Leptospirosis: An Update - Part 1 Of 2: Etiology, Ecology, Epidemiology, Prophylaxis And Contro

Leptospirose: Uma actualização - Parte 1 De 2: Etiologia, Ecologia, Epidemiologia, Profilaxia e Controlo

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Andréia Patrícia Gomes
Doctor of Science, Escola Nacional de Saúde Pública Sergio Arouca, ENSP/FIOCRUZ
Institution: Universidade Federal de Viçosa (UFV). Department of Medicine and Nursing
Address: PH Rolfs, s/n, Campus Universitário, Viçosa – MG, CEP: 36570- 900
E-mail: andreia.gomes@ufv.br

Diana Marques Gazola
Medical Student, Universidade Federal de Viçosa (UFV)
Institution:Universidade Federal de Viçosa (UFV). Department of Medicine and Nursing
Address: PH Rolfs, s/n, Campus Universitário, Viçosa – MG, CEP: 36570- 900
E-mail: dianagazola@hotmail.com

Luciene Muniz Braga
PhD Nursing - University Lisbon, Portugal
Institution:Universidade Federal de Viçosa (UFV). Department of Medicine and Nursing
Address: PH Rolfs, s/n, Campus Universitário, Viçosa – MG, CEP: 36570- 900
E-mail: luciene.muniz@ufv.br

Oswaldo Jesus Rodrigues da Motta
PhD in Bioethics, Applied Ethics and Public Health, Universidade Federal do Rio de Janeiro (UFRJ/PPGBIOS)
Institution:Universidade Federal de Viçosa (UFV). Department of Medicine and Nursing
Address: PH Rolfs, s/n, Campus Universitário, Viçosa – MG, CEP: 36570- 900
E-mail: oswaldo.motta@ufv.br

Jorge Luiz Dutra Gazineo
Master of Medicine - Infectious and Parasitic Diseases, Universidade Federal do Rio de Janeiro (UFRJ)
Institution:Universidade Federal do Rio de (UFRJ)
Address: R. Prof. Rodolpho Paulo Rocco, 255, Cidade Universitária, Rio de Janeiro - RJ, CEP: 21941-617
E-mail: jgazingo@yahoo.com.br

SUMMARY
Leptospirosis belongs to the category of neglected infectious diseases and, due to its great epidemic potential, its local distribution in tropical regions is of extreme importance. It is a worldwide public health problem, known for the emergence and reappearance of the disease, lack of sanitary conditions and abandonment of the disease. Human infections usually occur after skin contact with soil and/or water contaminated by the urine of chronically infected

mammals. The clinical manifestations of the disease range from mild fever, chills and flu-like symptoms to acute forms of the disease. Based on these brief considerations, this article - part 1 of 2 - aims to discuss the biological, ecoepidemiological, prophylactic and control aspects of leptospirosis in Brazil.

Keywords: leptospirosis, public health, vector control.

RESUMO
A leptospirose pertence à categoria das doenças infecciosas negligenciadas e, devido ao seu grande potencial epidémico, a sua distribuição local nas regiões tropicais é de extrema importância. É um problema de saúde pública mundial, conhecido pelo aparecimento e reaparição da doença, falta de condições sanitárias e abandono da doença. As infecções humanas ocorrem geralmente após o contacto da pele com o solo e/ou água contaminada pela urina de mamíferos cronicamente infectados. As manifestações clínicas da doença variam desde a febre ligeira, arrepios e sintomas semelhantes aos da gripe até às formas agudas da doença. Com base nestas breves considerações, este artigo - parte 1 de 2 - visa discutir os aspectos biológicos, ecoepidemiológicos, profiláticos e de controlo da leptospirose no Brasil.

Palavras-chave: leptospirose, saúde pública, controlo vectorial.

1 INTRODUCTION

Leptospirosis, with its variable clinical spectrum, usually affects humans and other species of animals, such as rodents, cattle and dogs. This zoonosis caused by bacteria of the genus *Leptospira* is an emerging public health problem, since it occurs on a global level and shows great magnitude. Although it is recognized as a treatable and preventable disease, little is known about its current and real incidence and, consequently, the disease is neglected. The global burden of leptospirosis has been estimated at 2.90 million DALYs per year. The disease burden of leptospirosis is greater than filariasis and rabies (also neglected tropical diseases), with a DALY incidence of 42/100.000 (TORGERSON *et al*., 2015). In addition, leptospirosis is among the leading zoonotic causes of morbidity worldwide. Its lethality is greater than or equal to other etiologies of hemorrhagic fever. It is estimated that the highest morbidity and mortality occur in countries with few resources, which include regions where the impact of leptospirosis has been underestimated (COSTA *et al*., 2015).

