Legionnaires' disease in the Netherlands, 1998-2006

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CHAPTER ONE

General introduction

HISTORICAL BACKGROUND

Legionnaires' disease (LD) is an airborne infectious disease named after a point-source outbreak of pneumonia among members of the American Legion. Between 21 and 24 July, 1976, this organisation of military veterans held a convention in the The Bellevue Stratford hotel in Philadelphia. In the two week following the convention, 149 attendees developed pneumonia. Furthermore, 72 visitors and bypassers of the convention hotel attracted LD. Of the 221 LD patients who were part of the outbreak, 34 (15%) died. Five months later, a gram-negative bacillus was shown to be the causative agent and named Legionella pneumophila. The same bacterium was later associated with Pontiac Fever (PF), a flu-like self-limiting illness named after an airborne infectious disease outbreak in 1968 involving 144 persons in a health department facility in Pontiac, Michigan. Pontiac Fever and LD are the only known clinical syndromes associated with Legionella bacteria and are collectively named legionellosis.

CLINICAL FEATURES AND DIAGNOSIS

LD patients initially present with cough, fever and nonspecific symptoms including malaise, myalgia, anorexia and headache, which are later followed by various stages of dyspnoe. Some patients develop shaking chills, chest pain, diarrhea, delirium or other neurologic symptoms. Extrapulmonary involvement is rare. Clinical presentation, physical examination, and radiographic findings do not differ from pneumonias caused by other micro-organisms. Although minor biochemical differences may exist, diagnosis of LD is therefore almost exclusively based on microbiology findings. Early diagnosis enables appropriate antimicrobial treatment early in the course of disease which is potentially life-saving.

THERAPY

Evaluation of treatment with different antibiotics in the initial outbreak showed beneficial effects for erythromycin. Since then, no clinical trials evaluating LD therapy have been published, but in vitro data and animal models suggest that newer macrolides and fluoroquinolones are superior to erythromycin. In the Netherlands, the Dutch thoracic society has issued guidelines accordingly.
MICROBIOLOGY

Description of the pathogen

*Legionella* is an intracellular parasite of protozoa. So far, 17 different hosts have been described, [14] of which *Hartmanella vermiformis* is the most frequently observed. [15] The resemblance of human alveolar macrophages to these protozoa is striking and has become a key issue in the understanding of the pathogenesis of *LD*. Cellular microbiology research has revealed that the focal point of infection by *Legionella* is the alveolar macrophage. [16]

Culture, serotyping and genotyping

*Legionella* must be grown on specific media and is tolerable to acid and chloride. [17] It can survive temperatures between 0 and 63°C and grows between 20 and 45°C with an optimum of 37°C. [18,19] The family of *Legionellaceae* [20] consists of 50 species and 70 serogroups. Nineteen species have been documented as human pathogen. [14] Worldwide, more than 90% of *LD* is caused by the species *Legionella pneumophila*, of which 92% is caused by *L. pneumophila* serogroup 1. [21] Molecular microbiology methods are used to further differentiate beyond the serogroup level. These techniques can be supportive to identify a source of infection, several of which have been used in outbreaks in the Netherlands. [22–27] In recent years the recommended DNA fingerprinting techniques of the European Working Group for *Legionella* Infections (EWGLI) [28–31] have been introduced in the Netherlands. [32–34] Since 2004, the genomic sequence of the original 1976 *Legionella pneumophila* isolate is known. [35]

EPIDEMIOLOGY

Case definition

According to the source of infection *LD* is commonly classified as community-acquired, nosocomial, or travel-related. Also a person-based classification can be used which differentiates single patients (sporadic cases), clusters (geographic or serial), and outbreaks. Furthermore, EWGLI differentiates between confirmed and probable *LD* patients on the basis of diagnostic criteria. [36]

