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INDOOR AND PERIDOMESTIC TRANSMISSION OF AMERICAN CUTANEOUS LEISHMANIASIS IN NORTHWESTERN ARGENTINA: A RETROSPECTIVE CASE-CONTROL STUDY

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Abstract. A case-control study was carried out during 1990–1994 to identify risk factors associated with American cutaneous leishmaniasis (ACL) in Santiago del Estero, Argentina. The study subjects consisted of 171 cases and 308 controls matched by age, sex, and place of residence. The analysis was performed by conditional logistic regression. Risk factors found to be significantly associated with ACL were related to indoor transmission (few rooms in the house, dirt floor, and a permanent opening in lieu of a window); peridomestic transmission (presence of a pond or woodland within 150 m of the house and an agricultural area within 200 m of the house); and human behavior (sleeping in the backyard, collecting water, bathing, and performing agricultural activities). Most transmission appears to have occurred indoors and in the peridomicile. These environments should be included in further research and control policies.

INTRODUCTION

Leishmaniasis is a group of vector-borne protozoan diseases caused by parasites of the genus *Leishmania* and transmitted in the New World by the bite of sandflies of the genus *Lutzomyia*. American cutaneous leishmaniasis (ACL) is endemic in most countries of Central and South America. Transmission of ACL has been reported in northern and northwestern Argentina since the 1920s, and is associated with deforestation.[1,2] In 1990 an outbreak of ACL occurred in four adjacent districts located in the southern part of the Santiago del Estero province, where no cases had been previously reported. *Leishmania* isolates from ulcers of eight ACL patients from Santiago del Estero (studied by monoclonal antibodies and isoenzymes) were classified as *Leishmania* (*Viannia*) *braziliensis.*[3] Reported cases occurred not only in young adults but also in children and the elderly, and were evenly distributed by sex. This pattern suggests indoor and peridomestic transmission along with the classic extradomestic transmission related to specific activities; in the latter, the majority of cases tended to be among young adult males.

To identify specific risk factors associated with ACL transmission in Santiago del Estero and to inform control measures, we carried out the present population-based case-control study.

MATERIALS AND METHODS

Study area. The study was carried out in four adjacent rural districts: San Martín, Loreto, Atamisqui, and Silípica, all in Santiago del Estero province in northern Argentina (Figure 1). The total population of the four districts combined is nearly 40,000. The study population consisted of people living in the study area during 1990–1993, mostly in dispersed rural settlements. The main economic activities were woodland exploitation, agriculture, and cattle breeding. Houses were scattered about 500 m apart, and built with dried mud on a wooden framework, with thatched roofs. Typically, the dwellings had an indoor environment (including 1–3 bedrooms) and a peridomestic environment (approximately 50–100 m^2 surrounding the house, with a small cultivated area, an outdoor latrine, a kitchen or mud stove, goat or pig corrals, and chicken coops) (Figure 2).

Study design. The case-control study conducted was population-based; two controls were selected per case. Cases and controls were matched by sex, age and census tract, which in this area includes roughly 70 inhabitants. Cases less than two years of age were matched to controls within two years, cases 2–4 years old within three years, cases 5–19 years old within five years, cases 20–59 years old within 10 years, and cases more than 60 years old within 20 years.

Data collection. Information about risk factors for ACL was collected in a standard questionnaire applied by a team of trained primary health workers unaware of the hypothesis of the study. The information collected included demographic data, characteristics of the house and peridomestic environment, and human behavior. In both cases and matched control, most of the information collected referred to the year of onset of the disease in the case. Some questions, such as those concerning insecticide spraying, were asked in relation to the whole study period.

All subjects received a physical examination and a Montenegro skin test (MST), which consisted of the application of 2×10^6 *Leishmania* promastigotes.[4] Skin reaction to MST and the size of the induration were measured after 48 or 72 hours by the ball-point method described by Sokal.[5] An induration of 5 mm or larger was considered a positive result for the MST. Ulcers or scars were recorded, including their number, characteristics, and anatomic site. Whenever ulcers were present, a sample was taken for parasitologic examination.

All the data pertaining to the disease, MST and other laboratory results, including parasitologic samples collected during field work, were recorded.

