumonia due to influenza virus had been recognized for quite some time [75]. Modern studies of patients who died in the 1918 influenza epidemic suggest that most of those deaths were, in fact, associated with secondary bacterial infection [76]. Outbreaks of pneumonia, thought to be viral and later identified as adenoviral [77], occurred in young adults, especially in military settings where crowding and physical and mental exhaustion were prevalent.

In the late 1930s, a pneumonia that behaved differently from pneumococcal pneumonia was attributed to an "atypical agent" [78, 79], subsequently called Eaton agent [80, 81] and eventually identified as *Mycoplasma pneumoniae* [82]. Recognized cases,
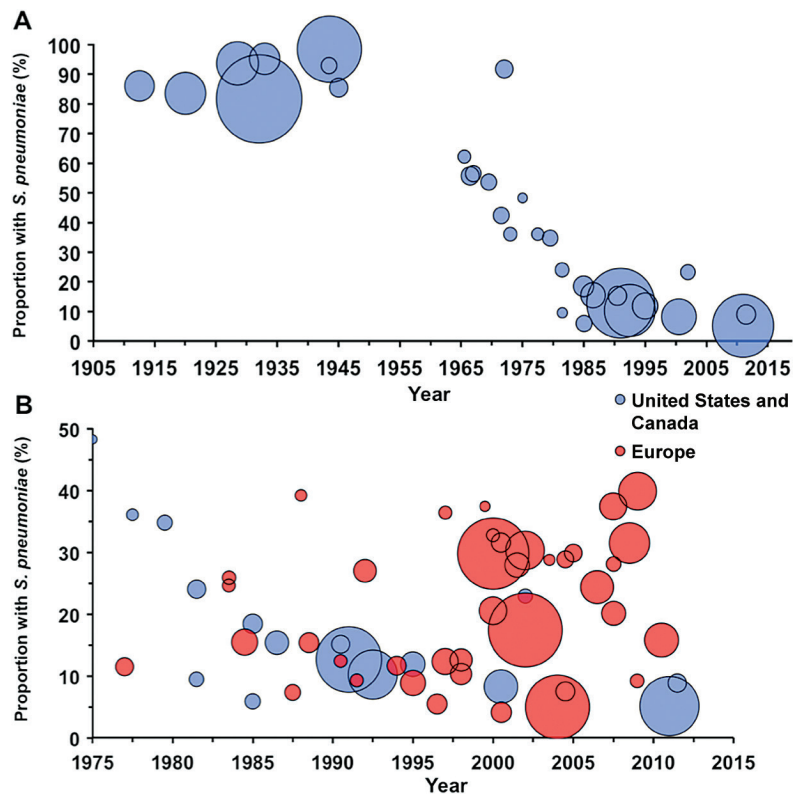
Figure 1. *A*, Frequency of *Streptococcus pneumoniae* as a cause of community-acquired pneumonia, United States/Canada. *B*, Comparison of the frequency of *S. pneumoniae* between the United States/Canada (blue) and Europe (red). The area of each circle is proportional to the number of patients in each study. For both figures, the year is the reported (or estimated) midyear of investigation (see Supplementary Material for details).

documented by culture, nearly always occurred in children, teenagers, and young adults (eg, military recruits [80]). Older adults were largely unaffected [83, 84], an observation that later came to be overlooked when diagnosis began to rely on serologic techniques. As a result, *Mycoplasma* pneumonia came to be greatly overdiagnosed. During World War II, an Armed Forces Commission, established to investigate outbreaks of pneumonia in military forces, identified the following 4 kinds of pneumonia: pneumococcal, mycoplasmal, influenzal, and acute respiratory disease of recruits, later shown to be adenoviral [85]. Nevertheless, pneumococcus was still regarded as the principal cause. In fact, through its 12th (1967) edition, the *Cecil-Loeb Textbook of Medicine* covered the subject of pneumonia under the rubric "Bacterial diseases: pneumococcal pneumonia" [86]. Although other causes were cited, "pneumococcal pneumonia … [remained] the most important of all pneumonias, not only in numerical terms, but because … [it was] the prototype of all the bacterial pneumonias" [86].

EARLY ANTIBIOTIC ERA THROUGH 1990

Pneumococcus

Our literature search revealed no pneumonia studies reporting the etiologic spectrum from 1947 through 1964. In 1965–1966, a report from Johns Hopkins Hospital [14] implicated

pneumococcus in 62% of cases. No cause was found in 34%, and no case was attributed to *H. influenzae,* but chocolate agar was not used routinely to culture sputum until the 1970s. In 1971–1972, at the same hospital [16], an "aggressive" approach to diagnosis identified pneumococcus in 30% of cases. *Haemophilus influenzae* was cultured from sputum in 29%. However, because only 1 patient was bacteremic, the authors stated that the "others can not critically be called *Haemophilus* pneumonia." By 1979–1980 and 1990–1991, reports from Johns Hopkins Hospital implicated pneumococcus in 35% [21] and 15% [27] of cases, respectively.

Anaerobic Flora

In the 1970s attention was directed toward anaerobic flora of the mouth and upper respiratory tract as a potential cause of pneumonia. In 1898 Veillon implicated anaerobic bacteria in lung infection [87]; their importance as the most common agents in lung abscess was subsequently emphasized by Smith [88] and confirmed by Cohen [89]. Further development of anaerobic bacteriology by Bartlett, Gorbach, and Finegold [90], together with the use of transtracheal aspiration, showed the importance of these organisms as a cause of pneumonia, especially in patients whose lifestyle suggested aspiration and who presented with a subacute syndrome of respiratory

infection characterized by putrid sputum, lung abscess, and/or empyema.

