FORUM

Lutzomyia longipalpis, Gone with the Wind and Other Variables

OD Salomon

Instituto Nacional de Medicina Tropical – INMeT, ANLIS Dr Carlos G Malbrán, Puerto Iguazu, Argentina

Abstract

Lutzomyia longipalpis (Lutz & Neiva) is the main vector of *Leishmania infantum* (Nicolle) in America, associated in turn with the current spread and urbanization of American visceral leishmaniasis (AVL). The vector distribution in AVL foci shows a spatial-temporal clustering despite the different epidemiological contexts. The factors associated with the macroscale distribution of *Lu. longipalpis* as a landscape stratification are discussed in the framework of the process of their adaptation to anthropized environments. On the other hand, the fact that *Lu. longipalpis* is clustered in only a few hot spots or critical sites suggests that microscale approaches that describe the trap surrounding environment and the availability of refuges and food sources are better at explaining the uneven distribution of this vector, and should contribute, together with macroscale variables, to design operational control strategies. With regard to temporal distribution and climatic or vegetation data obtained by remote sensing as variables to explain and forecast the abundance of *Lu. longipalpis*, it is necessary to take into account the time lags in relation to the life cycle of the vector, the difference between the level of daily activity and actual abundance, and the differences in critical variables and thresholds according to the region or season. In conclusion, this review shows that it is feasible to characterize the distribution of *Lu. longipalpis* at focus level and within it to identify the main critical sites, proposing a sequential cost-effectivity strategy for urban AVL surveillance and control.

Introduction

Lutzomyia longipalpis (Lutz & Neiva) has been associated with visceral leishmaniasis since the first studies in the Americas during the early twentieth century, usually in isolated rural foci. From then on, this species drew attention from the public health perspective to prevent and to control American visceral leishmaniasis (AVL), but also from a more theoretical epidemiological frame as an American Phlebotominae with vectorial competence for *Leishmania infantum* (Nicolle), an invasive alien parasite. Both these perspectives expanded during the following years, the public health one as the geographical spread and urbanization of the vector increased the incidence of the parasite infection in South America mainly since 1970–1980 (Salomón *et al* 2015), while the theoretical perspective also grew in importance as

a result of the relatively easy laboratory-bred colonies that put *Lu. longipalpis* in the hall of fame of "experimental species" to perform from genomics, microbiota, and parasite-vector interaction studies to saliva, pheromone, and behavioral research. The interest generated by *Lu. longipalpis* is reflected in the amount of research and publications that refer to this species, that is why in addition to the more significant or recent works cited in the text, a table that summarizes the main variables discussed in this review and most of the articles that reported them are presented as a supplementary file (Suppl 1).

However, two main obstacles prevented the generalization of these findings: (a) the genetic polymorphism of the *Lu. longipalpis* complex, with ongoing cryptic speciation processes and introgression between sibling species, with different vector capacity or spread potential (Casaril *et al* 2019);

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and (b) the plasticity that allows *Lu. longipalpis* dispersion and adaptation to different environments, probably caused by the aforementioned genetic heterogeneity, that consequently made different variables critical in different scenarios with disparate or even contradictory results (Lainson & Rangel 2005).

On the other hand, *Lu. longipalpis* distribution is spatially and temporally uneven, clustering in "hot spots" despite the geographical location and epidemiological contexts. Hence, many studies attempted to define the variables associated with the current and potential distribution of this vector, at different scales, to improve the current strategies of surveillance and control of AVL. But these approaches require careful examination of the consistency between sampling design and analysis scales, to avoid macrogeographic conclusions based on captures that represent only the phlebotomine populations around the trapping site, since the light traps separated by 5 m did not present mutual interference (Bell *et al* 2018). Otherwise, there is a risk of reaching conclusions on macro temporal and spatial scales based on captures with microfocal conditions, such as when the vector should be abundant by site and season but at the precise time of capture *Lu. longipalpis* "gone with the wind," an ephemeral variable that will be discussed later. Therefore, we will review the factors discriminated by scale that were associated with *Lu. longipalpis* distribution and the difficulties for their interpretation, whereas for AVL, as for many vector-borne diseases, we must take into account that while the biological variables contribute to the possibility of the outbreaks, its actual probability is modulated by the social determinants of risk and extraordinary climatic events.

