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Legionnaires' Disease Surveillance and Public Health Policies in Italy: A Mathematical Model for Assessing Prevention Strategies

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Abstract: *Legionella* is the pathogen that causes Legionnaires' disease, an increasingly prevalent and sometimes fatal disease worldwide. In 2021, 97% of cases in Europe were caused by *Legionella pneumophila*. We present a mathematical model that can be used by public health officials to assess the effectiveness and efficiency of different *Legionella* monitoring and control strategies to inform government requirements to prevent community-acquired Legionnaires' disease in non-hospital buildings. This simulation model was built using comprehensive data from multiple scientific and field-based sources. It is a tool for estimating the relative economic and human costs of monitoring and control efforts targeting either *L. pneumophila* or *Legionella* species and was designed to analyze the potential application of each approach to specific building classes across Italy. The model results consistently showed that targeting *L. pneumophila* is not only sufficient but preferable in optimizing total cost (direct and economic) for similar human health benefits, even when stress-tested with extreme inputs. This cost–benefit analytical tool allows the user to run different real-life scenarios with a broad range of epidemiological and prevalence assumptions across different geographies in Italy. With appropriate modifications, this tool can be localized and applied to other countries, states, or provinces.

Keywords: *Legionella*; Legionnaires' disease; water testing; model; surveillance; health policy; water safety plans

1. Introduction

1.1. Legionnaires' Disease Is a Significant Public Health Issue in Europe and Italy (as Well as Worldwide)

The burden of Legionnaires' disease in the European Union/European Economic Area (EU/EEA) has increased in the last decade, with notification rates rising from 1.2–1.4 per 100,000 population in 2012–2016 to 2.4/100,000 in 2021 [1,2]. In the same report, Italy was noted as having one of the highest rates at 4.6 cases per 100,000 population in 2021 [1,2]. Legionnaires' disease has a high individual and a high population burden, ranking as the fifth highest of infectious diseases in Europe, according to annual disability-adjusted life years [3]. Despite significant prevention efforts, data from the Italian Institute of Health suggest that cases in Italy have continued to rise and were 13% higher just one year later in 2022, at 5.19 cases per 100,000, returning to pre-pandemic levels [4]. In addition, fatality rates for community-acquired cases, at 15.1% in 2022, are well above the EU/EEA country average of 9% for all cases with known outcomes [1,2,4]. The fact that Italy has the third fastest aging population in the world is likely to exacerbate this pattern, making an analytical assessment of Italy's Legionnaires' disease prevention policy options particularly important and timely [5].

1.2. Legionella as the Causative Agent of Legionnaires' Disease

Legionella is an emerging pathogen worldwide [6] and is the causative agent of Legionnaires' disease, an illness with a high rate of morbidity and mortality [7]. Knowledge about legionellosis has increased in recent decades, but a full understanding of global incidence remains unknown, mainly because it is underdiagnosed and underreported. Several high-income countries and regions have well-established surveillance systems, but almost all data are collected through passive surveillance. *Legionella* species are ubiquitous in water but their presence in general is not necessarily indicative of community-acquired Legionnaires' disease. The species *Legionella pneumophila* has been responsible for more than 90% of cases worldwide [8]. In 2021, ~97% of cases in Europe were identified as being caused by *L. pneumophila*, with a significant percentage of those (82%) caused specifically by *L. pneumophila* serogroup 1 (*Lp*1) [1,2]. The epidemiology of infections caused by non-*pneumophila* species of *Legionella* is not as well documented as for those caused by *L. pneumophila*, but cases have been reported across various countries [9,10]. By far, most non-*pneumophila* cases are due to *L. longbeachae*, and have been consistently linked to exposure through gardening and contact with soil products rather than potable water in both Oceania and Europe [10–14]. A very small number of cases (<1%) that were confirmed through culturing were attributed to other non-pneumophila species: *L. anisa*, *L. bozemanii, L. micdadei*, and *L. cincinnatiensis* [1,2]. A method that is widely used to diagnose potential cases of Legionnaires' disease is the Urinary Antigen Test (UAT), which has a high specificity for *Legionella pneumophila* serogroup 1. Culture-based methods and polymerase chain reaction were used less often in Europe in 2021, constituting 11% and 12% of methods employed, respectively [1,2]. Primary UAT diagnoses lead to underreporting of cases caused by either *L. pneumophila* serogroups SG2-15 or other non-*pneumophila* species. However, data from large-scale studies in Europe and the U.S. including cases with and without an initial UAT diagnosis showed no substantial difference in the percentage of cases from non-*pneumophila* species (2% versus 3%) [15] and showed that, after widespread adoption of the UAT, surveillance data were more likely to undercount other serotypes of *L. pneumophila* than to undercount non-*pneumophila* species [16].

1.3. Differing Public Health Approaches to Reduce Legionnaires' Disease Risk

The World Health Organization has recommended adopting Water Safety Plan principles for risk assessment and management of water from the source to the tap [17]. Similarly, EU Directive 2020/2184 establishes minimum requirements to protect human health from the negative effects of contamination of waters. In particular, the Directive mandates the adoption of criteria for the assessment and management of potential risks associated with the internal distribution systems of water destined for human consumption (cold water and hot sanitary water) of priority buildings through inspection programs and analytical checks on specific parameters, particularly *Legionella* and lead. It also mandates the implementation of corrective measures in cases of non-compliance with threshold concentration limits. In Italy, Decree 18/2023 transposes the Directive (EU) 2020/2184, defines risk, and suggests preventive actions [18].

It is well established that building-level Water Safety Plans that reduce the risk of exposure to aerosolized *Legionella* lower Legionnaires' disease risk. The U.S. Centers for Disease Control and Prevention (CDC) found that 9 out of 10 outbreaks could have been prevented with effective Water Management (Safety) Plans in a study in which 44% of the outbreaks were at hotels or resorts [19]. The U.S. National Academies of Science, Engineering, and Mathematics came to the same conclusion [20]. Yet the most appropriate species of *Legionella* to target within these Water Safety Plans is still a topic of debate.

EU Directive 2020/2184 offers some leeway to Member States regarding the monitoring, sampling methods, and methods of analysis of *Legionella* which must be performed for priority building Water Safety Plans. Both historically and in their transpositions of the Directive, many countries have mandated testing and control of *Legionella* species at the genus level, including Italy, Spain, and Germany. Yet other countries and regions have heeded or are heeding their researchers' and experts' recommendations to focus their monitoring and control efforts specifically on reducing *L. pneumophila*, the species which creates the primary health risk. France has transposed EU Directive 2020/2184 to require control of *L. pneumophila* for all non-healthcare premises. The Dutch Ministry of Infrastructure published a similar pronouncement, that Dutch regulations should focus on *L. pneumophila* except in hospital-type settings [21]. Outside of Europe, Canada's regulations have exclusively focused on mandatory control of *L. pneumophila* [22], with recent Quantitative Microbial Risk Assessment (QMRA) research leading to recommendations of more frequent monitoring of *L. pneumophila* for high-risk sources of aerosolization [23].

Given the perennial challenges of competing priorities and pressures on finite public health funding, a tool that enables an objective analysis of the direct, economic, and total costs of a targeted *L. pneumophila* control strategy relative to a broader *Legionella* spp. control strategy could provide valuable insights for the policymakers responsible for setting those requirements.

1.4. Previous and New Social Economic Cost–Benefit Model Approaches

Understanding the economic burden of diseases is critical to informing sound policy decisions, useful in targeting interventions efficiently and equitably, and valuable in justifying investment in research and prevention strategies. To this end, researchers have attempted to estimate the economic burden of preventable diseases such as Malaria [24] and non-preventable diseases such as Parkinson's disease [25] using different approaches. Cost–benefit analysis is a well-established method for assessing public health interventions [26].

Many studies adopt the microeconomic approach to evaluate the economic burden of a disease by summing the impact of a disease on the individual patient or household, the government (using the healthcare system as a proxy), and/or the respective firms. This approach typically captures the costs of illness (medical care, travel costs) and indirect costs (the value of productivity losses). Colier et al. and Baker-Goering et al. estimated the lifetime economic burden of Legionnaires' disease in the U.S. by summing estimates of the medical costs for hospitalized patients and of productivity losses caused by absenteeism and premature deaths, based on historical data [27,28]. This approach was also used for models of Malaria [24] and Parkinson's disease [25].

Researchers in various countries have also adopted the computational technique Quantitative Microbial Risk Assessment (QMRA) to inform disease control policies. QMRAs of disease risk from *Legionella pneumophila* were published in 2007 by Armstrong et al. and continue to be employed today to better understand Legionnaires' disease prevention strategies and trade-offs [23,29–31]. The QMRA framework is often used to evaluate the health risks associated with exposure to a particular pathogen based on pathogen occurrence, exposure scenario, health endpoint, and population at risk [30]. We were not able to utilize QMRA techniques because of the lack of published QMRA data on Legionnaires' disease risk that distinguish between exposure to *Legionella* spp. or non-*pneumophila* species.

