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CLINICAL CHARACTERIZATION AND EPIDEMIOLOGICAL ASPECTS OF HUMAN VISCERAL LEISHMANIASIS IN THE PROVINCE OF SALTA. PERIOD 2008 - 2022

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Abstract: Leishmaniasis, a group of zoonotic-vectorial parasitic diseases, in humans the visceral presentation is the severe clinical form. In the province of Salta, the causal agent has been identified as *Leishmania (Leishmania) infantum* with *Lutzomyia longipalpis* as the main vector involved in urban transmission, with no reports on the epidemiological aspects of the same. This research generates knowledge on the clinical characteristics and its possible eco-epidemiological scenarios. Thirty-eight autochthonous cases of VL were reported between 2008 and 2022, with 3 isolated cases between 2008-2011 and in the period 2016-2022 the remaining cases in clusters and transmission foci in the Departments General San Martín and Rivadavia fulfilling criteria of vulnerability, receptivity and transmission, defining risk scenarios for acquiring the disease at an increasing transmission speed according to density of cases per 100 km^2 per triennium (0.1415 and 0.0116 cases/100km^2 to the year 2022 respectively) and a Triennial Composite Index of Visceral Leishmaniasis comprised between 1.51-3.00 (High Risk) for both in the same period. The 84.21% (32/38) of the cases have residence in General San Martín, 10.53% (4/38) in Rivadavia and 5.26% (2/38) in Anta with nexus in the previous one. The average age was 15.37±3.56 years (range between 0 and 77 years). 68.42% (26/38) are under 10 years old, and 84.61% (22/26) under 5 years old; 68.42% (26/38) are male. 68.42% (26/38) presented prolonged febrile syndrome with weight loss. Followed by hepatosplenomegaly ($p<0.0003$) and $p=0.0079$ when associated with fever and anemia. The average number of days between the onset of symptoms and the first consultation was 33 $IC_{95\%}$ [23 - 43 days]; 86.84% (33/38) required hospitalization and 9.09% (3/33) required intensive care and mechanical ventilation, 57.89% (22/28) were discharged from hospital and only one death was recorded. Specific treatment was recorded in 78.95% (30/38). All reported patients had at

least one laboratory study. The detection of specific antibodies by ELISA showed a sensitivity of 100% and the specificity is 100% with the exception of ELISA. Positive and negative predictive values had satisfactory results for all techniques and serological test concordance yields a Kappa of 0.84 $IC_{95\%}$ [1.05-0.64].
Keywords: Visceral leishmaniasis; VL; Risk stratification; Transmission risk, Triennial Combined Index of Visceral Leishmaniasis, ICTLv.

INTRODUCTION

Human visceral leishmaniasis (VL) is the severe clinical form of a group of zoonotic-vectorial diseases that together with cutaneous and mucocutaneous diseases constitute a major public health problem known as *"Leishmaniasis"*. Leishmaniasis is a chronic systemic disease whose main etiological agent is *Leishmania (Leishmania) infantum (L. (L. (L.) infantum); it* is clinically characterized by fever, hepatosplenomegaly, lymphadenopathy, anemia, leukocytopenia, thrombocytopenia, wasting and progressive weakness; asymptomatic cases may occur[1] ; is mainly vector-borne by infected female mosquitoes of the genus *Phlebotomus* and to a lesser extent there are other non-vector-borne forms of transmission through syringes shared by intravenous drug users, blood transfusions or congenital transmission from mother to child[2] .

They are present on five continents and are endemic in 98 countries or territories. About 80% of the global VL burden is concentrated in Brazil, Ethiopia, Eritrea, India, Kenya and Sudan and since 2011 a steady decline in cases has been observed as a result of the elimination plan in Bangladesh, India and Nepal[3] .

The latest epidemiological report for the Americas[4] reports 13 countries with endemic characteristics, including Argentina. The most affected group is males between 20 and 50 years of age (33%) followed by those over 50 years of age (17%) and those under 5 years of age (15%) with no differences between sexes. LV and HIV coinfection was reported in 16% of cases and represents the highest proportion reported since 2012. Regionally, 88% of the reported cases were diagnosed by laboratory tests and 12% by clinical-epidemiological criteria; 65% progress to cure and 9.4% die as a cause of this disease.

In our country, the geographical space where human and canine cases occur are related to the distribution of the vector; they define areas of disease transmission and belong to the northeastern and northwestern provinces of Argentina[5] ; where 175 cases were reported between 2001 and 2019[6] and 88 new cases up to SE 44 of the year 2023. The provinces with the highest number of cases reported by jurisdiction of residence in the period (2018 - 2023) were Salta (57%), Misiones (20%) and Corrientes (10%)[5] .

In the Province of Salta, the first reported case of VL, was diagnosed in 2008[7] ; between 2009 - 2018[1] three isolated cases were reported, and 21 in the following three-year period, all residents of the General San Martín Department[2] with a significant increase in the number of both human and canine cases registered in two of its five localities (Tartagal and General Mosconi); is an emerging disease, with less than 15 years of evolution since the first case was confirmed, of epidemiological priority, relevant to public health, with outbreaks described in 2018, 2019 and 2022[3] .

1. Case report SNVS (National Health Surveillance System) Component C2. File Epidemiological Surveillance Program. General Directorate of Epidemiological Coordination (DGCE). MSP - Salta

2. SNVS case report2.0 (National Health Surveillance System) clinical-epidemiological-laboratory component Epidemiological Surveillance Program. General Directorate of Epidemiological Coordination (DGCE). MSP - Salta

3. Outbreak reporting and investigation of VL outbreaks. Epidemiological Surveillance Program Archive. General Directorate

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Leishmaniasis is confined to certain ecoregions or natural foci where essential elements for its transmission are present: vectors, reservoirs, parasites and ecological conditions that make it possible: climate, humidity, temperature, vegetation. The problem must be approached from a broad perspective that links social and economic aspects in order to develop effective control measures. It represents a great challenge in the region due to the differences observed, constituting important obstacles and dificulties to carry out surveillance actions and adequate controls. In the last decades, important studies have been carried out that allow a better understanding of this parasitosis; however, there is a lack of knowledge about elements involved in transmission, risk factors and the relationship of the parasite with the host[8-13] . Currently, all efforts are aimed at ensuring early diagnosis, adequate and timely treatment of the disease, to avoid deaths caused by the disease; in addition, interventions related to the reservoirs and vectors in specific areas with transmission should be deepened.

