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Population-Based Assessment of Clinical Risk Factors for Legionnaires' Disease

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Abstract

We used US population-based surveillance data to characterize clinical risk factors for Legionnaires' disease (LD). The LD incidence increased by age and the risk was elevated for 12 clinical conditions, when compared to healthy adults. This information can be used to guide testing, treatment, and public health prevention efforts.

Keywords

Legionnaires' disease; risk factors; diagnosis; outbreak response; outbreak prevention

The incidence rate of Legionnaires' disease (LD), a pneumonia caused by the inhalation of water droplets containing the bacterium *Legionella*, increased 5.5-fold during 2000–2017 in the United States, from 0.42 to 2.29 reported cases per 100 000 persons (https://wonder.cdc.gov/nndss/nndss_annual_tables_menu.asp). Almost all reported LD patients require hospitalization, nearly half require intensive care, and the case fatality rate is approximately 9% [1].

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Notes

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Supplementary Data

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

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The early identification of LD reduces individual patient morbidity and mortality by leading to timely and appropriate treatment [2]. Identifying LD cases also triggers public health actions to identify the source of exposure, which can prevent additional cases and reduce outbreak sizes. To achieve early diagnoses, clinicians must order the correct tests for those patients with pneumonia who are at an increased risk for *Legionella* infection. However, the current understanding of these risk factors is based on limited information from small case control studies, an early case series, and an analysis of passive US LD surveillance data from 1980–1989 [3–8].

We leveraged 5 years of active, multi-state LD surveillance data, capturing more than 2000 LD cases, to conduct a national assessment of LD incidence rates by clinical condition—adjusting for age, race, and sex—and to evaluate clinical risk factors for the disease.

METHODS

Active Bacterial Core surveillance (ABCs), part of the Center for Disease Control and Prevention's Emerging Infections Programs, is an active, population-based surveillance system for invasive bacterial pathogens that is conducted at 10 US sites (in California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee; https://www.cdc.gov/abcs/). ABCs included active surveillance for LD for a 5-year period (2011–2015), during which the catchment area covered a population of approximately 36 million persons [1]. ABCs surveillance staff performed medical record reviews to collect demographic, clinical, and laboratory information, as well as data on chronic illnesses and health-related behaviors. A case of LD was defined using the Council of State and Territorial Epidemiologists' confirmed case definition, which requires the fulfillment of clinical and laboratory criteria (https://cdn.ymaws.com/www.cste.org/resource/resmgr/PS/09-ID-45.pdf).

The National Health Interview Survey (NHIS), conducted annually since 1957, is the largest US adult (≥18 years), in-person, household health survey (https://www.cdc.gov/nchs/nhis/). It uses a complex, multi-stage design to assess the health statuses of noninstitutionalized US civilians through questions about chronic illnesses and health-related behaviors.

We mapped variables from the ABCs case report form to NHIS, identifying 16 analyzable, clinical conditions. We used directly corresponding ABCs and NHIS variables when possible, and otherwise created approximations based upon content; several ABCs variables were excluded due to a lack of corresponding NHIS variables (Supplementary Table 1).

We used ABCs data to estimate the prevalence of the analyzable, clinical conditions among US adults with LD, as well as the aggregate proportion of adults with LD who had none of those 16 conditions (ie, "healthy" adults, comprising the referent population during 2011–2015; Table 1; https://www.cdc.gov/nchs/nvss/bridged_race.htm). We subdivided the cases and population by age, sex, and race categories, and then multiplied by the ratio of United States to surveillance population estimates. We used NHIS data to estimate the aggregate proportion of adults in the general US population with each condition during 2011–2015.

Because NHIS included only noninstitutionalized populations, 178 patients documented on the ABCs case report form as residing in long-term care facilities, long-term acute-care facilities, acute-care hospitals, or assisted living facilities—or who were listed as homeless or incarcerated—were excluded from this analysis. Persons <20 years old (n = 20) were also excluded.