1.5. The Development of a Simulation Model to Understand the Cost–Benefit Trade-Offs of Two Legionnaires' Disease Risk Reduction Strategies

Using a consistent valuation approach to assess the economic and societal burden of diseases is critical for accurately comparing health intervention strategies [26]. Here, we describe a collaborative effort to build a mathematical model and consistent process that allows national, regional, or municipal health policymakers to compare the costs and benefits of two approaches to preventing community-acquired Legionnaires' disease, both employing Legionella monitoring and control in the context of Water Safety Plans. Using the concrete example of Italy, we developed and tested the model as a practical, hands-on tool for estimating the disease, financial, and economic burden associated with surveillance and control of *L. pneumophila* relative to surveillance and control of *Legionella* species so that those findings could guide government policy. The model has a simple interface which allows the user to choose from a selection of variables and yields expected outcomes for different scenarios using conservative, data-driven assumptions. We further tested the limits of the model using minimum and maximum input values for several key variables.

2. Materials and Methods

2.1. Study Area

This work considered prior studies and utilized data from across Europe to inform a model specific to Italy. Italy is one of the four countries (along with France, Spain, and Germany) that, together, report 75% of the cases of Legionnaires' disease in Europe [1,2]. The approach taken by Italy to address this health issue follows the most recent European Directive (EU) 2020/2184 on the quality of water intended for human consumption, which sets criteria, requirements, and provisions for monitoring and ensuring water quality. Directive (EU) 2020/2184 requires Member States to define, then monitor and control, cold and hot sanitary water in "priority" buildings. The Italian transposition of this directive, Decreto 18/2023, sets the definition of six different classes of buildings, stratifying the risk on the basis of the vulnerability of the exposed subjects and suggesting the development of preventive actions within a wide perspective for risk assessment and the development of individualized Water Safety Plans. This stratification and specificity of building types and occupants are particularly well suited to a rigorous analysis of the societal and economic costs and benefits of different risk management approaches because the inputs can be specific to the realities of the implementation of each approach [32].

2.2. Overview of Study Design

We proposed and tested a framework to evaluate the total public health benefits and costs of reducing community-acquired Legionnaires' disease cases by addressing the causative agent. We first reviewed and leveraged data from different sources (>70 sources). These included peer-reviewed publications, reports from the European Center for Disease Prevention and Control (ECDC), and reports from The European Surveillance System (TESSy) [33]. Then, the specific situation in Italy was analyzed, taking into consideration epidemiological data, both clinical and environmental, and reports and bulletins from the

Ministry of Health, Instituto Superiore di Sanita, and the National Reference Laboratory for *Legionella*, as well as scientific papers. In addition, in-depth practical information relevant for the implementation of the different strategies was collected through surveys from Aquaitalia (the national Italian association of water treatment professionals and companies), ISTAT (the Italian National Institute of Statistics and Demography), and Statista [5] and qualitative data from interviews with experts and consultants in microbiology, epidemiology, management, and treatment of internal water distribution systems within buildings. The model was developed to incorporate the above data and simulate the costs and benefits of three potential *Legionella* monitoring and control strategies for certain categories of non-hospital priority buildings: (a) "no additional monitoring" for environmental surveillance and control; (b) the "monitor and control all *Legionella pneumophila*" strategy; and (c) the "monitor and control *Legionella* species" strategy.

From this model, for each strategy, we calculated (i) the estimated additional Legionnaires' disease cases prevented, (ii) the estimated direct remediation spending per case prevented, and (iii) the estimated total economic cost, which included costs from Legionnaires' disease cases not prevented, building remediation costs, costs of building shutdowns due to remediation, and legal costs associated with Legionnaires' disease cases.

2.3. Analytical Framework of the Model

The framework of the model (Figure 1) focuses on the Epidemiological Triad of the "environment" (building water), the "etiological agent" (*Legionella*), and the "hosts" (humans). Assumptions for the types of buildings and remediation efforts, exposure to *Legionella*, and expected cases of disease were made based on both the literature review and Italy-specific data sources. The model inputs and algorithms were set up very conservatively, that is, aiming to support current Italian guidelines (D.L. 18/23), which are primarily based on detection and remediation of *Legionella* spp. Detailed explanations of the assumptions and references are also further described in a User Guide (see Supplemental Material) and embedded in the model itself.

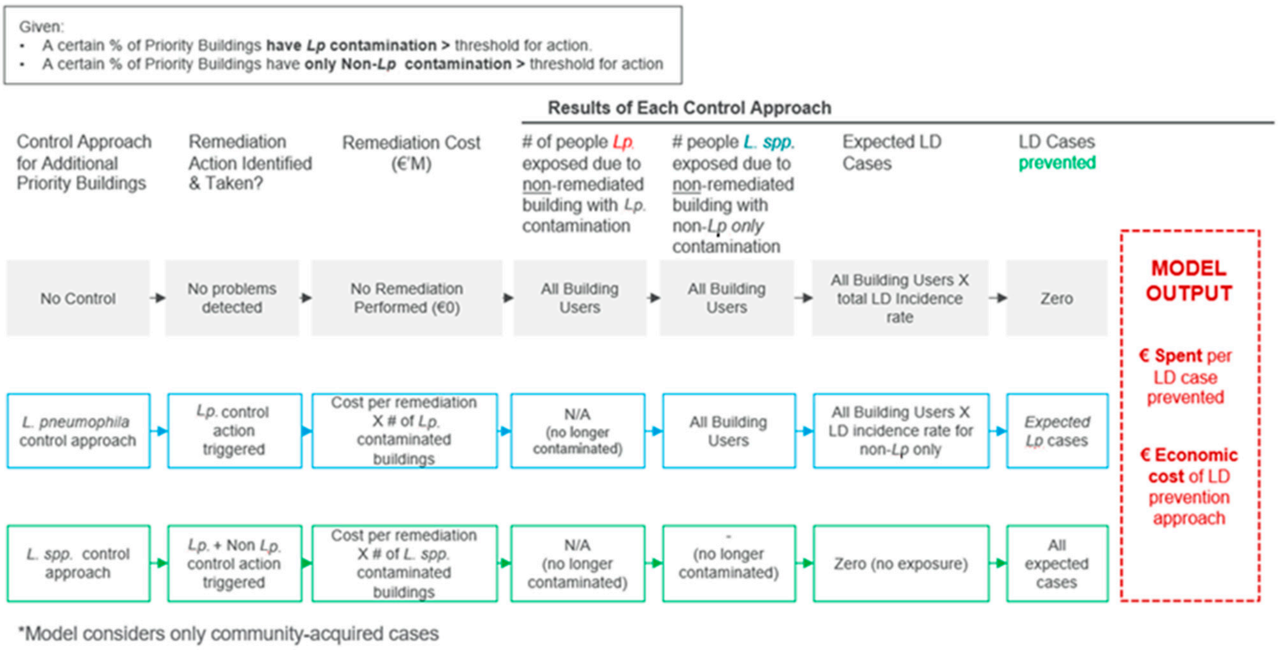


Figure 1. Analytical framework for estimating the financial and economic impact of different *Legionella* control strategies.

2.4. Parameters Related to the Building Environment

ISTISAN Report 22/23 defines six classes of priority and non-priority premises (A, B, C1, C2, D, and E) for Legionnaires' disease risk assessment and prevention in Italy (see Section 2.4.1 for descriptions) [34]. The action limit for the presence of *Legionella* and expected growth conditions for the bacteria were considered.

2.4.1. Priority Buildings

The model was designed to focus exclusively on community-acquired disease risk from non-hospital priority building types defined as priority class "B" and "C1" because of industry interest in Italian public policymakers clarifying the *L. pneumophila* and *Legionella* spp. requirements for these two priority building classes at the time of the study design [34]. Class B buildings include outpatient facilities, non-inpatient social welfare/rehab centers, and dental facilities. Buildings categorized as C1 include accommodations, penitentiaries, ships, stations, and airports. Data from ISTAT, Statista, and other sources were combined to estimate the total number of B and C1 buildings in Italy within these categories [34,35]. The study did not include buildings considered class "A" [34], such as hospitals and inpatient facilities, inpatient rehabilitation centers, or buildings for the ill or aging, because these may represent a very different situation given the specific subgroups of susceptible hosts. Priority building classes C2, D, and E were excluded from the study because, at the time of the study design, they were not expected to be reviewed in the near term (class C2: public and collective dining halls; class D: barracks, sports and spa centers including pools, and some penitentiaries; class E, non-priority: other buildings including condominiums, offices, and commercial spaces) [34].

