

# "The Philly Killer": Emergence of *Legionella pneumophila*, a ubiquitous environmental bacterium

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July 1976, Bellevue Stratford Hotel in Philadelphia (Pennsylvania - USA, see Figure 1). The heat is stifling, the air conditioning is running at full speed. Several hundred veterans of the American Legion have gathered there for a convention. Following the convention, a sudden epidemic of severe pneumonia developed over several consecutive days in surrounding cities: 147 legionnaires were hospitalized, 29 (16%) died. No classical etiology was found. A genuine police investigation was launched under the aegis of the Centers for Disease Control and Prevention (CDCP) in Atlanta, to detect the "killer": it remained unknown for several months. In fact, it was a new bacterium pathogenic to humans, later called "*Legionella pneumophila*", whose biotope was fresh water. A new environmental disease was born: legionellosis!

## 1. 50 years ago: the emergence of legionellosis



Figure 1. Historical photo of the Bellevue Stratford Hotel (1976). [Source: Jack E. Boucher, HABS photographer (Public domain)]

Two fundamental articles describe the circumstances and stages of the discovery of this "new" bacterium pathogenic to humans which caused the sudden outbreak of this epidemic of deadly pneumopathies. On December 1<sup>st</sup>, 1977, a year and a half after the outbreak, Fraser *et al.* [1] and J.E. McDade *et al.* [2] respectively published the description of the pneumonitis epidemic and the diagnostic process to detect the causative agent in the prestigious medical journal *The New England Journal of Medicine*. Their research was commissioned by the CDC [3], a US federal agency with powerful scientific, technical and financial resources, whose sole objective was to identify the "*Philly Killer*," as dubbed by the American press!

From the onset of the epidemic, a team of approximately fifty epidemiologists from the *Epidemic Intelligence Service* (EIS) were deployed in the State, supported by numerous microbiologists, chemists and toxicologists (Figure 2). However, all searches for known causing agents remained inconclusive. Six months later, McDade reverting to Robert Koch's postulates, inoculated a biopsy of lung tissue from a dead patient into a guinea pig and then into subcultures on embryonic eggs, which finally allowed the bacterial forms to be observed! During the following year, the main characteristics of the disease and the triggering infectious agent were defined: "*Pneumonia caused by a Gram-negative bacillus, of difficult culture, occurring most often in 'at-risk' subjects (elderly men, smokers), mortality rate of 10%, entry through the respiratory tract, probable cause of transmission: air conditioning systems.*" The epidemic was reported by the press worldwide and was even immortalized by a Bob Dylan's song "*Legionnaires' disease*"!

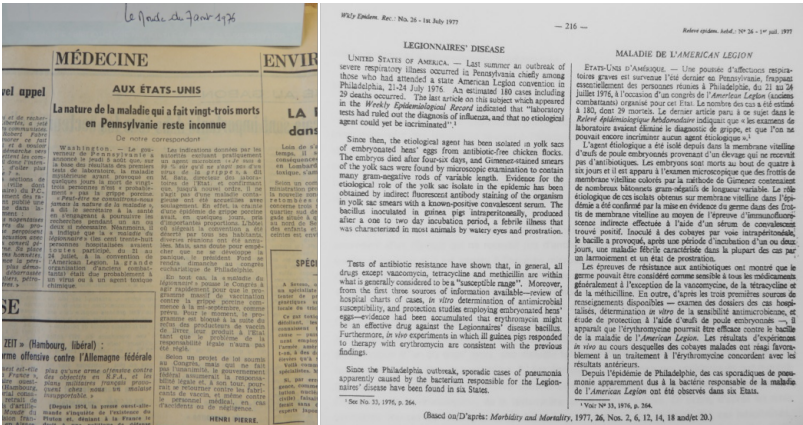


Figure 2. Left, article from the *Le Monde* newspaper of August 7, 1976. Right, article from the *Weekly Epidemiological Record* of July 1<sup>st</sup>, 1977 [Source: © personal photographs of J. Croizé]

The almost fortuitous discovery of the bacterium in 1981 was the subject of an exciting book entitled *Trauma* [4] which reads like a thriller. Authors G. Thomas and M. Morgan-Witts recount how, by tracking the patients, investigators, doctors and politicians, the most outlandish hypotheses were put forward (bird flu, plague, terrorist attack, chemical agents, toxins, etc.) before finally finding the solution. To date, after half a century of fundamental research on the infectious agent and epidemiological analysis of clinical cases, enormous progress has been made in the understanding, diagnosis and prevention of legionellosis. Nevertheless, the disease is still very topical, particularly in France (2,133 cases in 2018), because of its severity and the high proportion it represents among community-acquired pneumopathies (second cause of death after *Pneumococcus*).

