Journal of Infection and Chemotherapy 29 (2023) 90–94

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: www.elsevier.com/locate/jic

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Effect of the COVID-19 pandemic and state of emergency declarations on the relative incidence of legionellosis and invasive pneumococcal disease in Japan

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ARTICLE INFO

Keywords:
Japan
Legionella
COVID-19
Epidemiology
Invasive Pneumococcal Disease

ABSTRACT

Introduction: During the COVID-19 pandemic, the incidence of many droplet-transmitted infections decreased due to increased mask-wearing and social distancing. Contrastingly, there has been concern that COVID-19 countermeasures, such as lockdowns, may increase legionellosis incidence via water stagnation. During the pandemic in Japan, four state of emergency declarations were imposed between 2020 and 2021, which makes it particularly suitable to test this hypothesis.
Methods: We use country-level surveillance data from the National Institute of Infectious Diseases to track the relative incidence of legionellosis compared to invasive pneumococcal disease (IPD) during the COVID-19 pandemic in Japan, with a focus on the periods just after state of emergency declarations were lifted.
Results: The absolute number of legionellosis and IPD cases decreased in 2020 and 2021 compared to previous years. The average relative incidence of legionellosis as well as the variance of the relative incidence significantly increased during the pandemic compared to previous years. There were no increases in the relative incidence of legionellosis during the periods immediately following emergency declaration liftings, but the relative incidence did increase considerably during the first two states of emergency.
Conclusions: COVID-19 countermeasures appear more effective at decreasing the incidence of human-to-human transmitted infections, such as IPD, compared to environmentally-transmitted infections, such as legionellosis. Though no evidence was found to suggest that legionellosis cases increased after state of emergency declarations, public health efforts should continue to emphasize the importance of routine sanitation and water system maintenance to prevent water stagnation and *Legionella* spp. contamination.

Note

During the course of the COVID-19 pandemic in Japan, increased mask-wearing, improved personal hand hygiene, and widespread social distancing have led to decreased incidence of respiratory pathogens, including influenza, tuberculosis, respiratory syncytial virus, pertussis, mycoplasma pneumonia, and legionellosis, among others [1]. However, the decrease in legionellosis incidence has been found to be much less pronounced than those of typical droplet-transmitted infections [1,2]. In fact, the annual incidence of legionellosis uniquely increased between

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https://doi.org/10.1016/j.jiac.2022.08.016
Received 12 May 2022; Received in revised form 3 August 2022; Accepted 20 August 2022
Available online 16 September 2022
1341-321X/

2020 and 2021 in Taiwan [3].

Prolonged pandemic-associated building and business closures are associated with water stagnation and biofilm buildup, which promotes the growth of *Legionella* species [4]. Pandemic-era environmental studies of water samples taken from uninhabited dormitories and hospitals found that *Legionella* spp. contamination increased during closures [5]. A case report of Legionella pneumonia diagnosed in a dishwasher just after Rome's lockdown raised concern that pandemic-related activity restrictions may indirectly contribute to increased incidence of legionellosis via microbial contamination of poorly maintained water systems [6]. However, these hypotheses have not yet been tested at the national level using data with high temporal resolution (e.g., weekly or monthly reports).

Even prior to the pandemic, legionellosis was a global health concern with an estimated seroprevalence of 13.7% [7]. Sporadic cases of legionellosis are typically contracted in residential and large-building water systems, during car travel via aerosolized water that has accumulated on roads, and after contact with cooling towers [8]. However in Japan specifically, hot springs (*onsen*) and public baths (*sento¯*) are commonly-used, major sources of legionellosis transmission and have been linked to several large outbreaks [9]. Historically, the incidence of legionellosis in Japan has been highest in the Hokuriku Region, comprised of four prefectures along the Sea of Japan (Fukui, Ishikawa, Niigata, and Toyama) [10]. Legionellosis incidence in Japan has been increasing at a rate of approximately 11% since 2007, and mortality in recent years has been approximately 5% [10]. Japan's greying population has been implicated in the rise of legionellosis incidence, as more than 40% of cases occur in those aged 70 years and older [10].