2.4.2. Defined Action Limit

Water systems in buildings colonized with *Legionella* at >1000 organisms/L concentration level are defined as above the action limit per the European Directive (EU) 2020/2184 and the Italian transposition of the Directive [18]. Building owners are thus required to take necessary steps to remediate these facilities to minimize risk of infection and any potential cases or outbreaks. Data from Italian papers (n = 6) and a multi-region survey of *Legionella* management service providers by Aquaitalia estimated that 30–60% of buildings tested each year would be contaminated at above the recommended threshold for action for *Legionella* [36–42]. Additional qualitative data were gathered through interviews with *Legionella* management experts who corroborated this estimate across a cross-section of premises, including both buildings without previously installed disinfection systems and buildings with a range of different building disinfection systems. Consistent with the current Italian legislation, our model assumed the same *Legionella* threshold of 1000 organisms/L whether the detection parameter included the presence of any *Legionella* species (*L.* spp.) or focused specifically on *L. pneumophila*.

2.4.3. Building Water Temperature

Many factors contribute to the probability of *Legionella* proliferation in a domestic water system, such as water temperature, water age, disinfectant residual, or other variables. This study specifically included building water temperature as a variable because it impacts *L. pneumophila* and non-*pneumophila* species proliferation differently. While the optimal temperature range for growth of *Legionella* overall is estimated to be between 20 and 46 °C [43–45], more specific growth ranges have been demonstrated for *L. pneumophila* (20–42 °C) and for non-*pneumophila* species (18–35 °C) [45,46]. It was assumed that any species of *Legionella* would be inhibited at temperatures below 20 °C or above 45 °C, and buildings would not be contaminated regardless of any other input to the model. Within the favorable growth temperatures of 20–46 °C, the model conservatively included the following ratios of *L. pneumophila* (*Lp*) and non-*pneumophila* (non-*Lp*) for *Legionella*-contaminated buildings:

1. Estimated building water temperatures between 20 and 25 °C: 50% *Lp*/50% non-*Lp*;
2. Estimated building water temperatures between 25 and 35 °C: 60% *Lp*/40% non-*Lp*;
3. Estimated building water temperatures between 35 and 45 °C: 90% *Lp*/10% non-*Lp*;
4. Unknown building water temperatures: assumed ratio of 70% *Lp*/30% non-*Lp*;

The ratio that was used for contaminated buildings with unknown temperatures was derived from input from Aquaitalia members and six published Italian studies of non-hospital environments, which included more than 1000 building water sample results [36,37,39,41,42,47,48].

2.5. Parameters Related to the Etiological Agent Legionella

To estimate the percentage of projected Legionnaires' disease cases likely to be caused by *L. pneumophila* and non-*pneumophila* species, two published studies from Europe were used to set the minimum and maximum ratios for case etiologies used in the model. Data published by Beauté et al., in a study leveraging 10 years of data (2009–2018) from the ECDC, revealed that 97% of community-acquired cases were caused by *L. pneumophila* and 3% by non-*pneumophila*. The findings from this study were used to set a maximum *L. pneumophila*-to-non-*pneumophila* case ratio of 97%/3% in the model. An extensive epidemiological study of cases across Europe by the ECDC found *L. pneumophila* to be the primary pathogen of concern, causing between 95 and 99% of all culture-confirmed cases, with the lowest percentage (95%) reported in 2014 [1,2]. Data from the Italian National Surveillance System tell a similar story for Italy [4]. Nonetheless, to "test" our model with more extreme scenarios, the minimum ratio of *L. pneumophila* (*Lp*) to non-*pneumophila* (non-*Lp*) was set to 80%/20% based on estimates that cases attributed solely to *L. pneumophila* serogroup 1 represent 80–90% of Legionnaires' disease cases, and two intermediary choices between 80% and 95% were also included [20]. The scenarios used in the model are as follows:

- 97% *Lp*/3% non-*Lp*;
- 95% *Lp*/5% non-*Lp*;
- 90% *Lp*/10% non-*Lp*;
- 92.5% *Lp*/8.5% non-*Lp*;
- 80% *Lp*/20% non-*Lp*.

To estimate the number of cases likely to occur when different control approaches were used, the case etiology percentages were multiplied by the national Legionnaires' disease incidence rate, defined as the recent 5-year average (2018–2022) of Italy's incidence rate per hundred thousand population, and the total number of people exposed to a contaminated building under each control scenario. This approach allows the model to factor in the well-established differences in virulence, and, therefore, post-exposure Legionnaires' disease case rates, between *pneumophila* and non-*pneumophila* species. In the model, a base case *Lp.*/non-*Lp*. etiology ratio of 95%/5% was assumed. It was also assumed that the choice of control approach would determine the type of pathogen to which people are exposed. For instance, in an environment where building owners are required to adopt an *L. pneumophila*-specific control approach, buildings infected with *L. pneumophila* above the action limit would be identified and remediated in a timely fashion. Hence, the only potential cases in that environment would occur when non-*pneumophila* is present but is not identified or remediated.

2.6. Parameters Related to the Human Host

2.6.1. Estimation of Direct Exposure in Contaminated Buildings

The calculation used to determine the number of people who may be affected by each contaminated building was based on the estimated frequency of exposures for each type of building within each priority building class. This was defined as either point or repeat exposure depending on the length of time spent in a building. People with point or limited exposures include visitors (e.g., short-term hotel guests, travelers, cruise line passengers) who have a low risk of infection. The model assumes 2% of visitors with point exposure may be at risk of infection in a building contaminated at or above the action limit. People with repeated exposures are those with prolonged and frequent exposure to a contaminated building and have a higher chance of infection. Examples include workers within a building or residents of certain building types. Using data from ISTAT and Statista, the total number of repeat exposures was estimated by adding the total number of workers across class B and C1 priority buildings to the fraction (5–10%) of visitors/residents (e.g., inmates) with extended exposure to those buildings.

2.6.2. Estimation of Community-Acquired Cases

The number of Legionnaires' disease cases in Italy was estimated using the multiplier and schematic approaches developed by Cassini et al. and Rota et al., respectively. Incidence data were derived from Rota et al. (2018–2022) and were extracted from the National Surveillance System and the ISS National Reference Laboratory for Legionellosis databases [4]. Only confirmed community-acquired cases were considered in the model. This was derived by subtracting nosocomial cases from total confirmed cases and calculating the incidence rate per 100,000 population. The five-year average was then calculated using the most recent incidence rates (2018–2022) from the National Surveillance System and the ISS National Reference Laboratory for Legionellosis databases (Rota, 2018–2022). Underestimation and underdiagnosis multipliers were applied to this five-year average incidence rate of 4.53 Legionnaires' disease cases per 100,000 inhabitants, and were then apportioned to *L. pneumophila* or non-*pneumophila* exposures according to the etiology scenario selected when running the model. The incidence rate was then multiplied by the number of people estimated to have been exposed to class B or C1 buildings contaminated above the action limit with either *L. pneumophila* or with solely non-*pneumophila* species to estimate the Legionnaires' disease cases that would be associated with those buildings.

2.6.3. Underestimation Multiplier

Experts believe that Legionnaires' disease cases may be underestimated across Europe, including in Italy [49]. Cassini et al. classified EU countries into three groups based on the quality of their surveillance system, including system detection and reporting sensitivity [3]. The appropriate underestimation range was assumed to be that calculated by Cassini for Italy, which was from 1 to 3.03 times the number of national reported cases [3]. In the model, the upper end of this range was incorporated, a factor of 3.03 times the national report over the recent five-year period (2018–2022), in recognition of the multiple factors which influence the typical morbidity surveillance pyramid for Legionnaires' disease. Cassini notes that the underestimation factors they developed for infectious diseases in the EU/EEA countries include both under-ascertainments, "those cases that did not access the healthcare system", and underreporting, "those cases that are not reported to the surveillance system". Gibbons further explains that underreporting includes accounting for cases which are either not diagnosed at all or misdiagnosed, as well as accounting for under-notification, cases which are not reported to official surveillance systems with correct International Classification of Diseases codes [50]. The higher incidence rates for Legionnaires' disease than are used in this model could also be assumed. Other studies which looked at estimated undiagnosed Legionnaires' disease rates in certain areas of the Mediterranean and Central Europe detected disease in 3.4 and 5.5 percent of total community-acquired pneumonia cases (hospitalized and non-hospitalized) [51]. Applied to Italy, that would translate into 18.5 to 36.7 additional cases per 100,000 or a 4.7 to 8.5 multiplier for currently identified cases [52,53].

2.6.4. Underdiagnosis Multiplier

There are many potential reasons for underdiagnosis of Legionnaires' disease cases in Italy, as in the rest of Europe. One of the most often cited sources is related to the diagnostic method. In Italy, the Urine Antigen Test (UAT) is the most common diagnostic test, used for 96.9% of the 3030 confirmed cases in 2022, while culture and PCR tests constituted 1.1% and 2%, respectively [4]. The UAT has a high specificity for *L. pneumophila* serotype 1 and does not detect serogroups 2–15 or non-*pneumophila* species. For the model, it was assumed that the undiagnosed cases of both *L. pneumophila* serogroups 2–15 and other species of *Legionella* were captured in the underestimation multiplier described above. Hence, an underdiagnosis multiplier of 1× was applied to the model, meaning it was assumed there were no underdiagnoses.