Normal Respiratory Flora

Some adults who present with acute bacterial pneumonia were also shown to be infected by normal facultative or anaerobic organisms [90–98]. More recent reports on the etiology of pneumonia fail to mention these organisms, probably reflecting the failure to use transtracheal aspiration and/or anaerobic microbiology. Microscopic examination of good-quality sputum from patients with pneumonia may show large numbers of gram-positive cocci together with other organisms. Such findings suggest that so-called normal respiratory flora, including the *Streptococcus anginosus* group, *Streptococcus mitis,* and/or mixed respiratory flora, may cause a substantial proportion of cases of pneumonia when no recognized respiratory pathogen is identified.

Legionella

An outbreak of pneumonia in 1977 [99] led to identification of *Legionella* [100]. Implication of *Legionella* in other outbreaks [101] was soon followed by recognition of this organism as a cause of sporadic pneumonia, both in hospitals [102] and in the community [103, 104]. The relation to water sources [105, 106] and the association with geographical locations [104] was also documented.

Haemophilus influenzae

In 1983, Musher et al [107] showed that *H. influenzae* commonly caused pneumonia in older men, identifying 30 cases at a single hospital in a 2-year period. *Haemophilus* from 26 of these patients was nontypable; only 1 of these had associated bacteremia. Four patients had *H. influenzae* type b in their sputum, of whom 3 were bacteremic.

Chlamydia

In 1986, Grayston et al identified *Chlamydia pneumoniae* as an important cause of pneumonia in university students [108, 109]. As with *Mycoplasma*, this organism was not found commonly in older adults with pneumonia, raising question about more recent studies that have used only serologic techniques to implicate it as a common cause of pneumonia in hospitalized adults.

Viruses

During the 1980s, viral cultures of respiratory secretions increasingly documented a causative role for respiratory viruses in pneumonia. The potential importance of parainfluenza [14] and respiratory syncytial viruses [110] in adults was recognized; rhinovirus, coronavirus [111], and human metapneumovirus [112] were added later. Thus, by the end of the 1980s, most microorganisms that are currently known to cause CAP had been identified.

A landmark prospective study of CAP patients admitted to a private hospital, a university hospital, and a veterans' hospital in Pittsburgh in 1986–1987 [24] used classic bacteriologic techniques and identified pneumococcus in only 15% of cases, followed by *Haemophilus* in 11%. Serologic studies were positive for *Mycoplasma* or *Chlamydia* in 8%. *Legionella* was detected by antibody rise, immunofluorescence, and/or culture in 7%. Viruses were not sought. No cause was found in one-third of cases. The authors emphasized the decline of pneumococcus as a cause of pneumonia in the antibiotic era.

ANTIBIOTIC ERA WITH NEW TECHNIQUES, 1990–2010

After 2000, new techniques greatly increased the ability to identify respiratory pathogens. Tests to detect antigens of *S. pneumoniae* and *Legionella* in urine reliably increased recognition of the role played by these agents [67, 113–117]. Detection of capsular polysaccharides [118] or other pneumococcal constituents such as DNA that encode *lyt*A in sputum or nasal secretions [119] appeared to increase the diagnostic yield. However, these and other nonstandardized techniques may also lead to overdiagnosis [120], and further validation is required before they can be used in diagnosis. There is, however, little question that the availability of PCR has revolutionized our understanding of the role of respiratory viruses in pneumonia in adults.

More recent studies in the United States, that were designed to select a convenience sample of patients or to include patients in a pharmaceutical study (but not a complete evaluation of successive admissions), detected pneumococcus in 10%–14% of adults hospitalized for CAP [121, 122] (Figure 1A). During the same period, a greater proportion of cases have been attributed to pneumococcus in Europe than in the United States (Table 2). Lim et al [123] reported an etiologic agent in 75% of cases, including pneumococcus in 48% and "atypical organisms," principally *Chlamydia* and *Mycoplasma,* in 18%. Nearly one-third

Table 2. Etiology of Community-Acquired Pneumonia in Europe, 2001–2010

Pathogen	Percentage of Patients		
	England[a] [123]	Sweden[b] [40]	Netherlands[c] [126]
Streptococcus pneumoniae	48	38	37
Haemophilus	7	11	0
Staphylococcus aureus	1	1	1
Gram-negative rods	1	1	4
Legionella	3	1	4
Mycoplasma or *Chlamydia*	18	8	7
Virus	18	29	5
No pathogen	25	11	44

[a]Standard microbiology, urine pneumococcal antigen (UAg), and serologic tests for pneumococcus and "atypical" organisms.

[b]Standard microbiology, UAg, polymerase chain reaction on nasopharyngeal swabs and sputum.

[c]Standard microbiology, UAg, serology for "atypical" organisms.

of pneumococcal diagnoses were made serologically by rises in antibody to various pneumococcal constituents or by counter-immunoelectrophoresis (CIE) to detect capsular polysaccharides in sputum. However, these serologic tests have not been validated, and CIE is regularly positive in sputum that does not contain pneumococci (D. Musher and C. Stager, unpublished). If these serologic results are excluded, pneumococcus was found in 34% of cases. Diagnoses of *Chlamydia* and *Mycoplasma* were only made serologically. Interestingly, an earlier study by these same investigators [124] in which no special serologic techniques were used identified an etiologic agent in 54% of cases, with pneumococcus in 30%, *Haemophilus* in 8%, and "atypical organisms" in 1%. European investigators [125, 126] used only traditional microbiology and detection of pneumococcal cell wall antigen in urine to implicate *S. pneumoniae* in 37%–38% of cases of CAP.