Case definition and ascertainment. A list of potential cases was compiled, including all subjects with a diagnosis of ACL registered between January 1990 and April 1994 in all four public hospitals and primary health care facilities located in the study area, and in three referral hospitals located in the provincial capital of Santiago del Estero. Cases were also added to the list when named by other study subjects during fieldwork. Subjects in the list were visited at home, invited to participate in the study, and asked for informed consent (for children, parent or guardian consent was requested).

A definite case was defined as a subject with either a recorded clinical diagnosis of ACL and a positive MST result,

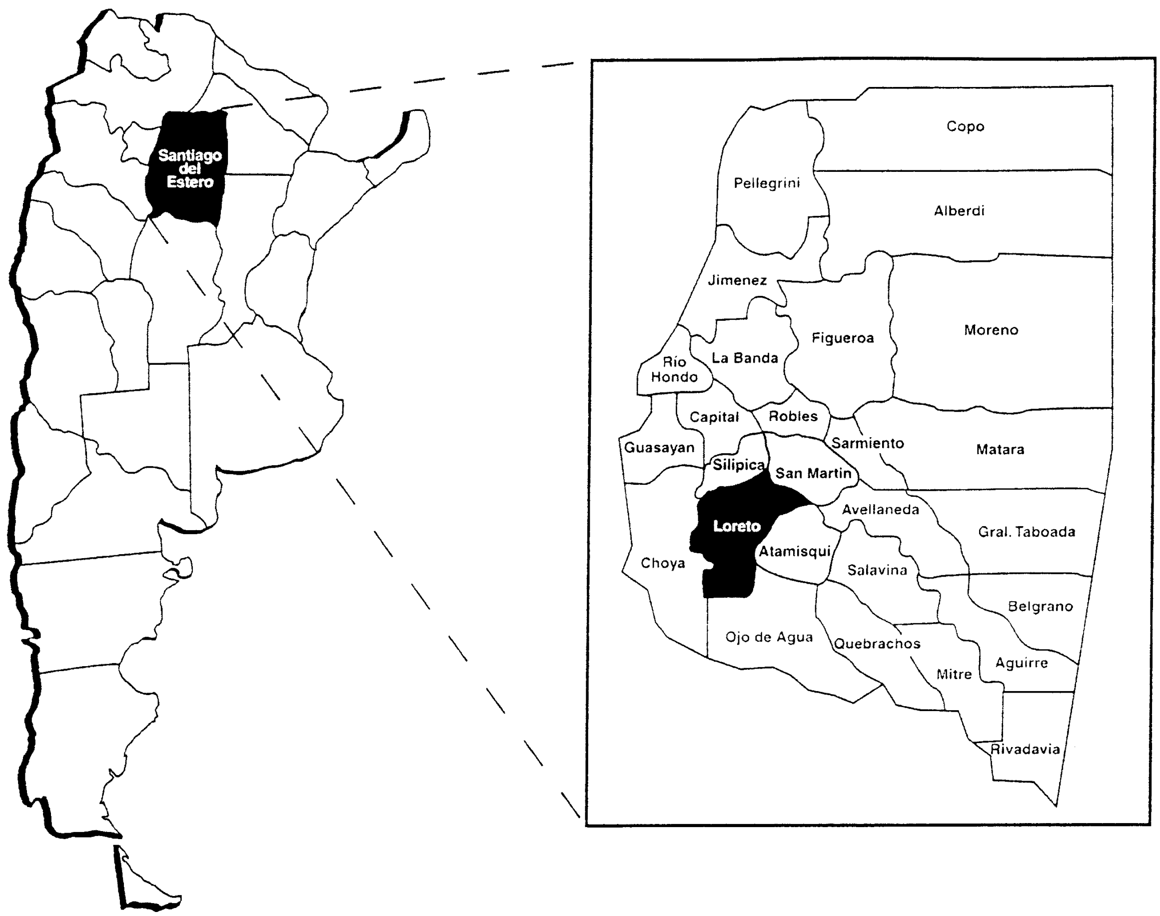

FIGURE 1. The study area of Atamisqui, Loreto, San MartÍn, and SilÍpica districts, Santiago del Estero province, Argentina, 1990–1994.

or a demonstration of *Leishmania* parasites by smear, culture, or hamster inoculation during the study period, whether while hospitalized or detected by the study. A probable case was defined as a subject with a clinical diagnosis of ACL in the hospital record, but either a negative MST result or absent laboratory confirmation even after tests conducted during fieldwork. Excluded from the study were subjects identified as ACL cases who did not display present or past signs of ACL during the physical examination.

