MAJOR ARTICLE

Increasing Incidence of Legionellosis in the United States, 1990–2005: Changing Epidemiologic Trends

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(See the editorial commentary by Ng et al. on pages 600–2)

Background. An abrupt increase in the incidence of legionellosis in the United States has been noted since 2003. Whether the recent increase is associated with shifting epidemiologic trends has not been well characterized.

Methods. We analyzed all cases of legionellosis reported to the Centers for Disease Control and Prevention through the National Notifiable Disease Surveillance System from 1990 through 2005.

Results. A total of 23,076 cases of legionellosis were reported to the Centers for Disease Control and Prevention from 1990 through 2005. The number of reported cases increased by 70% from 1310 cases in 2002 to 2223 cases in 2003, with a sustained increase to >2000 cases per year from 2003 through 2005. The eastern United States showed most of the increases in age-adjusted incidence rates after 2002, with the mean rate in the Middle Atlantic states during 2003–2005 exceeding that during 1990–2002 by 96%. During 2000–2005, legionellosis cases were most commonly reported in persons aged 45–64 years. Persons aged <65 years comprised 63% of total cases in 2000–2005. Age-adjusted incidence rates in males exceeded those in females for all age groups and years. Legionellosis incidence showed marked seasonality in eastern states, with most cases reported in the summer or fall.

Conclusions. Reported legionellosis cases have increased substantially in recent years, particularly in the eastern United States and among middle-aged adults. *Legionella* infection should be considered in the differential diagnosis of any patient with pneumonia. Public health professionals should focus increased attention on detection and prevention of this important and increasing public health problem.

More than 30 years have passed since the recognition of *Legionella* species as the cause of a severe pneumonia outbreak in Philadelphia in 1976 [1]. Since then, we have made great progress in understanding this disease and its environmental sources. Despite this, an abrupt increase in the incidence of legionellosis has been noted since 2003 [2], with recent increases in the Bronx prompting the New York City Department of Health to issue a press release in July 2007 [3]. This trend has also been noted internationally, as evidenced by a press release issued in August 2007 by the Health Protection Agency in England [4].

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Legionella species are weakly gram-negative bacteria found primarily around fresh water environments, such as lakes and streams, where the bacteria use free-living amoeba as hosts for intracellular survival and multiplication [5]. More than 45 species of *Legionella* have been identified. However, *Legionella pneumophila* is associated with ~90% of reported cases in the United States, with *L. pneumophila* serogroup 1 causing ~80% of these cases [5]. Disease is usually associated with man-made environments, such as cooling towers, whirlpools, and building water systems, where warm water (25°C–42°C) and biofilms support growth and survival of *Legionella* species [5]. Disease caused by *Legionella longbeachae* has been associated with use of potting soil and gardening [5].

Legionella species are implicated in 2 clinical syndromes: legionnaires disease and Pontiac fever, collectively known as legionellosis. Pontiac fever is generally a self-limited, influenza-like illness, whereas legionnaires disease is a common cause of serious bacterial pneumonia. Risk factors for legionnaires disease include older age, smoking, male sex, and underlying

diseases (immunosuppression, diabetes, chronic lung disease, and renal failure) [6]. Cases have been reported in otherwise healthy individuals [7–9] and in all age groups, including infants [8]. Although <20% of legionnaires disease cases are outbreak related [5, 6], outbreaks have been associated with whirlpool spas, cooling towers, decorative fountains, hotels, hospitals, nursing homes, and cruise ships [10–12]. To investigate whether the recent increase in legionellosis in the United States is associated with shifting epidemiologic trends, we analyzed data on cases reported to the Centers for Disease Control and Prevention (CDC) from 1990 through 2005.

METHODS

The CDC collects data on voluntarily nationally notifiable diseases through the National Notifiable Diseases Surveillance System. Legionellosis has been a nationally notifiable disease since 1980 [13]. Because only summary data are available before 1990, we analyzed legionellosis cases reported from 1990 through 2005, which is the last year for which finalized data were available.

DATA SET AND CASE DEFINITION

Subsequent to a data-use agreement, the CDC provided data on cases reported in states where legionellosis was designated as notifiable from 1990 through 2005 [14]. The 1990–2003 data included all reported legionellosis cases, whereas the 2004–2005 data were limited to "confirmed" cases of legionellosis with the exception of data from California [15]. Data set variables were year, event month (based on the report month), state, sex, race, ethnicity, and age, categorized as <1 year, 1–4 years, 5-year groups from 5 to 74 years, and ⩾75 years.

