

One health: a comprehensive approach to improve prevention and control strategies in Leptospirosis

Saúde única: abordagem abrangente para melhorar as estratégias de prevenção e controle da Leptospirose

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Submission: 18/08/2021 | Acceptance: 03/11/2021

ABSTRACT

Leptospirosis is a zoonosis caused by *Leptospira* spp., a spirochete that presents serovars diversity, whose prevalence, mode of transmission and circulation depend on the ecology and complex interrelation between humans, animals, and the environment in which they coexist. In animals, it affects reproduction causing economic losses and in terms of the environment, the evidence is limited. However, the survival of the bacteria is water favors; is for this, cases of leptospirosis increase with floods and rainfall. Despite its global distribution, epidemic potential, high human mortality rate, and socioeconomic burden, this zoonosis is neglected. Furthermore, worldwide zoonoses prioritization exercises based on the impact on agriculture, human and animal health have led to leptospirosis ranking among the most important zoonoses associated with poverty. This situation reflects the need for an integral management from the regulatory institutions of human, animal, and environmental health; but one main barrier of intersectionality is how the administration is designed for these events control. The current structures lead us to reflect and tend towards a holistic approach, seeking new forms of organization, new strategies to study, control and treat leptospirosis, the control of which is the responsibility of different sectors and disciplines. The comprehensive management of leptospirosis implies a higher level of understanding of the agent and of the biological, socioeconomic, and cultural risk factors in the regions and from a practical perspective, it is necessary to promote joint work initiatives; as well as present evidence of the need for work from a "one health" perspective for a zoonosis that has become an emerging problem in public health.

KEYWORDS: *Leptospira*; surveillance; risk factor; neglected zoonosis.

RESUMO

A leptospirose é uma zoonose causada por *Leptospira* spp., uma espiroqueta que apresenta diversidade de sorvares, cuja prevalência, modo de transmissão e circulação dependem da ecologia e da complexa inter-relação entre humanos, animais e o meio em que convivem. Em animais, afeta a reprodução causando prejuízos econômicos e em termos de meio ambiente as evidências são limitadas. Porém, a água favorece a sobrevivência da bactéria; portanto, enchentes e aumento das chuvas são fatores que têm sido associados ao aumento dos casos de leptospirose. Apesar de sua distribuição global, potencial epidêmico, alta taxa de mortalidade humana e carga socioeconômica, essa zoonose é negligenciada. Além disso, exercícios de priorização de zoonoses em todo o mundo com base no impacto na agricultura, saúde humana e animal levaram a leptospirose a ser classificada entre as zoonoses mais importantes associadas à pobreza. Esta situação reflete a necessidade de uma gestão integral por parte dos órgãos reguladores da saúde humana, animal e ambiental; mas uma das principais barreiras da intersetorialidade é a forma como a administração é projetada para o controle desses eventos. As estruturas atuais levam-nos a refletir e a tender para uma abordagem holística, buscando novas formas de organização, novas estratégias para estudar, controlar e tratar a leptospirose, cujo controle é responsabilidade de diferentes setores e disciplinas. A gestão integral da leptospirose implica um maior conhecimento do agente e dos fatores de risco biológicos, socioeconômicos e culturais das regiões e, do ponto de vista prático, é necessário promover iniciativas de trabalho conjunto; bem como, apresentar evidências da necessidade de trabalhar a partir de uma perspectiva de "uma saúde" para uma zoonose que se tornou um problema emergente de saúde pública.

PALAVRAS-CHAVE: *Leptospira*; vigilância; fator de risco; zoonose negligenciada.

INTRODUCTION

Leptospirosis is a zoonosis that affects the interface between humans, animals and ecosystems with different clinical manifestations and high mortality and morbidity rates in humans and animals in the world. In the human population, most infected are asymptomatic, the annual morbidity is higher than a million people; however, in those who trigger severe disease, it can lead to kidney or liver failure and pulmonary hemorrhage leading to death (CLEAVELAND et al. 2017).

