Spatial and Temporal Variability of Visceral Leishmaniasis in Colombia, 2007 to 2018

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Abstract. Visceral leishmaniasis (VL) is a neglected tropical disease associated with poverty and is endemic in 56 countries worldwide. Brazil, Venezuela, and Colombia are the most affected countries in South America. In Colombia, the National Public Health Surveillance System (SIVIGILA) consolidates epidemiological information and monitors all VL cases nationwide. However, to date, no studies have investigated the occurrence of VL in Colombia using metadata analysis. We studied the demographic data, the spatial and temporal distribution of VL cases, and the association with vector distribution of *Leishmania* species in Colombia from 2007 to 2018. We found 306 VL cases reported to SIVIGILA for this period, with a coverage of 25.5 cases/year, and a mortality of 2.28% (seven deaths). The highest number of confirmed cases ($N = 52$) occurred in 2007; the lowest ($N = 9$) occurred in 2012. The cases were reported mainly in children (< 7 years) affiliated with the subsidized health regimen. Regarding the geographic distribution, the cases were reported by 42 municipalities distributed in 10 departments. The occurrence of VL cases toward the northeast of Colombia, and the distribution of vectors, such as *Lutzomyia longipalpis* and *Lu. evansi*, may be changing the panorama of VL in the country. We conclude that VL, mainly in recent years, shows a temporal and spatial variability associated with the occurrence of cases in new settings. Our findings increase our understanding and knowledge of this disease, and suggest the need to monitor and prioritize areas with changes in geographic expansion to improve prevention and control actions in the country.

INTRODUCTION

Globally, vector-borne diseases constitute a major public health problem because of their high incidence and complex control—particularly in endemic areas, where transmission rates are high.^{1,2} This group of diseases includes leishmaniasis, which is transmitted primarily by the bite of the female sand fly of the Phlebotominae family that is infected with promastigotes of the protozoan parasite *Leishmania*.³ The disease has three main clinical forms, named according to the anatomic location affected in the host: cutaneous leishmaniasis (CL), mucosal leishmaniasis, and visceral leishmaniasis (VL).⁴ The presentation and evolution of each clinical form has been attributed to multifactorial characteristics of the parasite and the host.⁵

VL is recognized as the most serious form of leishmaniasis. In VL pathology, the amastigote stage of the parasite invades vital organs, such as the liver and spleen, and tissues such as bone marrow. Physiological and metabolic functions of the body are altered, leading to death if patients do not receive timely treatment.⁶ Historically, the etiology of VL has been attributed mainly to species of the *Leishmania donovani* complex^{3,7} and, to a lesser extent, species of the *L. enrietti* complex⁸; however, in recent years, there have been reported cases of VL associated with other species, including *L. colombiensis*,⁹ *L. amazonensis*,^{10,11} and *L. tropica*.¹²

According to official reports of the Global Leishmaniasis Program of the WHO for January 2020, 56 countries are endemic for VL, with 90% of the cases occurring in Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan.¹ Annually, there are an estimated 50,000 to 90,000 new cases worldwide; however, the disease may be underreported by as

much as 55% to 75%.¹³ According to reports by the Drugs for Neglected Diseases initiative, about 20,000 to 30,000 deaths are attributed to VL every year.¹⁴ In 2018, the majority of indigenous VL cases in the Americas was reported in Brazil ($N = 3,460$), Venezuela ($N = 43$), Paraguay ($N = 19$), and Colombia ($N = 16$).¹⁵ However, incidence has been greatly affected by climate change, migratory movements, and internal political crises. This last factor leads to health deficits and the disruption of public health programs.^{16–18}

