

Original Article

## Are the neglected tropical diseases under control in the tri-border region between Brazil, Argentina, and Paraguay?

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### Abstract

**Introduction:** Implementation of prevention and control measures for communicable diseases in border regions can be challenging and lead to inefficient attempts to control them. We describe evidences on the strengths, weaknesses, opportunities and challenges regarding implementation of health interventions for control, prevention and treatment of selected neglected tropical diseases (NTD), a group of transmissible diseases typically prevalent in tropical countries and vulnerable populations, in the tri-border between Brazil, Argentina, and Paraguay.

**Methodology:** A systematic literature review of observational and experimental studies was conducted, using PubMed and Bireme databases. Eligibility criteria were location (tri-border area) and subject (health interventions).

**Results:** Of a total of 595 references identified, 34 studies were included (18 pertaining to leishmaniasis, 11 to dengue, 2 to leprosy, 2 to soil-transmitted helminthiasis and 1 to Chagas' disease), with an inclusion rate of 6.4%. The main strengths were the similarity of health interventions between countries and easiness of mobility and communication flows. The main weaknesses were access to rural areas and discrepancies in the number of studies between countries. As for opportunities, we identified increased tourism, economic development and recent increasing research in this field. The main challenges were the absence of studies regarding other prevalent NTD in the region and movement of goods, animals and people across borders.

**Conclusions:** Although epidemiological studies are still needed to better understand and assess the prevalence of NTD in the area, mainly in Paraguay, these findings can inform decision-makers and health managers to plan a common strategy to address NTD.

**Key words:** Tri-border; Brazil; Argentina; Paraguay; neglected tropical diseases; border areas.

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### Introduction

Neglected tropical diseases (NTD) are a group of transmissible diseases, typically prevalent in tropical and subtropical countries, affecting more than a billion of people in the world [1-3], particularly vulnerable populations, children, pregnant women, and those living in poverty with limited access to effective treatments. In endemic places, NTD are responsible by poor health indicators (birth, fertility, morbidity, and mortality rates) [3] with high economic and social impact. NTD are associated with lower productivity, long-term incapacity and maintenance of poverty and sickness cycles [1-3]. The social and economic determinants associated with NTD highlight the need to address them with the introduction of simple and cost-effective interventions [2,3].

Border areas are critical, complex and vulnerable areas from a public health perspective, due to specific

political, juridical, technical, and operational issues concerning the control and treatment of diseases [4]. Border regions are usually remote areas, far from the commanding and decision-making stations, where major social, cultural, and economic differences occur. It is not uncommon to associate border regions with unemployment, low human development index, environmental problems, and illegal and criminal practices [5]. Therefore, health interventions in border areas must be flexible, adaptable, and include all the involved countries [6].

South America is still highly endemic for neglected tropical diseases [1], which makes the study of its prevalence, interventions and strategies a relevant issue. The tri-border region, where the cities Foz do Iguaçu (Paraná State, Brazil), Puerto Iguazú (Misiones Province, Argentina) and Ciudad del Este (Alto Paraná Department, Paraguay) meet, is the location of Iguazú

falls, classified as Humanity's Natural Heritage, and was identify as a particularly interesting spot for international health studies, for being a tourist attraction point with intensive trade and movement of goods and people across borders of three different countries [7].

A preliminary investigation was done, to access which neglected tropical diseases, among the list established by World Health Organization (WHO) [1], were prevalent in this region and should be studied [1,3], using official data available at institutional sites. The WHO list was chosen as a reference to this study because it is applicable worldwide and widely considered as the main reference about NTD. The identified diseases, classified as being possibly prevalent, were: Buruli ulcer [1,8], schistosomiasis [1,9-12], trachoma [1,10,12,13], echinococcosis [1,10,14,15], rabies [1,10,16,17], and foodborne trematodiasis [1,18]; and those classified as prevalent were: leprosy [1,10,12,15,16,19], Chagas' disease [1,9,10,15,16], leishmaniasis [1,10,15,16,19], taeniasis and cysticercosis [1,12,20,21], soil-transmitted helminthiasis [1,9,12,21,22], and dengue [1,9,10,15,16].

We aimed to describe the strengths, weaknesses, opportunities, and challenges for the prevention, control, and treatment of neglected tropical diseases in tri-border region, so that the findings can inform decision-makers and health managers to plan a common strategy to address these diseases.

## Methodology

The research question “what are the strengths, weaknesses, opportunities, and challenges for the prevention, control, and treatment of NTD in the tri-border?” was defined using the population, intervention, comparison, outcome (PICO) method

[23]. This method was chosen because of its sensibility, since there are not many published literature regarding this theme [24]. To achieve the objectives of the study, a Strengths Weaknesses Opportunities and Challenges (SWOC) analysis was chosen.

After the preliminary investigation, to identify which NTD were relevant to study we further identified the type of health interventions to control, prevent and treat NTD in the tri-border area, critically analysed those that have been performed and searched for epidemiologic data regarding these diseases in the region.

We conducted a systematic literature review of observational and experimental studies and used PRISMA to structure the report [24]. We approached local investigators for other relevant documentation or publication that could be included in the present study, but to our best knowledge no grey literature or other relevant local documents were identified at that time.

We used a protocol divided in five steps: 1) research within two different data bases (PubMed and Bireme), using MeSH terms, DeCS descriptors and Boolean indicators (Table 1) (the search timeline was from 2007 until 19<sup>th</sup> December 2018, and restricted to publications in Portuguese, English, Spanish, and French with full text available); 2) application of the inclusion and exclusion criteria to the abstracts using a flow-chart (Figure 1); in this phase, a random sample of 40 references was further evaluated by a second reviewer in order to access the sensitivity of the review process; 3) application of inclusion and exclusion criteria to the full text of the selected studies; 4) data collection on the disease, location, type of study, type of intervention, ethical review, results, and year of study of the selected studies; 5) SWOC analysis to identify strengths, weaknesses, opportunities and challenges.