Our present study shows a marked decline in the frequency with which pneumococcus causes pneumonia in the United States/Canada but no such decline in Europe (Figure 1B). An important limitation of our findings is between-study heterogeneity in patient population, severity of illness, microbiologic tests performed, and the thoroughness of diagnostic testing. We attempted to minimize the latter 2 factors by including only studies that performed pneumococcal testing in a significant proportion of cases. For studies that provided sufficiently granular data, we calculated the frequency of pneumococcal pneumonia by limiting the denominator to only those patients who underwent such testing. Also, we chose a case definition of pneumococcal pneumonia that emphasizes validated microbiologic tests that have been in clinical practice for decades. While an in-depth qualitative analysis is beyond the scope of this article, we provide preliminary evidence to suggest differences between the United States/Canada and Europe with respect to the relative frequency of pneumococcus as a cause of pneumonia.

Factors that contribute to this difference might include the widespread use of pneumococcal polysaccharide vaccine [127] and the decreased rate of cigarette smoking among adults in the United States [128]. The nearly universal administration of pneumococcal conjugate vaccine to US children beginning in 2000 further explains the decline [3]. In Europe and other parts of the world where pneumococcal vaccines have been recommended for routine use for adults and where the incidence of cigarette smoking remains high, pneumococcus remains responsible for a higher proportion of cases of CAP (Figure 1B) [40, 123, 126, 129–131]. Reliance on serologic techniques has probably led to overdiagnosis of *Mycoplasma* and *Chlamydia* [132]. As noted above, earlier studies that used culture for diagnosis suggested that these organisms only occasionally infect older adults. These findings have important implications for comparing results of CAP studies or following guidelines for management written on either side of the Atlantic.

STUDIES AFTER 2010

An intensive investigation of the causes of pneumonia included all patients hospitalized for pneumonia at a Veterans Affairs (VA) medical center from July 5, 2011 to June 30, 2012 [33]. Blood culture, urine pneumococcal and *Legionella* antigen, PCR for 15 respiratory viruses (but not *Mycoplasma* or *Chlamydia*), and serum procalcitonin were each performed in more than 95% of cases. Sputum was studied in 70%. Of 259 patients admitted from the emergency department with CAP, 44 (17%) were thought to be uninfected, an observation with important implications for reconciling quality improvement measures that relate to promptness of antibiotic therapy. Of the remaining 215 patients (Table 3), 29% had documented bacterial infection; *S. pneumoniae* was detected in only 9% of the 215 patients. PCR identified a respiratory virus in 23%. Bacterial and viral coinfection occurred in 6% of cases. Despite an intense search for an etiologic agent, the cause remained unknown in 55%.

Two subsequent studies (Table 3) yielded similar results. The Centers for Disease Control and Prevention's EPIC study [34] of more than 2000 patients at 8 medical centers reported an even lower proportion of pneumococcal pneumonia (5% vs 9%) and all bacterial pneumonia (15% vs 29%) than Musher et al [33]. Routine use of PCR for *Mycoplasma* and *Chlamydia* confirmed [132] that these organisms are very uncommon causes of CAP

Table 3. Etiology of Community-Acquired Pneumonia, Studies Since 2010

Pathogen	Percentage of Patients		
	Houston [33]	Centers for Disease Control and Prevention [34]	Netherlands [136]
Bacteria	29	15	30
Streptococcus pneumoniae	9	5	16
Haemophilus	6	<1	7
Staphylococcus aureus	5	2	3
Pseudomonas	3	<1	2
Legionella	1	1	1
Mycoplasma, Chlamydia	–	<3	1
Other	6	3	3
Nocardia	1	0	0
Mycobacteria	2	1	<1
Fungi (*Pneumocystis*)	3	1	2
Viruses	20	27	3
Rhinovirus	13	9	–
Coronavirus	3	2	–
Human metapneumovirus	2	4	–
Influenza	1	6	3
Parainfluenza	2	3	–
Respiratory syncytial virus	2	3	–
No pathogen	55	62	66

leading to hospitalization of adults, suggesting that serologic tests have contributed to marked overdiagnosis. Two more recent studies identified *Mycoplasma* as a cause of pneumonia in 6% of cases; however, 1 included 50% [133] and the other [134] included 25% of patients with a PORT (Patient Outcomes Research Team) score of ≤2. Such patients are generally not hospitalized and would not have been included in the VA study or the EPIC study.

Using a serotype-specific enzyme-linked immunosorbent assay (ELISA) on urine [135], a Dutch pneumococcal vaccine trial [136] identified pneumococcus in 16% of CAP in the control (nonvaccinated) group, consistent with the higher incidence of pneumococcus in Europe, although lower than some of the other European studies cited above [40, 123, 126]. The finding in these 3 studies [33, 34, 136] of *Legionella, Pseudomonas*, or *S. aureus* as a cause of 1%, ≤3%, or ≤5% of pneumonias, respectively, has important implications for the selection of empiric antibiotics used to treat CAP.

Perhaps the most important observation in these 3 studies was the failure to identify a cause for pneumonia in more than 50% of cases. The VA study [33] attempted to use clinical scenarios with support from laboratory and radiologic studies to distinguish bacterial from nonbacterial (largely viral) pneumonia. The investigators defined a likely bacterial pneumonia as 3 or more of the following: hyperacute presentation; septic shock; white blood cell count >15 000 or <6000 with increased band forms; dense segmental or lobar consolidation; absence of upper respiratory symptoms; biphasic illness with upper respiratory symptoms followed by a sudden deterioration; or an elevated procalcitonin level. Likely nonbacterial pneumonia had none of these findings plus 2 or more of the following: exposure to sick contact(s); upper respiratory symptoms; patchy infiltrates; and a low serum procalcitonin level. About 58% of patients with no identifiable cause stratified to likely bacterial disease and 15% to likely viral disease; 27% could not be categorized. The authors hypothesized that so-called normal respiratory flora play a prominent etiologic role in patients whose syndrome suggested likely bacterial pneumonia and in whom all other tests failed to reveal a recognized pathogen.