2.7. Estimating the Economic Burden

2.7.1. Cost of Remediation

In the event *Legionella* levels are above the action limit, remediation efforts might be required. The cost of remediation depends upon the complexity of the water system, the technology and equipment deployed, and the sampling techniques that are utilized. A survey of 175 buildings in Northern Italy found that remediation costs ranged from EUR 1800 to 5700, depending upon the extent of contamination [42]. For the model, it was assumed that a simple remediation process would be sufficient, and a conservative lower end of the range (EUR 1800) was included. The model also conservatively assumes that only 40% of buildings above the action limit are remediated. Thus, the overall cost of remediation was calculated by multiplying the number of contaminated buildings by the number of buildings that will be remediated (i.e., 40%) by the low end of the cost range (EUR 1800). Additionally, it is well established that the use of disinfecting chemicals to treat the water in contaminated buildings accelerates the rate of depreciation of specific water systems such as pipes and associated equipment. A conservative estimate of 1% of the cost of remediation was included to account for installing an internal disinfection system or replacing water lines. In the model, this replacement cost is calculated by multiplying a replacement rate of <1% of buildings by the low end of the cost to install or re-pipe a building, which is in the range of EUR 1500 to 17,500 [42,54,55]. Further expenses which occur in some situations for replacement or on-going costs of an internal disinfection system (e.g., Ag, H_2O_2, ClO_2, Chloramine) were not included.

2.7.2. Cost to Health System, Patients, and Caregivers

Because of the severity of Legionnaires' disease, cases typically have real and meaningful directly and indirectly attributable costs.

2.7.2.1. Hospitalization Costs

The acute phase of Legionnaires' disease requires hospitalization and may be severe or result in death. The model assumes a 70% hospitalization rate based on data suggesting that 69–74% of community-acquired cases required hospitalization [3,53,54]. Cassini (2018) categorizes Legionnaires' disease cases into three distinct groups: (1). uncomplicated cases requiring no hospitalizations; (2). complicated cases requiring hospitalization and non-intensive care treatment; and (3). severe cases requiring intensive care [3].

Applying Cassini's findings, the model assumes at least 30% of cases to be uncomplicated, 49% of cases to require hospitalization but not intensive care, and 21% of total cases to be severe. To estimate the hospital care cost, the model first assumes a conservative length of stay of 9.9 days, based on data from studies in Italy, the United Kingdom, and across Europe, for both severe and non-severe cases [3,4,55]. This value was multiplied by the low end of estimates for the cost per day for ICU stays, EUR 1700, and non-ICU stays, EUR 800. Hospitalization also incurs costs for prescription medications, and, again, a length of stay of 9.9 days was multiplied by the low end of the estimate for prescription costs of EUR 1600 for ICU patients and EUR 200 for non-ICU patients.

2.7.2.2. Productivity Loss

Productivity losses or indirect costs were defined as the economic burden of Legionnaires' disease illness borne by patients and their caregivers. Examples of these costs include decreases in earning ability due to illness or premature death, loss of productive hours due to illness, and loss of productive hours due to caring for a family member. Also taken into consideration was lost revenue due to temporary closures of businesses while remediation and control strategies are implemented.

Patient and Caregiver Productivity

The extent of productivity loss is different depending on the age range of each patient. In the model, patients above and below age 60 were considered separately using the case breakdown by age data from Rota et al., 2022. For those 60 years and above, no productive days are assumed to be lost due to the simple assumption that nearly 100% of this segment of the population in Italy is in retirement. On the other hand, for patients under 60 years of age, the conservative estimate of a 9.9-day hospital stay was multiplied by the average hours of work (8) per day and an estimated minimum wage rate of EUR 10 per hour [5] to calculate the presumed lost wages.

Indirect costs related to caregivers can include changes in productivity, absence from work, and decreased earning ability. The primary driver of these costs are the hours required for informal care and the earnings lost by their families. It was assumed that all hospitalized cases (severe or not) would require care from family, spouse, or friend. The economic burden on caregivers was then estimated by multiplying the productive hours (assumed 5 days, 50% of the 9.9 bed days) by the average number of work hours (8 h) and minimum wage rate (EUR 10) per hour, a conservative option which takes into consideration both caregivers who are not wage earners and caregivers who earn far above the minimum hourly wage.

Building Closures

To incorporate the productivity effects of building closures due to contamination into the model, data from published studies that focused on hotels were used as a proxy for commercial class B and C1 priority buildings. Based on three studies from different regions of Italy, 37–62% of a collective total of ~340 hotels required remediation and were potentially closed temporarily [39,40,56,57]. This range of percentages was included in the model. Remediation action requires varying levels of financial resources and shutdown time. The model includes a conservative estimate of two days as the minimum period required to effectively remediate a building and does not consider additional shutdown time for safety reasons prior to remediation. The economic cost of a business shutdown was calculated by multiplying the number of commercial buildings remediated by the number of days a business is closed (2 days) and the daily revenue foregone, EUR 1383 [58]. These estimates do not include additional costs or foregone revenues associated with the time and effort required to restart the business after a closure.

2.7.3. Legal Costs

Due to limited availability of data for Italy, the average potential legal costs of a *Legionella* case were estimated by evaluating recent *Legionella*-related lawsuits reported by the media in the UK, along with the damages imposed by the courts. The model assumes a 1% probability that the affected patients or their estate will resort to a legal action and a base case estimate of EUR 820,000 per legal action.

2.8. Adjustability of Model Variables

Model users may select among different scenarios (i.e., conservative, base, or optimistic assumptions) and may opt to focus on a specific region of Italy (i.e., Northern, Central, or Southern). Key variables have a drop-down feature so the user can select input data to vary the scenario and estimate the financial and economic impact of each control strategy in each situation. The key variables with this drop-down feature are:

1. Percentage of buildings contaminated at action level: Users may select eight different inputs in the model, ranging from 10% to 80%. Even though data from published studies ranged from 20–70%, the model extends this range to 10% and 80% to ensure all possible scenarios are effectively considered in the model. Also, see Section 2.4.2 for more details.
2. Building water temperature: Four data inputs, based on published studies, allow users to select different temperature ranges which have different repercussions for the

survival of each type of *Legionella*. However, due to limited data on actual building water temperatures, in the base case, the temperature is described as unknown, which assumes that the *Legionella* that are present include 70% *L. pneumophila* and 30% non-*pneumophila*. See Section 2.4.3 on "building water temperature" for more details.

3. Percent of cases caused by *L. pneumophila* or non-*pneumophila* species. Model inputs were based on virulence profiles described in Section 2.5.

3. Results

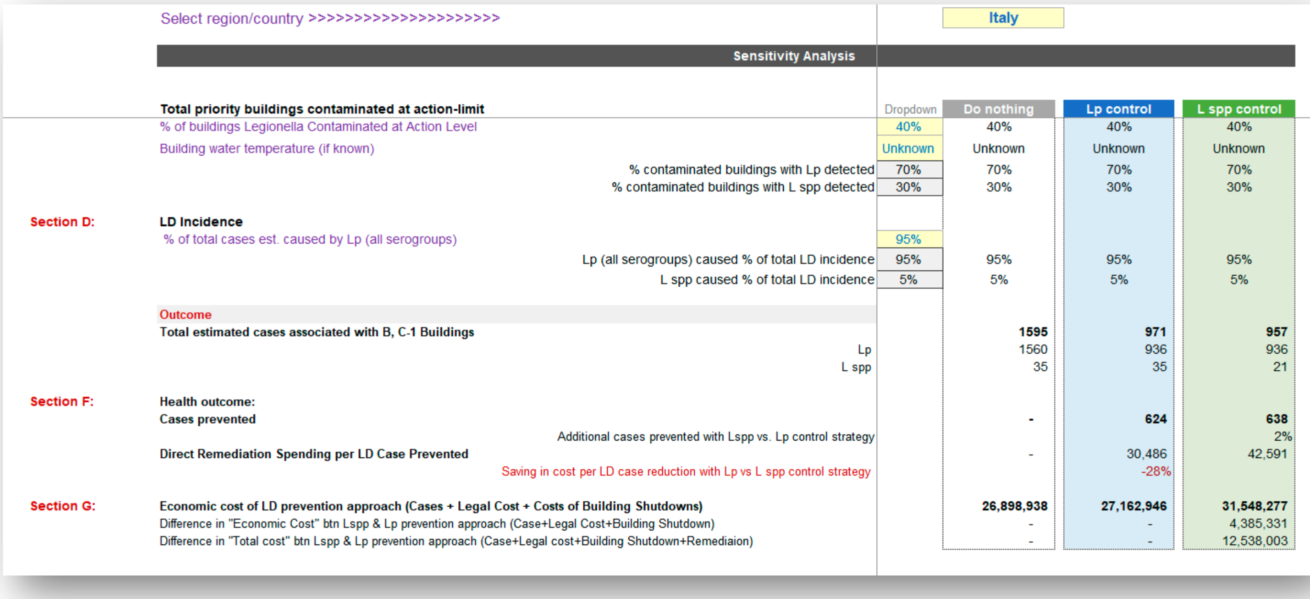
We have developed a simulation model that allows for customizable input to predict the costs and benefits of Legionnaires' disease monitoring and control approaches with a focus on determining whether monitoring and controlling *Legionella pneumophila*, the species that is overwhelmingly associated with the disease, are more effective or less effective as a public health strategy than monitoring and responding to a collection of *Legionella* species. Each assumption was selected conservatively with a bias toward the broader *Legionella* spp. monitoring and management strategy primarily and currently in place in Italy. To assess the effectiveness of each management strategy, we introduced a third scenario, the comparison group. This scenario assumes no monitoring and no subsequent remediation. The output includes economic resource considerations as well as costs and benefits to human health and life. It was designed for use by operators such as epidemiologists, policymakers, or operators involved in managing building safety or public health issues related to Legionnaires' disease. As described in the methods, this analysis excludes hospitals and residential rehabilitation facilities and instead focuses on community-acquired Legionnaires' disease in priority type B and C1 buildings in Italy. For any combination of assumptions chosen as inputs, the model generates the following citizen health results for each of the *Legionella* monitoring and control approach options:

