

A retrospective analysis of the leptospirosis research in Colombia

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Abstract

Introduction: Leptospirosis is a re-emerging infectious disease whose prevalence is often underestimated, not only in Colombia, but in most developing countries. The objective of this paper is to assess the research status of leptospirosis in Colombia in order to identify trends, knowledge gaps, and directions for future research.

Methodology: With the aim of gathering all the information available on leptospirosis in the country, a web search was conducted in various indexes and databases. The search terms used were: Leptospirosis + Colombia. A total of 95 publications were found and analyzed using descriptive statistics.

Results: The first report of leptospirosis in the country was published in 1957. More than 60% of the published works focus on the prevalence of the disease. The Central part of the country is the area with the highest number of publications. MAT was used in 84% of the prevalence studies and humans are the most studied taxonomic group, with 45% of the publications. The highest prevalence of the disease was registered for rodents (82.7%, 62/75), followed by humans (67.9%, 53/78), pigs (67.6%, 342/506), and dogs (67.2%, 41/61). The prevalence of the disease in the country is associated with occupational factors, hygiene conditions and contact with rodents.

Conclusion: Although leptospirosis is a prevalent disease in Colombia, the limitations of the diagnostic techniques used and the lack of a unified criteria on titers thresholds, make an accurate assessment of the prevalence of the disease in the country problematic.

Key words: Leptospirosis; research; Colombia; public health

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Introduction

Leptospirosis is a zoonosis caused by pathogenic bacteria of the genus *Leptospira*. It has worldwide distribution, although it is more frequent in tropical and subtropical areas. Over the past years, it has been recognized as an emerging disease [1-4], however, its occurrence is often underestimated due to the lack of awareness, non-specific symptomatology, and in many developing countries, to the lack of resources to confirm the diagnosis. It represents not only a public health problem but an economic one, since it causes large economic losses to the livestock industry [5].

Transmission in humans usually occurs through direct or indirect contact with the urine of an infected animal. Although exposure to the disease in humans has been primarily related to occupational factors (animal-associated activities), transmission through contaminated water (either by bathing, drinking, or exposure during flooding) has also been reported [2,6-8]. The clinical manifestations of the disease vary from mild to extremely severe symptoms and include: jaundice, anorexia, headache, vomiting, abdominal pain, nausea, coughing, diarrhea, and renal failure [9].

There are various methods that can be used to diagnose leptospirosis; however the microscopic agglutination test (MAT) is considered the “gold standard” method. Other methods include: dark field examination, immunofluorescence, culture, Elisa IgM, dot Elisa, and polymerase chain reaction (PCR). The literature on these methods is extensive, and several authors have discussed the advantages and limitations of each method, as well as the discrepancies between the diagnostic results [10-16].

Although an article describing the distribution of the disease in Latin America published in 1960 listed Colombia as a leptospirosis-free country [17], a national publication [18] had previously reported the occurrence of the disease in the country three years before. The first recorded outbreak of the disease in Colombia occurred in 1995, affecting people from poor neighborhoods on the Atlantic coast. This event was associated with exposure to rodents and flooding [8]. Another outbreak was reported among the people of Risaralda in 2006 which resulted in four fatalities [19].

The main objective of this paper is to assess the status of the scientific study of leptospirosis in Colombia. To my knowledge, this is the first attempt to gather all the available scientific information on leptospirosis in Colombia with the objective of identifying the trends in research, knowledge gaps, and directions for future research.

Methodology

During the month of February 2012, a web search with the aim of collecting all published works on leptospirosis in Colombia was conducted, searching the following indexes and databases: ISI Web of Knowledge (all databases), Science Direct, JSTOR and Medline/PubMed. In order to increase the number of results, a search in Google Scholar was also conducted, which includes a variety of databases such as: redalyc, SciELO and LILACS. The search terms used were: Leptospirosis + Colombia. Results used in the analysis only included original research and review articles focusing on leptospirosis that were published in peer reviewed journals. Meeting abstracts, dissertations, theses and technical reports were excluded. Data analysis was done through descriptive statistics. The results are presented according to the diagnostic test used, geographic region and subjects of study.

