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Environmental Science & Technology LETTERS

# The Role of Aspiration in Legionnaires' Disease: A Quantitative Microbial Risk Assessment (QMRA)-Based Comparison with Inhalation Exposures

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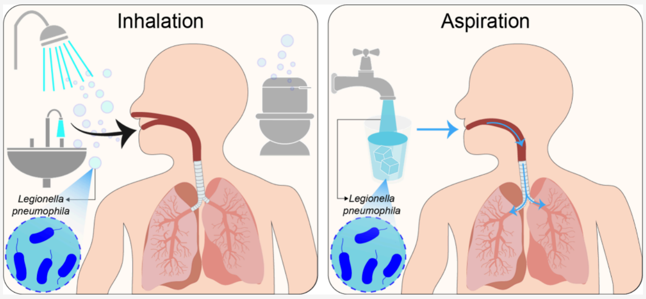
**ABSTRACT:** Legionellosis is generally attributed to the inhalation of aerosolized *Legionella pneumophila* from engineered water systems and/or soils. However, aspiration of contaminated water—a known cause of aspiration pneumonia—is seldom modeled in *L. pneumophila* risk assessment. Here, we develop a quantitative microbial risk assessment model to estimate the risks associated with aspiration exposures. Monte Carlo simulations, incorporating the aspiration water volume, the aspiration frequency, and the alveolar deposition fraction, reveal that low *L. pneumophila* concentrations in water can yield an appreciable infection risk in populations prone to aspiration. Under equal *L. pneumophila* concentrations, we find that an aspiration event can pose a higher infection risk than aerosol inhalation from showers or faucets. Sensitivity analyses identify the aspiration volume as a driver of risk. Our findings highlight the need for risk management strategies that address not only aerosol generation but also the aspiration of contaminated water.



**KEYWORDS:** *Pontiac fever, inhalation, aspiration, quantitative microbial risk assessment (QMRA), respiratory disease, premise plumbing, opportunistic pathogen*

## 1. INTRODUCTION

Legionellosis is caused by exposure to pathogenic *Legionella* spp. bacteria through the aspiration of contaminated water into the lungs or the inhalation of contaminated aerosols or dust. Legionellosis cases (including Legionnaires' disease and Pontiac Fever) contribute to a \$2.39 billion annual healthcare cost burden in the US[1] and are increasing in the US[2] and Europe.[3]

Aerosol inhalation (via water or soil aerosols) is thought to be the dominant exposure route for *Legionella* spp., but other exposures are not well-characterized.[4] An understudied but potentially important exposure route is pulmonary aspiration. Aspiration occurs when a small amount of oropharyngeal or gastric contents bypass the upper airway defenses and enter the lower respiratory tract.[5] While aspiration can affect anyone in the general population,[6] it is both more common and a greater concern in susceptible individuals, particularly those with physiological contributing factors such as dysphagia (swallowing disorder),[5] advanced age,[7,8] or neurological impairment.[9] Aspiration pneumonia can be caused by the aspiration of various substances, including liquids (such as drinking water and melted ice), food, and saliva. These infections can arise from the aspiration of pathogenic microorganisms from external environments or from the commensal microbial community of the respiratory tract, involving a wide range of species beyond *Legionella* such as viruses, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.[5,10]

Aspiration can develop into aspiration pneumonitis, or Mendelson's syndrome (a lung injury), or aspiration pneumonia, which is an infection from aspirating a liquid colonized by pathogenic bacteria, such as *L. pneumophila*.[5] Aspiration pneumonia can be difficult to distinguish from community- and hospital acquired-pneumonias due to similarities in symptoms.[11] For instance, an aspiration event that occurs overnight may go unnoticed,[12] making it challenging to directly link a pneumonia case with an aspirated pathogen and a specific aspiration event. Nonetheless, aspiration is recognized as a likely transmission route for *Legionella*. *Legionella* spp. have been detected in the oropharynx[13] and dental plaques[14] which can contribute to aspiration exposure. Guidance and management around aspiration-related *Legionella* generally focuses on the accidental introduction of water into the lungs during drinking or chewing ice.[15] In one

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**Table 1. Aspiration-Specific Monte Carlo Parameters**[a]

| Definition | Parameter | | Value or distribution | Units | Reference |
|---|---|---|---|---|---|
| Concentration of *L. pneumophila* | $C_{Leg}$ | | Varied | CFU/L | NA |
| Aspiration volume (assumes 100% comprised of water) | $V$ | Microaspiration | Uniform (1, 100) × $10^{-6}$ | L | 28 |
| | | Macroaspiration | Uniform (0.1, 1) × $10^{-3}$ | L | 29 |
| | | Severe aspiration | Uniform (1, 10) × $10^{-3}$ | L | 28,29 |
| Fraction of aspirated volume that reaches lower lungs | $f$ | | Uniform (0.001, 1) | Unitless | Assumption |
| Aspiration frequency | $a$ | Once | 1 | Aspiration events per year | Assumption |
| | | Monthly | 12 | | 26,27 |
| | | Weekly | 52 | | |
| | | Daily (during sleep, e.g.) | 365 | | |
| Dose−response (*Legionella pneumophila*, sub-clinical infection end point) | $r$ | Exponential model | Lognormal distribution ($\mu$ = −2.93, $\sigma$ = 0.49) | Unitless | 25 |