Control definition and ascertainment. Controls consisted of subjects living in the study area at the time the corresponding case presented signs of disease, and who tested negative for the MST, and had no clinical signs of cutaneous leishmaniasis. Controls were selected among residents of households in the same census tract as the index case. Index case homes were located on the census map, and houses within the same tract were listed. Houses were randomly allocated to a visiting order. All subjects with the same age group in the first house were examined. If the subjects had no signs of ACL, an MST was conducted and the questionnaire was applied. Household visits were repeated until two eligible controls were selected or the list of households was exhausted. If houses were empty or potential controls absent at the time of the visit, one return visit was made. All eligible controls in a household were included. After the result of the MST was read, individuals with positive results were excluded.

Sample size. The number of cases in the area during the study period determined the sample size. The study had at least 80% power at the 5% significance level to detect an odds ratio (OR) $\geq$ 2 for risk factors present in 50% of controls, and an OR $\geq$ 3 for those present in 20% of controls.

Data analysis. Potential risk factors were grouped into three categories for analysis: indoor factors, peridomestic factors, and factors related to human behavior (in either the peridomestic or extra domestic environments).

Indoor factors may affect the abundance of sandflies in the house. These factors include demographic variables and characteristics of the house: family size, number of rooms and bedrooms, crowding, lighting, construction materials, type of windows and main entrance, products stored, presence of domestic animals, and insecticide spraying by members of the household or the Chagas Control Program. Peridomestic factors included the presence of and distance to any structures, animal sheds, and sources of water, woodland, and agricultural areas. Human activities included those related to water (bathing, swimming, washing clothes, collecting water, and fishing), and subsistence activities (gathering firewood, hunting, and working or helping on a farm).

Initially, associations were investigated separately for each of the three groups of factors by univariate methods. For continuous and ordered categorical variables the chi-square test for trends was also calculated. A multivariate analysis was then conducted separately for each group of factors, starting with all factors that had a $P \leq 0.05$ or an OR ≤ 0.3 or an OR

