MAJOR ARTICLE

Incidence, Etiology, and Outcomes of Community-Acquired Pneumonia: A Population-Based Study

Agnar Bjarnason,[1,2] Johan Westin,[2,3] Magnus Lindh,[2,3] Lars-Magnus Andersson,[2,3] Karl G. Kristinsson,[1,4] Arthur Löve,[1,4] Olafur Baldursson,[4] and Magnus Gottfredsson[1,4]

[1]Faculty of Medicine, University of Iceland, Reykjavik; [2]Department of Infectious Diseases, Sahlgrenska University Hospital, Gothenburg, Sweden; [3]Department of Infectious Diseases/Clinical Virology, University of Gothenburg, Sweden; [4]Departments of Medicine, Microbiology and Virology, Landspitali University Hospital, Reykjavik, Iceland

Background. The microbial etiology of community-acquired pneumonia (CAP) is often unclear in clinical practice, and previous studies have produced variable results. Population-based studies examining etiology and incidence are lacking. This study examined the incidence and etiology of CAP requiring hospitalization in a population-based cohort as well as risk factors and outcomes for specific etiologies.

Methods. Consecutive admissions due to CAP in Reykjavik, Iceland were studied. Etiologic testing was performed with cultures, urine-antigen detection, and polymerase chain reaction analysis of airway samples. Outcomes were length of stay, intensive care unit admission, assisted ventilation, and mortality.

Results. The inclusion rate was 95%. The incidence of CAP requiring hospitalization was 20.6 cases per 10 000 adults/year. A potential pathogen was detected in 52% (164 of 310) of admissions and in 74% (43 of 58) with complete sample sets. *Streptococcus pneumoniae* was the most common pathogen (61 of 310, 20%; incidence: 4.1/10 000). Viruses were identified in 15% (47 of 310; incidence: 3.1/10 000), *Mycoplasma pneumoniae* were identified in 12% (36 of 310; incidence: 2.4/10 000), and multiple pathogens were identified in 10% (30 of 310; incidence: 2.0/10 000). Recent antimicrobial therapy was associated with increased detection of *M pneumoniae* ($P < .001$), whereas a lack of recent antimicrobial therapy was associated with increased detection of *S pneumoniae* ($P = .02$). Symptoms and outcomes were similar irrespective of microbial etiology.

Conclusions. Pneumococci, *M pneumoniae*, and viruses are the most common pathogens associated with CAP requiring hospital admission, and they all have a similar incidence that increases with age. Symptoms do not correlate with specific agents, and outcomes are similar irrespective of pathogens identified.

Keywords. community-acquired pneumonia; etiology; incidence; *Mycoplasma pneumoniae*; *Streptococcus pneumoniae*.

Lower respiratory tract infections are a leading infectious cause of death worldwide, according the recently published 2015 Global Burden of Disease Study, with rates increasing in many developed countries [1]. Community-acquired pneumonia (CAP) refers to infections acquired in the community, excluding healthcare-associated disease. Mild cases can be treated successfully at home, but severe cases require hospital admission and are associated with greater cost and suffer higher mortality [2]. Timely and appropriate antibiotic therapy is vital to improving outcomes, but minimizing unnecessary use of broad-spectrum agents is equally important [2].

Previous studies examining the etiology of CAP have provided widely differing results. Comparison is hampered by inherent epidemiologic differences in addition to lack of uniform inclusion criteria, study settings, and diagnostic methods. Despite rigorous attempts to identify a microbial etiology, 30%–64% of patients remain undiagnosed [3–12]. Studies applying molecular methods such as polymerase chain reaction (PCR) have yielded detection rates up to 86%, but highly specific patient selection criteria designed to optimize sample collection make comparisons difficult [13]. There is a dearth of population-based observational studies with high inclusion rates examining pneumonia incidence and etiology while avoiding overly selective inclusion criteria and applying modern diagnostic methods.

The aim of the present study was to prospectively investigate the frequency and etiology of CAP in a defined population, allowing for calculation of incidence, applying modern diagnostic tests, and comparing etiology with symptoms, risk factors, and outcomes.

MATERIALS AND METHODS

Patients and Study Design

This study took place at Landspitali University Hospital in Reykjavik Iceland (LUH). The LUH provides secondary care for the inhabitants of Reykjavik and nearby towns, comprising

Received 16 October 2017; editorial decision 28 December 2017; accepted 8 January 2018.
Correspondence: M. Gottfredssson MD, PhD, FACP, Landspitali University Hospital, Division of Infectious Diseases, Fossvogur, 108 Reykjavik, Iceland (magnusgo@landspitali.is).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofy010

63% of the national population. It also provides 90% of all intensive care in the country. Adults (≥18 years) admitted from December 1, 2008 to November 30, 2009 were screened for inclusion. Inclusion criteria were a new chest x-ray infiltrate and ≥2 additional symptoms: temperature >38.3°C or <36°C, diaphoresis, chills, new cough, chest pain, or new onset of dyspnea [6, 14]. Exclusion criteria were as follows: admission to an acute care facility during the preceding 14 days; use of immunosuppressive medications (corticosteroids equivalent to ≥10 mg prednisolone daily, methotrexate, hydroxyurea, adalimumab, infliximab, etenercept, azathioprine, mycophenolate mofetil, or cyclosporine); ongoing treatment for a malignancy; receipt of a solid organ transplant; or human immunodeficiency virus infection.

