MAJOR ARTICLE

Epidemiology of Severe Pneumonia Caused by *Legionella longbeachae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae:* 1-Year, Population-Based Surveillance for Severe Pneumonia in Thailand

Christina R. Phares,[1,2] Piyada Wangroongsarb,[3] Somrak Chantra,[5] Wantana Paveenkitiporn,[3] Maria-Lucia Tondella,[2] Robert F. Benson,[2] W. Lanier Thacker,[2] Barry S. Fields,[2] Matthew R. Moore,[2] Julie Fischer,[4] Scott F. Dowell,[4] and Sonja J. Olsen[4]

[1]Epidemic Intelligence Service Program, Office of Workforce and Career Development, and [2]Respiratory Diseases Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Thailand National Institute of Health and [4]International Emerging Infections Program, Thailand Ministry of Public Health–US Centers for Disease Control and Prevention Collaboration, Nonthaburi, and [5]Crown Prince General Hospital, Sa Kaeo, Thailand

Background. *Legionella* species, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* are recognized as important causes of pneumonia in high-income countries, but their significance in middle-income countries, such as Thailand, is unknown.

Methods. Population-based surveillance identified inpatient 3489 cases of clinically-defined pneumonia in a rural Thai province for 1 year. Patients who had a chest radiograph performed (for 2059 cases of pneumonia) were enrolled in an etiology study (which included 755 cases of pneumonia among 738 patients). Paired serum, nasopharyngeal swab, and urine specimens were obtained for diagnostic immunologic and molecular tests. Patients aged <18 years were not systematically tested for *Legionella* species. We report a lower limit of incidence (observed incidence) and an upper limit extrapolated to persons not tested or not enrolled in the study.

Results. The incidence of pneumonia due to *Legionella longbeachae* requiring hospitalization was 5–29 cases per 100,000 population. No case of *Legionella pneumophila* pneumonia was observed. The definite *C. pneumoniae* pneumonia incidence was 3–23 cases per 100,000 population; rates were highest among patients aged <1 year (18–166 cases per 100,000 population) and those aged ⩾70 years (23–201 cases per 100,000 population). *M. pneumoniae* pneumonia had a similar age distribution, with an overall incidence of 6–44 cases per 100,000 population. These pathogens were associated with 15% of all cases of pneumonia. A nonsignificantly higher proportion of patients with pneumonia associated with *L. longbeachae,* compared with patients with pneumonia associated with *M. pneumoniae* or *C. pneumoniae,* required supplemental oxygen or mechanical ventilation (45% vs. 18%; $P < .1$). Among patients with atypical pneumonia, only 15% received antibiotics with activity against the associated pathogen.

Conclusion. *M. pneumoniae, C. pneumoniae,* and *L. longbeachae,* but not *L. pneumophila,* are frequently associated with severe pneumonia in rural Thailand. Few patients receive antibiotics that cover atypical pathogens.

Pneumonia remains a leading cause of death worldwide, especially among children and older persons. The World Health Organization estimates that lower respiratory infections cause nearly 4 million deaths per year, a rate of >60 deaths per 100,000 population [1]. Among children aged <5 years, pneumonia is responsible for 10%–25% of all deaths in developing countries [2].

Accurate estimates of the incidence of specific pneumonia etiologies are valuable for appropriate allocation of public health resources, establishing vaccine priorities, and developing evidence-based standards for treatment. In high-income countries, recommendations for empirical antibiotic therapy are based on relative frequencies of individual pneumonia pathogens, as well as considerations of severity of illness, resistance pat-

Received 17 April 2007; accepted 7 August 2007; electronically published 9 November 2007.

Reprints or correspondence: Dr. Christina R. Phares, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, Mailstop E-03, Atlanta, GA 30333 (CPhares@cdc.gov).

Clinical Infectious Diseases 2007; 45:e147–55

1058-4838/2007/4512-00E3$15.00
DOI: 10.1086/523003

terns, and comorbid conditions [3]. Because pathogen probabilities vary across populations, regional data are needed, especially in understudied middle- and low-income countries, where the burden of pneumonia is high and diagnostic testing may be less readily available. Incidence data are additionally important for establishing a baseline for the burden of respiratory illness—a necessary first step in detecting departures from baseline that are attributable to emergent disease.

The present study provides some of the first population-based estimates of the incidence of severe pneumonia due to atypical respiratory pathogens *(Legionella* species, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae)* in Southeast Asia. Although these pathogens are increasingly recognized as important causes of pneumonia in other parts of the world, their significance in Thailand has not been well described. To estimate disease incidence, we conducted active, population-based surveillance for adult and pediatric inpatient cases of pneumonia in Sa Kaeo, a rural province in Thailand, and performed immunologic and molecular diagnostic testing for enrolled patients over a 1-year period.

METHODS

Case definition for severe clinical pneumonia. A patient with severe clinical pneumonia was defined as any person admitted to a study hospital who met the following 3 criteria: (1) residency in Sa Kaeo province (population, 438,557), (2) at least 1 sign of acute infection at hospital admission (self-reported history of fever or chills, documented temperature >38.2°C or <35.5°C, WBC count >11 or <3 $\times 10^3$ cells/mm^3, or abnormal WBC differential as defined by the clinical laboratory), and (3) at least 1 sign or symptom of respiratory disease at hospital admission (abnormal breath sounds, cough, sputum production, hemoptysis, dyspnea, or chest pain). Patients who were readmitted to a study hospital within 14 days after hospital discharge were classified as having a single episode of pneumonia, and patients who were readmitted to the hospital ⩾14 days after hospital discharge were classified as having recurrent pneumonia.

