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Potential environmental and health risk when returning to normal amidst COVID-19 vaccination
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Abstract
Due to the SARS-CoV-2 pandemic and restricted occupancy in work and school settings, there is a heightened risk for Legionella infection. An increase of stagnation in water pipe systems with limited water usage stimulates biofilm build-up, further facilitating Legionella proliferation. Individuals can inhale infected water aerosols and develop Legionellosis that can progress into mild flu-like symptoms or severe pneumonia. While SARS-CoV-2 vaccinations have been introduced globally, there is a concern for bacterial coinfections as individuals resume normal activities. Even with new SARS-CoV-2 variants circulating, Legionella persists as a public health threat as vulnerable communities’ restrictions fluctuate. Proper water monitoring and management are critical while reopening communities. This article features Legionella characteristics and novel case reports amidst the pandemic. This article encourages greater awareness for building managers to minimize water stagnancy by disinfecting water distribution systems and promotes healthcare professionals to properly diagnose other illnesses during the ongoing pandemic to reduce morbidity and mortality.

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Keywords
Legionella, Legionnaires’ disease, Coinfection, Biofilm, Water infrastructure, Inhalation risk.

Introduction
An emerging concern when returning to normal
In reaction to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, many local and national governments across the globe have imposed varying degrees of mandatory quarantines and closures (FT Visual & Data Journalism Team; URL: https://ig.ft.com/coronavirus-lockdowns/). However, these mandatory bans are now being lifted due to the introduction of SARS-CoV-2 vaccines, thereby decreasing daily confirmed cases. As of May 12, 2021, approximately 1.26 billion vaccine doses have been administered across the globe (WHO; URL: https://covid19.who.int/). In the United States (US) alone, as of May 17, 2021, approximately 47.33% (157.1 million) of the total American population has been administered at least one dose, while 37.33% (122.9 million) of all Americans are fully vaccinated. Notably, 47.1% of Americans over 18 years of age and 72.6% of Americans over 65 years of age are fully vaccinated (CDC; URL: https://covid.cdc.gov/covid-data-tracker/#vaccinations). Although public officials have high hope for these novel vaccines, a different threat to public health has arisen. As a result of unoccupied and/or under-used buildings during lockdown or restricted access periods, these conditions (stagnant water) have provided an ideal environment for the opportunistic pathogen, Legionella, to flourish [1]. When stagnant water sits for long periods of time in water distribution systems, the bacterium can proliferate and spread throughout the piping systems (Figure 1), which ultimately decreases the drinking water quality [2]. Currently, this is an emerging concern because when schools, offices, and other infrastructure reopen after COVID-19 lockdowns or remote work, there is a heightened risk for exposure to Legionella. The bacteria can cause Legionnaires’ Disease (LD), a severe form of pneumonia [3]. According to the CDC, in 2018, 10,000 cases of LD were reported annually in the US (CDC; URL: https://wonder.cdc.gov/nndss/static/2018/annual/2018-table2h.html), and roughly 1/10 cases are fatal [4,5]. Contrastingly, other reports estimate between 52,000 and 70,000 LD cases occur annually in the United States, suggesting that the true number of illnesses is severely underdiagnosed and misrepresented [6]. Amidst the current pandemic, it is expected that Legionellosis infection may dramatically increase [2], which is a concern for the immunocompromised population. Similarly, it is critical to note that throughout the 2009 H1N1 pandemic, mortality increased due to various bacterial coinfections and misdiagnosis [7,8].
Case reports of Legionellosis amidst the COVID-19 pandemic have slowly begun releasing around the world (Figure 1). Four unique cases document the varying degrees of Legionella infection and exposure sources, highlighting the importance of differential diagnosis during the COVID-19 pandemic (Table 1). Japan has reported a SARS-CoV-2 and Legionella coinfection in an elderly male [9], while another report documents a case of Legionella pneumonia when reopening a restaurant in Milan, Italy [1]. In Portugal in November 2020, the first large outbreak of Legionellosis was reported with 81 individuals infected via contaminated water sources [10]. Another case presents a male initially diagnosed with COVID-19 and failed improvement upon treatment, and was further diagnosed with a Legionella coinfection [11]. Therefore, the purpose of this paper is to raise awareness for doctors and clinicians to consider LD and other bacterial respiratory pathogens as a possible diagnosis in postlockdown populations. By increasing differential diagnoses, morbidity and mortality may be appropriately avoided around the world. Detailed Legionella characteristics, exposure routes, clinical manifestations, and mitigation strategies are thoroughly outlined.

While it is still unknown how Legionella interacts within the built and personal environments during the pandemic, this novel study addresses these possible environmental and health risks. During the ongoing COVID-19 pandemic, effective water disinfection measures must be enforced before reopenings to minimize the risk of possible Legionella infection in communities.