Data Collection

Potential participants were approached within 24 hours of admission and underwent a structured interview, and data were collected on underlying diseases, subjective symptoms, and antimicrobial use before admission. Pneumonia severity index (PSI) and CURB-65 scores were calculated [15, 16]. Outcomes were: length of stay (LOS), admission to intensive care units (ICUs), assisted ventilation, and in-house mortality. Outcomes were obtained retrospectively from patient charts. Vital status was cross-checked with national registry data after discharge from hospital.

Etiological Testing

The study was noninterventional but included additional diagnostic sampling. Sputum and blood were obtained for culture prior to in-hospital antimicrobial treatment and urine antigen testing was performed. An oropharyngeal swab was collected for PCR analysis. Results from physician-ordered etiological diagnostic testing were also included.

Sputum and blood were cultured with routine methods and susceptibly tested using the Clinical and Laboratory Standards Institute methods and criteria [17]. Only results from high-quality sputum samples were included [18]. Urine antigens were tested using commercially available tests (BinaxNow *Streptococcus pneumoniae* and BinaxNow *Legionella*; Inverness Medical Innovations).

Oropharyngeal swabs were frozen immediately at −80°C for batch analysis with PCR in 2 steps. Samples were initially tested for seasonal and pandemic influenza, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila* as previously described [19]. Samples were stored at −80°C and reanalyzed with multiplex real-time PCR for *S pneumoniae*, *Haemophilus influenzae*, influenza A and B, rhinovirus, adenovirus, parainfluenza 1–3, respiratory syncytial virus (RSV), coronavirus (NL63, OC43, HKU1), enterovirus, metapneumovirus, bocavirus, *C pneumoniae*, and *M pneumoniae* as previously described [20, 21]. Results of real-time PCR for *S pneumoniae* and *H influenzae* were considered positive at a cycle threshold of 35 or less to exclude false-positive results due to carriage [21].

Ethics Statement

This study was approved by the LUH ethics committee and was in accordance with the revised declaration of Helsinki. Informed consent was obtained from all individual participants or proxy included in the study.

Statistical Analysis

Statistical calculations were performed using IBM SPSS Statistics version 22.0.0.0 (IBM Corporation). Incidence was calculated with the average population of 2008 and 2009 derived from publically available official data (Statistics Iceland, http://www.hagstofa.is/Hagtolur/Mannfjoldi). Categorical data were compared using χ^2 and Fisher's exact test as appropriate. Continuous data were compared with 95% confidence intervals (CIs). Risk factors were examined in conjunction with specific etiologic results (*S pneumoniae*, *M pneumoniae*, and influenza) with direct comparison, as detailed above, as well as multinomial logistic regression. Variables that were included in the analysis were age, sex, any underlying disease, asthma, chronic obstructive pulmonary disease, ischemic heart disease, heart failure, diabetes mellitus type 2, underlying neurologic disease, chronic renal failure, malignancy, smoking status, recent use of antimicrobials, influenza vaccination, pneumococcal vaccination, fever, cough, purulent cough, hemoptysis, pleuritic chest pain, sweating, dyspnea, stomach pain, and diarrhea.

RESULTS

Study Population and Incidence

Of 511 cases approached with suspected pneumonia, 15 (3%) chose not to participate and 496 gave consent. Of these, 123 cases did not meet criteria for pneumonia, and exclusion criteria were present in 63 cases. Thus, 310 admissions were included in this study or 95% of all potential cases. The cohort is described in Table 1.

The overall incidence of CAP requiring hospital admission was 20.6 cases per 10 000 adults per year. Detailed incidence figures are displayed in Table 2.

Etiology and Yield of Diagnostic Methods

A potential pathogen was identified in 164 (53%) cases. Multiple agents were detected in 30 cases (10%; Table 3), and the most commonly identified organism was *S pneumoniae*, (61 cases, 20%). A respiratory virus was recovered in 47 cases (15%), and an atypical bacterial agent (*M pneumoniae*, *C pneumoniae*, or *Legionella* species) was recovered in 43 cases (14%). In addition, *Burkholderia pseudomallei* was detected in 1 instance, in a traveler returning from Southeast Asia.