## 2. Identity card of "the killer bacteria" *Legionella pneumophila*

### 2.1. What is it?

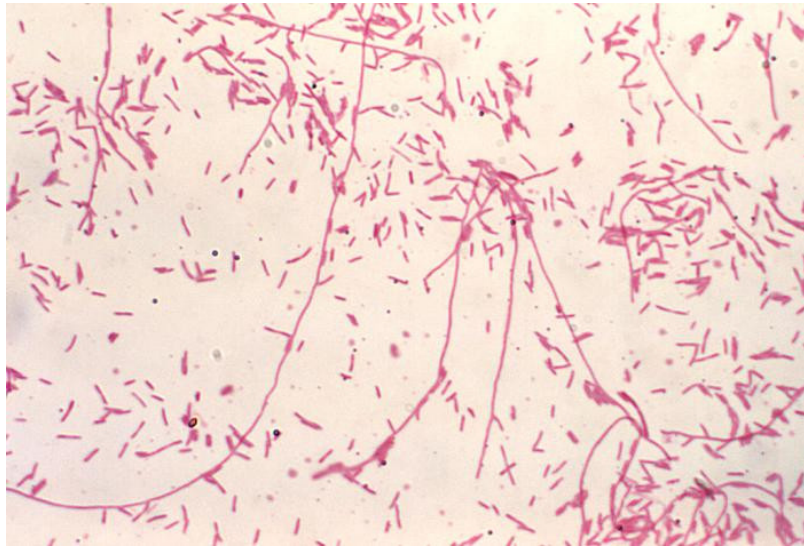


Figure 3. Gram staining of *Legionella pneumophila*. [Source: CDC-PHIL, Public domain]

The princeps [1] article on the taxonomy [2] of the bacterium was published in 1979 [5]. It is a small aerobic Gram-negative [3] bacillus, inaugurating a new family called *Legionellaceae* (in memory of the first patients affected) with only one genus *Legionella* (Figure 3). The first species was called *Legionella pneumophila* (Philein: love; Pneuma: breath) to remind us of the disease it causes: pneumonia. To date, 65 species have been described, of which only about twenty have been found jointly in humans and the environment. A remarkable phenomenon: its thermo-tolerance. The bacterium begins to multiply in temperatures from 25°C to 45°C. It can survive at a temperature of up to 60°C but dies off in temperatures above 70°C.

Initially, the bacterium is unable to multiply on existing media. In 1979, a new specific environment was described that is still relevant today. On average the division time of the bacterium is 4 hours; it explains, on the one hand, the time it takes for colonies to appear in cultures, between 2 to 5 days (Figure 4), and on the other, the incubation time of the disease, between 4 to 10 days. Several procedures for identifying colonies are possible: biochemical techniques, which were quickly abandoned, are now routinely replaced by immunological agglutination tests or mass spectrometry (MALDI-TOF-MS [4],[6]).

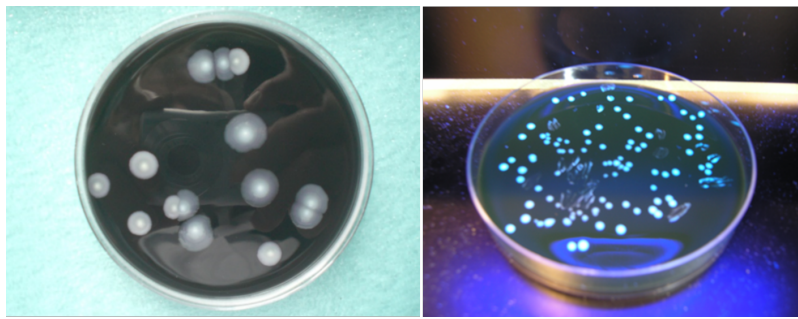


Figure 4. Colonies of *Legionella pneumophila* on selective BCYE media (left) and florescent colonies of *L. anisa* under UV light (right). [Source: © J. Croizé]

