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A Systematic Review of the geographic distribution of pathogenic *Leptospira* serovars in the Americas, 1930-2017

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Abstract: Leptospirosis is an important public health problem caused by Leptospira. The objective is to characterize the geographic distribution of pathogenic leptospira serovars in the Americas through a systematic review of the literature between 1930-2017. Searches were conducted in six scientific databases (PubMed, Web of Science, Embase, Lilacs, Scopus and Cochrane). We included studies conducted unambiguously in the Americas, that investigated infection of *Leptospira* in humans and animals in their natural environments with serovar identification. 283 articles were included, of which 69 were studies in humans, 86 in wild animals, and 182 in domestic animals. Most of them conducted in Brazil (104, 36.7%) and in rural environments (158, 55.8%). Bovines, equines and dogs where the most frequently studied domestic species. However, a large diversity including 80 species of wild animals were studied. Icterohaemorrhgiae, Canicola, Pomona and Grippotyphosa were the most common serovars, described in 46 (16.2%), 38 (13.3%), 32 (11.3%) and 26 (9%) of the articles, respectively. The Results indicate a large concentration of studies in Latin America, with emphasis on Brazil, in wild mammals and three main domestic animal groups. Our results emphasize the need for studies that delve into the relationships of the epidemiological cycle, environment, and health.

Key words: zoonosis, Leptospirosis, serovars, systematic review, distribution, Americas.

INTRODUCTION

Leptospirosis is a neglected infectious disease of remarkable social and economic impacts, whose etiologic agent are bacteria of the genus *Leptospira* (Ko et al. 2009). The pathogen has biological traits that make it viable in the environment for long periods of time, being an important factor for its transmissibility, as well as having a multitude of reservoir species (Ko et al. 2009). Leptospires have a cosmopolitan distribution, with higher incidence in warm and humid tropical and subtropical climates (Costa et al. 2015). The disease is considered the zoonosis with the widest distribution in the world, as well as a global public health concern (Costa et al. 2015). Leptospirosis presents a wide array of epidemiological patterns, including the transmission in urban, rural, and sylvatic areas. It is even linked to sport and recreative activities (Bourque & Vinetz 2018, Husbandry & Husbandry 2011). Thus, it is considered a zoonosis, whose management and control strategies is complicated (Ko et al. 2009, Schneider et al. 2017).

It is estimated that, Latin America, Costa Rica, Peru and Ecuador present the highest incidence rates of leptospirosis in the world (Schneider et al. 2017). In Brazil, several studies including those on leptospirosis have been conducted in domestic animals such as cattle, equines and caprids (Favero et al. 2017a, Meny et al. 2019). In bovines, leptospirosis affect milk production and reproduction, a cause of concern for cattle ranchers (Faine et al. 1999, Lucheis & Ferreira Jr. 2011).

Currently, there are 35 known species of *Leptospira*, genetically classified in three groups: pathogenic, intermediaries and saprophytes (Vincent et al. 2019). Serologically, there are over 260 serovars of leptospires, with several of them poorly studied. The serovars icterohaemorrhagiae, canicola, tarassovi, wolffi, bataviae, hardjo and grippotyphosa, copenhageni, djasiman, panama and patoc are involved frequently in human infection cases (Adler 2015). However, infection is mostly asymptomatic in animals, with occasional manifestations of clinical symptoms depending of the serovar involved (Vieira et al. 2018).

The geographic distribution of Leptospira is described in some articles, mainly in Latin American countries, such as Brazil (Pasquali et al. 2017) and Argentina (Orozco et al. 2014), and also in the USA (Pedersen et al. 2017) and Central America (Suepaul et al. 2010). Most of these studies were georeferenced with maps demonstration, and carried out in domestic and wild animals. However, none of them investigated the variability of reservoirs and serovars. Given these aspects of the cycle, it is important to highlight the geography of pathogenic leptospires and understand the diversity of serovars in the Americas, with the potential to enhance prevention and health promotion programs. Hence, this review aims to characterize the geographic distribution of pathogenic *Leptospira* serovars in the Americas.

MATERIALS AND METHODS

Search Strategy

The present study observed and followed the recommendations of the PRISMA statement for Systematic Reviews and Meta-analyses (Supplementary Material - Table SI). Searches were conducted in six scientific databases (PubMed, Web of Science, Embase, Lilacs, Scopus and Cochrane) employing the basic descriptors: "Leptospir OR Leptospira OR Leptospiral OR Leptospirosis AND [geographic region]", with [geographic region] being substituted, once at a time, by one of the following: Central America, Caribbean, North America, South America. And the regions: Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Bermuda, British Virgin Islands, Cayman Islands, Cuba, Dominica, Dominican republic, Grenada, Guadeloupe, Haiti, Jamaica, Martinique, Montserrat, Netherlands Antilles, Puerto Rico, St. Kitts and Nevis, St. Lucia, St. Vincent and the Grenadines, Trinidad and Tobago, Turks and Caicos Islands, U.S. Virgin Islands, Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Canada, Mexico, United States, Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela. Our Search Strategy took into consideration the specificities of each scientific database (Table SII).