TECHNIQUES TO IDENTIFY *S. PNEUMONIAE* CURRENTLY UNDER STUDY

A serotype-specific urinary ELISA increases the diagnostic yield for pneumococcus by 15%–20% [135]. Unfortunately, the available test only detects strains in the 13-valent conjugate pneumococcal vaccine, many of which have greatly declined in incidence [137]. Therefore, a new set of antigens needs to be studied and the method validated before it will provide useful information in the future.

Albrich et al [138] used a quantitative PCR on nasopharyngeal swabs to detect pneumococcal *lyt*A in human immunodeficiency virus (HIV)–infected South African patients with pneumonia. Patients who met criteria for pneumococcal infection had

1000-fold greater counts than patients without nonpneumococcal CAP and 100 000-fold greater counts than HIV-infected controls without CAP. To our knowledge, this work has not been validated in a study from a developed country. A quantitative, multiplex PCR detects 40 pneumococcal serotypes [139] but has yet to be studied as a diagnostic tool for CAP.

A recent study from the United Kingdom identified an etiologic agent by quantitative PCR in 87% of CAP patients, including *S. pneumoniae* in 36%, *H. influenzae* in 40%, *Moraxella* in 14%, *S. aureus* in 10%, *Klebsiella* in 4%, *Pseudomonas* in 3%, and *Mycoplasma* or *Legionella* in <2% each [140]. This technique appears to be either overly sensitive or nonspecific since 2 or more bacterial pathogens were found in 32% of cases and *Moraxella* was found in 14%. A respiratory virus was detected in 30% of cases but alone (without a bacterial respiratory pathogen) in only 6%.

CONCLUSION

In conclusion, principal trends in determining etiologic agents in pneumonia include the following: a marked but unexplained decline in the prevalence of pneumococcal disease; continued recognition of pneumococcus as the most commonly identified bacterial pathogen, especially in critically ill patients; a greater frequency of pneumococcus in Europe compared to the United States; a greatly increased role for respiratory viruses; detection of *Mycoplasma* and *Legionella* in a far smaller proportion of cases than had been reported in 1990–2010; and, perhaps most importantly, failure to establish an etiologic diagnosis in more than 50% patients. The principal challenges for the future appear to be to create a balance between overly sensitive and sufficiently sensitive diagnostic techniques, to identify an etiologic agent in the one-half of cases that now go undiagnosed, and to investigate the role of so-called normal respiratory flora in causing pneumonia. All these factors need to be considered as guidelines for management of community acquired pneumonia are formulated.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

References

1. Osler W. The Principles and Practice of Medicine: Designed for the Use of Practitioners and Students of Medicine. First ed. Edinburgh & London: Young J. Pentland, **1892**.
2. Osler W. The Principles and Practice of Medicine: Designed for the Use of Practitioners and Students of Medicine. 8th ed. New York and London: D. Appleton and Company, **1914**.

3. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med **2013**; 369:155–63.

4. Avery OT, Chickering HT, Cole R, Dochez AR. Acute lobar pneumonia: prevention and serum treatment. Monographs of the Rockefeller Institute for Medical Research. New York: Rockefeller Institute for Medical Research, **1917**.

5. Cecil RL, Larsen NP. Clinical and bacteriologic study of one thousand cases of lobar pneumonia. JAMA **1922**; 79:343–9.

6. Sutliff WD, Finland M. The significance of the newly classified types of pneumococci in disease: types IV to XX inclusive. JAMA **1933**; 101:1289–95.

7. Bullowa JGM. The Management of the Pneumonias: For Physicians and Medical Students. New York: Oxford University Press, **1937**.

8. Cecil RL, Lawrence EA. Pneumonia in private practice: a study of 911 patients. JAMA **1938**; 111:1889–94.

9. Warner GF, Li JG, Farber SM. A study of pneumonia in San Francisco, 1943–1944. Cal West Med **1945**; 62:161–2.

10. Warner GF, Gardner FH. A further study of pneumonia in San Francisco, 1944–1946. Calif Med **1948**; 68:32–4.

11. Dowling HF, Sweet LK, Hirsh HL. The Acute Bacterial Diseases. Philadelphia: W.B. Saunders Co., **1948**.

12. Tillotson JR, Finland M. Bacterial colonization and clinical superinfection of the respiratory tract complicating antibiotic treatment of pneumonia. J Infect Dis **1969**; 119:597–624.

13. Fiala M. A study of the combined role of viruses, mycoplasmas and bacteria in adult pneumonia. Am J Med Sci **1969**; 257:44–51.

14. Fekety FR Jr, Caldwell J, Gump D, et al. Bacteria, viruses, and mycoplasmas in acute pneumonia in adults. Am Rev Respir Dis **1971**; 104:499–507.

15. Dorff GJ, Rytel MW, Farmer SG, Scanlon G. Etiologies and characteristic features of pneumonias in a municipal hospital. Am J Med Sci **1973**; 266:349–58.

16. Moore MA, Merson MH, Charache P, Shepard RH. The characteristics and mortality of outpatient-acquired pneumonia. Johns Hopkins Med J **1977**; 140:9–14.

17. Oseasohn R, Skipper BE, Tempest B. Pneumonia in a Navajo community: a two-year experience. Am Rev Respir Dis **1978**; 117:1003–9.

18. Miller J, Sande MA, Gwaltney JM Jr, Hendley JO. Diagnosis of pneumococcal pneumonia by antigen detection in sputum. J Clin Microbiol **1978**; 7:459–62.