**A microbial threat**

**Understanding the water contaminant: Legionella**

Legionella bacteria are Gram-negative coccobacilli between 2 and 20 μm in length and 0.3–0.9 μm in width that can be found naturally in aerobic aquatic environments such as streams, lakes, and wet soils (Figure 2) [12]. Legionella species are facultative intracellular, meaning the bacterium can survive both inside and outside host cells [13]. These organisms can withstand temperatures between 0 and 68 °C and can even survive chlorination [12]. While Legionella spp. are normally found at low concentrations in natural freshwater bodies, their concentrations can be amplified in man-made water distribution systems (water pipes) and thereby become an opportunistic pathogen to humans.
Table 1

Summary of the case reports of *Legionella* across the globe. These reports document various routes of *Legionella* exposure and clinical manifestations while highlighting the importance of differential diagnosis during the COVID-19 pandemic. These cases reveal a diverse pool of antibiotics currently being used to treat *Legionella* infection.

| Location       | Case Timeline (2020) | Case Presentation | Antibiotics Administered | Epidemiological Investigation | Highlights | Reference                  |
|----------------|----------------------|-------------------|--------------------------|------------------------------|------------|----------------------------|
| Asahi, Japan   | Travel history: Feb. 26 – Mar. 4 | High risk 80-year-old male. | Azithromycin, Ceftriaxone | Legionella exposure source remains unknown, but suspected from the patient’s Nile cruise trip. | Importance of differential diagnosis during COVID-19 pandemic for illness with similar symptoms. | Arashiro, T. et al., 2020 |
| Johnstown, USA | N/A                  | 56-year-old male. | Azithromycin, Ceftriaxone | Legionella exposure source remains unknown, but the patient is categorized as a frequent traveler. | Legionella spp. was resistant to macrolides; emphasizes the need to change antibiotics if clinical improvement fails. | Hussain, K.M. et al., 2021 |
| Matosinhos, Portugal | Symptom onset: Oct. 15 | 81 cases of Legionnaires’ Disease. (+) culture tests for *L. pneumophila*. | Azithromycin, Ceftriaxone | Three cooling towers tested positive for *Legionella* spp. | First recorded outbreak (n = 81) of Legionnaires’ disease amidst COVID-19 pandemic. | Almeida, D.Q. et al., 2021 |
| Rome, Italy    | May 27 Diagnosis: June 4 | Male in 40s. | Levofloxacin | Patient returned to work in a restaurant that reopened on May 25, 2020, after COVID-19 bans were lifted. | Monitoring water systems is critical before reopening infrastructure in post-COVID-19 communities. | Palazzolo, C. et al., 2020 |

*PCR = Polymerase Chain Reaction.
*UAT = Urinary Antigen Test.
Essentially, *Legionella* can proliferate and spread in any water system when disinfection residuals are not strong enough to deactivate the bacteria, which can be very problematic for public health. Since *Legionella* can grow in different concentrations of chlorine, wide pH ranges, and broad temperatures, these water distribution systems offer idyllic living conditions for *Legionella* and their host, amoeba [14]. Water pipes provide optimal growing temperatures between 25 and 50 °C in addition to supplementing other nutrients, such as sediments and biofilms [12].

**Vaccines facilitate a ticking time bomb on water quality**

Many buildings across the world have had low occupancy or remained vacant for prolonged periods of time to control the spread of SARS-CoV-2. Consequently, water is no longer routinely used in such infrastructure and becomes stagnant in the distribution pies, which is a ticking time bomb for water quality due to shifts in microbial communities and biofilm buildup [15]. A study conducted between 2000 and 2014 concluded that Legionnaires’ Disease outbreaks in North America were related to buildings with limited occupancy, closures, and water disruptions [16]. As water ages and remains immobile in the pipes, sediments and particles containing chemicals and microorganisms will eventually settle on the inside wall of the pipes. These particles will continue to grow and mature, eventually forming biofilms inside the pipe wall and continue to utilize these nutrients along the pipe wall to survive [17]. *Legionella* can become virulent when they colonize these biofilms and interact with their amoeba hosts [13,17]. A recent study [18] noted that the pathogenesis and persistence of *Legionella* spp. depend on the type of amoeba host it infiltrates, with over 20 amoeba species vulnerable to *Legionella*. *Legionella* proliferation inside amoeba hosts was found to increase its ability to form biofilms, but *Legionella* outside amoebas did not increase the formation of biofilms [18]. Once *Legionella* establishes itself inside biofilms, including amoeba hosts, the bacteria are difficult to eradicate since the external shell of the biofilm protects it from the external environment, including disinfection residuals [17]. With the recent introduction of SARS-CoV-2 vaccinations, the risk escalates now that communities are returning to ‘normal’ functioning. When the water is turned back on in these piping systems, the water pressure breaks off particles from the largely grown
biofilms containing *Legionella*, dispersing throughout the pipes and contaminating the water. Chlorine and other residuals can be easily consumed by the accumulated organic matter inside the water pipes, which reduces the likelihood of deactivating free-floating *Legionella* [18].