Among cases with multiple pathogens detected (n = 30), the most common combination was *S pneumoniae* with a virus. *S pneumoniae* was detected with influenza in 5 cases (17%),

Table 1. Characteristics of Patients With Community-Acquired Pneumonia Displayed by Detected Pathogen

Patient Characteristic	Entire Group	*Streptococcus pneumoniae*	*Mycoplasma pneumoniae*	*Haemophilus influenzae*	*S aureus*	*Moraxella catarrhalis*	β-Hemolytic Streptococci	Influenza	Rhinovirus	RSV	Any Virus[a]	Any Atypical Bacteria[b]	Dual Pathogens
n	310	61	36	22	8	7	5	28	6	6	47	43	30
Age, years (95% CI)	62.8 (60.5–65.1)	64.2 (59.5–68.9)	44.8 (37.7–51.9)	66.9 (59.5–68.9)	73.3 (64.7–81.8)	67.4 (57.1–77.7)	52.8 (40.5–65.1)	50.1 (43.1–57.1)	78 (70.2–85.8)	71.8 (59.6–84.1)	59.5 (53.8–65.2)	47.5 (40.7–54.2)	62.2 (55.5–69.0)
Male	154 (50)	31 (51)	18 (50)	8 (36)	4 (50)	5 (71)	4 (80)	14 (50)	1 (17)	3 (50)	21 (45)	22 (51)	16 (53)
Underlying illness[c]	174 (56)	34 (56)	8 (22)	10 (46)	8 (100)	5 (71)	1 (20)	10 (36)	3 (50)	4 (67)	22 (47)	12 (28)	15 (50)
Asthma	43 (14)	7 (12)	2 (6)	3 (14)	1 (13)	2 (29)	0	4 (14)	1 (17)	1 (17)	7 (15)	3 (7)	5 (17)
COPD	80 (26)	19 (31)	5 (14)	4 (18)	5 (63)	4 (57)	0	2 (7)	2 (33)	1 (17)	7 (15)	6 (14)	7 (23)
Ischemic heart disease	63 (20)	9 (15)	5 (14)	2 (9)	2 (25)	3 (43)	1 (20)	3 (11)	0	1 (17)	6 (13)	8 (19)	4 (13)
Heart failure	36 (12)	8 (13)	2 (6)	1 (5)	2 (25)	2 (29)	0	2 (7)	0	0	3 (6)	5 (12)	2 (7)
Diabetes type 1or 2	42 (14)	4 (7)	4 (11)	0	3 (38)	2 (29)	0	1 (4)	1 (17)	1 (17)	3 (6)	4 (9)	2 (7)
Neurologic disease	43 (14)	4 (7)	3 (8)	2 (9)	3 (38)	0	0	2 (7)	0	1 (17)	4 (9)	4 (9)	2 (7)
Liver disease	6 (2)	3 (5)	0	3 (14)	0	0	0	1 (4)	0	1 (17)	2 (4)	0	3 (10)
Renal dysfunction	32 (10)	3 (5)	2 (6)	2 (9)	3 (38)	1 (14)	0	2 (7)	0	0	3 (6)	3 (7)	1 (3)
Active malignancy	9 (3)	2 (3)	0	3 (14)	0	1 (14)	0	0	0	1 (17)	1 (2)	0	2 (7)
Smoker	65 (21)	19 (31)	7 (19)	4 (18)	2 (25)	0	3 (60)	8 (29)	1 (17)	2 (33)	12 (26)	8 (19)	10 (33)
Former smoker	124 (40)	24 (39)	7 (19)	9 (41)	3 (38)	2 (29)	2 (40)	7 (25)	2 (33)	3 (50)	16 (34)	9 (21)	11 (37)
Recent antibiotic use	107 (35)	11 (18)	26 (72)	6 (27)	2 (25)	0	2 (40)	14 (43)	0	4 (67)	16 (34)	28 (65)	2 (27)
Influenza vaccination[d]	125 (40)	19 (31)	10 (28)	10 (46)	4 (50)	4 (57)	3 (60)	3 (11)	2 (33)	5 (83)	16 (34)	11 (26)	12 (40)
Prior Pneumococcal vaccination	43 (14)[e]	7 (12)	1 (3)	5 (23)	0	4 (57)	1 (20)	2 (7)	0	2 (33)	7 (15)	2 (5)	4 (13)
Reported symptoms													
Fever	262 (85)	52 (85)	31 (86)	20 (91)	6 (75)	4 (57)	4 (80)	27 (96)	5 (83)	6 (100)	43 (92)	38 (88)	27 (90)
Cough	246 (79)	50 (82)	31 (86)	21 (96)	5 (63)	6 (86)	3 (60)	25 (89)	5 (83)	6 (100)	40 (85)	37 (86)	26 (87)
Sputum	160 (52)	34 (56)	17 (47)	17 (77)	3 (38)	4 (57)	3 (60)	14 (50)	4 (67)	4 (67)	24 (51)	22 (51)	16 (53)
Hemoptysis	33 (10)	8 (13)	2 (6)	2 (9)	1 (13)	0	0	6 (21)	0	1 (17)	8 (17)	2 (5)	4 (13)
Chest pain	140 (45)	35 (57)	17 (39)	12 (55)	3 (38)	4 (57)	3 (60)	12 (43)	1 (17)	2 (33)	19 (40)	19 (44)	17 (57)
Diaphoresis	94 (30)	16 (26)	16 (44)	4 (18)	1 (13)	3 (43)	1 (20)	12 (43)	1 (17)	1 (17)	16 (34)	16 (37)	7 (23)
Dyspnea	218 (70)	45 (74)	27 (75)	13 (59)	6 (75)	2 (29)	1 (20)	24 (86)	2 (33)	5 (83)	37 (79)	33 (77)	19 (63)
Stomach pain	43 (14)	10 (16)	3 (8)	4 (18)	3 (38)	1 (14)	0	4 (14)	2 (33)	1 (17)	8 (17)	4 (9)	6 (20)
Diarrhea	49 (16)	12 (20)	9 (25)	3 (14)	1 (13)	0	1 (20)	8 (29)	0	2 (33)	10 (21)	9 (21)	5 (17)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; RSV, respiratory syncytial virus; *S*, *Staphylococcus*.