[a]The inhalation variable parameterization is described in ref 24.

documented case, a 79-year-old hospital patient with a swallowing disorder developed Legionnaires' disease, which was traced to an ice machine with high concentrations of *L. pneumophila* at the time.[16] Limited evidence also suggests *Legionella* can persist after gargling contaminated tap water; one study isolated *L. pneumophila* from the oropharynx up to 30 min after gargling.[17]

Due to the emphasis on water management activities for *Legionella* control within the built environment,[18,19] there is a need to understand the relative importance of different exposure routes and pathways. Opportunistic pathogen infections arise from numerous previously implicated potential water fixtures and sources, including toilets, faucets, decorative water features, hot tubs, water parks, HVAC systems, dehumidifiers, cooling towers, and showers.[20] Source apportionment for *Legionella* infections has been highlighted as an important gap for tackling this multipronged and persistent problem.[4,21]

Through hazard identification, exposure assessment, dose−response assessment, and risk characterization, quantitative microbial risk assessment (QMRA) has been used to model *Legionella pneumophila* fate, transport, and risk of infection, illness, and/or death.[22] Numerous models have been developed for assessing the risk of inhalation exposure of *Legionella* spp.[23] These models have been used to inform source apportionment goals, for example, identifying showers as a driver of indoor water fixture risks[24] and setting risk-based water monitoring targets. To date, a QMRA model has not been conducted for aspiration exposures to waterborne bacteria such as *Legionella* spp. Developing such a model would allow for evidence-based comparison of aspiration with other exposure routes to aid in prioritizing resources, informing management activities, and developing prevention policies. To achieve this goal, the objectives of this study are to (1) develop a QMRA model that considers aspiration as a route of exposure for *Legionella pneumophila*; (2) compare population level risks for aspiration and inhalation exposures; and (3) identify gaps for understanding aspiration contributions to the *Legionella* spp. burden of disease.

## 2. METHODS AND MATERIALS

To explore the risks of *L. pneumophila* infection through multiple routes, a model was developed using the QMRA framework[22] to compare aspiration with inhalation exposures, which have been previously explored and quantified as common routes of exposure and potential infection. In this study, aspiration is explored as a transmission pathway, as it can result in lung exposure to liquids and aerosols that may be contaminated, through a physiologically independent mechanism from inhalation.

**2.1. Aspiration QMRA.** Through the steps of the QMRA framework, the risk of infection was quantified for *Legionella pneumophila* (hazard identification) through aspiration (exposure assessment) using a dose−response relationship based on animal studies and epidemiological outbreak data.[25] First, the dose of *L. pneumophila* deposited into the lungs during an aspiration event was modeled with eq 1.

$$d = C_{\mathrm{Leg}} V f \tag{1}$$

Here, $d$ is the dose of viable *L. pneumophila* deposited into the lungs during a single aspiration event (colony-forming unit [CFU]), $C_{\mathrm{Leg}}$ is the concentration of viable *L. pneumophila* in water (CFU/L), $V$ is the volume of water that enters the respiratory tract during an aspiration event (L), and $f$ is the fraction of aspirated water that reaches the alveoli (unitless).

The annual risk of infection is then estimated based on an exponential dose−response model (eq 2) and compounded for annualized exposures (eq 3)

$$P_{\mathrm{inf}} = 1 - e^{-rd} \tag{2}$$

$$P_{\mathrm{annual}} = 1 - (1 - P_{\mathrm{inf}})^{a} \tag{3}$$

where $P_{\mathrm{inf}}$ is the risk of infection for one exposure, $r$ is the probability of an individual microorganism to survive and initiate infection (unitless), $P_{\mathrm{annual}}$ is the annual risk of infection, and $a$ is the aspiration frequency (per year), which can vary based on health status (e.g., presence of swallowing disorders) and age.[26,27] To quantify the variability in risk estimates, a Monte Carlo analysis was conducted using distributions for each variable, summarized in Table 1. A single run of 10,000 simulations was performed with random values from each of the theoretical distributions (with the random seed set to 56) defined in Table 1. Additional explanations for these parameters based on the literature can be found in the Supporting Information. All analysis was conducted using R v.4.2.2.

*2.1.1. Variable Parametrization: V, Volume Aspirated.* Literature reviews were performed in PubMed and Google Scholar to obtain information about aspiration volumes and frequencies. Available information suggested large uncertainty bounds surrounding volume and frequency as a function of the fluid aspirate chemistry,[30,31] individual susceptibilities such as