Three case definitions were used by the CDC from 1990 through 2005 [16–18]. For "confirmed" legionellosis, all 3 require a clinically compatible case plus either culture isolation of any *Legionella* organism from respiratory secretions, lung tissue, pleural fluid, or other normally sterile fluid; detection of *L. pneumophila* serogroup 1 antigen in urine; or at least a 4-fold increase in serum antibody titer for *L. pneumophila* serogroup 1 [17, 18]. Before 2005, criteria also included detection of *L. pneumophila* serogroup 1 by direct fluorescent antibody staining. Before 1996, a "probable" status based on a single convalescent-phase serum antibody titer of ⩾256 was included [17, 18].

DATA ANALYSIS

Data were analyzed using SAS statistical software, version 9.1 (SAS Institute). Analysis was limited to the 50 states and the District of Columbia. Broader age categories and US Census Bureau regions and divisions were coded. Event months were combined into seasons: spring was defined as March, April, and May; summer as June, July, and August; fall as September, October, and November; and winter as December, January, and February. Pediatric cases were defined as cases that occurred in individuals aged ⩽19 years.

Sex distribution was compared with the 2000 US Census population [19]. Crude and age-specific incidence rates were calculated using the case count and the corresponding yearly population estimate [20]. Populations of states where legionellosis was not notifiable in a given year were excluded in the denominator for affected rate calculations. Rates for periods >1 year were obtained by averaging annual rates. Age-adjusted rates were calculated using the 2000 US standard population [21].

RESULTS

A total of 23,076 cases of legionellosis were reported to the CDC from 1990 through 2005. The annual number ranged from 1094 to 2291 cases (figure 1). The number of reported cases increased by 70%, from 1310 cases in 2002 to 2223 cases in 2003, with a sustained increase to >2000 cases per year from 2003 through 2005. During 1990–2002, the mean (±SD) annual legionellosis case count was 1268 ± 139.40 cases (range, 1094–1610 cases), whereas from 2003 through 2005, the yearly mean was 2198 ± 107.15 cases (range, 2081–2291 cases). The age-adjusted incidence rate for legionellosis in the United States paralleled this rise, increasing 65%, from 0.45 cases per 100,000 residents in 2002 to 0.75 cases per 100,000 in 2003.

DEMOGRAPHIC DISTRIBUTION

Age. Age was known in 22,604 (98%) of the reported legionellosis cases. Mean age-specific incidence rates for the 1990–2005 period generally increased with increasing age group (figure 2). Legionellosis cases are now most commonly reported in persons aged 45–64 years (figure 3). From 1990 through 1999, the 65–74-year-old age group had the highest mean (±SD) number of reported cases annually (275 ± 38.48 cases per year). In contrast, from 2000 through 2005, the 55–64-year-old age group had the highest mean annual case count (388 ± 154.22 cases per year), followed by the 45–54-year-old age group. Persons aged <65 years comprised 63% of total cases in 2000–2005.

From 1990 through 2005, 375 cases (1.7%) were reported in pediatric age groups; 209 cases (0.93%) were reported in children aged ⩽14 years. Most pediatric cases were reported in children 15–19 years old (44.3%), followed by infants aged <1 year (18.1%).

Sex. Males comprised 61% of the 22,763 case patients for whom sex was known, compared with 49% of the 2000 US Census population. Rates in males exceeded those in females for all age groups and years. The gap between male and female incidence rates steadily widened in adults as the age group