Knowing the links involved in the transmission chain, both in the dynamics of the disease in humans (VL) and in its reservoir and vectors involved, allows establishing effective interventions for focus control as a multidisciplinary, coordinated and sustained work over time. Considering this background, and considering Argentina as a country with an expanding transmission[14] , we must have epidemiological surveillance tools adapted to the local reality focused on risk stratification with transmission scenarios defined in terms of receptivity to the presence of the vector and vulnerability, taking into account the geographical contiguity of localities with confirmed cases of VL and migratory movements to areas with confirmed transmission.

Therefore, the aim of this work is to understand the behavior of VL in the province of Salta by describing morbidity-mortality characteristics, transmission risk assessment, and eco-epidemiological and social aspects. The results obtained from interdisciplinary and interinstitutional activities will provide useful information to the surveillance system for the development of operational plans by public health decision-makers in the province.

MATERIALS AND METHODS

TYPE OF STUDY

Descriptive study with a retrospective, non-experimental, cross-sectional design.

SAMPLE

Patients reported in the event "Visceral Leishmaniasis" registered in the National Health Surveillance System (SNVS) (2008-2017) and SNVS[2.0] (2018 - 2022) with residence in the Province of Salta and who meet the criteria to confirm or rule out the disease, according to the criteria established in: "Definition and classification of cases"[15] .

METHODS

The historical reconstruction of the series of cases was carried out with the databases in the SNVS, SNVS[2.0] , the epidemiological records of the Epidemiological Surveillance Program of the General Directorate of Epidemiological Coordination of the MSP-Salta, the Laboratory of the Institute of Experimental Pathology "Dr. Miguel Ángel Basombrío" (Faculty of Health Sciences. Miguel Ángel Basombrío" (Faculty of Health Sciences. National University of Salta), the information provided by the Zoonosis Coordination of the National Directorate of Epidemiology and Analysis of the Health Situation, on 10/16/2019, zoonosisna-cion@gmail.com (case reported

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in 2008) and from the publications[7,8,10] . The clinical characterization and description of the epidemiological aspects of VL in the period 2008 - 2022 is performed taking into account the variables person, time and place.

STATISTICAL ANALYSIS

The series of cases were loaded into a Google Form developed for this research. The systematization of the data was carried out using Excel workbooks and the statistical processing of the data was treated with the following software packages: "Data analysis in Excel" (Excel / components / Tools for analysis) and "OpenEpi software version 3.01" file:///C:/OpenEpi/Menu/OE_Menu.htm.

Primary information on the location of confirmed VL cases were uploaded into an EpiCollect5 form[4] developed for this research work (https://five.epicollect.net/project/proyecto-tesis).

The definition of transmission areas, georeferencing of cases, spatial distribution, climatic conditions, epidemiological scenario and ecological characteristics were carried out using Google Earth Version 7.3.2.5491 type map models.

The calculation of Sensitivity, Specificity, Positive and Negative Predictive Value and Kappa index was performed with the SAMIUC (Andalusian Society of Intensive Care and Coronary Care Medicine) medical calculator available on the SAMIUC website:

https://www.samiuc.es/estadisticas-variables-binarias/medidas-de-concordancia/kappa-de-cohen/

CHARACTERIZATION OF THE EPIDEMIOLOGICAL SCENARIO

It is proposed to use a simple index combining the parameters that characterize each of the areas; it is self-developed and is identified as the "V-R-T Index (vulnerability, receptivity, transmissibility index)[5] according to the following definition:

It is the sum of the averages obtained in the observed values of vulnerability, receptivity and transmission, which correspond to a geographic area that coincides with the second administrative level of the country (Argentina) and is equivalent to Department[17].

The variables analyzed to define each of the parameters are as follows:

Vulnerability

- Favorable conditions for the presence of the vector: YES/NO
- Continuity with transmission areas: YES/NO
- Intense migratory traffic with areas with transmission: YES/NO
- Road networks shared with areas with transmission: YES/NO

Receptivity

- Recorded presence of the vector: YES/NO

Transmission

- Presence of autochthonous human cases of VL: YES/NO
- Presence of autochthonous canine cases of VL: YES/NO
- Presence of outbreak: YES/NO

4. EpiCollect5: Software developed by Imperial College London that combines Android, GPS technology and the free Google maps service.

5. V-R-T index: self-made index

TRANSMISSION RISK CALCULATION

It is performed using the Triennial Composite Index (ICTLv) according to the procedure described in the "Manual of Procedures for Surveillance and Control of Leishmaniasis in the Americas"[14] and was applied for the 2nd administrative level (Department) in triennial intervals between 2008 and 2002.

VL cases: Total number of new confirmed cases[6] of VL reported to the SNVS[2.0] between 2008 and 2022 by Department.

VL incidence rate: Total number of new cases of VL per year per 100,000 population by Department.

Population by department: It was obtained from the projections based on the results of the 2010 National Population, Households and Housing Census[18] .