**Table 1.** Key words used for the search.

<b>P [Population]</b>	Triple Border* OR Triple Frontier* OR Tri-border* OR Foz do Iguazú* OR Puerto Iguazú* OR Ciudad del Este* OR Paraná* OR Misiones* OR Alto Paraná* OR (Brazil AND Argentina AND Paraguay)
<b>I [Interventions]</b>	Border Areas OR Disease Prevention OR Primary Prevention OR Secondary Prevention OR Tertiary Prevention OR Communicable Disease Control OR Public Health OR Public Health Surveillance OR Health Promotion OR Health Education OR Health Policy OR Therapeutics OR Therapy
<b>C [Comparison]</b>	Not applicable
<b>O [Outcomes]</b>	Neglected Diseases OR Buruli Ulcer OR Mycobacterium ulcerans OR Schistosomiasis mansoni OR Schistosoma mansoni OR Mollusca OR Biomphalaria tenagophila* OR Trachoma OR Chlamydia trachomatis OR Leprosy OR Mycobacterium leprae OR Echinococcosis OR Echinococcus OR Chagas Disease OR Trypanosoma cruzi OR Trypanosomiasis OR Triatominae OR Rhodnius neglectus* OR Leishmaniasis OR Leishmania OR Phlebotomus* OR Leishmania infantum OR Rabies OR Rabies Virus OR Rabies Vaccines OR Taeniasis OR Neurocysticercosis OR Taenia OR Taenia solium OR Fascioliasis OR Fasciola hepatica OR Paragonimiasis OR Paragonimus OR Lymnaea OR Helminthiasis OR Ascaris lumbricoides OR Ascariasis OR Necator americanus OR Necatoriasis OR Ancylostomiasis OR Ancylostoma OR Trichuris OR Trichuriasis OR Dengue OR Severe Dengue OR Dengue Virus OR Aedes OR Haemorrhagic fever*

Terms with \* do not have a correspondent MeSH term.

The inclusion criteria applied to the full text of the studies were as follows:

1. The study was conducted or is related with tri-border or with one of the cities Foz do Iguacu, Puerto Iguazu and Ciudad del Este; and:
  - a. The subject analysed is related with health interventions for prevention, control or treatment of NTD; or
  - b. The subject analysed is related with NTD epidemiologic data in the tri-border region or in one of the cities Foz do Iguacu, Puerto Iguazu e Ciudad del Este.
2. The subject analysed is related with health interventions for prevention, control or treatment of NTD and the study was conducted in a distance below 100 km from the city centre of one of the tri-border’s cities, with interest or applicability in the tri-border region;
3. The subject analysed is related with cross-border care, international public health, health regulation or health policies, with interest or applicability in the tri-border region.

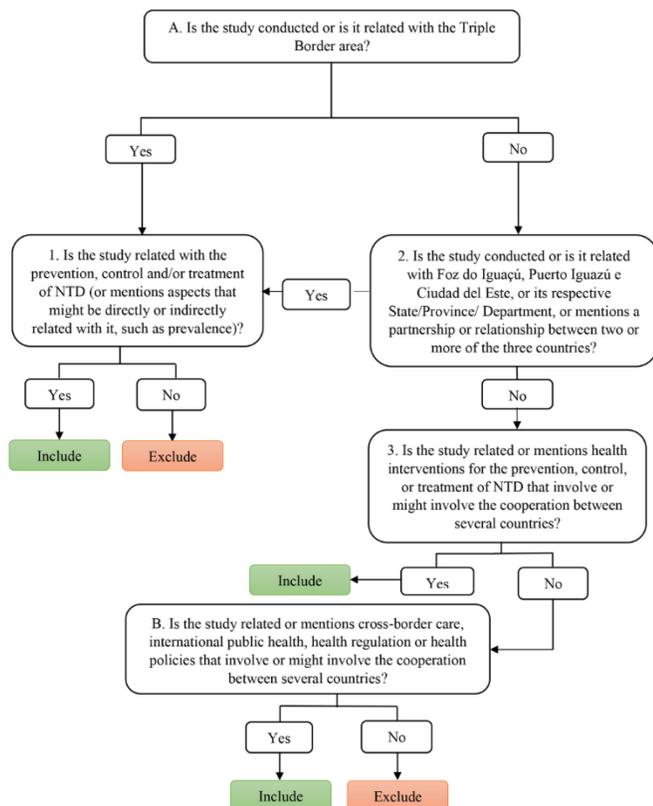
Studies were excluded from the full-text appraisal phase if any of the following exclusion criteria were met:

1. The study is not related with the tri-border region or was conducted in a distance above 100 km from the tri-border region;
2. The study/subject in analysis is about health interventions in areas other than NTD;
3. The subject under analysis is not related or does not connected with the implementation of health interventions in this region and/or regarding NTD;
4. The full text it is not available and/or an extra payment it needed for its access.

For this study, the area of interest was defined as the area within a radius of 100 km from the city centre of Foz do Iguacu, Puerto Iguazu or Ciudad del Este. This was adapted from the definition of borderland strip, which is the inside strip with 150 km of width, parallel to the terrestrial dividing line of the national territory as defined by the Brazilian Institute of Geography and Statistics [25].

Regarding the regular access to scientific magazines and online repositories, the access used was the b-on platform. We approached local investigators for other relevant documentation or publication that could be included in the present study, but no grey literature or other relevant local documents were identified.

**Figure 1.** Inclusion and exclusion criteria applicable to the studies abstracts.



**Results**

Between 20<sup>th</sup> February 2017 and 19<sup>th</sup> December 2018, 595 references were identified, 64 of which were duplicates and therefore excluded. Overall, 531 abstracts and later, 230 full texts were analysed.

Regarding abstract selection, the Kappa value calculated to assess the level of agreement between the first and the second reviewer was 0.352. The sensibility was 46% and the specificity 94%. At the end of the selection process, 34 studies were included, representing an inclusion rate of 6.4% (Figure 2).

The design of the included studies ranged from one (2.9%) community-based trial, four (11.8%) field trials, two (5.9%) cohort studies, two (5.9%) ecological studies, 18 (52.9%) cross-sectional studies, one (2.9%) cross-sectional and observational study, one (2.9%) cross-sectional and qualitative study, three (8.8%) observational studies, one (2.9%) qualitative study, and one (2.9%) documentary review and exploratory observational study. Fourteen (41.2%) of these studies were cross-sectional entomological studies, related to the control of vector populations of dengue and leishmaniasis; three (8.8%) were cross-sectional animal studies with dogs regarding the control of leishmaniasis; one (2.9%) was simultaneously a cross-

sectional entomological and animal study, and one (2.9%) was an observational retrospective study and cross-sectional entomological study, in a total of 18 (52.9%) out of 34 studies (Figure 2).

