

Chapter 1: Clinical Aspects of Legionellosis

1.1 Introduction

Infection with *Legionella* bacteria can cause two distinct clinical syndromes, grouped together under the name legionellosis. The first is pontiac fever, a self-limiting influenza-like illness. The incubation period is usually 24-48 hours. Patients recover spontaneously in 2-5 days. The second and the main subject of these guidelines is legionnaires' disease which is a severe and potentially fatal form of pneumonia. Symptoms include a flu-like illness, followed by a dry cough and progression to pneumonia. Diarrhoea, vomiting and mental confusion are common. The case fatality rate is about 12%, rising to about 30% in nosocomial cases.¹

Legionnaires' disease was first recognised in 1976 following an outbreak of pneumonia among delegates at the annual convention of the American Legion held in the Bellevue Stratford Hotel in Philadelphia. In that outbreak 221 persons became ill and 34 died of a previously unknown disease.² *Legionella pneumophila* was the organism isolated.

1.2 *Legionella* – natural history of the organism

Legionella are Gram-negative bacteria that live as intracellular parasites of a variety of species of amoebae, protozoa and slime moulds in aquatic environments. Figure 1 shows an electron micrograph of an amoeba entrapping a *L. pneumophila* bacterium with an extended pseudopod.

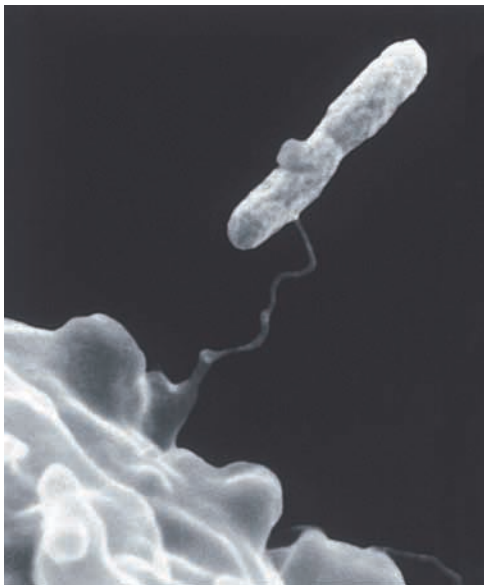


Figure 1. An amoeba entrapping a *L. pneumophila* bacterium. Courtesy of Fields BS. *Legionella and protozoa: interaction of a pathogen and its natural host. Legionella, current status and emerging perspectives.* Washington DC: ASM Press, 1993

To date, at least 50 *Legionella* species and 70 serotypes have been described.³ At least 20 species are associated with causing disease in humans.³ *L. pneumophila* serogroup 1 is the cause of 70-90% of all cases of legionnaires' disease where the aetiological agent has been isolated. *L. pneumophila* serogroup 1 can be further divided into many subtypes. One of these subtypes, the Pontiac subtype, is responsible for 85% of cases due to *L. pneumophila* serogroup 1.⁴ Other species identified as causing pneumonia in humans include *L. micdadei*, *L. bozemanii*, *L. dumoffii*, and *L. longbeachae*.³

Legionella bacteria are ubiquitous in nature and can be found naturally in environmental water sources such as rivers, lakes and reservoirs, usually in low numbers. *Legionella* bacteria have also been isolated from potting soils, particularly in Australia.⁵ From the natural source, the organism passes into sites that constitute an artificial reservoir (piped water in towns and cities, water networks, water systems in individual buildings, cooling towers, etc.).