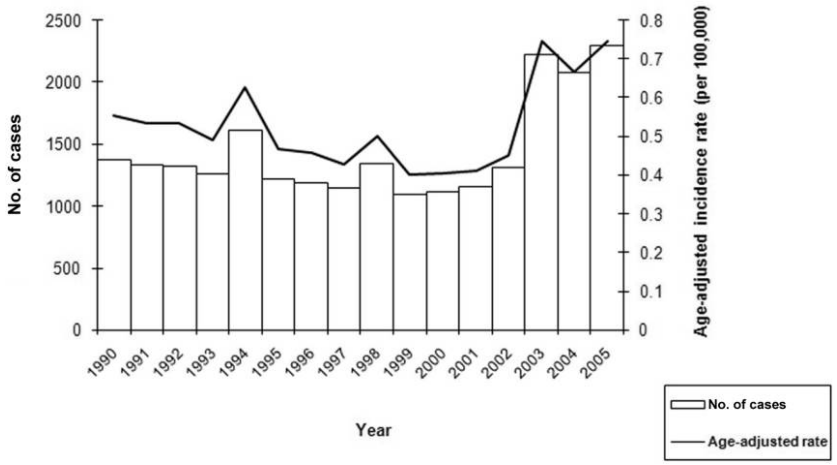

Figure 1. Annual number of legionellosis cases reported through the Centers for Disease Control and Prevention National Notifiable Disease Surveillance System and the corresponding annual age-adjusted incidence rate per 100,000 for 1990–2005.

increased. The male rate exceeded the female rate by 11% in the 15–24-year-old age group (0.073 vs. 0.066 cases per 100,000 residents). This sex difference increased to 116% in those aged ⩾75 years (2.62 vs. 1.21 cases per 100,000). The sex difference in annual incidence rates for legionellosis was highest in recent years. Yearly age-adjusted rates in males were >2 times higher than those in females from 2003 through 2005.

Geographic distribution. During 1990 through 2005, cases were reported from the District of Columbia and every state except Alaska. The Northeast region reported the largest percentage of cases (31.5%), followed by the Midwest (30.6%), the South (26.7%), and the West (11.2%). Most reported cases (69%) were concentrated in 3 contiguous eastern divisions: Middle Atlantic (26%), East North Central (25%), and South Atlantic (19%). The states with the highest reported case counts were Pennsylvania (11.5% of total cases), New York (11.0%), and Ohio (10.3%). Age-adjusted incidence rates were highest in Delaware (1.8 cases per 100,000 residents). Lowest age-adjusted rates were in North Dakota (0.04 cases per 100,000) and Oregon (0.07 cases per 100,000).

The increase in reported legionellosis cases after 2002 is mainly reflective of increased incidence in the states east of the Mississippi River (figure 4). The Northeast and South regions showed the greatest change in the mean annual number of cases from 1990–2002 to 2003–2005, increasing by 104% in the Northeast and 113% in the South. Regional mean age-adjusted incidence rates reveal similar findings. The mean rate (per 100,000) for 2003–2005 exceeded that for 1990–2002 by 82% in the Northeast (1.30 vs. 0.72), 76% in the South (0.60 vs. 0.34), 22% in the Midwest (0.81 vs. 0.66), and 4% in the West (0.30 vs. 0.29). By US Census Bureau division, the highest mean annual case counts for both the 1990–2002 and 2003–2005 periods were seen in the Middle Atlantic, East North Central, and South Atlantic divisions. The Middle Atlantic states showed the greatest increases in mean age-adjusted incidence rates, with the 2003–2005 rate exceeding the 1990–2002 rate by 96% (1.47 vs. 0.75), followed by the South Atlantic division (85%; 0.80 vs. 0.43). Divisional changes in age-adjusted incidence rates between these periods are shown in figure 5.

From 1990 through 2005, legionellosis cases were most frequently reported to the CDC in the fall and summer: 30% of the cases were reported in the fall, 29% in the summer, 23% in the winter, and 18% in the spring. Cases were reported most frequently in August (11.2%) and least frequently in February (5.6%). The West region had the least monthly variation in reported cases during this time (figure 6).

DISCUSSION

The number of reported legionellosis cases in the United States has increased substantially in recent years, particularly in the eastern United States. The number of reported legionellosis cases increased abruptly, from a mean of 1268 yearly cases before 2003 to >2000 cases per year from 2003 through 2005, with a brief spike in 1994, which appears to primarily reflect a few outbreaks in the South that year [22]. Final data from 2006 show a sustained increase: 2834 legionellosis cases were reported [23], which is the greatest number reported since legionellosis surveillance began.

