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Instructions on how to make an Outbreak of American Cutaneous Leishmaniasis

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Abstract

Outbreaks of American Cutaneous Leishmaniasis (ACL) are triggered by the confluence of multidimensional biological, climate, and social factors: the eco-epidemiological momentum. Despite the diversity of epidemiological scenarios, there are common "Ingredients for the recipe" to make an ACL outbreak. To describe the "Where", "When", and "Why" of this momentum could contribute to the understanding of the causes of epidemics, preventing their occurrence, and to define better strategies to control them. Typically, due to sylvatic-rural transmission, most urban ACL are still related in time and space to peripheral city deforestations, riparian forest, and green patches within the cities. Therefore, the "Where" of the ACL outbreaks could be characterized in the space as an edge effect, and afterwards the "When" of this edge could be categorized as an ephemeral, transient or permanent. The "Why" question is far more complex, as it includes the exposure of humans to vector due to anthropic activities in each edge scenario. The evidence for ACL outbreak control strategies: barricading the edge by chemical and physical barriers, environmental management, and individual prevention, were reviewed. Answers to questions regarding these "Where", "When", "Why", and "How to control" guided the content of the questions to be asked in the new focus of ACL transmission, not only to mitigate current transmission and prevent future outbreaks, but also to highlight the biological factors that might contribute to the possibility of an epidemic, and those conditions that modulate its actual probability, the climate and the social determination of risk.

Keywords: Eco-Epidemiology; Edge Effect; Phlebotominae; Urban Transmission

Introduction

Cutaneous leishmaniasis is a neglected tropical disease, categorized as emerging and uncontrolled, having the highest increase of prevalence among these diseases between 1990 and 2016 [1,2]. The estimated worldwide incidence is between 690,000 to 1,213,300 cases per year, including 48,915 reported cases in 17 countries of the Americas during 2016 [3,4].

American Cutaneous Leishmaniasis (ACL) is produced by several species of the genus *Leishmania*, transmitted by different species of Phlebotominae (Diptera: Psychodidae), with a broad spectrum of mammal reservoirs and epidemiological scenarios [5]. Despite this diversity in most of the cases, ACL transmission is restricted in space and time and reported as focal outbreaks, even in hyper-endemic areas, where it could be recurrent, but with an irregular pattern different from a seasonal trend [6,7]. These outbreaks were generated by the coincidence of multiple factors, both biological and social, a "Perfect storm" or an eco-epidemiological momentum, in the multidimensional sense of the eco-epidemiology definition by Susser [8].

The retrospective eco-epidemiology at the first sub-national jurisdiction was already used to understand the change in the transmission of ACL related to changes in land use [9], but a prospective eco-epidemiology at smaller spatial scales could be used to understand the outbreak generation and guide the studies of epidemic foci to mitigate transmission and prevent future epidemic events. While the studies from regional to global scales contribute to program policy and general advocacy [10], this review focuses in scales from site up to village, which are more useful for operational purposes in high-risk areas [11].

"Urban" ACL

Urban transmission of ACL has been proposed during the last decades, mirroring the urbanization of the American Visceral Leishmaniasis [12]. Risk of urban transmission of ACL is sometimes associated with mobilization of vectors due to deforestation near city borders or the creation of peripheral new neighborhoods, which generate ACL "Hot spots" [13-25]. ACL urban transmission has also be associated with environmental heterogeinity as secondary forest edges, riparian forests with periodic overflows [26-30], forest fragments within cities that harbor vectors and infected reservoirs [31-42], and zoological gardens or cemeteries [43-45].

Consequently, the urban ACL risk seems more closely linked to the organization of urban space than to actual urban transmission cycles. Contributing factors include the cities green belt and green preserved patches, the changes in land value—peripheral expansion, displacement of old settlements—, and the trend of returning to nature [46-50]. The unplanned growth of the city and its new scenarios of vector-human contact involve, with the social determination as a driving factor, work relations, housing quality, public services, and heath accessibility, as well as spatial segregation of people according to social status [51-53]. In turn, these situations pressure the vector-reservoir-parasite triad to adapt to new green-patched environments, but with a higher density of food sources for the vector and synanthropic reservoirs [54]. Further, the cases at urban borders could show a different spatial pattern from year to year, suggesting that transmission could be due to micro-local environmental interventions as deforestation in small areas or just around a new neighborhood, and so, in these foci, the urban peridomestic areas are not acting as a source population in the sense of the metapoplation dynamics [55-58]. However, in many cases city officials and politicians associated urban transmission with blanket spatial insecticide interventions over the whole city.