NOTE: Data presented as n (%) unless otherwise stated.

[a]All cases with an identified virus (bocavirus, coronavirus, influenza, metapneumovirus, parainfluenza, rhinovirus, or RSV).

[b]*M pneumoniae*, *Chlamydophila pneumoniae*, or *Legionella pneumophila* identified.

[c]Any combination of the following underlying conditions listed in the table.

[d]Vaccinated against seasonal influenza before actual season.

[e]Of 168 patients ≥65 years of age, 32 (19%) had received pneumococcal vaccination.

Table 2. Population Incidence of Community-Acquired Pneumonia Requiring Hospital Admission per 10 000 Adults[a]

Type of Pneumonia	All Adults	Age 18–49	Age 50–64	Age 65–79	Age ≥80
All-cause pneumonia	20.6	8.3	19.1	53.1	127.3
Streptococcus pneumoniae detected	4.1	1.6	3.9	11.1	23.3
S pneumoniae detected (polymerase chain reaction results excluded)	2.8	1.0	2.4	8.0	18.6
Mycoplasma pneumoniae detected	2.4	2.3	2.1	1.9	6.2
Virus detected	3.1	1.5	3.6	7.4	14.0
More than 1 pathogen detected	2.0	1.0	1.5	6.8	7.8

[a]Population statistics derived from publicly available official data (Statistics Iceland: http://www.hagstofa.is/Hagtolur/Mannfjoldi/).

with rhinovirus in 4 cases (13%), and with RSV in 3 cases (10%; see Table 3).

Sputum culture was positive in 54 cases (53% of available samples); however, only 101 participants (33%) could provide an adequate sample. In comparison, blood culture yielded relevant results in 16 (7%) of 231 cases. Polymerase chain reaction analysis of 201 available samples resulted in the identification of 43 (21%) atypical bacterial pathogens and 47 (23%) viruses. In addition, 31 (25%) possible cases of *S pneumoniae* and 12 (12%) possible cases of *H influenzae* were detected using PCR. For *S pneumoniae*, 19 cases were not confirmed by other methods, whereas 4 cases of *H influenzae* were not confirmed by other methods. *S pneumoniae* and *H influenzae* were identified in 22 and 30 additional cases, respectively, using multiplex PCR, but these were above the cycle threshold and thus excluded from further analysis.

A complete set of samples was available in 58 cases (19%) (Table 4), an etiological agent was detected in 45 cases (78%), and multiple pathogens were identified in 15 cases (26%). *S pneumoniae* and *H influenzae* were identified at a greater rate among patients without recent antibiotic use, whereas *M pneumoniae* was detected more frequently among patients with recent antimicrobial use (Table 4).

Seasonality

The admission rate due to pneumonia was stable during the study period. However, viral activity had 2 separate peaks. Viral pathogens were detected in 10 of 26 (38%) admissions in February and 12 of 29 (41%) in October. The later peak coincided with the 2009 H1N1 influenza pandemic.

Baseline Characteristics and Microbial Agents

Patient characteristics by probable microbial etiology are shown in Table 1. Comparison is hampered by the low number of participants in some groups. Patients with *M pneumoniae* and influenza were younger and had lower rates of underlying disease compared with other groups. The mean age of *M pneumoniae* cases was 44.8 years and the mean age of influenza cases was 50.1 years, compared with 62.8 years for the entire group (Table 1). Despite a low average age, 11 cases of *M pneumoniae* (31%) were over 60 years of age, and the age-specific incidence of *M pneumoniae* admission was highest among the oldest patients (6.2/10 000; Table 2). Symptoms were similar regardless of detected agent.

