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Review article

Legionellosis in the occupational setting

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ABSTRACT

Legionellosis is the common name for two infections, Legionnaires' disease (LD) and Pontiac fever (PF), both caused by *Legionella* bacteria. Although with low incidence, LD is an important cause of community- and hospital-acquired pneumonia. Among community-acquired cases, an increasing number was reported to be linked to the occupational setting, posing the need for better recognition of work activities at risk of legionellosis. In this work, we selected and reviewed relevant literature on cases of occupational legionellosis published between 1978 and 2016 in order to define the: *i*) etiology; *ii*) sources of infection, *iii*) work activities at risk, *iv*) infection rates, *v*) predisposing factors, *vi*) mortality and *vii*) country distribution. To our knowledge, this is the first review to provide an analysis of cases of occupational legionellosis.

A literature search in the PubMed website was started on January 31, 2015 and ended on June 30, 2016. Cases of occupational legionellosis documented in the scientific literature were retrieved from PubMed upon interrogation with the following keywords: "*Legionella pneumophila*", "Legionnaires' disease", "Pontiac fever", and "legionellosis", in combination with "employees", "workers", and "occupational". Abstracts were reviewed, and applicable articles were obtained. Only articles that met the inclusion criteria were considered.

Forty-seven articles were selected, reporting confirmed cases of legionellosis which occurred over 66 years (1949–2015), and involved 805 workers (221, LD; 584, PF). Fatalities were all associated with LD, resulting in 4.1% mortality. The most common etiologic agents were *Legionella pneumophila* (58.5%) and *Legionella feeleii* (39.4%), the latter being responsible for only one large outbreak of PF. Workplaces more frequently associated with occupational legionellosis were industrial settings (62.0%), office buildings (27.3%) and healthcare facilities (6.3%), though cases were also reported from a variety of workplaces, e.g. artesian excavation and horticultural sites, lorry parks, ships, water and sewage plants.

With few exceptions, cases occurred in industrialized countries of the northern hemisphere. Overall, our review highlights an extended spectrum of occupational categories at risk for legionellosis. For all categories, infection originated from exposure to work-generated aerosols contaminated with *Legionella* spp., and industrial facilities equipped with cooling towers or coolant systems were the most common occupational settings. These observations should raise awareness of the risk of acquiring legionellosis at work, and help to improve prevention and control measures for this infrequent but still problematic disease.

1. Introduction

Legionellosis is the common name for the infections Pontiac fever (PF) and Legionnaires' disease (LD), both caused by bacteria belonging to genus *Legionella*. The PF is a self-limited flu-like illness whose name recalls the town (Pontiac, Michigan, USA) where an unprecedented outbreak occurred in the Country Health Department building (Glick et al., 1978). Unlike LD, which can be a severe and deadly form of pneumonia, PF is never lethal. The LD was first recognized during an outbreak of pneumonia involving delegates to the 1976 American

Abbreviations: AFLP, Amplified Fragment Length Polymorphism; AP-PCR, Arbitrarily Primed PCR; CDC, Centers for Disease Control and Prevention; ECDC, European Centre for Disease Prevention and Control; ELDSNet, European Legionnaires' Disease Surveillance Network; ESGLI, European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for *Legionella* Infections; EU, European Union; EU-OSHA, European Agency for Safety and Health at Work; EWGLI, European Working Group for *Legionella* Infection; HACCP, Hazard-Analysis and Critical Control Points; ILO, International Labour Office; LD, Legionnaires' Disease; MLST, Multi Locus Sequence Typing; MLVA, Multi Locus Variable Number of Tandem Repeats; PF, Pontiac Fever; PFGE, Pulsed-Field Gel Electrophoresis; OSHA, Occupational Safety and Health Administration; PPE, Personal protective equipment; REA, Restriction Endonuclease Analysis; RFLP, Restriction Fragment Length Polymorphism; WHO, World Health Organization

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Legion convention at a Philadelphia hotel (McDade et al., 1979).