To contain the spread of COVID-19, the Japanese Government implemented between one and four state of emergency declarations (SoE) in each of its 47 prefectures. During SoEs, Japanese residents were asked to limit nonessential activities and outings, restaurants and bars halted in-person dining services, and many other businesses temporarily closed; however, SoE compliance in Japan was voluntary. There have been concerns that cases of legionellosis might increase when SoE declarations end [6], but they have yet to be substantiated using national data. In this study, we use national infectious disease surveillance data from December 2016 to December 2021 to assess the relative incidence of legionellosis compared to invasive pneumococcal disease (IPD) after the start of the COVID-19 pandemic, as well as after the lifting of SoEs in Japan.

National infectious disease surveillance data was obtained from the National Institute of Infectious Diseases (NIID) in Japan [11]. Weekly report counts for legionellosis and IPD were collected from 2016 week 50 to 2021 week 52. To assess whether legionellosis case counts were affected by SoEs, the use of a comparator infection is needed as the pandemic era is characterized by different health behaviors (e.g., widespread masking and social distancing), decreased exposure to environmental sources of *Legionella* (e.g., decreased use of public baths and fewer trips requiring hotel stays), and different surveillance reporting patterns. Because all SoEs happened during the pandemic, these events are not independent, so the use of a comparator infection enables us to control for various changes that occurred before and after the start of the pandemic and each of the subsequent SoEs. IPD was selected as the comparator because like legionellosis, both are nationally notifiable bacterial diseases (as opposed to sentinel surveillance infections, such as mycoplasma pneumonia), are transmitted via droplets (IPD: human-to-human; legionellosis: environmental aerosols), typically have incubation periods of less than one week, are primarily pulmonary infections that may present with extrapulmonary manifestations, have year-round incidence of roughly similar magnitude, and have been used as comparators in prior literature [3]. Of note, COVID-19 could not be used as the comparator as its incidence and SoEs are not independent events and it exhibits wave-like behavior due to the emergence of new variants and vaccination. Clinical features, diagnostic methods, and notification criteria for each infection are shown in Table 1.

We first calculated moving four-week average case counts for each infection and then applied seasonal and trend decomposition using Loess (STL). STL is a method to extract seasonality and polynomial trends from time-series data. After decomposition, the trend and remainder for each disease were summed to yield aseasonal counts. Any resultant values that were less than zero were treated as missing (4 of 520 values,

Table 1
Clinical features, diagnostic methods, and notification criteria for legionellosis and invasive pneumococcal disease as defined by the Ministry of Health, Labour and Welfare in Japan.

Notifiable infectious disease	Diagnoses	Clinical features	Diagnostic methods (specimen type)	Notification criteria
Legionellosis [12]	1. Legionnaire's disease (pneumonia type) 2. Pontiac fever (non-pneumonia type)	Abdominal pain, diarrhea, impaired consciousness, gait disturbance, pneumonia, multiorgan failure	1. Isolation and detection of *Legionella* spp. (lung tissue, sputum, pleural fluid, blood, other sterile sites, airway secretions) 2. Fluorescent antibody-mediated detection of *Legionella* spp. antigens (lung tissue, sputum, pleural fluid, blood, other sterile sites, airway secretions) 3. Detection of *Legionella* spp. antigens by enzyme immunoassay or immunochromatography (urine) 4. Detection of *Legionella* spp. genes by PCR (lung tissue, sputum, pleural fluid, blood, other sterile sites, airway secretions, urine) 5. Detection of *Legionella* spp. genes by LAMP (sputum) 6. Detection of *Legionella* spp. antibodies by indirect immunofluorescence or microplate agglutination (serum)	1. Symptomatic patient (see clinical features) with positive diagnostic test (see diagnostic methods) 2. Asymptomatic patient with positive diagnostic test (see diagnostic methods) 3. Previously symptomatic (see clinical features), expired patient with positive diagnostic test (see diagnostic methods) 4. Previously symptomatic (see clinical features) expired patient can be reported at physician's discretion if clinical suspicion is high
IPD [13]	Invasive *Streptococcus pneumoniae* infection of sterile sites, including: 1. Bacteremia 2. Meningitis	1. Children: fever with or without pneumonia; meningitis may be preceded by otitis media 2. Adults: pneumonia, fever, (productive) cough, shortness of breath, headache, convulsions, impaired consciousness	1. Isolation and detection of *S. pneumoniae* (CSF, blood, other sterile sites) 2. Detection of *S. pneumoniae* genes by PCR (CSF, blood, other sterile sites) 3. Detection of *S. pneumonia* antigens by latex agglutination or immunochromatography (CSF)	1. Symptomatic patient (see clinical features) with positive diagnostic test (see diagnostic methods) 2. Previously symptomatic (see clinical features), expired patient with positive diagnostic test (see diagnostic methods)