Water temperatures in the range 20°C to 45°C favour growth of *Legionella* bacteria. The organisms do not appear to multiply below 20°C and are killed within a few minutes at temperatures above 60°C.⁶ They are acid-tolerant and can withstand exposure to pH 2.0 for short periods. They have been isolated from environmental sources with pH ranging from 2.7 to 8.3.⁷

Legionella bacteria multiply within amoebae and protozoa. However, when environmental conditions are unfavourable e.g. absence of nutrients or temperature changes, the *Legionella*-infected amoebae encyst, allowing the survival of the host and the parasite until more favourable conditions allow excystment. In both natural and man-made water systems, *Legionella*-infected amoebae are found in association with microbial biofilm containing many different microorganisms (Figure 2).⁴ The presence of sediment, sludge, scale and other material within water systems, together with biofilms, are thought to play an important role in the persistence of *Legionella* bacteria, providing favourable conditions in which the *Legionella* bacteria may grow. Environmental changes can disrupt the biofilm or dislodge portions of it and lead to a sudden and massive release of *Legionella* bacteria into the water system. If the water is then aerosolised and inhaled by humans or aspirated by humans, the bacteria can cause illness in susceptible individuals. *Legionella* bacteria also exist as free living organisms.⁴

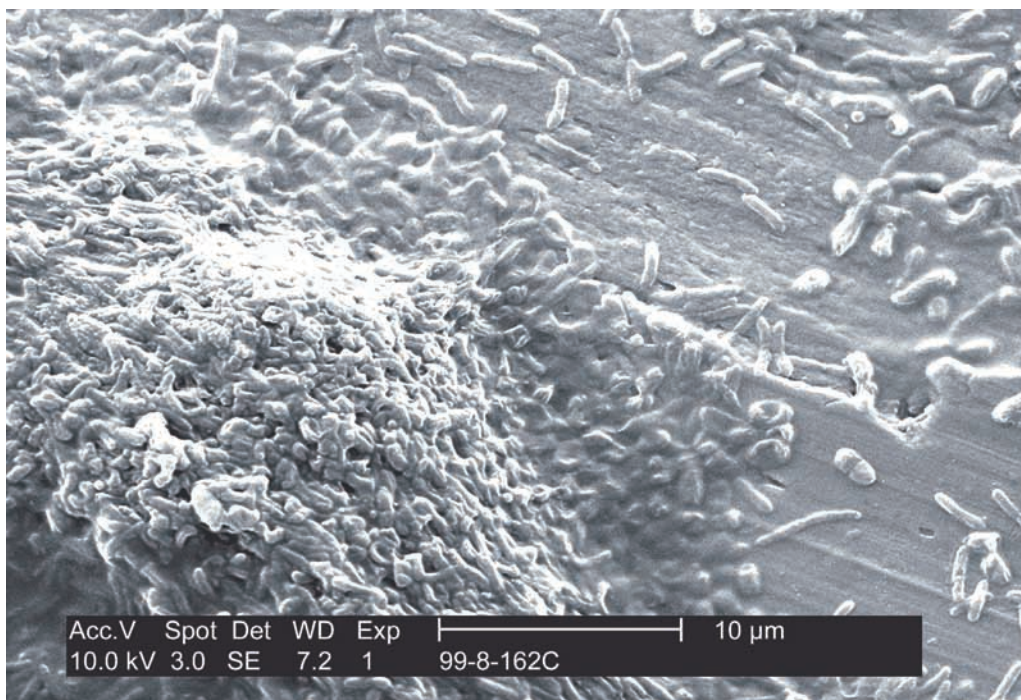


Figure 2. A scanning electron micrograph of *L. pneumophila* on potable water biofilms. Courtesy of Centers for Disease Control and Prevention/Janice Carr

Drinking water disinfectants such as free chlorine penetrate poorly into biofilms and *Legionella* bacteria are further shielded within the amoebae they parasitise.⁸ Free chlorine levels in municipal drinking water are generally sufficient to neutralise free floating coliform bacteria but are often too low to kill *Legionella* bacteria living in biofilm. In addition, many drinking water disinfectants such as free chlorine do not reach distal sites in a water distribution system, can dissipate quickly in heated water, are often sequestered by biofilm, sludge and scale and are often removed during water filtering such as occurs in spa pools. Biofilm and sludge play an important role in protecting *Legionella* from the effects of thermal and chemical disinfection.