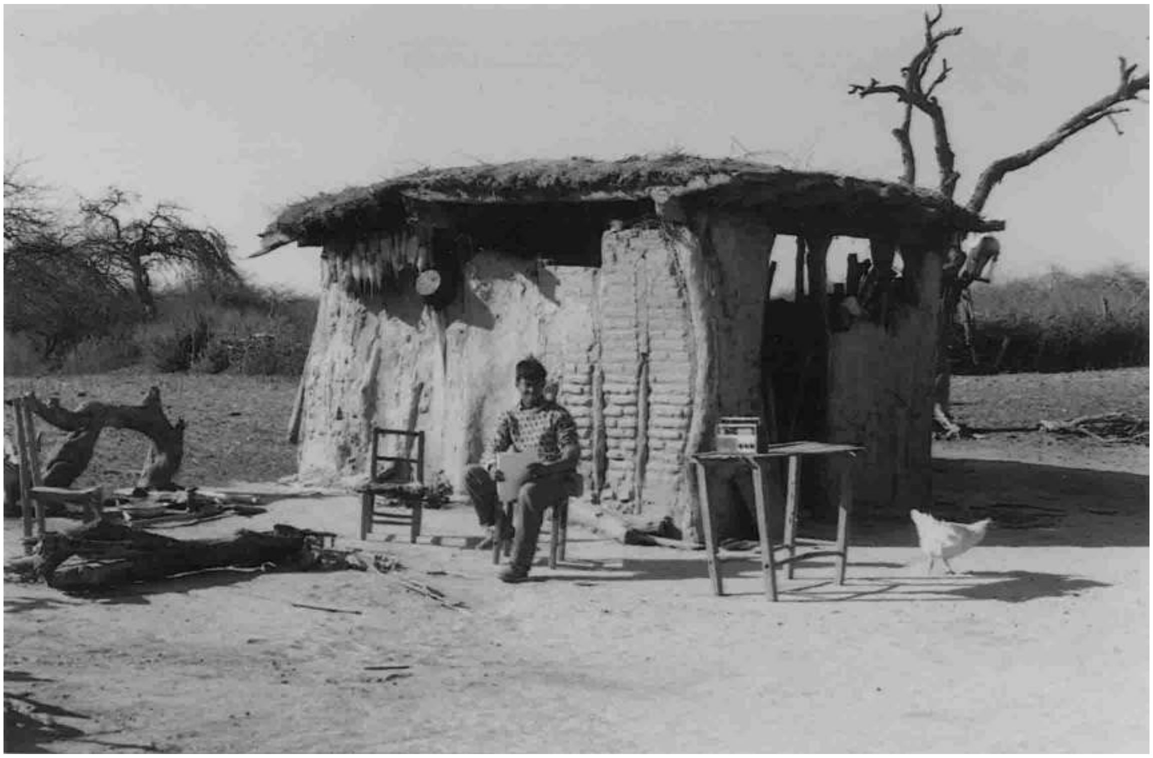

FIGURE 2. Typical residence and environment in the study area.

≥ 3.0 in the univariate analysis. A final model was defined, starting with the factors that were significant in the three group's model. Only those factors that remained in the groups and final models are presented. All the analyses were performed using Stata, Version 4.0 (Stata Corporation, College Station, TX).

Population attributable fractions were not estimated because there were too many statistically significant factors with frequent exposure and large ORs, and because in this setting it would have been difficult to predict the effect of removing one exposure at the risk associated with the remaining variables.

RESULTS

A total of 189 cases were identified in health facilities. Of those, 25 were not interviewed: 7 cases had died, 14 had moved away, 2 refused consent, and 2 could not be reached because of inaccessible roads. Fourteen additional cases of ACL were identified during fieldwork. Thus, a total of 178 cases were interviewed, of which 87% were definite cases and only 13% were classified as probable cases. Later, seven cases were excluded for lack of controls. Of 328 potential controls, 318 were interviewed. Twenty potential controls did not participate in the study: five were out of the study area at the time of the interview, five refused consent to the MST, and 10 were excluded because they turned out to be MST-positive. In summary, the study population consisted of 479 persons, 171 cases and 308 controls (Figure 3). The overall ratio of cases to controls was 1:1.8. This ratio varied: 37 cases had one control; 119 had two controls; 13 had three controls, and one case had four controls. As expected, the distribution of cases and controls did not differ by age, sex, or place of residence.

Factors related to indoor transmission (Group I). Factors that were significantly associated with ACL ($P < 0.05$) in this group model are shown in Table 1. In the multivariate analysis, adjusting for confounding, seven variables contributed significantly to this model: windows consisting of a permanent opening; number of rooms, type of floor, permanent opening as the main entrance; insect control by members of the household, type of roof, and products storage.

The risk of ACL related to windows or entrance doors consisting of permanent openings changed after allowing for other variables. The OR of windows consisting of a permanent opening was reduced from 9.7 to 5.3, and the OR of a permanent opening as the main entrance decreased from 5.7 to 3.4. Nevertheless, the ORs associated with these factors (which measures the openness of the house) still remained statistically significant after controlling for other factors. The ORs for number of rooms in the house and type of floor decreased after allowing for other variables. The adjusted OR of the association between products stored outside and inside the house when compared with no-storage showed a small decrease compared with the crude OR. Number of residents, number of bedrooms, poor illumination, and type of construction materials used in wall construction were no longer statistically significant in the group model, although they were significant in the univariate analysis.