Today, it is no longer one, but 65 species, that are described, the most frequent and most pathogenic for humans being *L. pneumophila* SG (serogroup) 1. Its pathogenicity is due mainly to the presence of a large number of factors involved in its intracellular multiplication, including the *Macrophage Infectivity Potentiator* (MIP) and three secretion systems, the most important of which is type IV [7]. Among the sequenced strains, *L. pneumophila* Paris and *L. pneumophila* Lens, show a genome of 3.7 million base pairs (Mbp). Their analysis shows, in particular, the presence of protein coding genes that have the same homology as their two known hosts: free living amoebae [5] and humans. Subsequently, homologous proteins from the different hosts were characterized which explains the adaptive capacity of this microorganism [8], and in particular, that of the species most pathogenic to humans: *L. pneumophila* serogroup 1.

## 2.2. What are its biotopes?



Figure 5. Freshwater, the natural biotope for *Legionella*. [Source: © J. Croizé]

The **natural habitat** for *Legionella* is **fresh water in all its diversity: lakes, rivers, ponds** (Figure 5) **and thermal waters**. They are, however, absent in seawater [9],[10]. This aquatic and hydro-telluric [6] bacteria can be found in natural environments in three different forms:

In **free living amoebae**: Non-parasitic protists [7] complete their life cycle entirely in the environment and in water feed on microorganisms, including *Legionella*, by phagocytosis. They also have a natural "resistance" to amoebas; they internalize themselves in a vacuole called *Legionella-Containing Vacuole* (LCV) which constitutes a privileged breeding site in the environment ; thereby allowing *Legionella* to "shelter" in amoebas and resist environmental stresses (Figure 6) [11]. These eukaryotes (genera *Acanthamoeba*, *Hartmannella*, etc.) now become a potential reservoir of contamination.

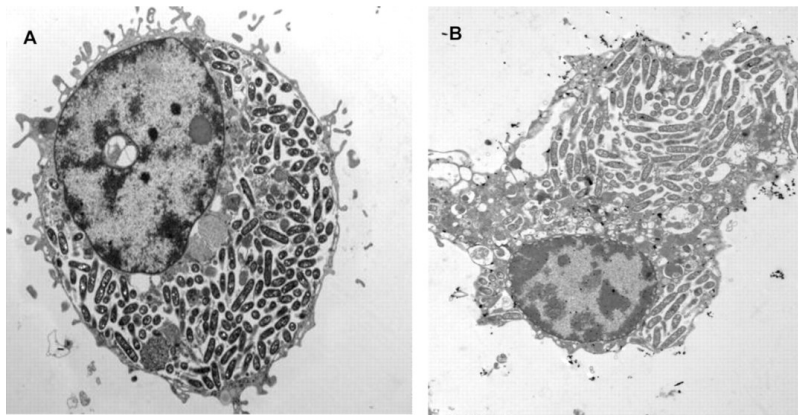


Figure 6. *Legionella pneumophila* infections in environmental amoebae and human macrophages. Electron micrographs of U937 macrophages (A) and *A. polyphaga* (B) infected by *L. pneumophila* (strain AA100) at 24 h. Image taken from Molmeret et al (see ref [11]) with the authorization of the American Society of Microbiology.)

In **bacterial biofilms** [8],[12]: A biofilm (see Bacterial Biofilms and Health) is composed from OF a dynamic environment where combined microorganisms enclosed in an extracellular matrix adhere to physiochemical surfaces: this model applies to *Legionella*. But biofilms can also be found on the surface of stagnant liquid media or "floating biofilms": these play a crucial role in the persistence of bacteria in tanks which may be inaccessible and the bacterial biofilms are therefore difficult to eradicate with disinfectant products.



Figure 7. Cooling tower. [Source : © J. Croizé]

In the **form of viable but non-cultivable bacteria** (VBNC) [13]: These appear under the effects of stress, which means that they are unable to multiply temporally because of their low metabolic activity. However, if conditions become favourable again, they can regain their pathogenicity.