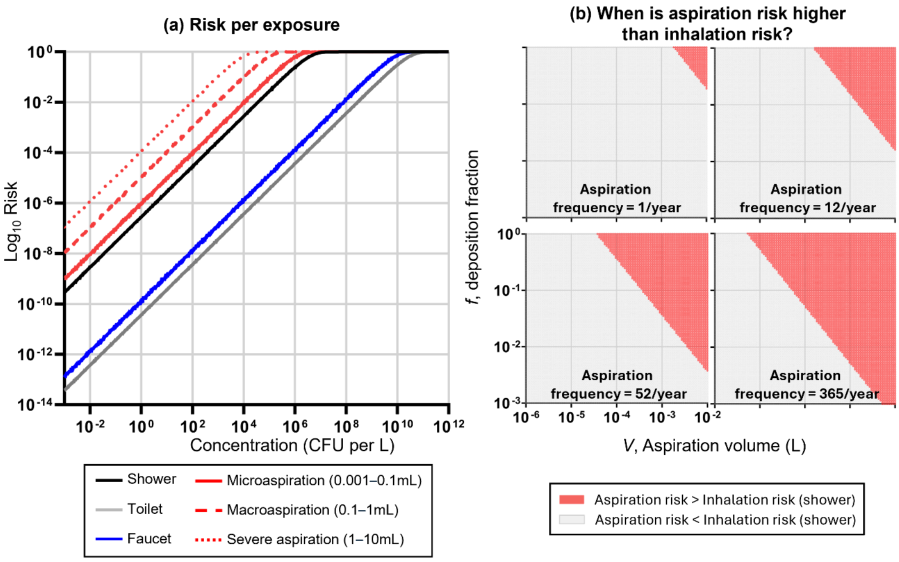

**Figure 1.** (**a**) Median *L. pneumophila* infection risk per exposure for inhalation and aspiration scenarios across a range of simulated concentrations. (**b**) Binary comparison of aspiration vs inhalation risk (showering) at 1 CFU/L. The grid shows conditions under which aspiration risk exceeds inhalation risk across varying aspirated volumes and frequencies ($a$ = 1, 12, 52, 365/year).

neuromuscular diseases, history of stroke, gastroesophageal reflux disease (GERD), and age,[32−36] exposures to medical devices and procedures,[37,38] surgery,[39] and other factors. “Microaspiration” of small volumes (≤0.1 mL) is assumed to occur once per week to once per month, although this is not well-documented and there is no firm cutoff for this volume.[28] “Macroaspiration” (volumes >0.5 mL) similarly can occur (unspecified frequency).[28] Macroaspiration is thought to occur during drinking, especially in those with susceptibilities or preexisting conditions, such as dysphagia or other swallowing disorders that increase aspiration rates (age and other conditions are consistently identified as contributing factors in increased aspiration).[40] “Silent aspiration” of saliva (<0.1 mL)[27] can occur during swallowing in ∼10−50% of individuals (approximately once per night during sleep) but typically does not cause harm.[26,27] In other studies, healthy patients have been shown to aspirate 0.01−0.15 mL, while other groups aspirated up to 3.64 mL during sleep.[28] In a human swallowing study[29] the mean aspirated volume was 5.53−6.72 mL of patients with underlying conditions. Another study on patients with dysphagia imaged and estimated <1% to 25% of the swallowed volume (75−100 mL) was aspirated.[41] This latter study, and a similar one on infants,[42] demonstrated imaging and quantification of aspirated liquid volumes into the lungs and subsequent clearance. Based on these findings, we defined ranges for our model as potential scenarios of microaspiration (0.001−0.1 mL), macroaspiration (0.1−1 mL), and more severe aspiration (1−10 mL). The large range in volumes is likely due to differences in the goals of the studies (e.g., ascertaining “background” rates of aspiration vs outcomes as severe as drowning and/or evaluation of severely susceptible populations), methodological differences, and study designs.

*2.1.2. Variable Parametrization: f, Fraction That Reaches Lower Lungs.* While the above studies note lung deposition of aspirated liquid, it remains uncertain the amount of which is in contact with the lower alveolar-bronchiolar region, which has been used to demonstrate and quantify *L. pnemuophila* inhalation exposure in previous models and clinical assessments,[43−45] particularly since the bacteria has demonstrated multiplication in alveolar macrophages.[46] While rich information is available on aerosol deposition,[47,48] limited to no information is available on nonaerosol deposition from aspirate. Thus, an additional factor, $f$, was included to capture this uncertainty, to represent a fraction of the aspirated volume that reaches the lower lungs, similar to the “deposition efficiency” that has been used in inhalation models.[24] Based on these findings, we defined ranges for our model as anywhere from 0.1 to 100% (Table 1), since portions of aspirate or liquid volumes may reach the lower lungs. While previous studies have demonstrated aspirate in both lungs,[41,42] we note the considerable uncertainty in estimating actual exposure.

**2.2. Inhalation QMRA.** Previously derived inhalation exposure models[24] were used for comparison with the aspiration exposure route proposed in our study. The exposure dose of *L. pneumophila* from three comparative indoor water fixtures is modeled in eqs 4−6. Here, $d$ is again the total dose of bacteria inhaled based on the concentration of bacteria in water ($C_{\mathrm{Leg}}$), the inhalation rate ($I$), the time exposed ($t$), the fraction of aerosols of diameter i ($F_{\mathrm{i}}$), the deposition efficiency in the alveolar-bronchiolar region of the lungs for aerosols of diameter i ($D_{\mathrm{i}}$), the concentration of aerosols per volume of air ($C_{\mathrm{aero,i}}$), the volume per aerosol of diameter i ($V_{\mathrm{aero,i}}$), and the partitioning coefficient ($P$).

$$d_{\mathrm{faucet}} = C_{\mathrm{Leg}} I t_{\mathrm{faucet}} P F_{\mathrm{i}} D_{\mathrm{i}} \tag{4}$$

$$d_{\mathrm{toilet}} = C_{\mathrm{Leg}} I t_{\mathrm{toilet}} \sum_{i=1}^{10} C_{\mathrm{aero,i}} V_{\mathrm{aero,i}} \sum_{i=1}^{10} F_{\mathrm{i}} D_{\mathrm{i}} \tag{5}$$

$$d_{\mathrm{shower}} = C_{\mathrm{Leg}} I t_{\mathrm{shower}} \sum_{i=1}^{10} C_{\mathrm{aero,i}} V_{\mathrm{aero,i}} \sum_{i=1}^{10} F_{\mathrm{i}} D_{\mathrm{i}} \tag{6}$$

All exposure parameters for the inhalation models are listed and defined in Table S1.