Legend: PCR = polymerase chain reaction; LAMP = loop-mediated isothermal amplification; CSF = cerebrospinal fluid.

0.77%). Because seasonality was calculated periodically, 2020 week 53 was excluded from the analysis. For all weeks between 2017 and 2021, the aseasonal counts for legionellosis were divided by the corresponding values for IPD to yield relative incidence ratios. Changes in the mean and variance of relative incidence ratios before and after the start of the pandemic were assessed using Student's t-test and Levene's test, respectively. For the purposes of this study, the pandemic was considered as starting in January 2020, when the first case of COVID-19 was identified in Japan.

The number of weekly reports, as well as the moving four-week average, for legionellosis and IPD are shown in Fig. 1A. When aggregated by year, the number of legionellosis reports was 1477, 1783, 2007, 1663, and 1753 for 2017, 2018, 2019, 2020, and 2021, respectively. The corresponding values for IPD were 2090, 2186, 2179, 1038, and 892. Both diseases showed decreased reporting in 2020 and 2021 compared to previous years.

The ratio of aseasonal reports of legionellosis vs IPD are shown in Fig. 1B. The average ratio between 2017 week 1 and 2019 week 52 was 0.84 (median 0.77) compared to 2.91 (1.52) between 2020 week 1 and 2021 week 52 ($p < 0.0001$). The variance of ratios increased significantly between these two time periods: 0.07 to 24.44 ($p < 0.001$). Two large peaks were observed roughly during the first two SoEs between weeks 16 and 22 of 2020 (peak 32.6) and 51 of 2020 and 9 of 2021 (32.1). A much smaller peak was observed during week 22 of 2021 (3.1), aligning with the third SoE. Peaks in the relative incidence of legionellosis were not observed within two weeks of SoE liftings or between SoEs.

Using Japanese national infectious disease surveillance data for legionellosis and IPD, we assessed the relative incidence of legionellosis compared to typical droplet-transmitted infections between 2017 and 2021. We found evidence for a statistically significant increase in the relative incidence of legionellosis and the variance of the relative incidence during the COVID-19 pandemic compared to previous years. Though we found that the relative incidence of legionellosis peaked during the first two SoEs, there was no evidence to suggest that the relative incidence increased when SoEs ended.

Water stagnation and insufficient cleaning during SoEs may have led to increased *Legionella* spp. contamination of water sources that were introduced to the population after emergency declarations. Prior research in Greece found that seasonal operation of hotels was a risk factor for Legionella contamination in water distribution systems [14] due to water stagnation [4]; the implementation of SoEs effectively introduced seasonality into the operation of businesses across Japan. Were this hypothesis clinically significant, we would have expected to see rises in the relative incidence of legionellosis within two weeks of SoE endings. However, concerns that the incidence of legionellosis would increase in Japan after SoEs were lifted did not come to fruition. Legionellosis case counts in 2020 and 2021 were lower than in previous years likely because of increased masking, social distancing, and decreased use of public baths and hotels, but these annual data alone are insufficient to prove that SoEs did not play a role in affecting legionellosis incidence. The use of a comparator infection, IPD, allowed us to control for these various changes during the pandemic era and determine that the relative incidence of legionellosis did not increase when SoEs ended.