Triennial Composite Index of VL (ICTLv): With the calculations of the last 3 years' averages of VL cases and incidence for the 2nd subnational administrative level, the overall mean and overall standard deviation are calculated for each indicator and normalization is done taking into account the following calculations:

- Average number of cases per three-year period $(M)_c$
- Overall mean of cumulative cases at the cut-off point $(M)_{gc}$
- Overall standard deviation of cases (at cutoff point) $(SD)_{gc}$
- Average incidence per three-year period $(M)_i$
- Overall mean cumulative incidence at the cut-off point $(M)_{gi}$
- Overall standard deviation of incidence (at cutoff point) $(SD)_{gi}$

RESULTS

CLASSIFICATION OF PATIENTS ACCORDING TO CLINICAL FEATURES, DIAGNOSIS AND EPIDEMIOLOGY

The epidemiological records and files of 143 patients residing in the province of Salta and notified in the period 2008-2022 were analyzed taking into account the three components: clinical, laboratory and epidemiological. The 26.57% (38/143) correspond to confirmed cases with VL, 7.69% (11/143) were invalidated for not meeting clinical epidemiological criteria and 65.74% (94/143) were discarded (Table 1) .

TEMPORAL DISTRIBUTION OF CASES

The series shows two moments of epidemiological significance, the first between 2008-2011 with 3 isolated cases and a second between 2015 and 2022 with a cluster of 35 confirmed cases (Figure 1).

GEOGRAPHICAL DISTRIBUTION

Notified cases were reported in 13 of the 23 Departments of the province of Salta; confirmed cases correspond to General San Martín and Rivadavia, where the foci of transmission are located, and Anta, with an epidemiological link to the latter. These VL cases are distributed in eight municipalities, with Tartagal having the highest number of cases (17) in the period 2008-2022 (Table 2). The geographic dispersion of confirmed cases can be seen in Map 1.

6. New cases confirmed according to the definition in force at the time of notification.

CHARACTERIZATION OF CASES

1 - Age groups: The 38 cases of VL show a wide range in their distribution from 0 to 77 years of age, with an average of 15.37±3.56 years (11.80-18.93 years). Of the confirmed cases, 68.42% (26/38) were under 10 years of age, and of these, 84.61% (22/26) were under 5 years of age; this distribution can be seen in Figure 2.

2 - Phenotypic sex: 68.42% (26/38) of the confirmed cases were males and 31.58% (12/38) were females.

3 - Clinical presentation: 60.84% (87/143) of the notified patients have an epidemiological record showing the signs and symptoms for which the disease is suspected and correspond to the 38 confirmed cases, the 46 discarded cases and the three invalidated cases.

In the series, 68.42% (26/38) of the cases confirmed at the time of consultation presented fever of more than 14 days of evolution (prolonged febrile syndrome - PFS) and weight loss, followed by hepatosplenomegaly (HEM) in 47.37% (18/38) and anemia with 44.74% (17/38); when these signs and symptoms are related to the final classification of cases it yields the following information:

- SFP: p=0.3730; OR=0.8535 $IC_{95\%}$ [0.3341-2.1800].
- Weight loss: p=0.0699; OR=1.9860 $IC_{95\%}$ [0.8109-4.8650].
- HEM: p<0.0003; OR=6.0000 $IC_{95\%}$ [2.0610-17.4700].
- Anemia: p=0.1822; OR=1.5180 $IC_{95\%}$ [0.6287-3.6650].

The association between the presence of PFS with the other signs or symptoms shows significant characteristics for the following pairs:

- SFP-weight loss: p=0.0125; OR=5.5580 $IC_{95\%}$ [1.2320-27.8300].
- SFP-HEM: p=0.0369; OR=3.9390 $IC_{95\%}$ [0.8834-21.7800].
- SFP-anemia: p=0.0079; OR=12.0800 $IC_{95\%}$ [1.6940-296.8000].

ANALYSIS OF THE MAIN VARIABLES REPORTED FOR CONFIRMED CASES

1 - Time (days) between the date of symptom onset and consultation: 89.47% (34/38) of the notifications show the date of symptom onset and the first medical consultation; this analysis yields an average of 33 days $IC_{95\%}$ [23 - 43 days]; with an interval ranging from 5 to 348 days.

2 - Hospitalization: 56.82% (75/132) of the reported patients recorded hospitalization, as did 86.84% (33/38) of those confirmed, and 9.09% (3/33) required intensive care and mechanical ventilation. The association between case confirmation and hospitalization yielded a p<0.0005; OR=8.0480 $CI_{95\%}$ [3.025 - 25.05].

3 - Other indicators: The analysis of the epidemiological records of confirmed patients also allows the following information to be analyzed:

- Records of evolution with medical discharge indicated in 57.89% (22/38).
- Only one death was recorded and it corresponds to the patient reported in 2008 with a post-mortem diagnosis.
- In 78.95% (30/38) of the notifications, the specific etiological treatment was registered in the SNVS $^{2.0}$; one with meglumine antimoniate and 29 with liposomal amphotericin.

LABORATORY ETIOLOGICAL DIAGNOSIS

1 - Analysis of data according to determinations and techniques: 100% (132/132) of the classified patients had at least one laboratory study. The diagnosis was made by direct methods of visualization of the parasite such as observation of smears, cultures and/or amplification of genetic

material by molecular biology (BM) and indirect methods using techniques for the determination of specific antibodies against *L. donovani/infantum* by Enzyme Linked Immunoassay (ELISA) and Immunochromatography rk 39 (Ic-rK39).

The analysis of Sensitivity (S), Specificity (S), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) was performed for each of the techniques applied and provides the following information:

- **Ic-rk39:** S = 88.24%, E = 100.00%, PPV= 100.00%, NPV = 95.29%.
- **ELISA:** S = 100.00%, E = 98.59%, VPP= 96.43%, VPN = 100.00%, VPN = 100.00%.
- **BM:** S = 84.00%, E = 100%, VPP = 100%, VPN = 91.11%, VPP = 100%, VPN=91.11%.

The combination of techniques used for case classification shows difference in S, E, PPV and NPV, results shown in Table 3.

The concordance analysis between the two serological tests used yields a Kappa value[7] (κ) of 0.84 $IC_{95\%}$ [1.05-0.64].