**Artificial or man-made water towers: air cooling towers** (Figure 7) and **domestic hot water (DHW)** installations [14],[15]. From natural sites, *Legionella* can colonize artificial sites and multiply if the temperature allows it to do so (25 to 45°C). Thus, any device or network containing hot water will constitute a potential niche for *Legionella*. Historically, air conditioning systems, cooling towers and evaporative condensers have been incriminated: hence, the word "air conditioning" is often synonymous with the word "legionellosis"! It has subsequently been proven that all "modern" domestic hot water networks could potentially be colonized with *Legionella*, and in zones more at risk, such as showers, whirlpools, decorative fountains, etc.

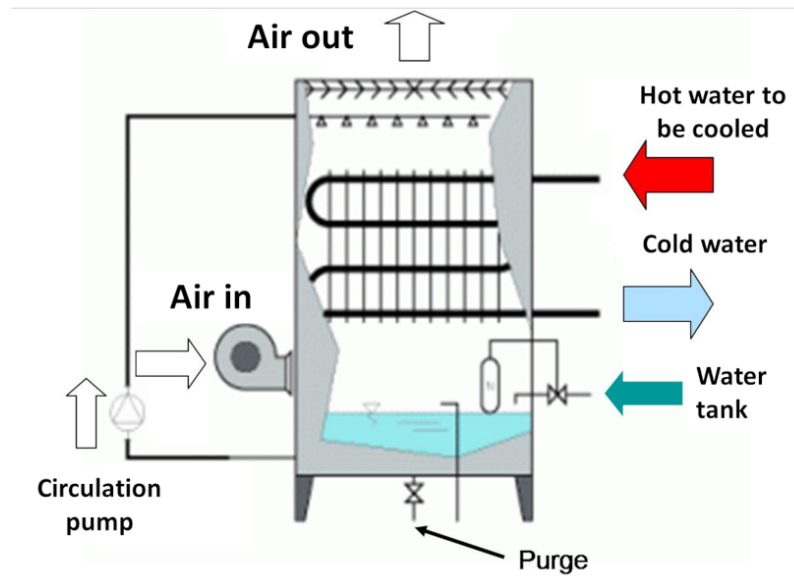


Figure 8. Fonctional diagram of an air-cooling tower. [Source: KW (CC BY-SA)]

**Air-cooling towers installations** were the first to be directly linked to the outbreak. Industrial hot water circuits or refrigeration units used in air conditioning (industry, trade) are favorable to the development of *Legionella* (water temperature and air/water contact in the installations). Humid air-cooling towers located outside buildings are cooling systems for these hot circuits, resulting in the formation of aerosols consisting of fine droplets which are released from the vents into the air. The extent of the risk will be greater or lesser depending on the location and density of the surrounding populations. Examples abound, a bus stop for golfers situated underneath the fallout, the involuntary recovery of vapors released by the buildings themselves or by neighboring buildings. The risks involving industrial cooling towers are less numerous. Albeit, the outbreak in Lens (1997) identified a cooling tower located 8 km, or even 16 km from the homes of contaminated patients (Figure 8)!



*Figure 9. Shower. [Source: Tanakawho (CC BY 2.0)]*

**Domestic hot water** (Figures 9 & 10) is initially cold water destined for domestic use, and intended for human consumption and which will be heated secondarily. This was the second area of contamination discovered after Susan Fisher-Hoch's observation of cases in England where the use of air conditioners is not very common [\[16\]](#). The water distributed to households through the supply network is heated by various means such as boilers, hot water tanks, etc., which are either individual or collective. It is then distributed through an average sized pipe to any water outlet (taps, showers) where it becomes domestic hot water.

*Legionella*, potentially present in cold water in very low concentrations, will be able to multiply rapidly if the temperature conditions permit. Contaminated hot water becomes dangerous when it is transformed into aerosols: this is the case for example, for showers, spas, atomizers and mist devices, decorative fountains, or even in car washing installations and water jets used in dentistry.



*Figure 10. Spa.*

In hospitals, the risks of contamination are identical but greatly increase with the admission of patients whose immunity has already been compromised (immunosuppression) or by their treatment (corticosteroid therapy). The epidemic of legionellosis which occurred in 2001 during the inauguration of the *Georges Pompidou European Hospital* remains a textbook case, underlining the importance of the composition of pipes as well as the time period of water stagnation in these pipes.

Other potential sites, although rarer, include wet soil such as "potting soil", where compost can be contaminated by a particular species, *L. longbeachae*, which is also pathogenic to humans.