To the best of our knowledge, this is one of the first studies to temporally link changes in the relative incidence of legionellosis to COVID-19 countermeasures. Our findings that the relative incidence of legionellosis increased during SoEs as well as at baseline during the pandemic period are consistent with the transmission dynamics of legionellosis and IPD. Social distancing policies are most effective at reducing the spread of human-to-human transmissible infections, such as IPD; however, legionellosis is only very rarely transmitted from person-to-person, and the large majority of cases are sporadic. Similarly, the widespread adoption of mask usage in Japan likely proved more effective in reducing rates of IPD, which are usually contracted from direct contact with sick persons. However, legionellosis is typically contracted in places where one typically does not wear masks: at home (i.e., residential water systems and air-conditioning units), in restaurants or hotels (i.e., water distribution systems), while driving (i.e., aerosolized road water), or in hot springs and public baths [8,9]. Thus, the baseline relative incidence of legionellosis compared to IPD after the initiation of social distancing precautions and universal masking is expected to increase, as was seen here.

Notably, the variance of relative incidence ratios increased significantly after the start of the pandemic. The effects of masking and other health behaviors, which have remained relatively stable since the beginning of the pandemic, ostensibly do not considerably contribute to this change in variance; it is more likely that the four rounds of SoEs introduced multiple, acute perturbations to the infection transmission landscape, resulting in fluctuations in relative incidence. The relative incidence of legionellosis increased most prominently during the first two SoEs, consistent with the notion that compliance with SoE measures decreased with each subsequent declaration [15]. Pandemic fatigue, which likely manifested with increased outings and decreased mask usage during later phases of the pandemic, would necessarily lead to a less pronounced increase in the relative incidence of legionellosis. Furthermore, many business and individuals began openly defying SoE measures during later declarations. Thus, human-to-human transmission of IPD likely did not decrease significantly from baseline during later SoEs, and no peak in the relative incidence of legionellosis was noted.

This study has limitations. First, we assume that the seasonality of each disease is stable over the analyzed time period (i.e., periodicity); it is possible that seasonality fluctuated slightly from year to year. Second, after extracting seasonality from weekly case counts and summing the trend and remainder terms, four negative values (0.77% of 520 total values) were created (only for IPD) and were treated as missing. However, all four values clustered during the two peaks observed in Fig. 1B during the first two SoEs, suggesting that they were akin to near-zero values that would have yielded high relative incidence ratios; thus, this limitation does not affect our interpretation of the results. Third, we did not have access to data reflecting actual changes in human behavior or environmental data regarding water sanitation. Fourth, surveillance reporting behavior may have been affected by the pandemic, but the use of a comparator infection should minimize the effects of these changes on our analyses. Finally, here we present the relative incidence of legionellosis, using IPD as a comparator; we are unable to definitively prove that the true incidence of legionellosis increased or decreased during SoEs because emergency declarations and the pandemic are not independent events and thus the effect of each on incidence cannot be untangled without the use of a comparator infection. However, given the stable relative incidence of legionellosis pre-COVID-19, IPD appears to have served as a reasonable comparator.

Patient consent statement

No human patients were involved in the design or performance of this study.

Data availability

Data are openly available on the Japan National Institute for Infectious Diseases (NIID) website (https://www.niid.go.jp/niid/ja/data.html).

Contributors

Conception/design of the work: CG, MI, DY, and SN; analysis of data: CG; data curation: CG and AE; creation of figures: CG; interpretation of findings: all authors; drafting of the work: CG; funding acquisition: DY and SN; substantially revised the work: all authors. All authors approve