None of the studies involved all the three countries: 21 (61.8%) were conducted in Argentina: 17 (80.9%) in Puerto Iguazú, one (4.8%) in Paranense Forest, one (4.8%) in Misiones and two (9.5%) in locations bellow 100 km from Puerto Iguazú (Puerto Libertad and Wanda); 12 (35.3%) were conducted in Brazil, all of them in Foz do Iguacu and eight (66.7%) of them also in other locations. Notoriously, only one (2.9%) study was conducted in Paraguay (Supplementary Table 1).

Of the included studies (n=34), 18 (52.9%) addressed leishmaniosis, 11 (32.3%) dengue, two (5.9%) leprosy, two (5.9%) soil-transmitted helminthiases and one (2.9%) Chagas' disease. Most of the studies entailed the surveillance and control of vectors: 19 (55.9%) studies were vector control interventions (11 about phlebotomine sandflies and 8 about *Aedes* spp.); two (5.9%) were prevention interventions; three (8.8%) studied the transmission

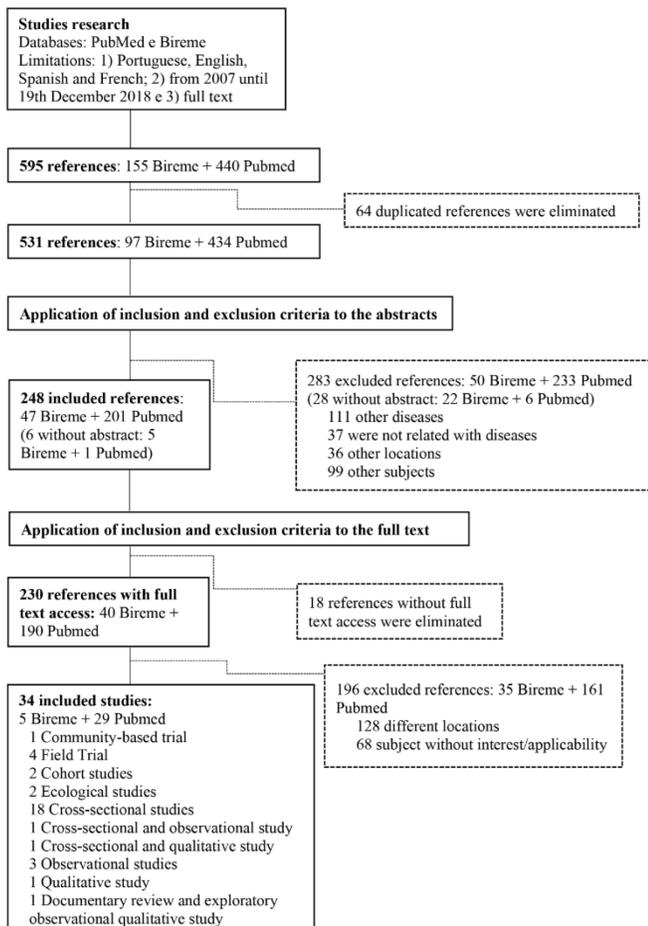
mechanisms; five (14.7%) studied its epidemiology, two (5.9%) were diagnosis and treatment interventions; two (5.9%) were control, diagnosis and treatment interventions and one (2.9%) was an eco-epidemiological study (Supplementary Table 1).

Notably, 16 (47.1%) studies out of 34 were published between the years 2017 (7 studies - 20.6%) and 2018 (9 studies - 26.5%). As for the other studies: one (2.9%) was published in 2007, three (8.8%) in 2008, two (5.9%) in 2009, two (5.9%) in 2010, two in 2011 (5.9%), three (8.8%) in 2012, two (5.9%) in 2013, one (2.9%) in 2014 and two (5.9%) in 2015 (Supplementary Table 1). The fact that 16 (47.1%) studies out of 34 were published between 2017 and 2018, demonstrates the exponential interest and investment in research in this area.

Most of the included studies aimed either at the control of the diseases, to minimize and monitor its dissemination and transmission or to assess its epidemiology. The studies conducted in Brazil, Argentine and Paraguay had in common the control and surveillance of the population of sandflies and the study of the epidemiologic profile of the regions (Supplementary Table 1).

In respect to surveillance and control of vectors only five (14.7%) studies were about an effective intervention to eliminate and/or treat domestic residencies or vectors' infested areas: one field trial conducted in Foz do Iguacu for the evaluation of adult trap specific for capturing *Aedes aegypti* females, in comparison with the technique of aspiration of specimens in artificial shelters [59]; one community-based trial conducted in Puerto Libertad, Misiones, for the evaluation of the efficacy of a new smoke-generating formulation containing 2% pyriproxyfen and 10% permethrin against *Ae. aegypti* and evaluation of community acceptance of this nonprofessional fumigant tablet and their perceptions and practices regarding dengue [51]; one field trial conducted in Puerto Iguazú in the area "2000 Hectáreas" that used impregnated curtains as a Phlebotomine control tool in experimental hen houses [40]; one field trial conducted in Wanda, Misiones, for the evaluation of a new ultralow volume formulation containing 15% permethrin and 3% pyriproxyfen, comparatively with a ultralow volume formulation of 15% permethrin against *Ae. aegypti* population [54]; one conducted in Puerto Iguazú, Wanda and Tartagal for the assessment of a new ovitrap to monitor population fluctuations of *Ae. aegypti*, in order to detect a peak of vector density and apply control measures or to evaluate their efficacy [56] (Supplementary Table 1).

**Figure 2.** Selected studies.



In Argentina, four studies were conducted at “2000 Hectáreas” area in leishmaniasis propagation context, namely one field trial regarding its control [40], one cross-sectional entomologic study regarding its transmission [42], one qualitative study regarding its ecoepidemiology [52] and one observational retrospective study and cross-sectional entomologic study regarding its epidemiology [55]. These studies have a valuable and interesting approach to the deforestation of primary forest and vulnerable population lack of resources and poverty problems (Supplementary Table 1).

Also, in Argentina, two studies conducted in the Mbyá-Guaraní indigene population stand out for their approach to the well-being and health of this vulnerable population. One was a household survey of children aged ≤ 15 years for parasitological and nutritional assessment of soil-transmitted helminthiases and other parasitosis, which concluded that 87.8% of children had at least one parasite and 87.0% malnutrition, being individual conditions, habits and literacy of the mother the most important socio-demographic determinants [26]. The other was an observational retrospective study regarding the estimation of the prevalence of Chagas Disease, Syphilis and Human Immunodeficiency Virus (HIV) 1, detected a prevalence of 6.7% of *Treponema pallidum*, *Trypanosoma cruzi* and HIV infections [37] (Supplementary Table 1).