1.3 Recognised and potential sources of *Legionella* infection

The following are all sources or potential sources of *Legionella* bacteria:

- Water systems incorporating a cooling tower
- Water systems incorporating an evaporative condenser
- Hot and cold water systems
- Spa pools
- Natural thermal springs and their distribution systems
- Respiratory and other therapy equipment
- Humidifiers
- Dental chair unit waterlines
- Fountains/sprinklers
- Water-cooled machine tools
- Vehicle washes
- Potting compost/soil in warmer climates
- Other plants and systems containing water which is likely to exceed 20°C, or have an electrical component that can transfer heat and cause localised heating, and which may release a spray or aerosol (i.e. a spray of droplets and/or droplet nuclei) during operation or when being maintained.

1.4 Methods of transmission

Legionellosis is usually acquired through the respiratory tract, by inhalation of aerosols contaminated with *Legionella* bacteria. Aspiration of water contaminated with *Legionella* has also been described as a route of transmission. This may occur predominantly in persons with swallowing disorders or in conjunction with nasogastric feeding.⁹ There is no evidence of person-to-person transmission.

1.5 Risk of infection

The infectious dose for *Legionella* bacteria in humans is unknown. Those at higher risk for legionnaires' disease include:

- People over 40 years of age³
- Males
- Smokers
- Those with excessive alcohol intake
- Immunocompromised organ transplant patients, patients with HIV/AIDS, and those receiving systemic steroids
- Patients with chronic underlying disease such as diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease and chronic liver failure.

The incubation period is usually between 2 and 10 days although longer periods have been reported.¹⁰ The risk of acquiring *Legionella* infection is principally related to the individual susceptibility of the subject exposed and the degree of intensity of exposure, represented by the quantity of *Legionella* present and the length of exposure. Attack rates during outbreaks of legionnaires' disease are low – less than 5%.¹ When a susceptible person inhales a contaminated aerosol consisting of droplets of the right size (1-5 micron), he or she can develop the disease.¹¹

1.6 Treatment

Current recommendations for empirical antimicrobial therapy of community-acquired pneumonia include agents which provide cover for *Legionella* infection.¹²⁻¹⁴ These recommendations incorporate evidence which increasingly favours combination empirical therapy for severe community-acquired pneumonia.

The inclusion of empirical cover for *Legionella* infection should also be considered in cases of nosocomial pneumonia, especially in severe cases and where there is a suspected risk of exposure to *Legionella* bacteria. Once the aetiology has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that specific pathogen.

The preferred antimicrobial treatment of legionnaires' disease should be guided by the severity of the disease, degree of immunocompromise, and the availability and potential toxicity of individual drugs.⁴ A detailed review by Diederer of current treatment options was published in January 2008.¹⁵ This review emphasises that retrospective, adequate size clinical trials of antimicrobial therapy for legionnaires' disease have not yet been published. Three observational studies suggesting the possible superiority of levofloxacin therapy over therapy with macrolides are cited with the recommendation that these should be interpreted with caution.¹⁶⁻¹⁸ In vitro data suggest that newer macrolides (azithromycin and clarithromycin) and many fluoroquinolone agents show the best activity against *Legionella* species. Newer macrolides and levofloxacin are licenced by the US Food and Drug Administration for the treatment of legionnaires' disease and are considered preferable to erythromycin. The duration of therapy has to be decided on an individual basis but two to three weeks of therapy is generally recommended.

The British Thoracic Society (BTS) guidelines recommend clarithromycin ± rifampicin as the treatment of choice for legionnaires' disease with a fluoroquinolone as an alternative.^{12;13} However, there is debate as to whether rifampicin provides additional benefit to patients with legionnaires' disease^{19;20} and some authors suggest that co-administration of rifampicin is of questionable benefit and do not recommend it.²¹

The BTS are currently reviewing their guidelines on the management of community-acquired pneumonia in adults. The consultation process has now closed and it is expected that the guidelines will be available later this year at www.brit-thoracic.org.uk/.