The most common route of infection in humans is contact with water, food and soil contaminated by urine from infected animals. The entrance of bacteria into the human body, besides abrasions on the skin, can also be through intact mucous membranes or through the whole skin being submerged for long periods. The people who are at greatest risk are workers and residents of endemic areas, mainly during the rainy season and in flood situations (VIJAYACHARI, SUGUNAN, SHRIRAM, 2008), where there is a greater spread of the bacteria through water, with consequent outbreaks of the disease. Because of this, the

encouragement and improvement of active surveillance and disease control measures in developing countries is essential to provide reliable epidemiological data to be translated into guiding knowledge for effective public health policies. In this sense, the present article - part 1 of 2- seeks to make a literature review to produce a scientific compilation of the various current aspects of leptospirosis.

1.1 THE *LEPTOSPIRA* GENUS

The bacteria of the genus *Leptospira* belong to the order *Spirochaetales,* which are found within the family *Leptospiraceae*. The comparison of ribosomal ARN sequences confirmed the results of phenotypic studies that the genus *Leptospira* constitutes a distinct group within the order *Spirochaetales*. Results from a recent study revealed that the genus *Leptospira* now contains 64 distinct species, including the species of a new subgroup phylogenetically very close to that which contained the traditional saprophytic species (PHILIP *et al*., 2020; VINCENT *et al*., 2019).

A comparative analysis of the genus *Leptospira* evaluated phylogenetic relationships among species in several independent ways, including single *locus, multilocus,* and full genome approaches. All approaches convincingly confirmed the separation of leptospira species into three groups: pathogenic, intermediate pathogenic and saprofitic. *Leptospirals* that can cause disease include members of the intermediate and pathogenic groups (FOUTS *et al*., 2016). Among the pathogenic species, *Leptospira interrogans* is the most relevant as an etiological agent of diseases in humans. The other species reported as etiology of leptospirosis are: *L. kirshneri, L. weilii, L. alexanderi, L. noguchii, L. borgpetersenii, L. mayottensis, L. santarosai, L. alstoni, L. kmetyl, L. fainei, L. broomi, L. wolffii, L. venezuelensis, L. licerasiae and L. inadai* (FOUTS *et al*.., 2016; LEHMANN *et al.,* 2014; PHILIP *et al.,* 2020; TSUBOI *et al.,* 2017; HAAKE, LEVETT, 2020).

The basic taxonomic unit is called serovars (serotypes), based on the expression of lipopolysaccharide (LPS) or lipoglycan exposed on the surface. The structural differences in the carbohydrate portion of LPS determine the antigenic diversity among the numerous serovar groups (HAAKE, LEVETT, 2020). Serovars containing overlapping antigenic determinants are classified into a larger serogroup. At least 25 serogroups and more than 300 serovars are described (AHMED *et al*., 2006; THIBEAUX *et al*., 2018), which explains the complexity of the pathogen, which entails diagnostic challenges and multiple infections. The disease can be caused by pathogenic *Leptospira* sp representing more than 250 serovars (LEHMANN *et al.,* 2014; PHILIP *et al.,* 2020).

The practical importance of the serovar concept is the epidemiological point of view, since one type of serovar can develop a commensal relationship with one host and be pathogenic for another. In view of this, it is known today that the serovar that most frequently affects cattle is *Hardjo*. In production animals, the greatest importance of leptospirosis is economic. In cattle, specifically, the economic losses are directly or indirectly related to reproductive failures such as infertility, abortion and fall in meat and milk production, in addition to costs with veterinary care, vaccines and laboratory tests (BABUDIERI, 1958; MINEIRO *et al*, 2007; OLIVEIRA, ARSKY, CALDAS, 2013).

