American cutaneous leishmaniasis (ACL) is a zoonosis caused by *Leishmania* species of subgenera *Viannia* and *Leishmania*. It is transmitted by phlebotomine sandflies and affects primarily sylvan mammalian hosts, mainly small rodents from tropical forests. It is an important public health problem, with clinical manifestations varying from simple cutaneous to mucocutaneous and disseminate lesions. It is highly endemic in several Brazilian regions. About 20,000 new cases have been notified annually over the last 5 years, and 10% of these cases are from the Southeast Region.1

Until the 1970s, human infection was only related to contact between humans and forests.2–5 However, in the last two decades, the disease has been described among individuals living in settled agricultural areas, where deforestation took place a long time ago.6 Recently, it has been suggested7–9 that there has been a modification in the transmission patterns, with the disease occurring in periurban populations. These new findings have lead to the ecological idea that environmental factors have changed sandflies’ behaviour. They are now living inside houses and outdoors close to the household.10 Little attention has been paid to the space and temporal dynamics of the transmission patterns of this disease and to the correlates between environmental factors and ACL.

In this paper we present the results of a continuous collection of ACL cases through a surveillance system carried out in Caratinga municipality, Southeast Brazil, where different transmission patterns have been hypothesized in the last three decades. The aims of this study were to estimate the incidence

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### Background
American cutaneous leishmaniasis (ACL) is endemic in many rural areas of Brazil where different transmission patterns of the disease have been described. This ecological study was carried out in a municipality located in Southeast Brazil and aimed to investigate the space-temporal patterns of the disease and environmental risk factors from 1966 to 1996.

### Methods
Incident ACL cases were defined by clinical diagnosis, confirmed by a positive skin test and/or parasitological examination. Age-adjusted morbidity rate of ACL was calculated by year for this municipality and their different census enumeration districts. The homogeneity $\chi^2$ test, Moran and empirical Bayes index and Knox procedure were employed for testing the significance of clusters in time, space and in time-space, respectively. A Poisson regression model was used to identify environmental factors related to rate variability.

### Results
A total of 1712 new ACL cases were reported with a yearly incidence rate of 48/100,000 inhabitants. Higher incidence rates were detected in 1968, 1974, and 1988 (100, 160, and 190 cases/100,000, respectively) with evidence of spatial clustering from 1986 to 1993. Significant space–time clustering with epidemic peaks followed by low incidence in subsequent periods was observed. The incidence rates of ACL were independently associated with rural areas; areas lacking sanitary installations and with higher proportion of exposed garbage ($P < 0.01$).

### Conclusions
This study suggests that ACL rates vary across space and time. Rural areas and some environmental factors could explain part of this variation. Environmental modifications in the vicinity of households over time and accumulation of susceptible individuals are discussed as possible factors responsible for variability.

### Keywords
American cutaneous leishmaniasis, cluster analysis, temporal–space patterns, temporal series, geography, herd immunity

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American cutaneous leishmaniasis (ACL) is a zoonosis caused by *Leishmania* species of subgenera *Viannia* and *Leishmania*. It is transmitted by phlebotomine sandflies and affects primarily sylvan mammalian hosts, mainly small rodents from tropical forests. It is an important public health problem, with clinical manifestations varying from simple cutaneous to mucocutaneous and disseminate lesions. It is highly endemic in several Brazilian regions. About 20,000 new cases have been notified annually over the last 5 years, and 10% of these cases are from the Southeast Region.1

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AMERICAN CUTANEOUS LEISHMANIASIS: SPACE–TIME CLUSTERING

Material and Methods

Study area
Caratinga is an endemic municipality for the disease. It is an area of 2234 km² located in Minas Gerais State, Southeast Brazil, and lying within the boundaries of 19°19' and 20°01'S, and 41°46' and 42°31'W. Caratinga Town, the administrative centre of the municipality, is situated at 575 m above sea level. The municipality has 12 districts, subdivided according to Brazilian Census Bureau into 130 census enumeration districts (CED). To permit comparisons, the CED were grouped in 21 urban and 53 rural CED (Figure 1).

Subjects
Incident ACL cases were patients attending for the first time a reference clinic in Caratinga during 1966–1996, and reported to a specific passive surveillance system for leishmaniasis. Patients with one or more active skin lesions, clearly demarcated, were diagnosed as cutaneous leishmaniasis. The presence of either concomitant/or not sequellae of mucous membranes, such as oral or naso-pharyngeal lesions defined the mucocutaneous form. All clinical diagnoses were confirmed by positive skin test (Montenegro) and/or parasitological examination.