In Colombia, the National Public Health Surveillance System (SIVIGILA) was created with Decree 3518 in 2006 to provide information rapidly and systematically on diseases of public health interest, and thus guide policies and programs aimed at the prevention, control, and monitoring. According to information provided by the Colombian government, the occurrence of indigenous VL cases has been limited primarily to two geographically defined areas known as the Magdalena River and the Montes de María subregion, San Andrés de Sotavento (Córdoba).¹⁹ In Magdalena River, there are four VL-endemic departments: Huila, Tolima, Cundinamarca, and Santander. In the Montes de María subregion, the endemic departments are Bolívar and Sucre. In addition, there have been cases reported in the department of Córdoba in the same subregion of the Caribbean coast. However, in recent years, SIVIGILA has recorded indigenous cases occurring in new departments, as well as cases imported from other countries.^{20–22}

In endemic municipalities, the public health laboratories perform surveillance and focus studies to understand VL transmission. During entomological studies, occurrences of *Lutzomyia longipalpis* and *Lu. evansi* infected with *L. infantum* have been reported in areas with cases of VL. Similarly, researchers have studied the distribution of vectors involved in the transmission of *L. infantum*,^{23–25} including *Lu. evansi* in the northwest of the country and *Lu. longipalpis* in the Andean region, with a high prevalence in Huila, Tolima, and Cundinamarca.²³ In addition, analysis of biological samples from

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canines has revealed different rates of infection in four endemic departments: Bolívar, 36%²⁶; Sucre, 33.6%²⁷ to 66.9%²⁸; Huila, 17.2%²⁹; and Tolima, 31.5%.³⁰ Furthermore, a similar panorama of infection rates has been observed in endemic areas of Venezuela, 24.1%³¹; Spain, > 34%³²; Brazil, 45.6%³³; and Bangladesh, 35%.³⁴

At the national level, metadata studies have shown changes in the demographic pattern and distribution of the disease and vectors in relation to CL as well as VL.^{35–37} However, despite the importance of this disease and the mandatory reporting of all VL cases in SIVIGILA, the combined geospatial and temporal variation of VL in Colombia has not yet been documented, and the full extent of the changes in the national distribution of this parasitic disease remains unknown. Therefore, this study aimed to describe the temporal and spatial distribution of VL in Colombia from 2007 to 2018 and to analyze descriptively the occurrence and distribution of the disease. Using publicly available information from official governmental sites and scientific data, we conducted statistical analyses and made biological associations with the vector distributions. Our results provide a scientific basis in relation to spatial and temporal changes and vector distribution for VL, which will help disease monitoring and deployment of public health strategies and programs aimed at the effective and efficient prevention and control of VL transmission in endemic areas of the country.

METHODS

Data collection and processing. The information recorded in the SIVIGILA platform are reported by the primary national data-generating units, which are obliged to report events of public health interest in Colombia. These events may be related to infectious diseases (including VL), noncommunicable diseases, or mortality-related events. The primary national data-generating units correspond to institutions providing health services at the municipal level (third sub-national territorial and administrative levels). The registered information was consolidated and checked at the department level (second sub-national territorial and administrative levels) by professionals of the public health surveillance department of INS (National Institute of Health) to verify cases and confirm their status.

We obtained the data available in reports of public health events from 2007 to 2018 and event microdata (for VL) from 2007 to 2017 from the SIVIGILA website (<https://www.ins.gov.co/Direcciones/Vigilancia/Paginas/SIVIGILA.aspx>). In addition, the 2018 *Leishmaniasis Events* report by the National Laboratory of Reference-Parasitology Group from the INS was used to corroborate the information. The tables for each year were consolidated with the addition of demographic data from the National Statistics Department (Departamento Administrativo Nacional de Estadística [DANE]) available in the document *Estimation and Projection of Total National, Departmental, and Municipal Population by Area 1985–2020* for 2007 to 2017 and *Population Projections 2018–2020* for 2018 to take advantage of the data updates by DANE, and thus obtain a more accurate estimate. The data on case occurrences were organized annually and biannually using Microsoft Excel (v. 2018; Microsoft Corp., Redmond, WA) at both the department and municipal levels.

For VL cases where there was no information about the municipality of origin were weighted in the department for the year of occurrence. Thus, the case was added to the municipality that had more cases reported by department during the year of analysis.