Results

Ninety five publications were found (information not shown). The largest number of articles were found in Google scholar (97.9%, 93/95), followed by ISI web of knowledge (37.9%, 36/95). Most of the articles (85.3%, 81/95) are written in Spanish, the official language of the country; while 14.7% (14/95) are written in other languages.

The first article on leptospirosis in Colombia was published in 1957 [18], and during the following four decades four, six, twelve, and nine articles were published, respectively, with an average of 1.7 articles per year (95 publications in 55 years). There was a marked increase in publications during the first decade of the 21st century, with 50 articles published in ten years. Six and seven articles were published in 2010 and 2011, respectively (Figure 1).

Publications by diagnostic test used

Most of the articles (64.2%, 61/95) reported results on the prevalence of the disease and described the diagnostic tests used in detail. MAT was the most frequently used test (83.6%, 51/61), followed by dark field examination (13.1%, 8/61), and IgM ELISA and

culture (both with 11.5%, 7/61). In 54.1% (33/61) of these studies only MAT was used, while in 32.8% (20/61) more than one diagnostic test was used (Figure 2).

Publications and prevalence by geographic region studied

Publications specific to a particular region accounted for 76.8% (73/95). The most studied area in the country is the central area, while the north, east, west and south are still relatively unstudied (Figure 3). The most studied geographic region is Antioquia with 17.8% (13/73) of the publications, followed by Risaralda and Caldas, with 13.7% (10/73) and 12.3% (9/73), respectively (Figure 3). The highest prevalence of the disease in the country was registered in the coffee zone (82.7%, 62/75), in the region of Córdoba (67.9%, 53/78), and in the region of Boyacá (67.2%, 41/61) (Table 1).

Publications and prevalence by subjects studied

87.4% (83/95) of the publications were specific in terms of subjects studied. Humans were the focus of 44.6% (37/83) of the publications, followed by cattle (27.7%, 23/83), pigs (16.9%, 14/83), and dogs (14.5%, 12/83) (Figure 4). The highest prevalence of the disease was registered for rodents (82.7%, 62/75), followed by humans (67.9%, 53/78), pigs (67.6%, 342/506), and dogs (67.2%, 41/61) (Table 2).

The serovars reported with the highest frequency in humans were: icterohaemorrhagiae, grippityphosa, hardjo-prajitno, bratislava, pomona, and bataviae. Those with the highest frequency for cattle were: hardjo, hebdomadis, icterohaemorrhagiae, and wolfii. In the case of pigs the most frequent serovars were: pomona, icterohaemorrhagiae, and bratislava, and in the case of dogs serovars with the highest frequency were: icterohaemorrhagiae, canicola, and grippityphosa. Common serovars registered for rodents included: grippityphosa, icterohaemorrhagiae, and bratislava. In the case of horses and goats, the information available is very limited. Although the disease has been studied in few wildlife species in Colombia, the most common serovars cited are: icterohaemorrhagiae, grippityphosa, copenhageni/icterohaemorrhagiae and tarassovi.

Figure 1. Number of publications on leptospirosis in Colombia per year.

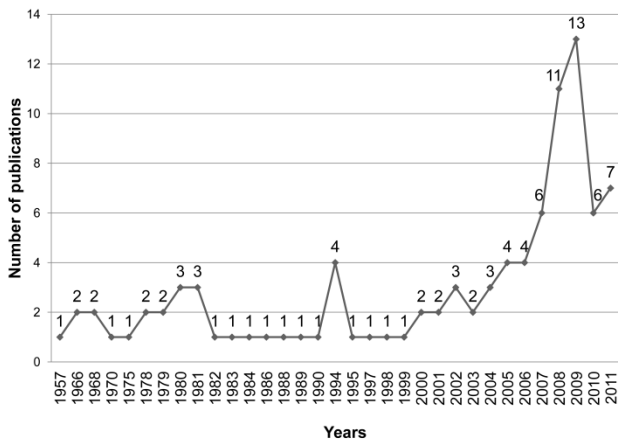


Figure 2. Number of publications by diagnostic technique used. Note that the sum of the results is higher than 61, this is because in 32.8% of the publications more than one diagnostic test was used