Population data
Demographic data for the study area were obtained through the official files supplied by ‘Instituto Brasileiro de Geografia e Estatística’, the official Brazilian Census Agency. The 1960, 1970, 1980 and 1991 census data for Caratinga stratified by age were used to calculate growth rates and to estimate the population size from 1966 to 1996.11–14 Regarding information on CED, only the 1980 and 1991 census data were available.

Morbidity rates
Direct standardized rates which took into account differences in the age population distribution among CED were calculated. The reference population was the 1980 local population in each age category.

Time homogeneity and time trend
Annual homogeneity of municipal level rates of ACL were tested using a $\chi^2$ test in order to compare the total number of ACL rates from 1966 to 1996, to test for space and temporal patterns in the rates and to correlate them to socio-geographic factors.

Figure 1 Caratinga municipality subdivided by rural and urban census enumeration districts, Minas Gerais State, Southeast Brazil
ACL cases observed with those expected under the assumption of constant rate across time.

The time trend of ACL rates were also tested using a log-linear model on the assumption of a Poisson distribution for cases using the population as offset. We assumed that the annual count of ACL cases in this region followed a Poisson distribution with mean equal to the population size times the underlying time-varying rate. The logarithm of annual rates follow a linear trend on time with parameters \(a\) and \(b\) estimated by maximum likelihood. Since the log-linear model is specific for time trend, it is more powerful for detecting this departure from the constant rate hypothesis than the \(\chi^2\) test for homogeneity.

Space clustering

Initially, we tested whether the underlying rates among the CED were spatially heterogeneous or not. Since the disease is rare, it was convenient to aggregate the counts of ACL cases with the aim of obtaining more stable rates. To investigate time variation on the endemic pattern, three time periods for which CED population data were available, were used: 1980–1985, 1986–1993, and 1994–1996. A powerful test for rates heterogeneity proposed by Oden was used.

Acceptance of the hypothesis of heterogeneous rates implies that there was some spatial variation of the underlying rates in the whole region but the scale of this variation could be smaller than the typical CED area. If the latter was true, we would have different rates among the areas but, if these rates were mapped by CED, they would not show a spatial pattern. The index proposed by Moran was used to test for spatial autocorrelation at the CED level. Moran’s index tests if rates from CED neighbours tend to be more similar than rates from CED chosen arbitrarily.

We considered as neighbours those CED sharing boundaries. The empirical Bayes index (EBI) proposed by Assunção and Reis is an adjustment of Moran’s index which takes into account the different population size used to calculate the rates. It is more robust to eventual outliers due to small population size and it is more powerful than Moran’s index.

Space and time clustering

The space-time interaction of cases of leishmaniasis was determined through the statistic of Knox. This test assumes that the number of ACL cases living near to each other and occurring close in time is higher than it could be due to chance alone. Note that the absence of spatial autocorrelation for each time period does not imply, as a consequence, an absence of space-time interaction. American cutaneous leishmaniasis cases were considered close in space if they belonged to the same CED and close in time if they belonged to the same season within a year.

To test for the presence of time periodicity each year was divided into two periods, rainy and dry, according to the pattern of rainfall in Caratinga, based on the information that the sandfly population size varies between seasons. The rainy season extends from October to March, and the dry season starts in April and ends in September.

Poisson regression analysis

In order to explain rate variability, a generalized linear model was fitted to the ACL case counts assuming a Poisson distribution with the population size as offset and with the logarithm of the underlying rates depending on the following covariates: population density, urban/rural indicator, household number, average of household inhabitants, proportion of houses without sanitary disposal, without water installation and with exposed garbage. Information on these covariates was available only for the 1991 census year.

Results

A total of 1712 new cases of ACL were reported in Caratinga from 1966 to 1996, with an average crude incidence rate of 48/100 000 inhabitants.

Table 1 shows selected demographic and clinical variables by area of residence. About 77% of all cases were from rural areas, except for Caratinga, Ipaba and Santa Rita districts where...
77.1%, 50% and 65% of cases, respectively, were from urban areas \((P < 0.01)\). Gender distribution was found similar across the area strata \((P = 0.06)\). The median age was 20.0 years and the average age was 25.5 (range 24.7–26.4 years). The age distribution of ACL cases according to the districts was significantly different \((P < 0.01)\), thus justifying age standardization. According to the clinical diagnosis, the majority of cases (96%) presented with the cutaneous form.

The incidence rates of ACL by year and the time trends are shown in Figure 2. There is strong evidence of annual variation during the three decades according to the \(\chi^2\) homogeneity test \((\chi^2 = 1411.1, \text{d.f.} = 30, P < 0.01)\). The trend test gives evidence of an increased rate of reported cases through the years (Table 2). According to the fitted generalized linear model, ACL morbidity increases at a rate of 5 cases/100 000 inhabitants a year and the underlying rates varied from 41.4 in 1966 to 57.2 in 1996.