Leptospirosis is a severely neglected tropical disease despite the high burden on human health and livestock production (GARBA et al. 2018). The agent responsible for zoonosis is *Leptospira* spp., a Gram-Negative bacterium with more than 300 serovars. From the clinical point of view, both in animal species and in humans, individuals can occur without any type of manifestation, with mild, acute, or chronic manifestations. As well, it is possible that in the disease the symptoms may be similar to those of other infections, being confused with dengue, influenza, viral hepatitis, brucellosis, borreliosis, mononucleosis, malaria, typhoid fever, yellow fever, rickettsiosis, Venezuelan hemorrhagic fever, pyelonephritis and poisonings (WORLD HEALTH ORGANIZATION 2011, CAIMI & RUYBAL 2020, ORLANDO et al. 2020).

Epidemiological risk factors such as occupational exposure, recreational activities, and international travel increase transmission in susceptible species, mainly in endemic regions. Also, the commercialization of domestic and wild animals in non-endemic regions is an important factor of transmission of leptospirosis from the perspective of one health (GARBA et al. 2018).

In animals, the prevalence of infections by the different *Leptospira* serovars in livestock farms in tropical and subtropical countries is unknown; this explains limitations in the standardization and availability of diagnostic tests. The prevalence is between 35-50% in livestock industry from United States. The serogroup most commonly associated with infection of livestock is Hardjo (GROOMS 2006). In Latin America this zoonosis is endemic and in world livestock it is one of the main causes of economic reduction in this industry (CAMPOS et al. 2017). Reproductive problems are the most notable effect in cattle of presence of *Leptospira* spp.; this causes losses in production, especially by difficulty in controlling the bacteria, that present in the herd, it becomes a reservoir and/or maintenance host, the Hardjo serovar is the one adapted in the bovine species (GUEDES et al. 2019).

The economic impact of disease in bovines is evidenced in reproductive aspects, treatments, and inefficient vaccination. Bovine reproduction is affected by abortions and embryonic mortality (RAJEEV et al. 2017). In Rio de Janeiro, Brazil, in a study carried out on 500 cows, the most important reproductive problem was strongly associated with leptospirosis was the repetition of estrus (LIBONATI et al. 2018). In Caribbean region, serum and kidney samples from cattle, pigs, sheep, and goats were collected in a local slaughterhouse between September 2016 and March 2017. Cattle had the highest seroprevalence (79.8%) followed by pigs (64.8%), sheep (39.4%) and goats (24.8%). DNA was amplified from kidney samples in 18/99 bovines (18.2%), 11/106 pigs (10.4%), 4/106 sheep (3.8%) and 2/105 goats (1.9%); these findings allowed the authors to conclude that more studies are justified and necessary to evaluate economic burden associated with leptospirosis (SHIOKAWA et al. 2019). Also, it is difficult to determine the economic losses, mainly by difficulties related with diagnosis; as well as the increase in global burden of leptospirosis caused by demographic changes that favor an increase in the urban population in tropical regions where floods and storms are more frequent (HAAKE & LEVETT 2015).

Environmental studies are limited; however, water sources are an important transmission vehicle for both humans and animals, and it should also be considered that disease is emergent associated with floods and rainy seasons (ARRIETA et al. 2010). Exposure to soil or water contaminated with the urine of *Leptospira* infected animals is the most common way that humans contract leptospirosis (BARRAGAN et al. 2017). A key factor in transmission to new hosts is ability of pathogenic *Leptospira*'s to persist in an aqueous environment (KURILUNG et al. 2017, THIBEAUX et al. 2017, BIERQUE et al. 2020).