Study triage and criteria

Article triage and classification was performed in two stages, involving review of article's abstract and title, and subsequent review of full-text in accordance with a carefully defined inclusion and exclusion criteria. After retrieving the results from the databases, each article had its title and abstract examined by two researchers. Each article was classified after evaluation, and an inter-observation concordance was evaluated by calculating the kappa statistic. Discordant articles were evaluated by another researcher in the group. Citations with no abstract available were retained for the next stage for full-text evaluation. We employed Mendeley® as the bibliographic database manager for the triage, manipulation and annotations of information obtained from the articles. All Search results were directly downloaded to Mendeley®, which also was used to flag duplicates.

Inclusion and Exclusion criteria

The inclusion criteria include only full-text articles published in Portuguese, English and Spanish, between 1930 and 2017, and performed in the Americas. Abstracts, literature reviews, editorials, letters to the editor, opinion papers, comments without original data and non-scientific communications were excluded from the screening process. The screening of articles took place in two stages; The first stage involved reading of titles and abstracts, and the other involved reading of the full text.

Screening of abstract and title of published articles

Specifically, article exclusion based on abstract and titles obeyed the following criteria: a) Non-target etiologic agent or disease; b) Experimental studies (either *in vitro* or *in vivo* cellular, biochemical or other assays that do not include data on natural occurrence of leptospires in humans, animals or the environment); c) Description of laboratory methods, drug therapeutics and vaccine tests; d) Leptospirosis as part of the diagnose evaluation or as part of differential diagnostics, but with no diagnosis of infection or exposure to leptospirosis established; e) Social Sciences or modelling studies that do not examine people or animals in the natural environment; and f) Continents or countries that do not belong to the Americas, or studies with no specified region.

Screening of full-text of published articles

After abstract and title evaluation, the articles went through a second triage, focusing on the diagnostic methods, considered as presented in (Table SIII). We excluded articles with non-specific serovar diagnostic tests or serogroup identification, or that are not CAAT, FSA (Factorial Seric Analysis), monoclonal antibodies, MAT and PFGE. In this stage, several articles were excluded after reading the full text, considering also the exclusion criteria of the previous stage, as described above (Figure 1). We did not intend to exclude articles based on serologic titer parameters. Nonetheless, to establish a methodologic quality cutoff, we opted to consider titers >50 for serovar diagnosis via MAT. These inclusion and exclusion criteria were established after consulting several Leptospirosis specialists and taking into account other studies in this thematic area.

Data extraction and synthesis

A digital data collection form was created using the digital platform Research Electronic Data Capture)/Fiocruz (RedCap) with all the criteria of interest for the study and the aim of organizing and facilitating posterior analysis. The form comprised of four sections: first, the article description (year, data collection period, study design, inclusion and exclusion criteria and type of diagnostics test); the second section included variables such as type of domestic animal reservoirs, present serovars and their respective incidences; the third section included variables on type of wild animal reservoirs (species and absolute frequency), involved serovars and their incidences; and the fourth section included details on human reservoirs (absolute frequency), present serovars and incidence.

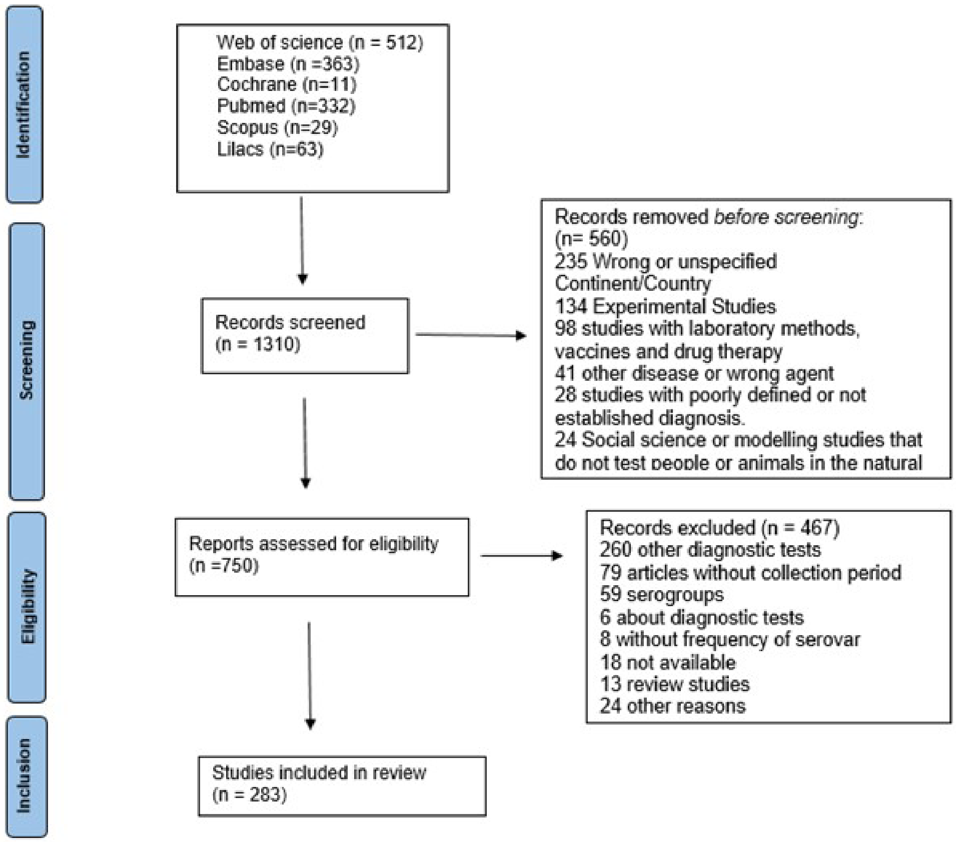

Figure 1. Flowchart of the article selection process.