In order to investigate if the trend of the disease was different among age categories, separated log-linear Poisson regression models were used. We tested for interactions between the trend of the incidence rates in the age classes, 0–9, 10–19, \(\geq 20\) years, stratified for rural and urban areas. Trend in the incident rates was not different for any age category, regardless of the area of residence. So, pooling the age for rural areas, the model showed increased rates of ACL cases over time, varying from 43.81 in 1970 to 169.08/100 000 in 1996 \((P < 0.01)\). On the other hand, the rates in urban areas presented a steady decrease over time varying from 61.12 in 1970 to 2.71/100 000 in 1996 \((P < 0.01)\) (Figure 3).

In Figure 4, the results of the ACL spatial distribution are presented for each CED from Caratinga. There was a wide variation on incidence rates over the three time periods. The results of Oden’s test (Table 3) provide strong evidence for rejecting the rate homogeneity hypothesis in each of the three periods. Moran’s index did not show a spatial autocorrelation, but the EBI test found evidence for this autocorrelation from 1986 to 1993. The EBI test was preferable to the Moran’s test because the population in each area was different.

Significant evidence of space-time clustering in rural areas for all decades and only for the 1970s and 1980s in urban areas was found using the Knox analysis (Table 4). The pattern of this space-time clustering was composed of epidemic peaks followed by small incidence in the subsequent periods (data not shown). Poisson regression analysis found a significant effect in the overall rate of ACL in this region. The incidence rates were independently associated with rural areas, areas without sanitary installations and areas with higher proportion of exposed garbage as compared to urban areas, areas with a higher proportion of sanitary disposal and less exposed garbage (Table 5). The model was able to explain 20% of the variation of the incident rates observed among CED. Due to strong correlation, all others covariates were not included in the final model. Because of a very small population and very high incidence rate, one CED was excluded from the model.

### Table 2

<table>
<thead>
<tr>
<th>Coefficientsa</th>
<th>Value</th>
<th>SE</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-8.50</td>
<td>0.22</td>
<td>-38.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Linear trend</td>
<td>0.01</td>
<td>0.003</td>
<td>4.07</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

a Log-linear model using Poisson distribution.

### Discussion

This study shows an increase in the incidence rates of reported ACL cases, with a significant positive trend over time, in a rural area located in Southeast Brazil over the last 30 years. American cutaneous leishmaniasis occurred in outbreaks, clustering in space and time. Three independent ecological factors were
Four possible explanations can be proposed: (1) variation of exposure related to environmental modifications, such as urbanization of endemic rural areas; (2) variation in sandfly habits and distribution as a consequence of the first argument; (3) variation in the number of mammalian hosts and, (4) variation in the number of susceptible individuals.

With respect to explanation (1), some studies in Brazil have shown an association between the environmental modifications of urbanization and the emergence or re-emergence of ACL cases.7–9 Although information on urbanization in this area is lacking, given that the incidence rates have been decreasing over time in urban areas, contrasting with the steady increase on incidence rates in rural areas, we postulate that environmental modifications could be occurring in both directions. For urban areas these modifications would result in a decreased exposure to several factors related to transmission. On the other hand, for rural areas, a continuous or maybe increased exposure of human beings within the sylvan environment could be able to maintain the transmission of the disease. To corroborate this argument the adjusted Poisson model showed a significant association with rural area after taking into account other social or geographic factors.

With respect to explanation (2), some articles have argued that the increase in ACL cases in children aged 0–9 years living either in urban or rural areas may be due to increased occurrence of sandflies in and around households, possibly resulting in a new transmission pattern for the disease.9,10,21 The absolute number of sandflies captured in this area has varied, as well as the relative proportion of different species. Also, data collected in this area have shown that most of the sandflies were captured in woodland (59%), around domestic sites (33.4%) and from the margins of rice fields (7.4%).6 Consequently, using the time increase on incidence rates regardless of age group as a surrogate marker for the transmission pattern in rural areas, the data do not support a new transmission pattern in this area due to increased sandfly occurrence in and around households over the last 30 years.

With respect to explanation (3), we observed that the risk was larger among the rural CED with a large number of houses associated with incidence rate variability: rural area, area with a higher proportion of households lacking sanitary disposal, and with a higher proportion of households with exposed garbage.