EPIDEMIOLOGICAL ASPECTS AND ECOLOGICAL CHARACTERIZATION

Geographic area

In the Province of Salta, the Departments of General San Martín and Rivadavia are the only ones that reported autochthonous cases of VL or cases related to a focus of transmission such as those residing in Anta. They occupy an area of 42,208.00 km^2 , representing 27.15% of the provincial total (155,488.00 km^2). The speed and occurrence of cases was quantified using the Density of cases/100 km2 by triennium/ Department.

The results obtained up to 2022 place General San Martín in first place with a density of 0.20 cases/100 km^2 compared to 0.02 in Rivadavia. The Professor Salvador Mazza Municipality presents the highest accumulated density for the study period, followed by Tartagal and Gral. Mosconi, as shown in Graph 3.

Vector. Phlebotomine vectors involved in the transmission of the disease

Information on the phlebotomine sandflies involved in the transmission of VL in Argentina and their distribution is obtained from the update made by the National Ministry of Health at the " National Zoonosis Meeting (September 19-20, 2023) ", proposed by the Leishmaniasis Research Network in Argentina (REDILA) (Map 2). In the province of Salta, the species involved are confirmed by means of different investigations:

Lutzomyia longipalpis (Lu. longipalpis): The literature review indicates that *Lu. longipalpis* was not found in captures made in Salta Province during the period 1988 - 2000[16] ; in 2013 Gómez Bravo et al. described for the first time its presence in the city of Tartagal during work carried out in northwestern Argentina[9] . The location of the capture sites indicated in the publication coincides with the presence of LV cases recorded subsequently.

In 2016 he made the first report of capture in the town of Salvador Mazza, confirming its presence on the Argentina-Bolivia border, not described so far and with typically peri-urban characteristics[12] .

In 2019, a focus study was conducted in the localities of Tartagal and General Mosconi, confirming the presence of this phleblotomine phlebotomine only in Barrio Norte Grande (Tartagal) in the area where the human case diagnosed that same year was described (22°30'21.5 "S 63°47'26.3 "W)[13] .

Migonemya migonei (Mg. migonei: The focus study conducted by Barroso A. P. et al. around the patients reported in 2010 and 2011 describes the presence of *Lu. migonei together* with *Lu. cortelezzii/Lu. sallesi (cortelezzii*

7. Cohen's Kappa Index (κ)

complex) as possible vectors involved in the transmission cycle of the disease in rural sites. The presence of these vectors associated with or in the vicinity of canine or human cases was also described in Tartagal[9,13] in Salvador Mazza[12] and in General Mosconi[13] .

Reservoir

The investigation of the reservoir or reservoirs involved in the transmission of this event in the province of Salta is carried out by means of two surveillance systems, one active and the other passive, and the survey of the different sources can be seen in Table 4.

Active surveillance (outbreak control intervention): The main objective is to know the prevalence of canine infection by *L. (L.) infantum* in a given area through census or sampling serological surveys, in order to verify the presence of infected dogs and to carry out surveillance and control actions for VL, which should be directed to areas related to the presence of human cases and requiring sanitary interest[3] .

In 2010, the notification of a human case with probable autochthonous characteristics allows for the first systematized focus study with investigations in canines that are directly related to the site of transmission; these studies were conducted in November 2010 and July 2011 in Curva de Juan (Municipality of Santa Victoria, Dept. Rivadavia) where 77 dogs were studied with a seroprevalence of 12.98% (10/77)[11] .

In 2017, a study was conducted in Professor Salvador Mazza on 40 canines, of which 4 (10%) were found to have positive rK39 serology, corresponding to a population-based study[12] .

The focus study conducted in 2019 studied 30 canines in Mosconi with a positivity of 10.00% (3/10) and 69 in Tartagal with 8.6% (6/69) positives[13] .

Passive surveillance: Corresponds to cases reported to the system through clinical suspicion in animals by veterinarians, who obtain blood samples and refer them to the reference laboratory (Laboratory of the Institute of Experimental Pathology "Dr. Miguel Ángel Basombrío". UNSa). The source of information consulted is the SNVS[2.0] and reflects the regular surveillance of canines with symptomatology. This process maintains a notification regulation since 2008.

Description of the epidemiological scenario of VL in the Province of Salta

The epidemiological scenario was defined taking into account the variables described for the ecological characterization, taking into account the concept of vulnerable, receptive, transmitted and/or endemic areas. Stratification was performed using the V-R-T Index. The interpretation of the results that can be obtained is shown in Table 5.

The results show that the Departments of General San Martín and Rivadavia have a V-R-T Index of 3.00, while Anta and Orán have a value of 1.00 and the rest of the departments have a value of 0.00, which indicates that:

Dpt. San Martín and Rivadavia: Epidemiological scenario with ecological characterization of the environment where VL transmission occurs.

Dpt. Anta and Oran: Epidemiological scenario with ecological characterization of the environment where VL transmission may occur.

Rest of the Departments: Epidemiological scenario with ecological characterization of the environment with very low or no probability of occurrence of VL transmission.

Estimation of epidemiological risk of VL

The Triennial Composite Index (ICTLv) was calculated taking into account the departments in which the cases occurred and corresponded to General San Martín,

Rivadavia and Anta; the latter corresponds to the residence of the patients, and the place of occurrence corresponds to Rivadavia. The indicators were then grouped by department and allowed categorization by disease transmission risk strata.

The analysis of the risk of VL transmission by Department and by triennium taking into account the series of cases 2008 - 2022 according to the ICTLv for the province of Salta is shown in Map 3 and allows observing the transition of this related to the moments described in the appearance of cases. Between 2008 and 2013 the risk is low to medium and between 2014 and 2022 it is medium to high.

DISCUSSION

In the province of Salta, VL is an emerging health problem; from the first case diagnosed in 2008 to the date of completion of this study, there is evidence of an increase in the speed of its transmission, being the General San Martín and Rivadavia Departments the only ones where it was evidenced; For the first of them, in these fifteen years the density of cases/100km^2 /triennium increased 23 times, taking it from a base value of 0.0061 to 0.1414, and for the other we observed a smaller increase, only three times, with a variation from 0.0038 to 0.0116. These values, projected for the next decades, would position the area as high risk.