The Infectious Disease Society of America (IDSA) in their 2003 guidelines recommends azithromycin or a fluoroquinolone (e.g. moxifloxacin or levofloxacin) as the preferred treatment for legionnaires' disease patients who are hospitalised. Erythromycin, azithromycin, clarithromycin, doxycycline, or a fluoroquinolone can be used for patients who do not require hospitalisation.²² The more recent IDSA/ATS (American Thoracic Society) consensus guidelines on the management of community-acquired pneumonia in adults recommend a fluoroquinolone or azithromycin as the preferred antimicrobials with doxycycline as an alternative for treatment of pneumonia caused by *Legionella* species.¹⁴ However, clarithromycin is the recommended macrolide in Ireland and the UK as intravenous azithromycin is currently not licenced in the UK or Ireland.

1.7 Definitions

Legionellosis is a statutorily notifiable disease in Ireland as defined by the Infectious Disease Regulations 1981 (S.I. No. 390 of 1981). Under the Infectious Diseases (Amendment) (No. 3) Regulations 2003 (S.I. No. 707 of 2003), which came into effect on 1 January 2004, laboratory and clinical notification of legionellosis is mandatory. Cases should be notified to the medical officer of health (MOH) in the relevant department of public health.

Clinical criteria

Any person with pneumonia

Laboratory criteria

Laboratory criteria for case confirmation

At least one of the following three:

- Isolation of any *Legionella* spp. from respiratory secretions or any normally sterile site
- Detection of *Legionella pneumophila* antigen in urine*
- *Legionella pneumophila* serogroup 1-specific antibody response

Laboratory criteria for a probable case

At least one of the following four:

- Detection of *Legionella pneumophila* antigen in respiratory secretions or lung tissue e.g. by direct fluorescent antibody (DFA) staining using monoclonal-antibody derived reagents
- Detection of *Legionella* spp. nucleic acid in a clinical specimen
- *Legionella pneumophila* non-serogroup 1 or other *Legionella* spp.-specific antibody response
- *L. Pneumophila* serogroup 1, other serogroups or other *Legionella* species: single high titre in specific serum antibody†

Epidemiological criteria

At least one of the following two epidemiological links:

- Environmental exposure
- Exposure to the same common source

Case classification

- a. *Possible case* – NA
- b. *Probable case*
Any person meeting the clinical criteria **and** at least one positive laboratory test for a probable case **or** an epidemiological link
- c. *Confirmed case*
Any person meeting the clinical and the laboratory criteria for case confirmation.

Source: European Commission Case Definitions for Communicable Diseases²³

*Currently available commercial urinary antigen tests only detect *L. pneumophila* serogroup 1

†In the UK, Health Protection Agency use a single titre of 1:128 or 1:64 in an outbreak

Nosocomial (healthcare-acquired) case

Laboratory-confirmed case of legionnaires' disease that occurs in a patient who was in a hospital or other healthcare institution during the 10 days before onset of symptoms.

The following sub-divisions are used for classifying nosocomial cases of legionellosis:

Definitely nosocomial

Patients who spent all of the ten days in a hospital or other healthcare institution before onset of symptoms.

Probably nosocomial

Patients who spent between one and nine of the ten days in a hospital or other healthcare institution prior to onset of symptoms and either:

- Became ill in a hospital or other healthcare institution associated with one or more cases of legionnaires' disease **or**
- Yielded an isolate that was indistinguishable by monoclonal antibody (mAb) subgrouping, or by molecular typing methods from isolates obtained from the hospital water system at about the same time.

Possibly nosocomial

Patients who spent between one and nine of the ten days prior to onset of symptoms, in a hospital or other healthcare institution not known to be associated with any other cases of legionnaires' disease and where no microbiological link has been established between the infection and the hospital.

Source: UK Health Protection Agency Legionella case definitions²⁴

Travel-associated cases*Single travel-associated case*

A case of travel-associated legionnaires' disease is defined as a case who, in the ten days before onset of illness, stayed at or visited an accommodation site that had not been associated with any other cases of legionnaires' disease, **or**

A case who stayed at an accommodation site linked to other cases of legionnaires' disease which had occurred **more than two years previously**.