- Estimated Legionnaires' disease cases caused by exposure in the set of class B and C1 priority buildings considered.
- Estimated direct remediation spending per Legionnaires' disease case prevented by each *Legionella* monitoring and control policy option.
- Savings per Legionnaires' disease case prevented.

Variables such as the total number of type B and C1 buildings, the proportion likely to be contaminated at or above the Italian action limit of >100 CFU/L, the impact on the exposed population, and the cost of remediation were all estimated as described in the Methods section. To focusing the model on the key variables, it was assumed that, if buildings were successfully remediated, they no longer posed a risk of *Legionella* exposure to their occupants for a period of time. For methods of testing, it was assumed that *Legionella* spp. monitoring would be performed with ISO 11731 [59], which detects both *L. pneumophila* and some non-*pneumophila* species, rather than, for example, a non-*pneumophila*-species-specific PCR protocol. For *L.-pneumophila*-targeted monitoring, it was also assumed that a culture method, whether ISO 11731 or a liquid culture method, would be used, which would specifically quantify *L. pneumophila* regardless of whether any other species were present. Using these parameters, the direct financial burden, described as the amount spent per Legionnaires' disease case prevented, and indirect economic burden, described as the economic impact of prevention approaches, for each control strategy were calculated using the model.

3.1. Predicting Health Outcomes Based on Monitoring Strategies

Applying the "base case" set of assumptions shown in the "drop-down" column in Figure 2, the *L. pneumophila* control strategy prevents an estimated 624 Legionnaires' disease cases per year which would have occurred if class B and C1 priority buildings had not been monitored and controlled.



		Dropdown	Do nothing	Lp control	L spp control
	Select region/country >>>>>>>>>>>>>>>>>>>>>>	Italy			
	Sensitivity Analysis				
	Total priority buildings contaminated at action-limit				
	% of buildings Legionella Contaminated at Action Level	40%	40%	40%	40%
	Building water temperature (if known)	Unknown	Unknown	Unknown	Unknown
	% contaminated buildings with Lp detected	70%	70%	70%	70%
	% contaminated buildings with L spp detected	30%	30%	30%	30%
Section D:	LD Incidence				
	% of total cases est. caused by Lp (all serogroups)	95%			
	Lp (all serogroups) caused % of total LD incidence	95%	95%	95%	95%
	L spp caused % of total LD incidence	5%	5%	5%	5%
	Outcome				
	Total estimated cases associated with B, C-1 Buildings		1595	971	957
	Lp		1560	936	936
	L spp		35	35	21
Section F:	Health outcome:				
	Cases prevented		-	624	638
	Additional cases prevented with Lspp vs. Lp control strategy				2%
	Direct Remediation Spending per LD Case Prevented		-	30,486	42,591
	Saving in cost per LD case reduction with Lp vs L spp control strategy			-28%	
Section G:	Economic cost of LD prevention approach (Cases + Legal Cost + Costs of Building Shutdowns)		26,898,938	27,162,946	31,548,277
	Difference in "Economic Cost" btn Lspp & Lp prevention approach (Case+Legal Cost+Building Shutdown)		-	-	4,385,331
	Difference in "Total cost" btn Lspp & Lp prevention approach (Case+Legal cost+Building Shutdown+Remediaion)		-	-	12,538,003

Figure 2. Model output for health outcomes of each *Legionella* control approach.

Using this output and applying the ECDC disease burden methodology and factors described in Cassini et al. (2018) [3], each additional Legionnaires' disease case prevented/not prevented can further be considered in terms of public health metrics such as YLL (years of life lost due to premature mortality), YLD (years lived with disability), and DALYs (disability-adjusted life years). In calculating the DALY metric for Italy, we adopted Cassini et al.'s Europe-wide approach to estimate the ratio of YLD to Legionnaires' disease incidence and the ratio of YLL to mortality incidence per 100,000 population for countries with high surveillance systems, which is the case for Italy. Applying the ratios above, the YLD, YLL, and DALYs for each control approach were calculated and are shown in Table 1.

Table 1. Estimating the YLL, YLD, and DALYs in Italy using the base case scenario.

***Legionella* Control Strategy**	**Estimated Annual Legionnaires' Disease Cases Prevented**	**Estimated YLL Prevented per 100K Population (Annual Rate)**	**Estimated YLD Prevented per 100K Population (Annual Rate)**	**Estimated DALYs Prevented per 100K Population (Annual Rate)**
No additional control and monitoring	0	N/A	N/A	N/A
L. pneumophila control and monitoring	624	3.77	0.0067	3.77
Legionella spp. control and monitoring	638	3.85	0.0068	3.86

Note: N/A= Not Applicable.

3.2. Estimating the Costs Associated with Each Monitoring Strategy

The model predicts that the *L. pneumophila* monitoring strategy will result in a EUR 30,000 remediation cost per Legionnaires' disease case prevented and a total spending of EUR 19 M, whereas *Legionella* spp. monitoring, which leads to a similar number of cases, will have a significantly higher remediation cost of EURO 27 M (Figure 3). The comparison is presented in Table 2.

			Do nothing	Lp control	L spp control
Section G:		**Additional Benefits (economic value of case reduction):**			
		Hospital care cost:	**11,828,130**	**7,201,244**	**7,096,878**
		total medical care cost (ICU)	5,637,707	3,432,369	3,382,624
		total medical care cost (non-ICU)	6,190,423	3,768,875	3,714,254
		Cost of prescription:	**731,372**	**445,277**	**438,823**
		total prescription cost (ICU)	535,967	326,310	321,580
		total prescription cost (non- ICU)	195,405	118,967	117,243
	G.1	**Total hospitalization cost**	**12,559,502**	**7,646,520**	**7,535,701**
		Productivity losses from LD cases:			
		Patients:	884,346	538,411	530,608
		Caregivers:	442,173	269,205	265,304
	G.2	**Total productivity losses**	**1,326,519**	**807,616**	**795,912**
		Shut down of commercial priority buildings (B&C1)			
		# of commercial priority businesses remediated		3,899	5,569
		# of days shut-down	-	2	2
		Avg daily turnover foregone (EUR)	-	1,383	1,383
	G.3	**Total cost of shut-downs (EUR)**	-	**10,786,240**	**15,408,914**
		% of affected people filing a suit	1%	1%	1%
		Legal "Fines" due to illness or outbreak	**12,447,567**	**7,578,372**	**7,468,540**
		Legal cost of lawsuit	**565,350**	**344,198**	**339,210**
	G.4	**Estimated legal costs**	**13,012,917**	**7,922,570**	**7,807,750**
		Economic cost of LD prevention approach (Cases + Legal Cost + Costs of Building Shutdowns)	**26,898,938**	**27,162,946**	**31,548,277**
		Difference in **"Economic Cost"** btn Lspp & Lp prevention approach (Case+Legal Cost+Building Shutdown)			4,385,331
		Total cost of LD prevention approach (Cases + Legal costs + Costs of Building Shutdowns+Remediation)	**26,898,938**	**46,185,848**	**58,723,851**
		Difference in **"Total cost"** btn Lspp & Lp prevention approach (Case+Legal cost+Building Shutdown+Remediaion)			12,538,003
		Incremental cost (savings) vs "Do Nothing Scenario		€ 19,286,910	€ 31,824,912

Figure 3. Model output estimating the economic and total cost of each Legionella control approach.

Table 2. Estimating the direct cost per case prevented of each control strategy.

Legionella Control Strategy	Estimated Total Direct Cost (Remediation, €'M)	Estimated Direct Cost (Remediation) per Legionnaires' Disease Case Prevented (€'K)	Relative Cost Difference per Legionnaires' Disease Case Prevented
No additional control and monitoring	N/A		
L. pneumophila control and monitoring	19.0	30.5	
Legionella spp. control and monitoring	27.2	42.6	+40% higher than *Lp* control and monitoring

Note: N/A= Not Applicable.