When analyzing other epidemiological aspects that take into account the presence of cases and their incidence rate mathematically summarized in the ICTLv, we also observe very important variations that accompany and support the results obtained when studying the density of cases. Thus, analyzing this index, proposed by PAHO as a surveillance tool, we observe that the Departments of General San Martín and Rivadavia follow the same corridor, defining scenarios that range from low risk to medium and high risk.

To complete the quantitative assessment of the risk scenario in epidemiological terms, it is necessary to take into account variables related to vulnerability, receptivity and transmission, so it was necessary to create a new index, not previously described, which is the "V-R-T index" by means of which we can have a general idea of the type of scenario in the area under study. The two departments involved in the event reach a maximum value of 3 and thus end up defining them in ecological and environmental terms. This index also shows an approximation value with what may happen with the neighboring departments (Anta and Orán), showing the phenomenon of continuity and contiguity, with an index equal to 1.

In these circumstances, we must intensify clinical and laboratory surveillance in human and canine cases and add entomological surveillance.

Handling these epidemiological concepts together with the clinical description of the cases allows us to understand the kinetics of the disease in our environment in order to define health policies that contribute to the mitigation of the event.

Once the links in the *"reservoir-vector-human"* transmission chain have been identified, multidisciplinary and intersectoral interventions can be carried out in a timely manner to control the outbreak, thus preventing the appearance of new cases and the spread of the area at risk.

The characterization of the described cases according to their signs and symptoms allows establishing that the diagnostic suspicion is not totally dependent on the presence of a prolonged febrile syndrome and/or weight loss, but that the possible presence of hepatosplenomegaly should be included in the definition of a suspected case ($p<0.0003$); as well as the association between the presence of fever for more than two weeks with anemia

(p<0.0079) and with hepatosplenomegaly (p<0.0079).0.0003); as well as the association between the presence of fever for more than two weeks with anemia (p<0.0079), and with hepatosplenomegaly (p<0.0369).

Advancing in the diagnostic methodology allows creating independence at the moment of making the etiological diagnosis of the disease, empowering primary health services as the first effectors in the recruitment of patients with clinical suspicion and proven epidemiology, where biochemical determinations with good sensitivity and specificity and proven quality in the field can be carried out within their reach. This review shows that the determination of specific antibodies to detect the disease by ELISA technique has a sensitivity of 100% related to the final classification of cases, and that when accompanied by another direct or indirect test, the specificity is increased. Similarly, for all the techniques reported in this series of cases, it can be seen that they reach a specificity of 100% or close to it. Likewise, the positive or negative predictive values are satisfactory for the classification of the cases. On the other hand, when analyzing the concordance between antibody determinations by ELISA or Immunochromatography methods, they yield a Kappa value (κ) of 0.84 *IC* 95% [1.05-0.64], reflecting a very good concordance between the two available tests.

Actions aimed at the three links must be carried out by health decision-makers. As far as the patient is concerned, early diagnosis, specific etiological treatment administered in a timely manner, sustained serological surveillance in the reservoirs identified in our environment such as the family dog or others that may arise as a consequence of future research, and the continuous search for vectors involved in the transmission of the disease will allow the development of mitigation plans supported by the scientific basis.

The integrated approach requires that the indicators described above be reviewed periodically to evaluate interventions and future strategies. The following should be considered annually:

- Laboratory diagnosis of at least 95 % of the cases
- Treatment of 100 % of cases
- Cures in at least 95 % of cases
- LV-HIV co-infection

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CONFLICTS OF INTEREST

This publication is based on the research studies carried out in the framework of the Thesis to obtain the degree of Master in Public Health with mention in PHC. Cohort 2021-2022. In the homonymous postgraduate career, dictated by the Faculty of Health Sciences of the University of Salta, approved by Resolution -D-N° 549-22 of the Faculty of Health Sciences of the UNSa on 30/09/2022. The thesis is directed by Ph. D. Paola Andrea Barroso, which is part of this publication.

I declare that I have no conflicts of interest with respect to the data published in this study and that they are of my own authorship.

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ANNEXES

TABLES

Ranking	Patients notified	Component		
		Clinical	Laboratory	Epidemiological
Confirmed	38	38	38	38
Discarded	94	46	94	0
Invalidated	11	3	0	0
Total	143	87	132	38

Table 1. Cases reported in the SNVS[2.0] to the event "Visceral leishmaniasis" according to final classification by component. Province of Salta. Years 2008-2022.

Source: *Notifications to SNVS and SNVS[2.0] . Epidemiological Surveillance Program. DGCE-MSP Salta*

Province of residence: Salta				
Department	**Municipality**	**LV Cases**	**% Dept.**	**% Municipality**
Anta		**2**	**5.26**	
	Apolinario Saravia	1		2.63
	El Quebrachal	0		0.00
	J. V. González	1		2.63
	Las Lajitas	0		0.00
Gral. San Martín		**32**	**84.21**	
	Aguaray	0		0.00
	Boat	1		2.63
	Gral. Ballivián	0		0.00
	Gral. Mosconi	11		28.95
	Prof. Salvador Mazza	3		7.89
	Tartagal	17		44.74
Rivadavia		**4**	**10.53**	
	Col. Juan Solá	1		2.63
	Rivadavia Banda Sur	0		0.00
	Santa Victoria East	3		7.89

Table 2. Distribution according to Department and Municipality (2nd and 3rd Administrative Level/ Argentina) of residence of VL cases notified to SNVS/SNVS2.0. Province of Salta. Years 2008 - 2022.