Travel-associated cases may involve travel within Ireland or travel abroad.

*Cluster of travel-associated cases**

A cluster is defined as two or more cases of legionnaires' disease who stayed at or visited the same accommodation site in the ten days before onset of illness and whose onset is within the same two-year period.

If any further cases associated with the cluster site occur more than two years after the last case, they will be reported as new single cases, although the country of infection will receive information on all previous cases regardless of the time period involved.

Source: European Working Group on Legionella Infection guidelines²⁵

*A cluster is not the same as an outbreak. It is a EWGLINET definition and refers to two or more cases in a single accommodation site within a specified period

A case must meet the clinical, microbiological and travel history criteria for it to be notified to the European Working Group on Legionella Infection (EWGLI) surveillance scheme for travel-associated legionnaires' disease (EWGLINET) (Appendix A).

Outbreak.

An outbreak is defined as two or more cases associated with the same geographical location or probable source of infection during the preceding six months.

Pontiac fever

A self-limiting influenza-like illness characterised by fever, headache, myalgia and non-productive cough. Patients recover spontaneously without therapy after two to five days. There is no evidence of pneumonia.

1.8 Epidemiology

Studies have estimated that legionnaires' disease accounts for between 0.5% to 10% of community-acquired pneumonia requiring hospitalisation in adults.⁴ In a review of nine studies of community-acquired pneumonia in which admission to intensive care was required, *L. pneumophila* was second only to *Streptococcus pneumoniae* as the aetiological agent most frequently identified.²⁶ Mortality from severe legionnaires' disease in these nine studies ranged from 0-25%. Overall, *Legionella* is probably the second to fourth most common cause of community-acquired pneumonia.

The proportion of hospital-acquired pneumonia due to legionnaires' disease has been reported as ranging from 0-47%.²⁷ Numerous species and serogroups of *Legionella* can be present in hospital water systems. It has been shown when an active search for *Legionella* infection is initiated, cases are frequently confirmed.^{27;28} Although *L. pneumophila* serogroup 1 accounts for the majority of cases, other serogroups have also been associated with infection in healthcare settings.^{28;29} This has important clinical implications as the most widely used test for diagnosing legionnaires' disease is the urinary antigen test and this test is specific for *L. pneumophila* serogroup 1 only.

Legionnaires' disease is thought to be rare in children. A review of the medical literature published in 2006, identified 76 cases of *Legionella* infection in children, 78% of whom had an underlying condition such as malignancy.³⁰ More recently, a large outbreak has been reported in a neonatal unit of a private hospital in Cyprus. Eleven cases were reported and three deaths.³¹

1.8.1 Legionnaires' disease in Ireland

The number of cases of legionnaires' disease notified to the Department of Health and Children (DoHC) and the Health Protection Surveillance Centre (HPSC) from 1994 to 2007 is shown in Table 1. HPSC took over responsibility for the collation of infectious diseases notifications on 1 July 2000.

Table 1. Number of legionnaires' disease cases per million population notified in Ireland, 1994-2007

Year	Number of cases	Crude rate per million population
1994	1	0.3
1995	1	0.3
1996	2	0.6
1997	6	1.7
1998	2	0.6
1999	2	0.6
2000	9	2.3
2001	3	0.8
2002	6	1.5
2003	7	1.8
2004	4	1.0
2005	9	2.3
2006	13	3.1
2007	16	3.8

1996 population: 3,626,087 – (1994-1999)

2002 population: 3,917,203 – (2000-2003)

2006 population: 4,239,848 – (2004-2007)

There were 67 cases of legionnaires' disease reported in Ireland during the period 2000 to 2007. There were six deaths due to legionnaires' disease during this period, giving a case fatality rate (CFR) of 9.0%. Forty-five cases (67.2%) were male, and 22 (32.8%) were female. Forty-one cases (61.2%) were travel-associated; three of these were associated with travel within Ireland. Twenty-one (31.3%) were community-acquired, and five (7.5%) were nosocomial.