We compared the occurrence of the underlying risk factors and symptoms displayed in Table 1 with etiology both directly and with regression analysis. *S pneumoniae* was more likely to be found in patients without recent antimicrobial use ($P = .002$, Fisher's exact test) (odds ratio [OR], 3.9; 95% CI, 1.6–9.3; $P = .002$). This association appeared stronger when PCR results were excluded (OR, 7.1; 95% CI, 2.1–23.6; $P = .001$) and was significant on direct comparison ($P = .003$, Fisher's exact test). Conversely, *M pneumoniae* was more likely to be identified if recent antibiotic use was reported ($P < .001$, Fisher's exact test), a link that was also found on regression analysis (OR, 11.6; 95% CI, 3.2–41.7; $P < .001$).

The likelihood of identifying influenza was higher amongst those not vaccinated against influenza when compared directly ($P < .001$, Fishers exact test) and with regression analysis (OR, 4.9; 95% CI, 1.1–20.8; $P = .03$). Hemoptysis was reported in 6 (21%) influenza cases. All influenza cases with hemoptysis were caused by A(H1N1)pdm09 (n = 22), and the association with hemoptysis was significant for these cases when compared with other participants ($P = .02$, Fishers exact test).

Severity Scores and Outcomes

The PSI and CURB-65 scores were lowest for patients with atypical bacterial infections and influenza (Table 5). Mortality was low with 9 deaths (3%). Despite higher rates of cultures obtained from these patients, a pathogen was detected in only 2 cases (*H influenzae* and *S pneumoniae*, respectively). Length of stay was similar between groups. Patients were admitted to the ICU and received ventilator care at similar rates, and no significant differences between patients with different pathogens were detected on direct comparison (Table 5) or using regression analysis (results not shown).

DISCUSSION

A major strength of this study was the high inclusion rate (95%) from a well defined population, allowing direct assessment of the incidence of CAP requiring hospital admission. The study was performed before the introduction of conjugated pneumococcal vaccination in the national childhood immunization

Table 3. Pathogen Combinations Among 27 Patients With Community-Acquired Pneumonia and Two Detected Agents[a]

	Haemophilus influenzae	*Moraxella catarrhalis*	*Legionella* species	*Chlamydophila pneumoniae*	*Mycoplasma pneumoniae*	Influenza	Rhinovirus	RSV	Parainfluenza	Bocavirus
Streptococcus pneumoniae	3	2	1			5	2	2		1
H influenzae		1	1	1	1		2	2		
Staphylococcus aureus					1					
β-hemolytic streptococci									1	
Burkholderia pseudomallei						1				

Abbreviations: RSV, respiratory syncytial virus.

[a]In 3 additional cases, 3 pathogens were recovered from the same patient: *S pneumoniae*, *H influenzae*, and rhinovirus; *S aureus*, *S pneumoniae*, and rhinovirus; and finally *S pneumoniae*, *H influenzae*, and RSV.

program, making it an important reference point for further studies.

To the authors' knowledge, only 2 previous studies have analyzed the incidence of pneumonia requiring hospital admission in conjunction with etiological testing utilizing PCR of similar scope. Takahashi et al [22] found the incidence of CAP in Vietnam to be 8 cases per 10 000 adults, but these results are difficult to compare with Western studies due to differences in healthcare systems in addition to being based on a much younger population. In a recent study, Jain et al [12] recruited 68% of eligible adult patients and estimated the overall incidence of CAP to be 24.8 cases per 10 000 adults per year, which is similar to our results. In comparison, Torres et al [23] recently determined in a review that the overall incidence of CAP in Europe was approximately 16 per 10 000 population.

Several studies have been published over the last decade utilizing nucleic acid amplification techniques to assess the etiology of pneumonia. A recent prospective study from the United States demonstrated that *S pneumoniae* accounted for 5% of pneumonia requiring admission compared with 20% in this study. A possible explanation may be that Jain et al [12] recovered high-quality sputum samples from only 12% of their participants compared with 31% in this study. Another contributing factor may be more widespread vaccination with the conjugated pneumococcal vaccine in the US population, which had not been introduced in Iceland when this study was performed. Another, smaller study set in the United States found *S pneumoniae* in 19% of their cohort, which is similar to our results [10]. From Europe, Holter et al [11] recently recovered pneumococci in 30% of admitted CAP patients in Norway where conjugated pneumococcal vaccine is included in the childhood vaccination program. Also of note, if results from nasopharyngeal culture and upper airway PCR are omitted, the rate was 18% [11]. Similarly, Bonten et al [24] found that 21% of CAP cases among those >65 years of age were due to *S pneumoniae* but did not use PCR diagnostics. In another recent study, Gadsby et al [13] achieved pathogen detection in 87% of patients using PCR methods on sputum samples, with *S pneumoniae* being identified in 36% of cases. Comparison with our work is difficult, however, because Gadsby et al [13] excluded patients unable to produce sputum. These recent studies support the results of the current study, that 20% of CAP is due to *S pneumoniae*.