In the same sense, alleged urbanization, with intra-domiciliary risk, could sometimes be related to towns of such size that have all the borders less than 250 m from the border with forested areas, relatively low captures of vectors, such as in Cochabamba, Bolivia [59], or villages promoted for eco-tourism or fishing close to reserves and hotels surrounded by forest [60-64]. Studies of vector distribution based on case-control designs or small sample sizes could also miss environmental associations when the cases are controlled by landscape or share a similar environment [65]. In larger cities, such as Manaus, Brazil, the ACL cases were clustered close to the Negro river and 76% lived within 500 m of forested areas inside the city, although the authors caution about that "It cannot be determined from these data whether transmission of these cases occurred within or outside the city of Manaus" [66]; further, as the surveillance notification systems usually records the residence or diagnosis of the cases site instead of the probable infections site.

The cases could be reported also as urban due to the residences recorded in their clinical files, but actually the cases are living in illegally occupied lands, where they make small deforestations for subsistence farms and domestic animal breeding in the forest fringe [67,68]; or they all live in an urban neighborhood from where they are recruited together for forest-related work [20]. Domestic-peridomestic transmission assumed by the presence of endophagic vectors or the gender-age distribution of the cases does not mean neither urban transmission, as indoor transmission could happen in relation to closeness to edges [69-71]**,** although the presence of vectors in human residential environments improves the probability of vector control [72], consistent with control guidelines [73,74].

This edge effect seems to explain many peri-urban ACL events, at the micro-scale, However, the edge effect could be extrapolated also to most of the ACL outbreaks as a conceptual frame of aanalysis? considering the broad spectra of interfaces between urban-rurban-rural-sylvatic landscapes, from indoor to extra-domestic transmission, from mixed urban and rural human practices [75-77] To answer this question, and to also know what questions to ask in ACL focus studies for managing outbreaks, except atypical ACL due to *Leishmania infantum-Lutzomyia longipalpis* [12], I will discuss the "Where", "When", "Why", and "How to control" described for ACL outbreaks. On the other hand, ACL urbanization is a circumstantial event by the effect of the pressure on vectors to be adapted to domestic environments, the selection and plasticity of species, and speciation trends within them, with different vectorial capacity.

"Where": The Edge Effect

As a general statement in anthropized landscapes with phlebotomine suitability, the species diversity decreases, while few species increase its relative and absolute abundance, mainly in domestic landscapes that could resemble forest microhabitats. Thus, the species composition varies according to the degree of fragmentation of the forest [39,41,78-94]. Phlebotomine collections in sylvatic environments could also have fewer collected individuals due to less blood availability close to the trap, as when light traps are used as the only method of capture [95].

Otherwise, when peridomestic environments still have great phlebotomine species diversity, the influence of nearby forest patches should be considered as population sources. In Brazil a higher species diversity in rural areas than in periurban areas was associated with the closeness to ecotopes, such as residual forests, rocky outcrops, and subsistence farms and its environmental gradients, together with the heterogeneity and density of sylvatic, synathropic, and domestic animals that provide blood sources in the ecotone area [96,97]. This availably of blood sources and a vector-feeding preference threshold could in turn modulate the short-range dispersion from the edges [98,99].

Even small modifications in the landscape led to an increase in the number of individuals of vector competent species, as was reported in a crop-forest interface in Argentina [100], or the generation of clustered ACL cases in forest intervened borders even in rural settlements [101,102]. These new edges, besides the concentrated source of blood and diversity of shelters, provide new breeding sites for vectors with soil enriched with fallen leaves and manure. Further, synathropic mammals also attracted to crops or domestic garbage, facilitate the possibility of multi-host reservoirs or a reservoir community linking sylvatic and peridomestic parasite transmission cycles [103-106].

In hyper-endemic areas the abundance of individuals of phlebotomine species was also associated with primary or secondary forest edges and vegetation coverage in a buffer area of 100 to 250 m or within small local surveillance units [7,33,107-111]. The relative abundance of phlebotomine between preserved areas and neighborhoods with forest fragments in a locality of Mato Grosso, Brazil, was 32:1 [112], while in the three-country border of Brazil-Bolivia-Peru, this value was 1.7:1 in peridomestic captures performed 200 m from the riparian forest continuous with the rainforest [113]. In the Argentina-Brazil-Paraguay three-country border, ACL peridomestic vectors are associated with proximity to natural reserves, residual forest, and rural forested edges in periruban areas [114,115].