ABCs and NHIS data were combined to calculate unadjusted LD incidence rates for adults ≥20 years old with any of the 16 conditions and for healthy adults. To estimate incidence rates by age, we modeled the surveillance incidence rates using log binomial regression with 7 age groups.

To derive rate ratios (RRs), we compared incidence rates among adults with a specified condition to incidence rates in healthy adults. We used log binomial regression to estimate RRs, and adjusted for age, race, and sex to control for known differences in LD incidences by these factors [1]. Confidence intervals (95% CI) were based on the parameter estimates from 1000 log binomial models, generated from a simulation (Supplementary Table 2). Analyses were performed using SAS 9.4 and R 3.4.2. This project was determined to be nonresearch, public health surveillance; Institutional Review Board approval was not required.

RESULTS

We included 2349 confirmed LD cases that were reported to ABCs during 2011−2015, for an estimated 5-year total of 19 750 US LD cases. Ages ranged from 20 to 101 years (median of 60); 63.5% of cases occurred in men.

The average LD incidence rate during 2011–2015 was 1.70 cases per 100 000 adults ≥20 years old. Incidence rates increased by age group, from 0.23 cases per 100 000 among persons 20–29 years old to 3.84 cases per 100 000 among those ≥80 years old (Supplementary Figure 1). The LD risk more than doubled between the age categories of 20–29 and 30–39 years and between the categories of 30–39 and 40–49 years. After age 50, the LD risk continued to rise, but incremental increases in incidences diminished. The LD risk was not significantly different for persons 70–79 years old, compared with persons ≥80 years old. Overall, 7.8% of cases were reported as fatal, ranging from 0% for persons 20–29 years old to 16.3% for persons ≥80 years old (Supplementary Figure 2).

Among adults with LD, 41.8% were noted to have at least 2 of the 16 conditions listed, and 17.5% had at least 3 of the conditions; 14.2% reported none of the 16 conditions, compared with almost a third (30.7%) of adults in the general US population. The estimated proportion of US adults with each condition varied from 1.6% (liver disease) to 34.6% (current tobacco smoking) among adults with LD and from 0.3% (dementia) to 22.6% (former tobacco smoking) in the general US population (Table 1).

The unadjusted LD incidence rate for healthy adults was 0.80 cases per 100 000, while the rates for adults with clinical conditions ranged from 0.84 (asthma) to 16.95 (hematologic malignancy). RRs were significantly elevated for 12 conditions, led by hematologic malignancy (RR 9.99, 95% CI 7.55–13.24), pharmacologic immunosuppression (RR 8.99,

95% CI 5.81–13.86), and dementia (RR 4.92, 95% CI 3.28–7.00). There were 3 conditions (liver disease, solid organ malignancy, and asthma) that were not associated with elevated RRs for LD. Former tobacco smoking appeared to be protective.

DISCUSSION

The clinical factors associated with increased risk for LD, based on active US population-based surveillance, had not been described previously. This documentation of increasing incidences by decade of age and associations with 12 of 16 clinical conditions, based upon a nationally representative collection of LD cases from 2011–2015, improves upon currently available information for clinicians to guide complex decision-making around ordering *Legionella* diagnostics for patients with pneumonia.

While the observed associations were consistent with previously published data, this analysis adds data on the magnitude of risk and documents the lack of a single inflection point for increased risk by age. Although 2 of the 3 conditions associated with the highest risks were the 2 rarest conditions at the population level (dementia and hematologic malignancy), such information at the individual level can inform testing and treatment decisions and may lead to improved patient outcomes and smaller LD outbreaks.

