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Emergence, control and re-emerging leptospirosis: dynamics of infection in the changing world

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Abstract

Globally, leptospirosis poses an increasing public health problem, as evidenced by markedly increasing incidence rates and multiple outbreaks in all continents. Yet, the disease is severely neglected and hence, its global burden is largely unknown. The estimated incidence of about half a million severe human cases annually is probably an underestimation while the burden for animal health is unknown. It is anticipated that current international initiatives will assess the global burden of leptospirosis, while mathematical modelling of transmission dynamics will allow the identification and testing of appropriate intervention and outbreak response measures within the coming years.

Keywords: Burden of disease, diagnosis, epidemiology, leptospirosis, modelling, public health, review, veterinary health, zoonosis
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Leptospirosis is an Existing and Growing Public and Veterinary Health Problem

Leptospirosis is probably the most widespread and prevalent zoonotic disease in the world [1]. Leptospirosis is difficult to diagnose both in the clinic and the laboratory. Therefore, the disease is frequently not recognized and consequently severely neglected. Leptospirosis is (re-)emerging globally and numerous outbreaks have occurred worldwide during the past decade. The most recent examples are the epidemics in Nicaragua in 2007 [2], in Sri Lanka in 2008 [3,4] and in the Philippines in 2009 [5], each affecting several thousands of people and causing hundreds of deaths. However, the true spread and increase of leptospirosis remains unknown, as the quality and availability of diagnostic tests, testing facilities and surveillance systems are highly variable and frequently absent.

Most mammalian species are natural carriers of pathogenic leptospires [6–8]. These include feral, semi-domestic and farm and pet animals as important infection sources. The risk of acquiring leptospirosis is associated with contact with animals. Therefore, leptospirosis is an important occupational disease, especially affecting farmers, slaughterhouse workers, pet traders, veterinarians, rodent catchers and sewer workers.

The main route of infection by these spirochetes is probably by transmission through indirect contact with leptospires secreted into the environment. Pathogenic leptospires survive longer in a warm and humid environment. Hence, the disease is particularly prevalent in wet tropical and subtropical regions [6–8].

Also of importance are increasing international travel and activities in tropical countries, with the subsequent introduction of leptospirosis cases from outside the industrialized world and the emergence of leptospirosis as a recreational disease. Leptospirosis is also a veterinary problem. Apart from farmers and slaughterhouse personnel acquiring leptospirosis, this zoonosis has a direct impact on the trade of animals or meat. The main economic impact, however, is caused by reproductive failures in livestock [9]. Usually animal leptospirosis is not routinely monitored. It is considered an endemic disease and surveillance is only carried out routinely for those endemic diseases for which there are control programmes. Therefore, surveillance is largely limited

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to diagnostic investigations and the subsequent collation of diagnostic data in some countries.

In summary, the relevance of leptospirosis is that it poses an existing and growing public and veterinary health problem. It is unlikely that leptospires (and leptospirosis) can be eradicated, as their main reservoirs are rodents, with rats notably forming major sources of highly virulent serovars.

Transmission, Epidemiology and Clinical Symptoms

Transmission

Pathogenic leptospires live in the kidneys of their natural hosts. In addition, the genital tracts of domestic animals act as sites of persistence [10–12]. A wide range of mammalian species are carriers. Humans are considered dead end hosts, although a recent report has shown that people can maintain leptospires in certain ecosystems [13]. Leptospires are excreted in urine into the environment, where they can survive for several months, depending on favourable environmental conditions. Infection of accidental hosts occurs via direct contact with the carrier's urine or indirectly through a urine-contaminated environment. Leptospires may also be excreted in the products of abortion in domestic animal species [10]. Pathogenic leptospires enter via skin abrasions and cuts, and through the mucous membranes of the eyes, nose (inhalation of contaminated aerosols) and mouth (consumption of contaminated beverage and predator chain transmission [14]) and genital tracts (domestic animals). Penetration through water-weakened skin is controversial. Unlike natural hosts, accidental hosts often develop disease [6–8].