However, as a word of caution on the "Where" question, at the local of infection or the smallest spatial scale, the distribution of ACL cases may have some bias due to differences between the distribution of infection and the distribution of clinically expressed cases, as the latter could actually be related with the distribution of the people with other co-infections, such as helminth ones that could immunomodulate the pathogenesis of *Leishmania* [116-118]. Other factors that could create bias regarding the ACL distribution are the stochastic or unknown distribution determinants of reservoir, parasites, vectors, infected vectors and reservoirs, and the genetic human predisposition for clinical signs or clustering of social determinants, such as familiar mucosal cases [119], while the hypothesis of endemic transmission by human reservoirs should require further population-based epidemiological evidence [120].

At these micro-spatial levels, the intra-domestic or peridomestic human infection could be related to the actual distribution of vectors as in an ACL focus in Chapare, Bolivia, where 99.3% of phlebotomine were collected outdoors [121], but also to the hourly distribution of vectors according to the hourly distribution of human exposure activities [122]. In Chaparral, Colombia, the peridomestic outdoor risk is from 19:00 to 20:00 hours and the indoor risk is from 23:00 to 24:00 hours [123], while in other scenarios the ratio between outdoor indoor vector abundance showed a linear correlation and with ACL incidence [15]. Besides, the housing quality, as its openness and crevices, the peridomestic suitability for vector breeding, and practices related to vector exposition—sleeping outdoors, collecting water, domestic or synanthropic and wild animals near the house—are factors associated with risk to infection, not only by vector accessibility to hosts, but also as it was stated above, to the social determination together with the closeness to woodland remnants [124-130].

"When": Ephemeral, Transient and Permanent Edges

The ACL transmission clusters in time, as in space, through extraordinary events, usually narrow peaks, even in endemic areas [131,132]. However, from the spatial conceptual frame of the edge effect described above, regarding the time the edge itself could be seen as ephemeral, transient, or permanent, and thus, the risk of transmission.

Ephemeral edges are associated with sporadic exposure, as is the case when humans in transit contact an endemic zoonotic cycle, the incidence is scattered in time and space, as it seems to be for ACL autochthonous cases in USA [133], or when researchers, students, officials, hunters, and eco-tourists visiting preserved areas [89,134-139]. ACL cases outside transmission areas, related to tourism, are frequently reported as exotic cases [140-143].

ACL outbreaks associated with military personnel, due to short-term training usually during nocturnal activities, battling, or after deployment, show a narrow shape-common-source epidemic curve [144-155], even reported in dogs involved in the training activities [156]. The larger number of articles about military cases reveals, not only an actual risk, but also better health accessibility than other populations at risk, and also, higher state-based social concern about these communities. In the city outbreaks associated with military deployment, although the number of cases could be as high as more than 3000 individuals, the estimated reproduction number close to one suggests the difficulties of sustaining the transmission cycle in the urban environment [157,158].

Transient edges are associated with temporary exposure due to provisional camps, occasional or ongoing deforestation as in "Fishbone" deforestation [159-161], and seasonal work or recreational activities in forest fragments concurrent with the seasonal peak of abundance of vectors [162,163]. New neighborhoods-related transmission became a transient edge if the incidence decreases after the deforestation event. Many times, these outbreaks are reported as sparse mini-epidemics, within an endemic area [164,165], or family clusters associated with secondary forest-unusable lands clearing for subsistence agriculture [166].

Permanent environmental edges after human settlements near the borders of the city, rural, or agricultural fields, from the "Back to nature" urban trend to smallholding farming, could generate endemic seasonal transmission, with outbreaks due to environmental modifications or exceptional climate events. The peridomestic or intra-domiciliary transmission depends on the edge closeness and the phlebotomine species present, as seen in the north-central Pacific region of Ecuador, where more than 90% of ACL cases live in farms surrounded by secondary forests and 30% are children below 10 years of age [167], or in the Brazilian Amazon of Manaus, where the intra-domiciliary transmission could be associated with the structural organization of rural settlements [91].