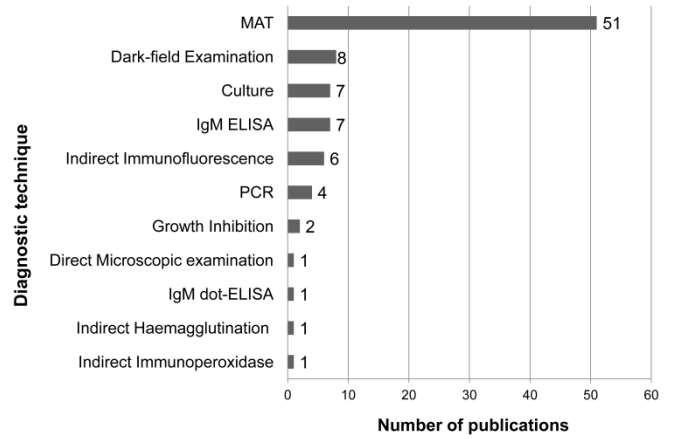


Figure 3. Information availability by geographic region. Eleven studies were excluded from this figure because they were conducted in larger areas and the regions included were not specified, i.e. Magdalena valley, Magdalena medio, south zone, Andean zone, Caribbean zone and Piedemonte zone, each was included in one publication. The western plains zone was included in five publications.

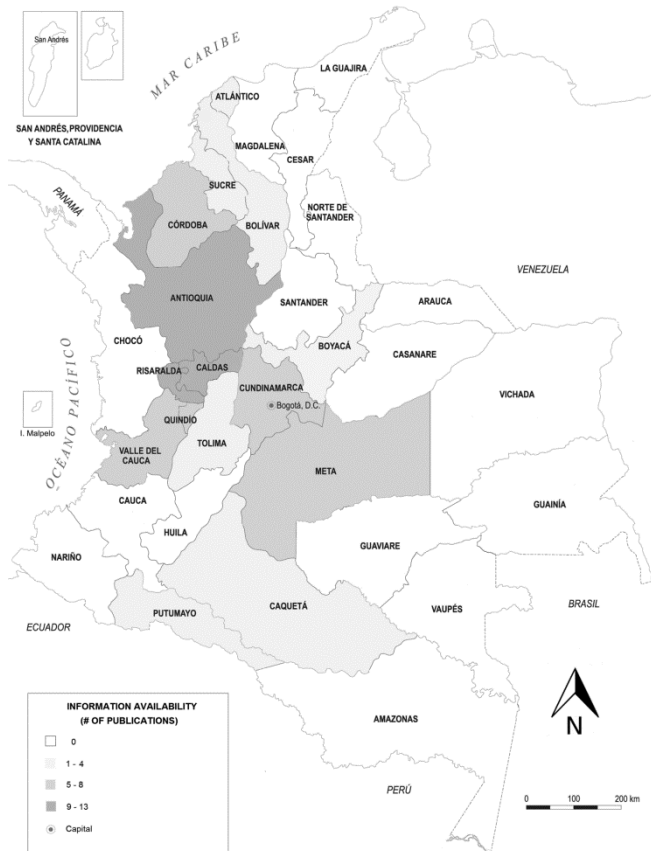


Figure 4. Number of publications by subject of study. Note that the sum of the results is higher than 83, this is because some publications included more than one group of study subjects