19. Ebright JR, Rytel MW. Bacterial pneumonia in the elderly. J Am Geriatr Soc **1980**; 28:220–3.

20. Boerner DF, Zwadyk P. The value of the sputum gram's stain in community-acquired pneumonia. JAMA **1982**; 247:642–5.

21. Dans PE, Charache P, Fahey M, Otter SE. Management of pneumonia in the prospective payment era. A need for more clinician and support service interaction. Arch Intern Med **1984**; 144:1392–7.

22. Marrie TJ, Haldane EV, Faulkner RS, Durant H, Kwan C. Community-acquired pneumonia requiring hospitalization. Is it different in the elderly? J Am Geriatr Soc **1985**; 33:671–80.

23. Larsen RA, Jacobson JA. Diagnosis of community-acquired pneumonia: experience at a community hospital. Compr Ther **1984**; 10:20–5.

24. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy. A prospective multicenter study of 359 cases. Medicine (Baltimore) **1990**; 69:307–16.

25. Farr BM, Sloman AJ, Fisch MJ. Predicting death in patients hospitalized for community-acquired pneumonia. Ann Intern Med **1991**; 115:428–36.

26. Bates JH, Campbell GD, Barron AL, et al. Microbial etiology of acute pneumonia in hospitalized patients. Chest **1992**; 101:1005–12.

27. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. Am J Respir Crit Care Med **1995**; 152:1309–15.

28. Marston BJ, Plouffe JF, File TM Jr, et al. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-based Pneumonia Incidence Study Group. Arch Intern Med **1997**; 157:1709–18.

29. Fine MJ, Stone RA, Singer DE, et al. Processes and outcomes of care for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team (PORT) cohort study. Arch Intern Med **1999**; 159:970–80.

30. Park DR, Sherbin VL, Goodman MS, et al; Harborview CAP Study Group. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. J Infect Dis **2001**; 184:268–77.

31. Yang S, Lin S, Khalil A, et al. Quantitative PCR assay using sputum samples for rapid diagnosis of pneumococcal pneumonia in adult emergency department patients. J Clin Microbiol **2005**; 43:3221–6.

32. Restrepo MI, Mortensen EM, Velez JA, Frei C, Anzueto A. A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. Chest **2008**; 133:610–7.

33. Musher DM, Roig IL, Cazares G, Stager CE, Logan N, Safar H. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. J Infect **2013**; 67:11–8.

34. Jain S, Self WH, Wunderink RG, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med **2015**; 373:415–27.

35. Hug B, Rossi M. A year's review of bacterial pneumonia at the central hospital of Lucerne, Switzerland. Swiss Med Wkly **2001**; 131:687–92.

36. Garbino J, Sommer R, Gerber A, et al. Prospective epidemiologic survey of patients with community-acquired pneumonia requiring hospitalization in Switzerland. Int J Infect Dis **2002**; 6:288–93.

37. Genné D, Siegrist HH, Lienhard R. Enhancing the etiologic diagnosis of community-acquired pneumonia in adults using the urinary antigen assay (Binax NOW). Int J Infect Dis **2006**; 10:124–8.

38. Piso RJ, Iven-Koller D, Koller MT, Bassetti S. The routine use of urinary pneumococcal antigen test in hospitalised patients with community acquired pneumonia has limited impact for adjustment of antibiotic treatment. Swiss Med Wkly **2012**; 142:w13679.

39. Strålin K, Olcén P, Törnqvist E, Holmberg H. Definite, probable, and possible bacterial aetiologies of community-acquired pneumonia at different CRB-65 scores. Scand J Infect Dis **2010**; 42:426–34.

40. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis **2010**; 50:202–9.

41. Pareja A, Bernal C, Leyva A, Piedrola G, Maroto MC. Etiologic study of patients with community-acquired pneumonia. Chest **1992**; 101:1207–10.

42. Almirall J, Morató I, Riera F, et al. Incidence of community-acquired pneumonia and *Chlamydia pneumoniae* infection: a prospective multicentre study. Eur Respir J **1993**; 6:14–8.

43. Lorente ML, Falguera M, Nogués A, González AR, Merino MT, Caballero MR. Diagnosis of pneumococcal pneumonia by polymerase chain reaction (PCR) in whole blood: a prospective clinical study. Thorax **2000**; 55:133–7.

44. Almirall J, Bolíbar I, Vidal J, et al. Epidemiology of community-acquired pneumonia in adults: a population-based study. Eur Respir J **2000**; 15:757–63.

45. Gutiérrez F, Masiá M, Rodríguez JC, et al. Epidemiology of community-acquired pneumonia in adult patients at the dawn of the 21st century: a prospective study on the Mediterranean coast of Spain. Clin Microbiol Infect **2005**; 11:788–800.

46. Andreo F, Domínguez J, Ruiz J, et al. Impact of rapid urine antigen tests to determine the etiology of community-acquired pneumonia in adults. Respir Med **2006**; 100:884–91.

47. Briones ML, Blanquer J, Ferrando D, Blasco ML, Gimeno C, Marín J. Assessment of analysis of urinary pneumococcal antigen by immunochromatography for etiologic diagnosis of community-acquired pneumonia in adults. Clin Vaccine Immunol **2006**; 13:1092–7.

48. Fernández Alvarez R, Suárez Toste I, Rubinos Cuadrado G, et al. Community-acquired pneumonia: aetiologic changes in a limited geographic area. An 11-year prospective study. Eur J Clin Microbiol Infect Dis **2007**; 26:495–9.

49. Falguera M, Carratalà J, Ruiz-Gonzalez A, et al. Risk factors and outcome of community-acquired pneumonia due to gram-negative bacilli. Respirology **2009**; 14:105–11.