Regarding the lag between the date of the event that contributes to the outbreak and the actual peak of clinical cases, there are considerations about the intrinsic incubation period, estimated from 8 to 22 weeks [123,168], but also periods from 3 months to 12 months due to long-term effects of rainfall on the population dynamics of the vector [15,169,170]. In this sense, extreme El Niño–Southern Oscillation (ENSO) years, with extreme rainfall, could be related to exceptional epidemic transmission, associated with the increase of the forest phlebotomine breeding and resting surfaces and forest growth getting closer the edge to human dwellings [171-176]. Furthermore, for major environmental modifications, migration and change of land use, the eco-epidemiological momentum for an ACL outbreak, could be reached after several years of the causative factors by a trigger threshold [177].

"Why": **Living in the Edge of the Edge**

The presumed original mode of transmission in ephemeral edges with human contact, with sylvatic cycles for forest-related activities, is still one recurrent cause of ACL cases. In old reports, a rural infection in humans and dogs was acquired during excursions into the surrounding forest [178]. However, in recent reports, the visits to primary climax forest, many times after sunset, were usually associated with extractivism (i.e., lumbering, poaching, harvesting forest goods), recreational, training, research activities, and migrants in transit [179,180]. However, when these irregular behaviors change to regular work by farming or gold mining, the borders of the camps, agriculture fields, or settlements of landless workers became transient edges [49,94,132,159,181-193].

Regarding the agricultural frontier, the deforestation and consequent local micro-climatic changes could have the shape of a lineal front as seen in industrial deforestation [100]. Thus, the ACL risk is associated with the times when the people go to the forest fringes to relieve themselves, to rest or to wait until they are transported to their residences; otherwise, the individual deforestation for subsistence farming, many times has a sickle shape so the edge is close to the house in almost all directions [194,195].

It is also noteworthy that although the gender in the transmission associated with male activities is still an important factor to define peridomestic transmission [196], the incidence in women and children could be related to the observation that the entire family goes to the place of work, mainly with babies kept under the shadow of wooden fringes or making temporary shelters in crop areas; in addition some male have the potential for a higher clinical susceptibility despite actual exposure [197-199], although in scenarios of high exposure this sex bias trends to decrease [139].

Besides, agriculture practices of cacao or coffee as soil-organic management, shadow and humidity distribution, and houses located close or inside the plantations seem to increase the risk of ACL [200-208], when the local Leishmanian ecological system is tolerant to the insertion of non native vegetation. For instance, in the case of Jari [Pará State, Brazil], insertion of *Gmelina* may produce suitable conditions for *L. amazonensis* enzootics and unsuitable for that of *L. guyanensis* [159]. Banana and sugar cane fields in many countries of South America were associated with larger populations of vectors of ACL that were explained by structural microhabitats to rest or carbohydrate food sources [209,210].

Changes in economic trends of global markets could promote the migration of immunological naïve people to endemic areas seeking economic improvement and so pioneering deforestation. Thus, ACL risk is associated with being a farmer migrant living close to the primary forest, in poor housing conditions with poultry and pigs near the house, and their average number of hours away from home, while the risk of ACL decreases when the plantations or nearby villages are far away of the forested areas [49,162,200,211-217]. On the other hand, the monoculture coffee crisis in Parana, Brazil, were associated with an increase in urban ACL reports due to rural to urban migration and seasonal migrant workers [218]. Even the ACL emergence in Ceará, Brazil, during the early twentieth century, was proposed to be due to migration to the Amazon region because of a catastrophic drought and smallpox epidemic, followed by the return of the people when the conditions were restored [219].

Massive migration, unplanned urbanization and poverty, together with ACL emergence and spread, were also associated with developmental projects, such as dams, pipe-lines construction, or trans-oceanic highways across the forest [219-228]. Other sources of migration, together with military activity, included ephemeral transit through the forest, transient camps, and unhealthy periurban housing where the people were displaced due to social disturbances. At the national level when the conflicts were categorized worldwide, ACL incidence was 2.38 times greater between the countries with higher and the lower level of conflict, and it was also significantly different from the lower level to no-conflict countries [229].

In Acre, Brazil, from 2007-2013, the three patterns of ACL transmission were reported simultaneously in different space-time clusters: ephemeral edge by transmission due to extractive activities as chestnut, rubber-tree bleeding, and fishing; transient edge among small-scale farmers close to natural reserves or riparian forest with peridomestic/intra-domestic occasional transmission; and a transitional situation between the sylvatic and the peridomestic cycle tending to be a permanent edge, the last one as the only growing high-risk cluster, while the reported urban cases were from visitors to the other clusters [130,230,231].