Surveillance. Active, population-based surveillance began in September 2002 and is ongoing in all Sa Kaeo hospitals (6 district hospitals, 1 large provincial hospital, and 1 military hospital). Inpatients who receive a diagnosis related to pneumonia are identified by daily review of admissions records, and a standardized case report form is completed for those who meet the case definition for severe clinical pneumonia [4]. A 2002 community survey confirmed that 80% of Sa Kaeo residents with symptoms of pneumonia sought hospital-based care; among those who sought hospital-based care, 98% did so at 1 of the 8 Sa Kaeo hospitals [4].

Etiology study. From 1 September 2003 through 31 August 2004, patients with severe clinical pneumonia who had a chest radiograph performed (at the treating physician's discretion) were invited to participate in an etiology study. After informed consent was obtained, study nurses collected acute serum, nasopharyngeal swab, and urine specimens from patients within 48 h after hospital admission. Convalescent serum specimens were collected 3 weeks later. This study was approved by the ethical review committee of the Thailand Ministry of Health and the institutional review board of the Centers for Disease Control and Prevention.

Laboratory methods. *M. pneumoniae* combined IgG and IgM titers were assessed using the *M. pneumoniae* IgG/IgM Antibody Test System (Remel). *C. pneumoniae* IgG and IgM titers were measured using a microimmunofluorescence assay (Focus Diagnostics), in accordance with current recommendations [5]. PCR assays were used to test nasopharyngeal swab specimens for *M. pneumoniae* and *C. pneumoniae* nucleic acid [6, 7]. *Legionella longbeachae* combined IgG, IgA, and IgM titers were measured using an indirect immunofluorescence assay [8, 9]. The antigen for indirect immunofluorescence assay was prepared by growing *L. longbeachae* serogroup 1, strain Long Beach 4, on buffered charcoal yeast extract agar slants at 37°C with 2.5% CO_2 for 24 h. *Legionella pneumophila* serogroup 1 urinary antigen level was measured by EIA (Binax).

Specimens were also tested for *Streptococcus pneumoniae* (by urine antigen test for patients aged ⩾18 years), *Coxiella burnetii* (by serologic testing), acid-fast bacilli (by sputum smear), influenza virus (by culture, RT-PCR, and serologic testing), respiratory syncitial virus (by culture, RT-PCR, and serologic testing), picornavirus (by RT-PCR and serologic testing), adenovirus (by culture, RT-PCR, and serologic testing), human parainfluenza viruses (by culture, RT-PCR, and serologic testing), and human metapneumovirus (by RT-PCR and serologic testing).

Etiologic diagnosis. Definite acute infection was defined as seroconversion for antibody to *M. pneumoniae* (IgG/IgM negative to IgG/IgM positive), a ⩾4-fold increase in antibody titer to *C. pneumoniae* (IgG or IgM), or a ⩾4-fold increase in antibody titer to *L. longbeachae* (IgG/IgA/IgM titer, ⩾1:128) in paired acute-phase and convalescent-phase serum specimens; a result of PCR of nasopharyngeal swab specimens that was positive for *C. pneumoniae* or *M. pneumoniae;* or a result of a urine antigen test that was positive for *L. pneumophila.* Possible acute infection with *C. pneumoniae* was defined as a single IgM titer ⩾1:16. When paired serum specimens were not available, a negative PCR result defined the absence of infection. Because the incidence of legionellosis in children and adolescents is rare [10], testing for *L. longbeachae* in patients aged <18 years was limited to a 71% convenience sample of those with paired serum samples available to confirm the absence of legionellosis in this age group, and no patients in this age group were tested

Table 1. Test results for 755 cases of acute infection with *Legionella longbeachae, Mycoplasma pneumoniae,* and/or *Chlamydia pneumoniae* among inpatients with clinically-defined pneumonia.

Pathogen[a]	Serologic testing[b]		PCR	Ratio of patients with concordant test results to those with discordant test results	Total
	Definite	Possible			
L. longbeachae[c]	20/397 (5.0)	…	…	…	20/397 (5.0)
M. pneumoniae	15/568 (2.6)	…	14/752 (1.9)	2:25	27/755 (3.6)
C. pneumoniae	14/568 (2.4)	69/568 (12.1)	2/752 (0.3)	2:81[d]	83/755 (11)

NOTE. Data are no. of patients with positive test results/no. of patients tested (%), unless otherwise indicated.

[a] Pathogen categories are not mutually exclusive.

[b] Paired serum specimens were obtained and tested for 392 (72%) of 547 adults and for 176 (85%) of 208 children and adolescents aged ⩽19 years. A diagnosis of definite infection was made on the basis of seroconversion or a ⩾4-fold increase in antibody titer in paired acute-phase and convalescent-phase serum specimens. A diagnosis of possible infection was made on the basis of presence of a single IgM titer ⩾1:16 and absence of a ⩾4-fold increase in IgG or IgM titer to *C. pneumoniae*.

[c] Excluding patients aged <18 years.

[d] The 2 serologic assay results that were concordant with PCR assay results were positive on the basis of a ⩾4-fold increase in antibody titer (i.e., definite *C. pneumoniae* infection).

for *L. pneumophila*. No attempt was made to assign a primary etiology when multiple pathogens were present.