Uniquely, the etiology of pneumonia was examined in the population of Reykjavik in 2 simultaneous studies undertaken 25 years before the current work, which found that *S pneumoniae* caused 39% and 26% of cases [25, 26]. This apparent decrease may in part be due to the fact that smoking, a risk factor for both CAP and invasive pneumococcal disease [27, 28], decreased by 50% in the population in the intervening period [29]. The decrease in *S pneumoniae* between these studies and the current one is also in line with the decline in rates of pneumococcal pneumonia during the last century, as reviewed

Table 4. Pathogens Detected in Cases of Community-Acquired Pneumonia and Results From Cases With Complete Sample Sets Available for Etiologic Testing[a]

		Complete Sample Sets Available		
	Entire Cohort	No Antimicrobial Before Admission[b]	Antimicrobial Before Admission[b]	All Cases
n	310	37	21	58
No pathogen detected	146 (47)	8 (22)	5 (24)	13 (22)
Single pathogen detected	134 (43)	16 (43)	14 (67)	30 (52)
More than 1 pathogen detected	30 (10)	13 (35)	2 (10)	15 (26)
Pathogens detected				
Mycoplasma pneumoniae	36 (12)	2 (5)[c]	10 (48)[c]	12 (21)
Streptococcus pneumoniae	61 (20)	12 (32)	3 (14)	18 (31)
Haemophilus influenzae	22 (7)	8 (22)	2 (10)	10 (17)
Influenza A	27 (9)	6 (16)	1 (5)	7 (12)
Moraxella catarrhalis	7 (2)	5 (14)	0 (0)	5 (9)
Rhinovirus	6 (2)	3 (8)	0 (0)	3 (5)
Chlamydophila pneumoniae	4 (1)	1 (3)	1 (5)	2 (3)
Metapneumovirus	3 (1)	2 (5)	0 (0)	2 (3)
RSV	6 (2)	1 (3)	1 (5)	2 (3)
Staphylococcus aureus	8 (3)	1 (3)	1 (5)	2 (3)
Burkholderia pseudomallei	1 (0.3)	1 (3)	0 (0)	1 (2)
Influenza B	1 (0.3)	1 (3)	0 (0)	1 (2)
Legionella species	3 (1)	-	-	-
Pseudomonas aeruginosa	2 (0.6)	-	-	-
Klebsiella pneumoniae	1 (0.3)	-	-	-
Mycobacterium avium	1 (0.3)	-	-	-
Coronavirus	2 (0.6)	-	-	-
Bocavirus	1 (0.3)	-	-	-
Parainfluenza	1 (0.3)	-	-	-
Oropharyngeal PCR results excluded				
S pneumoniae	42 (14)	10 (27)[d]	1 (5)[d]	11 (19)
H influenzae	18 (6)	8 (22)	2 (10)	10 (17)

Abbreviations: PCR, polymerase chain reaction; RSV, respiratory syncytial virus.

NOTE: Data presented as n (%).

[a]Tests performed were cultures of sputum and blood, antigen testing of urine, and PCR analysis of upper airway swabs.

[b]Patient reported data.

[c]The different detection rates of *M pneumoniae* among those with and without prior antimicrobial was statistically significant ($P < .001$; Fisher's exact test).

[d]The different detection rates of *S pneumoniae* among those with and without prior antimicrobial use was statistically significant when PCR results were excluded ($P < .05$; Fisher's exact test).

succinctly by Musher et al [30]. This has not been previously illustrated by repeated studies of the same population, to the author's knowledge.

The rate of *M pneumoniae* was relatively high in this study, i.e., identified in 36 cases (12%). In comparison, Jain et al [12] and Gadsby et al [13] identified *M pneumoniae* in 2% of their respective cohorts, whereas Holter et al [11] found this pathogen in 4% of patients. This result may be due to an ongoing local epidemic during the study period, but this question requires further study. Younger patients were relatively more likely to have *M pneumoniae* or influenza infections in this study. Although *M pneumoniae* infection is known to be common in younger individuals, approximately one third of cases were among older patients in this study, and the highest incidence was in this group [3]. *Mycoplasma pneumoniae* is also implicated in severe pneumonia; Miyashita et al [31] found that 6% of patients had severe disease requiring ICU admission. In this study, 4 (11%) of patients with *M pneumoniae* received ICU care. In comparison, 5 patients (8%) with *S pneumoniae* were admitted to ICUs.