Therefore, answers to the "Why" question show that the anthropogenic drivers are those that modulates the ACL risk in space and time, besides the climate and the environmental vector-reservoir suitability [232]. So, only when social marginality and exclusion are controlled, the climate becomes the most significant factor for ACL [233]. These social determinants include changes in demography and migration, land use, and land value, resulting in landscape edges that are overlapped with social spatial segregation, ethnic discrimination, housing deficiencies, labor practices and unfair regulations, protein–calorie malnutrition, and difficulties accessing the health system, which worsened by ACL treatment itself. There are also macro-factors associated with the political and economic crises, the urban structure, and market fashion trends from gold to the Brazilian chestnut or açai, from periurban marginality to enclosed private neighborhoods in pristine landscapes [234-238]. Therefore, as it was noted above in the section about urban transmission, case-control studies, if paired spatially and controlled by factors actually associated with social determination, could be biased, highlighting secondary individual risk variables instead of collective ones [239].

"How to Control": Barricading the Edge

To understand the "Where", "When", and "Why" components that come together to generate the eco-epidemiological momentum of an ACL outbreak, at focus and site spatial scales, could contribute to improve the effectiveness of control strategies, by focusing the interventions in the weakest links of the epidemic production chain.

Until 1993 DDT and afterward pyrethroids were empirically used for blocking transmission of endophilic-endophagic vectors of leishmaniasis, or the impact on leishmaniasis' vectors were "Collateral damage" of blanket spraying for other vector-borne diseases. Different degrees of success were attributed to these uncontrolled interventions [240-245]. Proposed outcomes ranged from dog ACL serology [246] to alleged cases for four years [247]. DDT was also tested outdoors due to its residual efficacy in tree buttresses, where the vector clustered to rest during the day, with a reduction in the vector population for three weeks [248], and in an oily emulsion to avoid the washing-out effect of tropical rains, by obtaining trunks not re-occupied for 11 months, but others re-colonized by vector immigration from nearby non treated areas [249]. Another report of interventions with an impact on ACL was helicopter-based insecticide campaigns, which lacked controls and protocol details [250].

For transient edges, mainly for military camps, some controlled trials that provided short-term chemical barriers in a buffer area (pushing away the edge) were tested. In the rain forest of Panama, the design involved experimental plots of 100 m in diameter, spaced 25 m apart from each other and periodical malathion spraying. However, the small and fluctuant amount of phlebotomine along the study relativized the results [251]. In another controlled trial, again with a buffer area of 100 m, back-pack sprayed 25% cyfluthrin, in a palm oil carrier, significantly reduced phlebotomine from reaching the cantonment area, and mainly its center, for more than 80 days [252].

Regarding transient to permanent edges, lambdacyhalothrin 10%, at a standard dose of 25 mg/m^2 as Indoor Residual Spraying, was evaluated in El Ingenio, Venezuela, between clustered houses according to its structure, showed short-term residually on walls and a short-term effect on the phlebotomine species *Pintomyia. ovallesi* up to 79 days, where the results improved if indoor females and the short season of highest vector abundance were considered [253]. Controlled by locality [nine houses], deltamethrin sprayed on indoor and outdoor walls, roofs, and premises around 10 m at the same 25 mg/m^2 dose reduced the indoor abundance of the species *Nyssomyia* intermedia 32% and *Migonemyia migonei* 42%, significant only in some months, while the intervention had no impact in peridomestic populations, and the pretreatment abundance was more than 50% higher than the highest abundance in the control houses during the study, which weakened the results on effectiveness [242].

Furthermore, any extrapolation should be taken with caution due to species-specific response, as in an ACL focus in Bolivia where the indoor-outdoor walls sprayed with deltamethrin had a beneficial impact against the vectors associated with visceral leishmaniasis, but not on the more exophilic vectors of ACL [254]. In the same sense, with indoor-outdoor thermal fogging with deltamethrin, controlled by house quality and seasonality, the overall indoor phlebotomine decreased from 90% to 40%, but one species, *Ny. trapidoi*, actually increased after fogging 5%, while the quality of the house was the most important factor related to the insecticide effect that lasted for 4 months [255,256]. The substrate factor is also essential for the impact on highly endophilic vectors in the Peruvian Andes scenarios, where lambda-cyhalothrin sprayed at 34 mg/m^2 every six months, with a follow up of two years, reduced the indoor abundance of the phlebotomine species of interest to 78%-83%, and the susceptible incidence of householders to 81% [202,257]. As a particular case of indoor intervention, the entomopathogenic fungus *Beauveria bassiana* did not demonstrate effectiveness in field applications (coffee plantation) [258]. Nevertheless, when the levels of evidence for different interventios were discriminated by a systematic review, only the Indoor Residual Spraying had moderate level of evidence, while the other control approaches had low level of evidence [259].