50. Cillóniz C, Ewig S, Polverino E, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. Thorax **2011**; 66:340–6.

51. Sordé R, Falcó V, Lowak M, et al. Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. Arch Intern Med **2011**; 171:166–72.

52. Capelastegui A, España PP, Bilbao A, et al; Poblational Study of Pneumonia (PSoP) Group. Etiology of community-acquired pneumonia in a population-based study: link between etiology and patients characteristics, process-of-care, clinical evolution and outcomes. BMC Infect Dis **2012**; 12:134.

53. Viasus D, Marinescu C, Villoslada A, et al; Influenza A (H1N1) Study Group of the Spanish Network for Research in Infectious Diseases (REIPI). Community-acquired pneumonia during the first post-pandemic influenza season: a prospective, multicentre cohort study. J Infect **2013**; 67:185–93.

54. Tudose C, Moisoiu A, Bogdan M. Mortality risk and etiologic spectrum of community-acquired pneumonia in hospitalized adult patients. Maedica (Buchar) **2010**; 5:258–64.

55. Røysted W, Simonsen Ø, Jenkins A, et al. Aetiology and risk factors of community-acquired pneumonia in hospitalized patients in Norway. Clin Respir J **2016**; 10:756–64.

56. Boersma WG, Löwenberg A, Holloway Y, Kuttschrütter H, Snijder JA, Koëter GH. Pneumococcal capsular antigen detection and pneumococcal serology in patients with community acquired pneumonia. Thorax **1991**; 46:902–6.

57. Bohte R, van Furth R, van den Broek PJ. Aetiology of community-acquired pneumonia: a prospective study among adults requiring admission to hospital. Thorax **1995**; 50:543–7.

58. Endeman H, Schelfhout V, Voorn GP, van Velzen-Blad H, Grutters JC, Biesma DH. Clinical features predicting failure of pathogen identification in patients with community acquired pneumonia. Scand J Infect Dis **2008**; 40:715–20.

59. Huijts SM, Boersma WG, Grobbee DE, et al; CAP Diagnostics Investigators. Predicting pneumococcal community-acquired pneumonia in the emergency department: evaluation of clinical parameters. Clin Microbiol Infect 2014; 20:1316–22.

60. Ruf B, Schürmann D, Horbach I, Fehrenbach FJ, Pohle HD. The incidence of legionella pneumonia: a 1-year prospective study in a large community hospital. Lung 1989; 167:11–22.

61. Kothe H, Bauer T, Marre R, Suttorp N, Welte T, Dalhoff K; Competence Network for Community-Acquired Pneumonia Study Group. Outcome of community-acquired pneumonia: influence of age, residence status and antimicrobial treatment. Eur Respir J 2008; 32:139–46.

62. Lévy M, Dromer F, Brion N, Leturdu F, Carbon C. Community-acquired pneumonia. importance of initial noninvasive bacteriologic and radiographic investigations. Chest 1988; 93:43–8.

63. Lehtomäki K, Leinonen M, Takala A, Hovi T, Herva E, Koskela M. Etiological diagnosis of pneumonia in military conscripts by combined use of bacterial culture and serological methods. Eur J Clin Microbiol Infect Dis 1988; 7:348–54.

64. Hohenthal U, Vainionpää R, Meurman O, et al. Aetiological diagnosis of community acquired pneumonia: utility of rapid microbiological methods with respect to disease severity. Scand J Infect Dis 2008; 40:131–8.

65. Leesik H, Ani U, Juhani A, Altraja A. Microbial pathogens of adult community-acquired pneumonia in Southern Estonia. Medicina (Kaunas) 2006; 42:384–94.

66. White RJ, Blainey AD, Harrison KJ, Clarke SK. Causes of pneumonia presenting to a district general hospital. Thorax 1981; 36:566–70.

67. Bewick T, Sheppard C, Greenwood S, et al. Serotype prevalence in adults hospitalised with pneumococcal non-invasive community-acquired pneumonia. Thorax 2012; 67:540–5.

68. Ostergaard L, Andersen PL. Etiology of community-acquired pneumonia. Evaluation by transtracheal aspiration, blood culture, or serology. Chest 1993; 104:1400–7.

69. Mareković I, Plecko V, Boras Z, et al. Evaluation of PCR as rapid microbiological method in diagnosis of pneumococcal pneumonia. Scand J Infect Dis 2008; 40:843–5.

70. Blasi F, Cosentini R, Legnani D, Denti F, Allegra L. Incidence of community-acquired pneumonia caused by *Chlamydia pneumoniae* in Italian patients. Eur J Clin Microbiol Infect Dis 1993; 12:696–9.

71. Logroscino CD, Penza O, Locicero S, et al. Community-acquired pneumonia in adults: a multicentric observational AIPO study. Monaldi Arch Chest Dis 1999; 54:11–7.

72. Cecil RL, Baldwin HS, Larsen NP. Clinical and bacteriological study of 2000 typed cases of lobar pneumonia. Arch Intern Med 1927; 40: 253–80.

73. Cole RI. Acute pulmonary infections, Delamar Lectures. Baltimore: Williams and Wilkins Co, 1927.

74. Heffron R. Pneumonia with special reference to pneumococcus lobar pneumonia. New York: The Commonwealth Fund, 1939.

75. Francis T Jr. Influenza. In: Rivers TM, Horsfall FL, Jr. Viral and Rickettsial Diseases of Man. Third ed. Philadelphia: J. B. Lippincott:633–72.

76. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis 2008; 198:962–70.

77. Hilleman MR, Werner JH. Recovery of new agent from patients with acute respiratory illness. Proc Soc Exp Biol Med 1954; 85:183–8.