Factors related to peridomestic transmission (Group II). Of those factors fitted in the multivariate analysis, seven remained significantly associated with ACL: presence of a pond or waterway or woodland less than 150 m away from the

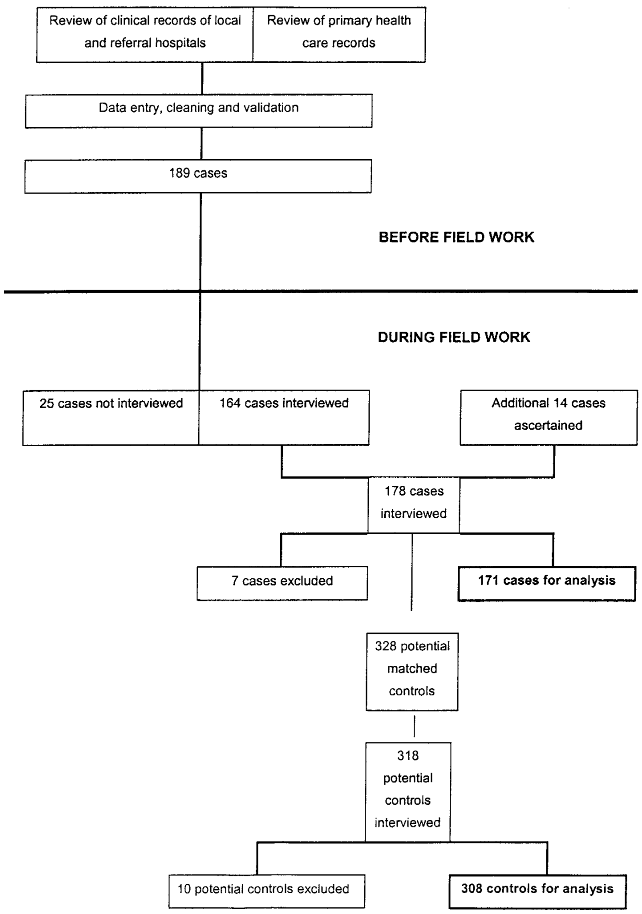

FIGURE 3. Flow diagram of selection of cases and controls before and during fieldwork.

house; presence of a road or agricultural area more than 50 m and 200 m from the house, respectively; open garbage disposal, and sighting of armadillos around the house (Table 2). The OR for house near a pond increased from 12.1 to 15.1 after allowing for the other variables fitted in the model. However, the ORs for presence of waterway and woodland near the house decreased from 7.5 to 4.4 and from 11.3 to 5.8, respectively.

Factors related to human behavior (Group III). Table 3 shows crude and adjusted ORs with the corresponding confidence intervals and *P* values of the "group model" for factors related to human behavior that may increase the probability of contact between sandflies and humans. Of eight factors included in the multivariate analysis, six remained significant after controlling for other factors: increasing number of months sleeping in the backyard, gathering firewood, bathing, collecting water, and working or helping in agriculture.

After adjusting for confounders, the number of months sleeping in the backyard became more strongly associated with ACL. Similarly, the association between working or helping in agricultural activities and risk increased after allowing for other factors. After controlling for other factors, the risk associated with gathering firewood, bathing, and collecting water found in the crude analysis decreased, but remained statistically significant.

Final model. Table 4 shows the distribution of cases and controls for the variables that remained in the final model, with corresponding crude and adjusted OR. The adjusted ORs for indoor transmission were 4 for less than three rooms in the house, 8 for a window consisting of a permanent opening, and 6 for a dirt floor in the house. For peridomestic transmission, the ORs were 15 for a pond less than 150 m from the house, 4 for woodland less than 150 m from the

TABLE 1
Crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for factors related to indoor transmission