## 2.3. How did the bacteria emerge in humans?

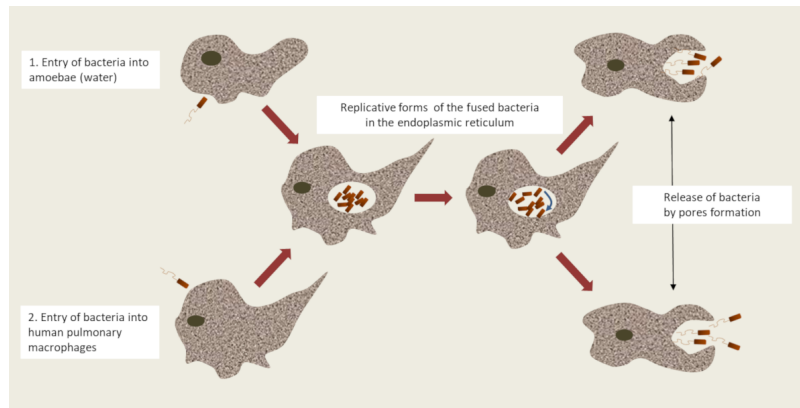


Figure 11. Life cycle of *L. pneumophila* in both amoebae and human macrophages. Diagram adapted from ref. [15]

It has now been proven that human infection occurs *via hot water aerosol inhalation contaminated* with *Legionella*: droplets less than 5  $\mu\text{m}$  but large enough to contain the bacteria (greater than 2  $\mu\text{m}$  in diameter) [17]. Any healthy subject is normally able, during microbial exposure, to defend him or herself thanks to the pulmonary macrophages which are natural "lung cleaners" and which destroy the microorganisms that have been ingested. But if an abnormality occurs in the process of phagocytosis, or the infecting strain has a particular virulence, or if the concentration of bacteria is high, then the macrophage is transformed into an "accidental host." *Legionella* multiplies in the phagolysosome vacuole (LCV) as it does in amoebae, before escaping with increased virulence (bacteria becomes flagellated again). This process is mainly found with *L. pneumophila*, a species responsible for more than 90% of all cases of legionellosis (Figure 11). The bacteria are classified as intracellular multiplying bacteria which will require the use of antibiotics with intracellular diffusion.

These particularities suggest that legionellosis is not a human communicable disease (only one exception was recorded in Portugal in 2016), but an opportunistic disease, the occurrence of which depends very much on many individual risk factors!

## 2.4. What is legionellosis?

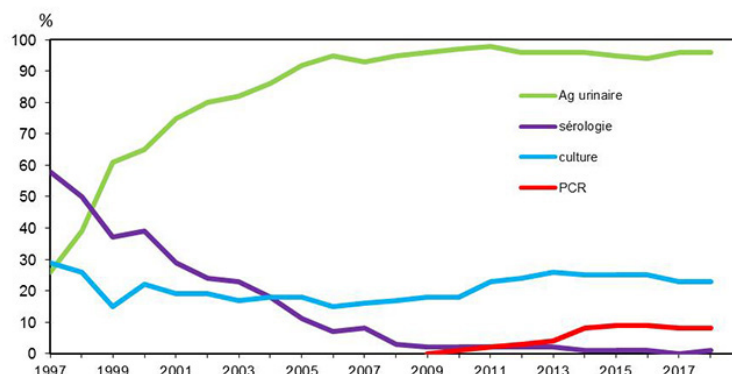


Figure 12. Comparative breakdown of the 4 diagnostic methods for legionellosis cases, France 1997-2018. Reproduced with the authorization of "Données de Santé Publique France" [19].

Legionellosis is a pneumopathy [17] which has an incubation period of approximately 5 days after exposure; the infectious dose is 1000 CFU (Colony Forming Unit) of *L. pneumophila per liter*. Some groups of people are more "at risk" than others (although in 20 to 30% of cases, no risk factors are detected). Three contributing factors are now well identified:

age over 50 years (legionellosis is rare in children and in young adults)

smokers (45% of cases)

males (75% of cases).

Other patients with a weakened immune system (malignant hemopathies, cancers, immunosuppressive treatments, prolonged corticosteroid therapy), chronic cardiac or pulmonary pathologies and diabetes will need to have highly regulated and supervised prevention and monitoring measures in place, including a mandatory "Zero *Legionella*" threshold for domestic hot water (DHW).