**2.3. Comparison of Aspiration and Inhalation Risk.** To further explore the uncertainty in parametrization for the aspiration model and find where the aspiration risk is higher than the inhalation risk, combinations of parameters were explored alongside the Monte Carlo simulation. With the ranges of parameters $V$, $f$, and $a$ presented (Table 1), the aspiration dose and resulting annual infection risk was calculated and compared with annual risk of inhalation from showering. The *L. pneumophila* concentration was set to 1 CFU/L for both scenarios.

**2.4. Sensitivity Analysis.** A sensitivity analysis was performed to examine the impact of uncertainty in the volume aspirated ($V$), the fraction of aspirated water that reaches the lower lungs ($f$) (deposition efficiency for inhalation models), and aspiration frequency ($a$) informed by estimates of aspiration volume[28,29,31] and frequency.[26,27] The ranges used for this analysis reflect the ranges from the model (Table 1) and are also listed in Table S2. The sensitivity analysis was evaluated by using bivariate Spearman rank correlations.

## 3. RESULTS

The risk of infection for single aspiration events is plotted in Figure 1a alongside the single-exposure infection risks for the previously modeled plumbing fixtures for *L. pneumophila*. The median risk of infection through aspiration for a single exposure event was higher than for the other exposures, even at small volumes (microaspiration).

To explore the impact of the exposure assumptions and inherent uncertainty on annual infection risk, Figure 1b shows the combination of aspiration volume ($V$) and lung deposition ($f$) that results in annual risk exceeding that of showering (assuming one shower per day). This threshold was evaluated across multiple aspiration frequencies ($a$ = 365, 52, 12, and 1 for daily, weekly, monthly, and single events, respectively). Based on the distributions chosen for $f$ and $V$ (where $V$ is represented as a continuous sequence from $10^{-6}$ to $10^{-2}$ L), the probability that the annual infection risk exceeds that of showering was 44.2%, 24.6%, 13.5%, and 2.2% for daily, weekly, monthly, and single events, respectively. For comparison to the aspiration volumes, the median single-shower inhaled exposure volume (eq 2) was estimated as $5.4 \times 10^{-6}$ L. Therefore, assuming the same *L. pneumophila* concentration in water, even infrequent aspiration events can pose a comparable or greater infection risk than inhalation exposures under certain combinations of aspirated volume and lung deposition. This highlights how variability (and inherent uncertainty) in the aspiration volume and deposition efficiency can influence risk outcomes.

Spearman Rank sensitivity analysis resulted in volume aspirated, $V$, as most impactful on the infection risk ($\rho$ = 0.893, compared with 0.263 for $f$ and 0.247 for $a$). These results and parameter ranges can be found in Figure S1 and Table S2.

## 4. DISCUSSION

**4.1. Implications of Aspiration Risk Models.** Based on the current risk assessment, even low concentrations of *L. pneumophila* in drinking water (e.g., 1 CFU/L) correspond to higher infection risk for single aspiration events compared to common exposures such as showering, faucet aerosolization, and toilet flushing (Figure 1). This highlights pulmonary aspiration as an underexplored route for potential respiratory infections within the context of building water management. As noted in the literature, higher frequencies and volumes of aspiration events are more common for individuals at higher risk, such as the elderly or those with underlying conditions or illnesses. Opportunistic pathogens such as *L. pneumophila* are already noted for being of greater concern for these same individuals, posing a higher risk and with higher mortality rates.[49,50]

**4.2. Limitations and Recommendations for Additional Aspiration Risk Analysis.** This QMRA model highlights that a better understanding of the volume, frequency, and deposition of aspirated water/liquid as a function of host susceptibility and microbiomes (in both water and the human body) is needed. Limited quantitative information is available regarding these factors, and the literature can be more systematically evaluated (e.g., using systematic literature reviews[51]) to better translate clinical studies (e.g.,[52]) of swallowing and aspiration challenges to quantitative outcomes, for example, using the penetration-aspiration scale.[53] Development of a mechanistic model for aspiration may aid in further estimating this volume.[41,42] While aspiration fluid volume and frequency may be related in a way that is not captured here, limited data are available, pointing to this as a key area for further research and quantification. Additional comparison of inhaled and aspirated volumes and risk results between models is in the Supporting Information (Figure S2).

In the current model, the aspiration volume was assumed to be composed completely of drinking water; however, other oropharyngeal or gastric fluids are likely to be present, and a more precise composition would improve the model. Incorporation of a more nuanced characterization of aspiration fluid in view of drinking, swallowing, sleeping, or other activities would provide insight into refining this quantitatively. Given the potential for colonization with *Legionella* spp. in the human microbiome,[13,14] other approaches could be taken to examine transition probabilities from colonization to disease progression as has been performed for other pathogens in QMRA models such as for *Staphylococcus aureus*.[54] Currently available dose−response models have inhalation, rather than aspiration, routes of exposure, and additional harmonization is needed to account for an aspiration route of exposure.