The passive nature of the notifiable disease system likely leads to underreporting of cases: 1 population-based study estimated that *Legionella* species cause 8000–18,000 pneumonia cases annually [24], suggesting that more than three-quarters of cases are currently undiagnosed or unreported. Whether the recent increase in reported legionellosis cases and the predilection for cases in the eastern states reflect true changes in the incidence

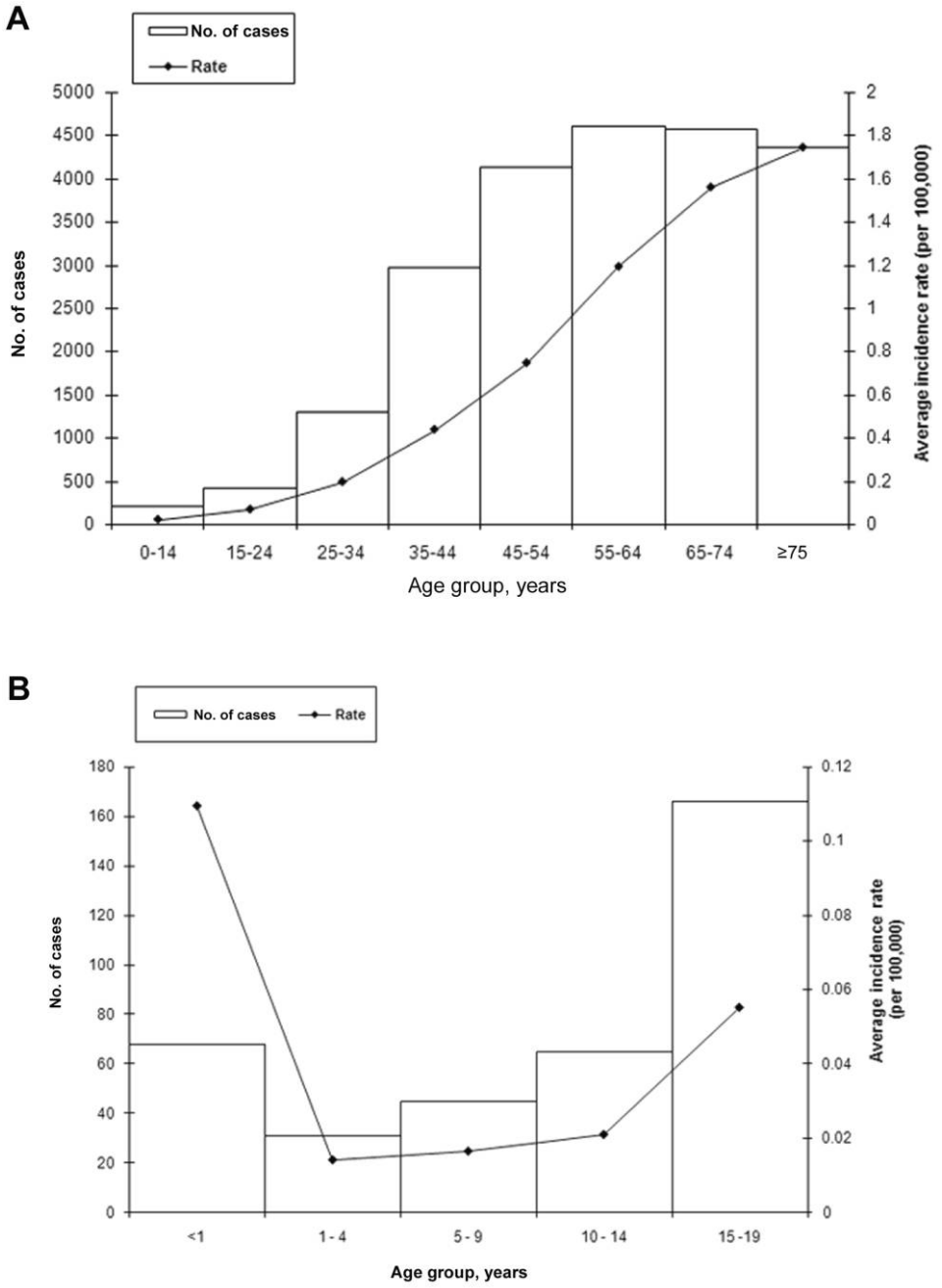

Figure 2. Total number of legionellosis cases reported for 1990–2005 and mean age group–specific incidence rates (per 100,000) for this period by all age groups *(A)* and pediatric age groups *(B)*.

of legionellosis, rather than artifact due to changes in legionellosis testing or reporting practices over time is unclear. We found no evidence that changes in diagnostic testing were responsible for the increase after 2000. Increased use of urine antigen testing had already occurred in the 1990s, when diagnosis by this test increased from 0% to 69% [13]. Currently, there is no commercially available PCR approved for clinical diagnostic use in the United States, making widespread routine use of PCR for diagnosis of legionellosis less likely. An increase due to introduction of other new diagnostic methods or changes in reimbursement in ~2003 is also unlikely (V. Baselski, personal communication).