Figure 13. Detection of antigen in the urine for the diagnosis of legionellosis. [Source: © J Croizé]

Clinically, the disease has two distinct forms: **Pontiac fever** (flu-like symptoms without pneumonia; symptoms disappear in 2 to 5 days without treatment, after an incubation period of a few hours to 48 hours). And **legionnaires disease**, a severe clinical and radiological pneumonia evoking influenza-like symptoms, without pathognomonic signs. If untreated, death occurs in 10% of cases. Appropriate antibiotic therapy (antibiotics to treat intracellular fighting bacteria such as macrolides, fluoroquinolones or rifampicin) is prescribed. It complies with the recommendations of the *National Agency for the Safety of Medicines and Health Products* (ANSM) [18], which take into account the gravity of the infection and allows for an estimated recovery time of less than one month.

Legionellosis is a serious disease, hence the importance of an accurate diagnosis for therapeutic purposes but also for surveillance purposes. It is based on an association with pneumonia and the presence of at least one of the following 4 microbiological criteria [19] (Figure 12):

The presence of *Legionella soluble* antigens in the NOW *Legionella* urinary test (Figure 13);

DNA isolation using direct PCR technology on the bronchopulmonary sample;

Isolation of bacteria cultures from pulmonary samples (sputum or bronchoalveolar lavage) then coding the isolated strain;

Confirmation posteriori may be given if seroconversion is proven.

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### **3. Today what is known about the epidemiology of Legionellosis in France and Europe?**

Epidemiology is a branch of medical science which deals with the incidence and prevalence of a disease in large populations and the detection of the source and causative agent of such disease.

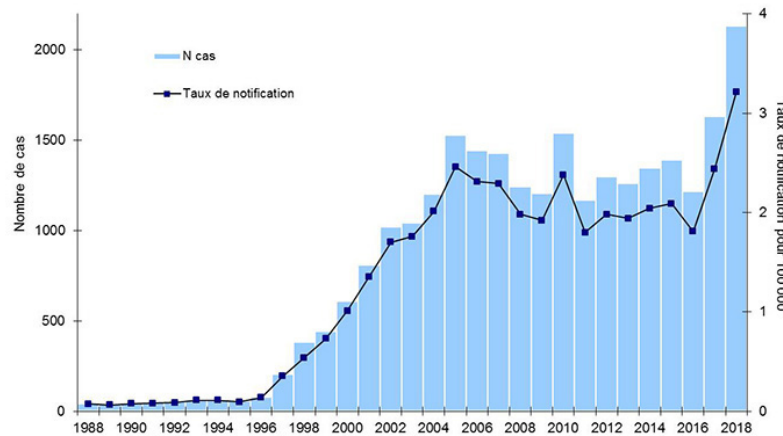


Figure 14. Evolution of the number and annual incidence rates of notified cases of legionellosis in France, 1988-2018. [Source : Reproduced with permission from Santé Publique France (see Ref. [19]).

The epidemiological investigation into the outbreak of Legionellosis is considered a role of fundamental importance. Recognized as a significant public health problem, legionellosis was added to the list of diseases subject to compulsory declaration. In France, the notification of this disease has been mandatory since 1987. All new cases need to be reported and a notification issued. Thanks to the availability of a reliable diagnostic test (search for soluble antigens in urine - 1997) and the obligation to transmit the isolated strain to the "Centre National de Référence (CNR) des *Legionelles*" in Lyon [20] - an effective surveillance system exists in France (Figure 14). This is based on the study of *Legionella* strains which were isolated from Legionellosis infected patients and strains isolated from the environment. The aim of the CNR is to identify the source of contamination. The comparative study of "sick and environmental" strains is based on various coding methods (phenotypic [9], genomic).

Today, different methods for data analysis are carried out, which have led to a reliable descriptive epidemiology:

Guidelines have been implemented by the regulatory authorities which require the documentation and classification of all cases of legionellosis as "confirmed" or "probable," according to biological test results;

Classification of "nosocomial [10] cases" or "community cases" according to where the disease was acquired;

Recording the spread of the disease based on the number of people affected by the same strain: isolated cases or grouped cases or epidemic cases (see Table 1); and

Finally, cases related to travel to another country other than France are reported to the *European Legionella Surveillance Network* EldsNet [21].