Epidemiology

To date nearly 300 pathogenic *Leptospira* serovars have been identified and many more will follow. In general, each serovar is adapted to a certain mammalian host; rodents, insectivores, dogs, pigs and cattle comprise the best known ones. Serovars can be adapted to several hosts, while one host might carry several distinct serovars. In addition, serovars continue to adapt to new hosts because the cycle is complex and dynamic. Vaccination pressures may also alter the distribution of serovars in a species. Distribution and infection patterns may thus change both by adaptation of serovars to other hosts, and by the introduction of new host animals into an area. Also climatic (global warming, El Niño) and ecological changes (e.g. introduction of new crops, expanding cities and deforestation) will affect the distribution of *Leptospira* serovars and consequently the prevalence and clinical features of human cases, while anthropogenic practices and animal management systems are likely to determine exposure and infection risks [6,8].

Clinical symptoms

The lack of awareness of leptospirosis is mainly due to the wide variety of symptoms seen in infected persons, the often subclinical nature of the disease in animals, and technically demanding laboratory tests making the disease difficult to diagnose both in the clinic and the laboratory [15–18].

The illness varies from mild to severe, potentially fatal [6,7,16–18], depending on a number of known and unknown factors, among which the causal serovar and the host's immune status might be important. Worldwide, case fatality rates range from 3 to >50% [7,15,19]. Clinical manifestations may comprise fever, myalgias, severe headache, chills, diarrhoea, nausea and vomiting, oliguria/anuria, jaundice, conjunctival suffusion, aseptic meningitis, haemorrhages, joint pain, skin rash, cough, cardiac arrhythmia, psychosis and/or delirium. Early acute disease presents with non-specific symptoms of fever, myalgia and headache lacking any diagnostic hallmarks suggestive of leptospirosis [7,15–20].

Because of its protean manifestations, leptospirosis mimics many other infectious diseases, namely influenza, hepatitis, dengue, Hantavirus infections or other viral haemorrhagic fevers, yellow fever, malaria, brucellosis, borreliosis, typhoid fever or other enteric diseases, and pneumonia [6–8,20–22], together with a range of abortifacient diseases in animals (such as brucellosis, neospirosis bovine virus diarrhoea, infectious bovine rhinotracheitis and porcine circa virus). Therefore, it is often misdiagnosed as any of these other diseases, which generally encounter more awareness [20,21]. This contributes to the cycle: under-diagnosis – under-reporting – lack of awareness and neglect.

Diagnostic Methods

Confirmation of a clinically suspected leptospirosis case in the laboratory also has many bottlenecks. Standard tests, such as culturing and the microscopic agglutination test (MAT), are tedious, laborious and require well-equipped laboratories with experienced staff and, therefore, are restricted to a few 'expert' centres. Because MAT is the reference test in serodiagnosis, an international proficiency testing scheme has been developed to standardize its performance level at a global scale [23]. However, novel or adapted simplified diagnostic tests for diagnosis in both humans and animals are badly needed. Several rapid tests for human use are currently available (Table 1). Meaningful multicentre comparisons have not

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TABLE 1. Common diagnostic tests for leptospirosis