Leptospirosis is a neglected zoonosis with impact humans by epidemic potential, the high mortality rate, and the socioeconomic burden; in the animals, affects the reproduction, the production, and the economy of sector. Also, affect the environment due to its global distribution and because water facilitates growth, maintenance, transmission and distribution of the bacteria (BOUSCAREN et al. 2019). This situation reflects the need for comprehensive management due to impact on agriculture, human and animal health, where a holistic approach is promoted among government entities responsible for controlling and treating leptospirosis. Additionally, leptospirosis is the second zoonosis associated with prioritized poverty out of 13 selected among 286 for having a human mortality >1,000 deaths per year, a morbidity >1 million affected people, a high impact on livestock and a wildlife interface (DOMACHOWSKE 2019). Human population of countries with low economic resources are the most affected and with highest health burden by zoonoses;

especially because they do not have access to drinking water, they have greater contact with rodents and wild animals (ESCANDÓN-VARGAS et al. 2019). In addition, many populations carry out agricultural and livestock practices in a precarious way in rural areas or in urban perimeters, obtaining products of poor quality despite the fact that consumption of meat and other derivatives is low (GRACE 2015).

The comprehensive management of leptospirosis implies a higher level of understanding of disease, the agent, and biological, socioeconomic, and cultural risk factors in the regions. Also, it is important to promote joint work initiatives and present evidence of need for work from "one health" perspective for a zoonosis that has become an emerging problem in public health.

Epidemiology and importance leptospirosis

Global burden of leptospirosis has not been calculated but according to the estimated figures of more than 1.03 million cases per year with an approximate total of 2.90 million years of life adjusted for disability, it has been considered that it represents more than 70% of global burden of cholera (TORGERSON et al. 2015). Leptospirosis has a worldwide distribution can cause fatal clinical problems such as pulmonary hemorrhage syndrome with high morbidity and mortality and presents an occupational risk by direct or indirect contact with the urine of infected animals (PAL & HADUSH 2017).

For a zoonosis such as leptospirosis, risk factors are established that enhance its presentation mainly in tropical and humid regions (ESCAMILLA et al. 2007, HERNÁNDEZ-RODRÍGUEZ et al. 2017). Likewise, the role of rodents in epidemiology and transmission of *Leptospira* is important, especially because they carry pathogenic serovars capable of causing disease in humans and animals (BOEY et al. 2019). The distribution of zoonotic pathogens has been facilitated by geographic, environmental, and biological factors and changes social, cultural, and climatic that affect species and their environments. This undoubtedly requires new approaches that modify the way of facing complex zoonosis in public health. It is necessary to explore new ways of addressing health problems because, despite global, national and regional efforts, mortality, due to care failures, especially in marginalized populations, is still very high (RAMOS & TOVAR 2012).

In developing countries, there is still a lack of integration between sectors of human, animal, and environmental health for the control of diseases, especially zoonoses, causing an increase in their frequency; as well as, controlled ones have reemerged, affecting the population's morbidity and mortality. Like other zoonoses, impacts are related to the increasingly frequent presence of animals in human environments, increasing contact and the possibility of infections, with approximately 75% of recent outbreaks of global importance being of zoonotic origin. Another relevant aspect is diversity of pathogens, bacteria, fungi, parasites and viruses associated with zoonoses, whose data are limited in some regions such as Africa (ASANTE et al. 2019). The prevalence of leptospirosis has been associated with increment of maintenance hosts, wild animal, and poverty some localities. Control strategies must take into consideration the region, number of animals infecting serovar maintenance host and the control epidemiological available (AGUDELO-FLÓREZ et al. 2010). Type of host plays a fundamental role (VAN SEVENTER & HOCHBERG 2016); this, related with ability of *Leptospira*'s to survive in urine and permanent contamination of the environment, constitute outstanding epidemiological characteristics. Humid conditions, the presence of puddles, lagoons and stagnant waters that are easily contaminated become a permanent source of transmission. Aspects such as urbanization in natural areas change the natural environment by providing artificial sources of humidity, changes in temperature and alterations in dynamics of zoonotic pathogens such as *Leptospira* spp. (MILLÁN et al. 2018). Considering epidemiology of leptospirosis and maintenance of *Leptospira* in the ecosystems, it can be inferred that the interrelationship between humans, animals, reservoirs, and the environment is complex, and ecosystems are defining the prevalent serovar, the mode of transmission and epidemic outbreaks.