Variables	Cases (n = 171) No.	Cases %	Controls (n = 308) No.	Controls %	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*
Permanent opening for window							
No	55	33.0	233	75.0	1	1	
Yes	116	67.0	75	25.0	9.7 (5.5–17.2)	5.3 (2.4–11.7)	< 0.001
Number of rooms							
≥4	30	18.0	160	52.0	1	1	
1–3	141	82.0	148	48.0	7.6 (4.3–14.2)	5.0 (2.3–11.1)	< 0.001
Type of floor							
Cement/others	21	12.0	123	40.0	1	1	
Soil-earth	150	88.0	185	60.0	10.0 (5.0–20.0)	5.0 (1.1–5.0)	0.018
Permanent opening for main entrance							
No	107	63.0	279	90.0	1	1	
Yes	64	37.0	29	10.0	5.7 (3.3–9.9)	3.4 (1.6–7.2)	0.001
Type of roof							
Thatched	121	71.0	161	53.0	1	1	
Corrugated iron	41	24.0	103	33.0	0.4 (0.2–0.6)	2.9 (1.2–7.3)	0.018
Cement	9	5.0	44	14.0	0.1 (0.05–0.4)	2.6 (0.6–10.8)	0.116
Insect control by householder							
None	41	24.0	21	7.0	1	1	
Insecticides (DDT)	64	37.0	174	56.0	0.1 (0.1–0.3)	0.3 (0.1–0.8)	0.017
Smoke	46	27.0	64	21.0	0.3 (0.1–0.7)	0.3 (0.1–0.9)	0.033
Both insecticide and smoke	20	12.0	49	16.0	0.1 (0.08–0.4)	0.2 (0.09–0.7)	0.017
Storage of products							
No	48	28.0	132	43.0	1	1	
Yes, outside the house	114	67.0	167	54.0	2.3 (1.4–3.7)	2.8 (1.4–5.8)	0.003
Yes, inside the house	9	5.0	9	3.0	5.9 (1.5–22.7)	4.9 (0.9–26.8)	0.062

TABLE 2
Crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for factors related to peridomestic transmission

Variables	Cases		Controls		Crude OR (95% CI)	Adjusted OR (95% CI)	P
	No.	%	No.	%			
Distance to a pond							
≥151 m	87	49.0	273	89.0	1	1	
≤150 m	84	51.0	35	11.0	12.0 (6.1–23.4)	15.1 (6.1–7.3)	< 0.001
Distance to a road							
≤50 m	55	32.0	196	64.0	1	1	
≥51 m	116	68.0	112	36.0	10.0 (3.3–10.0)	3.3 (1.6–10.0)	0.001
Distance to waterway							
≥151 m	122	71.0	282	92.0	1	1	
≤150 m	49	29.0	26	8.0	7.5 (3.6–15.6)	4.4 (1.5–13.1)	0.007
Distance to woodland							
≥151 m	15	9.0	63	20.0	1	1	
≤150 m	156	91.0	245	80.0	11.3 (3.4–37.7)	5.8 (1.2–28.2)	0.027
Distance to a cultivated area							
≥201 m	65	38.0	169	55.0			
≤200 m	106	62.0	139	45.0	2.3 (1.5–3.7)	2.6 (1.2–5.5)	0.010
The sighting of armadillo							
No	111	65.0	268	87.0	1	1	
Yes	60	35.0	40	13.0	3.8 (2.3–6.3)	4.0 (1.8–9.1)	0.001
Garbage disposal							
Closed	36	21.0	141	46.0	1	1	
Open	135	79.0	167	54.0	3.2 (2.0–5.0)	3.1 (1.5–6.1)	0.001

house, and 5 for cultivated area less than 200 m from the house. For behavior-related factors, the ORs were 10 for sleeping in the backyard for more than four months, 13 for collecting water, 9 for bathing, and 6 for working in agriculture. The ORs associated with indoor and peridomestic transmission were large, and some exposures were very frequent. Had we calculated the population-attributable fraction (PAF) for the independent effect of these variables, some factors associated with indoor transmission (e.g., type of floor) and others associated with peridomestic transmission (e.g., presence of woodland within 150 m) would have had a PAF of approximately 50%.

DISCUSSION

The risk of acquiring ACL in Santiago del Estero province during the early 1990s was significantly enhanced by factors likely to be associated with indoor, peridomestic, and extra-domestic transmission. Evidence for indoor transmission comes from the increased risk for persons inhabiting houses that have fewer rooms, dirt floors, or permanent openings for windows. These characteristics were also found to increase the risk of ACL in other endemic areas where domestic transmission was suspected (Llanos-Cuentas EA, unpublished data).[6–9] While these factors may be a proxy indicator for poverty in our study, and thus be confounded by poverty, it makes biologic sense that endophagic sandflies will have more opportunity to bite people living in houses with permanent openings.[7] The sandfly vectors in this study site have not yet been identified, but two possible vector species have been previously collected in Santiago del Estero, i.e., *Lu. intermedia* and *Lu. migonei*. Both have been incriminated as ACL vectors in Brazil by the detection of natural infections with *L. braziliensis*.[10–14] *Lutzomyia intermedia* is highly anthropo-