Source: *Notifications to SNVS and SNVS[2.0] . Epidemiological Surveillance Program. DGCE - MSP Salta*

Method	Sensitivity	95% CI	Specificity	95% CI
Ic-rK39	88.24%	75.93% - 100.00 %	100.00%	99.38% - 100.00%
ELISA	100.00%	98.15% - 100.00%	98.59%	95.15% - 100.00%
Ic-rk39/ELISA	100.00%	97.83% - 100.00%	100.00%	99.14% -100.00%
BM	84.00%	67.63% - 100.00%	100.00%	98.78% -100.00%
Ic-rK39/BM	83.33%	66.34% - 100.00%	100.00%	98.28% - 100.00%
ELISA/BM	85.71%	68.37% - 100.00%	100.00%	98.68% -100.00%
Ic-rK39/ELISA/BM	85.00%	66.85% - 100.00%	100.00%	98.21% -100.00%

Method	VPP	95% CI	VPN	95% CI
Ic-rK39	100.00%	98.33% - 100.00%	95.29%	90.20% - 100.00%
ELISA	96.43%	87.77% - 100.00%	100.00%	99.19% - 100.00%
Ic-rk39/ELISA	100.00%	97.83% - 100.00%	92.68%	99.14% - 100.00%
BM	100.00%	97.62% - 100.00%	91.11%	81.69% - 100.00%
Ic-rK39/BM	100.00%	97.50% - 100.00%	87.88%	75.23% - 100.00%
ELISA/BM	100.00%	97.22% - 100.00%	92.68%	83.49% - 100.00%
Ic-rK39/ELISA/BM	100.00%	97.06% - 100.00%	90.32%	78.30% - 100.00%

Table 3. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value of the techniques used for the diagnosis of visceral Leishmaniasis according to final classification. Province of Salta. Years 2008 - 2022. n=132

Source: *Notifications to SNVS and SNVS[2.0] . Epidemiological Surveillance Program. DGCE - MSP Salta*

Year	Surveil-lance	Action	Department	Location/Location	rK39 seroprevalence in canines			Source
					Est.	Pos.	%	
2010/ 2011	Activate	Focus control	Rivadavia	Curva de Juan (Santa V. Este)	77	10	12.99	Barroso et al, 2015
2017	Activate	Population study	Gral. San Martín	Prof. Salvador Mazza	40	4	10.00	SNVS 2.0
2019	Activate	Focus control	Gral. San Martín	Gral. Mosconi	30	3	10.00	Barroso et al, 2022
2019	Passive	Veterinary Clinic	Gral. San Martín	Aguaray	2	1	50.00	SNVS 2.0
2019	Passive	Veterinary Clinic	Gral. San Martín	Gral. Mosconi	1	1	100.00	SNVS 2.0
2019	Passive	Veterinary Clinic	Gral. San Martín	Prof. Salvador Mazza	1	0	0.00	SNVS 2.0
2019	Passive	Veterinary Clinic	Gral. San Martín	Tartagal	94	75	79.79	SNVS 2.0
2019	Passive	Veterinary Clinic	Capital	Salta	1	0	0.00	SNVS 2.0
2019	Passive	Veterinary Clinic	Oran	San Ramón de la Nueva Orán	2	2	100.00	SNVS 2.0
2020	Passive	Veterinary Clinic	Gral. San Martín	Aguaray	1	1	100.00	SNVS 2.0
2020	Passive	Veterinary Clinic	Gral. San Martín	Gral. Mosconi	2	1	50.00	SNVS 2.0
2020	Passive	Veterinary Clinic	Gral. San Martín	Prof. Salvador Mazza	1	1	100.00	SNVS 2.0
2020	Passive	Veterinary Clinic	Gral. San Martín	Tartagal	99	81	81.82	SNVS 2.0
2021	Passive	Veterinary Clinic	Gral. San Martín	Tartagal	2	1	50.00	SNVS 2.0
2021	Passive	Veterinary Clinic	Capital	Salta	1	1	100.00	SNVS 2.0
2022	Passive	Veterinary Clinic	Gral. San Martín	Aguaray	3	1	33.33	SNVS 2.0
2022	Passive	Veterinary Clinic	Gral. San Martín	Gral. Ballivian	3	1	33.33	SNVS 2.0
2022	Passive	Veterinary Clinic	Gral. San Martín	Gral. Mosconi	27	10	37.04	SNVS 2.0
2022	Passive	Veterinary Clinic	Gral. San Martín	Prof. Salvador Mazza	12	8	66.67	SNVS 2.0
2022	Passive	Veterinary Clinic	Gral. San Martín	Tartagal	156	87	55.77	SNVS 2.0
2022	Passive	Veterinary Clinic	Gral. San Martín	Vespucio	6	1	16.67	SNVS 2.0
2022	Passive	Veterinary Clinic	Rivadavia	Rivadavia Bda. Norte	1	0	0.00	SNVS 2.0
2022	Passive	Veterinary Clinic	Capital	Salta	5	4	80.00	SNVS 2.0
2022	Passive	Veterinary Clinic	Oran	San Ramón de la Nueva Orán	3	2	66.67	SNVS 2.0

Table 4. Seroprevalence in canines by determination of rK39 according to surveillance strategy by Department and year of study. Province of Salta. Years 2010-2022.

