EDITORIAL COMMENTARY

Our Evolving Understanding of Legionellosis Epidemiology: Learning to Count

Victoria Ng,[1,3] Patrick Tang,[2] and David N. Fisman[1,2]

[1]Research Institute of the Hospital for Sick Children and [2]Ontario Public Health Laboratories Branch, Toronto, Canada; and [3]The Australian National University, Canberra, Australia

(See the article by Neil and Berkelman on pages 591–9)

"A disease is also farther on the road to being cured when it breaks forth from concealment and manifests its power" (Seneca, ca. 4 BC–65 AD) [1].

Legionella pneumophila burst onto the medical scene ~3 decades ago as the causative pathogen in a respiratory disease outbreak among American Legion conventioneers at Philadelphia's grand Bellevue Stratford Hotel [2]. As a result of the outbreak, 182 people became sick, 29 died, the hotel went out of business, and, ultimately, clinicians were introduced to a novel, virulent pathogen. The initial identification of legionellosis in the context of a large and virulent outbreak and the subsequent recognition of case clusters associated with cooling towers, fountains, and grocery store mist machines [3] did much to cement the perception of *L. pneumophila* as an agent of respiratory outbreaks associated with inhalation of contaminated droplets. In the nosocomial field, such outbreaks have been associated with case-fatality rates exceeding 40% [4].

However, many clinicians now recognize that legionellosis is an important cause of sporadic community-acquired pneumonia and a relatively common cause of community-acquired pneumonia requiring admission to the intensive care unit [5]. As sensitive and noninvasive diagnostic options have expanded, so has the perceived spectrum of illness associated with *Legionella* species. A recent article by von Baum and colleagues [6] suggested that, when individuals with ambulatory community-acquired pneumonia are tested for legionellosis by urine antigen testing, nearly 4% may receive a diagnosis of legionellosis.

Understanding of the links between the physical environment and legionellosis risk has undergone a parallel evolution. *Legionella* species are present in surface waters and ground water [7], and pathogenic species of *Legionella* frequently can be isolated from home and hospital water-distribution systems, even in the presence of chlorine (and in the absence of identified outbreaks). The finding that monochloramination of potable water supplies (which is far more effective at killing *Legionella* species than is chlorination) is associated with a reduction in nosocomial legionellosis outbreaks [8] suggests that exposure to this "uncommon" pathogen via drinking water may actually be common. The association among advanced

age, deficient immune status, and severe legionellosis likely results from a high frequency of microaspiration and the inability to clear aspirated organisms in individuals with these characteristics.

In this issue of *Clinical Infectious Diseases,* Neil and Berkelman [9] provide a succinct and thought-provoking summary of recent trends in legionellosis in the United States. They report that the incidence of legionellosis increased markedly in the United States from 2002 through 2005. Should we be concerned that the incidence of a virulent infectious disease is increasing? Or, given the history of legionellosis as a difficult-to-diagnose disease entity, should we take comfort in the increased recognition of an infectious process that may, historically, have been underrecognized? If the latter is true, we might heed Seneca's wise words above and regard increased case numbers as a harbinger of better control of this disease through improved understanding.

As anyone familiar with the function of most public health surveillance systems might suggest, the answers to these questions are not straightforward. However, consideration of the possible mechanisms underlying this increase may guide future surveillance and disease-control efforts. Of course, any apparent trend in time series data may simply reflect our innate human desire to impose order or meaning on a

chaotic pattern [10], but appropriate statistical models can help reassure us that year-on-year increases during a multiyear period do not simply represent random fluctuations in disease counts.

That said, the dependence of public health surveillance systems on passive reporting of cases means that even a real increase in measured incidence is not necessarily synonymous with a true increase in disease activity. Apparent increases in disease activity in passive surveillance systems can be driven by changing test technologies (e.g., introduction of more-sensitive or less specific tests), changing test submissions (e.g., more test submissions by clinicians or the establishment of mass screening programs or alternative venues for testing), or an interaction between test technology and submission volumes, even if the true disease epidemiology remains entirely stable. In the context of legionellosis, the advent of highly sensitive urine antigen testing for *L. pneumophila* has almost certainly increased the frequency of identification of this disease, but as Neil and Berkelman [9] point out, this technology had been available for approximately a decade before the observed surge in legionellosis cases occurred.