A community trial conducted in Puerto Libertad, Misiones [51] and an ecoepidemiological study conducted in “2000 Hectáreas” area [52], promoted a community approach, empowering and valorising the role, intervention, perceptions and practices of the

community, regarding dengue and the local inhabitants perceptions, knowledge and representations regarding leishmaniasis, respectively (Supplementary Table 1).

Only two studies about leprosy were included, both conducted in Brazil regarding its epidemiology in Paraná State [58] and Foz do Iguazú [30], despite leprosy being present in the three countries and a well-known prevalent disease in Misiones, Paraná and Foz do Iguazú [10,16,-58]. Overall, the five epidemiological studies included were related with past diseases outbreaks, namely two about leishmaniasis in Paraná [29] and Puerto Iguazú [55], one about dengue in Paraná [53] and the two about leprosy in Paraná [58] and Foz do Iguazú [30].

Four studies addressed diagnosis and treatment: two in the Mbyá-Guaraní indigene population, regarding parasitological assessment and estimation of the prevalence of Chagas Disease, Syphilis and HIV-1 [26,37]; one in children aged ≤ 15 years in Puerto Iguazú for parasitological assessment and the parasitic environmental contamination and socio-demographic characteristics [36] and one in Alto Paraná regarding the epidemiologic situation, interventions for vector control, health care treatment and stakeholders perceptions of American cutaneous leishmaniasis [38] (Supplementary Table 1).

The two simulated cohort studies, addressed cost-effectiveness approaches, using a Markov model, for American tegumentary leishmaniasis [45] and dengue [33]. Both recommended the implementation of primary and secondary prevention measures to avoid disease transmission, since these were more cost-effective than the traditional approach to treat detected

**Table 2.** SWOC analysis.

<b>Internal Factors</b>	
<b>Strengths</b>	<b>Weaknesses</b>
Similarities of the interventions conducted in Brazil and Argentina for the control and prevention of leishmaniasis and dengue; Increased mobility and communication; History of joint strategies; Linguistic, cultural, socio-political, health-care systems differences between countries; Human resources, logistical and economic differences between countries.	Access to rural areas (e.g., “2,000 Hectáreas”); Discrepancy in the number of studies conducted in Paraguay (one) and Brazil (12) and Argentina (21); Lack of ethical review; Linguistic, cultural, socio-political, health-care systems differences between countries; Human resources, logistical and financial differences between countries.
<b>External Factors</b>	
<b>Opportunities</b>	<b>Challenges</b>
Similitude of interventions between countries; Increased tourism and local visibility; Increased trade activities and economic development; Increased number of published papers and research in the area in the last two years of the research period.	Absence of studies regarding other prevalent NTD in the region (taeniasis and cysticercosis) and scarce information on leprosy, soil-transmitted helminthiases and Chagas disease Barriers in the cooperation and collaboration between countries Circulation/mobility of goods, animal and people.

cases. In the first case, the adoption of insecticide-impregnated curtains and clothing was highly cost-effective when compared to early diagnosis strategy [45]. The later, recommended vaccination as the main strategy to decrease the seroprevalence of dengue set at 79% in Misiones [34] (Supplementary Table 1).

Through the SWOC analysis of all included studies (Table 2) it was possible to identify as strengths: the similarities of the interventions conducted in Brazil and Argentina for the control of leishmaniasis and dengue (vector vigilance, monitoring and elimination); the facility of mobility and communication and the past history of joint strategies, such as the Southern Cone Initiative to the elimination of Chagas's disease [60]. On the other hand, we identified as weaknesses: the access to rural areas, such as "2.000 Hectáreas" area, in terms of health system accessibility and existent social barriers, the discrepancy in the number of studies conducted in Paraguay (1), Brazil (12) and Argentina (21) and the lack of ethical review. The linguistic, cultural, socio-political, health-care systems and human resources, logistical and economic differences between countries were simultaneously considerate strengths and weaknesses, depending on how they are perceived and managed by the countries and their political, health professional players, population and different stakeholders.

As for opportunities, we identified increased tourism and local visibility, increased trade activities, growing economic development of the area, increase of published papers and research in the last two years and the similitude of interventions between countries.

As challenges, we identified the absence of studies regarding other prevalent NTD, such as taeniasis and cysticercosis; the barriers in cooperation and collaboration between countries and the circulation/mobility of goods, animal and people (Table 2).

## Discussion

The aim of this study was to understand how NTD have been prevented, controlled and treated in the tri-border region, highlighting the interactions between the three countries. Thus, we expect to use the results of this study to inform the design of strategies aimed at the elimination of the prevalent NTD.

According to our study, in the past decade, several studies were conducted in this area, particularly in 2017 and 2018, mostly regarding vector borne diseases such as leishmaniasis and dengue, which are well-known diseases affecting South America [1,10,15,16]. The studies were conducted in Argentina or Brazil, except

for one conducted in Paraguay, and none involved all countries.

These results highlight the problematic prevalence of vector-borne diseases in this region and some of the efforts that have been put into place to address them. The NTD under consideration do not respect borders and have a rapid dissemination at this region with subtropical mesothermal humid climate. As so, any strategy for controlling NTD should include the three countries to maximise efforts and produce more efficient, cost-effective and long-term sustainable results. The lack of joint studies seems to point out the need to develop an international wide approach that will surely improve the control of the diseases and capitalize efforts and resources.

Despite their prevalence, studies on leprosy, soil-transmitted helminthiasis and Chagas' disease in the analysed period were scarce and no studies were found for taeniasis and cysticercosis [9,10,12,15,16,19,20-22]. No further evidences or relevant information regarding Buruli ulcer, schistosomiasis, rabies, foodborne trematodiasis, trachoma or echinococcosis, classified as possible prevalent, were found. In order to avoid future outbreaks of unknown prevalent diseases and to prevent their silent dissemination, additional epidemiologic studies in the region are recommended.