The form was tested several times with mock datasets and improved accordingly during data collection. Data synthesis was also performed using RedCap, where basic descriptive statistics were performed such as mean, median, mode and standard deviation. We built tables with the variables referring to reservoir and serovar, and the data was also used to georeference cases using QGIS 3.8. This study, despite focusing on pathogenic species, also collected data from intermediate species such as Wolffi and saprophytes such as Patoc, which do not cause infections in humans and animals, but contribute to the leptospirosis transmission cycle, as the host may be contaminated with one or more serovars.

Critical evaluation of methodological validity and bias assessment

Selection bias is common and expected in systematic review studies; thus, the present study applied strictly the PRISMA protocol guidelines, respecting the criteria for methodological quality and the stepwise article selection process. Studies without an explicit methodology were excluded, as their data can be deemed unreliable. Information bias might also be present in studies with large volume of data. To minimize this, we applied the RedCap/ Fiocruz form, containing the variables of interest for this study.

Finally, this study presents some limitations, such as the possibility of overestimating the serovar frequency, as some samples present co-agglutination in MAT tests. However, despite this limitation, this test is widely used to identify serogroups as commonly found in literatures. As such, only 59 articles related to serogroups were excluded, which does not compromise the results presented here.

Another important limitation observed during the screening of studies was the lack of specification of the country or continent where the study was carried out, resulting in the exclusion of a large part of the literature (235 excluded articles), which might have influenced the results presented here.

RESULTS

A total of 1310 articles were retrieved according to the search criteria (Table SII). However, only 750 (57%) were selected following already established inclusion and exclusion criteria. After full-text analysis, 481 articles were excluded (Figure 1). Of the remaining 283 articles, 8 had their period of investigation between 1970-1979, 32 between 1980-1989, 16 between 1990-1999, 4 between 2000-2009, and 81 between 2010 and 2017. Most of the studies were carried out in Brazil (104; 36.7%). Regarding study design, 243 (86.8%) studies were cross-sectional and 15 (5.4%) were case control; with 158 (55.8%) performed in rural areas. More than 90% of the studies used only the MAT test in association with other tests (Table I). One hundred and eighty-two (49.2%) of the studies were on domestic animals, 86 (30.7%) with wild animals and 69 (18.6%) with humans (Table II).

Most studies examined dogs (59, 32.4%), bovines (48, 26.4%), and equines (25, 13.7%) (Table II). Amongst wild animals, the most frequent were the boar, *Sus scrofa* (6, 7%), the racoon, *Procyon lotor* (6, 7%), California sea lion, *Zalophus californianus* (7, 8%), and the White-tailed deer, *Odocoileus Virginianus* (3, 3.4%). The most prevalent serovars were Icterohaemorrhagiae (221, 61.2%), Pomona (212, 58.7%), Canicola (188, 52.1%), Grippotyphosa (172, 47.6%), Bratislava (153,

Table I. Diagnostic tests used in articles between 1930-1970.

Reservoir	Test	Article (N, %)
Human (N=69)	MAT	68(98.5%)
	CAAT	1(1%)
	FSA	0
	MoAB	0
	PFGE	1(1%)
	ELISA/EIA	17(24.6%)
	PCR	3(4%)
	IFA	3(4%)
	DNA TEST	2(2%)
	MLVA	0
Domestic animal (N=182)		
	MAT	151(83%)
	CAAT	0
	FSA	1(0%)
	MoAB	1(0%)
	PFGE	2(1%)
	ELISA/EIA	7 (4%)
	PCR	12(6.5%)
	IFA	6(3%)
	DNA TEST	3(1.6%)
	MLVA	0
Wild animal (N=86)		
	MAT	81(94.1%)
	CAAT	1(1%)
	FSA	0
	MoAB	0
	PFGE	4(4.75%)
	ELISA/EIA	2(3.3%)
	PCR	8(9.3%)
	IFA	4(4.75%)
	DNA TEST	1(1%)
	MLVA	0

Microscopic agglutination test (MAT), Cross-agglutinin absorption test (CAAT), Factor serum analysis (FSA), Monoclonal antibodies (MoAB), Pulsed-field Gel Electrophoresis (PFGE), ELISA or EIA (Enzyme-Linked Immunosorbent Assay), PCR(Polymerase Chain Reaction), IFA (Indirect Immunofluorescence Assay), DNA test, MLVA(Multiple-Locus Variable number tandem repeat Analysis).

42.4%), Hardjo (155, 42.9%), Autumnalis (107, 29.6%) and Copenhageni (78, 21.6%).

Regarding serovars, the studies registered a wide variety (Table II), and all groups classified as saprophytes and intermediary pathogenic were included for posterior refinement. As expected, the repetition of several serovars in different studies was a consequence of the use of panels established diagnostic protocols.

