Intra-urban differences underlying leprosy spatial distribution in central Brazil: geospatial techniques as potential tools for surveillance

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Abstract

This ecological study identified an aggregation of urban neighbourhoods spatial patterns in the cumulative new case detection rate (NCDR) of leprosy in the municipality of Rondonópolis, central Brazil, as well as intra-urban socioeconomic differences underlying this distribution. Scan statistics of all leprosy cases reported in the area from 2011 to 2017 were used to investigate spatial and spatiotemporal clusters of the disease at the neighbourhood level. The associations between the log of the smoothed NCDR and demographic, socioeconomic, and structural characteristics were explored by comparing multivariate models based on ordinary least squares (OLS) regression, spatial lag, spatial error, and geographically weighted regression (GWR). Leprosy cases were observed in 84.1% of the neighbourhoods of Rondonópolis, where 848 new cases of leprosy were reported corresponding to a cumulative NCDR of 57.9 cases/100,000 inhabitants. Spatial and spatiotemporal high-risk clusters were identified in western and northern neighbourhoods, whereas central and southern areas comprised low-risk areas. The GWR model was selected as the most appropriate modelling strategy (adjusted R^2: 0.305; AIC: 242.85). By mapping the GWR coefficients, we identified that low literacy rate and low mean monthly nominal income per household were associated with a high NCDR of leprosy, especially in the neighbourhoods located within high-risk areas. In conclusion, leprosy presented a heterogeneous and peripheral spatial distribution at the neighbourhood level, which seems to have been shaped by intra-urban differences related to deprivation and poor living conditions. This information should be considered by decision-makers while implementing surveillance measures aimed at leprosy control.

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Introduction

Leprosy, or Hansen's disease, is a chronic infectious disease mainly caused by the bacillus *Mycobacterium leprae*, which primarily affects the skin and peripheral nervous system. If left untreated, leprosy can result in severe physical impairment and deformities. It has been suggested that *M. leprae* is predominantly transmitted during prolonged contact with bacilliferous and untreated individuals by skin-to-skin contact and aerosols/droplets (Bratschi *et al*., 2015). In high-burden countries, transmission is largely driven by poor socioeconomic and sanitary conditions, low levels of schooling and food insecurity (Pescarini *et al*., 2018). According to the World Health Organization (WHO), more than 200,000 new cases were reported worldwide in 2019, with India, Indonesia, and Brazil together accounting for over 80% of all cases (WHO, 2020a).

In Brazil, according to the Ministry of Health (MoH), the control of leprosy is essentially based on early case detection, treatment of all cases with multidrug therapy, and health education (MoH, 2016). Nonetheless, these strategies have not been sufficient to significantly reduce the transmission of the disease (Barreto *et al*., 2011). From 2015 to 2019, an annual average of 27,477 new leprosy cases was recorded in Brazil. In 2019, the overall new case detection rate (NCDR) was calculated at 13.2 cases/100,000 inhabitants, but this value was disproportionally higher among the Brazilian states covered by the Amazon rainforest (MoH, 2021). For example, the state of Mato Grosso, located in central-western Brazil in the southern Amazon region, historically presents the highest NCDRs of leprosy in the country (MoH, 2021). In the period 2008-2017, an annual average rate of 89.4 cases/100,000 inhabitants was observed state-wide. Moreover, high-risk areas for leprosy comprised more than half of the 141 municipalities and 35.6% of the whole population in Mato Grosso (Carvalho *et al*., 2020). Thus, the strengthening of control actions of leprosy has been highly recommended in the municipalities of the state (Miguel *et al*., 2020).

Analyses based on geographic information system (GIS) have been successfully employed to guide surveillance and control actions of leprosy at different spatial scales (Silva *et al*., 2017a), such as districts (Bulstra *et al*., 2021), municipalities (Rodrigues *et al*., 2020) and neighbourhoods (Duarte-Cunha *et al*., 2016). These analyses provide reliable information for decision-makers on the factors underlying the dynamics of leprosy occurrence and identification of priority areas for interventions (Silva *et al*., 2017a). This is particularly desirable for municipal health coordinators, as leprosy control measures are performed at the municipality level with great involvement of the primary healthcare network within the Brazilian Unified Health System (Miguel *et al*., 2020).