Spatial Distribution

Landscape Stratification (Macroscale)

The spatial distribution of *Lu. longipalpis* at the macroscale is usually discriminated in forest, rural, urban/peri-urban, and urban environments, although rarely accurately characterized. The proportion of this species among others Phlebotominae barely reaches more than 5% in the forest (Thomaz-Soccol *et al* 2018), but its abundance and relative abundance tends to increase with the anthropic disturbances of the landscape. Thus, in the Tocantins River in Brazil, 90% of *Lu. longipalpis* was found on the edge of the forest, but in the same river, after the construction of a hydroelectric plant, the abundance in the most modified urbanized environment was 4.8 times greater than in the rural-forest area (Oliveira *et al* 2011, Vilela *et al* 2011), while in tourist developments the relative abundance is as high as 26% (Fonteles *et al* 2018). These figures increase even more once *Lu. longipalpis* is adapted to domestic environments such as

rural endemic AVL foci located in xerophilic or semi-arid regions. In these habitats, the proportion of *Lu. longipalpis* is again up to 3% in the forest, but reaches over 99% in the bush (caatinga), and 78% in the highly anthropized environment or 42% in the coastal Atlantic landscape (Dias-Lima *et al* 2003, de Souza Freitas *et al* 2018). The number of individuals captured also increases in the forest to peridomestic environments by 5–7 times to 250 times (Ferreira *et al* 2013, Pereira Filho *et al* 2015).

In relation to the urban colonization of *Lu. longipalpis* reported since the last decades of the twentieth century, its spread from city to city was associated with the construction of highways and fishbone deforestation, and the network of roads and intensity of exchange between nearby towns (Oliveira *et al* 2018). In this way, the main cities, once established *Lu. longipalpis*, act as an infestation and infection hub, generating a radial spread which slows down as the surrounding localities more favorable to the vector are colonized, in São Paulo from 200 km/year to less than 25 km/year (Oliveira *et al* 2016). This urban dispersion of AVL and the urban increase in abundance of *Lu. longipalpis* at macroscale was related to vector populations with the pheromone chemotype (S)-9-methylgermacrane-B, in contrast with the cembrene-1 chemotype (Casanova *et al* 2015). However, in terms of genetic diversity, hybridization between *Lu. longipalpis* newly arrived urban settlers and older resident rural ones better adapted to local environments was also likely (Quintana *et al* 2019).

The dispersal of *Lu. longipalpis* within the city at the macrohabitat scale is explained by occasional introductions of the vector, which function as source populations spreading it to the outskirts, through successive colonizations of the most suitable peridomestic microhabitats. In Presidente Prudente, São Paulo, the apparent "seed" of *Lu. longipalpis* was located in a flower nursery with abundant organic fertilizer, and then this species progressively advanced through backyards with henhouses (Prestes-Carneiro *et al* 2019), while in Rio de Janeiro, *Lu. longipalpis* introduced in the Caju Cemetery was unable to colonize the surroundings with completely urbanized blocks (Brazil 2013). In Salvador, Bahia, the dispersion was directed toward the beach front while in Fortaleza, Ceará, it remained far from the beach, demonstrating the different spatial distribution of sites with environments conducive to the vector (Silva *et al* 2014, Mota *et al* 2019).

Therefore, the urban abundance of *Lu. longipalpis* depends not only on environmental strata but also on the date-stage of colonization. The proportion of vectors may increase from 9% in the early stages of urbanization, to 40% in the shared scenarios of AVL with cutaneous leishmaniasis (Ribeiro da Silva *et al* 2019), to 90% in a period of 10 years as in Campo Grande, Mato Grosso do Sul, Brazil (Oliveira *et al* 2012). In established urban foci, the relative abundance of *Lu. longipalpis* usually ranges from 80 to 100%

in mixed landscapes of shrubs, trees, animal shelters, and human houses, although its presence may be low or nil in non-urban surroundings and in the densely populated downtown, such as a city in the State of São Paulo where the rural:peri-urban:urban ratio was 1:8.6:3.3: respectively (Colla-Jacques *et al* 2010). Therefore, the Normalized Difference Vegetation Index (NDVI) or its variance as a measure of environmental heterogeneity of each stratum may be better to explain the distribution of the vector, than political boundaries, sectors of the health system, or cadastral characterization as urban or rural.