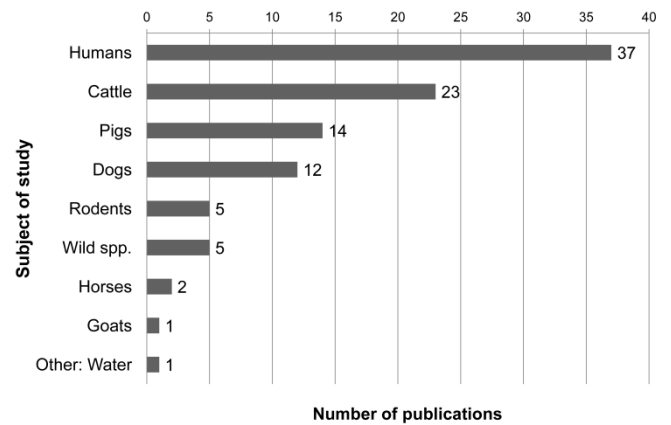


Table 1. Leptospirosis prevalence by geographic region

Geographic Region with prevalence data	Prevalence Range (min,max*)	Sample Size (n)	Subject	Diagnostic Test	Other Observations
Antioquia	7.4% [32]	27	Primates	MAT, \geq 1:50	Primates in captivity
	35.6% [22]	642	Humans	MAT, \geq 1:100	Rural area in Necoclí
Atlántico	9.7% [33]	970	Humans	MAT, \geq 1:400	
Boyacá	11% [23]	82	Humans	MAT, \geq 1:100	
	67.2% [34]	61	Dogs	MAT, \geq 1:100	
Coffee zone (Caldas, Quindío, Risaralda)	0 [35]	45	Humans	MAT, 1:50	Workers from the Manizales's Central Slaughterhouse
	82.7% [36]	75	Rodents	Dark field examination & culture	Swine farms
Córdoba	12% [37]	200	Dogs	MAT, \geq 1:100	
	67.9% [24]	78	Humans	MAT, \geq 1:100	
Cundinamarca	31% [38]	200	Pigs	Indirect immunoperoxidase	
	52.2% [39]	46	Bulls	MAT, \geq 1:25	
Meta**	0 [41]	\geq 56	Wild animals	MAT, non-mentioned cut-off, culture	56 species of wild animals
	48% [42,25]	27	Humans	ELISA	Fish farm workers.
South zone	18.4% [43]	353	Humans	MAT, \geq 1:100	
Sucre	13.3% [44]	90	Humans	ELISA	
Tolima***	6% [46]	850	Humans	MAT, \geq 1:100	
	21.4% [46]	850	Dogs	MAT, \geq 1:100	
Valle del Cauca	20.6% [47]	150	Humans	MAT, \geq 1:800	
	41.1% [48]	197	Dogs	MAT, \geq 1:100	

* Range provided when more than one study is available

** In this region a 100% prevalence was registered in humans, however it was not included in the results due to its lack of representativity (n=5) [40].

*** Another study conducted in this geographic region reported a 36.7% seropositivity (n = 1543, MAT, > 1:50) in a variety of organisms (Humans, pigs, cattle, dogs etc.) [45], however it was not included in the results, due to the fact that the sample size per group of organisms was not reported, and therefore the representativity of the results is unknown.

Table 2. Leptospirosis prevalence by subject of study

Subject of the Study	Prevalence Range (min,max*)	Sample size (n)	Geographic Region	Diagnostic Test	Other Observations
Cattle	10.5% [49]	598	Magdalena Medio	MAT, 1:100	
	62.5% [50]	264	Multi-regional	MAT, \geq 1:100	
Dogs	12% [37]	200	Córdoba	MAT, \geq 1:100	
	67.2% [34]	61	Boyacá	MAT, \geq 1:100	
Humans**	0 [35]	45	Caldas	MAT, 1:50	Workers from the Central slaughterhouse
	67.9% [24]	78	Córdoba	MAT, \geq 1:100	People displaced by Colombia's armed conflict
Pigs	10.3% [51,52]	68	Antioquia	MAT, \geq 1:10	
	67.6% [53]	506	Coffee growth zone	Sum of positives in MAT 1:50 and growth inhibition test	
Rodents***	20.5% [26]	254	Antioquia	Culture	At farmers' market
	82.7% [36]	75	Coffee growth zone	Dark field examination, culture	
Water	20.5% [54]	292	Coffee growth zone	Dark field examination	Drinking water
	66% [54]	47	Coffee growth zone	Dark field examination	Wastewater
Wild spp.	0 [41]	\geq 56	Meta	MAT, non-mentioned cut-off, Culture	56 species in the wild
	30.8% [55]	52	Antioquia	Culture, PCR	Primates in captivity

* Range provided when more than one study is available

** Excluding a breakout reported in the geographic region of Risaralda in 2006 [19] and a report of 100 % prevalence in a study with a sample size of five individuals [40].