As described in the Methods section, the model attempts to take into account various quantifiable indirect costs to society (labeled here as "economic costs") as a result of Legionnaires' disease in the population. These include patient hospitalization and prescriptions, productivity losses for hospitalized patients and their caregivers, commercial revenue loss when buildings are shut down for remediation, and legal costs associated with Legionnaires' disease patients. Figure 3 is a snapshot of the model output estimating the costs associated with disease cases for each of the three scenarios.

The model predicts a much lower economic cost and total cost when monitoring for *L. pneumophila* relative to *Legionella* spp. (Table 3). The estimate is 27% lower costs overall when monitoring specifically for *L. pneumophila* rather than *Legionella* spp.

To predict what these costs might be over the next 10 years as a forward-looking projection, three variables in the model were changed to reflect (a) an increasing number of priority class B and C1 buildings, (b) the impact of expected slight rises in average building water temperature due to climate change in Italy (and therefore the effect on *Legionella* spp. and *L. pneumophila* growth potential), and (c) inflation. The output showed that the total cost and difference between the *L. pneumophila* and *Legionella* spp. control approaches become even more meaningful with similar health benefits (Figure 4).

Table 3. Estimating the total cost of each monitoring approach.

***Legionella* Control Strategy**	**Economic Cost of LD Prevention Approach (€'M)**	**Total Cost of LD Prevention Approach (€'M)**	**Difference in Total Cost: *Legionella* spp. Relative to *Lp* Control Strategy (€'M)**
No additional control and monitoring	26.9	26.9	N/A
L. pneumophila control and monitoring	27.2	46.2	N/A
Legionella spp. control and monitoring	31.5	58.8	12.5 (+27% higher than *Lp*)

Note: N/A = Not Applicable.

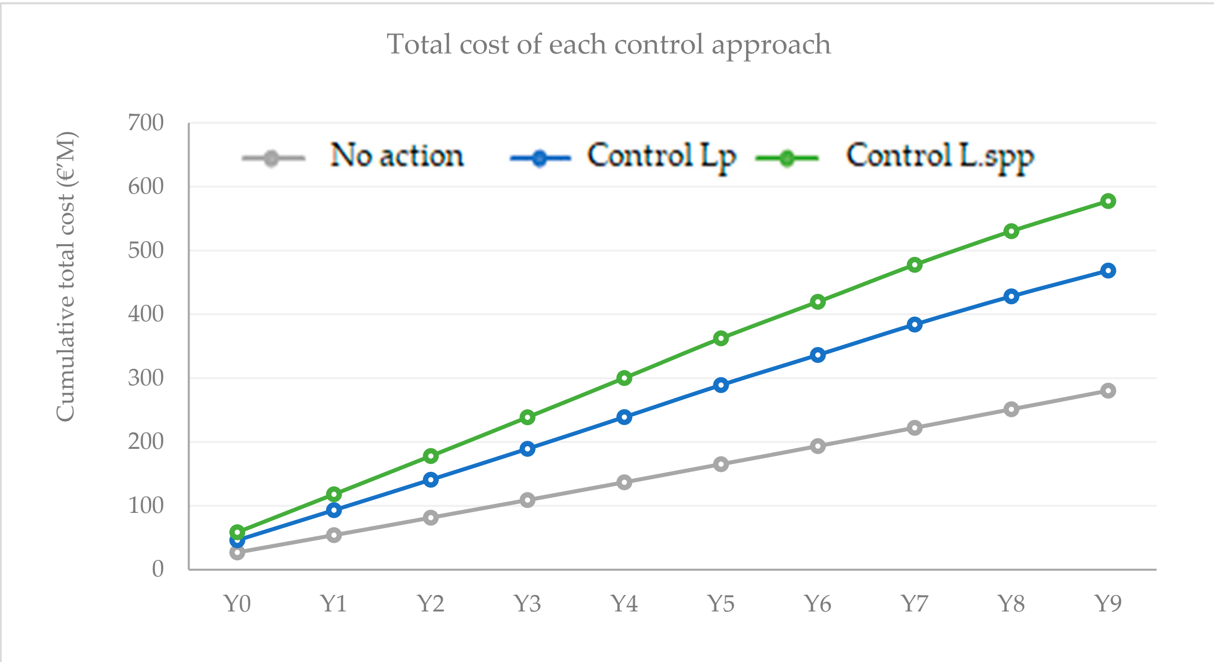


Figure 4. Projected total 10-year cost of each control approach using base case assumptions.

As shown in Table 4, an *L. pneumophila* control strategy delivers very similar health benefits (i.e., 97% of total cases prevented) to the *Legionella* spp. approach; however, the cost of an *Legionella* spp. approach over the same period is estimated to be 23% higher.

Table 4. Total and economic cost projected over time (10-year simulation of base case).

***Legionella* Control Strategy**	**# of Cases Prevented**	**Direct Cost of LD Prevention Approach (€'M)**	**Economic Cost of LD Prevention Approach (€'M)**	**Total Cost of LD Prevention Approach (€'M)**	***Legionella* spp. vs. *Lp* (€'M)**
No additional control and monitoring	N/A	N/A	280.5	280.5	N/A
L. pneumophila control and monitoring	6.5K	194.3	274.4	468.7	N/A
Legionella spp. control and monitoring	6.7K	265.8	295.5	577.5	109 (+23% above *Lp*)

Note: N/A= Not Applicable.

3.3. Comparing Monitoring Strategies at High and Low Limits for Key Variables

The model allows users to select different inputs for certain variables. Accordingly, we tested combinations of the extremes of three variables: percent of buildings contaminated overall, percent of contaminated buildings with detectable *L. pneumophila*, and percent of cases caused by *L. pneumophila* (Table 5). To explore the upper and lower limits of the model and compare the two different control strategies, each of these variables was set to the minimum and maximum as per values published in the literature (and highlighted in the Methods section).

Table 5. Min–max inputs across three dynamic variables.

% of Buildings Contaminated with *Legionella* at the Action Level			**% Buildings Contaminated with *Lp* Detected**			**% of Total Cases Est. Caused by *Lp* (All Serogroups)**		
Low (L)	**Base (B)**	**High (H)**	**Low (L)**	**Base (B)**	**High (H)**	**Low (L)**	**Base (B)**	**High (H)**
10%	40%	80%	50%	70%	90%	80%	95%	97%

The output from the model is shown in Table 6. The two control strategies are predicted to provide similar health benefit in terms of Legionnaires' disease cases prevented. However, for health and economic outcomes, which are defined as total cost to society and total cost to society per Legionnaires' disease case prevented, an *L. pneumophila* control approach has a much better outcome across all scenarios than an *L.* spp. strategy. An *L. pneumophila* control strategy is most attractive relative to an *L.* spp. control strategy when buildings are contaminated with a relatively lower proportion of *L. pneumophila* than *L.* spp. at the highest level of *L. pneumophila*-caused cases (scenario LLH or HLH) (i.e., where *L. pneumophila* % of disease cases is at its highest of 97%). In this case, an *L.* spp. control approach is projected to cost 63% more than an *L. pneumophila* control strategy but delivers only 3% more Legionnaires' disease cases avoided.

Table 6. Estimating health-adjusted outcome at the lower and upper limits of the variables.

	LD Cases Prevented			**Total Costs (Economic + Direct)**				**Total Cost per LD Case Avoided**			
Scenarios	**No Actions**	***Lp Control***	***L. spp. Control***	**No Actions (€'M)**	***Lp Control (€'M)***	***L. spp. Control (€'M)***	***L. spp. vs. Lp* (%)**	**No actions**	***Lp Control (€'K)***	***L. spp. Control (€'K)***	***L. spp. vs. Lp* (%)**
LLL	N/A	94	117	5	9	14	57%	N/A	93	116	25%
LLH	N/A	114	117	5	8	14	63%	N/A	73	116	58%
LHL	N/A	169	174	7	14	15	7%	N/A	83	87	4%
LHH	N/A	205	205	9	15	16	7%	N/A	72	77	7%
Base case	**N/A**	**624**	**638**	**27**	**46**	**59**	**27%**	**N/A**	**74**	**92**	**24%**
HLL	N/A	751	938	40	69	109	57%	N/A	93	116	25%
HLH	N/A	910	938	40	67	109	63%	N/A	73	116	58%
HHL	N/A	1351	1389	59	112	120	7%	N/A	83	87	4%
HHH	N/A	1638	1644	69	118	127	7%	N/A	72	77	7%

Notes: LLL: low % building contamination, low % of buildings with *Lp*., low range of cases caused by *Lp*; LLH: low % building contamination, low % of buildings with *Lp*, high range of cases caused by *Lp*; LHL: low % building contamination, high % of buildings with *Lp*, low range of cases caused by *Lp*; LHH: low % building contamination, high % of buildings with *Lp*, high range of cases caused by *Lp*; HLL: high % building contamination, low % of buildings with *Lp*, high range of cases caused by *Lp*; HLH: high % building contamination, low % of buildings with *Lp*, high range of cases caused by *Lp*; HHL: high % building contamination, high % of buildings with *Lp*, low range of cases caused by *Lp*; HHH: high % building contamination, high % of buildings with *Lp*, high range of cases caused by *Lp;* N/A: Not Applicable.