TABLE 3
Crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for factors related to human behavior transmission

Variables	Cases		Controls		Crude OR (95% CI)	Adjusted OR (95% CI)	P
	No.	%	No.	%			
Months sleeping in the backyard							
None	23	13.0	123	40.0	1	1	
1–3	10	6.0	34	11.0	2.1 (0.8–5.2)	5.6 (1.7–18.43)	0.004
4	23	13.0	76	25.0	1.6 (0.8–3.2)	2.3 (0.9–5.5)	0.052
5–12	115	68.0	75	24.0	9.0 (4.9–16.8)	11.9 (5.0–28.5)	0.000
Gathering firewood in the past year							
No	35	20.0	146	47.0	1	1	
Yes	136	80.0	162	53.0	10.2 (4.5–4.8)	4.6 (1.6–13.4)	0.004
Bathing in the past year							
No	125	73.0	288	93.0	1	1	
Yes	46	27.0	20	7.0	11.7 (4.9–7.8)	4.8 (1.6–14.2)	0.000
Collecting water in the past year							
No	47	27.0	175	57.0	1	1	
Yes	124	73.0	133	43.0	16.1 (6.6–40.5)	12.9 (4.3–39.1)	0.000
Work/help on a farm past year							
No	108	63.0	243	79.0	1	1	
Yes	63	37.0	65	21.0	2.8 (2.5–7.8)	3.5 (1.6–7.6)	0.002

TABLE 4

Final model: crude and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for factors related to cutaneous leishmaniasis transmission

Variables	Cases		Controls		Crude OR (95% CI)	Adjusted OR (95% CI)	P
	No.	%	No.	%			
Number of rooms							
≥4	30	18.0	160	52.0	1	1	
1–3	141	82.0	148	48.0	7.6 (4.2–13.9)	4.4 (1.4–13.8)	0.010
Permanent opening for window							
No	55	33.0	233	75.0	1	1	
Yes	116	67.0	75	25.0	9.7 (5.5–17.2)	8.0 (2.5–25.5)	0.000
Type of floor							
Cement/others	21	12.0	123	40.0	1	1	
Soil-earth	150	88.0	185	60.0	9.1 (4.3–19.2)	6.1 (1.1–34.3)	0.037
Distance to a pond							
≥151 m	87	51.0	273	89.0	1	1	
≤150 m	84	49.0	35	11.0	12.0 (6.1–23.4)	15.1 (4.5–50.1)	0.000
Distance to woodland							
≥151 m	15	9.0	63	20.0	1	1	
≤150 m	156	91.0	245	80.0	11.3 (3.4–37.7)	4.4 (0.8–23.2)	0.075
Distance to a cultivated area							
≥201 m	65	38.0	169	55.0	1		
≤200 m	106	62.0	139	45.0	2.3 (1.5–3.7)	5.2 (1.5–18.4)	0.009
Months sleeping in the backyard							
0–4/year	56	33.0	233	76.0	1	1	
5–12/year	115	67.0	75	24.0	6.5 (4.0–10.6)	10.0 (3.4–29.6)	0.000
Collecting water							
No	47	27.0	175	57.0		1	
Yes	124	73.0	133	43.0	16.1 (6.6–40.5)	13.2 (2.7–62.8)	0.001
Bathing in the past year							
No	125	73.0	288	93.0	1	1	
Yes	46	27.0	20	7.0	11.7 (4.9–27.8)	8.9 (1.5–50.7)	0.013
Working/helping in agriculture area							
No	108	63.0	243	79.0	1	1	
Yes	63	37.0	65	21.0	2.8 (2.5–7.8)	5.7 (1.5–20.7)	0.008

philic, apparently well adapted to the peridomestic environment,[15–19] and frequently enters human dwellings at night to blood feed.[20,21] Although *Lu. migonei* is also found in the peridomestic environment, it tends to be less abundant than *Lu. intermedia* (where both species coexist) and is less anthropophilic than *Lu. intermedia*, preferring to feed on donkeys, chicken and dogs.[22–26]