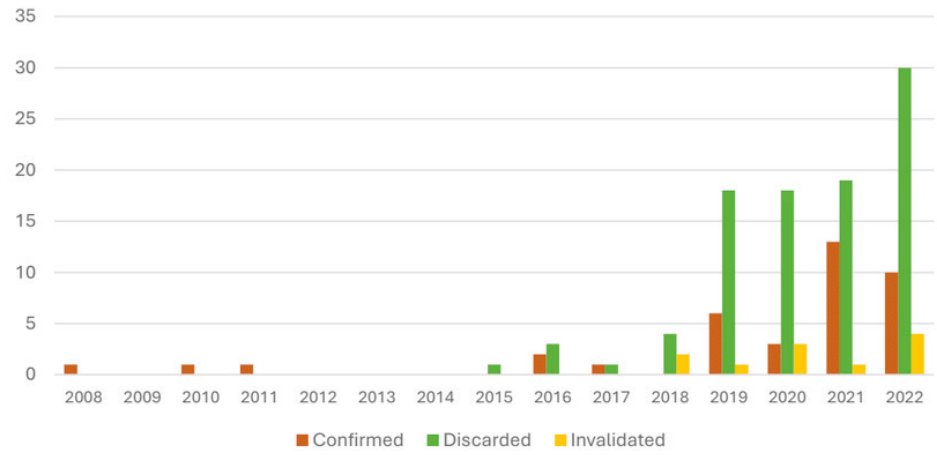
Source: *Notifications to SNVS and SNVS[2.0] . Epidemiological Surveillance Program. DGCE - MSP Salta*

V-R-T Index Range	Characteristics of the epidemiological scenario of VL
0.00 a 0.99	Epidemiological scenario with ecological characterization of the environment with very low or no probability of occurrence of VL transmission.
1.00 a 1.99	Epidemiological scenario with ecological characterization of the environment where VL transmission may occur. Vulnerability, receptivity and transmission should be assessed to define the interventions to be carried out in the epidemiological surveillance area.
2.00 a 3.00	Epidemiological scenario with ecological characterization of the environment where VL transmission occurs. Clinical and laboratory surveillance of human and canine cases and entomological surveillance should be kept active.

Table 5. Interpretation of the V-R-T Index defining the characteristics of the epidemiological scenario of VL.

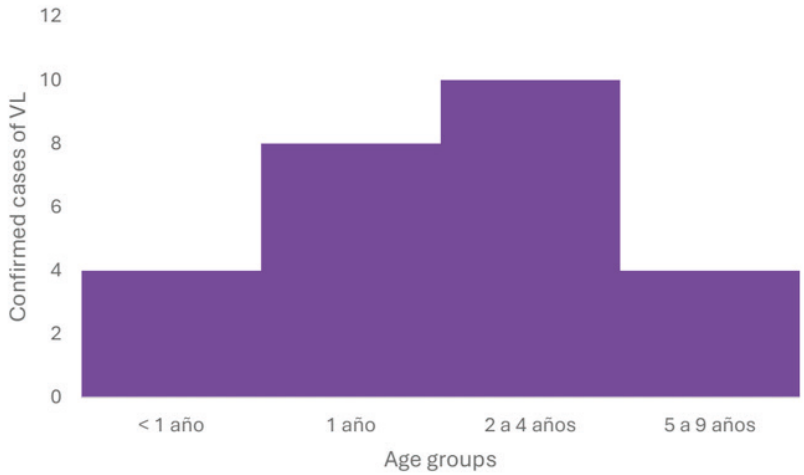
Source: *Own elaboration. Based on the Thesis "Clinical characterization and eco-epidemiological aspects of human visceral Leishmaniasis in the Province of Salta. Period (2008-2022). (García Campos, 2024)*

GRAPHICS



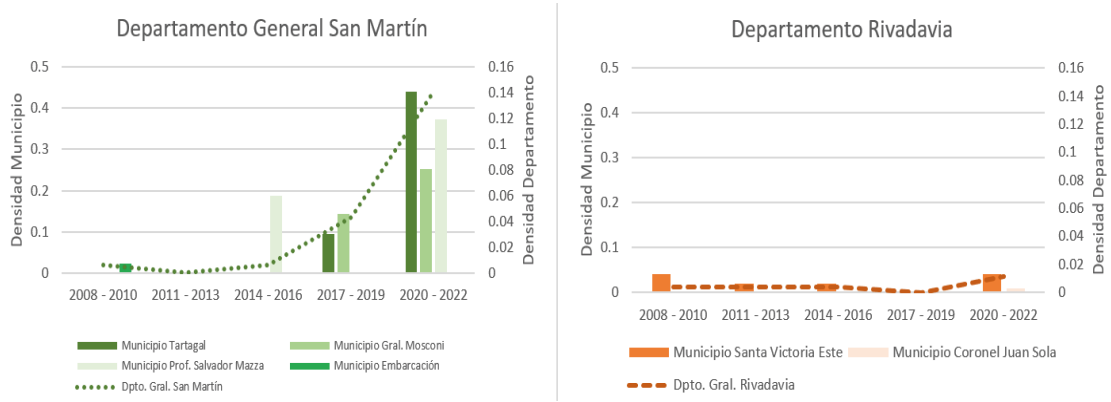
Graph 1. Confirmed, discarded and invalidated cases of VL according to year of notification. Province of Salta. Years 2008 - 2022. n=143

Source: *Notifications to SNVS and SNVS[2.0] . Epidemiological Surveillance Program. DGCE - MSP Salta*



Graph 2. Distribution by age group of children under 10 years of age classified as confirmed cases of human visceral leishmaniasis. Province of Salta. Years 2008 - 2022. n=26

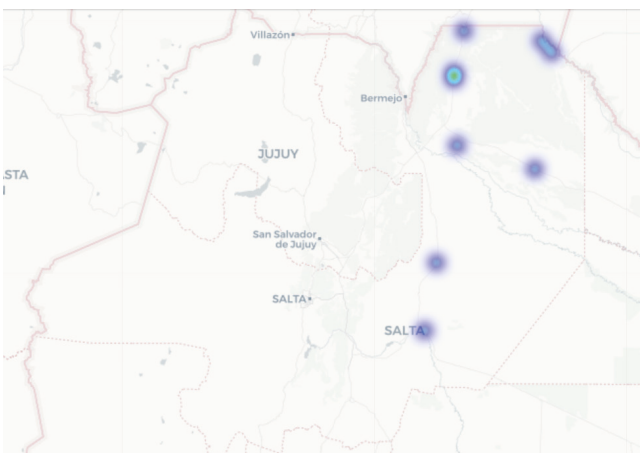
Source: *Notifications to SNVS and SNVS[2.0] . Epidemiological Surveillance Program. DGCE - MSP Salta*