Statistical methods. To calculate the lower limit of incidence of severe clinical pneumonia due to a specific pathogen, we divided the observed number of cases with laboratory evidence of a specific infection by 2001 provincial census data. To extrapolate the upper limit of incidence, we first determined, among tested patients, the proportion of patients with positive test results for each pathogen by 5-year age strata and applied those proportions to the entire population of patients with severe clinical pneumonia that was captured by surveillance. Then, because 20% of surveillance-area residents do not seek hospital-based care for pneumonia [4], we adjusted for access to care by age. Incidence is reported as a range, from the lower limit to upper limit. The prevalence of pathogen-specific severe clinical pneumonia is the proportion of patients testing positive for each pathogen among all patients tested. A 3-month moving average was used to calculate monthly incidence, except for the first and last observations, wherein a 2-month average was used. The χ^2 test or Fisher's exact test were used to compare proportions.

RESULTS

Study population. From 1 September 2003 through 31 August 2004, active surveillance identified 3489 cases of severe clinical pneumonia; a chest radiograph was performed for 2059 (59%) of these cases. Among cases for which a chest radiograph was performed, 755 (37%) cases were included in the study, including 17 recurrent cases. Of these included cases, 463 (61%) were in male patients, 292 (39%) were in female patients, 547 (72%) were in adult patients (age, >19 years), and 208 (28%) were in children and adolescents. The median age was 60 years (first and third quartiles, 43–72 years) for adults and 2 years (first and third quartiles, 0–5 years) for children and adolescents. Six cases occurred in neonates (age, <1 month). Compared with enrolled patients, among the unenrolled, the proportion of cases in male patients was significantly lower (61% vs. 56%; $P < .05$, by χ^2 test), and the proportion of cases in pediatric and adolescent patients was significantly higher (28% vs. 48%; $P < .05$, by χ^2 test).

Test results. Among the 755 cases in enrolled patients with severe clinical pneumonia, paired serum specimens were obtained a median of 22 days apart and were tested for 568 cases (75%); nasopharyngeal swab specimens for 752 cases (>99%) were tested by PCR. Collectively, 117 cases (15%) were in patients with evidence of 130 acute infections due to ⩾1 atypical pathogen. Table 1 shows the distribution of test results for each atypical pathogen.

Among 554 cases of severe clinical pneumonia in patients

Table 2. Lower and upper limits of incidence of clinical pneumonia associated with *Legionella longbeachae, Mycoplasma pneumoniae,* and/or *Chlamydia pneumoniae,* by age group.

Age group[a]	Lower and upper incidence of infection, cases per 100,000 population			
			C. pneumoniae[b]	
	L. longbeachae (n = 20)	*M. pneumoniae* (n = 27)	Definite (n = 14)	Definite and possible (n = 83)
Children	…	9.8–84	2.0–20	5.2–54
Adults	7–45	4.2–23	3.9–24	27–176
All	4.6–29	6.2–44	3.2–23	19–133

[a] Children were patients aged ⩽19 years, and adults were aged >19 years.

[b] Diagnosis of definite *C. pneumoniae* infection was based on a ⩾4-fold increase in antibody titer to *C. pneumoniae* (IgG or IgM) in paired acute-phase and convalescent-phase serum samples. Possible *C. pneumoniae* infection was diagnosed on the basis of a single IgM titer ⩾1:16.