Physical and chemical barriers were applied together to "Block the edge" effect in an ACL outbreak in a new village—created by clearing the forest in French Guiana shore—where the sylvatic enzootic cycle had been already described. The actual fringe with active transmission was identified as 12 ha of peripheral residual forest and riparian vegetation, although all the houses of the locality are located less than 250 m from these borders. The physical barrier was a deforested belt of 200 m, together with a chemical barrier of dimethyl-1, 2-dibromo-2, 2-dichloro-ethyl phosphate. No human cases were recorded during the deforestation, or during the next season, while the abundance of phlebotomine and potential reservoirs dropped dramatically inside the village and the borders [260,261].

Regarding environmental management, with or without insecticide spraying, it is usually focused in the micro-environmental management of the household unit. However, as with chemical interventions, the environmental interventions should consider a buffer area according to the estimated dispersal of the vectors, usually taken as a radius of 100 to 250 m. unfortunately, many times the actual impact of the interventions on the landscape and related cultural practices are not assessed [262]. Further, the environmental management protocols are discontinuous and unstandardized so the results are negligible, and even contradictory as in a 7-year follow up where the vector relative abundance increased [263,264]. In micro-scale studies, such as one conducted in Jacarepaguá, Rio de Janeiro, Brazil, the reduction of animals in the peridomicile and the improvement in the housing were the main interventions that reduced indoor collections of *Ny. intermedia* and *Mg. migonei* [265]. When the cost-efectivenes of different intervention measures were estimated environmental management has a larger intial cost to be instrumented, the larger lag until the results were observed, but the higher and more sustainable impact [266].

Regarding barriers for ephemeral edges, DEET on net jackets or permethrin-treated clothing did not provide protection in skin uncovered areas, while soap with DEET 20% and 0.5% permethrin had short-term effects but indistinguishable from the placebo [267,268]. Conversely, permethrin uniforms at 850 mg/m^2 reduced the incidence of leishmaniasis from 12% in the control group to 3% in uncovered skin areas of the experimental group [269]. Further, pre-exposure preventive education for military personnel (insect repellents, long-sleeve clothing, sleeping in protected areas) lowered the incidence up to no-transmission at all [154,270], while planning the training to avoid the vector's most abundant season also show effectiveness [271].

The difficulties of some phlebotomine to bite through fabrics were reported by cloth protection [272], but also encouraged the testing of nets and curtains as alternative preventive tools for ephemeral to permanent edges. Pyrethroid-Long Lasting Insecticidal Nets reduced vector landing rates, increased mortality of females in contact with the net, and induces exhophily by repellency [273,274]. Pyrethroid impregnated curtains that did not cover all the phlebotomine entrances, reduced the number of vectors that entered to experimental hen houses, and even non-impregnated curtains had a significant effect with fewer phlebotomine trapped than in the control chicken coops without curtains [275]. In the same sense, in trials controlled by clusters of city sectors, polyester curtains (mesh 0.05 mm) impregnated twice in a year with 12.5 mg/m^2 of lambdacyhalothrin and loosely hanged, reduced vector indoor trapping, even with open doors, and the incidence after 12 months in the control houses with non-impregnated curtains was 8% while in experimental ones was 0% [276,277]. In another experiment, deltamethrin (26 mg a.i./m^2) impregnated bed nets and curtains showed fewer phlebotomine caught by human bait under the nets (0.14 phlebotomine/man-hour) than outside the nets in the same room (1.91 phlebotomine/man-hour) or in unprotected rooms (3.29 phlebotomine/man-hour) [278] A trail controlled by village clustering, which involved nets impregnated with deltamethrin, repellent (20% DEET and 0.5% permethrin) delivered to each residence, whitewash painting of tree bases up to 50 m from the house, and health education, showed the greatest effect in lowering the incidence in children younger than 10 years old and people living on the periphery of the village, but the low incidence of cases also in the control group during the follow up period reduced the statistic significance of the results [279]. Hence, the effectiveness of a net-curtain strategy to lowering the ACL incidence depends on the degree of coverage of the whole human population at risk with intact nets, it requires relatively negligible transmission out of the net during the hours of vector highest acitvity, and hinges on the total abundance of vectors during peaks, so the proportion that can cross the fabric.