Fifty-nine cases (88.1%) were classified as confirmed and eight (11.9%) as probable. *L. pneumophila* serogroup 1 was responsible for 82.1% of cases, *L. pneumophila* serogroup unknown (3.0%), and *Legionella* species unknown (14.9%).

The median age was 48 years, with a range from 18 to 80 years. The median age for females was 45 years and 49 years for males. The cumulative number of cases in each age group is shown in Figure 3.

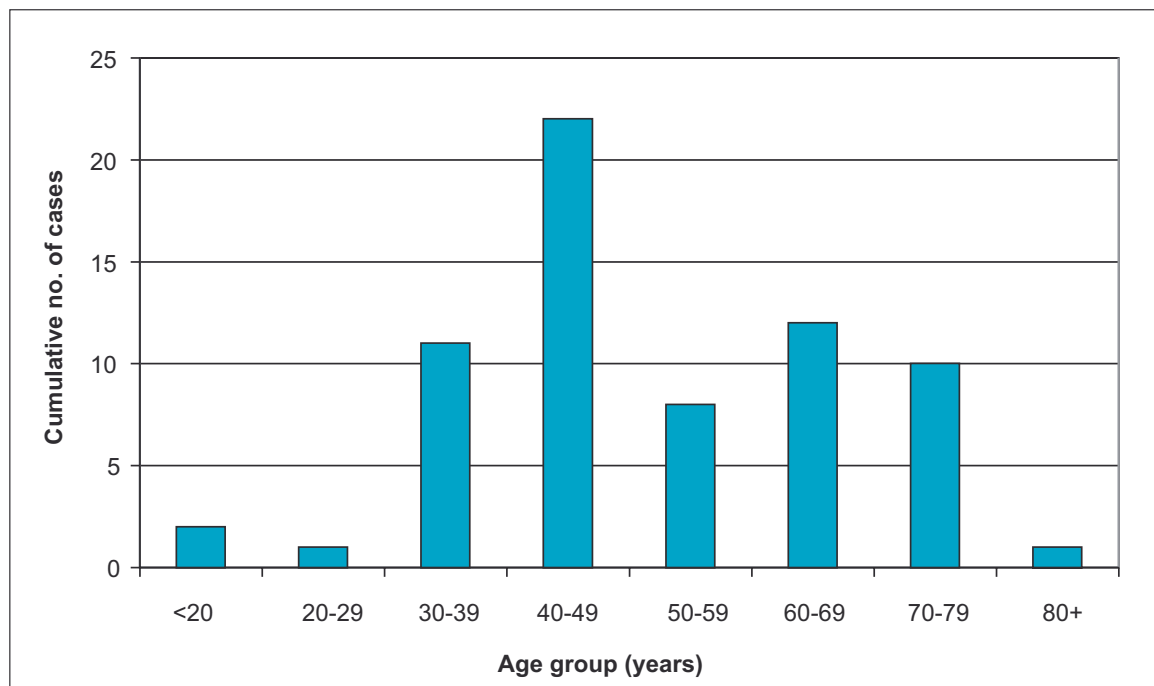


Figure 3. Cumulative number of cases of legionnaires' disease in each age group, 2000 to 2007

The peak month of notification was September (Figure 4). The main method of diagnosis was urinary antigen in fifty cases (74.6%), serology in fifteen (22.4%), culture in one case (1.5%), and the method was unspecified in one case (1.5%).