Cases of unknown department origin or Venezuelan origin were not used when analyzing incidence. Data on the national distribution of *Leishmania* vectors (mainly the sand flies associated with species transmitting VL) were taken from the entomological surveillance report for leishmaniasis of the INS³⁸ and research articles by Ferro et al.²³ and Bejarano et al.³⁹ The data were consolidated and filtered to construct a map of Colombia showing the geographic distribution of the *Leishmania* vectors (*Lutzomyia* spp.) and their relationship to VL cases. The map was made using QGIS software (v. 3.24.1, Washington, DC).

Statistical analysis. Descriptive statistical analysis of the data was performed to determine the demographic characteristics of the population with VL. The variables analyzed were age, gender, department of origin, affiliation to the health system, and number of deaths. The variable “affiliation to the health system” included four categories: contributory regimen (workers and pensioners contributing to the health system for their care and that of their family members), subsidized regimen (unemployed people from socioeconomic strata 1 and 2 who receive many health services free of charge), other (special regimes, such as those for indigenous, military, or state teachers), and none (no affiliation to any health regimen).

To show differences in infection by gender, a normality test was performed for age in both groups (male and female). Because the data were not distributed normally, we proceeded to present the data with median and interquartile range values. Later, a Mann-Whitney U test was performed to evaluate the existence of differences among ages by gender.

These demographic variables were also used to perform a multivariate linear regression to determine whether the cases had an association with the covariates available in the public databases used. Given the small number of cases, we collated all cases in the study period into a single analysis by departments. We calculated standardized incidences based on the total population by department. Standardized incidence ratios (SIRs) were calculated from the total number of cases in Colombia over the study period using empirical Bayesian smoothing as described by Clayton and Kaldor.⁴⁰ We constructed probability maps based on the empirical negative binomial distribution for the data. Last, we calculated measures of spatial autocorrelation in several ways. A global Moran's I randomization test on the SIRs was performed, and spatial weight matrices were based on first-order queen contiguity.

Municipal crude incidence (Io) was calculated by dividing the number of VL cases per year by the population, and the result was recorded per 100,000 inhabitants. The same calculation was made at the department level, and the data were plotted on a heat map using ggplot2 (R package, v. 3.6.1). To display the cases and incidences data in a timeline, the number of cases and Io data were smoothed using Lowess regression. To show the geographic evolution of VL cases during the analyzed period, a map of Colombia was drawn showing the VL biannual incidence rates from 2007 to 2018 by department using QGIS software.

RESULTS

Description of sociodemographic data of patients with VL in Colombia. For the years analyzed, 306 laboratory-confirmed cases of VL in Colombia were reported to SIVIGILA. Four of these cases were associated with a department of unknown origin and one originated abroad (Venezuela), and thus were discarded from the statistical analyses. In general, most VL cases occurred in children; 75% of the patients were between 0 and 7 years old, with a median of 2 years. The remaining 25% of patients were between 8 and 78 years old (Table 1). There were no statistically significant differences in cases of VL between the sexes at the national level ($\chi^2 = 0.40199$, $P = 0.5261$). Regarding social security affiliation, most of the patients were in the subsidized regimen (73.2%) or they were not affiliated with any health system regimen (15.6%), which can be extrapolated to represent conditions of vulnerability associated with poverty because, in the subsidized regimen of the health system in Colombia, people from socioeconomic strata 1 and 2 are affiliated to this one. Similarly, not being affiliated with any health regimen implies greater vulnerability in relation to the difficulty of accessing health services coupled with poverty. For the years analyzed, seven (2.29%) cases reported to SIVIGILA were individuals who had died.

Characterization of VL cases and incidence by department.