78. Reimann HA. An acute infection of the respiratory tract with atypical pneumonia. A disease entity probably caused by a filterable virus. JAMA 1938; 111: 2377–84.

79. Reimann HA. Pneumococcal and "virus" pneumonia. Bull N Y Acad Med 1941; 17:187–94.

80. Chanock RM, Mufson MA, Bloom HH, James WD, Fox HH, Kingston JR. Eaton agent pneumonia. JAMA 1961; 175:213–20.

81. Eaton MD, Van Herick W. Serological and epidemiological studies on primary atypical pneumonia and related acute upper respiratory disease. Am J Hyg 1947; 45:82–95.

82. Chanock RM, Rifkind D, Kravetz HM, Kinght V, Johnson KM. Respiratory disease in volunteers infected with Eaton agent: a preliminary report. Proc Natl Acad Sci USA 1961; 47:887–90.

83. Mufson MA, Chang V, Gill V, Wood SC, Romansky MJ, Chanock RM. The role of viruses, mycoplasmas and bacteria in acute pneumonia in civilian adults. Am J Epidemiol 1967; 86:526–44.

84. Foy HM, Kenny GE, McMahan R, Mansy AM, Grayston JT. *Mycoplasma pneumoniae* pneumonia in an urban area. Five years of surveillance. JAMA 1970; 214:1666–12.

85. Clinical patterns of undifferentiated and other acute respiratory diseases in Army recruits. Medicine (Baltimore) 1947; 26:441–64.

86. Wood WBJ. Pneumonia. Pneumococcal pneumonia. In: Beeson PB, McDermott W. Cecil-Loeb Textbook of Medicine. Twelfth ed. Philadelphia and London: W. B. Saunders Co., 1967:145–59.

87. Veillon A, Zuber A. Recherches sur quelques microbes strictement anaerobies et leur role en pathologie. Arch MedExper d'Anat Path 1898; 10:517–45.

88. Smith DT. Fusospirochetal disease of the lungs, its bacteriology, pathology and experimental reproduction. Amer Rev Tuberc 1927; 16: 584–98.

89. Cohen J. The bacteriology of abscess of the lung and methods for its study. Arch Surg 1932; 24:171–88.

90. Bartlett JG, Gorbach SL, Finegold SM. The bacteriology of aspiration pneumonia. Am J Med 1974; 56:202–7.

91. Bartlett JG. Anaerobic bacterial infections of the lung and pleural space. Clin Infect Dis 1993; 16 Suppl 4:S248–55.

92. Hahn HH, Beaty HN. Transtracheal aspiration in the evaluation of patients with pneumonia. Ann Intern Med 1970; 72:183–7.

93. Hoeprich PD. Etiologic diagnosis of lower respiratory tract infections. Calif Med 1970; 112:1–8.

94. Bartlett JG, Rosenblatt JE, Finegold SM. Percutaneous transtracheal aspiration in the diagnosis of anaerobic pulmonary infection. Ann Intern Med 1973; 79:535–40.

95. Ries K, Levison ME, Kaye D. Transtracheal aspiration in pulmonary infection. Arch Intern Med 1974; 133:453–8.

96. Thorsteinsson SB, Musher DM, Fagan T. The diagnostic value of sputum culture in acute pneumonia. JAMA 1975; 233:894–5.

97. Bartlett JG. Anaerobic bacterial infections of the lung. Chest 1987; 91:901–9.

98. Bartlett JG. Diagnostic accuracy of transtracheal aspiration bacteriologic studies. Am Rev Respir Dis 1977; 115:777–82.

99. Fraser DW, Tsai TR, Orenstein W, et al. Legionnaires' disease: description of an epidemic of pneumonia. N Engl J Med 1977; 297:1189–97.

100. McDade JE, Shepard CC, Fraser DW, Tsai TR, Redus MA, Dowdle WR. Legionnaires' disease: isolation of a bacterium and demonstration of its role in other respiratory disease. N Engl J Med 1977; 297:1197–203.

101. Macrae AD, Lewis MJ. Legionnaires' disease in Nottingham. Lancet 1977; 2:1225–6.

102. Gorman GW, Yu VL, Brown A, et al. Isolation of *Pittsburgh pneumonia* agent from nebulizers used in respiratory therapy. Ann Intern Med 1980; 93:572–3.

103. Muder RR, Yu VL, Zuravleff JJ. Pneumonia due to the *Pittsburgh pneumonia* agent: new clinical perspective with a review of the literature. Medicine (Baltimore) 1983; 62:120–8.

104. Yu VL, Kroboth FJ, Shonnard J, Brown A, McDearman S, Magnussen M. Legionnaires' disease: new clinical perspective from a prospective pneumonia study. Am J Med 1982; 73:357–61.

105. Wadowsky RM, Yee RB, Mezmar L, Wing EJ, Dowling JN. Hot water systems as sources of *Legionella pneumophila* in hospital and nonhospital plumbing fixtures. Appl Environ Microbiol 1982; 43:1104–10.

106. Stout J, Yu VL, Vickers RM, et al. Ubiquitousness of *Legionella pneumophila* in the water supply of a hospital with endemic Legionnaires' disease. N Engl J Med 1982; 306:466–8.

107. Musher DM, Kubitschek KR, Crennan J, Baughn RE. Pneumonia and acute febrile tracheobronchitis due to *Haemophilus influenzae*. Ann Intern Med 1983; 99:444–50.

108. Grayston JT, Kuo CC, Wang SP, Altman J. A new *Chlamydia psittaci* strain, TWAR, isolated in acute respiratory tract infections. N Engl J Med 1986; 315:161–8.

109. Marrie TJ, Grayston JT, Wang SP, Kuo CC. Pneumonia associated with the TWAR strain of *Chlamydia*. Ann Intern Med 1987; 106:507–11.