There are several limitations to this analysis. Direct comparisons between ABCs and NHIS for all conditions were not possible; thus, all possibly relevant conditions could not be evaluated. The exclusion of long-term care facilities, due to limitations in available NHIS data, removed a population that is of interest due to its inherent vulnerability. Due to limitations of both data sets, this analysis accounted for clinical risk factors only. There are a number of important epidemiologic risk factors—such as recent travel, healthcare exposure, and epidemiologic ties to an ongoing outbreak—that should be considered when making decisions about LD testing, regardless of the patient's clinical status. Likewise, we could not determine the reasons for the observed relationships using these data sources; additional analyses using a different study design would be needed to understand causal pathways. Finally, if decisions to order LD testing were influenced by the knowledge of previously published risk factors, the burden of LD among healthy persons could be underestimated. The impact of this, however, is likely minimal, as multiple analyses have demonstrated that clinician adherence to available LD testing recommendations [9] is sub-optimal [10, 11] and similar underlying conditions have been observed among patients with LD since the first documented outbreak, prior to the publication of risk factors [12].

CONCLUSION

Because the clinical consequences of LD can be severe and because recognizing LD cases is key to identifying environmental sources of *Legionella*, prompt diagnoses are paramount. Our characterization of the associations between the LD risk and age and certain clinical conditions provides information that could improve testing practices, potentially leading to timelier, tailored treatments, as well as swifter public health interventions and the prevention of additional cases. Moving forward, these data could be used with other factors (eg,

geographic differences in disease prevalence, morbidity and mortality estimates, testing resources) to inform the creation of standard, population-level LD testing criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Adults With Legionnaires' Disease and in the General Population With Specified Conditions

Condition	Proportion of Adults[a] With Legionnaires' Disease and Specified Condition, ABCs, 2011–2015, %[b]	Proportion of Adults[a] in General Population With Specified Condition, NHIS, 2011–2015, %[b]	Unadjusted Incidence Rate,[c] Cases Per 100 000 Adults[a]	Rate Ratio[c] (95% CI) Adjusted for Age, Race, and Sex	
Asthma	6.0	12.3	0.84	0.83	(0.67–1.02)
Chronic obstructive pulmonary disease[d]	15.2	6.3	4.18	**2.45**	**(2.05–2.92)**
Coronary artery disease	15.1	6.6	3.98	**2.04**	**(1.73–2.43)**
Current alcohol abuse	5.1	5.1	1.73	**1.60**	**(1.27–2.01)**
Current tobacco smoking	34.6	17.5	3.42	**3.35**	**(2.93–3.80)**
Dementia[e]	1.7	0.3	9.28	**4.92**	**(3.28–700)**
Diabetes mellitus	25.8	9.5	4.68	**3.03**	**(2.56–3.55)**
Former tobacco smoking	12.6	22.6	0.96	**0.64**	**(0.54–0.76)**
Hematologic malignancy	4.3	0.4	16.95	**9.99**	**(7.55–13.24)**
Immunosuppression due to disease[f]	12.5	6.0	3.89	**4.43**	**(2.93–6.61)**
Immunosuppression, pharmacological[f]	9.7	2.2	8.23	**8.99**	**(5.81–13.86)**
Kidney disease	8.1	2.1	6.67	**3.89**	**(3.22–4.72)**
Liver disease	1.6	1.9	1.46	1.01	(0.69–1.41)
Neurological disease	4.6	2.1	3.9	**3.80**	**(2.96–4.83)**
Solid organ malignancy	5.8	6.2	1.61	0.95	(0.75–1.16)
Stroke	4.3	2.8	2.67	**1.42**	**(1.12–1.81)**
None of these conditions	14.2	30.7	0.80	Referent	Referent

Data show proportions, incidence rates, and rate ratios from ABCs and NHIS, United States, 2011–2015. Referent denotes the persons in ABCs and NHIS (2011–2015) with none of the 16 conditions listed in the table (see Methods paragraph 4). Bolded values indicate the confidence intervals that do not cross 1 (for the intervals that cross 1, the direction of the association is unclear).

Abbreviations: ABCs, Active Bacterial Core surveillance; CI, confidence interval; NHIS, National Health Interview Survey.

[a] Includes persons ≥20 years old.

[b] Aggregate proportion (2011–2015).

[c] Derived using ABCs and NHIS data.

[d] Includes 2012–2015 data only.

[e] Includes persons ≥50 years old.

[f] Includes 2013 data only.