Chapter 34
Leptospirosis and Leptospires—The Silent Assassins

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Abstract Leptospirosis is one of the most common yet under reported zoonoses. Leptospires, the etiological agents of leptospirosis are ubiquitous pathogens, with a world-wide distribution, causing a spectrum of disease ranging from a mild influenza-like illness to Weil's disease, which manifests itself in multi-organ failure. The following chapter reports on the epidemiology and transmission of the disease in humans and animals. The chapter will also delineate the symptoms observed in humans and animals and in concluding outline unresolved and evolving issues for microbiologists, epidemiologists and public health officials.

34.1 Introduction

Leptospires are 6–20 μm in length and 0.1–0.2 μm in diameter and have optimal growth at 30°C (Levett 2001). In the genus there are some 20 leptospiral species (nine pathogenic, six saprophytic/environmental and five intermediate species). Serologically there are more than 300 serovars and leptospirosis has been reported in over 150 mammalian species (Picardeau 2013; Ko et al. 2009). The main animal reservoirs include rodents, dogs, cattle, horses and pigs. These animals may act as maintenance hosts for adapted serovers such as serovar Canicola in dogs or serovars Ballum, Icterohaemorrhagiae or Copenhageni in rodents. Renal colonization and shedding of leptospires in the urine of infected animals sets the scene for the

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transmission of the organism to infect humans and other animals who are incidental hosts (Adler and de la Pena Moctezuma 2010; Faine et al. 1999).

34.2 Epidemiology in Animals

Epidemiological studies in animal populations, particularly in endemic regions have relied on the use of serosurveys. Roqueplo et al. (2013) conducted a cross sectional survey to estimate the prevalence of leptospiral antibodies in wild and domestic animals in New Caledonia. This study reported that 43 % of cattle, 72 % of Rusa deer, 80 % of horses, 43 % of dogs and 100 % of cats ($n=8$) had reactive leptospiral titres. Interestingly, members from the serogroups Icterohaemorrhagiae, Australis, Canicola, Ballum and Cynopteri appeared to circulate in the majority of hosts investigated.

Similarly, Desvars et al. (2013) conducted a serosurvey of 574 animals belonging to 12 species on Reunion Island and reported reactive leptospiral titres in approximately 80 % of rats, 34 % of cattle, 48 % of pigs, 26 % of cats and 47 % of dogs. This study also investigated the renal carriage (leptospires in kidney tissues) of ten animal species by qPCR and reported renal carriage in approximately 18 % of cattle, 16 % of pigs, 66 % of rats, 85 % of mice and 30 % in cats and dogs. leptospiral DNA was also detected in two bat urines echoing previous suggestions of a rodent-bat infection cycle (Matthias et al. 2005).

In a meta review of leptospiral serosurveys undertaken over a 20 year period in Rio de Janeiro, Brazil, Martins and Lilenbaum (2013) reported a seroprevalence rates of approximately 36 % of rats, 73 % of dogs, 38 % of cattle, 40 % of horses, 66 % of pigs, 40 % of wild animals excluding felines, 15 % of wild felines and tamarins. The predominant infecting serogroups were Icterohaemorrhagiae, Sejroe, Australis and Pomona. Another study from Brazil also reported high seropositivity (71 %) in 119 racehorses to serovar Copenhageni (Hamond et al. 2012). Leptospirosis in horses is of interest because of the association with post infection recurrent uveitis which has been postulated to cost the United States equine industry in the vicinity of 100–250 million dollars per year (Verma and Stevenson 2012). The high prevalence of reactive antibody titres and carriage of leptospires in rodents is well known in the Leptospirosis community. Recently in an ecological study of *Leptospira interrogans* in rats in Vancouver it was noted that an increase in weight or body fat and bite wounds increased the probability of infection in rodents (Himsworth et al. 2013).