Analysis showed the existence of two geographically defined groups for the presentation of VL in the country—one in the north and the other toward the center of the country—in the departments that converge on the Magdalena River (Figure 1). Each area contains three main departments: the North Zone consists of Bolívar, Sucre, and Córdoba, whereas the Central Zone contains Huila, Tolima, and Cundinamarca. The comparison between observed and expected cases showed SIR values that demonstrated the high level of risk of VL occurrence mainly in the North Zone (Bolívar, Sucre, and Córdoba), where the transmission of the parasite and the presentation of the disease are historically recorded (Figure 1) and the population is lower in comparison with the departments in the Central Zone.

The clear pattern in the geographic distribution of VL in Colombia had an impact on the occurrence and incidence of cases per 100,000 inhabitants at the department and

municipal levels. The departments with the greatest occurrence were Bolívar (105 cases), Sucre (76 cases), and Córdoba (70 cases), followed by Huila (28 cases) and Tolima (11 cases) (Figure 2A). Since 2016, the number of VL cases in Huila began to exceed those in Sucre and Córdoba. Interestingly, between 2010 and 2012, there was a marked decrease in the number of cases in the three departments that generally have the greatest number of cases per year. In 2012, only nine cases were reported in Colombia, seven in Huila, and the other two in Sucre and Tolima (Supplemental Table 1). We then analyzed annual incidence by department (Figure 2B), and although, until 2015, the department with the greatest number of cases was Bolívar, Sucre had the greatest annual incidence. As of 2016, both the incidence and number of cases reported in Bolívar were the greatest in the entire country. However, Huila has also begun to be an important department for VL in recent years; in 2017, the incidence exceeded that of Sucre and Córdoba. In 2018, the number of cases exceeded those of the two regions.

In congruence with the previous analyses, the histograms of observed cases and their trends showed that, in Colombia, the presentation of VL is a highly variable phenomenon over time and that it does not follow a certain pattern. It has a tendency to increase or decrease in the number of cases per year (Supplemental Figures 1 and 2). In addition to this finding, it noticed that during the first months of each year, there is a seasonality factor, with an increase in the number of cases reported (Supplemental Figure 2).

Characterization of VL cases and incidence by municipality.

When we analyzed the crude incidence of VL at the inter-department and municipal levels, we observed high data variation and congruence in their distribution (Figure 3A). At a lower level, we found 42 municipalities reporting VL cases in the analyzed period. The municipalities with the greatest historical incidence per year were El Carmen de Bolívar, Ovejas, and San Andrés de Sotavento (Figure 3B), in the departments of Bolívar, Sucre, and Córdoba, respectively. However, the greatest incidence was reported in Chalán (Sucre), with 34.46 and 34.34 cases/inhabitant in 2010 and 2009, respectively. In Huila, the annual VL cases were reported by different municipalities, and the number of cases reported was not constant over time. Notably, in the department of La Guajira, all VL cases were limited to the municipality of Hatonuevo (Figure 3b).

TABLE 1

Sociodemographic characteristics of patients with visceral leishmaniasis in Colombia reported to the National Public Health Surveillance System from 2007 to 2018

Variable	Location in Colombia										Total
	Bolívar	Córdoba	Sucre	Cesar	Huila	Tolima	Cundinamarca	Santander	Norte de Santander	La Guajira	
No. of cases	105	70	76	1	28	11	6	1	1	2	301
No. of deaths	2	2	1	0	2	0	0	0	1	0	8
Age, y; median (IQR)	3 (1–7)	2 (1–8)	2 (1–8)	*	1 (1–3)	2 (1–2)	26 (22.75–77.26)	†	*	‡	2 (1–7)
Gender											
Female	50	31	32	1	19	9	2	0	0	0	144
Male	55	39	44	0	9	2	2	1	1	2	155
Regimen in the health system											
Contributive	4	9	1	0	6	2	4	0	0	0	26
Subsidized	79	52	62	1	21	5	2	1	0	2	225
None	22	8	13	0	0	4	0	0	1	0	48
Other	0	1	0	0	1	0	0	0	0	0	2

IQR = interquartile range.

* Only case (15 y).