**Human exposure**

There are two routes of exposure to humans. In most cases, an individual may inhale tiny aerosols from infected water [19]. In rare cases, an individual may unintentionally swallow infected water into their lungs. *Legionella* outbreaks have previously been associated with complex water systems in hospitals, hotels, and cruise ships. In 2021, a *Legionella* outbreak hit a senior housing complex in Portland, Oregon, with one fatality and four hospitalized (Cambosa, T.; URL: http://outbreaknewstoday.com/legionnaires-disease-outbreak-in-portland-1-dead-4-hospitalized-24560/); meanwhile, a similar outbreak infiltrated New Jersey prisons, with one fatality and one induced coma (Lacy, A.; URL: https://theintercept.com/2021/04/29/new-jersey-prison-legionnaires-disease/). Cooling towers pose a high risk of exposure [20], in addition to showerhead faucets and hot tubs (Figure 2). Another high-risk exposure scenario would be indoor water park settings where high aerosol generation and inhalation exposure can happen, especially when people resume their recreation after periods of limited travel. Once exposed to the bacteria, *Legionella* can cause a disease called Legionellosis, and transmission does not spread between humans.

On November 3, 2020, the first outbreak of Legionnaires’ Disease was reported during the COVID-19 pandemic in Matosinhos, Portugal [10]. An epidemiological investigation was conducted, and within a few days, the municipal water management company concluded that various cooling towers tested positive for *Legionella* spp. The outbreak hit its peak on November 7, and by November 20th, 2020, the outbreak was determined under control. A total of 81 individuals tested positive for *Legionella* with a 16.1% case fatality rate, and 12.3% of patients were diagnosed with a COVID-19 coinfection. It should be noted that the investigation took a total of 10 days from the first patient diagnosis to taking action to shut down the cooling towers. By raising *Legionella* awareness amidst the ongoing pandemic, delayed public health responses could be prevented in the future to reduce morbidity and mortality.

**Human health implications**

Currently, there are over 60 species within the genus *Legionella* [21], and roughly 24 of these species are probable pathogens to humans [22]. In accounting for nearly 90% of all human infections [21], *Legionella pneumophila* is the most studied and common species that causes Legionellosis in humans, which may be due to its greater virulence and/or higher prevalence in the environment compared to other species [22,23]; however, some recent reports have documented *Legionella micdadei* as the second most human disease-causing species [24].

When *Legionella* spp. reach the lungs, the bacteria are ingested by alveolar macrophages. Since *Legionella* has a type IV secretion system, these proteins prevent normal phagosome-lysosome fusion, allowing for increased cell proliferation inside the macrophages [22]. Each infected cell will grow and eventually burst, killing the host cell while releasing *Legionella* into the extracellular space, further infecting other surrounding cells. After extreme bacterial growth and alveolar macrophage death, severe pneumonia may inhibit the human body by compromising respiratory function. There are two clinical entities of *Legionellosis* in humans: Legionnaires’ Disease (severe pneumonia) and Pontiac Fever (milder respiratory illness).

**The severe form: Legionnaires’ Disease**

Legionnaires’ Disease (LD) clinically manifests as pneumonia with severe multisystem disease [12]. People who are 50 years or older, smokers, alcohol users, and/or have weakened immune systems are at the highest risk of LD [5]. Cough, shortness of breath, muscle aches, headaches, chills, and fever may arise 2–14 days after *Legionella* exposure [23]. Although LD is mainly characterized by a severe form of pneumonia (most similar to pneumococcal or other bacterial pneumonia), LD may exhibit other neurological and gastrointestinal illnesses, such as confusion, nausea, and abdominal pain [25]. Treatment includes antimicrobial therapy, and most cases require hospital care. 1/10 people die from complications, and for patients who stay in a healthcare facility, fatality increases to 1/4 [5,6]. While LD cases occur year-round, most cases are reported during the summer and early autumn [25].