Consequently, depending on the scale, the attributes used for stratification, and the characteristics of the peridomestic habitats, captures between neighboring sites within a city can result in 1 to 1000 *Lu. longipalpis*, with a relative proportion of this species ranging from 0.18 to 100% (Ximenes *et al* 2000, Figueiredo *et al* 2016). Furthermore, the clustering of *Lu. longipalpis* in few sites and few traps discussed in the next sections, recorded in rural and urban scenarios, from Honduras to Brazil and Argentina, suggests that the microscale is the best scale to explain the spatial distribution of this vector, in order to obtain models that allow the development of operational tools for its surveillance and control at the focus level.

However, before discussing the microscale variables associated with *Lu. longipalpis*, it is necessary to review some studies on the distribution of canine AVL and human AVL at the macroscale. The spatial spread of human and dog cases was associated with massive human migrations due to development projects or the search for better living conditions. These events also generate changes in the landscape that favor the colonization of *Lu. longipalpis* such as unplanned urbanization. This synergistic confluence of cultural, environmental, and biological drivers for the AVL was reported during the construction of the Bolivia-Brazil pipeline in the State of Mato Grosso do Sul (Pasquali *et al* 2019). Later, the first urban records of *Lu. longipalpis* in the state of São Paulo, in a locality near the border with Mato Grosso do Sul, date from 1997, but by 2014 the vector had been recorded in 164 São Paulo municipalities. Regarding the temporal distribution, 2 years and 2 months passed between the first capture of *Lu. longipalpis* and the first report of canine AVL, and one more year until the first case of human AVL (Casanova *et al* 2015, Oliveira *et al* 2016). On the other hand, in established urban foci, the canine AVL may or may not overlap with the distribution of *Lu. longipalpis*, as occurs in downtown areas with a high prevalence of infected dogs but without vectors. These inconsistencies may be due to vertical and horizontal transmission of AVL from dog to dog, to dog breeding and sales networks, the structure of the stray dog population, and the time elapsed since the introduction of the vector and the parasite to a given locality, since more time may imply less spatial agreement by the previous cited reasons.

Critical Site Characterization (Microscale)

Vectorial transmission of *L. infantum* in the Americas is mainly a microfocal event around domestic areas of rural and urban environments. Human AVL incidence is a proxy of the distribution of parasites, infected reservoirs, and people prone to manifest the infection clinically, but also of the contagious *Lu. longipalpis* distribution (Casanova *et al* 2013). Regardless of whether the environments are urban or rural settings, one of the variables more frequently associated with the clustered abundance of this vector at the microscale is the availability of blood sources surrounding the trap.

In this sense, *Lu. longipalpis* can be collected in several places within an AVL focus, yet high abundance can only be found in few areas, in few "critical sites" among them, and usually in few animal shelters or hot spots within these sites. The spatial auto-correlation of abundance for *Lu. longipalpis* was estimated to be around 600 to 700 m (Fernández *et al* 2013), but their abundance can vary up to 1770 times between critical sites of the same focus, and even almost 30 times between a trap in an animal shed and one located 100 m away (Quinnell and Dye 1994). This clustering is favored by a low dispersion trend at the microscale when food is available; capture-recapture studies in Brazil and Colombia reported more than 90% recaptures at the release site, or 98% within 100 m to 300 m (Morrison *et al* 1993; De Oliveira *et al* 2013a, Galvis-Ovallos *et al* 2018). Therefore, chicken pens can act as a hot spot for vector clustering both as initial colonization sites and in already established populations (Fernández *et al* 2010, Silva *et al* 2019), as well as pigpens (Figueiredo *et al* 2016), horse stalls in a Cavalry Regiment (Dorval *et al* 2009), and a dog kennel in a peri-urban backyard (Dos Santos Brighente *et al* 2018), while the abundance of *Lu. longipalpis* in aphotic areas of caves stresses the notion of this species plasticity related to bat as a food source (de Almeida *et al* 2019).