The aspiration model here provides some quantitative context for comparing aspiration with other routes of exposure but highlights the larger range of uncertainties for exposure volumes and frequencies compared to inhalation with more information available for parametrization.[24] With better quantification of these variables, aspiration models could be considered in additional models of comparative *Legionella* risks and source apportionment to inform holistic risk management efforts.

**4.3. Implications for Risk Assessment and Management.** By demonstrating that aspiration of drinking water can potentially deliver a higher *L. pneumophila* dose to the alveolar region than inhalation exposures, the study underscores the need to expand QMRA frameworks beyond inhalation. It exposes key data gaps, particularly on aspirate volumes and their deposition fractions in the lower respiratory tract. These gaps limit the precision of existing models and warrant further investigations. Our findings suggest that risk management strategies must evolve to address aspiration as a distinct and potentially dominant exposure route, especially among vulnerable populations. Closer integration of drinking water safety planning with clinical protocols for aspiration prevention is essential.

Several recommendations based on the reviewed literature were compiled (Table 2). Proper swallowing function is

Table 2. Risk Management Recommendations for Aspiration Exposure

| High risk patients | General population | Water systems |
|---|---|---|
| ●Ensure **upright posture** during meals (≥45°), and for ventilated patients[60]<br>●Provide **modified diet** (thicker liquids if advised)[59]<br>●Monitor swallowing using **clinical assessments** or **video fluoroscopy**[68]<br>●Encourage small sips and slow eating or **assisted feeding** for severe swallowing problems[7]<br>●Consider **swallow** or respiratory therapy[7]<br>●**Pharmacotherapies** such as folic acid supplementation[57] or amantadine to modulate dopamine metabolism for stroke patients[58] | ●**Elevate the head** of the bed (30°–45°) **during sleep**[61]<br>●**Minimize sedative use** that affects swallowing reflexes[5]<br>●Regular **dental hygiene** to reduce oral bacterial load[62,64]<br>●Use **suctioning devices** when appropriate[63] | ●Control growth of *Legionella* in water systems to minimize both inhalation and aspiration exposures (e.g., **water management plan** and follow applicable guidance)[66]<br>●Use **highly treated water** or sterile water for high-risk applications where possible[38,67] |

necessary to reduce or prevent aspiration and can decrease with age.[55,56] Swallowing therapies may improve this reflex in those with swallowing disorders.[7] Pharmacotherapies have been tested for their effects on preventing aspiration pneumonia in stroke patients and may be considered, such as folic acid supplementation[57] and drugs to modulate dopamine metabolism.[58] For high-risk patients, other recommendations include dietary modifications regarding food textures,[59] assisted feeding strategies,[7] and an elevated position rather than supine, especially for ventilated patients.[60] Individuals can also elevate the head during sleep, minimize sedative use, engage in regular dental hygiene practices, and use suctioning devices where appropriate.[5,61−64]

Water management plans can be implemented within buildings (with a focus on healthcare environments) to control the growth of *Legionella* to minimize overall exposures.[65,66] The use of more highly treated, or "sterile", water can also reduce aspiration risks, although interpretations and feasibility of its implementation varies.[38,67]

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.5c00488.

> Additional volume and risk results for individual parameter variations, sensitivity analysis results, tabulated parameters for inhalation models, and full model code (PDF)

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) Collier, S. A.; Deng, L.; Adam, E. A.; Benedict, K. M.; Beshearse, E. M.; Blackstock, A. J.; Bruce, B. B.; Derado, G.; Edens, C.; Fullerton, K. E.; Gargano, J. W.; Geissler, A. L.; Hall, A. J.; Havelaar, A. H.; Hill, V. R.; Hoekstra, R. M.; Reddy, S. C.; Scallan, E.; Stokes, E. K.; et al. Estimate of Burden and Direct Healthcare Cost of Infectious Waterborne Disease in the United States. *Emerg. Infect. Dis.* **2021**, *27* (1), 140−149.

(2) Moffa, M. A.; Rock, C.; Galiatsatos, P.; Gamage, S. D.; Schwab, K. J.; Exum, N. G. Legionellosis on the Rise: A Scoping Review of Sporadic, Community-Acquired Incidence in the United States. *Epidemiol. Infect.* **2023**, *151*, No. e133.

(3) European Centre for Disease Prevention and Control (ECDC). *Legionnaires' Disease Annual Epidemiological Report for 2021*; ECDC: Stockholm, Sweden, 2023.

(4) NASEM. *Management of Legionella in Water Systems*; National Academies Press: Washington, D.C., 2019. DOI: 10.17226/25474.

(5) Marik, P. E. Aspiration Pneumonitis and Aspiration Pneumonia. *N. Engl. J. Med.* **2001**, *344* (9), 665−671.

(6) Ramsey, D.; Smithard, D.; Kalra, L. Silent Aspiration: What Do We Know? *Dysphagia* **2005**, *20* (3), 218−225.

(7) Kikawada, M.; Iwamoto, T.; Takasaki, M. Aspiration and Infection in the Elderly: Epidemiology, Diagnosis and Management. *Drugs Aging* **2005**, *22* (2), 115−130.

(8) Steele, C. M.; Cichero, J. A. Y. Physiological Factors Related to Aspiration Risk: A Systematic Review. *Dysphagia* **2014**, *29* (3), 295−304.