Although *S pneumoniae* was identified in 37% of diagnosed cases, viruses were also commonly recovered (31%), whereas atypical bacteria were found in 28%. Previous studies have found viral pathogens in 15%–32% of patients with CAP [6–8, 12, 13, 32]. Influenza was the most common virus, and most cases were infected with the H1N1 pandemic strain and admitted during October 2009. It has previously been shown that the elderly population was relatively protected from the pandemic influenza A(H1N1)pdm09 strain, likely due to cross-reactive immune responses [33].

We found that 107 (35%) patients reported receiving antibiotics before admission, similar to previous reports (11%–32%) [6,

Table 5. Outcomes and Severity Scores of Patients Admitted With Community-Acquired Pneumonia by Detected Etiological Agent

	Entire Group	*Streptococcus pneumoniae*	*Mycoplasma pneumoniae*	*Haemophilus influenzae*	*Staphylococcus aureus*	*Moraxella catarrhalis*	β-hemolytic Streptococci	Influenza	Rhinovirus	RSV	Any Virus[a]	Any Atypical[b]	Dual Pathogens
n	310	61	36	22	8	7	5	28	6	6	47	43	30
Length of stay	7.5 (6.9–8.1)	7.7 (6.3–9.1)	7.1 (5.6–8.6)	7.9 (5.9–9.9)	14.5 (7.1–21.9)	9.6 (1.5–17.6)	8.8 (4.2–13.4)	8.8 (6.2–11.5)	8.0 (5.5–10.5)	7.5 (4.5–10.5)	8.4 (6.7–10.1)	7.1 (5.7–8.6)	8.4 (5.9–10.9)
In-house mortality, n (%)	9 (3)	1 (2)	0	1 (5)	0	0	0	0	0	0	0	0	0
ICU admission	25 (8)	5 (8)	4 (11)	2 (9)	2 (25)	1 (14)	0	9 (32)	1 (17)	0	10 (21)	5 (12)	4 (13)
Required mechanical ventilation	8 (3)	2 (3)	2 (6)	1 (5)	1 (13)	1 (14)	0	3 (11)	0	0	3 (6)	2 (5)	2 (7)
PSI score	77.1 (73.3–81.0)	79.7 (71.6–87.8)	51.6 (41.2–62.0)	87.1 (73.3–100.9)	100.8 (76.3–125.2)	93.1 (78.4–107.9)	62.8 (48.4–77.2)	63.7 (51.6–75.8)	88.0 (70.1–105.9)	95.2 (67.1–123.3	73.7 (64.1–83.4)	54.3 (44.6–64)	79.6 (68.1–91.3)
CURB-65 score	1.3 (1.2–1.4)	1.4 (1.2–1.7)	0.6 (0.4–0.9)	1.5 (1.0–2.0)	2.3 (1.4–3.1)	1.4 (0.7–2.2)	0.2 (0–0.6)	0.8 (0.4–1.2)	2.0 (1.3–2.7)	1.8 (1.1–2.6)	1.2 (0.9–1.5)	0.8 (0.5–1.0)	1.4 (1.0–1.8)

Abbreviations: CURB-65, confusion, urea, respiratory rate, blood pressure, age over 65; ICU, intensive care unit; PSI, pneumonia severity index; RSV, respiratory syncytial virus.

NOTE: Data presented as mean (95% confidence interval) unless otherwise stated.

[a]All cases with an identified virus (bocavirus, coronavirus, influenza, metapneumovirus, parainfluenza, rhinovirus, or RSV).

[b]*M pneumoniae*, *Chlamydophila pneumoniae*, or *Legionella pneumophila* identified.

7, 12, 34]. Prior antibiotic use was associated with detection of *M pneumoniae*, a correlation that has been noted previously [35]. It is possible that this reflects the lack of therapeutic response to empiric antimicrobial therapy against pneumonia in the outpatient setting, which commonly consists of β-lactams, but would be worthy of further study. Conversely, the odds of identifying *S pneumoniae* were increased in patients without recent antimicrobial use. It is also possible that participants who had received prior treatment had more drawn out symptoms indicative of different etiology. Some previous studies have excluded patients unable to produce sputum or with recent antimicrobial use to improve diagnostic yield [6, 13]. Our results, which include the vast majority of eligible patients, indicate that such an approach may introduce a major selection bias by excluding infections caused by "atypical" bacteria and viruses and preferentially include pneumonia caused by *S pneumoniae*.

Despite our diagnostic attempts, we did not find any etiology for 47% of patients in this study. This is common and 2 recent studies found no etiology in 37%–62% of patients [11, 12]. The reasons for this are unclear, and this is an important area for further study.