In the municipality of Rondonópolis, a highly endemic area for leprosy in the state of Mato Grosso, many epidemiological studies have addressed the occurrence of the disease (Jarduli *et al*., 2014; Silva *et al*., 2017b; Pinto *et al*., 2021). However, updated GIS-based investigations are lacking in the area. Therefore, this study aimed to identify spatial patterns of the NCDRs of leprosy in the municipality of Rondonópolis from 2011 to 2017 at the neighbourhood level, and associated demographic, socioeconomic, and structural characteristics underlying this distribution.

Materials and methods

Study design and area

This is an ecological study using data aggregated to neighbourhood level to investigate spatial patterns of NCDRs of leprosy in the municipality of Rondonópolis between 2011 and 2017.

According to the Brazilian Institute of Geography and Statistics (IBGE), Rondonópolis, situated around the geographical coordinates of 16º28′15″S and 54º38′08″W, has a surface area close to 4200 km² composed of 230 urban neighbourhoods (IBGE, 2010), with an estimated population of approximately 240,000 inhabitants (IBGE, 2022). There are large differences in demographic, socioeconomic, and structural features. Despite surveillance and control measures, Rondonópolis has been classified as a hyperendemic area for leprosy (NCDR > 40.0 cases/100,000 inhabitants) between 2000 and 2010 (Marciano *et al*., 2018). More recently, it ranked among the municipalities with the highest absolute number of new leprosy cases reported in the state of Mato Grosso (Carvalho *et al*., 2020).

Data collection, study population, and variables

Data on the occurrence of leprosy were collated from the Brazilian Notifiable Diseases Information System (MoH, 2023). All new leprosy cases reported in the municipality of Rondonópolis between 2011 and 2017 were included. We excluded relapses, duplicate records, institutionalized individuals, those residing outside the urban area of Rondonópolis and records with indication of error, unidentifiable residence address, or change in the diagnosis. For each case, we recorded data on the year of reporting, year of diagnosis, and neighbourhood of residence. Furthermore, the records were grouped by neighbourhood according to the year of reporting.

Information on the following demographic, socioeconomic and structural characteristics of the neighbourhoods were extracted from the Demographic Census (IBGE, 2010): number of inhabitants, percentage of non-white individuals (*i.e.* black, mixed, indigenous), mean number of inhabitants per private permanent household (PPH), literacy rate among individuals aged five years and older, mean monthly nominal income per PPH (in Brazilian minimum wages), percentage of PPHs without household income, percentage of PPHs without bathroom, percentage of PPHs with public electricity supply, percentage of PPHs with public water supply, percentage of PPHs with public garbage collection, and percentage of PPHs with sanitary sewage service. These variables were selected based on previous studies that assessed their association with the occurrence of leprosy in Brazilian urban areas (Kerr-Pontes *et al*., 2004; Castro *et al*., 2016; Duarte-Cunha *et al*., 2016; Pescarini *et al*., 2018). Annual population estimates for the whole municipality were obtained from IBGE.

For further spatial analyses, we employed the digital georeferenced database of neighbourhoods of Rondonópolis provided by the Municipal Health Department of Rondonópolis in 2016. Due to data unavailability and analytical limitations, we did not consider neighbourhoods that emerged after 2010 and therefore were not listed in the Demographic Census carried out that year (IBGE, 2010), as well as four island neighbourhoods that did not share borders with others (*i.e.* neighbourless). In addition, homonymous neighbourhoods that share a border were pooled and considered as one single spatial unit. These procedures resulted in 183 neighbourhoods. Given the still high number of analytical units, reducing the number of neighbourhoods from 230 to 183 would have limited impact on the overall analysis.

Statistical analysis

Data were tabulated and checked in Microsoft Office Excel (Microsoft Corporation, 2022). To describe temporal patterns, we first calculated the overall and annual NCDR (cases/100,000 inhabitants) of leprosy for the whole municipality by dividing the annual number of leprosy cases by the annual estimated population. In sequence, we calculated the overall and annual NCDR for each neighbourhood. For the annual NCDR, we considered the population count from the Demographic Census (IBGE, 2010) as constant over years. Neighbourhoods were further classified according to the magnitude of leprosy endemicity using the annual NCDR as recommended by the Brazilian Ministry of Health (MoH, 2016): hyperendemic (>40.0/100,000), very high (20.0-39.9/100,000), high (10-19.9/100,000), medium (2.0-9.9 /100,000) and low (< 2.0 /100,000). In addition, the overall NCDR per neighbourhood was smoothed using a global empirical Bayesian estimator in GeoDa 1.20 (Anselin *et al*., 2006). This method decreases data instability and random fluctuations by converging crude rates towards an overall mean (Marshall, 1991).