(9) Thomson, J.; Hall, M.; Ambroggio, L.; Stone, B.; Srivastava, R.; Shah, S. S.; Berry, J. G. Aspiration and Non-Aspiration Pneumonia in Hospitalized Children With Neurologic Impairment. *Pediatrics* **2016**, *137* (2), No. e20151612.

(10) Almirall, J.; Boixeda, R.; de la Torre, M. C.; Torres, A. Aspiration Pneumonia: A Renewed Perspective and Practical Approach. *Respir. Med.* **2021**, *185*, 106485.

(11) DiBardino, D. M.; Wunderink, R. G. Aspiration Pneumonia: A Review of Modern Trends. *J. Crit. Care* **2015**, *30* (1), 40−48.

(12) Kakeshpour, T.; Fennelly, K. P.; Bax, A. Snoring-Generated Fluid Droplets as a Potential Mechanistic Link between Sleep-Disordered Breathing and Pneumonia. *Respir. Res.* **2024**, *25* (1), 224.

(13) Jaresova, M.; Hlozanek, I.; Striz, I.; Petrickova, K.; Kocmoud, Z. Legionella Detection in Oropharyngeal Aspirates of Transplant Patients Prior to Surgery. *Eur. J. Clin. Microbiol. Infect. Dis.* **2006**, *25* (1), 63−64.

(14) Tesauro, M.; Petrelli, F.; Lizioli, A. Presence of Legionella Spp. in Human Dental Plaque. *Ann. Ig. Med. Prev. E Comunità* **2018**, No. 5, 387−390.

(15) CDC. Developing a Water Management Program to Reduce Legionella Growth & Spread in Buildings. CDC, 2017.

(16) Bencini, M. A.; Yzerman, E. P. F.; Koornstra, R. H. T.; Nolte, C. C. M.; Den Boer, J. W.; Bruin, J. P. A Case of Legionnaires' Disease Caused by Aspiration of Ice Water. *Arch. Environ. Occup. Health* **2005**, *60* (6), 302−306.

(17) Yu, V. L. Could Aspiration Be the Major Mode of Transmission for Legionella. *Am. J. Med.* **1993**, *95* (1), 13−15.

(18) Julien, R.; Dreelin, E.; Whelton, A. J.; Lee, J.; Aw, T. G.; Dean, K.; Mitchell, J. Knowledge Gaps and Risks Associated with Premise Plumbing Drinking Water Quality. *AWWA Water Sci.* **2020**, *2* (3), No. e1177.

(19) Singh, R.; Hamilton, K. A.; Rasheduzzaman, M.; Yang, Z.; Kar, S.; Fasnacht, A.; Masters, S. V.; Gurian, P. L. Managing Water Quality in Premise Plumbing: Subject Matter Experts' Perspectives and a Systematic Review of Guidance Documents. *Water* **2020**, *12* (2), 347.

(20) Hamilton, K.; Bartrand, T. Microenvironment-Associated Water Microbiomes and Priorities for Public Health Research. *NAE Bridge* **2022**, *52* (3).

(21) Fischer, F. B.; Bigler, M.; Mäusezahl, D.; Hattendorf, J.; Egli, A.; Julian, T. R.; Rölli, F.; Gaia, V.; Wymann, M.; Fridez, F.; Bertschi, S.; Akers, I.; Albrich, W. C.; Bandeira, D.; Bernasconi, E.; Berthod, D.; Boesing, M.; Calligaris-Maibach, R.; Clerc, O.; Croxatto, A.; et al. Legionnaires' Disease in Switzerland: Rationale and Study Protocol of a Prospective National Case-Control and Molecular Source Attribution Study (SwissLEGIO). *Infection* **2023**, *51* (5), 1467−1479.

(22) Haas, C. N.; Rose, J. B.; Gerba, C. P. *Quantitative Microbial Risk Assessment*; 2nd ed.; Wiley Blackwell, 2014. DOI: 10.1002/9781118910030.

(23) Tang, L.; Rhoads, W. J.; Eichelberg, A.; Hamilton, K. A.; Julian, T. R. Applications of Quantitative Microbial Risk Assessment to Respiratory Pathogens and Implications for Uptake in Policy: A State-of-the-Science Review. *Environ. Health Perspect.* **2024**, *132* (5), 056001.

(24) Hamilton, K.; Hamilton, M.; Johnson, W.; Jjemba, P.; Bukhari, Z.; LeChevallier, M.; Haas, C. N.; Gurian, P. L. Risk-Based Critical Concentrations of *Legionella Pneumophila* for Indoor Residential Water Uses. *Environ. Sci. Technol.* **2019**, *53* (8), 4528−4541.

(25) Armstrong, T. W.; Haas, C. N. A Quantitative Microbial Risk Assessment Model for Legionnaires' Disease: Animal Model Selection and Dose-Response Modeling. *Risk Anal. Off. Publ. Soc. Risk Anal.* **2007**, *27* (6), 1581−1596.

(26) Butler, S. G.; Stuart, A.; Leng, X.; Wilhelm, E.; Rees, C.; Williamson, J.; Kritchevsky, S. B. The Relationship of Aspiration Status With Tongue and Handgrip Strength in Healthy Older Adults. *J. Gerontol. A. Biol. Sci. Med. Sci.* **2011**, *66A* (4), 452−458.