Legionellosis is acquired from the inhalation of aerosols containing *Legionella* bacteria. The family of *Legionellaceae* consists of the single genus *Legionella*, which currently includes more than 57 known species (see http://www.bacterio.net). *Legionella pneumophila* is the most common among pathogenic *Legionella* species and includes 15 serogroups, though the majority of human disease (84% worldwide, 95% in Europe) is caused by *L. pneumophila* serogroup 1 (sg. 1) (Harrison et al., 2007). In addition to *L. pneumophila*, at least 27 *Legionella* species have been documented as human pathogens on the basis of their isolation from clinical samples of sick patients (Pearce et al., 2012). While *L. pneumophila* can infect otherwise healthy individuals, the majority of confirmed infections involving non-*Legionella pneumophila* species occurred in immunosuppressed or otherwise predisposed patients (Diederen, 2008; Knirsch et al., 2000; Muder and Yu, 2002; Parry et al., 1985). Notably, legionellosis caused by these species is probably under-reported due to the difficulty in their identification and the absence of simple serodiagnostic reagents for most of them (Fields et al., 2002; Vaccaro et al., 2016).

Legionella spp. are ubiquitous, but limited information is available on the geographic distribution of non-*L. pneumophila* species. The only exceptions are Australia and New Zealand, where *L. pneumophila* accounts for only 50% of the cases, while *L. longbeachae* accounts for 30% and even up to 50% of cases in South Australia (Yu et al., 2002). In New Zealand, the Ministry of Health reported that, in 2011, *L. longbeachae* was responsible for more cases than *L. pneumophila,* with 42% (67 cases) and 30% (49 cases) of laboratory reported cases of infection, respectively (Currie et al., 2014; The Institute of Environmental Science and Research Ltd – New Zealand, 2012). In Europe, the incidence of *L. longbeachae* has historically been low (Currie et al., 2014; Lindsay et al., 2012). However, geographical variation in the incidence of legionellosis can be biased by differences in case definitions, diagnostic methods, surveillance systems, and data presentation among countries (Bhopal, 1993). This variation could be reduced if EU case definition for LD was widely applied (http://ecdc.europa.eu/en/healthtopics/legionnaires_disease/surveillance/Pages/EU-case-definition.aspx). Irrespective of the causative species, legionellosis is worldwide distributed, whereas most cases have so far been reported from the industrialized countries (Ambrose et al., 2014; Castor et al., 2005; Den Boer et al., 2002; Fields et al., 2002; Gilmour et al., 2007; Mitchell et al., 1990).

Legionella spp. and strains colonize soils and water supplies throughout the world. Indeed, legionellae can be found in natural aquatic environments (streams, rivers, ponds, lakes, and thermal pools), as well as in moist soils and mud, although in the environment the concentration is low (Diederen, 2008; Fields et al., 2002; Steinert et al., 2002). The early discover that *L. pneumophila* is ubiquitous in aquatic environments and exists as an intracellular parasite of amoebae has provided a link between bacterial ecology and human disease (Rowbotham, 1980). Notably, the virulence of *Legionella* may be increased by replication in amoebae (Cirillo et al., 1994). Inside amoebae, legionellae are able to survive in moist environments for long periods of time, withstanding temperatures of 0–68 °C and a pH range of 5.0–8.5, and they are also protected against chlorine disinfection, commonly used in urban water systems (Berjeaud et al., 2016). The presence of encrusted deposits and biofilms can offer nutrients for algal and fungal biomasses and have been shown to support the growth of *L. pneumophila* (Muraca et al., 1988).

Modern urban environment provides a wide diversity of sites for *Legionella* to colonize and, should environmental conditions suit, to multiply until high bacterial concentrations are reached (Fields et al., 2002). Multiplication in water systems is facilitated if nutrients are available, temperature is appropriate, and the water system is shutdown, occasionally used, poorly maintained or the pipework contains "dead-legs" (i.e. without outlets). Thus, contact between humans and *Legionella* in both natural and urban environments is certainly common (Berjeaud et al., 2016; Diederen, 2008; Fields et al., 2002).