Test	Sensitivity[a,b,c,]	Specificity[a,b]	Costs[d]	Advantages	Disadvantages[e]	Reference
Culture	5–50%	100%	€20[f]	Provides evidence. Veterinary and human applicability	Too slow and difficult	[6,7,16]
Dark-Field Microscopy (DFM)	10^4 bacteria/ml	Low; confusion with protein fibres	<€1	Quick and early diagnosis. Veterinary and human applicability	Unreliable, requires confirmation	[6,7,16]
Microscopic Agglutination Test (MAT)	90%	>90%	€160[f,g]	Gold standard. Veterinary and human applicability	Requires a panel of life antigens, difficult (expertise), laborious (3 h), serology. Problems with seronegative carrier animals	[6,7,16]
IgM-ELISA[h]	84%	99%	€48[f,g]	Cost effective, can be done without ELISA Reader	Laborious (4 h), serology Limited veterinary use	[7,16]
IgM-ELISA[i]	>90%	88–95%	€9–16[g,j]	Cost effective and relatively rapid (1–2 h)	Serology	[7,16]
IgG-ELISA for cattle	ca.90%	95%	€6[j]	1 h	Misses early immune response	[53]
DriDot test	82%	95%	€5–7[g,j]	Easy, quick (30 s), cost effective	Serology, needs confirmation by MAT. No veterinary use	[7,16]
Lateral flow test	81%	96%	€2–5[g,j]	Easy, quick (10 min), finger prick blood, cost effective	Serology, needs confirmation by MAT	[7,16]
Real-time PCR	100%	93%	€100[f]	Early diagnosis. Veterinary and human applicability	Few tests validated (ref 56, 57), sophisticated expensive equipment, expertise	[7,16,55,56]

[a]Several studies indicate different percentages.
[b]Sensitivity and specificity largely depends on a number of factors; stage of illness, type and producer of test and panel of clinical materials used for testing [6,57].
[c]Sensitivity of culture depends mainly on the route and transport time to the laboratory. MAT is the gold standard and should be 100%. However, when comparing with culture this gold standard appears not optimal. Sensitivities of other serological tests are compared with MAT.
[d]Excluding costs for equipment.
[e]Serology has the disadvantage that it detects antibodies 7–10 days after the onset of the disease. This is too late for antibiotic treatment, which should start within the first 4 days.
[f]Includes personnel costs for execution of test based on costs formally recognized by The health assurance authority in The Netherlands (year 2011).
[g]Based on performance of one test. Please notice that serological confirmation requires testing of both acute and convalescence serum samples for seroconversion or significant titre rise.
[h]In-house ELISA.
[i]Commercial ELISA.
[j]Costs may vary, amongst other factors, due to the subjection to different import taxes raised in distinct countries.

been carried out between these tests, using sera from adequately defined cases, to ascertain their relative merits as diagnostic tools. Also, these tests are for screening purposes only, and results must be confirmed by standard tests. In addition, they are applicable only at a later stage of disease when effective treatment with antibiotics is likely to fail. Moreover, *Leptospira* related to reproductive failure in animals is a chronic condition associated with declining antibody titres or the absence of detectable antibody titres. There is an urgent need for robust and easy to use diagnostics, particularly during acute infection among humans and domestic animals. In addition, it must be remembered that human and veterinary diagnostic requirements differ in some respects, as follows. In human leptospirosis the first requirement is to get a diagnosis and genus specific tests are suitable, whereas in animals the individual is less important than the population from which it comes. Therefore, it is important to get an early diagnosis of the infecting serovar as control measures such as vaccination are serovar dependant. Improved diagnostics will contribute to an improved case detection and a consequent increased awareness and control of leptospirosis and, hence, be beneficial for veterinary public health care and (national) economies.

Treatment and Control

In the past, adequate treatment has been shown to markedly increase the chances of surviving leptospirosis and reduce the number of days of illness [24]. For example, introduction of peritoneal dialysis in cases of renal failure has markedly reduced fatality rates [7]. Early antibiotic treatment is generally thought to be beneficial to the course of disease while treatment later on might reduce recovery periods and minimize sequelae [25]. However, treatment with penicillin, the drug of choice, is sometimes problematic, with rapid clearance of leptospires associated with the life-threatening Jarish-Herxheimer reaction.

In severe cases, high doses of intravenous penicillin (four times a day, 2 million units) are recommended. In less severe

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cases, oral antibiotics such as amoxicillin, ampicillin, doxycycline or erythromycin can be prescribed. Third-generation cephalosporins and quinolone antibiotics also seem to be effective [7]. A number of antibiotics, in particular dihydrostreptomycin, have been shown to be useful in the elimination of leptospires from carrier animals [26].