34.3 Epidemiology in Humans

The global burden of human leptospirosis is currently unknown, however, estimates of the annual incidence range from 0.1 to 1 case/100,000 people in temperate areas to 100 cases/100,000 during epidemics in tropical regions (Everard and Everard

1993; Levett 2001). In addition, the incidence of leptospirosios is also higher in those environments prone to flooding (Lau et al. 2010a). An estimated 300,000–500,000 severe cases occur each year, with case fatality reports of up to 30 % (WHO 2003; Hartskeerl 2006). In an attempt to develop a better understanding of the burden of leptospiral disease, the WHO (2011) estimates that the global incidence in endemic areas exceeds five severe cases per 100,000. Given the lack of reporting in many developing areas, misdiagnosis, lack of awareness, patients failing to present for treatment and those with subclinical infections, it is almost impossible to determine the true incidence. The source of infection in humans is usually through either direct or indirect contact with the urine of an infected animal. Further, the usual portal of entry is via compromised cutaneous or mucosal membranes (Levett 2001). Occupation is a significant risk factor as dairy and cattle farmers, veterinarians, abattoir workers, meat inspectors, rodent control workers and other occupations where intermit contact with animals is required, all have a greater chance of direct contact with the urine of infected animals. Occupations that bring humans into indirect contact with animal urine are also at risk of infection, e.g. sewer workers, miners, soldiers, septic tank cleaners, fish farmers, gamekeepers, canal workers, rice field workers, taro farmers, banana farmers and sugar cane workers (Faine et al. 1999; Levett 2001; Tulsiani et al. 2011). Recreational activities while travelling are also considered a risk factor for the disease (Lau et al. 2010b).

In Europe as a whole, the overall incidence rate in 2010 was 0.13 per 100,000 inhabitants (Dupouey et al. 2014). In Germany, there were 2694 reported cases of leptospirosis from 1962 to 2003. During this time period, the highest mean annual incidence was 0.11 per 100,000 in 1962–1967. The lowest mean annual incidence was 0.04 per 100,000 between 1992 and 1997 (Jansen et al. 2005). In the Netherlands, there were 2553 (mainly severe) cases of leptospirosis reported from 1925 to 2008 although the average incidence was 0.25 per 100,000 population. The incidence in the Netherlands showed a small decrease over the 84 year period and as in Germany male patients accounted for the majority of infections (Goris et al. 2013a, b; Jansen et al. 2005). In France, approximately 600 cases per year are diagnosed, however, half of them are from French overseas principalities. The incidence of 0.5 per 100,000 in mainland France is similar to that seen in Germany and the Netherlands. However, in the overseas territories, an average incidence of 1060 per 100,000 was reported between 2007 and 2009. In French Polynesia, the average incidence is 39 per 100,000 and in New Caledonia, the average incidence is 45 per 100,000 (Picardeau 2013).

The Asia Pacific region has some of the highest incidence rates for leptospirosis since high population densities are potentially a risk factor for leptospirosis (Victoriano et al. 2009). This is not surprising given the frequent climatic calamities, overcrowding, poor sanitation, proximity of domestic and wild animals and occupational risks. In China over the past two decades, the average annual incidence was 0.7 per 100,000 inhabitants. Major outbreaks have occurred following flooding and heavy rainfall. Interestingly, 60 % of cases in China are due to infection with *L. interrogans* serovar Lai. The principle vector for transmission are rats such as *Apodemus agrarius* (Zhang et al. 2012). In South Korea, the predominate infecting

serovar and vector are similar to that seen in China however, the incidence is lower. Between 1998 and 2011 in South Korea there were 1528 reported cases of leptospirosis giving rise to an incidence rate of 0.22 per 100,000 inhabitants (Kim 2013).

In Australia, the annual incidence is 8.9 cases per million (Pappas et al. 2008). In North Queensland, leptospirosis is endemic as agriculture such as banana and sugar cane farming, which are common to these areas, are high-risk industries. Seasonal changes have a direct impact on the incidence of the disease as the frequency of infection is highest during the wet season (January–April) whilst being relatively low during the dry season (June–December). Although the organism was only identified in the late 1990s, *L. borgpetersenii* serovar Arborea has emerged as the most predominate infecting serovar in Queensland (Tulsiani et al. 2011; Wynwood et al. 2014).

Leptospirosis is endemic in the Caribbean Islands and in many parts of Central and Southern America. Pappas et al. (2008) reported that the incidence in Trinidad and Tobago is 120.4 per million, Barbados 100.3 per million and Jamaica 78 per million. In El Salvador, Brazil and Argentina the incidence is 358, 12.8 and 9.5 per million respectively.

34.4 Evidence of Human-to-Human Transmission

Currently, reported evidence of human-to-human transmission is scarce. However, diagnosis of such transmission has been confirmed by serological testing. Bolin and Koellner (1988) reported the case of a 29 year old breast feeding mother who worked as a veterinarian and had a confirmed *L. interrogans* serovar Hardjo infection. The mother continued to breast feed during her illness and 21 days post-onset of symptoms, the infant displayed clinical signs consistent with leptospirosis. A positive result was confirmed by the microscopic agglutination test (MAT). In another report detailing possible human-to-human transmission, Harrison and Fitzgerald (1988) discussed the advent of possible sexual transmission of *L. interrogans* serovar Icterohaemorrhagie. The diagnosis of this condition was also confirmed serologically by MAT.