Figure 3 Time trend and incidence rate (per 100 000) of American cutaneous leishmaniasis (ACL) according to residence area, age and year of diagnosis, Caratinga, Southeast Brazil, 1970–1996
Table 3: Comparison of estimates using Moran's, empirical Bayes and Oden's indexes to evaluated the heterogeneity and autocorrelation spatial of the incidence rates of American cutaneous leishmaniasis in Caratinga, Southeast Brazil, 1980–1996

<table>
<thead>
<tr>
<th>Period</th>
<th>Moran's index</th>
<th></th>
<th>Empirical Bayes index</th>
<th></th>
<th>Oden's index</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-value</td>
<td>P-value</td>
<td>EBI</td>
<td>Z-value</td>
<td>P-value</td>
<td>Z-value</td>
</tr>
<tr>
<td>1980–1985</td>
<td>-0.28</td>
<td>0.78</td>
<td>10.43</td>
<td>0.18</td>
<td>43.94</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1986–1993</td>
<td>1.37</td>
<td>0.17</td>
<td>30.24</td>
<td>0.02</td>
<td>364.35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1994–1996</td>
<td>-0.66</td>
<td>0.50</td>
<td>18.14</td>
<td>0.31</td>
<td>78.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1980–1996</td>
<td>0.80</td>
<td>0.42</td>
<td>28.59</td>
<td>0.04</td>
<td>459.36</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 4: Space-time interaction of American cutaneous leishmaniasis cases according to the residence area (urban/rural) in decades, Caratinga, Southeast Brazil, 1966–1996

<table>
<thead>
<tr>
<th>Decade</th>
<th>Urban areas</th>
<th></th>
<th>Rural areas</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-value</td>
<td>P-value</td>
<td>Z-value</td>
<td>P-value</td>
<td>Z-value</td>
<td>P-value</td>
</tr>
<tr>
<td>60</td>
<td>1.34</td>
<td>0.090</td>
<td>2.27</td>
<td>0.012</td>
<td>3.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>70</td>
<td>2.36</td>
<td>0.009</td>
<td>10.03</td>
<td>&lt;0.001</td>
<td>8.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>80</td>
<td>3.25</td>
<td>0.001</td>
<td>10.04</td>
<td>&lt;0.001</td>
<td>11.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90</td>
<td>0.70</td>
<td>0.242</td>
<td>4.37</td>
<td>&lt;0.001</td>
<td>4.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>6.99</td>
<td>&lt;0.001</td>
<td>26.97</td>
<td>&lt;0.001</td>
<td>37.88</td>
<td>0.000</td>
</tr>
</tbody>
</table>
without sanitary installations and with exposed garbage. These findings suggest that human activity could attract the zoonotic hosts to the domestic environment, as observed by other authors.10,22,23

Arguments (2) and (3) support the idea of formation of an ACL artificial biocenosis around the household, contributing to the argument of transmission in this area.

With respect to explanation (4), some authors21 have suggested that, in Brazilian regions, ACL has explosive outbreaks with very low incident case rates in the subsequent period. There is a strong evidence that, following clinically apparent infection, treated individuals acquire lifelong resistance,24 increasing the herd immunity. In this region, which has a very low rate of migration into the area, three epidemic peaks were observed in the last three decades. These peaks could be explained by the birth of new susceptible cohorts of individuals with a subsequent accumulation of susceptible individuals reaching a threshold sufficient to initiate an epidemic. When the susceptibles pool was depleted, the epidemics declined until a new large susceptible pool was formed again.

Also, considering that the population growth rate was constant over time, variation in the susceptible pool due to migration and death rates does not seem a plausible explanation for ACL case variation in this region.

These ecological associations could be spurious if the variation in incidence was due to changes in the surveillance system during the epidemic period, with diagnosis, notification and flow of information improvement, as well as changes in popular knowledge of the disease, resulting in more medical care seeking behaviour. Also, changes in the disease classification and diagnostic criteria were not observed in this area during the study. In Caratinga, the continuous existence of collaboration between the Federal University of Minas Gerais and the public health service created a consistent surveillance system over the last 30 years. Surveillance bias would not be expected to produce a distorted trend in the observed ACL rates in this setting.

Despite the impossibility of accurately measuring relevant exposures at the individual level in this large number of subjects, this study suggests an apparent cluster of ACL in small rural areas over time.25 Differences in the communities that might explain a large amount of the incidence rate variability could be an increased sandfly population in the vicinity of dwellings due to low sanitation including higher proportion of exposed garbage, associated with cyclic provision of susceptible individuals. This suggests the creation of a very susceptible biocenosis that would be responsible for occasional peaks of incidence within small regions.

Further studies, combining individual-level analysis in each group, followed by an ecological analysis of all the group using the results from the individual level will be able to clarify the findings described here.

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