This last issue about the amount of biting females during the epidemic peaks relativizes the extrapolation of modeling or control trials based on abundance data during endemic transmission periods. The population explosions of vectors that produce outbreaks are usually outlier peaks with different dynamics and behavior than those computed from inter-epidemic parameters. Furthermore, the actual abundance of vectors and their infection rates during these outbreaks, despite a proportional reduction by control measures, could still be above the transmission threshold. During inter-epidemic periods in rural areas surrounded by forest in the Orinoquia Region of Colombia, the ratio between indoor:outdoor:forest phlebotomine abundance was 1:7.8:18.3 so a peak of the forest population could increase the transmission despite the reduction of the domestic ones by any intervention, as in Panama where after deltamethrin fogging the vector infection rates increased while the blood sources for the phlebotomine were sustained [280,281]. However, by modeling we can forecast the "Where", "When", and "Why" the transmission could take place, which would allow us to focus regular surveillance protocols, in space and time, instead of blanket surveillance strategies what are impractical due to the lack of financial, human, or logistical resources.

Larger Scales: Diluting the Edge Effect

At the second and third subnational jurisdictional level in Colombia, ACL cases could still be correlated with natural vegetation, mainly, due to riparian forest from the hydrographic corridors and residual forest, permanent crops, and heterogeneous agricultural zones, while urbanization and shrub coverage was negatively associated with ACL prevalence [237,282]. However, at larger modeling scales, the aggregated data and variables that correlated with opposite plus/minus signs could compensate the actual micro-focal trends of individual risk in a kind of "Ecological fallacy", while big extensions of new agroecosystems or forested areas can dilute the edge effect. Therefore, at these scales, climate could be the driving factor that better explains the distribution of transmission or climate together with vegetation indexes [283-286], rather than anthropic or cultural factors [175].

In the conceptual frame of larger scales, the deforestation would reduce ACL transmission, and so happen during the first half of the twentieth century. Nonetheless, ACL reemerged during 1970-1980, mainly in rural foci along new edges with clustered sources of blood [244,287,288]. Further, climate change forecasting models for the Neotropical region predict that some phlebotomine vector species will reduce their spatial distribution but increase their presence at higher altitudes [289], while other phlebotomine vector species will expand their distribution [290,291], without considering changes in land use that could also be driven by climate change. However, even in broad regional events, such as ENSO, the transmission clustered in some sites, so it is not synchronous in different areas close to each other [175].

Intermediate vegetation density at larger spatial scales could imply at smaller scales, forest remnants and wastelands that are intermingled with human settlements and ongoing changes in land use. Therefore, the positive association of the amount of phlebotomine collected with these intermediate vegetation indexes is related to environmental heterogeneity and edges [83,166,292]. In the same sense, the incidence of ACL at municipality levels was positively associated with the development of a human index instead of deforestation [293], but when residual and gallery forests were identified, the incidence was associated with the size of the deforested and urbanized areas, and thus, with the closeness of the edges to human dwellings [294,295].

Conclusion

Focus Research in ACL Outbreaks

The answers about the "Where", "When", "Why" of ACL transmission contribute to refine the questions to ask during the research of an active focus once an outbreak of ACL happens. To weigh each of the confluent factors that generate the eco-epidemiological momentum of an ACL epidemic, allows evaluating the feasibility and sustainability of the alternative strategies for control.

The questions begin when the ACL event is suspected, or better if confirmed, before any eco-epidemiological field work is initiated. Any useful background information should be gathered to design a research protocol and to estimate the resources needed: potential vectors, reservoirs, and parasite species known in the area, their biology, bionomy, and time-space distribution at different scales from micro-habitat to village focus (i.e., vector endophily-endophagy, reservoir synanthropy), clinical and epidemiological antecedents, the currently reported situation, climatic and geographic data, local available human and logistic resources, and any recorded changes from environment to demography in the last decade. The experts in the local settings and the locals should be included in the team, or at least its perception of the causes of the outbreak event. Regarding the active or recent ACL human cases in this stage of the research, the clinical files should be enough as a source for preliminary information. It is better to avoid asking patients several times with the same topics until the in-depth epidemiological interview, otherwise the reiteration of the questions by agents of the health system tend to reiterative answers of the surveyed person based on precoinceived concepts rather than actual antecedents. The clinical files also contribute to identifying the need of parasite characterization if there are differences with the previously reported clinical expression, and the complexity of the entomological studies if there are differences with the known pattern of transmission that require *a priori* a study for incrimination of new potential vectors.