This table considers the total of serovars independently of the country of identification. Posteriorly, with the georeferenced data and stratification by locality and reservoir, it is possible to note that part of the domestic and wild reservoirs has homogeneous distribution (Figure 2), but with different serovar frequencies between countries. Studies involving domestic and wild animals were mainly conducted in Brazil (wild animals: N=15; 14.4%; domestic animals N=97; 53.2%), with the United States being a heavy contributor on wild animal studies (40; 46.5%). Studies on domestic animals in Brazil were mainly conducted with dogs (23; 22.1%) and bovines (28; 26.9%). Studies on humans were mainly conducted in Latin America, especially in Brazil and Colombia.

The geographic analysis makes evident that countries present different serovar frequencies and diversity, even when comparing the same reservoirs.

Serovar distribution in humans was very diverse considering the 69 studies recovered, with serovars of Bratislava (42%) and Grippotyphosa (43%) being the most frequent and located in Colombia. On the other hand, the serovars responsible for the more serious clinical manifestations such as Icterohaemorrhagiae and Canicola, were more common in Brazil (23%) and Argentina (7%) (Figure 3).

Studies conducted in humans in the USA and Canada showed a low frequency of serovars, with the most common been Canicola and Hardjo respectively.

Amongst the domestic animals analyzed, only dogs, bovines and equines were mapped (Figure 4). The other domestic reservoirs registered were swine, caprids, sheep and cats. Regarding serovar diversity, the number of articles per reservoir was 28 for dogs, 11 for cats, 11 for caprids, 17 for sheep, 18 for swine, 22 for equines and 24 for bovines. The most frequent serovar found in cats were Icterohaemorrhagiae, Canicola, and Autumnalis. These serovars were located in Brazil, the USA, and Colombia. In goats, the most frequent serovars were Autumnalis, Pomona, Hardjo, and Icterohaemirrhagiae, located mainly in Northeastern Brazil. In this same region, the most frequent serovars in sheep were Autumnalis, Pomona, and Bratislava. In pigs, serovars of Autumnalis, Icterohaemorrhagiae, and Pomona, were identified more frequently in the northeast region of Brazil and the USA, Texas, Oregon, California, Iowa, and Hawaii.

Brazil was the leading country in number of studies on domestic animals. Studies on bovines detected the serovars Wollfi (77%), Bratislava (57%) and Icterohaemorrhagiae (55%); and in dogs, the most common serovars were Bratislava (41%), and for equines, Gippotyphosa (43%) and Bratislava (55%) (Figure 4 a, b, c).

Regarding wild animals, 86 studies registered over 80 species in the Americas, with the most concentration observed in the USA (40) and Brazil (15). The majority of the animals studied were terrestrial, in special boars and racoons, but we also identified aquatic animals such as sea lions and manatees, as well as reptiles such as Boas and crocodiles. For these reservoirs, the most common serovars were Icterohaemorrhagiae, Pomona, Grippotyphosa and Canicola (Figure 5). Most animals were examined in forests, zoos, parks and reserves.

Table II. **Most frequent serovars for humans, domestic and wild animals, in 283 articles from 1930-2017.**

Reservoir	No (%) of studies[a]	Serovars identified	No (%) of studies[b]
Humans	69 (19%)		
		Icterohaemorrhagiae	47 (68%)
		Canicola	38 (55%)
		Pomona	32 (46%)
		Grippotyphosa	27 (39%)
		Bratislava	22 (32%)
Dogs[c]	59 (32%)		
		Canicola	52 (88.1%)
		Icterohaemorrhagiae	42 (71.1%)
		Pomona	40 (67.7%)
		Grippotyphosa	38 (64.4%)
Bovines	48 (26.3%)		
		Hardjo	35 (72.9%)
		Pomona	32 (66.6%)
		Icterohaemorrhagiae	30 (62.5%)
		Grippotyphosa	28 (58.3%)
Equines	25 (13.7%)		
		Pomona	21 (84%)
		Bratislava	20 (80%)
		Hardjo	19 (76%)
		Grippotyphosa	18 (72%)
		Icterohaemorrhagiae	18 (72%)
Pigs[d]	15 (8.2%)		
		Pomona	14 (93.3%)
		Icterohaemorrhagiae	8 (53.3%)
		Autumnalis	7 (46.4%)
		Canicola	5 (33.3%)
		Hardjo	4 (26.6%)
Rattus	7 (3.8%)		
		Icterohaemorrhagiae	4 (57.1%)
		Grippotyphosa	1 (14.2%)
		Pomona	2 (28.5%)
		Tarassovi	2 (28.5%)
Wild Animals	86 (30.7%)		
		Pomona	48 (55%)
		Canicola	45 (52.3%)
		Icterohaemorrhagiae	43 (50%)
		Grippotyphosa	39 (45.3%)

[a]Number and proportion of studies stating information on a reservoir between 283 studies. [b]Number and proportion of studies stating information on a serovar identified in a specific reservoir. The sum of proportion exceeds 100% because several serovars are reported per study. [c]From a sample of 59 dogs. [d]Domestic pigs (total=182: domestic animal). Obs: The articles presented more than one host and more than one serovar. In this way, the calculation of the proportion is based on inexact proportions.