34.5 Evidence of Animal-to-Human Transmission

Reports of human-to-human transmission are rare and as such Adler and de la Pena Moctezuma (2010, p. 289) submit that ‘human to human transmission for practical purposes is non-existent and that leptospirosis is recognised globally as a zoonosis.’ Since cases and outbreaks of leptospirosis are either unreported or misdiagnosed, it is not surprising that reports, which attempt to identify and track the course of leptospirosis outbreaks, are rare. Recently, Li et al. (2013a, b) used molecular methods such as multi locus sequence typing and multiple locus variable-number tandem

repeat analysis to type isolates recovered from rodents in the Guizhou province in China. The authors found that the newly sequenced strains were consistent with serological investigations undertaken in leptospirosis patients from Guizhou province. Desvars et al. (2013) reported that 16S RNA gene sequencing identified four pathogenic genomospecies, which are responsible for human leptospirosis, have also been isolated in Mayotte rats.

34.6 Disease Symptoms in Humans

At present, the minimum infecting dose leading to leptospirosis is unknown, however, the incubation period is assumed to be inversely correlated with the size of the inoculum. For example, a high infecting dose may engender a short incubation period when compared to a low infecting dose. Conversely, small doses may result in prolonged incubation times which may extend into the immune phase. It is anticipated that these small infecting doses might be responsible for mild or even sub clinical infection (Faine et al. 1999). Once in the blood, leptospires are capable of circulating to all tissues. Leptospires that evade phagocytic cells of the recticuloendothelial system grow in an exponential manner doubling every eight hours (Faine et al. 1999). There is evidence to suggest that phagocytosed leptospires do not survive long within the interior of the phagocyte (Vinh et al. 1982; Wang et al. 1984). Virulent strains have the ability to attenuate phagocytic responses by activating apoptosis in the macrophage (Merien et al. 1998). Moreover, Adler and de la Pena Moctezuma (2010) write that the ability to resist complement and death by neutrophilic destruction may be a feature of virulent leptospires in non-immune hosts. Central to the pathology observed in leptospirosis is the damage caused to the endothelium of small blood vessels. This engenders ischaemia in target organs thus resulting in renal, hepatic and pulmonary damage and thrombocytopenia. A number of leptospiral virulence factors such as haemolysins, fibronectin binding proteins and numerous surface proteins such as LipL32, Lig A, Lig B, lipoprotein Loa22 and the 6 Len proteins (LenABCDEF) are postulated to play a role in pathogenesis (Adler and de la Pena Moctezuma 2010; Bulach et al. 2006; Hoke et al. 2008; Matsunaga et al. 2003; Merien et al. 2000; Picardeau et al. 2008; Ristow et al. 2007; Stevenson et al. 2007). Recently, *L. interrogans* catalase KatE and HtpG (high-temperature protein G is the bacterial homolog to the highly conserved molecular chaperone Hsp90) have also been shown to be virulence factors in leptospirosis (Eshghi et al. 2012; King et al. 2014).

Following the initial incubation period, the infection enters the acute phase of the disease which can last up to ten days (Tulsiani et al. 2011). Clinically, during the acute phase, patients typically present with headache, fever, excruciating myalgia and arthralgia and sometimes rigiours, vomiting, photophobia and a mucosal rash (Faine et al. 1999). Haemoptysis, hypotension and bradycardia are also common presentations. These symptoms are considered non-specific thereby making the diagnosis of leptospirosis difficult. Hepatosplenomegaly, jaundice (produced as a

result of hepatocellular damage, increased erythrocyte destruction and the resulting increase in circulating haemoglobin and bilirubin), renal failure, liver failure and acute respiratory distress are common features of the more acute form of the disease (Sutliff et al. 1953; Solbrig et al. 1987; Faine et al. 1999, Levett 2001). Host factors, or more specifically, the activation of the innate immune system in which a myriad of cytokines are released (cytokine storm) in response to the invading pathogen also play a central role in the clinical outcome (Reis et al. 2013). Following the acute phase, patients enter the immune phase where immunoglobulins, specific for the destruction of leptospires, are produced to resolve the infection (Levett 2001).