**The mild form: Pontiac Fever**

The clinical characterization of Pontiac Fever (PF) is often debated with no agreed-upon definition [25]; however, it is accepted that PF is the nonfatal and nonpneumonic illness associated with *Legionella* exposure [12]. PF symptoms include muscle aches, fever, and mild flu-like, which typically emerge within 72 h, without developing pneumonia [26]. There are no known risk factors associated with PF [12]. Healthy individuals are able to fight Legionellosis infection and eradicate the bacteria before it reaches the lungs. Thus, PF is usually overlooked since most recover on their own without the need for antimicrobial treatment. As a result, PF is reported less frequently than Legionnaires’ Disease [25].
Additional COVID-19 Co-infections
In addition to *Legionella* spp., there is still a concern for other secondary infections alongside SARS-CoV-2. Recent studies note that at the beginning of the pandemic, antimicrobial usage has increased in comparison to prepandemic [27,28]. The true incidence of bacterial, viral, and fungal coinfections remains unknown across the world. One study reported that bacterial coinfections were more dominant compared to viral and fungal infections in COVID-19 patients [29]. Several studies found that the most common respiratory pathogens with COVID-19 infection include: *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Aspergillus*, *Myoplasma pneumoniae*, *EB Virus*, *Escherichia coli*, and *Pseudomonas aeruginosa* [29–31]. Most reports describe that between 5% and 30% of hospitalized COVID-19 patients developed any type of secondary infection [32]. Overall, COVID-19 patients diagnosed with a secondary bacterial infection are more likely to suffer from worse health outcomes compared to COVID-19 patients without a secondary bacterial infection [33,34].

**Recommendations**

**Diagnosis and treatment**

Since people with LD suffer from pneumonia, doctors can confirm via chest X-ray. There are two preferred methods for diagnosing if the infection is caused by *Legionella* bacteria. The first and most commonly used diagnostic test is the urinary antigen test (UAT), which is rapid and relatively inexpensive, with 70–86% sensitivity and 100% specificity [35]. The UAT only detects *L. pneumophila*, but this serogroup causes about 90% of *Legionella* infections, so this is the initial and preferred practice [36]. The second method is isolating *Legionella* by culture to detect non-*L. pneumophila* species, which is more time-consuming and costly than UATs [37]. Clinicians can also use a blood test to determine if patients have the less severe form of PF. Amidst the COVID-19 pandemic, clinicians must consider *L. pneumophila* as a potential diagnosis in reopening populations. While the majority of people hospitalized from Legionellosis suffer from LD, the most effective treatment method is antibiotic therapy [21]. Even while waiting for diagnostic results, antibiotic treatment has normally already begun. Rapid diagnosis and administration of correct antibiotics are recommended to decrease the risk of developing serious conditions. Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, trovafloxacin) and macrolides (azithromycin) are the antibiotics of choice (Legionella.org; URL: https://legionella.org/about-the-disease/what-is-legionnaires-disease/treatment/). One reported case [11] of *Legionella* infection reported resistance to macrolides, and levofloxacin proved to be effective (Table 1). People with underlying conditions may receive additional treatment, including oxygen and fluids. There is no vaccine for Legionellosis, so the best way to prevent infection is by reducing exposure risk. Most notably, clinicians in reopening communities must be more aware of diagnosing COVID-19 coinfections to reduce avoidable mortality and morbidity across the world.

**Mitigation**

With the release of COVID-19 vaccinations around the globe, communities have begun resuming normal prepandemic livelihoods. Employees are returning to the workforce, students are returning to in-person school, and individuals are resuming recreational and social activities. As a result, these offices, schools, restaurants, shopping malls, and indoor amusement parks will be increasing their building capacity and water usage. Although it may be difficult, there are effective water management practices that can eradicate *Legionella* colonies and prevent recolonization within distribution systems when reopening infrastructure. The key is to design, implement, and regularly update a water safety plan that is unique to each water system. Monochloramine, chlorine, chlorine dioxide, copper-silver ionization, ozone, and UV disinfection have all been shown to be successful in some way against *Legionella* [38]. One method alone is not enough, and a routine combination must be used to inhibit bacterial growth. The CDC (CDC; URL: https://www.cdc.gov/coronavirus/2019-ncov/php/building-water-system.html) and additional resources provide a thorough recommendation for campus reopenings and building owners to follow to reduce stagnant water conditions [2,6,39,40].

Meanwhile, SARS-CoV-2 variants have been recently emerging and spreading around the globe [41]. While some populations and countries with lower vaccination rates remain more vulnerable to variants, epidemics may continue to resurface globally. *Legionella* may remain a public health threat as communities shift in and out of COVID-19 lockdown practices. After these restrictions, inspecting and monitoring water systems is critical before reopening infrastructure to reduce the risk of *Legionella* exposure. Future interventions should work to incorporate *Legionella* building inspection and management in local and regional public policy to mitigate public health implications. Additional clinical research studies should aim to develop an inexpensive and rapid urinary antigen test that can accurately detect all *Legionella* serogroups, not just *L. pneumophila*. With proper management policies and diagnostic tests, *Legionella* may no longer threaten global public health.

**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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