Spatial and spatiotemporal clusters for the occurrence of leprosy were investigated using spatial scan statistics (Kulldorff & Nagarwalla, 1995) implemented in SaTScan™ 9.3 software (Kulldorff & Information Management Services Inc., 2021). For each neighbourhood we considered the population count and the number of new leprosy cases, which was assumed to follow a Poisson distribution. The whole area was scanned for low- and high-risk circular clusters, with the maximum size equal to 50% of the population at risk and without geographical overlapping. The p-value of the clusters was estimated under the Monte Carlo hypothesis test with 999 replications. For spatiotemporal analysis, we considered the precision in years and the maximum size of the temporal cluster as equal to 50% of the entire study period. High- and low-risk clusters at $p < 0.05$ were considered statistically significant. To investigate intra-urban differences underlying the occurrence of leprosy at the neighbourhood level, we employed different statistical methods to model the smoothed NCDR (*i.e.* outcome) as a function of potential demographic, socioeconomic, and structural explanatory variables. For that, we first performed a logarithmic transformation of the outcome. Following, the correlation between the transformed outcome and the explanatory variables were checked by a correlation matrix using the Pearson's correlation coefficient (r). All variables of p-value <0.20 and not highly correlated with other covariates (r>0.60) were selected for multivariate modelling by ordinary least squares (OLS) regression as follows:

$$\log(Y_i)= \beta_0+\beta_1 X_{1i}+...+ \beta_n X_{ni} + \varepsilon_i \qquad \text{Eq.1}$$

where Y is the outcome in neighbourhood i; β_0 the intercept; $\beta_1 \dots \beta_n$ the regression coefficients for the n explanatory variables ($X_1 \dots X_n$) in neighbourhood i; and ε the error term (the residuals).

The OLS model was developed by a stepwise forward procedure using the Akaike information criterion (AIC) to assess whether the addition of explanatory variables improved the model fit. The OLS assumption of a normal distribution of residuals was graphically checked (with a histogram and quantile-quantile plot) followed by the Shapiro-Wilk test (Shapiro & Wilk, 1965). An inspection for heteroscedasticity was performed by plotting the residuals and using the Breusch-Pagan test (Breusch & Pagan, 1979). Moreover, the variance inflation factor was employed to check for multi-collinearity among the variables in the model.

The classical OLS model does not take the spatial autocorrelation of the variables into account, which may result in a mis-specified model (Anselin & Arribas-Bel, 2013). In addition, our OLS regression residuals were not uniformly distributed across neighbourhoods, which suggested the existence of spatial autocorrelation. Therefore, we also modelled the dependent variable using global spatial regression analyses, namely, the spatial lag model (SLM) and the spatial error model (SEM). Briefly, global spatial models assume that the spatial autocorrelation structure can be captured by incorporating a single parameter in the OLS regression (Câmara *et al*., 2014). The SLM attributes the spatial autocorrelation to the dependent variable by adding a spatially-lagged dependent variable ($\rho W_i Y_i$) to the OLS model as follows (Mollalo *et al*., 2020):

$$log(Y_i)= \beta_0+\beta_1 X_{1i}+...+ \beta_n X_{ni}+\rho W_i Y_i+ \varepsilon_i \qquad \text{Eq.2}$$

where ρ is the spatial autoregressive coefficient; W the spatial weights matrix that defines the neighbours of the neighbourhood i and links the outcome to the explanatory variables at each neighbourhood (Câmara *et al*., 2014; Mollalo *et al*., 2020).

In contrast, the SEM assumes the ignored spatial autocorrelation in the residuals of the OLS regression:

$$log(Y_i)= \beta_0+\beta_1 X_{1i}+...+ \beta_n X_{ni}+\lambda W_i \xi_i+\varepsilon_i \qquad \text{Eq.3}$$

where ξ represents the spatial component of the error at neighbourhood i, λ the correlation between these terms; and ε_i is the spatially uncorrelated error component (Mollalo *et al*., 2020).