The LD accounts for 2%–15% of community-acquired pneumonia (Seenivasan et al., 2005). Legionellosis can present as a sporadic or epidemic form. Some people have lower resistance to infection and are more likely to develop legionellosis (Farnham et al., 2014; Ginevra et al., 2009). Well known risk factors are organ transplants (kidney, heart, etc.), age (> 50; older persons are more predisposed), heavy smoking, heavy consumption of alcoholic beverages, underlying medical problem (respiratory disease, diabetes, cancer, renal dialysis, etc.), weakened immune system (immunosuppressive therapies, e.g., corticosteroids) (Farnham et al., 2014; Ginevra et al., 2009). The link between legionellosis and HIV infection is controversial since LD has infrequently been described in patients infected with HIV (Sandkovsky et al., 2008). Nevertheless, some studies suggest that pneumonia caused by *Legionella* tends to present with more severe clinical features and complications in the HIV-infected population (Robbins et al., 2012; Sandkovsky et al., 2008). Interestingly, a genetically-determined susceptibility of humans to LD was also described (Hawn et al., 2003; Hilbi et al., 2010).

Despite its low incidence, LD is a relevant cause of community- and hospital-acquired pneumonia (Seenivasan et al., 2005). Among community-acquired legionellosis, an increasing fraction of cases linked to the work environment has been reported (Ambrose et al., 2014; Castor et al., 2005; Den Boer et al., 2002; Gilmour et al., 2007; Mitchell et al., 1990). It is generally accepted that there is a foreseeable risk of exposure to *Legionella* bacteria in any undertaking involving a work activity, trade or business where water is used or stored and where there is a mean of creating and transmitting water droplets/mists which can be inhaled. The majority of occupational legionellosis cases occur sporadically, and the transmission mechanism is difficult to identify. Inter-human transmission, although statistically very unlikely, has recently been described (Borges et al., 2016; Correia et al., 2016). In every occupational setting investigated so far, an aerosol-producing device has invariably been implicated in the transmission of *Legionella* to susceptible workers (Ambrose et al., 2014; Castor et al., 2005; Den Boer et al., 2002; Gilmour et al., 2007; Mitchell et al., 1990).

The role of *Legionella*-contaminated distribution systems for potable water as a source of occupational legionellosis has been well established in many workplace investigations (Castellani Pastoris et al., 1987; Castor et al., 2005; Chikte et al., 2011; Colville et al., 1993; Israeli et al., 1985; Muraca et al., 1988; Oggioni et al., 2016; Stout and Yu, 1997; Vanaclocha et al., 2012). Cases of LD have been traced to a wide variety of man-made poorly maintained water sources, including cooling towers and coolant systems (i.e., systems to remove excess heat using heat exchange with water), evaporative condensers, whirlpool and spas, fountains, ice machines, and vegetable misters (Berjeaud et al., 2016; CDR Wkly, 1992; Conwill et al., 1982; Den Boer et al., 2002; Diederen, 2008; Fields et al., 2002; Herwaldt et al., 1984). Improved characterization of the environmental exposures that increase the risk of transmission of legionellosis may provide a rational basis for targeting prevention efforts, and may also help to determine the source of infection. In fact, tracing *Legionella* infections to an environmental source is a primary goal in the epidemiological investigation. The main reason for genotyping *L. pneumophila* is to help identifying environmental reservoirs giving rise to cases of LD, thus allowing control measures to be implemented in order to prevent further cases. Different methods such as ribotyping, restriction fragment length polymorphism (RFLP) analysis, restriction endonuclease analysis (REA), arbitrarily primed PCR (AP-PCR), amplified fragment length polymorphism (AFLP) analysis, pulsed-field gel electrophoresis (PFGE), multi locus sequence typing (MLST), and multi locus variable number of tandem repeats analysis (MLVA) have been developed during time (reviewed by Mercante and Winchell, 2015). More recently, a scheme for the sequence-based typing (SBT) of *L. pneumophila* that uses the sequences of seven genes has been described (Farhat et al., 2011; Mentasti et al., 2014;