Impact on human health

Human leptospirosis is related to various risk factors, such as interaction with animals. In rural areas increases the transmission of *Leptospira* spp. by the presence of wild and domestic animals, increasing the spread of the bacteria and the risk of this zoonosis among rural workers. Studies carried out in family farms in Minas Gerais Brazil have identified the simultaneous occurrence of *Leptospira* spp. with some viruses such as BTV (bluetongue virus), BoHV-1 (bovine alphaherpesvirus), BVDV (bovine viral diarrhea virus) in the 476 cattle in the 46 farms. This co-infection with *Leptospira* spp. has shown high seroprevalence, which needs control measures to reduce the economic loss related to these zoonoses. The results of this study showed a seroprevalence of 76.1% for *Leptospira* spp., mainly associated with abortions in cattle evaluated of the 46 farms; therefore, the economy of farms is affected and the risk of transmission in humans is increased by contact with livestock, which has been commonly associated with an increased risk (HAAS et al. 2020).

Leptospirosis can represent up to 20% of febrile pathologies of unknown origin (WORLD HEALTH ORGANIZATION 2011), approximately 17% of people hospitalized for this disease suffer acute lung damage and of these 25% die. It has an endemic global annual average incidence of 5 per 100,000 inhabitants. In the case of Americas, the incidence is 12.5 per 100,000 inhabitants (SCHNEIDER et al. 2017). The diagnosis is established with MAT test; however, it is recommended to include representative serovars of all serogroups for its performance; as well as the local or characteristic circulating serovars of the region in order to limit the number of false negatives due to an incomplete diagnostic panel (WYNWOOD et al. 2015). Additionally, confirmation between two paired serum samples (two weeks apart) that shows a four-fold or more increase in antibody titers is necessary to identify serogroup. This aspect is very important, however, in some countries it is difficult to obtain a second sample, this can be deduced from a study carried out in Colombia where it is reported that 69% of cases of human leptospirosis are not confirmed (unique samples) and this trend has been maintained over the years as the number of paired samples (confirmed cases) have been decreasing; the authors report that from 2007 to 2011 only 31% of the cases have been confirmed; and situation is not very different in other countries of the tropics (BELLO et al. 2013).

Leptospirosis is recognized as an occupational disease that affects certain groups at risk, such as workers in rice fields and other agricultural products, those who perform maintenance of sewers and soldiers, but mainly people who work with animals, whether they are farm workers, slaughterhouses. And veterinarians (GUERRA 2013). People who work in rural areas are at risk when they have contact with water contaminated with *Leptospira* spp. This was evidenced by a study that sought to identify the frequency of seropositive against *Leptospira* by evaluating 1,164 sera from five rodent species by the MAT test. A 6.9% (22/317) was found in *Rattus exulans*, 5.0% (23/464) in *R. rattus*, 3.5% (6/170) in *Bandicota indica*, 2.6% (1/38) in *B. savilei* and 2.3% (4/175) in *R. norvegicus*; the predominant serogroup being Pyrogenes. Additionally, the researchers reported a correlation between rodent data with the predominant human serogroups (WANGROONGSARB et al. 2002, BOEY et al. 2019). The interaction between humans, animals and the environment enhance transmission and risk. In this way, addressing this disease from the One Health concept and with interdisciplinary vision for to understand it and intensify control measures.

Impact on animal health

Generally, *Leptospira* serovars are associated with certain animal species, for example pigs with Pomona and Bratislava, cattle with Hardjo, canines with Canicola, and wildlife with Grippotyphosa and Tarassovi. Despite this, any species can not only be infected with the serovars it maintains but also with serovars maintained by other species, highlighting importance of knowing the serovars and maintenance hosts in each region to understand the epidemiology and carry out adequate control (PINTO et al. 2017, MIOTTO et al. 2018, ZHANG et al. 2019). In the world has been know *Leptospira borgpetersenii* serovar Hardjo (hardjo-bovis) has been recognized as the most common cause of cattle leptospirosis, on the contrary, *Leptospira interrogans* serovar Hardjo (hardjoprajitno) has been isolated in cattle from specific regions of the United Kingdom (GROOMS 2006). Infections caused by *L. interrogans* serovar Pomona and *L. interrogans* serovar Grippotyphosa have also been found to be associated with reproductive failure causing significant economic losses (LIBONATI et al. 2018).