Due to the complex and dynamic epidemiology, there are no general rules in the prevention and control of leptospirosis in humans. However, domestic animal control measures are often much simpler because they may be addressed on a population basis and there is the possibility to isolate that population. Direct or indirect contact with the urine of excreting animals is the basis of infection. Prevention and control thus mainly focus on the reduction of the infection source and the prevention of penetration of leptospires into the accidental host. Leptospires cannot usually be eradicated as rodents and insectivores form major natural reservoirs. Hardjo infection is probably the only exception where this serovar is maintained by cattle and sheep and there are no known wildlife hosts.

It will be obvious that a rational design of prevention and control measures is based on the identification of the infection source(s) and that the dynamic epidemiology requires a permanent surveillance system. By definition, prevention and control measures are tailor-made.

Prevention of transmission can be achieved by wearing protective clothes (e.g. gloves, safety glasses and boots), but this is not always practical; it is, for example, not an option to wear boots in a paddy field. Intervention can also be achieved by improving water and food storages but, probably, increasing awareness about the disease and the infection risks in clinicians, the population (notably risk groups) and public health decision makers is an effective approach for reducing infection risks.

Control of rodents can only be achieved by a constant and intensive management of populations (e.g. muskrat control in the Netherlands). The use of rodenticides is risky (generation of a resistant population) and needs expertise in the composition and applicability of such control agents [27]. Changing the environment in order to reduce attractive ecological niches (cleaning up garbage and improving sanitation) is only feasible and realistic for major urban areas in the industrialized world.

Infection risk from and between domestic animals can be reduced by herd control measures. These include treatment of carriers and/or vaccination. Treatment of Hardjo infections in cattle herds is applied in the Netherlands [26]. The Dutch Hardjo control programme consists of a regular surveillance that is undertaken by testing bulk-milk with a Hardjo-specific ELISA. Infected cattle are then treated with dihydrostreptomycin and Hardjo-free farms are certified. Participation in the programme led to a virtual eradication of 'dairy fever' in the country. Outside the Netherlands, vaccination is the most common approach. Nevertheless, it should be noted that both curative and prophylactic measures do not prevent *Leptospira* transmission but will largely reduce excretion of leptospires [9,28,29]. Both approaches should be combined with herd management.

There are vaccines available for cattle, dogs and pigs. These whole-leptospire-based vaccines consist of a limited panel of local serovars and give a short-term serovar-specific protection. There has been a movement away from cheap multivalent vaccines that produced very limited protection [30] to more expensive monovalent products, which has led to the development of vaccines that can provide at least 12 months of microbiological protection in cattle [31,32]. Vaccines for use in other domestic animals are being subjected to more critical evaluation of the protection provided than was the case in the past.

The use of subunit vaccine candidates is increasingly being advocated because of their anticipated stronger or long-term immunity and availability of non-toxic, potent adjuvants [33]. This may well be the way forward for vaccines for use in humans and companion animals, particularly where cross-serovar protection may be an important consideration. It may not be the most appropriate route for vaccines for use in food producing animals where costs are critical and where immunity is only required to a very limited number of serovars in a species. The major production cost for such vaccines is the cost of the bovine albumin used in growing the organism and its subsequent removal from the final product. This has been obviated in some vaccines by the use of protein-free culture media. Many of the vaccines available in Europe, but also in other continents, notably in Latin America, are manufactured in the USA. These vaccines are not necessarily appropriate to regional requirements as they are not based on cultural evidence of what are the local major problems, although there is a trend for companies to better focus on at least European needs. Studies on cattle maintaining with serovar Hardjo, have shown that cell-mediated immunity is important in protective immunity in that species [32,34] but protective immunity in other animal species is poorly understood.