The dog is considered the natural host of the sorovar *Canicola* and the sewer rat (*Rattus norvegicus*), the natural host of the sorovars *Icterohaemorrhagiae*, *Copenhageni* and *Pyrogenes*, which commonly infect dogs. The *Mus musculus* (mouse) is the main reservoir of *L. ballum (*BABUDIERI, 1958). It is known that the most commonly associated and known serovars of classic canine leptospirosis are *Icterohaemorrahagiae* and *Canicola*. (BLAZIUS, *et al*., 2005). The prevalence of leptospirosis found in Brazilian canine populations has varied from 10 to 22%. In swine, the most commonly found *leptospirosis* serovars are infectious and causative of disease: *Pomona, Icterohaemorrhagiae, Tarassovi, Canicola, Gryppotyphosa, Bratislava and Muenchen*, the first four being already isolated from pi*gs in Brazil.*

Swine leptospirosis is classified as a B-list disease in the *Office International des Épizooties*, a group to which transmissible diseases of great importance from a socioeconomic and/or sanitary point of view belong, with considerable repercussion in the international trade of animals and animal products (OLIVEIRA, ARSKY, CALDAS, 2013). In birds, natural infection by *Leptospira* spp is not known; there is speculation if they have only the role of temporary hosts (BABUDIERI, 1958). Among the serovars of the *interrogans* species in Brazil, the sorovar *Icterohaemorrahagiae* seems to be the most common in humans (BLAZIUS *et al*., 2005). In studies by ROMERO *et al*., (2003) in São Paulo, Brazil 54.8% of positive samples for this serovar were observed between 1969 and 1997. In Recife, Salvador and São Paulo, this serovar was identified as a causal agent in more than 50% of the cases described (SILVA *et al*., 2003).

Leptospira sp is a helicoidal microorganism, shows one or both of its ends curved, or hook-shaped, is endowed with great motility conferred by an axostile, fine bacilli (0.1 x 6 to 12µm) and spiral. The *Spirochaetes* are thin, mobile, flexible and unicellular. The survival period of pathogenic in water varies according to temperature, pH, salinity and degree of pollution; their multiplication is optimal in pH between 7.2 and 7.4 (MANUAL DE

LEPTOSPIROSE, 1997; LEVETT, 2001). Its various serovars cannot be differentiated just by morphology.

The most relevant microbiological characteristics are: better visualization in dark field microscopes, since they are very small and cannot be visible in the common microscope; growth only in specific cultures. The most used medium is tween-albumin or EMJH (Ellinghausen-McCullough modified by Johnson and Harris) medium which is commercialized. EMJH adds 1% bovine serum albumin and tween 80 (source of long chain fatty acids); commercial formulations are commercially available. Liquid and semi-solid media containing serum include: Korthof medium (Peptone, NaCl, NaHCO3, KCl, CaCl2, KH2PO4, Na2HPO4) and Fletcher (Peptone, meat extract, NaCl, and agar) (LEVETT, 2001). *Leptospira* spp growth is slow in primary isolation and these crops must be kept for at least 13 weeks before being discarded. Some strains grow very slowly and may require even longer incubation time (EVANGELISTA; COBURN, 2010), (BHARTI *et al*., 2003).

2 ECOLOGY AND EPIDEMIOLOGY

Described on almost all continents, leptospirosis is considered a zoonosis of endemic behavior. Its estimated incidence is one case per 100.000 inhabitants, and increases to 10 in every 100.000 inhabitants in tropical climate regions. Its lethality is estimated to vary between five and 30%. It is a seasonally distributed disease: its peak incidence occurs during the rainy season in tropical regions, while in temperate regions its peak occurs from late summer to early autumn (WAR, 2013).

In Africa, the incidence is expected to increase due to improvements in surveillance and diagnostic conditions coupled with disorderly urban growth. In Hawaii, the actual incidence of the disease is estimated to be twice that reported. In Gabon, one study found a seroprevalence of *Leptospira spp.* infections higher than 15% in residents of marginalized communities. A study in Burkina Faso suggests that leptospirosis is probably endemic in that country (ZIDA *et al*, 2018).

A study conducted in Peru showed that under-recognition of serious complications and underdiagnosis already reach high levels, especially in urban areas. Concomitant with progressive climate change and disorderly urbanization, unusual flooding in Sri Lanka, India and Bangladesh has caused rat-infested sewers to overflow, causing leptospirosis outbreaks. In 2016 it was reported that leptospirosis, which is endemic in India, was expanding to other regions of that country (PATIL *et al*., 2016).

The cases of leptospirosis in China have gradually decreased in recent years, but it is still a zoonotic infectious disease of epidemiological importance (HU, LIN, YAN, 2014). In 1998, after Hurricane Mitch, there was a significant increase in leptospirosis cases in Central American countries. In short, it is possible to affirm that the factors that corroborate the beginning of outbreaks of the disease are: hot and humid climate, poor living conditions associated with close and repeated contact with natural reservoirs and situations of natural disasters and/or humanitarian crises (VIJAYACHARI, SUGUNAN, SHRIRAM, 2008).