The most direct evidence for peridomestic transmission comes from the finding that ACL risk was greatest for those who most frequently slept outdoors in the backyard. A marked dose-response effect was observed with the number of months per year spent sleeping outdoors. Additional circumstantial evidence comes from the finding that the risk of ACL was significantly greater for people living close to woodland, a cultivated area, or a pond. All three factors could potentially have an impact on the sandfly population density around the home. The increased risk associated with houses located near a source of water is consistent with previous reports (Llanos-Cuentas EA, unpublished data).[27,28] The edges of sources of water may provide suitable conditions for sandfly breeding sites (low temperature, moderate humidity, and presence of living organic matter). Immature sandfly stages have been recovered from soil taken at the edge of water sources in Brazil and Panama.[29–32] Woodland and crops provide suitable habitat for adult sandflies as well as their immature stages. Proximity of houses to both woodland,[28,33–35] and crops[36–41] have been identified as risk factors for ACL in other settings.

The biologic explanation for risk associated with these environmental features close to houses lies in the increased rates of vector-human contact. It is unclear to what extent this increase is due to greater sandfly densities in the domestic habitat (when sandflies fly into the home in search of a blood meal) or to an increase in the chance of humans moving into high density environments (e.g., to collect wood or to irrigate their crops). In southern Brazil there is some evidence for the former hypothesis, since the indoor and peridomestic abundance of *Lu. intermedia* was found to be highest for houses located less than 300 m from the edge of a secondary forest.[31] No entomologic data was collected in our study; however, it is interesting to note that these environmental features were significant risk factors even after adjusting for detected human activity risk factors (suggesting that their impact is mainly through their effect on domestic sandfly abundance). Specifically, we showed that working or helping in an agricultural area or water collection, and bathing in any source of water were associated with an increased risk of ACL. Agricultural activities are often found to be associated with ACL risk (especially where domestic transmission is not common), notably in studies in Brazil,[41,42] Colombia,[33] Costa Rica,[6] Venezuela,[43] and Peru (Llanos-Cuentas EA, unpublished data).

With respect to control strategies, it is important to identify risks that can be reduced by feasible interventions. For example, it is unlikely that people will take into account the risk of acquiring a vector-borne disease when deciding where to build their dwelling; therefore, a strategy that advises avoidance of building close to forests, plantations, or rivers is unlikely to be effective. However, the risk associated with many factors identified in this study could be reduced by means of residual insecticide spraying, dwelling improvements or changes in behavior.

Residual insecticide spraying has been effective in other areas endemic for leishmaniasis, particularly where the transmission is domestic and peridomestic.[44–48] Restricting sandfly access to the house by providing glass windows for dwellings that have only permanent openings in the wall would probably be effective, but expensive. Cheaper alternatives include screens (metallic, plastic, or other type) or permethrin-impregnated curtains. Trials using impregnated curtains in Colombia have shown that homes treated this way have fewer sandflies than untreated houses.[49] Risk factors related to human behavior are the appropriate targets for interventions, such as encouraging sleeping under bed nets, and the use of repellent soap or repellent clothing when undertaking risky activities.[49–51]

We chose not to quantify the relative importance of indoor, peridomestic, and extra domestic transmission. However, it appears from a comparison of the ORs and percentage exposed to the factors in the three groups that transmission during extra domestic activity is likely to be relatively unimportant, and that most transmission takes place in or around the house. Estimating the relative contribution of factors within groups is even more complex. Had we attempted to estimate population attributable fractions, we would have found about 22% of the cases attributable to the presence of a window consisting of a permanent opening in the home. Does this mean that we would reduce incidence by 22% if all windows were screened effectively? What if this was done in conjunction with spraying the peridomestic area? In such a situation, where factors overlap and can influence each other, we suggest that predicting the effect of removing one of the variables alone is futile. A reliable measure of effectiveness of different interventions is unlikely, unless they can be applied in a more controlled situation, such as an intervention trial. Studies like this, however, provide a rational basis for prioritizing interventions.

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