Incidence

In the Netherlands, *LD* became a notifiable disease on June 4th, 1987, eleven years after the first Dutch *LD* patient had been diagnosed. [37] For the 1987–1999 period the mean yearly incidence in the Netherlands was 2.7 per million for an average of 42 notified *LD* patients per year. Half of these patients suffered from confirmed *LD* and half from probable *LD*. [38] The mean incidence in the 1987–1999 period was 50% lower than that of Europe and the US. [39,40]
Several small outbreaks were described during that period, three of which were associated with travel abroad, [41–43] four were hospital associated [24,26,44,45] and two were community-acquired. [25,46] In 1999, a large outbreak involving 188 patients (this thesis, chapter two) [27] marked a sharp rise in notified LD incidence to 11 per million, excluding the outbreak patients. [38] The incidence has continued to rise to 26 per million in 2006, excluding 30 patients who were part of a cooling-tower outbreak in that year. [34]

Geographic distribution
LD incidence differs between countries in Europe [47], but also within countries. [48] In the Netherlands, a fivefold difference in LD incidence was observed using province as geographic entity. [38] In this thesis, in chapter four, geographic differences are further explored at the municipal level.

Temporal influence
Seasonality has been reported for LD, with peaks in spring and autumn. [49] Since prospective incidence studies did not confirm this pattern, [50] the peaks could also be attributed to ascertainment bias or to unnoticed cooling tower outbreaks. [51] Humidity seems to play a role in increased endemic situations. [52,53]

Risk factors
Although most environmental *Legionella* strains are not pathogenic they can infect humans with an impaired immune system, [54] as is seen in nosocomial LD. For community-acquired LD, smoking is the strongest host-related risk factor for sporadic [55] as well as outbreak-related patients. [1]

TRANSMISSION

Reservoir
The natural habitat for *Legionella* is surface water of lakes, rivers as well as thermally polluted water. [56] In these aquatic environments *Legionella* bacteria live as parasites in protozoa. [57] The same observation was made in manmade water systems where biofilm provided a favorable environment sometimes leading to high concentrations of *Legionella*. [58,59]

Route
The transmission route from these habitats to the human lung has predominantly been postulated to result from inhalation of infected aerosols. Also, drinking of contaminated water and subsequent aspiration has been described as a route of transmission. [33,60,61]
While the exact mechanism of transmission remains unsolved, several facilities and water systems are associated with LD outbreaks: hospitals, [62] cooling towers, [63–65] saunas, [65] and whirlpool spas. [66] Numerous serosurveys have demonstrated high prevalences of antibody titers against *Legionella* suggesting that humans are regularly exposed to the bacterium without developing pneumonia. [67,68]

**Aerosols**

It is rather *Legionella* bacteria than aerosols which are inhaled in the pathogenesis of LD. Aerosols that find their origin in the aquatic environment vary in size between 12–2000 μm. Those measuring 10 μm can float and spread over larger distances. However at 65% air humidity these aerosols are evaporated in milliseconds to seconds. At 100% air humidity they evaporate within 100 seconds. The role of aerosols therefore seems to be *Legionella*’s escape from the aquatic environment.

**Virulence**

Soon after its discovery it was demonstrated that *Legionella* lose their pathogenic capacity in artificial media. [69] Contrastingly, they become more virulent after passage in protozoa like amoebae. [70,71] In the interaction with protozoa, lack of nutrition for *Legionella* accelerates the development of virulent traits like mobility and penetration capacity. Subtyping of *L. pneumophila* using monoclonal antibodies (MAb) suggests higher virulence for strains reacting with MAb2 (international panel) or MAb3 (Dresden panel) since they are more often associated with outbreaks and less often with nosocomial LD. [72,73] Several outer membrane proteins have been associated with virulence, the macrophage infectivity potentiator (Mip) most convincingly as its absence lead to a 80-fold decrease in infectivity for human macrophages. [74]

**Infective dose**

Environmental research has shown high concentrations of *Legionella* in aerosol producing water systems and devices as well as in potable water worldwide without the occurrence of LD patients. [75–77] Indeed, the omnipresence of *Legionella* is in sharp contrast to its low incidence. This has been described as the “infective dose paradox”. [78] Low incidence suggests that the infective dose is very high. Indeed, extrapolation of animal research suggested a high infective dose of 14 million bacteria. At the same time microbiologic research suggests a low infective dose for three reasons. First, to reach the alveoli particles should be smaller than 1 μm, which is the size of a few hundred *Legionella* bacteria. [79] Second, LD patients who are part of cooling tower related outbreaks are infected a kilometer or more away from the source, [65,80,81] whereas a high concentration of airborne *Legionella* at such a distance seems highly unlikely. Third, exceptional routes of transmission have been described involving very low calculated numbers of bacteria. [33]
Host