Leptospirosis is a compulsory notification disease in Brazil. It is essential that health professionals be aware of the need to provide epidemiological data of an underreported disease such as leptospirosis, as such neglect adds to the factors that make it a neglected disease. Both the occurrence of isolated suspected cases and outbreaks should be notified, as soon as possible, for the triggering of epidemiological surveillance and control actions. Notification is made through the Leptospirosis Investigation Form, which must be registered in the Aggravates Notification Information System (SINAN).

The number of confirmed cases of leptospirosis notified at SINAN between 2007 and 2019 varied from 3.005 to 4.967, while the number of leptospirosis deaths notified in the same period varied from 270 to 390. There are records of leptospirosis in all of the states in Brazil, with a higher number of cases in the south and southeast regions. The disease shows an average lethality rate of 9%. Among confirmed cases, male patients between 20 and 49 years old are among the most affected, although there is no gender or age predisposition to contract the infection. As for the characteristics of the probable site of infection, the majority occur in urban areas and in home environments. (Brazil, MS, 2020).

The main natural reservoirs are several wild and domestic animals (LEVETT, 2001; LEHMANN *et al*., 2014). All animals are susceptible to the disease and can act as a source of infection (OLIVEIRA, ARSKY, CALDAS, 2013). Human is only an accidental and terminal host within the transmission chain. Almost 200 animals have already been described as reservoirs of the bacteria. Among animals, the main reservoir are the rodents *Rattus norvegicus* (rat or sewer rat), *Rattus rattus* (black mouse or roof mouse) and *Mus musculus (mouse)* (LEVETT, 2001). However, among them, the sewer rat stands out for being the main reservoir of the virulent sorovar for humans, the *Icterohaemorraghiae* (LEHMANN *et al*., 2014). Other frequent reservoirs of the disease are dogs, cattle and other livestock (GUERNIER *et al*., 2018).

Most infected animals do not get sick, but it is possible that they may eventually die. However, *Leptospira spp*. spreads and lodges in several organs of these animals and, due to the colonization of the renal tubules, the bacteria is eliminated alive in urine in large quantities,

contaminating water, soil and food. These microorganisms can remain viable for days or months in water or soil that has neutral pH (LEHMANN *et al*., 2014).

3 TRANSMISSION

Human infection is the result of direct or indirect contact with the urine of infected animals. Indirect transmission is the most common, and occurs mainly when the individual comes into contact with contaminated water, either in occasional situations such as flooding or in recreational or work activities. In these situations, bacteria crosses intact skin (only if submerged for long periods), mucous membranes and skin with abrasions or excoriations. This is the most frequent form of transmission in developing countries such as Brazil, where the seasonality of the peaks has statistical epidemiological importance, with an increase in the incidence in the summer, with the occurrence of floods due to the rain season.

Thus, vulnerable groups in regions with precarious sanitation systems and lack of public policies to control transmitters are always at great risk of indirect infection. There is a possibility of infection from ingestion of food contaminated with urine or aerosol, but it is infrequent (NICK, 2014b). Other less frequent infection modalities are possible and are usually related to accidents in laboratories, contact with contaminated tissues without personal protective equipment, inhalation of airborne urine droplets during some procedures and direct contact with urine contaminated with *Leptospira spp*. In developed countries, at-risk populations are workers dealing with tissues or live animals who become directly infected, however these incidents are sporadic.

Other professions also have high risk as military and health professionals working in areas of disasters and humanitarian crises. Inter-human transmission has already been described, and is extremely rare, but has been documented through sexual intercourse and breastfeeding (NICK, 2014b). Transmission has also rarely occurred through animal bites (CDC, 2020a). Transplacental infection has been described and although the rate of fetal transmission is unknown and information on complications and sequelae in newborns is scarce, some studies have shown that active disease in the mother is a risk factor for abortion and fetal death (NICK, 2014a).