With regard to the relative attraction of each host to determine a critical site, traps in pigpens yield 99% of the *Lu. longipalpis* caught at a rural AVL focus, almost 30 times more productive than the most productive intradomicile (Ferro *et al* 1995), but pigs were deemed equivalent to cows when forage ratio-biomass was computed (Morrison *et al* 1993). In a focus of atypical AVL in Honduras, *Lu. longipalpis* was caught 200 times more around cows than pigs (Carrasco *et al* 1998), or horses in Brazil (Ximenes *et al* 1999). On the other hand, related to the most frequent hosts in peri-urban domestic landscapes, in one study, humans were more attractive than dogs and equivalent to six chickens in terms of body size (Quinnell *et al* 1992), although in other foci this vector shows low anthropophilia (Morrrison *et al* 1993). In a modeling attempt, the abundance of *Lu. longipalpis* was weakly associated with the number of animals (Quinnell &

Dye [1994]), while in the field, a dwelling with 100 chickens was 6 times more attracitve than peridomiciles with 45 to 50 chickens and dogs (Lopes *et al* [2019]). A possible explanation of these disparate results in addition to differences in accessibility and host exposed surface biomass may be that some approaches assume a linear response of the insects to the gradient of olfactory cues, but this stimulus would increase in shape by steps with the square root of the number of sources, along with the influence of velocity, turbulence and convection of the odor plume, and the size of the release patch (Andersson *et al* [2013]).

The attractiveness of domestic animals could also generate design bias when as a precondition traps are located close to henhouses or chicken perching trees to improve the capture success rate, underestimating the "chicken" variable in modeling attempts, and skewing results as to infection prevalence or blood index. Therefore, results from gut content vary according to proximity to blood sources, thus reporting that chickens are the main host in the outdoors and dog indoors (Afonso *et al* [2012]), or these are humans (Sales *et al* [2015]), marsupials, and combined sources involving human indoors and birds outdoors (Missawa *et al* [2008]), or birds and human equally and 8 times higher than dogs (de Oliveira *et al* [2008]).

Besides food, animal shelters provide themselves a relatively undisturbed resting and breeding place, with shadow and humidity. In a peri-urban/urban AVL focus in Sâo Paulo State, Brazil, emerging traps had recently molted adults only in houses with chicken coops, where the traps located around chicken sheds were 7 times more productive than the traps in leaf litter, clustering 61% of the captures in just four traps (Casanova *et al* [2013]). On the other hand, the pigpens in rural Colombia, although also identified as a breeding site, showed a more dispersed pattern at microscale level (Ferro *et al* [1997]), even though both in pigpens and in chicken sheds, most of the larvae or emerging adults were found surrounding the animal dwellings where organic matter such as stool and fodder is degraded, dried, and mixed with the soil instead of inside the shelter with water-urine saturated and trampled ground.

The type of vegetation was also associated with the vector at microscale, even specific trees, such as banana, guava, coconut, and mango trees (Ribeiro da Silva *et al* [2019]). These trees provide shelter for the vectors by means of the structure of their exposed roots, bark, and leaf axils, and they could also serve as the preferred sugar sources, such as those plants belonging to the Fabaceae family (Lima *et al* [2016]); however, the variable recorded as proportion of vegetation coverage is more related to the shielding from sun irradiance and rainfall flooding. Consistently, more *Lu. longipalpis* are in cultivated areas and secondary woodland than in the savanna (Quinnell & Dye [1994]). Vegetation-related variables were associated with the presence of *Lu. longipalpis* in urban-rural

areas, in the State of Paraná, Brazil, in an area of 250 m around the trap with mixed urban and herbaceous environments (Thomaz-Soccol *et al* [2018]), and in different foci of Argentina this vector was correlated with vegetation coverage (Quintana *et al* [2019]), and landscape NDVI microheterogeneity (Berrozpe *et al* [2019]). As for microheterogeneity in highly urbanized backyards, the hot spots of *Lu. longipalpis* abundance were associated with the number of tree species, mean distance to water, and flower pots (Santini *et al* [2012]), the latter having also been associated with probable "seed" colonization of cities discussed at macroscale.

Besides the animal blood sources and the vegetation, other variable associated with *Lu. longipalpis* in the articles cited in the last paragraph and other modeling attempts was the proximity to river shores (Menezes *et al* [2015], Thomaz-Soccol *et al* [2018]). However, these results should be analyzed in the context of the spatial distribution within the locality of the human density, of the riparian gallery forest and microclimate patches including soil moisture saturation, and of different qualities of housing and peridomestic yards. With regard to house features, other studies with variables recorded at microscale prove the bathroom or kitchen being located outdoors to represent an environmental risk factor for human, but also the landscape suitability for *Lu. longipalpis* by presence of gardens and decaying fruit in the backyard (Luz *et al* [2020]). In this sense, the house quality is a proxy for a socio-economic complex of variables, as in a city of Misiones, Argentina, where *Lu. longipalpis* in a hot spot modeling showed that their abundance was associated negatively with the percentage of households with lack of building materials and economic deprivation, and positively with the percentage of surface covered by trees and bushes up to 50 m near the house, and with the percentage of houses without electricity, so the area with more vectors seems to be halfway between urban downtown and rural outskirts (Fernández *et al* [2010]).