**Table 1.** Epidemiology data on Legionellosis cases in 2018 extracted from "Données de Santé Publique France 2019" (see Ref. [19]).

<b>Number of cases</b>	<b>2133</b>
<b>Isolated strain</b>	<i>L. pneumophila</i> Lp1:2065/2133
<b>Average age</b>	64 years
<b>Sex ratio M:F</b>	2.7 (3 times more males than females)
<b>Incidence</b>	- 3.2/100,000 inhabitants - 10.4/100,000 for people >80 years
<b>Fatality</b>	8%
<b>Diagnosis</b>	96% (antigen test)
<b>Risk factors</b>	- Smoking (44%) - Diabetes (18%) - Cancer/hemopathy (11% approx.) - At least 1 risk factor (73%)
<b>Profile</b>	- Hospitals - Tourism - Hotels/camping sites - Thermal spas

Data collected from the 2018 legionellosis epidemic in **France** (figures published in August 2019) highlights the different characteristics of the disease as summarized in Table 1; in its commentary *Santé Publique France* [22], emphasizes this clear increase: 2,133 cases and a national incidence rate of 3.2%, the highest figure recorded since surveillance began in 1988.

No particular reason was found to explain this except for a net increase in cases in June (favorable meteorological factors), numerous sporadic cases and no new risk factors.

In **Europe, case notification is the responsibility of the ECDC** (*European Centers for Disease Prevention and Control*). This monitoring activity is effective in thirty European countries. The number of reported cases has increased from 5,835 in 2013 to 9,238 in 2017 [23]. The incidence is 1.8/100,000 inhabitants.

The four countries that reported the most cases of legionellosis were: in first place Italy: 2013 cases; France in second place: 1,630 cases; Spain in third place: 1,363 cases; and Germany in fourth place: 1,280 cases. But these figures should be interpreted with caution as not all of the countries use the most recent diagnostic methods. However, the present tests used and the monitoring systems in place are considered very important for the accuracy of the data.

Note that for the USA, the annual incidence rate in 2014 was 1.62 cases per 100,000 inhabitants, an increase from 0.42 cases reported since 2000.

## 4. Is it possible to prevent legionellosis?

### 4.1. How can we monitor water quality systems?

**There are no vaccines that can prevent legionellosis!** Therefore, the entire prevention strategy is based on individual or collective measures.

**Prevention measures** targeting domestic hot water and cooling tower systems are based on **several fundamental regulatory texts** [24]: *Guide for investigation and management assistance of the High Council for Public Health, July 11, 2013 - Decree of February 1<sup>st</sup>, 2010 – Circular of December 23, 2010 - Decree of December 14, 2013.*

**The general guidelines regulating the use of domestic hot water** (see the *monitoring sheet published by the Ile-de-France Regional Health Agency*) **are**:

Whether it be for individual or collective use, it is necessary to **continually control the temperature of hot water storage tanks**, which must always be:

above 55°C at the end of production;

above 50°C at any distribution point;

The temperature of cold water must be below 20°C.

**Regular maintenance and monitoring of hot water installations** must be ensured by removing stagnant water in the piping

system, checking for the presence of corrosion in the pipes and by descaling taps and shower heads, as well as rectifying poor maintenance practices of the water supply network.

**Individual prevention "at home."** In addition to the above rules, there are two further important precautions to take:

**After a prolonged absence** from a property (holiday vacation, for example), it is essential to let **run** all hot water taps and shower heads for **several minutes**.

**Be cautious with rarely used water points**, as they are potential reservoirs of *Legionella*.

**Risky installations are classified into two groups according to their anthropogenic activity:**

**Group A:** installations at high risk of *Legionella* dispersal:

**A1:** over an area of one or more municipalities (measuring several hundred square meters or several square kilometers). This is the case for roof-mounted cooling towers installed in buildings or industrial sites, for air conditioning requirements. Contamination is caused by the release of hot water vapor into the atmosphere. To prevent such contamination, the cooling towers must be regularly maintained, cleaned and disinfected using biocides.

**A2:** several square meters around communal water sources: collective domestic hot water systems.

**Group B:**

**B1:** collective water-misting equipment, spas, vehicle washers, lagoon systems for wastewater treatment plants, professional high-pressure cleaners.