4 PROPHYLAXIS AND CONTROL

In Brazil, the main form of leptospirosis transmission is the indirect route through contact with water contaminated by rodent urine (Brazil, MS, 2019). Therefore, to reduce the numbers of leptospirosis infected, some measures should be directed at the bacterial reservoirs,

the protection of workers at risk and the improvement of environmental and sanitary conditions of the population: a) avoid contact with water or mud from floods and prevent children from swimming or playing in these waters; b) people who work in the cleaning of mud, debris and sewage unclogging should wear rubber boots and gloves (or double plastic bags tied on hands and feet); c) sanitary water (sodium hypochlorite at 2.5%) eradicates *leptospirosis*, and is used to disinfect water reservoirs, in the proportion of one liter of sanitary water per 1.000 liters of water from the reservoir; d) cleaning and disinfection of places and objects that came in contact with contaminated water or mud, the orientation is to dilute 2 cups (400ml) of sanitary water in a bucket of 20 liters of water, leaving to sit for 15 minutes (Brazil, MS, 2020). In addition, epidemiological surveillance is fundamental, not only to guide public prevention policies, but also to contain outbreaks. Because of this, there is a compulsory disease notification.

The most important collective measures are rodent control, basic sanitation, herd immunization and improvement in socioeconomic conditions for extremely vulnerable populations, positively impacting housing, feeding and schooling conditions of these individuals. In addition to herds, domestic animals should be vaccinated, although this does not prevent a vaccinated dog, for example, from developing a subclinical form of leptospirosis with elimination of leptospirosis in the urine (NICK, 2014b).

For travelers should be avoided environments that may be contaminated with urine from rats and other animals, as well as coming into contact with water or mud from floods or suspicious rivers and lakes,. It is suggested to look for information about the occurrence of leptospirosis in the region you are visiting. If you fall ill on your return, do not forget to report your trip and the likely risk situations you went through during the trip (floods, camps, rivers and lakes) (Brazil, MS, 2020; CDCb, 2020.

Although there are licensed vaccines for use in France, Cuba and some Asian countries (XU, YE, 2018; HAAKE, LEVETT, 2020), it is important to note that there is currently no vaccine available for humans with proven efficacy against leptospirosis. The vaccine project is a major challenge for leptospirosis until today, since the discovery of the disease in 1886. This is because there are at least 250 serovars and also the pathogenesis of the infection is not fully understood. Like different strains of *Leptospira* sp are circulating around the world it is hard to create a single universal vaccine.

Both vaccines made from dead bacteria and recombinant vaccines have failed to confer immunity for a long time (KARPAGAM, GANESH, 2020). Despite the large number of published studies on protective immunological activity, there has been little progress in discovering a vaccine that is truly effective against leptospirosis. Vaccine efficacy data

presented in the literature are conflicting, regardless of the protein or adjuvant used (LPS or OMPs) (TEIXEIRA *et al*., 2019).

In fact, the forms of individual protection are quite limited depending on the reality of individuals, but health education, with simple guidance on the risk of prolonged contact with water from suspect sources and measures after contact are very relevant. Among the individual protection measures, chemoprophylaxis (pre- or post-exposure) also stands out, which despite the evidence of its benefit, there is still no universal consensus regarding its use in medical literature (TAKAFUJI *et al*, 1984; SEHGAL *et al*., 2000; EDWARDS, LEVETT, 2004; BRETT-MAJOR, LIPNICK, 2009; GUERRA, 2013; SCHNEIDER *et al.*, 2017; ALIKHANI *et al.*, 2018). Drug prophylaxis is not 100% effective, but is probably an adequate measure in cases of short periods of exposure, such as floods or floods; in this case, doxycycline, a long-acting tetracycline at a dose of 200 mg/day for two to five days, is the drug of choice. In endemic areas, with risk of recurrent exposure, a dosage of 200 mg/week should be used, with protection of up to 95%. Regarding pre-exposure prophylaxis, azithromycin, like doxycycline, reduces serum positivity (infection) but has no significant effect on the appearance of clinical forms of leptospirosis (ALIKHANI, *et al*., 2018). In situations of major outbreaks, the use of mass chemoprophylaxis is not recommended (MARTINS, CASTIÑEIRAS, 2020).

5 FINAL CONSIDERATIONS

The study of such a neglected disease with a significant impact on public health worldwide represents a challenge due to the lack of actual data reported while observing the documentation of numerous individuals still dying from an old and treatable disease. Therefore, the individual and collective efforts to combat it become fundamental, by highlighting these flaws and synthesizing their main aspects from the epidemiological point of view, forms of transmission and, to this end, their preventive and prophylactic measures - as well as, the understanding of their pathophysiology, methods of diagnosis and treatment, which will be more adequately addressed in part 2 of this review.

After all, orientation based on updated evidence is necessary, so that doctors may become aware and choose effective measures in their practice, when organizations and institutions responsible for the management of a country's health may act to confront the regrettable partial or complete loss of human health for a disease that has already advanced a great deal in scientific terms long enough to have a drastically lower magnitude than it does.

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