Neglected diseases have been studied in this area for the past 10 years, but, as already mentioned, separately for the three countries. Probably, leishmaniasis and dengue are most commonly studied due to recent outbreaks, and detection of cases of visceral leishmaniasis, both in human and dogs, and increasing need to control and eliminate *Ae. aegypti*, a common vector of dengue, chikungunya, yellow fever, and zika, the former with a recent rapid dissemination through Latin America [1,41].

Other prevalent diseases, such as leprosy, Chagas' disease and soil-transmitted helminthiasis appear to be less the focus of studies or the target of health interventions. Nevertheless, importance must be given to community circulation and transmission of the *Mycobacterium leprae* and to patients and their caregivers needs and health [30,58], to the implementation of measures to avoid congenital transmission of Chagas' disease [37] and to treat and prevent child infection with soil-transmitted helminthiasis and other parasitosis [26,36]. Other important factor that might influence which diseases are subject to a health intervention is the political importance that is given to their prevention, control or treatment and health strategies.

The findings of these studies reflect the importance of vector control interventions in the region, together with the study of the epidemiology and of the transmission mechanisms, in particular for Dengue and Leishmaniosis. The rapid spread across borders of NTD can be better exemplified using Leishmaniosis as example. In 2004, there was an outbreak of American Tegumentary Leishmaniasis in Puerto Iguazú (“2000 Hectáreas”) [52] and in 2012, *Lutzomyia Longipalpis* was first detected in the State of Paraná [47]. Following these events, *Leishmania infantum*, the parasite responsible for Visceral Leishmaniosis, was first detected in dogs in 2013 Puerto Iguazú [43]. On the following year, *L. infantum* natural infection was first detected in *Nyssomyia whitmani* and *Migonemyia migonei* [42] and in 2015, *L. infantum* was detected in *Lutzomyia Longipalpis*, *Ny. whitmani*, and *Micropygomyia quinquefer*, also in Puerto Iguazú [39]. In 2015, the prevalence rate of *L. infantum* in dogs was 23.8% in Foz do Iguazú [35], while *Lu. longipalpis* was the prevalent sandfly species, with its respective distribution related to the abundance of dogs in Foz do Iguazú [31]. Although no data was found about the prevalence of Visceral Leishmaniosis in Ciudad del Este, a study published in 2017, identified that there were more cases of American Cutaneous Leishmaniasis in the districts close to the tri-border in relation to the rest of the Department [38]. Across years it is notorious how Visceral Leishmaniosis has spread across borders within the tri-border region and have become prevalent, highlighting the importance of integrated strategies and harmonized control interventions in border areas.

The following limitations were identified: lack of studies and information about Paraguay; absence of studies and information regarding other prevalent diseases in tri-border region (taeniasis and cysticercosis) and regarding other possible prevalent diseases (echinococcosis, schistosomiasis, Buruli ulcer, trachoma, rabies, and foodborne trematodiasis); undisclosed data and information, given that a health intervention does not necessary implies the publication of a study; research in only two databases (PubMed and Bireme); utilization of PubMed database, a database of studies related with biomedicine field and that may lack studies in health policy and evaluation of health interventions; the fact that this subject area is developing and there are few published studies; low Kappa value calculated to assess the level of agreement between the first and the second reviewer and low sensitivity value related with the application of the inclusion and exclusion criteria to the abstracts, possibly because the first reviewer did not excluded

articles that could have been excluded thought the application of the diagram (Figure 1). As for keywords, few limitations were found: the use of keywords with low interest for the investigational question, such as “Mollusca”, “Chlamydia trachomatis”, “Haemorrhagic fever” or obsolete terms, such as “Phlebotomus”; and not using keywords for other relevant vectors for Cutaneous Leishmaniosis and Chagas Disease. Despite this, we believe that these limitations were mitigated using MeSH terms, which allowed for a broader research, including the relevant words for each one of the studied NTD. Also, it is important to mention that at the time the preliminary study started, to access the prevalence of NTD in the tri-border, snake bites were not included on the WHO list. Nevertheless, some results related with this disease were found thanks to the term neglected diseases used as a MeSH term. The WHO list was chosen as a reference to this study because it is applicable worldwide and widely considered as the main reference about NTD, but other references could have been chosen instead, such as the PAHO list or specific countries classification lists.

## Conclusions

This review identified that health interventions to control NTD in the tri-border area are similar between countries, with satisfactory mobility and communications between them, although access to rural areas and knowledge gaps on epidemiology might hamper their implementation. Nevertheless, increasing interest with accompanied increase in population flows in the tri-border area might pose an opportunity for greater collaboration between countries, through an intersectoral, holistic and collaborative approach.

Considering the identified strengths, we believed that countries could share human resources, equipment and transports across sectors, in order to reduce operational cost and increase health outcomes. The differences in terms of national regulations (including disease reporting at national level), implementation of mandatory responsibilities in international health regulations and health sovereignty, as well as agroforest and touristic projects with economic impact, should be taken into consideration when planning common regular surveillance and border-based intervention and research.

We recommend the implementation of health interventions that empower and engage local communities and of environmental studies to address the ecological impact of the deforestation and its effects both in animal and human health. We also recommend additional epidemiological studies to understand and

assess the prevalence of NTD in the area, particularly in Paraguay, through the implementation of regular diagnostic testing, both in humans and animals.

The results of this study may be helpful to political decision-makers, stakeholders and health managers to plan a common strategy, in international health perspective, to fight NTD and to design tailored interventions that jointly address human, animal and environment health, in a one health perspective.

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## Annex – Supplementary Items

Supplementary Table 1. Summary of the included studies.