The agreed preconditions for selecting capture sites, labeled as worse scenarios, best scenarios, or critical sites, act as a quasi-controlled natural experiment design and so could minimize certain associations. This statement has already been discussed for chickens and animal dwellings, but is also valid for organic matter in soil, trees, and relative humidity vegetation (Costa *et al* [2019]). Further, when these factors, taken as qualitative variables with dichotomous or trichotomous values, were added to characterize "receptivity levels" for *Lu. longipalpis* presence, there was no association between the environmental theoretical risk and the actual abundance of this species, but the analysis was performed with different efforts of capture, and a mix of microhabitat and macrohabitat factors; so the house with the greater capture of *Lu. longipalpis* was assigned to the intermediate level of receptivity, although it had a large chicken coop, trees,

and large quantities of organic matter in the soil (Vianna *et al* 2016).

The relationship between indoor and outdoor *Lu. longipalpis* abundance is also modulated by the presence of clustered animals in the peridomestic area, so this vector is still the prevalent one in an anthropic domestic area but it is usually up to 20 times higher in peridomicile than in domicile, and it is 5 to almost 300 times more abundant in the peridomicile than in the extradomicile, where it is more plentiful in the ground than in the canopy (Fonteles *et al* 2018, Mejía *et al* 2018). However, the absolute and relative abundance of *Lu. longipalpis* in the intradomicile may be higher than or similar to that of the peridomicile depending on the season and need for shelter, the structure-openness of the roof, the distribution and competition from different blood sources, and the domestic behavior of the other sympatric Phlebotomine species (de Souza Freitas *et al* 2018). With regard to intermediate domestic-peridomestic habitats as verandas in tropical areas, these are sites of special interest for AVL epidemiology at microscale, because the people can be there during the peak of activity of *Lu. longipalpis* dressed in indoor clothes yet exposed to an outdoor risk (Santini *et al* 2010). In an ecotourism area of Mato Grosso do Sul, Brazil, the house with the highest captures had 83 times more *Lu. longipalpis* in the chicken shed than the veranda, but in the second house with more vectors (20 times more than the remaining sites), their number was similar between the chicken shed and the veranda (Andrade *et al* 2009).

Another usual measure associated with *Lu. longipalpis* distribution at microscale is the sex ratio. Males tend to be more abundant than females in light traps but also in host-baited traps, but the ratio could vary slighter larger than one to have only males, even between equivalent sites of the same area, and between captures from different hours (de Almeida *et al* 2019, Mota *et al* 2019). It was proposed that the male bias in the sex ratio would increase with the amount of captured individuals as a density-dependent event to improve the recruitment rate success by swarming (Quinnell and Dye 1994), so male pheromone adds individuals and arrests both sexes at the site of the semiochemical release (Bell *et al* 2018). In this sense, the male sex pheromones on the host placed as lures increase five times the whole *Lu. longipalpis* capture, the aggregated males toward the night potentiates the attractiveness of the host odors, and the response could also be modulated by the physiological age of the *Lu. longipalpis* females or its infection (Bray *et al* 2014). Conversely, the sex ratio found indoor or in resting places can have a higher proportion of females than the peridomestic captures (Figueiredo *et al* 2016), while the 1:1 ratio was associated with peridomestic-domestic habitats where the oviposition, breeding, resting and feeding place, and the trap were located in the same spot (Pereira Filho *et al* 2015 Silva *et al* 2016).

Temporal Distribution

The study of *Lu. longipalpis* distribution of presence and abundance over time also requires defining the temporal scale of analyses discriminating (a) macroscale long-period trends in climate and environmental change, (b) seasonal or annual modality due to population dynamics of the vector, and (c) microscale hourly pattern that reflects the threshold and level of phlebotomine activity.