† Two cases (15 and 34 y).

‡ Two cases (1 and 5 y).

FIGURE 1. Exploratory data analysis of the occurrence and incidence of visceral leishmaniasis cases in Colombia. The political map of Colombia divided into departments the occurrence of observed cases (left), the occurrence of expected cases (middle), and standardized incidence ratio (SIR) (right) per year from 2007 to 2018. This figure appears in color at www.ajtmh.org.

Analysis of the changes in VL distribution demonstrated by biannual incidence. By plotting the biannual Io of VL both temporarily and spatially by department, we see that, initially, from 2007 to 2010, there were two geographically defined areas of VL occurrence (Figures 1 and 4). Historically, the northern departments have been mostly affected; for example, incidences of more than 1.2/100,000 inhabitants have occurred in Sucre, compared with the more stable and lower VL incidence in the entire country (0.31–0.60/100,000 inhabitants during the years analyzed) (Figure 4). When we compared the distribution and initial incidence of VL of the 2007–08 biennial data with the 2017 to 2018 data, it was seen that, as VL incidence of departments in central Colombia decreased, sporadic instances of new cases began to be reported in the departments of Santander, Cesar, and La Guajira, shifting the VL distribution toward the northwest.

When we calculated measures of spatial autocorrelation, we did not obtain evidence of significant spatial autocorrelation (Moran's I randomization test on the SIRs, $z = -0.082$, pseudo- $P = 0.39$). We then constructed a probability map based on the empirical negative binomial distribution of the data (Figure 5).

Because we did not have evidence of significant spatial autocorrelation, we chose not to calibrate any models.

Species specificity in the distribution of vectors and VL foci cases. We compared the entomological data registered from various research groups and the data from the Entomology Reference Laboratory of the INS with the national distribution of sandflies in relation to the VL endemic departments (Figure 6). The geographic correlation performed fits a spatial ecological association inference. The distribution of *Lu. evansi* was related mainly to the distribution of VL cases in northern Colombia (Bolívar, Sucre, and Córdoba) and in the northeastern departments (Norte de Santander, Cesar, and La Guajira). In these latter departments, VL cases have been reported in the past few years.

In contrast, in Huila, Tolima, and Cundinamarca, *Lu. longipalpis* was the primary vector distributed in these departments. *Lutzomyia longipalpis* has also been reported in some foci of the Montes de María subregion, Norte de Santander and La Guajira. Similar concomitance was observed in the distribution of *Lu. gomezi* (CL *Leishmania* spp. vector) with VL cases from the Andean area to northern Colombia. Last, *Lu.*

FIGURE 2. (A) Occurrence and (B) incidence per 100,000 inhabitants of visceral leishmaniasis (VL) at the departmental level. Lowess fit was used to smooth the frequency of VL (cases, incidence) by department in a time-series graph. The single point represents a department in which a unique case was reported. This figure appears in color at www.ajtmh.org.

FIGURE 3. Heat map of visceral leishmaniasis incidence variation at the (A) department and (B) municipal levels. Incidence is 100,000 inhabitants/year. BOL = Bolívar; SUC = Sucre; COR = Córdoba; CES = Cesar; HUI = Huila; TOL = Tolima; CUN = Cundinamarca; SAN = Santander; NSAN = Norte de Santander; LAG = La Guajira. This figure appears in color at www.ajtmh.org.

columbiana (CL *Leishmania* spp. vector) was only found in the Andean area, and the absence of vectors associated with the transmission of VL in other departments bordering Venezuela is evident, such as in Arauca, Vichada, and Guaviare (Figure 6).