Information on human vaccines is limited. These are available only in certain countries, such as China [35], Cuba [36,37], France [38] and Russia [39]. As in animals, these vaccines are largely serovar-specific and protect for a relatively short period. Boosting at regular intervals is necessary to maintain protective titres of antibodies [7,35]. These vaccines are also focused on the local situation and do not cover the needs in other regions where other serovars are

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endemic. Like the animal vaccines, those for humans are composed of crude antigens consisting of leptospires killed by phenol or formaldehyde that give unwanted side effects (Shi Manhua, personal communication).

Geographical Distribution

Leptospirosis has a worldwide distribution but it is particularly endemic in tropical and subtropical regions. It should be noted that only a few countries have a notification system for leptospirosis and mainly hospitalized cases are recognized. While it is generally accepted that leptospirosis is re-emerging globally, and that notably lung haemorrhagic forms are increasing in number [19,21], the true spread and increase of leptospirosis cases remain unknown.

Numbers of confirmed cases and fatalities provided by national reference centres are likely to represent a marked underestimation. This is based on the following considerations:

1. The vast majority of countries do not have a notification system or notification is not mandatory [38].
2. In The Netherlands, reporting is mandatory and notification is effective. Yet, our estimation for The Netherlands is that we miss at least 30% of the severe cases. An estimated 3- to 10-fold under-reporting of severe cases has been indicated by several national reference centres in Europe (Hartskeerl, personal observation).
3. Incidences are based on severe leptospirosis cases only. In 70 – 90% of such cases hospitalization is needed (Table 2) and confirmation is often limited to hospitalized patients.
4. The number of mild leptospirosis cases is unknown but might be many times that of the severe cases.
5. Late sequelae occur but are not well assessed [40,41]. A preliminary estimate of a 10-year investigation in the Netherlands indicated the following: about 27% of the patients had long-term complaints (especially with tiredness, myalgias, joint/back pain, headache, tinnitus and psychotic complaints); 11% of the patients had serious complaints (defined as complaints for more than 1 year or requiring reference to a clinician); and 1.3% of the patients remained permanently unfit for work.
6. Worldwide incidences are (i) 0.1–1 cases per 100 000 population per year in regions with a temperate climate, (ii) >10 cases per 100 000 population in humid (sub) tropical regions and >100 cases per 100 000 population affected during outbreaks [7]. The average case fatality rate is about 10%.

Identification of Specific Factors Triggering Changes in the Distribution of the Disease

Survival of pathogenic *Leptospira* serovars outside the host, being a unique feature within spirochetes, contributes to the maintenance of infection cycles in reservoirs and to an increased infection risk for accidental hosts, including humans. Survival outside the host largely depends on humid and warm conditions. Global warming and increased rainfall are thus predictors of an increasing leptospirosis incidence. Additionally, environmental changes that lead to migration of natural hosts and improved conditions for the survival of pathogenic leptospires, as well as socio-economic and political factors resulting in increased human exposure, might influence the occurrence of leptospirosis. Indeed, from the end of the 20th century, massive urban and rural outbreaks of leptospirosis have been observed in virtually all continents [2–4,15–18,42]. These outbreaks involving thousands of cases and many hundreds of deaths frequently occur in slums peripheral to large cities [21]. The increasing world population and urbanization in the 21st century will favour such events.

Tropical countries benefit from an increasing popularity as holiday destinations, often with activities with a high risk of infection, such as rafting, jungle tracking and caving. Notably

TABLE 2. Days of illness and of hospitalization due to leptospirosis

Days of acute disease[a]		Days of hospitalization				
Median	Spread	Hospitalized cases (%)	Median	Spread	Intensive care (%)	Reference/source
14	2–84	68.0	ND	ND	ND	[18]
15	6–36	88.0	8	1–30	64.0	Unpublished data, The Netherlands (n = 49)[b]
17	2–90	100	10	1–35	33.0	[54] (n = 119)[b]

ND, not determined.
[a]Total number of days of illness before and during hospitalization.
[b]Between brackets the number of cases involved in the evaluation.