With an intact host defence, inhaled Legionella are removed from the bronchial tree by mucociliary clearance and subsequently killed by gastric acid in the stomach. Cell-mediated immunity is the primary host defense against Legionella infection. \cite{82,83} Human monocytes and alveolar macrophages activated by lymphokines inhibit intracellular multiplication of Legionella. Innate and humoral immunity do not seem to play an important role. \cite{16}

CONTROL AND PREVENTION

Long term prevention

Removing dead legs and setting the water temperature above 60 degrees Celsius is a widely advised preventive measure. Few of the environmental Legionella strains that humans are exposed to on a daily basis are in fact capable of causing LD. With this knowledge, general preventive measures are not very effective. Three observations are ingredients for a potential successful prevention scheme. One is that outbreaks are often preceded by small clusters or solitary LD patients, \cite{86} the second that apparently sporadic LD patients are in fact clustered around the same source of infection \cite{87} and the third that time clusters of LD patients can span up to seventeen years. \cite{62}

Disinfection

Despite very promising results on residual disinfection of municipal drinking water with monochloramine \cite{88–90} there is little support for disinfection of potable water in the Netherlands. Although several emergency decontamination methods exist, in the Netherlands the “superheat and flush” method is the most widely used. \cite{84} For cooling towers decontamination in the Netherlands, chlorination has been used. \cite{85}

LEGISLATION ON LEGIONELLA

In the Netherlands, the Ministry of Housing, Spatial Planning and the Environment (VROM) is responsible for the quality of drinking water. After the 1999 outbreak, VROM issued a new Drinking Water Law aimed at reducing the level of Legionella contamination of drinking water. The Water Law is based on the precaution principle that use of water should lead to less than one death per one million person years. Despite extensive investments to arrive at the reduced contamination, over the last eight years the incidence of LD in the Netherlands has continued to rise.
OUTLINE OF THE THESIS

In part one the epidemiology of LD in the Netherlands is described. A large outbreak involving 188 patients and a prospective case-control study to identify risk factors are presented. Furthermore, geographic differences in LD incidence in the Netherlands are explored.

In part two the transmission of LD is elaborated on. A rare transmission route involving potting soil is shown to exist in the Netherlands and a prospective study comparing patient isolates as well as environmental Legionella strains indicates that current knowledge on transmission is still incomplete.

In part three the laboratory diagnosis of LD is explored and several diagnostic assays are discussed in detail.

In part four control and prevention of LD is discussed. The first results of a newly installed outbreak detection and prevention scheme in the Netherlands are described. Part four ends with a general discussion and conclusion.

INSTITUTES AT WHICH THE STUDIES WERE PERFORMED

The 1999 outbreak investigation was studied at the Epidemiology and Surveillance (epi) department of the National Institute of Public Health and the Environment (rivm) in Bilthoven. First, in 2000 and 2001 three national rivm reports (nrs. 213690006, 213690003 and 213690004) were published that preceded an international publication in 2002 that is presented in part 1 of this thesis. Most other studies were performed at the Municipal Health Service Kennemerland in Haarlem. This institute received several grants, among them three grants from the Haarlem Tuberculosis Foundation that helped realise the two other studies presented in part 1 of this thesis. Also, a four-year grant was provided by the Public Health Foundation (Fonds Oogz). This grant enabled the formation of a National Legionella Outbreak Detection Programme (BEL) which ran from 2002–2006 and has moved since to the Regional Public Health Laboratory (RPHL) Kennemerland where it has become part of the rivm. Data for the studies presented in parts 2 and 4 of this thesis were collected by BEL. The studies in part 3 of the thesis were performed at the RPHL Kennemerland in Haarlem.

REFERENCES