Author and reference	Disease	Location	Type of study	Type of intervention	Ethical Review	Results	Year of study
Rivero <i>et al.</i> , 2018 [26]	STH and P	Puerto Iguazú (Mbyá-Guaraní communities)	Cross-sectional study	Diagnosis and treatment (parasitological and nutritional assessment and statistical analysis of socio-demographic determinants - household survey of children aged ≤ 15 years)	Yes	87.8% of children had at least one parasite. 79.7% multiparasitism, 60.7% hookworms, 41.9% <i>Strongyloides stercoris</i> . 87% malnutrition. Individual conditions, habits and mother's literacy were important determinants.	Mar 2017 to Dec 2017
Pech-May <i>et al.</i> , 2018 [27]	VL	Argentina (six sites including Puerto Iguazú) and samples from eight America Latin countries	Cross-sectional entomologic study	Control (analysis of the genetic diversity and structure and re-evaluation of the phylogeography of <i>Lutzomyia longipalpis</i> )	No	Two primary genetic clusters in Argentina, cluster 1: Tartagal, Santo Tomé and San Ignacio; cluster 2: Puerto Iguazú, Clorinda and Corrientes. Eight haplogroups (three of these in Argentina).	Not indicated
Santini <i>et al.</i> , 2018 [28]	VL and TL	Puerto Iguazú	Cross-sectional entomologic study	Control (distribution of Phlebotominae abundance in time and space)	Yes	5,110 individuals captured, 98.3% were <i>Lu. longipalpis</i> and <i>Nyssomyia whitmani</i> . Vector persistence throughout the year in special patches of high abundance even during less favourable season.	2011 to 2012
Melo <i>et al.</i> , 2018 [29]	CL	Paraná, including Foz do Iguazú	Ecological study	Epidemiology (analysing the influence of the remaining native vegetation on CL prevalence - statistical analysis using georeferencing)	No	In general, the spatial regression of the detection coefficient revealed statistical significance for spatial density (vegetation influences the incidence of CL). No statistical significance was observed for Foz do Iguazú.	2012 to 2016
Simionato de Assis <i>et al.</i> , 2018 [30]	L	Foz do Iguazú	Ecological study	Epidemiology (evaluation of the relationship of social determinants with risk of leprosy and temporal trend of its occurrence - multivariate analysis)	Yes	The proportion of households with monthly nominal household income per capita greater than 1 minimum wage (negative association) and people of brown race (positive association – possibly ecological fallacy), were statically-significantly associated with risk of illness. A decrease of 4% per year was observed in the rate of detection of new cases. The multibacillary form was observed predominantly (may indicate late diagnosis).	2003 to 2015
Thomaz-Soccol <i>et al.</i> , 2018 [31]	VL	Foz do Iguazú, Santa Teresinha do Itaipu and two transects	Cross-sectional entomologic study	Control (determination of the Phlebotominae fauna, the factors that affect its presence and abundance and the presence of <i>Leishmania infantum</i> )	No	<i>Lu. longipalpis</i> was the prevalent species and its distribution was related to the abundance of dogs. <i>L. infantum</i> was found in <i>Lu. longipalpis</i> , <i>Ny. whitmani</i> , <i>Nyssomyia neivai</i> and <i>Lutzomyia sp. Leishmania braziliensis</i> was detected in <i>Ny. whitmani</i> (possible transmission of both VL and CL).	Oct 2014 to Nov 2015
Fernández <i>et al.</i> , 2018 [32]	TL	Puerto Iguazú	Cross-sectional animal study and entomologic study	Transmission (assessment of the role of small mammals in the transmission cycle of TL caused by <i>L. braziliensis</i> – temporal and spatial association)	No	Co-occurrence of phlebotominae and small mammal captures in four out of 16 stations, which were all the stations with small mammal captures and yielded 97% of the total phlebotominae captures (small mammals may provide a potential source of blood for phlebotominae females). Presence of <i>L. braziliensis</i> in two sigmodontinae small mammals.	2007 to 2009
Orellano <i>et al.</i> , 2018 [33]	D	Argentina (Misiones, Salta and Buenos Aires)	Cohort study (simulated study using a Markov model)	Prevention (vaccination of children's age 0 to 9 years)	NA	Seroprevalence for Misiones was 79%, therefore a vaccination strategy is recommended.	Epidemiological surveillance data from 2007 to 2016
Rivas <i>et al.</i> , 2018 [34]	D	Foz do Iguazú	Cross-sectional entomologic study	Control (evaluation of Larval Index for <i>Aedes aegypti</i> and the relationship between the Building Infestation Index and climate variables for dengue cases)	No	Positive correlations between Building Infestation Index and cases and between mean temperature and cases at two months. Weak correlation between precipitation and cases at three months.	2001 to 2016 (different months over the years)
Thomaz Soccol <i>et al.</i> , 2017 [35]	cVL	Foz do Iguazú, Santa Teresinha do Itaipu and two transects	Cross-sectional animal study	Control (assessment of the prevalence, distribution and risk variables of cVL)	Yes	<i>L. infantum</i> prevalence rate was 23.8% in Foz do Iguazú, 4.7% in Santa Teresinha do Itaipu and 9.1% in the transects areas. The number of vectors and the presence of infected dogs in the neighbouring were positively correlated with the occurrence of infected dogs. Dog size (positive) and quality of the dog's nutrition (negative) were correlated with cVL. First registry of dogs infected with <i>L. braziliensis</i> in the region.	Nov 2014 to Nov 2015
Rivero <i>et al.</i> , 2017 [36]	STH and P	Puerto Iguazú	Cross-sectional study and qualitative study	Control, diagnosis and treatment (co-infection of parasites in children, parasitic environmental contamination and socio-demographic characteristics - children aged ≤ 15 years and soil and dog feces samples)	Yes	Soil and dog samples: 71.5% of sites contaminated, 62.0% hookworms, <i>Trichuris</i> spp. 15.2%; Children: 58.8% parasitoses prevalence, 34.2% multiple-parasitism; 4.4% hookworms; Determinants; presence of trash, street density, age 5-9, playing with soil, previous treatment, mother's literacy, hygiene habits and household characteristics	Jun 2013 to May 2016
Eirin <i>et al.</i> , 2017 [37]	CD, SF, HIV	Argentina (five Amerindian population, including Mbyá-Guaraní of Puerto Iguazú)	Observational retrospective study	Diagnosis and treatment (estimation of infections prevalence)	Yes	In the Mbyá-Guaraní population a prevalence of 6.7% of <i>Treponema pallidum</i> infection was detected and no <i>Trypanosoma cruzi</i> and Human Immunodeficiency Virus infections were detected	2007 to 2010
Giménez-Ayala <i>et al.</i> , 2017 [38]	ACL	Alto Paraná, including Ciudad del Este	Documentary review and exploratory observational qualitative study	Control, diagnosis and treatment (epidemiologic situation, interventions for vector control, health care treatment and stakeholders' perceptions)	Yes	There were more cases of ACL in the districts close to the triple border in relation to the rest of the Department. The diagnosis is centralised in the Health Centers and in the Regional Hospital of Ciudad del Este. The main complications for treatment are its discontinuity and the economic problems of the population to move to the city.	Epidemiologic data from 2003 to 2016, vector data from 2008 to 2013, dates of interviews are not indicated March 2015
Moya <i>et al.</i> , 2017 [39]	VL	Puerto Iguazú	Cross-sectional entomologic study	Control (detection of <i>L. infantum</i> DNA in phlebotomine species)	No	Detection of <i>L. infantum</i> in 3.9% of the captured female sandflies (3 <i>Lu. longipalpis</i> , 1 <i>Ny. whitmani</i> and 1 <i>Micropygomyia quinquefer</i> )	March 2015
Acosta <i>et al.</i> , 2017 [40]	ACL	Puerto Iguazú ("2,000 Hectáreas")	Field trial	Control (use of impregnated curtains as a Phlebotomine control tool in experimental hen houses)	No	59.7% sand flies captured in the no curtain treatment, 26.3% in the non-impregnated curtain, 8.0% in the impregnated curtain and 6.1% in the without chicken conditions	Feb 2012 to Jan 2013
Aguirre-Obando <i>et al.</i> , 2017 [41]	D	Several Brazilian municipalities, including Foz do Iguazú	Cross-sectional entomologic study	Control (insecticide resistance – Phe1534Cys kdr mutation in natural populations of <i>Aedes albopictus</i> )	No	10% 1534Cys kdr allele variation in Foz do Iguazú, (emergence of pyrethroid resistance)	2009 to 2014