Although completeness of notifiable disease reporting is difficult to assess, we found no evidence that variations in case-reporting procedures or completeness contributed to the increased incidence over time. Although physicians in states with

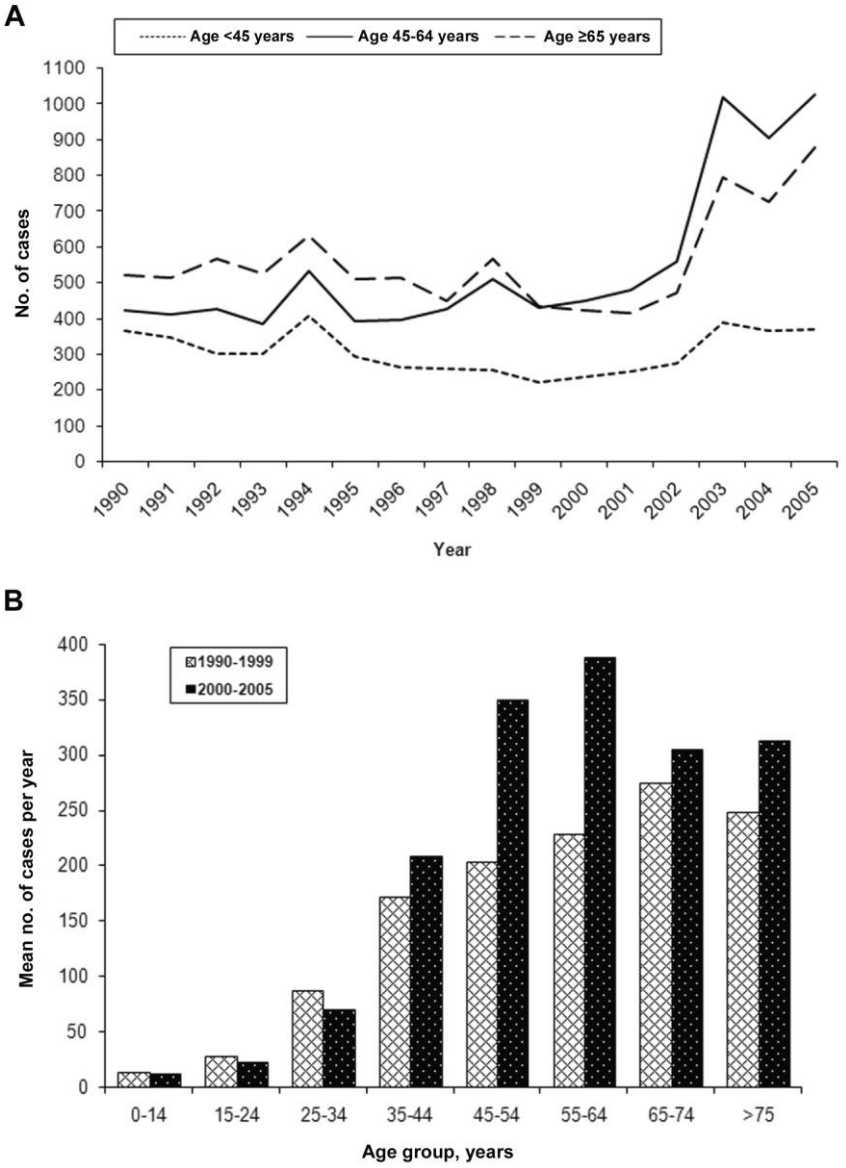

Figure 3. Trends in age distribution of reported legionellosis cases. *A,* Annual number of reported legionellosis cases by 0–45 years of age, 45–64 years of age, and ⩾65 years of age during 1990–2005. *B,* Comparison of the mean number of legionellosis cases per year for the 1990–1999 versus 2000–2005 periods among different age groups. Note that cases in the 45–64-year-old age group surpassed those in the ⩾65-year-old age group in ~2000.