DISCUSSION

VL continues to be a major global public health problem in terms of the number of people at risk, related mortality-morbidity rates, and the increasing emergence of resistance to commonly used drugs.^{41–43} The occurrence of VL in Colombia shows an expansion in its geographic distribution, probably related to the presence of *Lu. evansi* and *Lu. longipalpis* on new transmission foci (Figure 6). Likewise, the population most affected by this parasitic disease are the children affiliated with the subsidized regimen of the Colombian health system. The results of our study show that cases of VL have occurred mainly in children in situations of vulnerability associated with poverty (Table 1), considered as one of the greatest risk factors for the development and evolution of the disease.^{44,45} In the case of Colombia, not being affiliated with any health system regimen or being in the subsidized regimen is related to belonging to socioeconomic strata 1 and 2, which implies a greater state of economic vulnerability and difficult access to medical and hospital services. According to official reports, in Colombia, people from these socioeconomic strata have a daily income of less than \$2.50.

In terms of age, the epidemiological behavior of VL in Colombia is similar to that in Central American countries,¹⁵ Venezuela,¹⁵ Alagoas (Brazil),⁴⁶ and western and central China,⁴⁷ where children are the most affected by this disease. In contrast, countries with a high prevalence of the disease, such as Brazil (national data), India, and Nepal, show that the adult population is the most affected by VL,^{15,48,49} with a growing number of HIV-positive patients.⁵⁰ In this sense, the marked difference between the populations affected by VL, according to geographic location of occurrence, may be the result of various factors such as the intraspecific genetic

variability and divergence of *L. infantum* in the New World and the interspecies genetic variability against species of *L. donovani* complex of the Old World,^{7,51,52} in which, for example, *L. donovani* has shown a large number of polymorphisms and high genetic diversity.^{7,51,53} In the human host, susceptibility to VL is associated with some human leukocyte antigen type I and II genes,^{54–56} nutritional factors, and immunization rates, which have been found to have protective effects for other infectious diseases,⁵² and there are associations at the vector level in relation to the behavior and adaptation to the ecological niche of the main vectors for *Leishmania*.^{25,57–59}

However, concurrent with studies carried out by the WHO in Brazil,⁶⁰ the presentation of cases in Colombia was not significantly different between genders. Likewise, this variable in conjunction with the other covariates included in our study did not show a direct association with the occurrence of VL cases in the country. This contrasts with a meta-analysis study by Cloots et al.,⁴⁸ who reported males in Bangladesh, India, and Nepal are more prone to developing the disease, and have higher seroprevalence rates and risks for seroconversion. However, population studies in relation to the latter two variables have not been conducted in endemic areas in Colombia.

Regarding geographic distribution, VL was found to affect six main departments, with consistent behavior over time, but variability in the number of cases (Figures 1–4), mainly in the municipalities of El Carmen de Bolívar, Ovejas, San Andrés de Sotavento, and Tuchin (Figure 3B). In the other municipalities, the occurrences were usually not sustained over time. In Colombia, there is a trend of an increase of case notifications of VL during the first quarter of each year (Supplemental Figure 2). This fact is possibly associated with the increase in the vector population and its parasite transmission capacity during the rainy season⁶¹ of the last quarter of the previous year in the foci (<http://www.ideam.gov.co/web/tiempo-y-climate/precipitation-monthly-per-year>) and the average incubation time of *Leishmania* in the host, which ranges from 2 to 6 months after infection in the case of VL.¹

FIGURE 4. Changes in geospatial distribution of visceral leishmaniasis incidence through time by biannual segmentation of department data. Incidence is per 100,000 inhabitants. The map was constructed using QGIS software. This figure appears in color at www.ajtmh.org.

Population abundance and distribution of VL vectors in Latin America, such as *L. evansi* and *L. longipalpis*, have been studied in Colombia, Brazil, and Argentina. In general, a direct relationship has been found between increased rainfall and vector abundance, in addition to other environmental factors such as the vegetation richness index.^{23,62,63} However, regarding the abundance levels of *L. longipalpis*, the climatic conditions can affect each focus of VL in a different way.^{57,63–66} Therefore, keeping the information on population density and vector distribution updated can help entomological surveillance systems improve vector control activities and thus mitigate the incidence of the disease in the country.