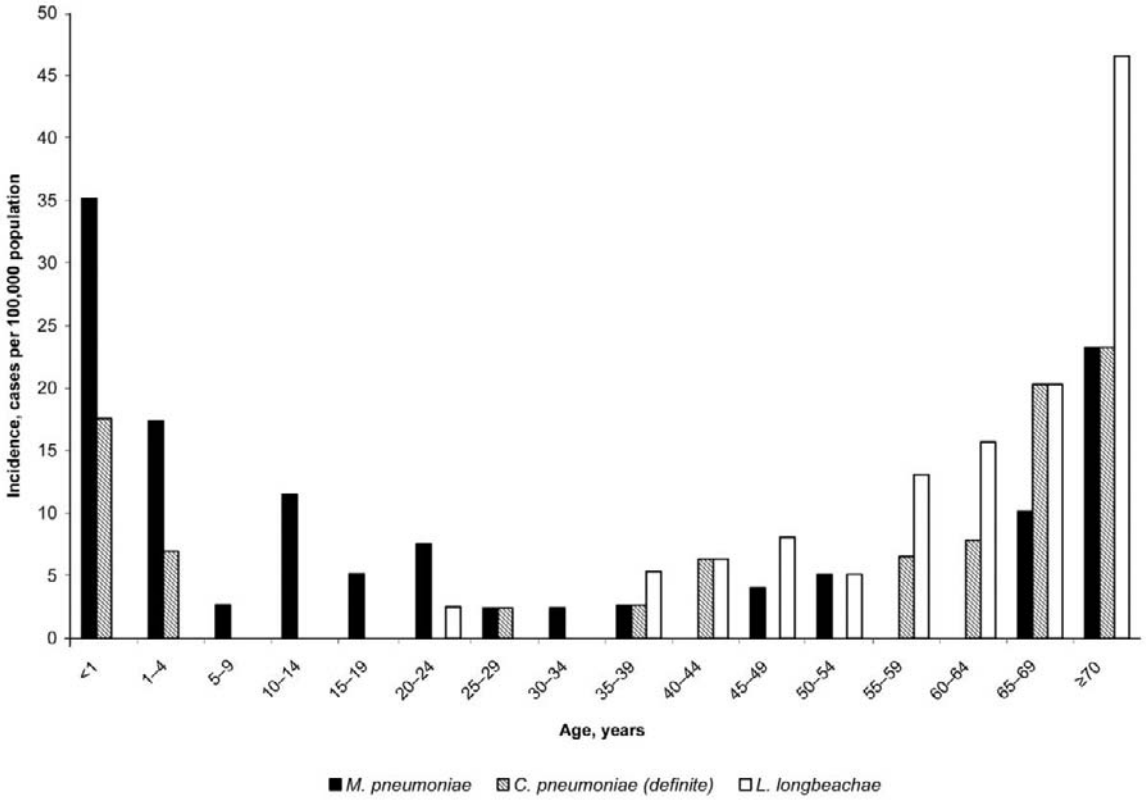

Figure 1. Minimum incidence of infection with *Legionella longbeachae* (adults aged >19 years only), *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae,* by age.

who were ⩾18 years of age (the only age group tested for both *L. pneumophila* and *L. longbeachae*), none were in patients with evidence of *L. pneumophila* infection, but 20 (5.0%) of 397 cases were in patients with serologic evidence of acute *L. longbeachae* infection. Among 201 cases in patients aged <18 years who had paired serum specimens available, 121 (71%) cases were in patients tested for *L. longbeachae,* with no positive results.

M. pneumoniae was detected in 27 (3.6%) of 755 cases. Diagnoses of *M. pneumoniae* infection were based on seroconversion alone for 13 cases, PCR results alone for 12 cases, and concordant results for 2 cases. Eleven (92%) of 12 cases were in patients who had positive PCR results alone and who had serologic evidence of persistent or recent past infection (both acute-phase and convalescent-phase serum specimens were positive for antibody to *M. pneumoniae).* In comparison, among 537 cases in patients who had negative PCR results and had paired serum samples available, only 139 (26%) were in patients with evidence of persistent or recent past infection (92% vs. 26%; $P < .05$, by Fisher's exact test).

Eighty-three (11%) of 755 cases were in patients with evidence of definite or possible acute *C. pneumoniae* infection: 14 (2.4%) of 568 cases were in patients who were tested and received a diagnosis on the basis of a ⩾4-fold increase in antibody titer; 2 cases (and no other cases) were in patients who also had a positive PCR result. Another 69 cases were in patients who received a diagnosis on the basis of a single high IgM titer. Seroreversion for antibody to *M. pneumoniae* (i.e., from antibody positive to antibody negative in paired serum specimens) was rare (occurring in <0.2% of cases), as were ⩾4-fold decreases in antibody titer to *C. pneumoniae* (0.5%) or *L. longbeachae* (<0.2%).

Age and sex distribution. Table 2 shows the lower and upper limits of incidence for severe clinical pneumonia due to each atypical pathogen by age. The incidence of *L. longbeachae* pneumonia was highest among adults aged >34 years and increased with advancing age, reaching a minimum incidence of 47 cases per 100,000 population among patients aged ⩾70 years (figure 1). The proportion of cases due to *L. longbeachae* varied from 4% to 6% among patients aged >24 years (figure 2). The incidence of *L. longbeachae* infection was higher among male patients in every age stratum, with an overall male-to-female rate ratio (RR) of 1.6 (95% CI, 1.1–2.3).

For *M. pneumoniae* pneumonia, incidence was highest among infants (age, <1 year), at 35–289 cases per 100,000 population, and among elderly patients (age, ⩾70 years), at 23–