110. Dowell SF, Anderson LJ, Gary HE Jr, et al. Respiratory syncytial virus is an important cause of community-acquired lower respiratory infection among hospitalized adults. J Infect Dis 1996; 174:456–62.

111. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. Am J Med 1997; 102:2–9; discussion 25–6.

112. Stockton J, Stephenson I, Fleming D, Zambon M. Human metapneumovirus as a cause of community-acquired respiratory illness. Emerg Infect Dis 2002; 8:897–901.

113. Gutiérrez F, Masiá M, Rodríguez JC, et al. Evaluation of the immunochromatographic Binax NOW assay for detection of *Streptococcus pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. Clin Infect Dis 2003; 36:286–92.

114. Rosón B, Fernández-Sabé N, Carratalà J, et al. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis 2004; 38:222–6.

115. Boulware DR, Daley CL, Merrifield C, Hopewell PC, Janoff EN. Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection. J Infect 2007; 55:300–9.

116. Ishida T, Hashimoto T, Arita M, Tojo Y, Tachibana H, Jinnai M. A 3-year prospective study of a urinary antigen-detection test for *Streptococcus pneumoniae* in community-acquired pneumonia: utility and clinical impact on the reported etiology. J Infect Chemother 2004; 10:359–63.

117. Sinclair A, Xie X, Teltscher M, Dendukuri N. Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired

pneumonia caused by *Streptococcus pneumoniae*. J Clin Microbiol **2013**; 51:2303–10.

118. Sheppard CL, Harrison TG, Smith MD, George RC. Development of a sensitive, multiplexed immunoassay using xMAP beads for detection of serotype-specific *Streptococcus pneumoniae* antigen in urine samples. J Med Microbiol **2011**; 60:49–55.

119. Strålin K, Herrmann B, Abdeldaim G, Olcén P, Holmberg H, Mölling P. Comparison of sputum and nasopharyngeal aspirate samples and of the PCR gene targets lytA and Spn9802 for quantitative PCR for rapid detection of pneumococcal pneumonia. J Clin Microbiol **2014**; 52:83–9.

120. Musher DM, Mediwala R, Phan HM, Chen G, Baughn RE. Nonspecificity of assaying for IgG antibody to pneumolysin in circulating immune complexes as a means to diagnose pneumococcal pneumonia. Clin Infect Dis **2001**; 32:534–8.

121. File TM Jr, Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis **2010**; 51:1395–405.

122. Sherwin RL, Gray S, Alexander R, et al. Distribution of 13-valent pneumococcal conjugate vaccine *Streptococcus pneumoniae* serotypes in US adults aged ≥50 years with community-acquired pneumonia. J Infect Dis **2013**; 208:1813–20.

123. Lim WS, Macfarlane JT, Boswell TC, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax **2001**; 56:296–301.

124. Macfarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. Lancet **1993**; 341:511–4.

125. Johansson N, Kalin M, Hedlund J. Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. Scand J Infect Dis **2011**; 43:609–15.

126. Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med **2010**; 181:975–82.

127. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev **2013**; 1:CD000422.

128. Centers for Disease Control and Prevention. Current cigarette smoking among adults—United States, 2011. MMWR Morb Mortal Wkly Rep **2012**: 889–94.

129. Rozenbaum MH, Pechlivanoglou P, van der Werf TS, Lo-Ten-Foe JR, Postma MJ, Hak E. The role of *Streptococcus pneumoniae* in community-acquired pneumonia among adults in Europe: a meta-analysis. Eur J Clin Microbiol Infect Dis **2013**; 32:305–16.

130. Huijts SM, Pride MW, Vos JM, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. Eur Respir J **2013**; 42:1283–90.

131. Karhu J, Ala-Kokko TI, Vuorinen T, Ohtonen P, Syrjälä H. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Infect Dis **2014**; 59:62–70.

132. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med **2014**; 371:1619–28.

133. Barrera CM, Mykietiuk A, Metev H, et al; SOLITAIRE-ORAL Pneumonia Team. Efficacy and safety of oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia: a global, double-blind, multicentre, randomised, active-controlled, non-inferiority trial (SOLITAIRE-ORAL). Lancet Infect Dis **2016**; 16:421–30.

134. File TM Jr, Rewerska B, Vucinic-Mihailovic V, et al. SOLITAIRE-IV: a randomized, double-blind, multicenter study comparing the efficacy and safety of intravenous-to-oral solithromycin to intravenous-to-oral moxifloxacin for treatment of community-acquired bacterial pneumonia. Clin Infect Dis **2016**; 63:1007–16.

135. Leeming JP, Cartwright K, Morris R, Martin SA, Smith MD; South-West Pneumococcus Study Group. Diagnosis of invasive pneumococcal infection by serotype-specific urinary antigen detection. J Clin Microbiol **2005**; 43:4972–6.

136. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med **2015**; 372:1114–25.

137. Kobayashi M, Bennett NM, Gierke R, et al. Intervals between PCV13 and PPSV23 vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep **2015**; 64:944–7.

138. Albrich WC, Madhi SA, Adrian PV, et al. Use of a rapid test of pneumococcal colonization density to diagnose pneumococcal pneumonia. Clin Infect Dis **2012**; 54:601–9.

139. Messaoudi M, Milenkov M, Albrich WC, et al. The relevance of a novel quantitative assay to detect up to 40 major *Streptococcus pneumoniae* serotypes directly in clinical nasopharyngeal and blood specimens. PLoS One **2016**; 11:e0151428.

140. Gadsby NJ, Russell CD, McHugh MP, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. Clin Infect Dis **2016**; 62:817–23.