However, as in the spatial-based studies, many factors may interact between the scales, increasing the dispersion of the results if they are not accurately controlled in the analyses. The *Lu. longipalpis* abundance in a given day for example correlates with climate variables with different lags of time, as the trapping success is conformed by the size of the population concurrent with the capture, the size of the successive previous incremental or decremental cohorts, and the activity during the trapping.

In the macroscale, the uneven distribution of *Lu. longipalpis* abundance from 1 year to the next may be due to long-term trends, pluri-annual cycles, or differences in weather between the sampled years (Resende *et al* 2006). However, in longitudinal studies, modifications also at spatial microscale in food availability, habitats conducive to *Lu. longipalpis*, and human interventions and practices at that scale can be related to the difference in abundance or prevalence between years up to 4 times, not merely climate variables (de Oliveira *et al* 2013b, Holcman *et al* 2013). Conversely, captures in animal dwellings are more stable in successive captures than open-air sites, acting as a microclimate buffer that attenuates external weather conditions (Quinnell and Dye 1994). In addition, some designs to study the long-term temporal distribution of vectors at the regional level change the capture site yearly or bi-yearly to avoid the impact of the trapping on phlebotomine population or the refusal of the householders, and so also changed the microhabitat modulators of *Lu. longipalpis* abundance.

The studies of annual distribution of *Lu. longipalpis* usually show that it is present throughout the year, with a seasonal pattern related with climate variables, except in areas with periods of extreme weather conditions, when the adult vector disappear. With respect to the peaks of capture and the climate modulation of previous generations, the time lags are conditioned by biological parameters related with the life cycle, for instance the length of the larval or egg to adult periods estimated in 38–56 days (Morrison *et al* 1995a), 7 days for female longevity (Cortez *et al* 2007), 0.90 or 0.69–0.79 daily for male survival rate, and 0.69–0.89 for female survival rate, and 5 days for minimum gonotrophic cycle (De Oliveira *et al* 2013a, Galvis-Ovallos *et al* 2018). Furthermore, the correlation between abundance and climate also depends on the recording of the appropriate dependent variables as for instance the imaginal emergence

peak that relies on larval cycles may be strongly related with variables such as water deficit (Casanova *et al* 2013). On the other hand, the time intervals between the peaks of *Lu. longipalpis* and the peaks of human or canine AVL cases, on this annual time scale, are also shifted from each other, as the latter are related to the incubation period of the parasites in the mammalian host (de Ximenes *et al* 2006). Thus, simultaneous surveys of vectors and infection can link different seasons of transmission, the vectors peak related to the next AVL incidence rate, and the host infection prevalence related with the previous vector peak although they may have a similar but displaced pattern (Michalsky *et al* 2009, Silva *et al* 2014).

The seasonal current and potential distribution of vector abundance in ecological niche modeling at different spatial scales was associated with climate variables but also with vegetation-related variables as a proxy of climate and environmental suitability such as the normalized difference vegetation index (NDVI). In Brazil, at country level, *Lu. longipalpis* maximum entropy predictive models show precipitation, day temperature, and precipitation of the warmest quarter as the main predictors of abundance (Andrade-Filho *et al* 2017). Also in Brazil, but at state scale, the annual precipitation and NDVI are the variables that most contribute to explain the temporal distribution of *Lu. longipalpis* or the cases of AVL, while temperature seasonality, or precipitation either in wettest or in the driest periods, varies in relative weight according to semi-arid environments of Bahia or tropical ones in Mato Grosso do Sul (Almeida *et al* 2013, Rodgers *et al* 2019). Still at regional scale in Colombian Andes region together with the mean and seasonal precipitation-related variables, the slope also explains the vector distribution, suggesting that these variables could be a proxy for the moisture of the soil (Ferro *et al* 2015).

In the AVL focus spatial scale, *Lu. longipalpis* in Corrientes city, Argentina, NDVI and land surface temperature (LST) were the significant variables during the summer and low urban coverage during the winter (Berrozpe *et al* 2019), while in Clorinda city, Argentina, LST was during the day and night but with lags of 2 months, and NDVI and normalized difference water index (NDWI) with lags of 2 and 3 months (Gómez-Bravo *et al* 2017). Additionally, at the same spatial level in Mato Grosso do Sul, Brazil, *Lu. longipalpis* abundance was correlated by use of the Spearman coefficient with maximum temperature and relative humidity (Almeida *et al* 2010), with temperature and less with rainfall (Lara-Silva Fde *et al* 2015), and with the mean temperature, cumulative rainfall, and negatively with relative humidity (Michalsky *et al* 2009).