*** A study reported a 100 prevalence in this taxonomic group [40], however, it was excluded from the range due to the low sample size (n = 15) and therefore the low representativity.

Discussion

Although the first work on leptospirosis in the country was published 56 years ago, it was not until the first decade of the 21st century that the research reached its highest point. It is important to note that the publication rate found may be underestimated due to the fact that some national journals may still not be indexed. Although the overall prevalence of the disease is widespread in the country, results vary greatly among areas and among organisms.

MAT was the most frequently used diagnostic test but there is a lack of unified criteria for determining positive MAT titers/cut off points. Interpretations of the MAT are difficult due to the fact that agglutinating antibodies remain for long periods of time in the body after infection. Also, there is an ongoing debate about when a leptospira agglutination titer is positive and significant (cut-off); some consider a titer to be positive at 1:100 while others consider it to be positive at higher values. According to the US Center for Disease Control and Prevention [20], a titer of $\geq 1:200$ (in combination with clinical symptoms) is used to define a probable case, however, in places where the prevalence of the disease is common, as in the case of most tropical countries, a titer of 1:200 may not have a diagnostic value and a higher cut-off value is necessary [2].

Since, due to previous infections, antibodies may be more persistent in areas with higher prevalence of the disease, the cut-off should be specific to the region in question [21]. It is recommended that the serological results should be analyzed considering specific regional characteristics (such as prevalence of the disease, risks of exposure, etc.). In addition, it is recommended to analyze two consecutive serum samples in order to identify a significant, four-fold or greater increase in titers [21].

Based on the results reported for Colombia and considering: 1) that more than 80% of the studies on the prevalence of the disease were based on the MAT, 2) the difficulties of interpreting the MAT and low titers, and 3) the doubtful results on the efficacy of diagnostic tests, including the MAT [11-15], it can be concluded that the real prevalence of the disease in the country is still unknown and that there is a need to continue to search for methods that can accurately assess its prevalence. Work at molecular level is revealing interesting results in various parts of the world and should be considered in future works [10-16].

There is still no information on the prevalence of the disease in several of the 32 geographic regions,

and with exception for the central area, most of the country is still relatively unstudied. There is a need to expand the geographical scope of the research, giving priority to regions with the highest prevalence of leptospirosis where actions to control and reduce the disease are most urgent.

Humans are the most studied taxonomic group. Factors associated with the prevalence of the disease, as established through research, include: occupational factors, hygiene conditions, frequent contact with rodents, and owning/working with animals, all of which considerably increase the risks of contagion [22-26]. Medical treatment depends on the severity of the symptoms. Severe leptospirosis may be treated with intravenous penicillin, less severe cases may be treated with antibiotics such as amoxicillin, ampicillin, doxycycline or erythromycin. Ceftriaxone also appears to be effective [27]. On the other hand, results from a review assessing seven clinical trials that tested antibiotics to treat leptospirosis showed that the benefit of antibiotic therapy remains unclear, particularly for severe cases [28]. Although the use of antibiotics is controversial, the World Health Organization [21] recommends that treatment be initiated with antibiotics as soon as leptospirosis is suspected.

The prevalence of serovars among the different taxonomic groups is consistent with what has been reported in the literature [2,29]. The few studies done on wild animals in Colombia, reported a low prevalence of the disease. Small mammals like opossums and rodents are more frequent carrier hosts of leptospira than are larger mammals. Similar results were reported in Peru [30], where leptospira was found to be frequent in small mammals like bats, rodents and marsupials. In Brazil, studies on tapirs (*Tapirus terrestris*) have shown negative results for *Leptospira* spp. (0/10) [31].

Finally, future work in Colombia should provide information not only on the prevalence of the disease, but on other topics such as the effectiveness of the diagnostic tests, factors associated to the occurrence of the disease, as well as on the environmental, social and political strategies necessary to reduce the prevalence of the disease in the country.

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