In swine, significantly incidental infections include strain bellowing to the Canicola, Icterohaemorrhagiae and Grippotyphosa serogroups. In the infection of pig the serogroups most commonly are they Pomona, Australis and Tarassovi groups but all of which have alternative wildlife maintenance host (ELLIS 2012, ADLER 2015).

Epidemiological importance of the canine species in leptospirosis allows us to understand the variables related to the acquisition of the disease. This is important for the design of control policies and the number of annual deaths in humans and canines exposed to risk factors such as living with infected animals, relationship with environments contaminated with spirochete, and wild animals (MARAMI et al. 2021, SANTOS et al. 2021).

Environmental factors are determining and are associated with epidemiology of canine leptospirosis (RAGHAVAN et al. 2012) found an association ($p < 0.1$) between hydrological variables and the soil with the status of canine leptospirosis, indicating a lower risk of leptospirosis in dogs with distant residence of water (OR = 0.82; 95% C). Likewise, a study that evaluated the association of canine leptospirosis with the information obtained from an agricultural census found 94 dogs positive for leptospirosis with a significant association of leptospirosis with risk factors such as: houses with a lack of complete sanitary facilities (P = 0.00), poverty situation (P = 0.02), proximity to parks and forests (P = 0.02) (RAGHAVAN et al. 2012).

Leptospirosis model a current health challenge

Leptospirosis is bacterial zoonoses most common in the world, mainly because mammals, including

rodents, livestock, wildlife, and pets, are the main hosts of *Leptospira*, etiological agent of this zoonosis (MAYFIELD et al. 2018). In leptospirosis, the relationship between humans, animals, and ecosystems is evident, which is why it has been classified as a good model of "one health" and from a holistic approach, understanding the disease and control strategies can be improved. In addition, it is increasingly necessary to seek integration for its management due to the impact in various sectors, in numerous risk groups, in many countries, and in various settings. Also, because the control of leptospirosis is difficult due to lack of diagnosis in human population and because it is a disease that is not sufficiently reported, is not recognized and resources are limited, evidencing a lack of interest by governments for its knowledge and management of this zoonosis. In the case of leptospirosis in animals, resources are precarious, generating an inadequate global understanding of this zoonosis (LAU 2016).

Leptospirosis is an excellent example of "one health", which despite the increasing number of cases and the increase in outbreaks around the world continues to be a neglected zoonosis (BENACER et al. 2016). Currently, with the effects of climate change, a considerable increase in leptospirosis cases is projected in various regions; therefore, control in human populations is highly dependent on the control of animals that become infected with *Leptospira* spp., a rather complex and unusual bacterium as considered through genetic studies. The absence of understanding of disease on regional can impact health planning; in some cases, this may affect how authorities manage leptospirosis control programs. Therefore, is necessary integrate professionals of different disciplines to study a zoonosis that affects the human-animal-environment interface (Figure 1). The situation is complicated because the knowledge of the diversity of *Leptospira* is incomplete; serovars are discovered periodically and new species less frequently. Furthermore, studies on the effectiveness of culture media are limited and show that a culture medium may be suitable for cultivating a serovar but other serovars do not have the same response to the culture medium (DELLA ROSSA et al. 2016, GUERNIER et al. 2018). Likewise, the knowledge and perception of human and veterinary doctors about leptospirosis is diverse and it is considered an important problem, especially because the surveillance of this infection in humans is important and in animals it is vital; however, surveillance for veterinary leptospirosis is very limited.