3.4. Comparing Monitoring Strategies over a Range for Each Individual Variable

The assumptions in the model were further tested by exploring a range of the key variables to assess the limits of our framework and assess the two control strategies. Each of the three variables from Table 5 (% of buildings contaminated at action level, % of buildings in which *L. pneumophila* was detected, and % of total cases of Legionnaires' disease) was varied. A variable rate of hospitalization was also included because it is a major driver of the economic costs, as was the expected compliance with remediation when an action limit has been exceeded. In each case, a single input was varied while other assumptions were held constant. In each case, the health outcome was very similar whether the *L. pneumophila*. control strategy was used or the *Legionella* spp. strategy was used (Table 7).

Table 7. Legionnaires' disease cases were prevented at different levels of contaminated buildings with *L. pneumophila* detected and at different percentages of total LD cases estimated to be caused by *L. pneumophila* (all serogroups).

LD cases prevented at different building contamination levels												
% of buildings contaminated at action level	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%		100%
No actions	-	-	-	-	-	-	-	-	-	-		-
Lp strategy	78	156	312	468	624	780	936	1092	1248	1404		1560
*L*spp. strategy	80	160	319	479	638	798	957	1117	1276	1436		1595
LD cases prevented at different % of contaminated buildings with *Lp* detected												
% of building water contaminated by *Lp*	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%		100%
No actions	-	-	-	-	-	-	-	-	-	-		-
Lp strategy	45	89	178	267	357	446	535	624	713	802		891
*L*spp. strategy	89	131	216	300	385	469	554	638	723	807		891
LD cases prevented at different % of total LD cases est. caused by *Lp* (all serogroups)												
Lp % total incidence of cases							60%	70%	80%	90%	95%	100%
No actions							-	-	-	-	-	-
Lp strategy							394	460	525	591	624	657
*L*spp. strategy							507	544	582	619	638	657

However, in terms of total cost to society, the *L. pneumophila* control strategy was consistently advantageous regardless of the variable tested (Figure 5A–E).

The difference in relative cost between the two control approaches was most sensitive to changes in two specific variables: "% of contaminated buildings with *L. pneumophila* detection" and "rate of compliance with remediation when the action limit is exceeded". When the percentage of buildings for which a remediation action was taken was varied, the *Legionella* spp. control strategy consistently led to a higher cost (Figure 5B). However, when *L. pneumophila* represented the minimum of over-action-limit samples (only 5%), there was a substantial difference in cost between the two strategies, EUR 35 M per year, or 770%. When *L. pneumophila* was 90% of over-action-limit contaminations, the difference was much less, although still notable at EUR 4 M or 7%. At all rates of building owner compliance with the requirements to take remedial action as a result of *Legionella* detected above the action limit, the total costs were consistently higher for the *Legionella* spp. control strategy (Figure 5E). Yet the cost of an *Legionella* spp. strategy was estimated at EUR 1.6 M higher per year than an *L. pneumophila* strategy when 5% compliance with the remediation requirement was assumed, and more than EUR 31 M higher each year, 42% higher, at 100% compliance, when public health policies were assumed to be fully implemented.

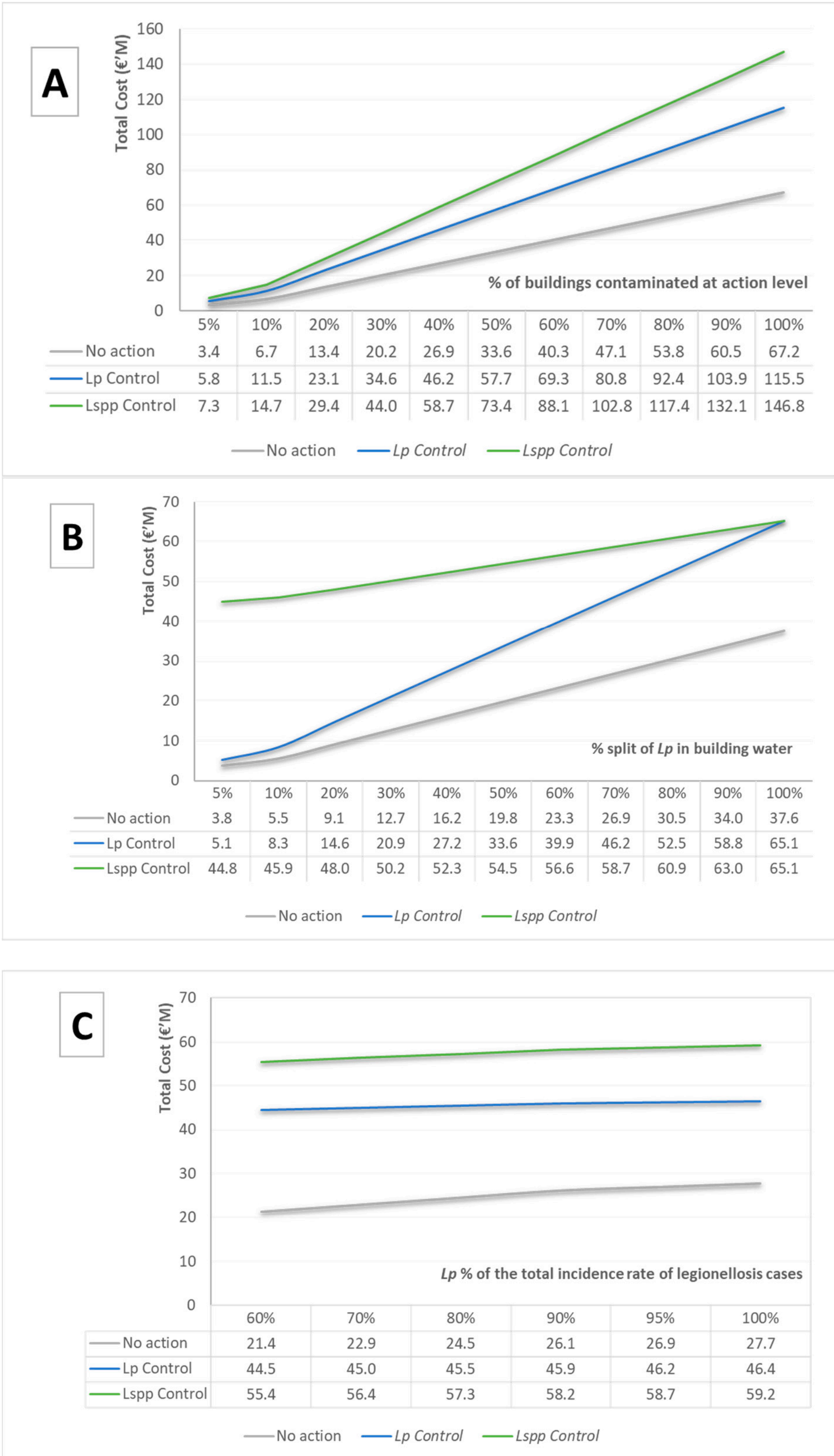


Figure 5. *Cont*.