Author and reference	Disease	Location	Type of study	Type of intervention	Ethical Review	Results	Year of study
Moya <i>et al.</i> , 2015 [42]	VL	Puerto Iguazú "2,000 Hectáreas"	Cross-sectional entomologic study	Transmission (determination of <i>L. infantum</i> infection in Phlebotominae population in the rural area)	No	Two <i>Ny. whitmani</i> and one <i>Migonemyia migonei</i> were infected with <i>L. infantum</i> . First report of <i>L. infantum</i> natural infection in these sandflies species in Argentina.	Apr 2014
Acosta <i>et al.</i> , 2015 [43]	cVL	Puerto Iguazú	Cross-sectional animal study	Control (determination of <i>L. infantum</i> as the etiologic agent of cVL in domestic dogs from the city)	Yes	7.2% (15/209) of the surveyed dogs were identified as positive for cVL by serological and/or parasitological methods. First molecular characterization of <i>L. infantum</i> from dogs in this area (in 14 amplified samples).	May 2013
Espinosa <i>et al.</i> , [44]	D	Puerto Iguazú	Cross-sectional entomologic study	Transmission (analysing the existence of virus vertical transmission in <i>Ae. aegypti</i> )	No	Finding of vertical transmission of the DEN 3 virus in male specimens of <i>Ae. aegypti</i> .	Apr 2009 to Sep 2009
Orellano <i>et al.</i> , 2013 [45]	ATL	Argentina (subtropical forest Yungas, dry and humid Chaco, and Paranaense forest)	Cohort study (simulated study using a Markov model)	Prevention (estimation of the cost-effectiveness of implementing one primary and one secondary prevention strategies, comparing to the actual model of diagnosis and treatment of detected cases)	NA	The incremental cost-effectiveness ratio for early diagnosis strategy was estimated at US\$ 156.46 per DALY averted (cost-effective), while that of prevention of transmission with insecticide-impregnated curtains and clothing was US\$ 13,155.52 per DALY averted (highly cost-effective)	Epidemiologic data of 2010
Santini <i>et al.</i> , 2013 [46]	VL	Puerto Iguazú	Cross-sectional entomologic study	Control (spatial distribution of <i>Lu. longipalpis</i> abundance)	No	<i>Lu. Longipalpis</i> proved to be exclusively urban and was found in 31% of the households' samples (67% low abundance, 20% moderate abundance and 13% high abundance). <i>Ny. whitmani</i> was the only species found both in urban and peri-urban environments and <i>Mi. migonei</i> was only found on the outskirts of the city. 49 specimens of <i>Lu. longipalpis</i> and 54 other sandflies specimens were captured. First record of <i>Lu. longipalpis</i> in the State of Paraná.	Sep 2011
Santos <i>et al.</i> , 2012 [47]	VL	Foz do Iguazú	Cross-sectional entomologic study	Control (characterisation of Phlebotominae population in the urban area)	No	191 premises were identified as positive for <i>Ae. aegypti</i> (house index of 9.6%), 9% residential and 22% vacant lots. 29,600 containers were surveyed, and the overall container index was 1.1. Water tanks were the most frequently infected.	Jul 2005 to Nov 2005
Costa <i>et al.</i> , 2012 [48]	D	Puerto Iguazú	Cross-sectional entomologic study	Control (characterisation of <i>Ae. aegypti</i> oviposition sites in the city – containers and buildings)	No	<i>Ny. whitmani</i> and <i>Mi. migonei</i> were the most and second most abundant species, respectively and were present throughout the year (potential long period of ATL transmission). Both species were positively associated with temperature and with precipitation. The abundance of sandflies was higher in pigsties than in houses.	Jun 2006 to Feb 2008
Fernández <i>et al.</i> , 2012 [49]	ATL	Puerto Iguazú	Cross-sectional entomologic study	Control (characterisation of Phlebotominae fauna along time in farms located near primary and secondary forest in houses and pigsties, two years after deforestation)	No	Of the 345 ovitraps installed, 63% were positive for eggs (11,220), 53% <i>Ae. aegypti</i> e 47% <i>Ae. albopictus</i> . Coexistence and aggregation of their eggs were observed at all the sites in Paraná. In Foz do Iguazú the <i>Ae. Aegypti</i> populations showed alteration in susceptibility status to the organophosphate temephos, revealing incipient resistance.	Summer 2006-2007
Prophiro <i>et al.</i> , 2011 [50]	D	Foz do Iguazú (North and South), Santa Helena and Ubiratã (Paraná) and Tubarão (Santa Catarina)	Cross-sectional entomologic study	Control (verification of the coexistence between <i>Ae. aegypti</i> and <i>Ae. albopictus</i> populations and evaluate their susceptibility to the organophosphate temephos)	No	Immediately after treatment, the adult index fell almost to zero in all treated areas, including the area where the residents applied the fumigant tablet themselves. There were no significant differences between treatments. More than 80% of the residents applied the fumigant tablets and preferred participating in a vector control program by using a nonprofessional mosquito control tool, instead of attending meetings and workshops promoting cultural changes.	2009
Harburguer <i>et al.</i> , 2011 [51]	D	Puerto Libertad, Misiones	Community-based trial	Control (evaluation of the efficacy of a new smoke-generating formulation containing 2% pyriproxyfen and 10% permethrin against <i>Ae. aegypti</i> and evaluation of community acceptance of this nonprofessional fumigant tablet and their perceptions and practices regarding D)	No	18% of the people settled in the forest edge (77% living less than 100 m), associated the forest and an insect with ATL origin, but represented themselves living in a risk-free area. Among farmers, the urban origin of the disease was the prevalent idea. Mobility and mistrust of drugs influence the access to treatment and implementation of prevention measures.	2008
Mastrángelo <i>et al.</i> , 2010 [52]	ATL	Puerto Iguazú ("2,000 Hectáreas")	Qualitative study	Ecoepidemiology (human-environment relation during an ATL outbreak in 2004 – micro-social research on local inhabitants' practices and representations about illness - interviews and participant observation)	No	There were three D outbreaks in 1995/96, 2002/03 and 2006/07. The urban areas with more incidence of the disease are Londrina, Maingá and Foz do Iguazú. Positive correlation with Paraguay [ $r=0.71$ , $p=0.006$ ] and negative with Argentine [ $r=-0.15$ , $p=0.61$ ]. In Foz do Iguazú there were three outbreaks between 1998 and 2002. The adulticide effect was similar for both formulations, whereas the inhibition of adult emergence was higher with the new formulation (initial values of 96% maintained until 35 days after versus values not greater than 20% of inhibition). Larval indexes showed a greater, long-lasting effect with the new formulation.	1995 to 2007
Duque <i>et al.</i> , 2010 [53]	D	Paraná, including Foz do Iguazú	Observational retrospective study	Epidemiology (temporal and spatial distribution of D in the State of Paraná)	No	The adulticide effect was similar for both formulations, whereas the inhibition of adult emergence was higher with the new formulation (initial values of 96% maintained until 35 days after versus values not greater than 20% of inhibition). Larval indexes showed a greater, long-lasting effect with the new formulation.	Mar 2007 to May 2007
Lucia <i>et al.</i> , 2009 [54]	D	Wanda (Misiones)	Field trial	Control (evaluation of a new ultralow volume formulation containing 15% permethrin and 3% pyriproxyfen, comparatively with an ultralow volume formulation of 15% permethrin against <i>Ae. aegypti</i> population)	No	Most of the 36 (75%) cases of human ACL reported have involved males over 15 years old infected during deforestation to establish individual farms. In 31 (86%) cases the transmission had occurred in the area "2,000 Hectáreas". 18,438 sand flies were captured. The most prevalent species were <i>Ny. whitmani</i> (87.4%) and <i>My. migonei</i> (7.6%). The risk of ACL outbreak is associated with economic and leisure activities in primary-secondary forest, including deforestation, rural settlements, fishing, hunting, and ecotourism.	2004 to 2005
Salomón <i>et al.</i> , 2009 [55]	ACL	Puerto Iguazú (city and "2,000 Hectáreas")	Observational retrospective study and cross-sectional entomologic study	Epidemiology (description of the scenario for ACL transmission from entomological and parasitological perspectives – analysis of clinical records of Hospital Samic and capture of sand flies in primary forest, peri-urban areas, and deforested land sites)	No	In the different situations assayed, the ovitraps resulted in the effective monitoring of mosquito populations in urban areas at high risk of dengue in Argentina, even in areas difficult to access.	Not indicated
Masuh <i>et al.</i> , 2008 [56]	D	Puerto Iguazú, Wanda (Misiones) and Tartagal (Salta)	Field trial	Control (assay of a new ovitrap to monitoring population fluctuations of <i>Ae. aegypti</i> , in order to detect a peak of vector density and apply control measures or to evaluate their efficacy)	No	38,662 specimens of 23 different species were captured: 75.6% <i>Ny. neivai</i> , 10.1% <i>Ny. whitmani</i> , 7.8% <i>Mg. migonei</i> e 3.7% others. <i>Lu. Longipalpis</i> was not captured.	From Mar 2004 to Nov 2005
Silva <i>et al.</i> , 2008 [57]	VL	Paraná (37 municipalities, including Foz do Iguazú)	Cross-sectional entomologic study	Control (identification of the sandfly fauna and aspects of the species' behaviour in forest and anthropic environments)	No		