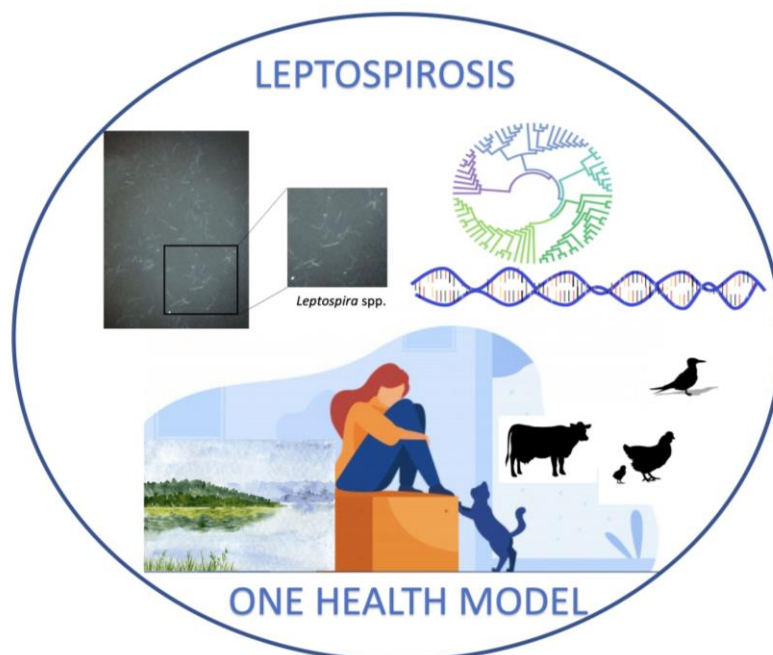


Figure 1. Leptospirosis is an example "one health" by la interaction of animals-human and environment interface. In this model, professionals must participate in different disciplines and diverse experiences that contribute to diagnosis, prevention, control, and surveillance of a zoonosis with worldwide impact.

Taking into account the aspects as mentioned earlier, comprehensive management of this zoonosis is necessary, where the "one health" approach gains strength, especially if the need for joint work is recognized; in this sense, the International Leptospirosis Society (ILS), founded in 1994, is an international resource because it promotes knowledge of this zoonosis, facilitates communication, provides information and provides support through a network of laboratories around the world, facilitating training and the

confirmation of medical and veterinary tests with comparable results worldwide; however, many other available proficiency testing schemes are restricted to medical or veterinary testing (GRACE 2014). Based on global data collected by Global Environmental Action Network against Leptospirosis (GLEAN) is necessary must make research on socioeconomic and environmental factors in different geographic regions that influence the presentation of animal and human leptospirosis cases (GRACE et al. 2012). A support for this comprehensive management of leptospirosis is that the reference centers guide diagnostic laboratories and research institutions by donating strains and reagents and providing recommendations and instructions on various topics to researchers and national and international organizations. Local reference centers provide regional support by confirming diagnoses and the identification of *Leptospira* serovars, the unequivocal characterization of new species, and provide guidelines for the maintenance and integrity of the strains (HARTSKEER & SMYTHE 2015). For their part, international reference centers design, validate and implement diagnostic technologies to ensure quality and carry out international monitoring with recommendations on global burden, distribution, prevention and control of leptospirosis, advising health decision makers to define guidelines and national and international policies (HARTSKEER & SMYTHE 2015, POLO et al. 2019).

CONCLUSION AND AUTHORS INSIGHTS ON THE TOPIC

An integrated vision against leptospirosis is necessary for the prediction, detection, prevention, and response in the animal-human-ecosystem interface for guides the knowledge and management of this zoonosis whose complexity in transmission as too the lack of practical tools to operate locally is a challenge for human and animal health authorities. Similarly, it is a challenge for the scientific community in promoting the development of research, collaboration mechanisms and innovative ideas that can reduce the global impact on human and animal health, livestock production, agriculture and food.

In leptospirosis, the interactions between species and changes in ecosystems affect the dynamics of this zoonosis; therefore, fostering the “one health” approach can favor its understanding and facilitate health processes from the formation of collective work units for establish of joint solutions from the human-animal-environment interface.

The study of leptospirosis should be promoted from the integration of human, animal, and ecosystem health because multiple risk factors and social determinants condition the presentation and distribution of this zoonosis, generating a strong influence on prevention and control measures.

ACKNOWLEDGMENTS

To the Universidad de La Salle, School of Basic and Applied Sciences and School of Agricultural Sciences.

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