Could the increase in legionellosis cases described by Neil and Berkelman be entirely due to changes in clinician testing patterns? Theoretically, this might be so, although the "test denominators" needed to answer this question definitively are an important Achilles heel for most public health surveillance systems. Supposing that there was no change at all in the per-test probability of identifying legionellosis, test submissions would have to have approximately doubled after 2002 to account for patterns reported here, and one might ask what would precipitate such an extreme change in diagnostic testing patterns.

In our jurisdiction (the Canadian province of Ontario), we are fortunate enough to have centralized testing for several pathogens of public health importance, including *Legionella* species. This allows us

to consider test denominators in evaluating disease trends and also permits evaluation of the complex, bidirectional relationships among test positivity, test submission volume, and apparent rates of disease. There are both theoretical and empirical reasons to think that increasing identification of legionellosis, as a result of urine antigen testing, could reinforce clinician testing patterns. Clinicians are well documented to operate under an "availability heuristic" with respect to clinical decision making [11]. This heuristic leads to more consideration of diagnostic possibilities that have been the subject of recent experience. In this context, availability of highly sensitive urine antigen test methods creates an ongoing "positive feedback loop" with more cases of legionellosis identified leading to more tests submitted and thus to more positive results obtained, and so on.

This effect can be documented quantitatively at our laboratory, with use of data on legionellosis test submissions and legionellosis cases identified from 1992 through 2006 (figure 1). It can be seen that there is a strong linear relationship between the current month's test submissions and the prior month's case count (figure 1, black squares and black regres-

sion line; $r^2 = 0.14$; $P < .001$) but no significant relationship between the current month's case count and the prior month's test submissions (gray circles and gray regression line; $r^2 = 0.002$; $P = .57$). Similar relationships are detected using 2- and 3-month lags.

However, although such a positive feedback loop may account for some component of the increase in disease incidence reported by Neil and Berkelman [9], we agree with their suggestion that observed trends likely represent true changes in legionellosis epidemiology, not least because they are regional in nature. As the authors note, there is an increasing body of evidence linking the risk of legionellosis occurrence to environmental conditions in general and to warm, humid weather and precipitation events in particular [12]. At the time of writing, climate change due to anthropogenic greenhouse gas generation seems well under way in North America, and projected changes in temperatures and precipitation patterns might be expected to result in increases in the incidence of legionellosis, as well as other important infectious diseases with environmental reservoirs [13]. Measuring the impact of such changes and interpreting the surveillance data for infectious diseases
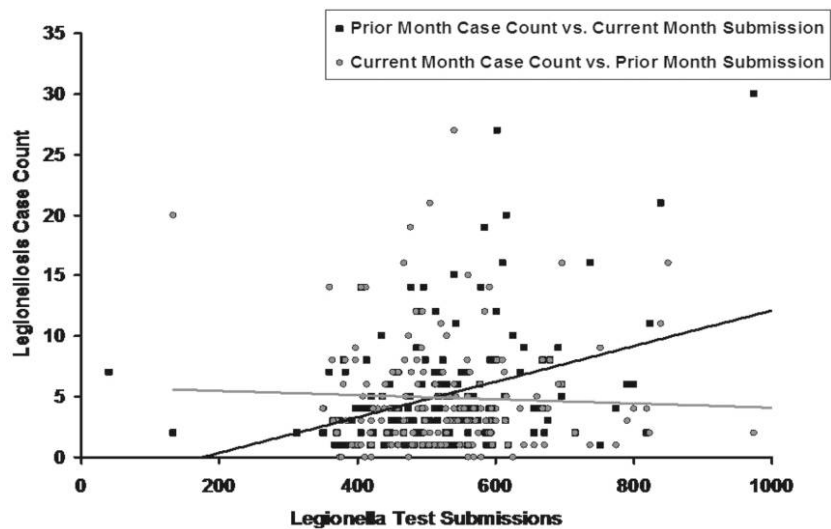

Figure 1. Relationship between the number of legionellosis cases identified (in the current or prior month) and test submissions (in the prior or current month), Ontario Public Health Laboratory, 1992–2006.

with environmental reservoirs in the face of rapid environmental change will remain difficult in the absence of surveillance systems that not only capture disease counts but also account for changing laboratory methods and clinical practices.

Acknowledgments

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