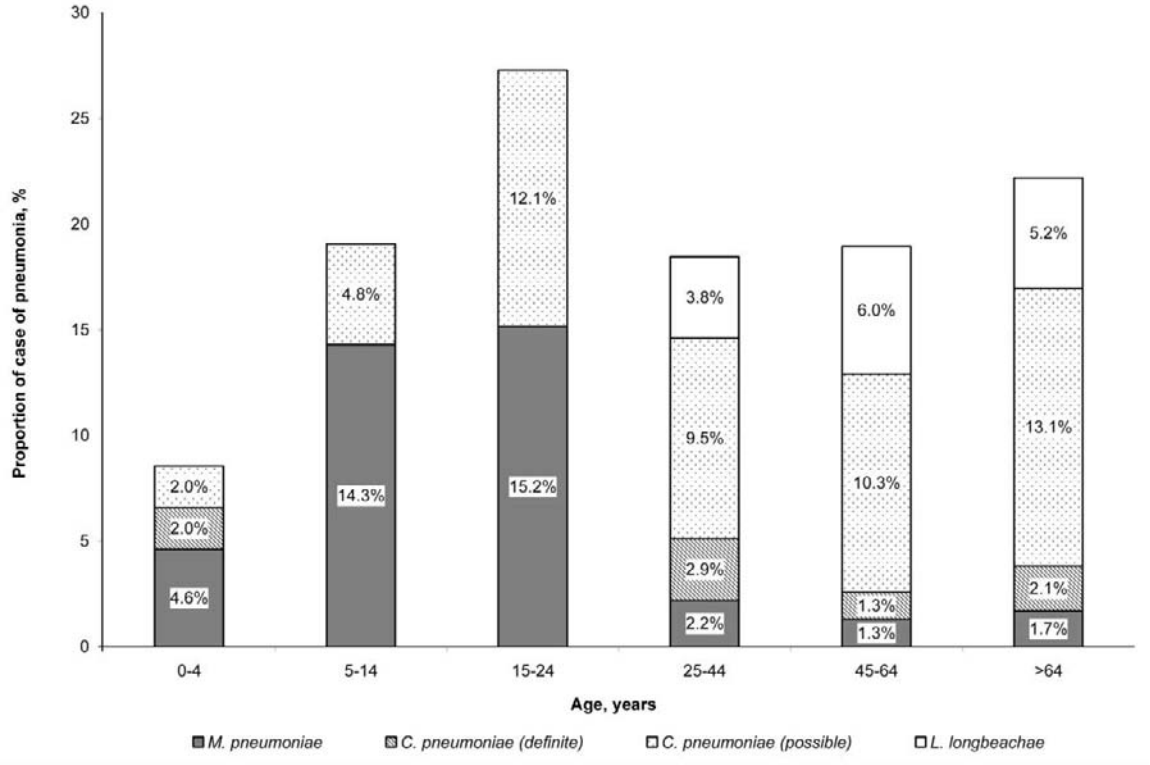

Figure 2. Proportion of all cases of pneumonia associated with *Legionella longbeachae* (adults aged >19 years only), *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae,* by age. The proportion of cases of *L. longbeachae* infection among patients aged 20–24 years are not included in the figure; 3.4% of patients tested in this age group were positive for *L. longbeachae.*

110 cases per 100,000 population (figure 1). *M. pneumoniae* was also the most commonly identified atypical pathogen in children and adolescents, associated with nearly 5% of cases of pediatric pneumonia in children aged <5 years and almost 15% of cases of pneumonia in patients aged 5–24 years (figure 2). The male-to-female RR for *M. pneumoniae* pneumonia varied by age: among children and adolescents, the incidence was significantly higher among boys than among girls (RR, 2.6; 95% CI, 1.7–3.9); among adults, the incidence was higher among women than among men (RR, 0.3; 95% CI, 0.1–0.5).

The overall incidence of definite *C. pneumoniae* pneumonia was 3.2–23 cases per 100,000 population. When cases associated with possible *C. pneumoniae* infection were added, incidence increased >6-fold. This change was age-dependent, increasing 3-fold among patients aged ⩽19 years, 6-fold among patients aged 20–70 years, and 10-fold among those aged ⩾70 years, on the basis of observed incidence calculations. *C. pneumoniae* infection (definite and possible) was associated with 14% of cases of pneumonia among patients aged >19 years and 4% of pediatric cases; however, when only cases associated with definite infection were considered, the prevalence of cases associated with this pathogen was substantially lower, at 2% among adults and 1.4% among children and adolescents (figure 2). The incidence of *C. pneumoniae* pneumonia (definite and possible) was higher among men than among women (RR, 1.5; 95% CI, 1.2–1.9) and much higher among boys than among girls (RR, 7.1; 95% CI, 3.4–15).

Temporal distribution. Figure 3 shows the number of cases of clinical pneumonia due to each pathogen, by month, and includes the number of cases of all-cause, chest radiograph–confirmed pneumonia for comparison. The number of cases of all-cause pneumonia peaked between February and April, and the number case of *M. pneumoniae, C. pneumoniae,* and *L. longbeachae* pneumonia peaked between September and December. Pneumonia due to *M. pneumoniae* and *C. pneumoniae* was largely absent from April through June. The temporal distribution of cases of possible *C. pneumoniae* infection was similar to that of cases of definite *C. pneumoniae* infection (data not shown).

Coinfection and clinical course. Coinfections were common among the 117 cases of pneumonia associated with definite and possible atypical infections (table 3). Sixty-five percent of cases of *L. longbeachae* infection were in patients with evidence of infection with at least 1 other pathogen, and 40%–50% of cases of *M. pneumoniae* or *C. pneumoniae* infection were also in coinfected patients. Influenza virus was the most common copathogen.