34.7 Disease Symptoms in Animals

34.7.1 Canines

The severity of leptospirosis in canines may be dependent on the size of the infecting dose, infecting serovar, age and health of the dog as well as vaccination status. Clinical signs may vary from the sub-clinical or asymptomatic infection with infections due to *L. interrogans* sv Canicola to chronic infection characterised by chronic hepatitis and uveitis, sub-acute disease accompanied by pyrexia, anorexia, vomiting, renal failure and petechiae (Prescott 2008; Sykes et al. 2011). The acute and peracute disease while uncommon, may result in coagulopathy, vascular injury and death (Prescott 2008). Other clinical signs include arched back, swollen tender kidneys, depression, melena and blood stained urine. Death can occur 36 hours to four days after the onset of symptoms. Serovars causing the more sinister clinical picture include serovars Australis, Grippotyphosa, Icterohaemorrhagiae, Autumnalis and Pomona. Regular vaccinations may assist to prevent severe disease however, the vaccines are serovar specific and do not engender protection against all possible infecting serovars (Faine et al. 1999).

34.7.2 Felines

Given the predatory activities of cats towards rodents, it is reasonable to conclude that cats are at high risk for contracting leptospirosis. Surprisingly, the clinical presentation of diseased cats is rare even though there is greater seroprevalence of leptospiral antibodies in cats than in dogs (Roqueplo et al. 2013). In addition, renal insufficiency and hepatic inflammation may be evident in those animals that present with leptospirosis (Arbour et al. 2012; Bryson and Ellis 1976; Lapointe et al. 2013).

34.7.3 Equines

Clinical features of leptospirosis disease in horses include fever, anorexia, jaundice, mucosal petechiae and depression. Severe forms of the disease (respiratory failure) are more likely to occur in foals than adult horses. Reproductive catastrophies are common in infected mares. Antibodies directed towards leptospiral LruA and LruB proteins have been shown to cross-react with structures in the eye, thus resulting in an auto-immune basis for equine recurrent uveitis or moon blindness (Verma and Stevenson 2012; Verma et al. 2013).

34.7.4 Bovines

Cattle infected with serovars for which they are not maintenance hosts are more likely to display clinical disease, especially if the host is young, i.e. a calf. Clinical signs in cattle with acute disease include fever, pulmonary congestion, jaundice, haemoglobinuria and anaemia. Renal lesions may be observed at slaughter. In cows, the milk drop syndrome has also been observed. Chronic infections may also engender reproductive catastrophies (Faine et al. 1999; Pearson et al. 1980).

34.7.5 Swine

Younger pigs are more likely to display acute leptospirosis compared with more mature ovines. Clinical features are similar to those observed in other animals and include jaundice, weakness, haematuria, anorexia, renal failure and convulsions. Adult pigs are usually asymptomatic, however, may have renal lesions. Again reproductive catastrophies (abortions and stillbirths) occur as a result of maternal infection (Baker et al. 1989; Faine et al. 1999).

34.7.6 Unresolved Issues

There are numerous unresolved issues which the Leptospirosis community needs to address. Firstly, for nearly a century, culture and serology have underpinned the diagnostic practices of laboratories with an interest in this field (Martin and Pettit 1918). With the dawn and rapid advances in molecular diagnostics, there is now a plethora of molecular techniques available for laboratories to undertake primary diagnostic and reference services. However, as Goarant (2014) eloquently argued, reconciling historical serological knowledge with modern molecular epidemiological practices remains a challenge as does identifying the most appropriate DNA targets and techniques for *Leptospira* spp. typing. As whole genome sequencing becomes less costly, less time consuming and less technically demanding, we are hopeful of gaining consensus and resolving these issues.

Secondly, the issue of chronic illness and the occurrence of post-leptospirosis symptoms in patients need a more comprehensive investigation. While neuropathies and mental illness may be considered persistent sequelae, 10 % of patients may complain of uveitis and headaches for years (Faine et al. 1999; Shpilberg et al. 1990). In an interesting and much needed attempt to add framework to understand the burden of human leptospirosis, Goris et al. (2013b) reported that 21.1 % of their patient cohort frequently reported complaints such as myalgia and headache beyond 24 months post infection.

Finally, governments around the world are encouraged to invest more in public health initiatives centring on surveillance and reporting structures for Leptospirosis and educating medical officers and the public of the disease. Until such initiatives are universal, leptospires will remain silent assassins and serious attempts to understand and prevent leptospirosis will be futile.

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