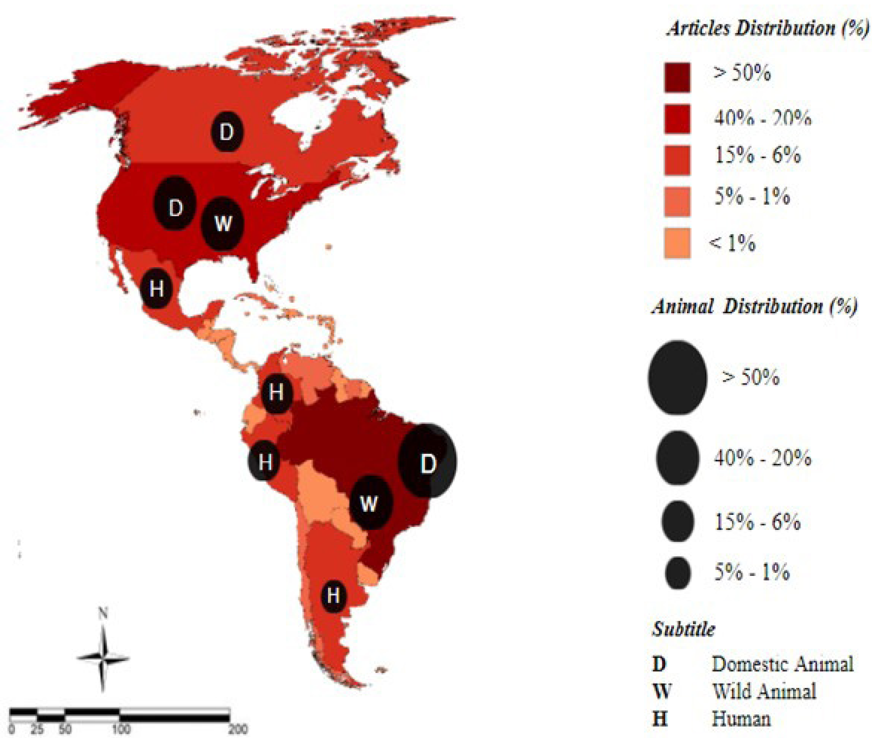

Figure 2. Spatial distribution of studies by reservoir groups,1930-2017.

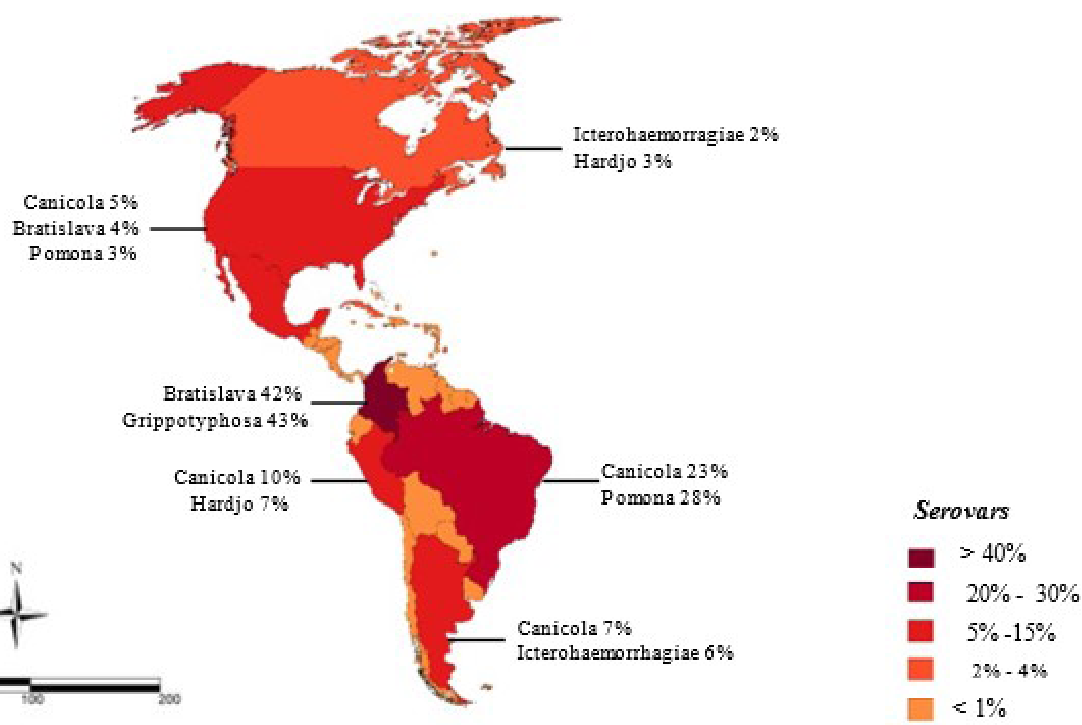

Figure 3. Geographical distribution of the serovars present in humans, 1930-2017.