(27) Gleeson, K.; Maxwell, S. L.; Eggli, D. F. Quantitative Aspiration During Sleep in Normal Subjects. *CHEST* **1997**, *111* (5), 1266−1272.

(28) Beal, M.; Chesson, A.; Garcia, T.; Caldito, G.; Stucker, F.; Nathan, C. A Pilot Study of Quantitative Aspiration in Patients with Symptoms of Obstructive Sleep Apnea: Comparison to a Historic Control Group. *Laryngoscope* **2004**, *114* (6), 965−968.

(29) Hwang, C. H. Swallowing Study Using Water-Soluble Contrast Agents May Increase Aspiration Sensitivity and Antedate Oral Feeding without Respiratory and Drug Complications: A STROBE-Compliant Prospective, Observational, Case-Control Trial. *Medicine (Baltimore)* **2022**, *101* (27), No. e29422.

(30) James, C. F.; Modell, J. H.; Gibbs, C. P.; Kuck, E. J.; Ruiz, B. C. Pulmonary Aspiration-Effects of Volume and pH in the Rat. *Anesth. Analg.* **1984**, *63* (7), 665−668.

(31) Raidoo, D. M.; Rocke, D. A.; Brock-Utne, J. G.; Marszalek, A.; Engelbrecht, H. E. Critical Volume for Pulmonary Acid Aspiration: Reappraisal in a Primate Model. *BJA Br. J. Anaesth.* **1990**, *65* (2), 248−250.

(32) Blatt, S. P.; Parkinson, M. D.; Pace, E.; Hoffman, P.; Dolan, D.; Lauderdale, P.; Zajac, R. A.; Melcher, G. P. Nosocomial Legionnaires' Disease: Aspiration as a Primary Mode of Disease Acquisition. *Am. J. Med.* **1993**, *95* (1), 16−22.

(33) Cvejic, L.; Bardin, P. G. Swallow and Aspiration in Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **2018**, *198* (9), 1122−1129.

(34) Ficke, B.; Rajasurya, V.; Sanghavi, D. K.; Cascella, M. Chronic Aspiration. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.

(35) Kikuchi, R.; Watabe, N.; Konno, T.; Mishina, N.; Sekizawa, K.; Sasaki, H. High Incidence of Silent Aspiration in Elderly Patients with Community-Acquired Pneumonia. *Am. J. Respir. Crit. Care Med.* **1994**, *150* (1), 251−253.

(36) Kollmeier, B. R.; Keenaghan, M. Aspiration Risk. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.

(37) Muder, R. R.; Yu, V. L.; Woo, A. H. Mode of Transmission of Legionella Pneumophila: A Critical Review. *Arch. Int. Med.* **1986**, *146* (8), 1607−1612.

(38) Venezia, R. A.; Agresta, M. D.; Hanley, E. M.; Urquhart, K.; Schoonmaker, D. Nosocomial Legionellosis Associated with Aspiration of Nasogastric Feedings Diluted in Tap Water. *Infect. Control Hosp. Epidemiol.* **1994**, *15* (8), 529−533.

(39) Neilipovitz, D. T.; Crosby, E. T. No Evidence for Decreased Incidence of Aspiration after Rapid Sequence Induction. *Can. J. Anaesth. J. Can. Anesth.* **2007**, *54* (9), 748−764.

(40) Metheny, N. A. Risk Factors for Aspiration. *J. Parenter. Enter. Nutr.* **2002**, *26* (6S). DOI: 10.1177/014860710202600605.

(41) Silver, K. H.; Van Nostrand, D. The Use of Scintigraphy in the Management of Patients with Pulmonary Aspiration. *Dysphagia* **1994**, *9* (2), 107−115.

(42) Laube, B. L.; Katz, R.; Loughlin, G. M.; Pinto, J. M.; Lefton-Greif, M. A. Quantification of the Source, Amount and Duration of Aspiration in the Lungs of Infants Using Gamma Scintigraphy. *Paediatr. Respir. Rev.* **2019**, *32*, 23−27.

(43) Baskerville, A.; Broster, M.; Fitzgeorge, R. B.; Hambleton, P.; Dennis, P. J. EXPERIMENTAL TRANSMISSION OF LEGIONNAIRES' DISEASE BY EXPOSURE TO AEROSOLS OF LEGIONELLA PNEUMOPHILA. *Lancet* **1981**, *318* (8260), 1389−1390.

(44) Lim, K.-Y.; Hamilton, A. J.; Jiang, S. C. Assessment of Public Health Risk Associated with Viral Contamination in Harvested Urban Stormwater for Domestic Applications. *Sci. Total Environ.* **2015**, *523*, 95−108.

(45) Quon, H.; Allaire, M.; Jiang, S. C. Assessing the Risk of Legionella Infection through Showering with Untreated Rain Cistern Water in a Tropical Environment. *Water* **2021**, *13* (7), 889.

(46) Nash, T. W.; Libby, D. M.; Horwitz, M. A. Interaction between the Legionnaires' Disease Bacterium (Legionella Pneumophila) and Human Alveolar Macrophages. Influence of Antibody, Lymphokines, and Hydrocortisone. *J. Clin. Invest.* **1984**, *74* (3), 771−782.