We observed no significant differences in clinical findings at

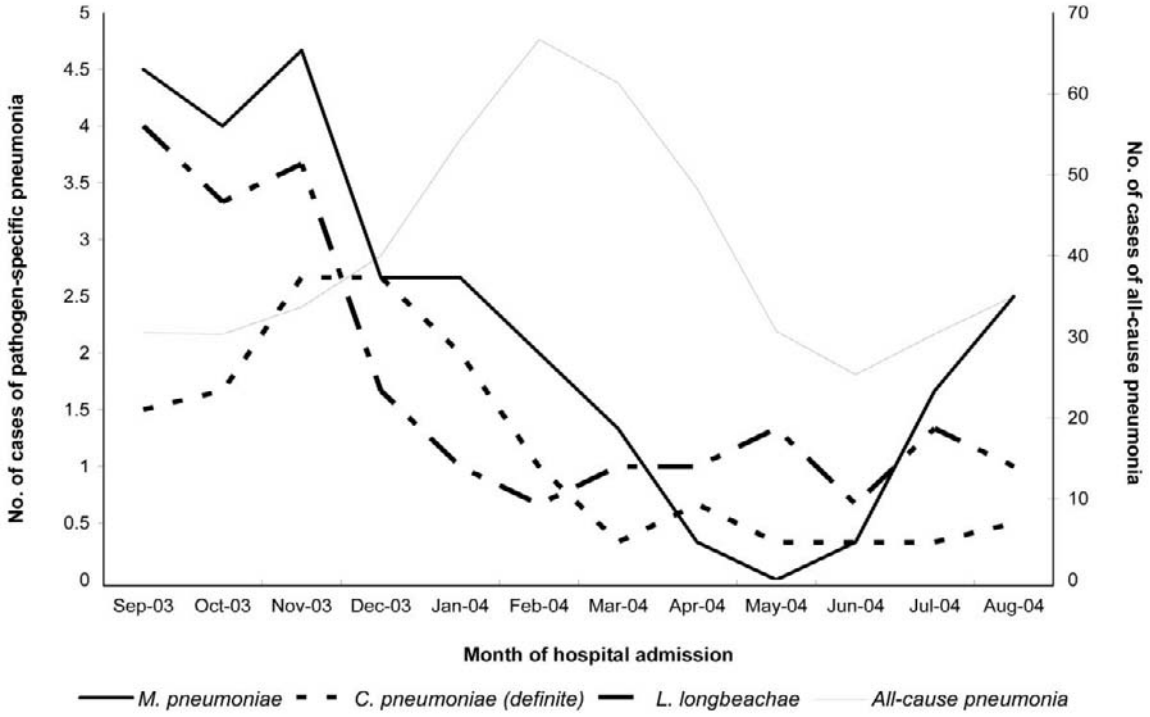

Figure 3. Number of cases of *Legionella longbeachae, Mycoplasma pneumoniae, Chlamydia pneumoniae,* and all-cause pneumonia, by month, with a 3-month moving average.

presentation or chest radiograph patterns by etiology (table 3). During hospitalization, a nonsignificantly higher proportion of adult patients infected with *L. longbeachae* required medical procedures indicative of severe disease (mechanical ventilation or supplemental oxygen), compared with patients infected with *M. pneumoniae* or *C. pneumoniae* (45% vs. 18%; $P < .1$, by Fisher's exact test). Among all 95 adult patients infected with at least 1 atypical bacterial pathogen, 47 (49%) had significant underlying illness, including heart, liver, or renal disease; chronic obstructive pulmonary disease; asthma; diabetes; stroke; malignancy; or HIV infection. Of 23 children and adolescents, 3 (13%) had underlying illness (asthma or anemia).

Among the 117 patients infected with an atypical pathogen, the majority (79% of patients) received a β-lactam antibiotic alone (57%) or in combination with another antibiotic (22%). Aminoglycosides was the second most commonly prescribed class of antibiotics. Only 18 patients (15%) received antibiotics that have activity against atypical infections (e.g., macrolides or quinolones). Of these 18 patients, 15 were adults. Sixteen patients (14%), 14 of whom were children, received no antimicrobial therapy.

DISCUSSION

Our study is one of the first to describe the importance of *L. longbeachae* infection in Southeast Asia. Previous studies of legionellosis in Asia have focused on *L. pneumophila*—the species that causes ~90% of cases of Legionnaires disease in the United States and Europe [11, 12]—and have reported that *L. pneumophila* serogroup 1 accounts for 2%–5% of cases of pneumonia in hospitalized adults in urban Thailand and 0%–25% of cases in other Asian countries, predominately in urban settings [13–15]. In contrast, our population-based data indicate that severe pneumonia due to *L. pneumophila* serogroup 1 is rare or absent in a rural Thai surveillance population, but that pneumonia due to *L. longbeachae* occurs with some frequency.

Although uncommon in the United States and Europe, *L. longbeachae* accounts for approximately one-half of all cases of Legionnaires disease in Australia and New Zealand [16]. In 2004, passive surveillance in Australia documented a national incidence of *L. longbeachae* pneumonia of 0.7 cases per 100,000 population [16]. In comparison, active surveillance in Sa Kaeo found the incidence of *L. longbeachae* pneumonia in adults to be 5–29 cases per 100,000 population. *L. longbeachae* is the only soil-dwelling pathogenic *Legionella* species, and transmission has been linked to gardening and exposure to potting soil [17]. In Sa Kaeo, 70% of industry is in the agricultural sector [18], which indicates high exposure to soil and, thus, high potential for transmission. We speculate that populations predominately engaged in small-scale agriculture are at increased and underappreciated risk for acquiring *L. longbeachae* infection. Furthermore, the temporal distribution of *L. longbeachae,* which reached its nadir from April through June, suggests that sea-

Table 3. Coinfections and radiographic findings for 117 cases of clinical pneumonia associated with *Legionella longbeachae, Mycoplasma pneumoniae,* and/or *Chlamydia pneumoniae.*

Variable	No. (%) of patients			
	L. longbeachaea[a] (n = 20)	*M. pneumoniae* (n = 27)	*C. pneumoniae*	
			Definite (n = 14)	Possible (n = 69)
Coinfection				
None	7 (35)	16 (59)	7 (50)	44 (64)
Single other pathogen	10 (50)[b]	8 (30)[c]	4 (29)[d]	20 (29)[e]
Multiple other pathogens	3 (15)	3 (11)	3 (21)	5 (7)
Radiograph finding				
Alveolar consolidation	4 (20)	12 (44)	4 (29)	17 (25)
Interstitial infiltrates	8 (40)	10 (37)	5 (36)	36 (52)
Other	2 (10)	2 (7)	1 (7)	5 (7)
No interpretation available	6 (30)	3 (11)	4 (29)	11 (16)