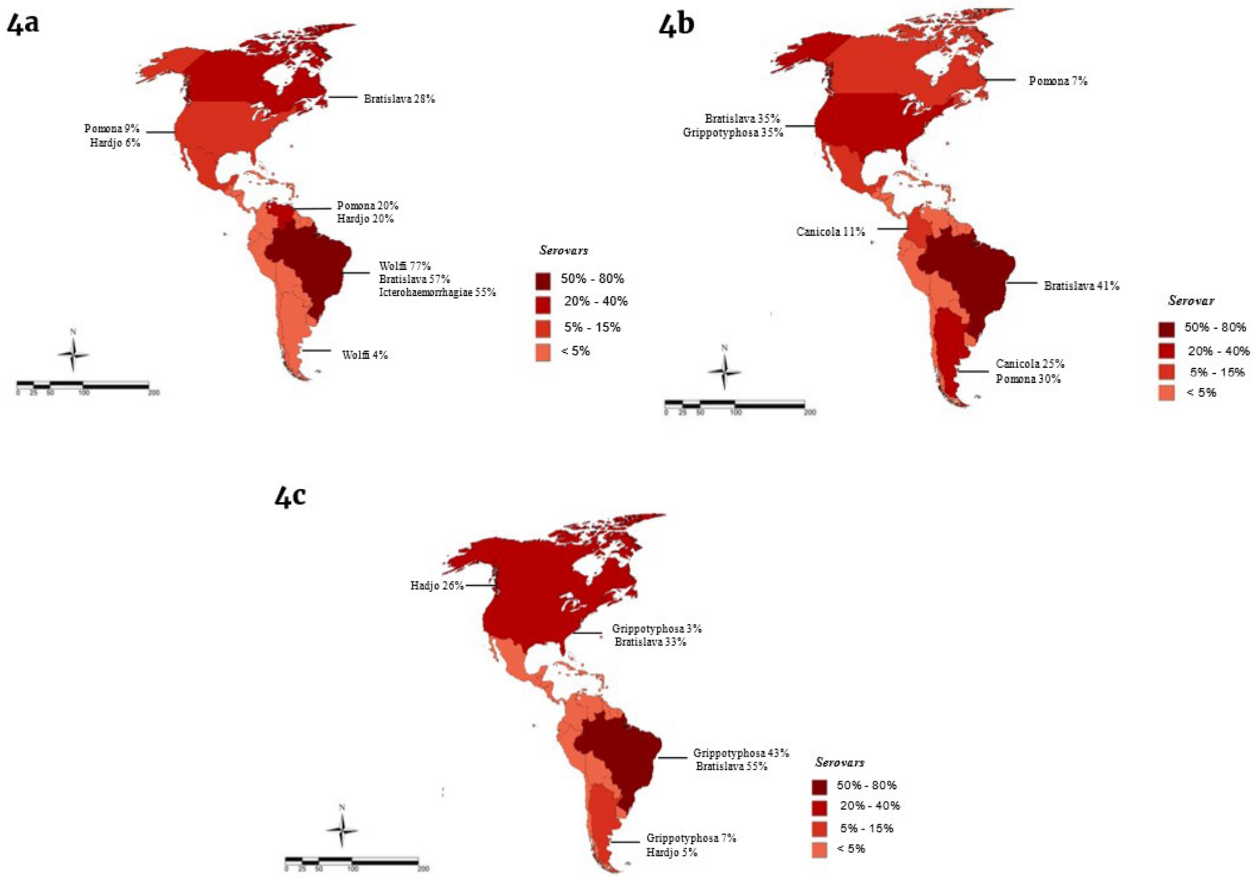

Figure 4. Geographical distribution of serovars present in the three main domestic reservoirs, 1930-2017. 4a. Bovines. 4b. Dogs. 4c. Equines.

DISCUSSION

This study demonstrated a predominant distribution of seven Leptospira serovars (Icterohaemorrhagiae, Pomona, Canicola, Bratislava, Wolffi, Hardjo, and Grippotyphosa) in the Americas, with major concentration in Brazil, the USA, Canada, Argentina, and Colombia. This variability of serovars in humans is clearly seen, as the study encompasses all countries in the Americas, especially Colombia and Brazil. However, the variability of serovars in domestic and wild animals is more pronounced in Brazil and the USA.

There are about 35 pathogenic species of leptospiras, and over 250 serovars, with *Leptospira interrogans*, *Leptospira kirschneri* and *Leptospira noguchii* causing the most infections in humans (Vincent et al. 2019). Serovar or serotype is a variation of the types of bacteria characterized from the composition of its plasma membrane and represents the basic taxonomic unit. In Brazil, the serovars Icterohaemorrhagiae and Copenhageni are often related to the most severe cases (Adler et al. 2015).

The transmission of leptospirosis is influenced by the characteristics of the infectious