This study indicated that the likelihood of detecting pandemic influenza A(H1N1)pdm09 was increased for patients reporting hemoptysis. This strain has been associated with more severe disease than seasonal influenza [19]. Blood in sputum was reported in 30% of the first influenza A(H1N1) pdm09 cases from Mexico in 2009, whereas hemorrhagic tracheitis and bronchitis has been noted as a histological feature in severe cases in prior influenza pandemics [36, 37]. Other reported symptoms were similar in all groups and did not help in discerning between different etiologies. The lack of correlation of symptoms with etiology has been demonstrated previously and is confirmed by these results [38].

Mortality was relatively low (3%) compared with many previous studies (2%–15%), possibly due to differences in setting and inclusion criteria [3, 4, 7, 12, 39]. Jain et al [12] found a similar mortality (2%) in their cohort and a similar PSI score despite being younger, whereas 21% of their patients were admitted to ICU and 6% required invasive ventilation. Corresponding results from this study are 5% and 2%, respectively, if cases due to the H1N1 pandemic are excluded (Table 5). Conversely, the median LOS was 3 days in the study by Jain et al [12] compared with 7 in the current study, probably reflecting major differences in management approaches to this problem between a Nordic country and the United States. Holter et al [11] examined a Norwegian cohort with an identical median age to ours and found a similar LOS (7 days), and although 18% were admitted to ICU, the mortality was 4%. It is likely that systemic factors and different thresholds for ICU admission, timing of switching from intravenous to oral, and transfer to outpatient management may explain some of these differences [11, 12].

Rates of ICU admissions, use of assisted ventilation, and LOS were similar for patients irrespective of organisms identified. It is notable that patients with atypical pathogens had lower PSI and CURB-65 scores than other patients but required similar ICU care and LOS. Because both scores include age as risk factors, the relatively low age of influenza and *M pneumoniae* patients may offer a partial explanation. Severity scores and outcomes were also similar for patients with an identified virus when compared with other patients. Although pandemic influenza cases heavily influenced this result, they did not account for all morbidity in this group. Patients with dual pathogens had a trend towards worse outcomes, but the number of patients was low and therefore a great potential for type II error.

This study has several limitations. As in similar studies, no potential etiology was identified for a sizeable group of participants. Despite the high level of patient inclusion, we were not able to collect all tests for all participants: a more complete sample set might have resulted in the detection of more potential pathogens. We chose to collect oropharyngeal swabs for PCR analysis to optimize sample collection and patient recruitment. It is possible that use of nasopharyngeal samples may have increased sensitivity for respiratory viruses [40]. In addition, an organism identified from the upper airway cannot always be assumed to be the causative agent for pneumonia, and PCR results for some organisms must be interpreted as suggestive for possible etiology. It is also possible that our method of batch analysis and storage may have decreased the sensitivity of our laboratory methods. When comparing the statistical results of this study, the number of relevant variables in comparison with the cohort size, particularly for individual etiologies, must be kept in mind as in other comparable studies. We applied multinomial regression as part of our analysis, but there is a risk of overfitting due to small numbers of individual outcomes, cohort size, and number of variables. The results of direct comparisons are reported alongside these results but must also be interpreted with the number of comparisons in mind. Both of these factors increase the risk of type I error.

CONCLUSIONS

This population-based study with a 95% inclusion rate demonstrates an incidence of CAP requiring hospitalization of 20.6 cases per 10 000 adults/year. *S pneumoniae* was the most frequently identified pathogen. The incidence of *M pneumoniae* was highest amongst the oldest patients, similar to the other pathogens examined. Study designs that exclude participants with prior antibiotic use or unable to produce sputum to increase diagnostic yield may lead to biased results and miss certain pathogens. Clinical signs and symptoms were of limited use for identifying patients with a respiratory virus or atypical bacterial infection, and, despite lower severity scores among these patients, LOS and rates of ICU admission and need for assisted ventilation were similar regardless of microbial etiology.

Acknowledgments

We thank Drs. Hilmir Asgeirsson, Janus F. Gudnason, and Kristinn L. Hallgrimsson (Department of Medicine, Landspitali University Hospital, Reykjavik) and Berglind Kristjansdottir and Gunnsteinn Haraldsson (University of Iceland) for their work in recruiting participants and processing clinical samples. We also thank the house staff, nurses, and laboratory personnel of Landspitali University Hospital for help in recruiting participants and preserving samples. Finally, we thank the personnel of the Department of Microbiology and Department of Virology at Landspitali University Hospital as well as the personnel at the Department of Microbiology at the Sahlgrenska University Hospital for help in processing samples.

Financial support. This work was funded by the Icelandic Center for Research, Rannís (grant number 100436021), the Landspitali University Hospital Science Fund, and the University of Iceland Research Fund.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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