The disparate results presented in previous paragraphs about the association between *Lu. longipalpis* with climate variables shows that the results can vary according to the climate range in each region. In addition, the weight of these

explanatory variables can change throughout the year, becoming significant above or below a threshold during critical periods or lack significance in periods when these variables fluctuate within an optimal "window." This inconsistency in the correlation of variables with the temporal distribution of *Lu. longipalpis* is evident with a discontinuous variable such as rainfall, with vectors peaking before, during, or after the rain peak (Mota *et al* 2019, Ribeiro da Silva *et al* 2019) according to the characteristics of the landscape that provides shelter or prevents flooding. However, again these correlations become more significant when lag times are contemplated so positive association was found between female abundance and relative humidity-rainfall 21 days earlier (Morrison *et al* 1995a), and the abundance of both sexes with the rainfall 30–60 days before the collection (Holcman *et al* 2013, Costa *et al* 2019) with the temperature 20 days before collection (Lopes *et al* 2019), or with rainfall and humidity but with negative correlation with temperature (Pereira Filho *et al* 2015). Regarding annual modality and climate variables lag times, *Lu. longipalpis* was trimodal in Mato Grosso do Sul and Colombia (Morrison *et al* 1995a, Brilhante *et al* 2015); in Natal, the males were bimodal correlated with relative humidity and wind up to 6 weeks earlier, and females were unimodal peaking 3 months after peak of temperature and 2 weeks after the increase of wind, but with a lag of 11 weeks with relative humidity (Ximenes *et al* 2006).

On the other hand, many studies did not find a significant correlation between climate variables and *Lu. longipalpis* temporal distribution, although the authors usually highlight the similar pattern between the plotted rainfall or temperature curves and the vector histogram. This lack of statistical significance besides the issues already discussed above may be due to the low range of variation of the variable measured along the year or a variable with large variation but with its correlation not disaggregated by season. Additional sources of inconsistencies are related to design problems, weather data recorded on meteorological stations up to 100 km from the captures sites, "mean" data without relation with the actual date of capture so averaging values before and after the trapping, and linear coefficients to explain not-linear associations.

The microscale temporal distribution, the hourly pattern, also varies between places and habitats, showing peaks in the evening in rural peridomiciles (Morrison *et al* 1995b), at 10 or 11 PM according to the sex (Ximenes *et al* 2006), at midnight in intradomiciles (Rebêlo *et al* 2001), or bimodal in the twilight hours of dusk and dawn (Infran *et al* 2017). The hourly activity seems more related to the light cycles, sunset time, and even artificial lighting than to internal clocks, since in the photic zone of caves nocturnal activity is 33 times greater than diurnal activity, while in the aphotic area it is only 0.66 times (Campos *et al* 2017). With regard to moonlight, it was not correlated with the abundance of *Lu.*
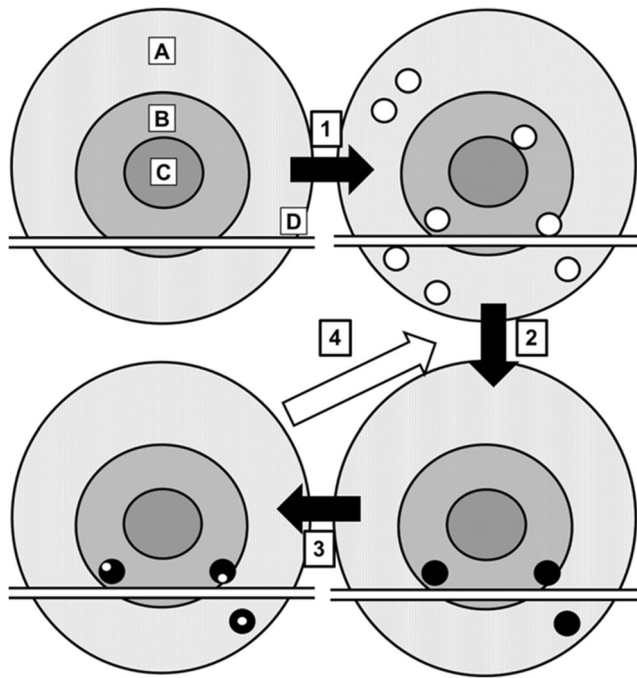
Fig 1 Proposal for surveillance-control of *Lutzomyia longipalpis* in a schematic city stratified as a center (A); heterogeneous landscape of green patches, urban construction and peri-urban population density (B); peri-urban-rural periphery (C); and a river crossing the city (D), by selecting the possible critical sites of the macrohabitat (600 m buffer zone) (1), most probable macrohabitat critical sites (2), most likely microhabitat hotspots (50 m buffer zone), and feedback if critical conditions change (4)