historically higher legionellosis rates or recent outbreaks may have increased awareness and may be more likely to test for and report *Legionella* species, evaluation of the Middle Atlantic, East North Central, and South Atlantic divisions on a state-by-state basis reveals that the number of case reports increased across almost all these states after 2002, rather than being limited to a few states. This makes the geographic variation and post-2002 increase less suggestive of state-specific reporting artifacts. We also found no changes in national water-quality standards that would promote increased of risk of proliferation of *Legionella* species in water sources.

Past research has suggested a link between weather and legionellosis. A 1990–2003 study by Hicks et al. [25] analyzing the 2003 increase in the incidence of legionellosis in several Middle Atlantic states correlated the 2003 increase in legionellosis with increased total monthly rainfall. Because legionellosis occurrence has continued to increase after 2003 despite decreased rainfall in some areas—for example, case reports increased in South Atlantic states through 2006 despite a drought in that area [23, 26]—the correlation to total rainfall is less certain. A separate study by Fisman et al. [27] that evaluated the association of weather patterns and legionellosis

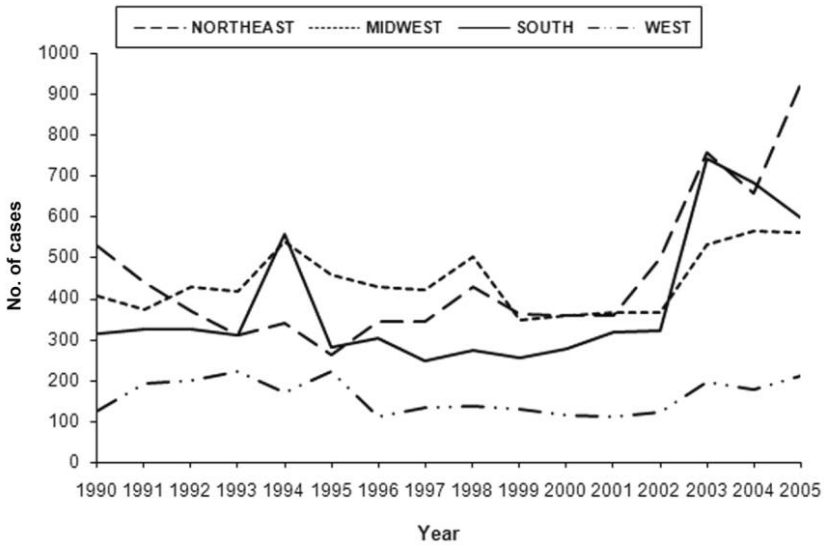

Figure 4. Annual number of reported legionellosis cases by US Census Bureau region, 1990–2005

in Philadelphia from 1995 through 2003 alludes to a more complex weather pattern than just increased monthly rainfall. Although this study did not find an association between monthly incidence of legionellosis and total monthly precipitation after controlling for other meteorologic variables, it identified a short-term association between legionellosis and the presence of precipitation and increased humidity at 6–10 days before disease [27]. Given that climate trends predict continued precipitation increases in northeastern states [28], more detailed analyses are needed to clarify the association among climate, weather, and temporal and geographic variations in legionellosis occurrence.

In our analysis, as in previous studies [6, 13], annual reported incidence rates for legionellosis increased with age across all age groups older than 1 year. However, we noted a trend toward younger ages in recent years. Despite the common perception that legionnaires disease is a disease primarily of elderly people, since the year 2000 the highest number of legionellosis cases has been reported in persons 45–64 years old, rather than the ⩾65-year-old age group as seen before 2000.

This study highlights the importance of considering *Legionella* species as a cause of pneumonia in all age groups. A continued misperception that legionnaires disease is a disease of elderly people may lead to preferential testing of older patients and missed cases in children and young adults if legionellosis is not considered in the differential diagnosis. For example, McDonough et al. [9] recently reported 5 cases of legionnaires disease in military recruits aged 18–28 years in the same training company that were identified only retrospectively through PCR analysis of throat swabs as part of a pneumonia surveillance study. Pediatric cases comprise ~1% of the cases reported from 1990 through 2005, yet evidence-based pediatric management guidelines for community-acquired pneumonia [29, 30] do not discuss legionnaires disease in the differential diagnosis or as part of the testing recommendations, potentially leading to misdiagnosis and underreporting of cases.