Graph 3. Density of cases (accumulated per three-year period) of VL per 100 km^2 according to municipality of residence or occurrence in the Departments of General San Martín and Rivadavia. Province of Salta. Years 2008 - 2022. n=38

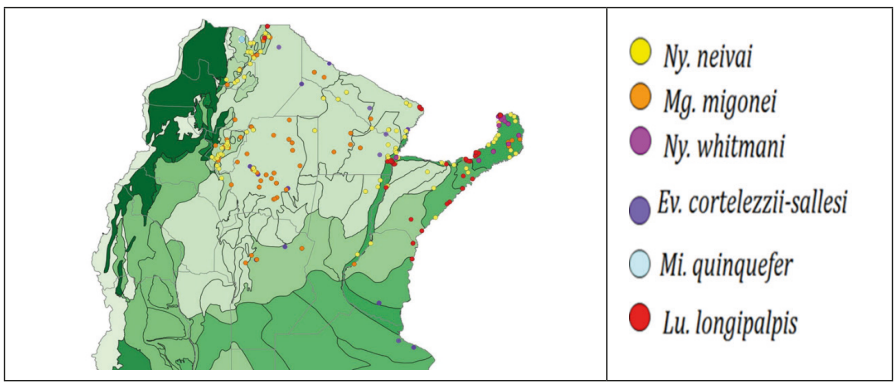
Source: *Notifications to SNVS and SNVS$^{2.0}$. Epidemiological Surveillance Program. DGCE - MSP Salta*

MAPS



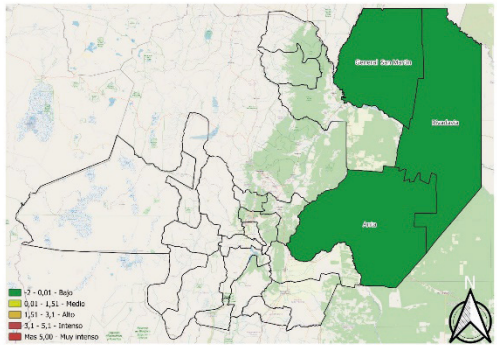
Map 1. Heat map with the distribution of VL cases reported to SNVS/SNVS2.0. Province of Salta. Years 2008 - 2022.

Source: *Own elaboration. Taken from the information recorded on the location of confirmed VL cases uploaded in the EpiCollect form5. (https://five.epicollect.net/project/proyecto-tesis).*

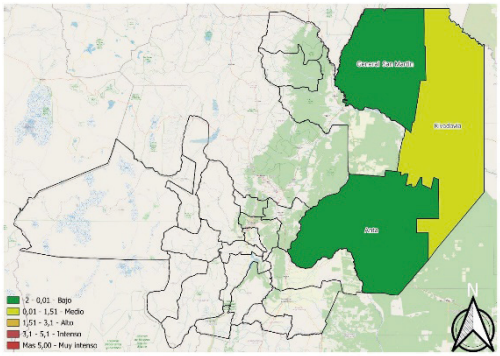


Map 2. Distribution of the main phlebotomine sandflies involved in the transmission of parasites related to tegumentary and visceral Leishmaniasis in Argentina. REDILA 2022.

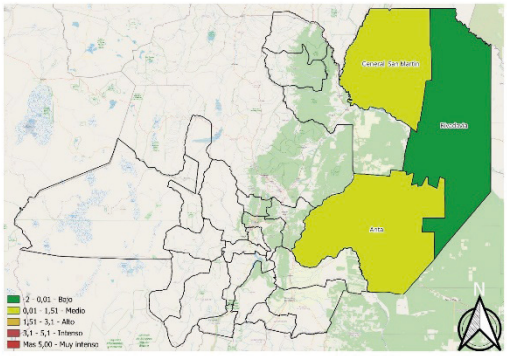
Source: *National Zoonosis Meeting (September 19-20, 2023) "National Leishmaniasis Program, canine visceral leishmaniasis and its approach from Public Health". MSN*



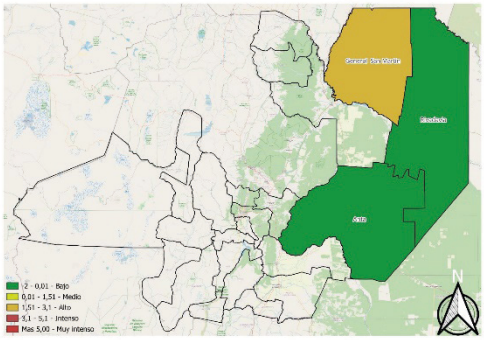
ICTLv 2008-2010



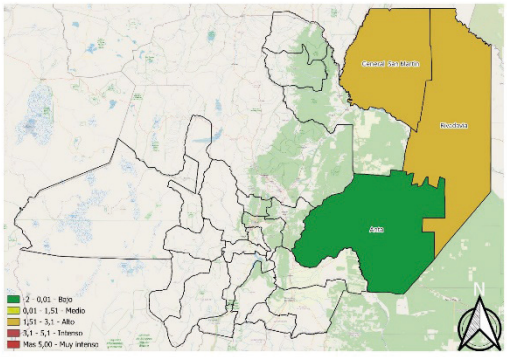
ICTLV 2011-2013



ICTLv 2014-2016



ICTLv 2017-2019



ICTLv 2020-2022

Reference	ICTLv	Risk of transmission
	- 2.00 a 0.00	Under
	0.01 a 1.50	Medium
	1.51 a 3.00	High
	3.01 a 5.00	Intense
	plus 5.00	Very intense

Map 3. Evolution of the risk of VL transmission by Department and three-year period according to the ICTLv, Province of Salta. Year 2008 - 2022

Source: *Own elaboration. Based on the Thesis "Clinical characterization and eco-epidemiological aspects of human visceral Leishmaniasis in the Province of Salta. Period (2008-2022). (García Campos, 2024)*