Author and reference	Disease	Location	Type of study	Type of intervention	Ethical Review	Results	Year of study
Sobrinho and Mathis, 2008 [58]	L	Paraná, including Foz do Iguaçu	Observational retrospective study	Epidemiology (analysis of the prospects for the elimination of L, based on detection and prevalence rates and other epidemiologic variables)	Yes	The L detection rates were high or very high in most of the health districts (1.62, 1.82 e 1.60 cases per 10,000 inhabitants in 2000, 2003 e 2005, respectively). In terms of prevalence, eight health districts had reached the goal of eliminating the disease. In Foz do Iguaçu, the detection rate is high in inhabitants < 15 years (0.58 cases per 10,000 inhabitants), the prevalence rate is 2.68 cases per 10,000 inhabitants and the multibacillary cases represent 82.4%.	Epidemiologic data from 2000 to 2005
Gomes <i>et al.</i> , 2007 [59]	D	Foz do Iguaçu	Field trial	Control (evaluation of Adultrap specific for capturing <i>Ae. aegypti</i> females in comparison with the technique of aspiration of specimens in artificial shelters)	No	The Adultrap captured 24/26 females of <i>Ae. aegypti</i> , while aspiration captures 29/700 females and another five species. In peridomiciles, Adultrap captured significantly more females than aspiration did. Demonstration of sensitivity of Adultrap for detecting females in low-frequency situations.	Nov 2004 to Mar 2005

ACL: American Cutaneous Leishmaniasis; ATL: American Tegumentary Leishmaniasis; CD: Chagas' Disease; CL: Cutaneous Leishmaniasis; cVL: canine Visceral Leishmaniasis; D: Dengue; HIV: Human immunodeficiency virus 1; L: Leprosy; NA: Not applicable; P: other parasitoses; STH: Soil-transmitted helminths; SF: Syphilis; TL: Tegumentary leishmaniasis; VL: Visceral Leishmaniasis.