The global parameter estimates of SLM and SEM are assumed to be constant over the geographic space, which may not properly explain the relationship between variables. This is called spatial stationarity and can be overcome with a geographically weighted regression (GWR) (Brunsdon *et al*., 1996). GWR is based on kernel-weighted regression and estimates specific parameters in the model for each locality under analysis, rather than one single set of parameters (Brunsdon *et al*., 1996; Fotheringham & Oshan, 2016; Mollalo *et al*., 2020):

$$log(Y_i)= \beta_{i0}+\beta_{1i} X_{1i}+...+ \beta_{ni} X_{ni}+\varepsilon_i \qquad \text{Eq.4}$$

where, the dependent variable (Y) is a set of estimated parameter values for each explanatory variable at each neighbourhood i obtained via weighted least squares (Fotheringham & Oshan, 2016).

All the aforementioned analyses were performed in R 3.4.0 and R Studio 3.6.2 software (R Studio Team, 2021). Mapping was performed using QGIS 3.6.1 (QGIS, 2019). To test for spatial autocorrelation, we used the global Moran's I and a first order and queen contiguity-based spatial weights matrix. Positive and negative values of Moran's I indicate direct and inverse autocorrelation, respectively, whereas values close to zero supports a random spatial distribution. The values of adjusted R^2 and AIC were used to compare the OLS model with SLM, SEM, and GWR models fitted with the same predictors. The model with the highest adjusted R^2 and lowest AIC was defined as the most appropriate. In particular, an adaptive spatial kernel was used to select the optimal bandwidth for the GWR model.

Results

Spatial and spatiotemporal patterns of leprosy

From 2011 to 2017, 848 new cases of leprosy were reported in the municipality of Rondonópolis, which corresponds to an overall NCDR of 57.9/100,000. The annual number of new cases ranged between 75 and 150 with a peak in 2013 (Figure 1A). The annual NCDR showed a stable trend between 2011 and 2014, ranging between 58.1 and 73.4/100,000. However, from 2015 and onwards it decreased. In 2017, the NCDR was 33.7/100,000, which is below the threshold for hyperendemic classification (Figure 1B).

More than 80% (149/183) of the assessed neighbourhoods reported at least one new leprosy case during the study period. The overall number of cases per neighbourhood ranged from 0 to 52, with greater notification in those located in the northern and western parts of the municipality (Figure 2A). The cumulative NCDRs varied widely among neighbourhoods (range 0.0 to 714.3/100,000); the highest rates were observed in northern and western neighbourhoods, whereas the lowest ones appeared in the southern and central areas (Figure 2B). Cumulative smoothed NCDRs presented less variation (range 11.9 to 239.3/100,000), but the heterogeneous and peripheral spatial pattern was still observed (Figure 2C). In fact, three spatial clusters of high risk for leprosy encompassing 45 neighbourhoods were detected in the western [relative risk (RR) = 2.91, p<0.001] and northern (RR=8.28, p=0.039 and RR=1.58, p<0.001] areas. In contrast, 85 central and southern neighbourhoods composed a low-risk area for leprosy (RR=0.48, p<0.001).

Figure 3 shows the spatiotemporal patterns of the NCDR of leprosy at the neighbourhood level over time. The observed patterns supported the heterogeneous and peripheral distribution found in the purely spatial analysis. The highest number of neighbourhoods classified as hyperendemic was observed between 2011 and 2013 (*Supplementary materials, file no. 1*). During this period, a spatiotemporal high-risk cluster for leprosy (RR=2.06, p<0.001) was formed in the northern region of the municipality with 27 neighbourhoods. From 2014 onwards, the number of hyperendemic areas decreased (*Supplementary Materials, file no. 1*), but the northern and western regions remained with the highest NCDRs. In 2015, a spatiotemporal high-risk cluster (RR=7.13, p<0.001) composed of four western neighbourhoods was detected. As the number of areas classified as having very high endemicity slightly increased, a spatiotemporal low-risk cluster (RR=0.38, p<0.001) encompassing 86 central and southern neighbourhoods was formed between 2015 and 2017.