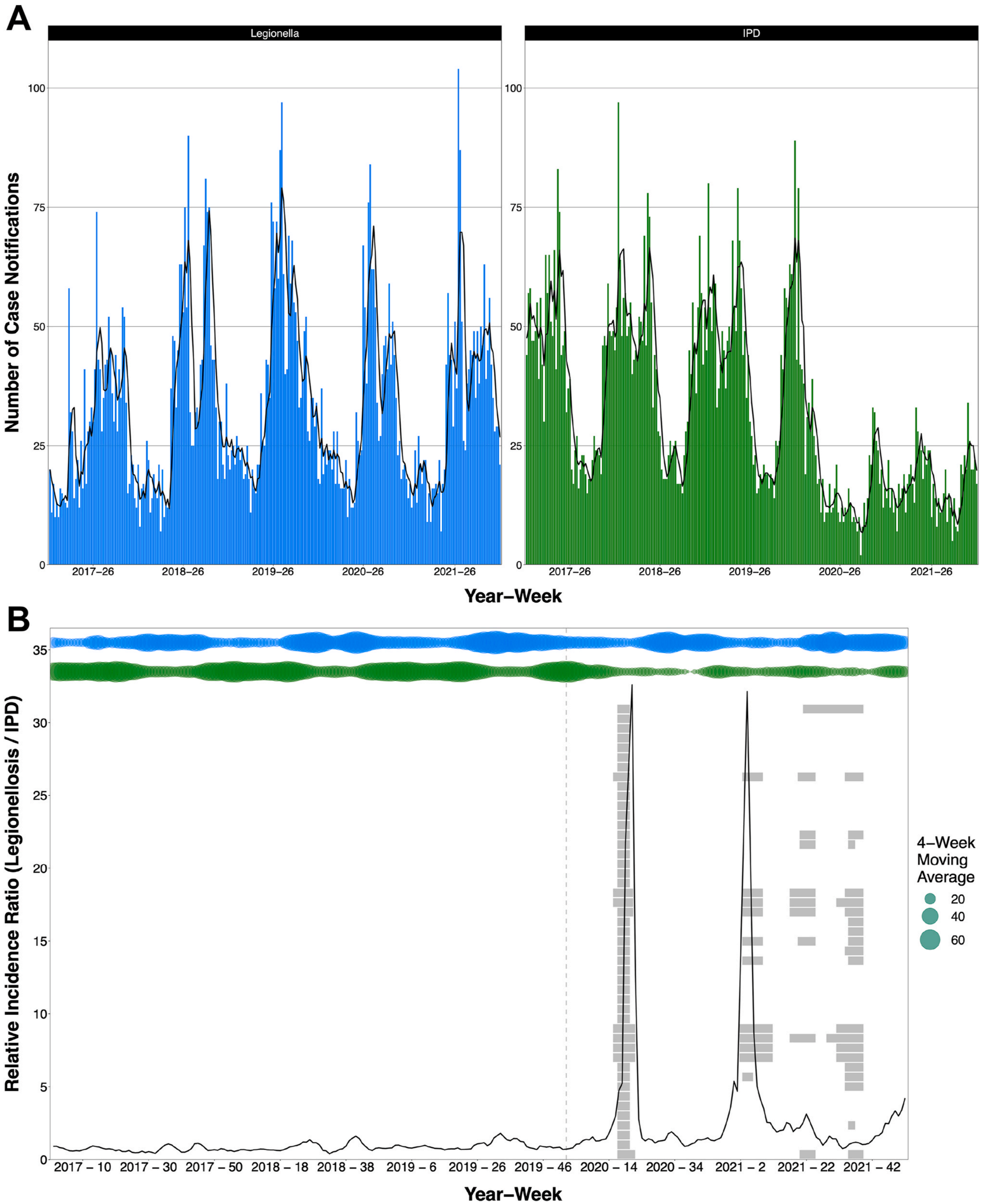

Fig. 1. General trends in and relative incidence ratios of legionellosis and IPD, 2017 to 2021.
Legend: A) Number of case notifications, by week, for legionellosis and IPD. Bars show weekly case notifications. Black lines show four-week moving averages. B) Relative incidence ratios, by week, for legionellosis and IPD. Black lines show relative incidence ratios. The dashed, grey line denotes the start of the COVID-19 pandemic in January 2020. Grey rectangles show state of emergency declarations in each of Japan's 47 prefectures (each row of rectangles corresponds to one prefecture). Bubble plots at the top of the plot illustrate the four-week moving average of case notifications during the corresponding week (legionellosis in blue; IPD in green)

of the final version of the manuscript.

Funding

The present work was supported in part by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (21H03203), and by Precursory Research for Embryonic Science and Technology from the Japan Science and Technology Agency (JPMJPR21RC).

Ethics statement

Ethical review was not required because this study uses open data.

Declaration of competing interest

The authors have declared no conflicts of interest.

Acknowledgment

The funding source of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The views expressed in this paper are solely those of the authors.

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