**B2:** equipment used in oxygen therapy, sleep apnea, nebulization, dental care.

## 4.2. How do we know that the water network is contaminated?

Research into water network systems is well codified by the AFNOR Standard NF T 90-431: "*Water Quality. Search for and enumeration of Legionella spp. and Legionella pneumophila.*" This is a method by direct inoculation and after concentration. It applies to all types of water: both clean and dirty. Since 2010, the NF T90-471 standard using detection by molecular biology type PCR has existed: this technique is carried out in the case of a specific request by the health authorities.

## 4.3. What are the obligations of public institutions?

For these institutions, the decree of February 1<sup>st</sup>, 2010, and the circular of December 21, 2010 (see ref. [\[19\]](#)) must be applied in order to prevent contamination of the domestic hot water systems. They relate to the monitoring of *Legionella* in facilities dealing with the supply, storage and distribution of domestic hot water in healthcare institutions, medical social facilities and prisons, hotels and tourist residences, campsites and other establishments which are open to the public.

Other guidelines, which can be consulted on the Internet, apply specifically to all types of establishments open to the public, from campsites to hotels:

*Legionella* monitoring of spas and pools,

*Legionella* monitoring of thermal springs,

*Legionella* monitoring of car washers,

*Legionella* monitoring of tourist establishments,

*Legionella* monitoring of cooling towers (January 20, 2014),

Recommendations for residential buildings.

Regarding hospitals, the distribution of circulars from the *Direction Générale des Soins* and the *Conseil Supérieur d'Hygiène de France* have helped healthcare professionals to understand the risks for hospitalized patients and have led to the development of

a response guide. In the field, the Committees for the *Control of Nosocomial Infections* (CLIN) and the Hygiene Units have developed procedures, including the establishment of a "water quality monitoring logbook" [25].

#### 4.4. What to do in case of contamination?



Figure 15. Diagram appearing on the "Legionellosis" file of the Ile-de-France Regional Health Agency.

If the water system is contaminated with *Legionella*, the system operator must immediately take the appropriate measures according to risk levels [26].

For a simple disinfection intervention, various processes are applied, used alone or in combination. They can be:

**Mechanical:** pipe descaling or repair;

**Physical:** in particular thermal shock. Used only in hot water systems, it consists in maintaining the water temperature at 70°C for at least 30 minutes. This procedure has been used in medium-sized hospitals, but during the heating process, no one can use the water and it requires the presence of personnel at each point-of-use to avoid burns; or

**Chemical:** these are highly controlled chemical agents, the main ones of which are chlorinated compounds that generate hypochlorites.

## 5. Messages to remember

During the 1970s and 1980s, three major infectious diseases of bacterial origin emerged: (1) *Borrelia burgdorferi* agent of Lyme disease, (2) *Helicobacter pylori* responsible for gastric ulcers, and (3) *Legionella pneumophila* and Legionellosis.

Each time, it was chance circumstances that led to the discovery of the causative bacteria. In fact, they had existed for a long time, but had simply been ignored!

*Legionella* most certainly existed in environmental waters long before the Philadelphia outbreak, but they were not well known because they had not yet had an opportunity to infect humans.

It is we humans with our hot water demands and its multiple uses for comfort, pleasure or industry requirements, that has given rise to a new and totally unpredictable disease.

As *Legionella* is ubiquitous in environmental freshwater, its eradication in the environment is impossible.

It is the responsibility of all of us to promote and enforce strict rules for the proper use of hot water and the prevention of its contamination; rules that must, above all, be put into practice in order to protect the people most "at risk".

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## Notes and references

**Cover image.** Some press coverage.

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[21] ELDSNet : *European Legionnaires' Disease Surveillance Network*, coordinated by ECDC (*European Center for Disease Prevention and Control*), created in 2005. EWGLI (*European Working Group for Legionella Infections*), created in 1986, will become EWGLINET and then in 2010 becomes ELDSNet.

[22] Santé Publique France. Since 1 May 2016, it has included: INVS (*Institut National Veille Sanitaire*), Inpes (*Institut national de prévention et d'éducation pour la santé*), Eprus (*Etablissement de préparation et de réponse aux urgences sanitaires*).

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