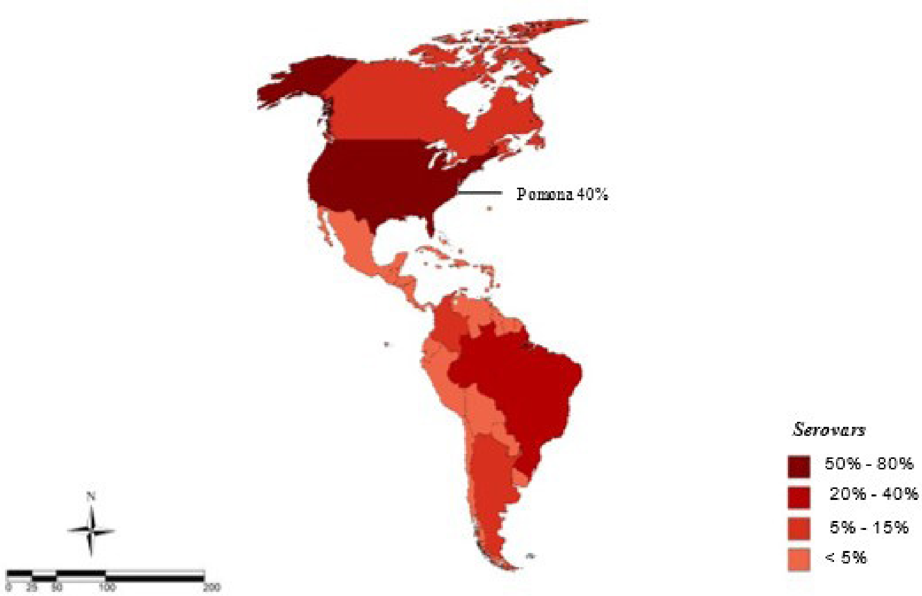

Figure 5. Geographic distribution of serovars found in wild animals,1930-2017.

agent, the susceptibility of hosts, demographic clustering, movement, the interaction between species and populations, the purpose of animal use, and, above all, the environmental conditions that allow the maintenance and multiplication of the infectious agent (Adler et al. 2015). The Leptospira cycle basically involves three components: environment, reservoirs, and humans (accidental host). The main reservoir host for the pathogens are rodents, however, other domestic and wild animals can act as secondary reservoirs. Transmission therefore occur when there is direct contact with infected animals, or indirectly, when there is contact with soil or water contaminated with infected urine of the rodents (Haake & Levett 2015a, Levett 2015). Humans therefore acts as an accidental host, and are not essential for the maintenance of Leptospira's biological cycle. Transmission between humans is rare, but can occur, through semen and breast milk or directly through sexual contact or artificial insemination. In this perspective, humans have a very important role in epidemiologic and public health aspects (Haake & Levett 2015b, Ullmann & Langoni 2011a). Studies have demonstrated that some serovars are more frequently found in human population, such as Icteroahemorrhagiae, Canicola and Pomona (Adler & la Pena Moctezuma 2010). However, the reason for this specificity, and the mechanism of interaction between serovars and humans is still unknown. Nonetheless, these serovars are capable of causing severe forms of the disease in humans, such as Weil's syndrome (Ko et al. 2009).

The distribution of these serovars in humans, as observed in this study, is concentrated in the equatorial and tropical regions, where temperatures and humidity are higher (Ullmann & Langoni 2011b). Although no spatial correlation tests was performed in this study, this phenomenon is well established, as *Leptospira* presents high biological adaptive capabilities to survive and stay viable in environment with temperatures around 26°C, thus increasing its transmissibility (Faine et al. 1999).

The serovar Icterohaemorrhagiae was more frequent in Brazil and Colombia. In the former, Other serovars such as Hardjo, Canicola and Grippotyphosa were also reported, which could be justified by the high number of studies conducted in the country (Bello et al.

2013). In Colombia, the most frequent serovars were Bratislava and Canicola. The presence of Pomona, Icterohaemorrhagiae and Canicola is widely cited in literature (Lacerda et al. 2008). The serovar Bratislava was not common in humans as expected, given its higher affinity for swine reservoirs (Brown et al. 2011). The presence of serovar Hardjo in humans might be linked to the proximity with cattle raising, for example, as it is known that this serovar is frequent in bovines,and could be transmitted to humans through contact with animal waste and milk (Favero et al. 2017a). The main serovars associated to the severe forms of leptospirosis are Icterohaemorrhagiae and Canicola, which include manifestations such as jaundice, renal insufficiency and hemorrhage (frequently in the lungs) known as Weil's syndrome (Brito, 2018; Ko et al. 2009). A very high number of studies on domestic animals, mostly on bovines were reported from Brazil. This could be attributed to the tradition of been a beef producing country, with high interest in the international market. The predominant serovar was Bratislava, followed by Icterohaemorrhagiae and Hardjo (Dewes et al. 2020, Otaka et al. 2012). This data deviated from what is normally observed in literature, which reports that the serovar Hardjo has specificity for bovine reservoirs (Magalhães et al. 2020). Nonetheless, the serovar Hardjo is the one of the most frequently found serovar in domestic animal, and it is responsible for several health problems such as infertility, premature calves, miscarriages and mastitis (Loureiro & Lilenbaum 2020, Mineiro et al. 2007).

In bovines, *Leptospira* infection could be characterized into two groups, with the first group involving strains that are adapted to animals and are not dependent on climate and region, such as Hardjo, and another involving strains transported from other animals, either wild or domestic and are dependent on environmental factors, such as Wolffi, Pomona, Grippothyphosa, Canicola and Icterohaemorrhagiae serovars (Favero et al. 2017b). Studies of serological surveys carried out in Minas Gerais (Ribeiro 1983), Mato Grosso (Madruga et al. 1980), Rio de Janeiro (Martins & Lilenbaum 2013), São Paulo (Langoni et al. 2000) and Pernambuco (Oliveira et al. 2001) presents a high frequency of reactive cattle for Hardjo. This shows the strain is of priority concern in Brazil, thus requiring appropriate management actions and control measures. In addition, there are related evidence on the importance of cattle as a reservoir in the transmission of leptospirosis, as they can be directly or indirectly related to the transmission of leptospirosis to humans, as these animals are close to production in rural areas, through beef and dairy farming.