[a] Excluding children and adolescents aged ⩽19 years.
[b] Coinfecting pathogens: *C. pneumoniae* (5), influenza virus (2), *Streptococcus pneumoniae* (1) acid-fast bacillus (1), and picornavirus (1).
[c] Coinfecting pathogens: influenza virus (4), *C. pneumoniae* (2), adenovirus (1), and respiratory syncitial virus (1).
[d] Coinfecting pathogens: *L. longbeachae* (2), *M. pneumoniae* (1), and picornavirus (1).
[e] Coinfecting pathogens: Influenza virus (11), *L. longbeachae* (3), *S. pneumoniae* (2), *M. pneumoniae* (1), acid-fast bacillus (1), adenovirus (1), and human metapneumovirus (1).

sonal factors may affect the occurrence of disease, although multiple years of surveillance data are needed to establish periodicity.

The results of our study also implicate *M. pneumoniae* and *C. pneumoniae* as being frequently associated with severe pneumonia in some segments of the population. Among children, we found that the incidence of both *M. pneumoniae* pneumonia and *C. pneumoniae* pneumonia was highest among patients aged <1 year and second highest among those aged 1–4 years. In contrast, early population-based studies from the United States and Europe found that the incidence of *M. pneumoniae* and *C. pneumoniae* pediatric pneumonia was lowest among patients aged 0–5 years and highest among those aged 5–14 years [19, 20]. This difference in age-specific incidence may relate to differences among study populations in the timing and frequency with which small children are exposed to other children. Although incidence was highest in the youngest age groups, the relative contributions of *M. pneumoniae* and *C. pneumoniae* to severe pediatric pneumonia increased with age, emphasizing the continuing importance of these pathogens in these age groups, as has been formerly reported [21–23].

In adulthood, the incidence of both *M. pneumoniae* pneumonia and *C. pneumoniae* pneumonia is highest among the older population. In addition, the incidence of *M. pneumoniae* pneumonia is significantly higher among women than among men—a finding that has been described previously and has been attributed to mothers having heightened contact with children [19]. Relative to other causes of pneumonia, adult inpatient pneumonia caused by *M. pneumoniae* was rarer (<3%) in the surveillance population than has been reported in population-based studies of inpatient pneumonia in the United States and Europe (5%–8%) [24, 25], and the proportion of cases of pneumonia associated with definite *C. pneumoniae* infection (2.4%) was similar to that seen in other populations [25].

Clinical presentation and radiographic findings are poor predictors of atypical etiology [26]. Therefore, the need for antibiotics that have activity against atypical pathogens cannot easily be determined at presentation. Other studies have revealed that initial treatment of community-acquired pneumonia requiring hospitalization with regimens that cover atypical pathogens, such as a quinolone alone or a macrolide plus a β-lactam antibiotic, leads to improved outcomes [27], and current treatment guidelines for North America reflect these findings [28]. Because few patients in our study received antibiotics from these classes, we were unable to evaluate the impact of type of antimicrobial therapy on outcome.

The diagnosis of atypical infections remains problematic, and much of the variability in frequency across studies is likely because of differences in the diagnostic tests and criteria used. We used recommended serologic criteria and validated molecular techniques to conservatively characterize definite infection. To support the conclusion that seroconversion to antibody to *M. pneumoniae* or a ⩾4-fold increase in antibody titer to *C. pneumoniae* or *L. longbeachae* resulted from infection—and not merely from poorly reproducible testing—we examined the

number of seroreversions and comparable decreases in antibody levels and note that such events were reassuringly rare (frequency of seroreverions and ⩾4-fold decreases in antibody titer, ⩽0.5%). The diagnosis of *C. pneumoniae* infection in particular continues to evolve, although efforts have been made to promote a standard diagnostic approach to *C. pneumoniae* assays [5, 29].

The strengths of our study include nearly complete case ascertainment of severe (inpatient) clinical pneumonia among a well-defined source population, coupled with extensive diagnostic testing, in a region of the world where little is known about the epidemiology of pneumonia. Our study also had certain weaknesses. In addition to the limitations of diagnostic testing, not all patients with signs and symptoms of pneumonia presented to a hospital. Among patients who presented to a hospital, not all had a chest radiograph performed; among those who had a chest radiograph performed, not all were enrolled in the etiology study, and not all enrollees had paired serum samples obtained. Moreover, because the case definition of severe pneumonia relies on clinical rather than radiographic criteria, its specificity may be reduced. Thus, we were unable to measure a precise incidence of severe pneumonia and, instead, presented a lower limit based on observed incidence among the patients enrolled and an upper limit based on an extrapolation. Finally, Sa Kaeo province may not be representative of the whole of rural Thailand.

In summary, *L. longbeachae* but not *L. pneumophila* is frequently associated with severe adult pneumonia in parts of rural Thailand, and *C. pneumoniae* and *M. pneumoniae* are associated with both adult and pediatric pneumonia. Few patients with pneumonia receive antibiotics that have activity against these pathogens. The observed incidence of pneumonia associated with atypical etiologies suggests that initial therapy with antibiotics that cover atypical pathogens would produce benefits that are similar to those seen in other patient populations, although local outcome studies are needed, in addition to considerations of availability and cost.