Legionella species are arguably the most important waterborne organisms in the United States with regard to serious morbidity and mortality. Legionnaires disease has been identified as a significant cause of community-acquired pneumonia leading to hospitalization, identified in 2%–8% of cases in North American and European studies [24, 31–33]. In several studies of severe community-acquired pneumonia, *Legionella* species have been the second most commonly identified organism, after pneumococcus [34, 35]. It is also a significant cause of waterborne-disease outbreaks. In the most recent Waterborne-Disease Outbreak Surveillance System summary [11], *Legionella* species were the most commonly identified infectious organisms in waterborne outbreaks associated with drinking water and with water not intended for drinking (excluding recreational water). *Legionella* species were also linked to all the deaths associated with these outbreaks [11].

Given the significant morbidity associated with legionnaires disease and its apparent rising incidence in recent years, legionnaires disease is increasingly important as a public health threat. Approximately 20%–25% of legionellosis cases are travel related [13, 36]. Because pneumonia caused by *Legionella* species is clinically indistinguishable from other bacterial pneumonias [5, 31], clinicians should consider *Legionella* species in the differential diagnosis of any patient with pneumonia, regardless of age, especially for patients with immunosuppression; a recent history of travel, especially if it included stays in hotels or on cruiseships; or exposure to environmental water sources, such as whirlpool spas or decorative fountains. Current guide-