As shown in Figure 3B, there was a significant decrease in reported VL cases in 2012 at the national level, with only nine cases occurring in three locations: Neiva ($N = 7$), Ovejas ($N =$

1), and Coyaima ($N = 1$). This interesting change in the pattern of VL occurrence can be related to climate changes that affect the life cycle of the vector. We inferred that the marked decrease in the number of cases could be related to the El Niño–Southern Oscillation phenomenon and hurricane activity in the Atlantic Ocean during 2012.⁶⁷ These meteorological events trigger changes in rainfall, humidity, and continental temperature patterns,⁶⁸ and, when rainfall increases above average, there is less organic matter available for the development of sandflies,^{69–71} leading to a reduction in leishmaniasis transmission rates.⁷² This negative impact on the occurrence of VL has been documented in the Andean region⁷³ and Venezuela.⁷⁴ However, da Silva Neto et al.⁶⁸ showed that, in 2012, VL had an increase in incidence (12.37 cases/100,000 inhabitants) in the state of Mato Grosso do Sul, an area in southern Brazil with particular geographic

Negative Binomial p-values

0.008 - 0.050 0.050 - 0.174 0.174 - 0.257 0.257 - 0.340

FIGURE 5. Map of empirical negative binomial distribution for the visceral leishmaniasis data in Colombia from 2007 to 2018. This figure appears in color at www.ajtmh.org.

conditions, and concluded this natural phenomena was related to the greatest VL index recorded in this population.

In general, the areas historically endemic for VL are confined to the North (Montes de María and Córdoba) and Central Zones of the country (Figures 1, 4, and 5). These zones have a wide distribution of *Leishmania* species-transmitting vectors, such as *Lu. longipalpis*, *Lu. evansi* for VL, and *Lu. gomezi* for CL (Figure 6), and an abundance of reservoir mammals for the parasite,^{37,75} which aid the pathogen's epidemiological circuit and, therefore, maintain the transmission rates. Regarding mammalian reservoirs, canines are the main reservoirs for the domestic and peri-domestic transmission of VL⁷⁶ in Brazil,^{77,78} Spain,⁷⁹ and other endemic countries. Studies have been conducted to measure the impact of canines on the incidence of VL, and the effectiveness of euthanasia and other control strategies to interrupt transmission.^{80,81} However, to carry out effective control of leishmaniasis in endemic areas, it is necessary to resort to One Health strategies,^{82,83} including the concept that the prevention of leishmaniasis requires targeting both canines and the environment in which the insects perpetuate their life cycle.⁸⁴

For VL in Colombia, the epidemiological behavior of the disease in Santander and La Guajira is misleading. By the 19th

century, one case of VL had been reported in each of the two departments, in San Vicente de Chucurí-Santander in 1943 (the first case of VL documented in Colombia)⁸⁵ and in Barrancas-La Guajira in 1987,⁸⁶ both of which were in infants from rural areas. Curiously, there were reports of cases of CL, but not VL, in various municipalities until VL cases reemerged in 2017 and 2018 (Figure 3B). This panorama, which is similar to that seen in India and Sri Lanka, involving the recent emergence of this clinical form of the disease in new foci,⁸⁷ jeopardizes strategies to control and eliminate leishmaniasis in these territories. New studies are needed specifically in these departments to understand more fully the emerging transmission dynamics of the parasite.

It is important to highlight the presence of different vector species for *Leishmania* in the new foci mentioned in our study and in other border departments, as parasitological and entomological surveillance should be increased in these areas to control and prevent leishmaniasis outbreaks.^{3,23} In addition, studies on the rates of infection and coinfection in various Phlebotominae species and domestic/peri-domestic/sylvatic reservoirs by the various *Leishmania* species are necessary to facilitate the prediction of likely VL-causing species in vulnerable populations. This could increase the effectiveness