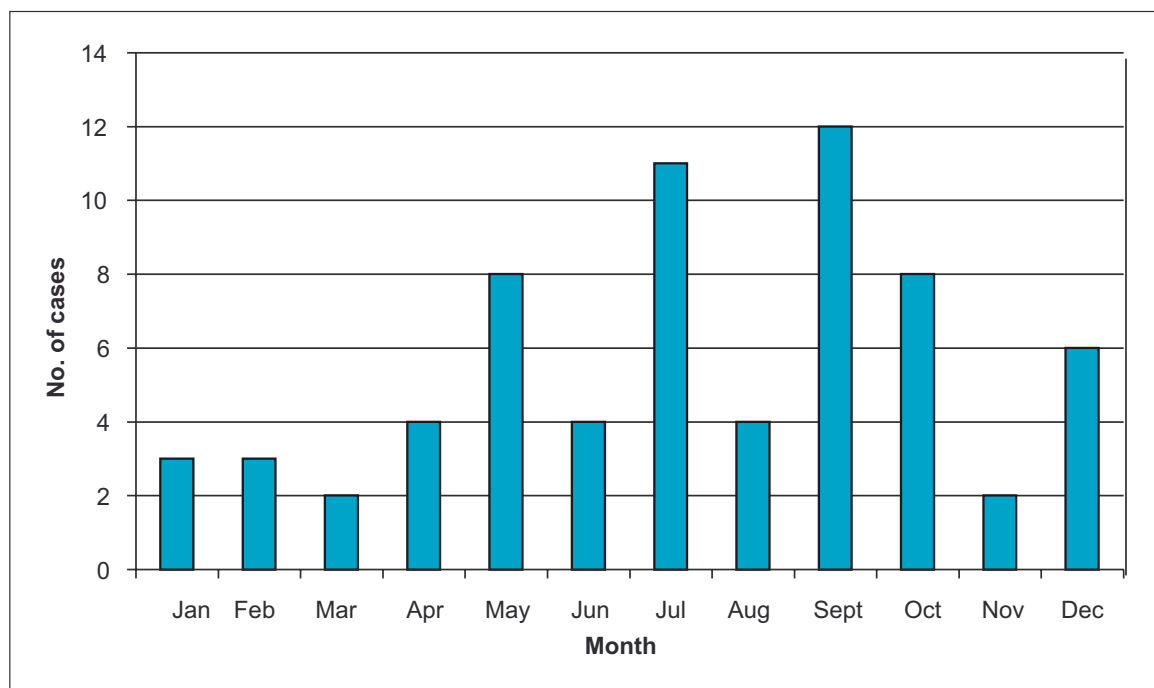


Figure 4. Cumulative number of cases by month, 2000 to 2007

1.8.2 Legionnaires' disease in Europe

Legionnaires' disease is a statutorily notifiable disease in many but not all European countries. In 2007, the overall European rate of infection was 11.4 cases per million population (based on a population of 520.3 million in 33 countries).³² Table 2 shows the incidence rate in various European countries in 2007.

Table 2. Number of legionnaires' disease cases and rate per million population in various European countries in 2007

Country	Number of cases	Rate per million population
Spain	1,098	24.8
France	1,428	22.8
Denmark	133	24.4
Netherlands	321	19.6
Sweden	130	14.2
Scotland	43	8.4
England & Wales	441	8.2
Northern Ireland	11	6.3
Ireland	16	3.8
Poland	13	0.3
Norway	35	7.5

There were 391 deaths associated with legionnaires' disease in Europe in 2007, a CFR of 6.6%. The majority of cases were male (71.6%). The number of cases in each age group in Europe is shown in Figure 5.