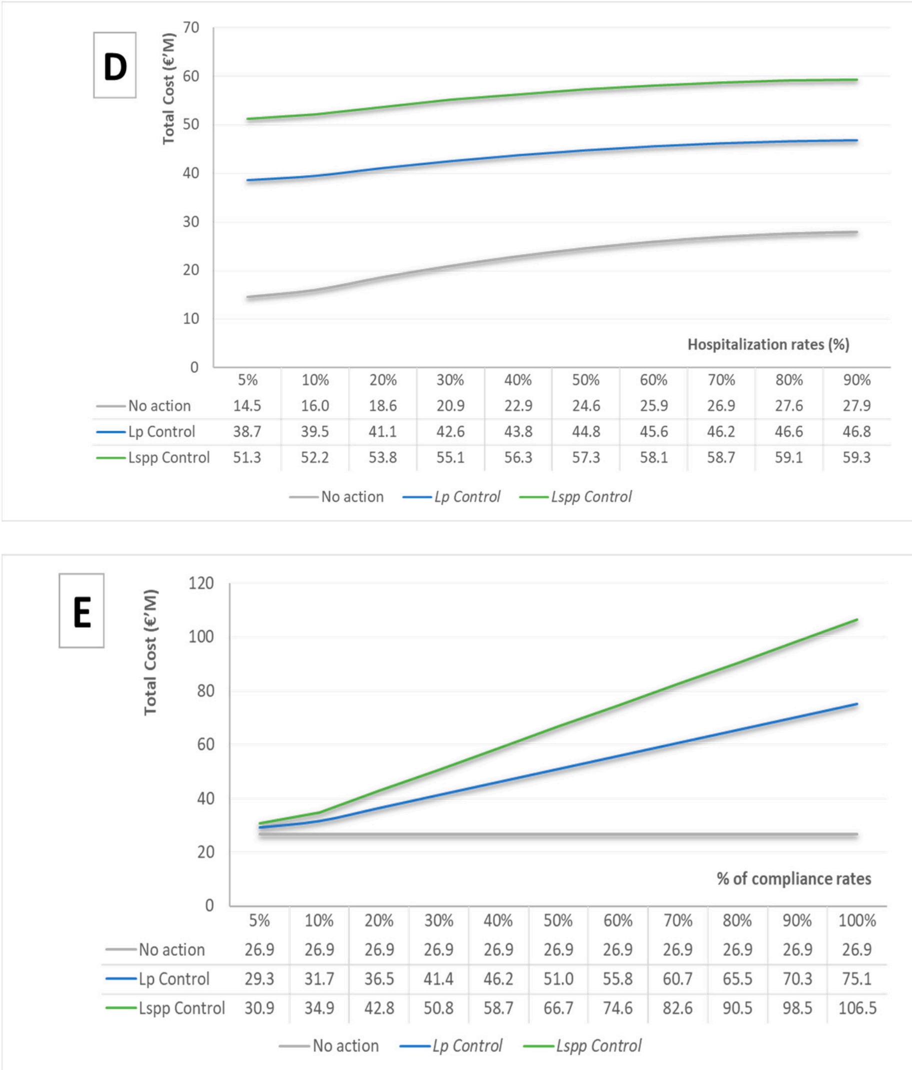


Figure 5. The cost of each control strategy with individual input options varied. (**A**) Varying "the % of buildings contaminated at action level" while holding the three other base case assumptions constant. (**B**) Varying "% of contaminated buildings with *L. pneumophila* detection" while holding the three other base case assumptions constant. (**C**) Varying "the % of total Legionnaires' disease cases est. caused by *L. pneumophila* (all serogroups)" while holding the three other base case assumptions constant. (**D**) Varied rate of hospitalization (%) while holding the three other base case assumptions constant and (**E**) varied rate of compliance with remediation when the action limit is exceeded while holding the other base case assumptions constant.

4. Discussion

The simulation model presented here was designed using an in-depth set of data from multiple sources as a tool for predicting the economic and human costs of different monitoring and control efforts meant to reduce Legionnaires' disease risk in Italy. The simulation allows for the user to input a range of variables to generate outputs which reflect a range of scenarios. We used the model to compare two different approaches for monitoring and controlling *Legionella*: the first approach detects and responds to any *Legionella* species found above a threshold action limit, and the second approach specifically monitors and takes action against *Legionella pneumophila*, the species known to be the cause of the vast majority of Legionnaires' disease cases contracted through building water sources. Our results consistently show that an approach targeting *Legionella pneumophila* is not only sufficient but, in most cases, preferable in terms of cost, both direct and indirect, and human health benefits.

A reliance on UAT diagnoses is often cited as a caveat to epidemiological case data which documents *L. pneumophila* serogroup 1 (*Lp*1) as responsible for 80–90% of cases. However, recent analyses of case etiologies with and without UAT diagnoses (Pan-European data) and before and after widespread use of UATs (New York state data over 40 years) reveal that UAT diagnoses do not underestimate the percentage of non-*pneumophila* species relative to cases caused by *L. pneumophila* when all serogroups are considered. See full discussion in Supplementary Information [15,16]. Nonetheless, we ran a sensitivity analysis to consider a broad range of hypothetical etiology situations, from *L pneumophila* (any serogroup) causing only 60% of cases (far more conservative than the lowest estimates of waterborne *Legionella* etiologies of 80% of cases due solely to *Lp*1) to the other extreme, in which *L. pneumophila* bacteria cause 100% of Legionnaires' disease cases (Figure 5C). The result along this continuum was a minimal change from the total cost of an *Legionella* spp. control approach being 24% higher than for a targeted *Lp* approach at 60% of cases being caused by *L. pneumophila* versus 28% higher at 100% of case etiologies being traced back to *L. pneumophila*. The difference in cost per case prevented ranged from 3% less for an *Lp* approach with 60% *L. pneumophila* etiology to costing 28% more when 100% of cases are attributed to *L. pneumophila*.

This study focused on a single health outcome, preventing Legionnaires' disease cases. As such, both the DALYs calculated and the economic costs (hospitalization and prescription cost, lost productivity of patients and caregivers, and legal costs) were limited to costs provoked by Legionnaires' disease. Other health risks for each control strategy could also be compared and/or incorporated, for example, the unintended consequence of exposures to chemicals used in remediations, as was considered by Tolofari et al. for the *Mycobacterium avium* complex, total trihalomethanes (THMs), and total haloacetic acids (THAs) [60]. Disinfectant byproducts could be assumed to increase with the total number of buildings remediated, leading to greater exposure and risk under the broader *Legionella* spp. control strategy than under the more targeted *L. pneumophila* approach. A more in-depth analysis could be performed to quantify this additional public health and economic cost burden.

This study was run with the assumption that traditional environmental plate culture testing methods, specifically ISO:11731, can be used to analyze all water samples for *Legionella*, followed by a final step to identify the species if the targeted *L. pneumophila* control approach is utilized. The availability and increasing use in the last decade of alternative testing methodologies specific to *L. pneumophila* move the assessments of costs and benefits of identifying and responding to this more specific target bacterium from a theoretical discussion to a very practical one. As the EU Directive references in Annex III Part A, newer technologies, such as qPCR, liquid culture, LAMP, and other *Legionella* detection methods, have widened the range of environmental surveillance strategies that can be practically implemented based on the needs and public health policy decisions of a particular country or region.

An important limitation of this study is that the current versions of this cost–benefit model only assess monitoring and control strategies specific to certain types of non-hospital buildings (class B and C1) and explicitly exclude any inpatient rehabilitation facilities. An appropriate range of variables from the literature and practice would need to be gathered and incorporated into the model to offer any policy insights for a more vulnerable, immunocompromised population such as may be treated or housed in these settings. Another limitation is that, consistent with the Italian Legionella Guidelines 18/23, the model does not consider potential exposure risks that are not directly associated with internal building water distribution systems destined for human consumption, so it excludes risks from cooling towers, fire prevention sprinklers, and others following a different approach and regulation.

From a policy perspective, given the many competing priorities and pressures on public health funding in countries around the world, an objective analysis of the direct, economic, and total costs of a targeted *L. pneumophila* strategy relative to a broader *Legionella* spp. control strategy can provide valuable insights for policymakers. This tool is customized with data from Italy and allows a variety of scenarios to be easily analyzed.

Other countries may benefit from using this same framework and simulation model and applying inputs specific to their country or region. For example, this approach could be used to assess the cost–benefits of following recent recommendations of researchers in Germany who stated the following: "In the future, mainly *L. pneumophila* should be taken into account, when evaluating drinking water plumbing systems", explaining that "evidenced-based clinical and epidemiological studies underpin that the vast majority of clinical legionellosis cases are linked to *L. pneumophila*. Against this background, it does not seem justified to attribute virtually the same virulence to all strains of environmental *Legionella* spp., to initiate control measures without considering strain-specific health risks" [61].

Adapting this model to other jurisdictions would require revising, and, as needed, changing, the geography-specific inputs described in Sections 2.4–2.6. This would include, for example, the type of number of buildings controlled, the number of people potentially exposed per building, building contamination estimates, estimates of the proportion of *L. pneumophila* and non-*pneumophila* species found in buildings, Legionnaires' disease incidence rates factoring in country-specific underestimation factors, and local costs for remediation, hospital care, and/or productivity losses.

5. Conclusions

The EU Drinking Water Directive 2020/2184 requires a risk-based approach to controlling *Legionella* and offers the possibility for Member States to take a practical and proportionate public health policy approach to *Legionella* monitoring and control.

A simulation model based on conservative assumptions from the state-of-the-art peer-reviewed literature and current local practitioner data provides a valuable and user-friendly tool to assess the public health costs and ramifications of different monitoring and control approaches.

This model was developed and tested with academic and real-world inputs representing the current Italian situation. The model was also tested under stress conditions, providing consistent and reproducible results. The various simulations were set up conservatively, favoring a *Legionella* spp. monitoring and control approach. However, under all conditions, the costs of a strategy based on broadly monitoring *Legionella* species were consistently higher than those of a strategy focused on *L. pneumophila*, including all serogroups, with similar health outcomes. The various simulations, both those chosen on the basis of scientific evidence and those representing hypothetic extreme assumptions, strongly support the effectiveness and appropriateness of surveillance focused on *L. pneumophila* for buildings of type B and C1, suggesting its greater appropriateness in the context of public health choices and policies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/w16152167/s1, Supplementary Information & Figures S1: Impact of UAT Diagnostic Methods on Estimates of Legionnaires' disease Caused by non-pneumophila *Legionella*. Supplemental Material S2: Mathematical Model Users Guide. References [1,8,15,16,62–68] are cited in the supplementary materials

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