The serovars of Grippotyphosa and Bratislava reported among dogs in the USA and Brazil, respectively, demonstrates the diversity of the presence of other serovars besides Pomona, which is the most frequently found serovar in this species (Kikuti et al. 2012). This diversity of non-specific serovars is a characteristic that might be present in any reservoir, owing to the presence of co-agglutination in samples collected for testing (Cortez et al. 2020). Dogs have important roles in the epidemiological cycle of leptospirosis, as it can transmit the disease to humans through prolonged domestic contact. They are thus considered maintenance hosts and are usually asymptomatic. These animals are part of the sentinel species, and are important for precocious detection of leptospirosis in the environment because they are more exposed to risk factors and environmental contamination. Their contamination may occur from direct contact with water or soil contaminated with leptospires, or when they have primary contact with other contaminated animals, or when they act as predators of rodents (Cortez et al. 2020, Ghneim et al. 2007).

The USA and Brazil were the countries with the most studies on equines, with Pomona and Bratislava/Icterohaemorrhagiae being the most frequent serovars, respectively. This corroborates with some studies in literature, where horses are considered maintenance hosts for these serovars, with several cases of infection (Alves et al. 2016, Arent et al. 2016, Pinna et al. 2011). The main clinical manifestations in these animals are uveitis, miscarriages, stillbirths, premature delivery and hepatic and kidney disfunction (Divers et al. 2019). Some studies indicate that serovar Pomona is responsible for reproductive abnormalities and ocular syndromes in equines (Carpio & Iversen 1979, Donahue et al. 1991). Although leptospirosis in horses is considered uncommon, but despite this, its importance should not be neglected, as it can be a source of infection and transmission to humans and other animals (Tirosh-Levy et al. 2021).

Studies in wild animals shows that there is interest in knowing the serovars in these reservoirs, especially in controlled environments such as zoos, as they are potential transmission sites Vieira et al. 2018 (Table SIV). Among reported animals, mammals such as racoons and boars were frequently studied in Brazil and the USA. Racoons are animals that frequently occupy rural environments, but can be easily found in urban settings and could be carriers of several diseases such as canine distemper and feline parvovirus, as well as *Leptospira interrogans,* with its most frequent serovars being Icterohamorrhagiae, Grippothyphosa and Pomona (Allen et al. 2014, Junge et al. 2007).

Boars (or wild hogs) are considered potential leptospirosis spreaders, and their population growth increases the risk of contact with humans and domestic animals which therefore increases the risk of transmission. The main serovars found were Bratislava, Icterohaemorrhagiae and Pomona (Pedersen et al. 2017), and the clinical manifestations are limited to miscarriage, muscle spasms, muscle weakness and stiffness, rarely resulting in death. Although the majority of the identified animals were mammals, and that the main leptospirosis transmission route is through their urine, it is important to highlight the cases of infected reptiles observed, as there is little information about the epidemiology of leptospirosis and its serovars in this group, which forms a knowledge gap on this kind of transmission (Biscola et al. 2011, Rodrigues et al. 2016). However, according to some studies, snakes might be important leptospire reservoirs, especially given their diet rich in rodents, the main leptospirosis reservoirs. Leptospirosis in snakes normally is not associated to any clinical symptoms, but they can carry the bacteria in their kidneys for long periods of time (Abdulla & Karstad 1962, Hyakutake et al. 1980).

The importance of studying domestic and wild animals is based in the complexity of the transmission cycle of *Leptospira*, as these animals might have contact with humans directly or indirectly through, for example, recreational activities or people working in their environments, or by contact with domestic animals. In view of these aspects, and knowing this complexity of the epidemiological cycle of leptospirosis, it is expected that measures and actions aimed at the primary prevention of leptospirosis are based on decreasing human contact with animals potentially contaminated with leptospires, thus avoiding cases of the disease and its socioeconomic consequences. This study therefore presents some inherent biases of systematic review, such as, for example, selection and information biases, which could underestimate the frequency of some serovars in detriment of others. Also, during the process, for some studies, we observed some issues with concepts, or absence of definition of serogroup and serovar, prevalence and rates.

CONCLUSIONS

Leptospirosis is a neglected disease worldwide, with huge repercussions in human and animal health, as well as being an economic burden in endemic countries. This systematic review therefore adds some important contributions to the knowledge of leptospires and their geographic distribution. The variability of pathogenic leptospire serovars (Hardjo, Bratislava, Icterohaemorrhagiae, Grippotyphosa and Pomona) in the regions of the Americas, mainly from Brazil, USA Argentina, Canada and Colombia is important to support development and planning of preventive measures and more efficient control actions. These actions could ultimately contribute to reduced transmission of leptospirosis and other human and animal diseases. Finally, more profound studies on the environmental influence on serovars are important, to complement available evidence on the interaction between these components for pathogen survival.

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SUPPLEMENTARY MATERIAL

Table SI. PRISMA checklist items to be included in the narrative report of the systematic review.

Table SII. Search strategies for each database used in the systematic review.

Table SIII. Diagnostic tests used for *Leptospira* serovar identification considered in this study.

Table SIV. Wild animal article, 1930-2017.

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