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TABLE 3. Factors triggering changes in the distribution of leptospirosis

Factors increasing incidence	Factors reducing incidence	Factors triggering changes in distribution
Increased rainfall	Decreased rainfall	
Local food availability and increased rodent-densities	Decreased food availability and lower rodent-densities	
Global warming		
Urbanization (socio-economic deprived areas)	Improved sanitation	
Lacking legislation on surveillance, notification and control/prevention	Improved vaccination and/or prophylaxis	
Growing communities without timely expansion of legislation (e.g. the growing EU)		
Holidays in tropical countries		
Military expeditions		Changes in agriculture land use and deforestation
		Trade in animals and products

South East Asia and Latin America, where incidences are high, are exceedingly popular for tourists. This leads to a higher import of leptospirosis cases into the industrialized world, often with exotic serovars. Factors triggering changes in the distribution of leptospirosis are listed in Table 3.

Burden and Transmission Dynamics Modelling

As a true neglected infectious disease, the global burden of leptospirosis is unknown. Current estimates of 350 000 to 500 000 severe cases annually [2,18,43] are likely to represent an underestimation. The magnitude of mild cases is completely unknown. Considering the high case fatality rates reported for severe leptospirosis, one might hypothesize that the global burden of leptospirosis is similar to that of, for example, dengue fever. Moreover, leptospirosis also poses a veterinary burden, which might be considerable. Probably, leptospirosis would rank high in the list of neglected tropical diseases [44]. A major drawback in the assessment of the burden of leptospirosis is the scarcity of models and hence the lack of understanding of its dynamic transmission [45]. Available models concern basic aspects of the spread of leptospirosis in Thailand [46], the infection dynamics of rodents in Tanzania [47] and responses to some environmental drivers [48]. The worldwide effects of climate change are apparent from the evidence of global destabilization of natural systems [49]. The study of the impacts of climate on human health is an emerging research area. Thus, predictive modelling for the impacts of climate change on health is limited, firstly because most aspects of human systems are not readily amenable to modelling and, secondly, because of insufficient long-term data series on health outcomes. Recently, the WHO has initiated the assessment of the global burden of human leptospirosis and for that purpose has established a Leptospirosis Burden Epidemiology Reference Group (LERG). To date this initiative has provided the design of basic transmission and susceptibility-infection (SI) models [50,51] and will pursue this work on mathematical modelling towards both the estimation of the global burden of the disease and the rational formulation of effective control and prevention measures. It is hoped that the Food and Agriculture Organization (FAO) and Office International des Epizooties (OIE) will join the effort to include the veterinary side of the burden in line with the one-world-one-health concept [52]. Until adequate models are available, general adaptation measures can be effective at avoiding/reducing the impacts on health, such as: (i) primary actions taken to prevent or reduce human exposure to leptospires, through improved housing and availability of potable water and sanitation drainage; (ii) specific prevention measures regarding changes in health risk or health status through the introduction of environmental controls (e.g. rodenticides, traps and food protection) in response to an increase in the abundance of rodents and a higher risk of *Leptospira* transmission; (iii) increased disaster response capacity, with improved diagnosis and treatment of cases; (iv) use of genomic and proteomic knowledge to understand leptospiral biology, with direct application in improved curative and prophylactic measures, especially for impoverished populations; (v) established national and international databases and improved accessibility to monitored data from unusual environmental events; (vi) improved disease surveillance to reduce the number of undetected and/or unreported cases; and (vii) improved public education programmes to avoid leptospiral infection.

Conclusion

Leptospirosis is a prototype neglected infectious disease with an unknown but probably considerable impact on veterinary and public health. Leptospirosis will undoubtedly remain a significant veterinary public health threat for the coming years regardless of the extent of climate changes that are anticipated to favour an increase in its global incidence. Therefore, the use of mathematical modelling in the assessment of the global burden and infection risks, as initiated by the WHO, will be a valuable tool for the future design of adequate intervention and control measures.

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Transparency Declaration

Conflicts of interest: nothing to declare.

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