longipalpis by one study (Ximenes *et al* 2006), but different wavelengths showed different attractiveness yet barely no alteration of the sex ratio (Lima-Neto *et al* 2018).

However, *Lu. longipalpis* abundance by hour and by night, like most of the data used looking for correlations at temporal and spatial scale, is modulated by spatial and temporal microscale events. One of these, the wind, referred to in the title of this review, can suddenly change speed and direction around the capture site. Thus, the wind not only has a direct effect on the flight capability, but also has a modulatory effect on the abundance of vectors via the velocity and intensity of attractive, repellent, or pheromonal volatile plumes that reach different *Lu. longipalpis* populations at different distances from the trap.

Conclusions: Modeling for Surveillance and Control

Control-successful interventions reported up to now were designed as blanket insecticide application in small localities. In Isla Margarita, Venezuela, it was performed with intradomestic residual spraying with *λ*-cyhalothrin 25 mg/m² and spatial fogging of fenitrothion 30 g/ha around the houses (Feliciangeli *et al* 2003). In La Paz department, Bolivia, it was sprayed deltamethrin 25 mg/m² indoors, outdoors,

and in peridomestic dwellings, controlling the *Lu. longipalpis* population inside the house for up to 10 months, although the initial indoor density was as low as 0.7 females/house/night and the results were not controlled by seasonality (Le Pont *et al* 1989).

However, regular city-wide intervention strategies are not cost-effective in large cities, besides the fact that the concept of intervention around each case after the diagnosis is less effective than that in arbovirus due to leishmaniasis' longer periods of incubation. In addition, in some urban foci, the human AVL tends to decrease along the years despite the presence of *Lu. longipalpis* and canine AVL as in Dracena, Brazil (Cortez *et al* 2007), and Puerto Iguazú, Argentina (Lamattina *et al* 2019), so with few human cases it is more difficult to justify a budget for blanket interventions when so many other actions in public health must be prioritized.

This review shows that it is feasible to characterize the uneven spatial distribution of *Lu. longipalpis* to identify at least at microscale the critical site-hot spots of initial vector presence, so as to focus the surveillance on them for early warning and timely intervention. In addition, since these critical site-hot spots are also the places where *Lu. longipalpis* is most abundant and persistent over time, if these sites behave as source populations for surrounding places, a focused intervention only on the critical sites could effectively control vectorial transmission of AVL throughout locality. This population dynamics hypothesis is supported by the gene flow between domestic and forest populations (Márquez *et al* 2001), although sink populations could act as temporary shelters during insecticide intervention (Oliveira *et al* 2012). Therefore, this approach would allow an operational strategy by concentrating the effort only on the few sites more suitable for *Lu. longipalpis*. Thus, after an analytical review of the models, to find the most significant and frequent explanatory variables of the presence and abundance of *Lu. longipalpis* according to their degree of evidence, a "model of models" would be proposed for field validation. This resulting model should be able to identify sequentially the following: (1) the sites most possible to be critical at macrohabitat scale (buffer up to 600 m) with remote sensor images and census secondary data; (2) among these sites, the places most probable to be macrohabitat critical sites according to local knowledge and field surveys; and (3) within the macrohabitat most probable critical sites the hot spots most likely to be the microhabitat critical sites (up to 50 m), through field surveys that include the amount and distribution of blood sources and vegetation coverage; and (4) finally the strategy should be able in turn to feed back the site selection if any of the critical conditions change (Fig 1).

Likewise, for this model to be operational, controlled field validation in different scenarios will be required, as well as a user-friendly interface and an application manual for local

agents describing the methodology for identifying critical sites, suitable intervention alternatives, and follow-up through appropriate impact indicators. Interventions will range from risk awareness at possible critical sites to integrated vector management at probable ones, with different degrees of intensity between the microhabitat and the macrohabitat areas, according to the significant variables identified by the model.

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