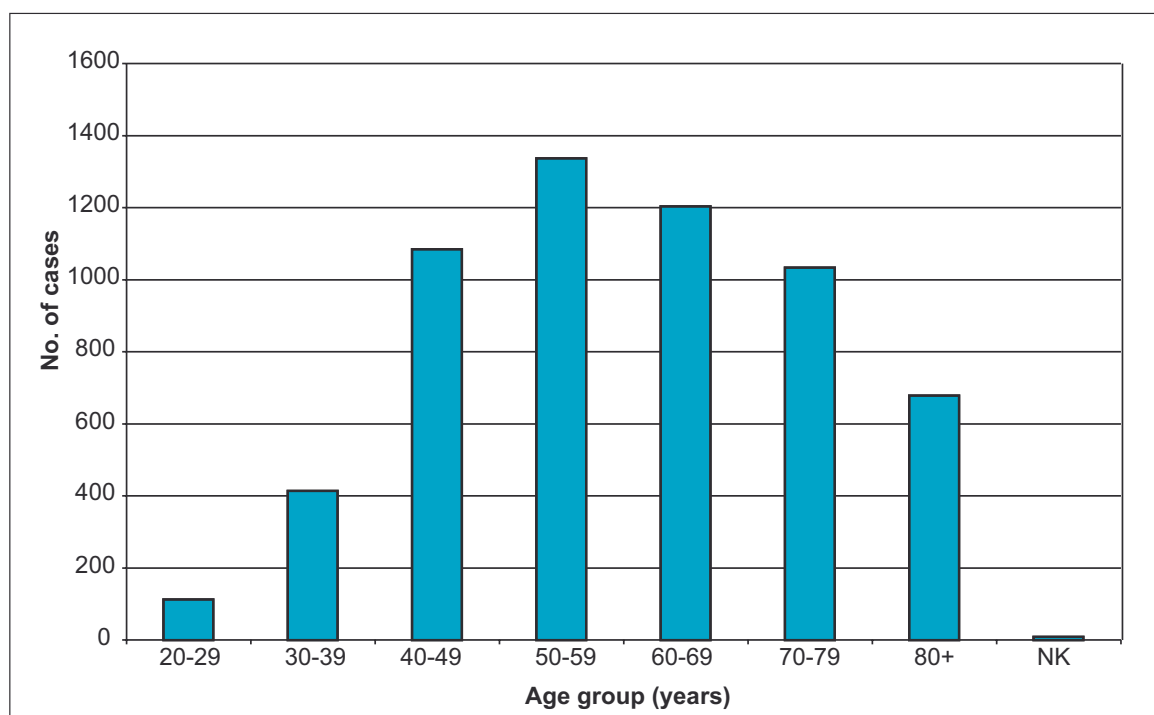


Figure 5. The number of legionnaires' disease cases in each age group in Europe, 2007

The majority of cases were community-acquired (62.1%), 21.7% were travel-associated, 5.6% were nosocomial, 0.9% other, and 9.6% unspecified. The cases were classified as confirmed in 89.8% of cases, 8.9% were presumptive and 1.3% were unknown. The main method of diagnosis was by urinary antigen (80.6%), culture (8.7%), serology (7.1%), PCR (2.2%), other (0.2%), unknown (1.2%).

1.8.3 Under-diagnosis and under-reporting

Under-diagnosis and under-reporting are thought to lead to a significant under-estimation of incidence of legionnaires' disease in many countries. The causes include:

- Pneumonia being treated with antibiotics which cover *Legionella* and patients recovering without the need to establish the cause of pneumonia
- Lack of sensitivity and specificity of diagnostic methods e.g. serology
- Cases not being notified.

Denmark has consistently had a higher rate of infection (around 20/million population) than most other countries. The factors probably associated with this are that it is a small country which carries out high levels of testing for *Legionella* in patients with pneumonia and it has a centralised reference laboratory for diagnosing and reporting cases. In recent years, EWGLI has adopted the rate of 20/million population as the 'gold standard' for countries to reach in order to reflect a truer incidence of infection.

The reported incidence of legionnaires' disease in Ireland has increased from 0.3/million population in 1994 to 3.8/million in 2007. However, the rate is still low compared with many European countries and the rate falls well short of the 'gold standard' as set by EWGLI. This could suggest that a major degree of under-diagnosis and under-reporting currently exists in Ireland or that the rate in Ireland may actually be lower than in some European countries. It is critical to the control of legionnaires' disease that enhanced surveillance is maintained at a high level. Significantly, it has been reported that delay of appropriate therapy results in poor outcome.³³ A rapid urine antigen test is available in Ireland. Consideration should be given for the more widespread use of this test when a patient presents with pneumonia. The importance of specimens for culture should also be considered.