Acknowledgments

Financial support. Centers for Disease Control and Prevention.
Potential conflicts of interest. All authors: no conflicts.

References

1. World Health Organization. World health report 2004 statistical annex. Available at: http://www.who.int/whr/2004/annex/en/. Accessed 13 July 2006.
2. Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet Infect Dis **2002**; 2:25–32.
3. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. Clin Infect Dis **2000**; 31:347–82.
4. Olsen SJ, Laosiritaworn Y, Siasiriwattana S, Chunsuttiwat S, Dowell SF. The incidence of pneumonia in rural Thailand. Int J Infect Dis **2006**; 10:439–45.
5. Dowell SF, Peeling RW, Boman J, et al. Standardizing *Chlamydia pneumoniae* assays: recommendations from the Centers for Disease Control and Prevention (USA) and the Laboratory Centre for Disease Control (Canada). Clin Infect Dis **2001**; 33:492–503.
6. Tondella ML, Talkington DF, Holloway BP, et al. Development and evaluation of real-time PCR-based fluorescence assays for detection of *Chlamydia pneumoniae.* J Clin Microbiol **2002**; 40:575–83.
7. Zhang M, Holloway B, Thacker W, Schwartz S, Talkington D. Development of TaqMan probe-based PCR with customized internal controls for detecting *Mycoplasma pneumoniae* and *Mycoplasma fermentans* [abstract G-18]. In: Program and abstracts of the 99th General Meeting of the American Society for Microbiology (Chicago). Washington, DC: ASM Press, **1999**:325.
8. Wilkinson HW. Hospital-laboratory diagnosis of *Legionella* infections. Revised ed. Atlanta: Centers for Disease Control and Prevention, **1988**.
9. Wilkinson HW, Reingold AL, Brake BJ, McGiboney DL, Gorman GW, Broome CV. Reactivity of serum from patients with suspected legionellosis against 29 antigens of legionellaceae and *Legionella*-like organisms by indirect immunofluorescence assay. J Infect Dis **1983**; 147: 23–31.
10. Jajosky RA, Hall PA, Adams DA, et al. Summary of notifiable diseases—United States, 2004. MMWR Morb Mortal Wkly Rep **2006**; 53:1–81.
11. Yu VL, Plouffe JF, Pastoris MC, et al. Distribution of *Legionella* species and serogroups isolated by culture in patients with sporadic community-acquired legionellosis: an international collaborative survey. J Infect Dis **2002**; 186:127–8.
12. Fields BS, Benson RF, Besser RE. *Legionella* and Legionnaires' disease: 25 years of investigation. Clin Microbiol Rev **2002**; 15:506–26.
13. Wattanathum A, Chaoprasong C, Nunthapisud P, et al. Community-acquired pneumonia in southeast Asia: the microbial differences between ambulatory and hospitalized patients. Chest **2003**; 123:1512–9.
14. Ngeow YF, Suwanjutha S, Chantarojanasriri T, et al. An Asian study on the prevalence of atypical respiratory pathogens in community-acquired pneumonia. Int J Infect Dis **2005**; 9:144–53.
15. Prapphal N, Suwanjutha S, Durongkaveroj P, et al. Prevalence and clinical presentations of atypical pathogens infection in community acquired pneumonia in Thailand. J Med Assoc Thai **2006**; 89:1412–9.
16. Yohannes K, Roche PW, Roberts A, et al. Australia's notifiable diseases status, 2004, annual report of the National Notifiable Diseases Surveillance System. Commun Dis Intell **2006**; 30:1–79.
17. Centers for Disease Control and Prevention. Legionnaires' disease associated with potting soil—California, Oregon, and Washington, May–June 2000. MMWR Morb Mortal Wkly Rep **2000**; 49:777–8.
18. National Statistical Office Thailand. Population and housing census 2000. Available at: http://web.nso.go.th/pop2000/finalrep/sakaeofn.pdf. Accessed 02 April 2007.
19. Foy HM, Kenny GE, Cooney MK, Allan ID. Long-term epidemiology of infections with *Mycoplasma pneumoniae.* J Infect Dis **1979**; 139: 681–7.
20. Heiskanen-Kosma T, Korppi M, Jokinen C, et al. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. Pediatr Infect Dis J **1998**; 17:986–91.
21. Block S, Hedrick J, Hammerschlag MR, Cassell GH, Craft JC. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. Pediatr Infect Dis J **1995**; 14: 471–7.
22. Harris JA, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. Pediatr Infect Dis J **1998**; 17:865–71.
23. Principi N, Esposito S, Blasi F, Allegra L. Role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in children with community-ac-

quired lower respiratory tract infections. Clin Infect Dis **2001**; 32: 1281–9.
24. Gutierrez F, Masia M, Mirete C, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. J Infect **2006**; 53:166–74.
25. 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.
26. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med **2001**; 163:1730–54.
27. Restrepo MI, Anzueto A. Antimicrobial treatment of community-acquired pneumonia. Clin Chest Med **2005**; 26:65–73.
28. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis **2007**; 44(Suppl 2):S27–72.
29. Kumar S, Hammerschlag MR. Acute respiratory infection due to *Chlamydia pneumoniae:* current status of diagnostic methods. Clin Infect Dis **2007**; 44:568–76.