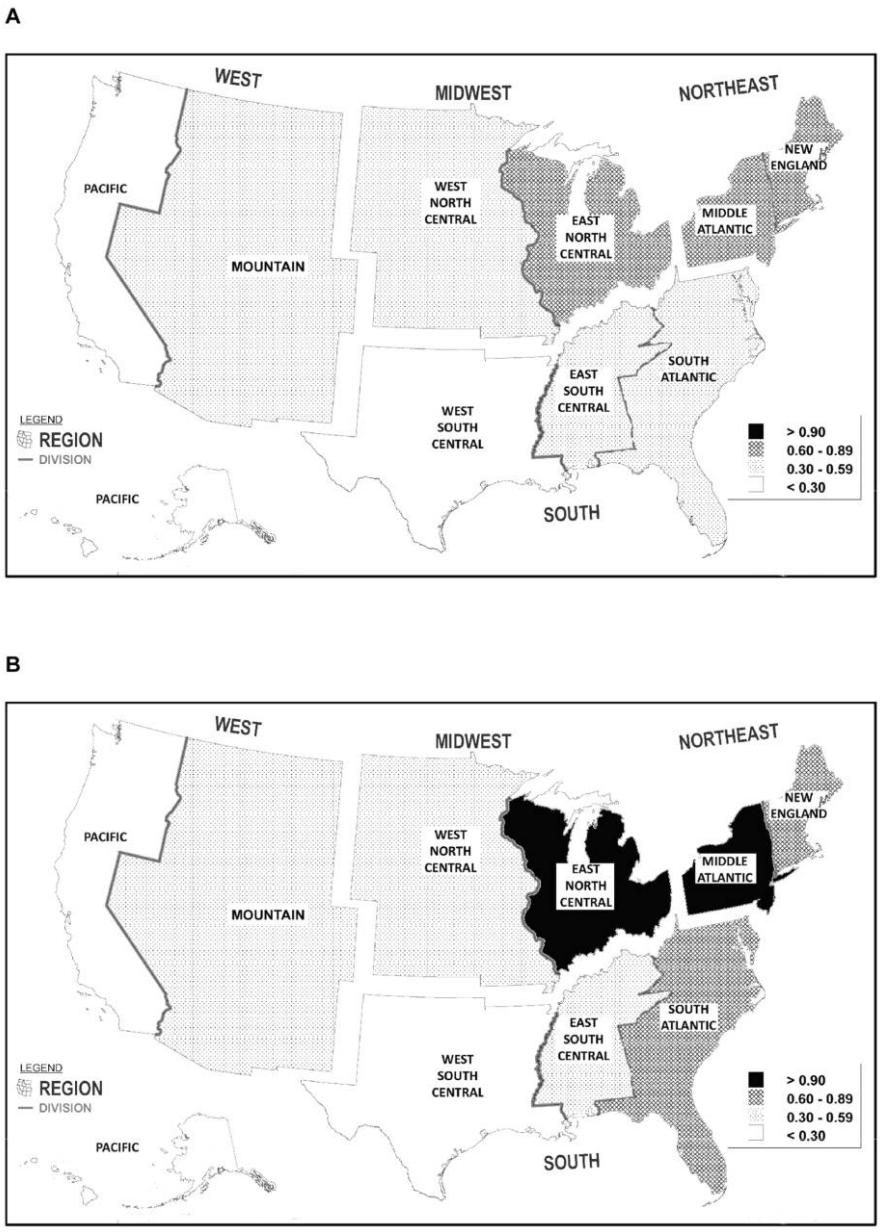

Figure 5. Mean age-adjusted incidence rates for legionellosis (cases per 100,000) by US Census Bureau division during 2 periods: 1990–2002 *(A)* and 2003–2005 *(B)*. Maps have been modified from the Census Regions and Divisions of the United States map prepared by the Geography Division, US Census Bureau (http://www.census.gov/geo/www/maps/CP_MapProducts.htm).

lines for management of community-acquired pneumonia in adults [37] recommend *Legionella* testing in patients with a history of travel within 2 weeks before the onset of symptoms, community-acquired pneumonia requiring admission to the intensive care unit, failure of outpatient antibiotic therapy or other nonresponding pneumonia, history of active alcohol abuse, presence of a pleural effusion, or exposure as part of a legionellosis outbreak or suspected outbreak. Current health care–associated pneumonia guidelines [38] recommend that clinicians maintain a high index of suspicion for legionnaires disease in patients with health care–associated pneumonia, especially in those who have recently undergone transplantation, who have immunosuppression, who have chronic underlying diseases, or who are aged ⩾65 years. Clinical guidelines for *Legionella* testing in pediatric pneumonia are lacking and should be developed.

Further research is required to explain the recent increases in legionellosis. Routine collection and dissemination to researchers of more-comprehensive patient risk factor, laboratory diagnostic testing, and other epidemiologic information by na-

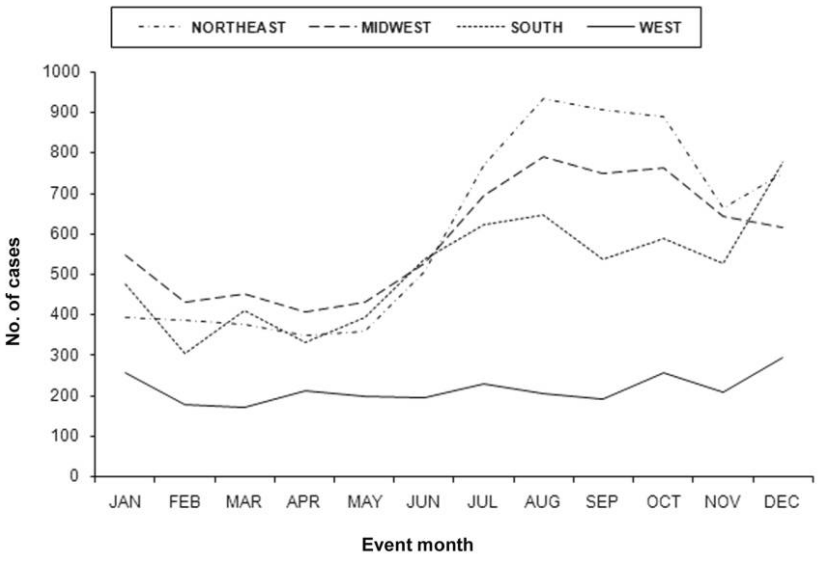

Figure 6. Monthly number of reported legionellosis cases by US Census Bureau region, 1990–2005

tional surveillance systems would aid these efforts. Programs of routine environmental water monitoring for *Legionella* species with reduction or elimination of the bacteria from water systems when detected, are increasingly being implemented as a prevention strategy [39, 40], and the impact of these programs requires further assessment. In addition, more research is needed on the effectiveness of various water disinfection systems for reduction of *Legionella* species in water systems.

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