(47) Heyder, J. Deposition of Inhaled Particles in the Human Respiratory Tract and Consequences for Regional Targeting in Respiratory Drug Delivery. *Proc. Am. Thorac. Soc.* **2004**, *1* (4), 315−320.

(48) Heyder, J.; Gebhart, J.; Rudolf, G.; Schiller, C.; Stahlhofen, W. Deposition of Particles in the Human Respiratory Tract in the Size Range 0.005−15 Micrometers. *J. Aerosol Sci.* **1986**, *17* (5), 811−825.

(49) Bauer, M.; Mathieu, L.; Deloge-Abarkan, M.; Remen, T.; Tossa, P.; Hartemann, P.; Zmirou-Navier, D. Legionella Bacteria in Shower Aerosols Increase the Risk of Pontiac Fever among Older People in Retirement Homes. *J. Epidemiol. Community Health* **2008**, *62* (10), 913−920.

(50) Sopena, N.; Pedro-Botet, L.; Mateu, L.; Tolschinsky, G.; Rey-Joly, C.; Sabrià, M. Community-Acquired Legionella Pneumonia in Elderly Patients: Characteristics and Outcome. *J. Am. Geriatr. Soc.* **2007**, *55* (1), 114−119.

(51) Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D. G. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* **2009**, *6* (7), No. e1000097.

(52) Garon, B. R.; Engle, M.; Ormiston, C. A Randomized Control Study to Determine the Effects of Unlimited Oral Intake of Water in Patients with Identified Aspiration. *J. Neurol. Rehabil.* **1997**, *11* (3), 139−148.

(53) Rosenbek, J. C.; Robbins, J. A.; Roecker, E. B.; Coyle, J. L.; Wood, J. L. A Penetration-Aspiration Scale. *Dysphagia* **1996**, *11* (2), 93−98.

(54) Schoen, M. E.; Jahne, M. A.; Garland, J.; Ramirez, L.; Lopatkin, A. J.; Hamilton, K. A. Quantitative Microbial Risk Assessment of Antimicrobial Resistant and Susceptible Staphylococcus Aureus in Reclaimed Wastewaters. *Environ. Sci. Technol.* **2021**, *55* (22), 15246−15255.

(55) Jaradeh, S. Neurophysiology of Swallowing in the Aged. *Dysphagia* **1994**, *9* (4), 218−220.

(56) Nilsson, H.; Ekberg, O.; Olsson, R.; Hindfelt, B. Quantitative Aspects of Swallowing in an Elderly Nondysphagic Population. *Dysphagia* **1996**, *11* (3), 180−184.

(57) Sato, E.; Ohrui, T.; Matsui, T.; Arai, H.; Sasaki, H. Folate Deficiency and Risk of Pneumonia in Older People. *J. Am. Geriatr. Soc.* **2001**, *49* (12), 1739−1741.

(58) Nakagawa, T.; Wada, H.; Sekizawa, K.; Arai, H.; Sasaki, H. Amantadine and Pneumonia. *Lancet* **1999**, *353* (9159), 1157.

(59) Finestone, H. M.; Greene-Finestone, L. S. Rehabilitation Medicine: 2 Diagnosis of Dysphagia and Its Nutritional Management for Stroke Patients. *cmaj* **2003**, *169* (10), 1041−1044.

(60) Kollef, M. H. Ventilator-Associated Pneumonia: A Multivariate Analysis. *JAMA* **1993**, *270* (16), 1965.

(61) Kalinowski, C. P. H.; Kirsch, J. R. Strategies for Prophylaxis and Treatment for Aspiration. *Best Pract. Res. Clin. Anaesthesiol.* **2004**, *18* (4), 719−737.

(62) Langmore, S. E.; Terpenning, M. S.; Schork, A.; Chen, Y.; Murray, J. T.; Lopatin, D.; Loesche, W. J. Predictors of Aspiration Pneumonia: How Important Is Dysphagia? *Dysphagia* **1998**, *13* (2), 69−81.

(63) Shannon, A.; Goldsmith, A. Suction Devices. *Anaesth. Intensive Care Med.* **2009**, *10* (10), 468−470.

(64) Tada, A.; Miura, H. Prevention of Aspiration Pneumonia (AP) with Oral Care. *Arch. Gerontol. Geriatr.* **2012**, *55* (1), 16−21.

(65) Cazals, M.; Bédard, E.; Soucy, C.; Savard, P.; Prévost, M. How Clean Is Your Ice Machine? Revealing Microbial Amplification and Presence of Opportunistic Pathogens in Hospital Ice-Water Machines. *J. Hosp. Infect.* **2023**, *141*, 9−16.

(66) Springston, J. P.; Yocavitch, L. Existence and Control of Legionella Bacteria in Building Water Systems: A Review. *J. Occup. Environ. Hyg.* **2017**, *14* (2), 124−134.

(67) Marrie, T. J.; Haldane, D.; Macdonald, S.; Clarke, K.; Fanning, C.; Le Fort-Jost, S.; Bezanson, G.; Joly, J. Control of Endemic Nosocomial Legionnaires' Disease by Using Sterile Potable Water for High Risk Patients. *Epidemiol. Infect.* **1991**, *107* (3), 591−605.

(68) Leonard, R. Predicting Aspiration Risk in Patients with Dysphagia: Evidence from Fluoroscopy. *Laryngoscope Investig. Otolaryngol.* **2019**, *4* (1), 83−88.