FIGURE 6. Map of visceral leishmaniasis cases and *Leishmania* vectors implicated in the transmission of the pathogen. The map shows the overlap between vector diversity and total number of departmental cases across the study periods. Pink shading, endemic department with current cases; violet shading, endemic department with cases until 2010; yellow shading, department with new cases. The map was constructed using QGIS software. This figure appears in color at www.ajtmh.org.

of species-specific therapeutic management strategies, which is crucial considering the different intra- and inter-species susceptibility profiles that have been documented worldwide.^{88–90}

However, in addition to the presence of vectors and reservoirs, the emergence of VL in new geographic areas may be associated with environmental factors, such as climate fluctuation⁹¹; the local intensification of extractive activities⁹²; human migration^{93,94}; parasite–host interaction factors⁹⁵; host factors, such as nutritional and immunological deficiencies, which are sometimes related to, for example, limited economic resources and limited access to basic

sanitation services, education, and self-protection measures⁴⁴; and the intrinsic evolution of parasites, including adaptation to new environments, reduction in life cycle duration, and changes in host immune system evasion. Regarding the immigration of people from Venezuela during the past decade, the cross-border dispersal of *Leishmania* species has been apparent in both CL and VL cases, as shown in Table 1. In addition to the data used in our study, four cases of VL in the Venezuelan migrant population were reported to SIVIGILA in 2019 and 2020 (<http://www.ins.gov.co/buscadoreventos/BoletinEpidemiologico>). This phenomenon has been seen for other vector-borne diseases,

such as Chagas disease, malaria, and arboviral infections, which implies there is a substantial risk of pathogen transmission to the countries bordering Venezuela.

Likewise, considering that although all the official data for VL was used for this 12-year period, the amount of data and the nature of it do not allow statistical analysis of inferences, as is done in countries such as India and Brazil, where the high prevalence of the disease, availability of data, and population studies have allowed generating these types of associations. The low number of nationwide cases reported to SIVIGILA and confirmed by the laboratory may be associated with technical difficulties or medical staff ignorance of the pathology in some areas. Likewise, this possible under-registration of cases and the precarious demographic information available may be a result of the negative impact of the armed conflict in Colombia experienced during this period, which made it difficult for the community to access health services and timely diagnosis and treatment, and affected indirectly the real-time reporting of information in SIVIGILA. Negative effects on war-associated leishmaniasis have been seen in different countries worldwide.^{47,50,96–98} This situation can lead to under-reporting of the disease, overestimating the effectiveness of the current VL promotion and prevention programs, and generating possible biases in our data analyses.

Considering this scenario along with the high variability of ecological niches, different geographic profiles of VL foci in Colombia, and the various characteristics of the population at risk, we consider that, at this time, to make predictions about the transmission rate and detail the risk factors associated with the acquisition of infection and development of VL could lead to fallacies and erroneous hypotheses at the national and even department levels. Therefore, we suggest that, in addition to using the data on changes in the spatial-temporal distribution of infectious diseases generated by our study, researchers must carry out eco-epidemiological analyses that involve the main actors of VL transmission (parasite/vector/reservoir/human) and the relationship among with the different determinants and risk factors associated with them.^{48,99} One of the shortcomings of our study is the lack of information related to domestic canines, because they are an important host for the transmission of this zoonotic parasite.¹⁰⁰ Unfortunately, there are no population data that show the incidence of this parasitosis in canines in a sustained manner over time, nor with the coverage of all transmission foci in the country, which represents a knowledge gap for the country.

CONCLUSION

Because ours is the first study to analyze the spatial and temporal evolution of VL from 2007 to 2018 in Colombia, it is highly important that both the scientific community and national regulatory institutions consider the findings of this study regarding the current situation of the disease. Furthermore, population studies and robust predictive models of the disease should be integrated with epidemiological, sociodemographic, zoonotic, and environmental studies to facilitate effective decision making in relation to the surveillance, prevention, and control of these parasites at the national and regional levels, focusing on those populations with a greater risk for infection.

Note: Supplemental tables and figure appear at www.ajtmh.org.

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