In the field the focus research of the ACL outbreak involves defining the probable edges of transmission, the "Where" question, from the spatial distribution of cases and their autochthony contribution to the potential indoor transmission. The hypotheses that arise from the answers could then be specifically tested by proper controlled entomological protocols, indoor-outdoor collections, and sites nearby the domestic ones, but with better vector suitability. The in-depth interview to the ACL patient and his household members discriminated by gender and age implies to recollect domestic, recreational, and work-related activities before the case clinical expression appearence, period that varies according to the estimated intrinsic period of the parasite species and the date of the outbreak onset. To avoid biasing the answers, it is important to start with the site of perceived transmission before asking specific questions of places visited. The questionnaire should include even sites incidentally visited but with known environmental risk, and also the perception of the ACL case about the place where the transmission happened. These putative places perceived by the community as risky, although the actual risk of transmission at these sites may not have a biological bases, it should also be assessed by entomological captures. The results of entomological captures should be shared afterward with the community to discuss the places with actual risk of transmission, mainly in the localities where all vector-borne diseases knowledge, perception and attitudes are based on mosquito-arbovirus information.

While the "When" question to discriminate ephemeral and transient of permanent edges contributes to design the optimal period for entomological collections at local levels, it is also asked to understand the timing of the eco-epidemiological momentum and its probability to happen again. Once the "Where" suggests probable areas of transmission, the "When" question can look for any changes or exceptional events in climate, environment (new edges), demography, practices, and activities that could be associated with increasing exposure. To draw the epidemic curve, the probable date of infection should be determined for each case, by computing a mobile average period according to the parasite's estimated intrinsic cycle, and the recalled start date that clinical signs began. The anamnesis is required to identify and record which was the first manifestation recognized (redness, itching, bumps, ulcer, actual lesion, etc.), and if the date is too vague, to use before-after a milestone-date (Christmas, popular festivity, birthday, etc.). The lag between a trigger event and the outbreak goes from more than a year of delay as for extraordinary climate events, few months as the coming of electricity to town that changes the hours-site of domestic practices, to few days due to a religious assembly at the hour-place of risk that convenes the community. Furthermore, primarily in outbreaks in urban edges, we need to assess if the cases are sporadic or if the incidence has seasonal regularity, as well as if there are clusters with spatial recurrences.

Despite the active search of current and past ACL cases (ulcers and scars) based on the previous questions, and the review of historical clinical files for suspected, undiagnosed cases during the previous years, it is recommended to ask the patients about other cases to drive a "Snow-ball" search approach in the affected community, or even emigrants residing in the community during the transmission event. On the other hand, when the information provided in the interview starts to be redundant, the principle of saturation could be applied.

The "Why" question used to figure out how the "Where-when" changes in the area trigger the eco-epidemiological momentum involves the in-depth interview of the cases, but also other sources and key informants. Additionally, as the review of the literature above suggests, biological factors determine the possibility of an ACL outbreak, but the climate and mainly the social context actually modulates its probability. Therefore, despite the immediate, more visible "Why" determinants on individual lifestyles or health status, the structural ones, such as changes in the trends of economic global, regional and local economic markets, the correlated changes in land use and massive migration of people seeking economic opportunities or safety, compels the ACL researchers to include a social determination assessment and to advocate for the right of health as a human right [296,297]. From the control standpoint, this public health attitude requires identification of the more vulnerable links of the transmission process that can be feasibly changed in short-, medium- and long-term interventions, and to involve the players within an agency to change them, including the legal responsibility of public and private "Constructor of edges" in prevention, mitigantion and control ACL transmission. From a personal standpoint, the social responsibility of the medical entomologist as builder of the risk concepts and as a public health professional must be realized, that besides the immediate recommendations at focal time-space scales, we need to be aware on what Ulrich Beck in "World at risk" [298] and Zygmunt Bauman in "Wasted Lives: modernity and its outcasts" [299] told us about the use of 'risk' as a tool for social control, so to avoid claiming the persons for individual solutions to structural problems.

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