Intra-urban differences underlying leprosy spatial distribution

Table 1 summarizes the correlation coefficients between smoothed NCDRs per neighbourhood and demographic, socioeconomic, and structural characteristics. A positive correlation was

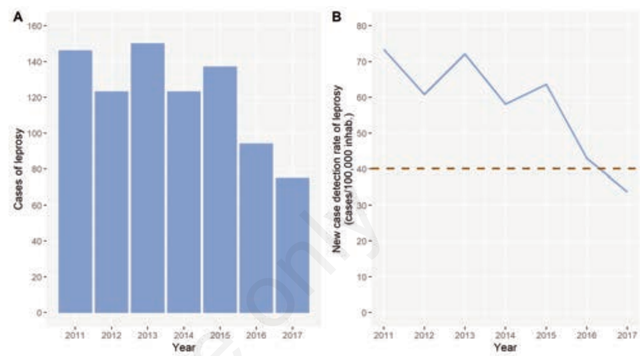

Figure 1. Temporal distribution of leprosy in the urban area of the municipality of Rondonópolis, Mato Grosso, Brazil (2011-2017). A) Annual number of new cases; B) Annual new case detection rate. The dotted black line represents the hyperendemicity threshold defined by the Brazilian Ministry of Health (MoH, 2016).

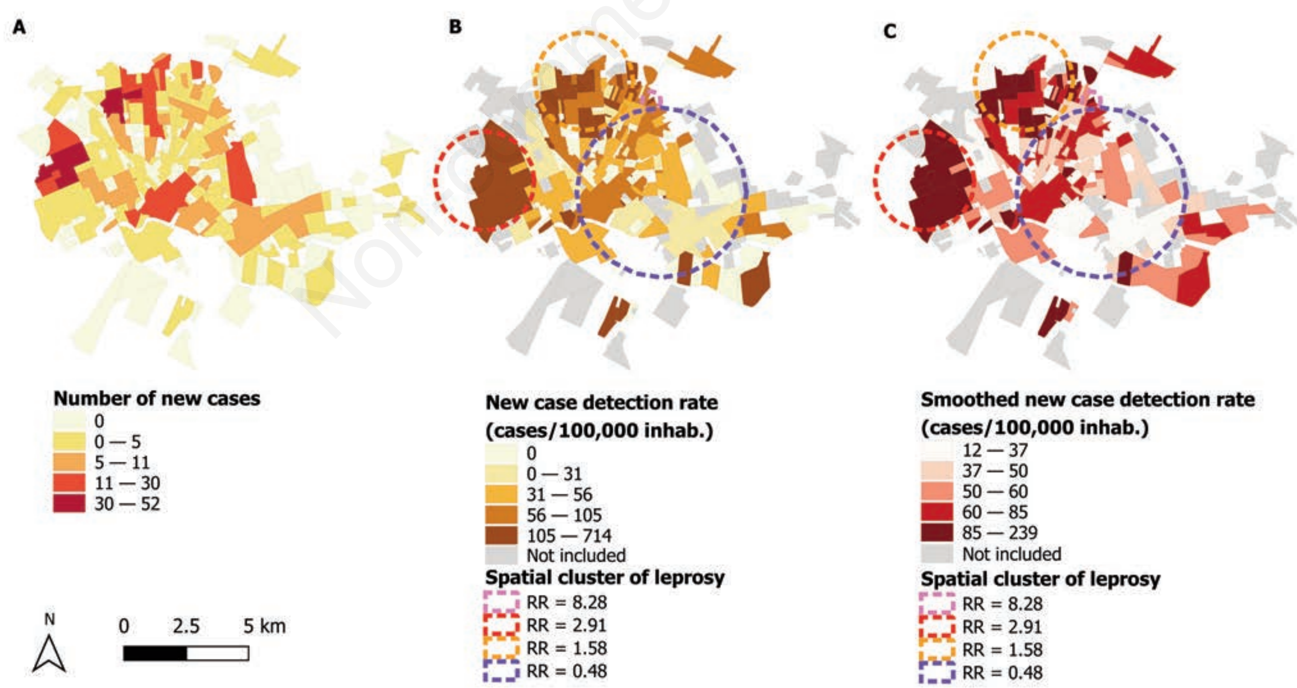

Figure 2. Spatial distribution of leprosy at the neighbourhood level in the urban area of the municipality of Rondonópolis, Mato Grosso, Brazil (2011-2017). A) Absolute number of new cases; B) Crude rates with significant spatial clusters for the disease; C) Smoothed rates with significant spatial clusters for the disease. The dotted circles in B) and C) show spatial clusters detected by spatial scan statistics. In the legends, the upper bounds are included within the intervals. Class intervals in A) were defined using natural breaks and in B) and C) by the quintile distribution of the variables. The grey neighbourhoods were not included in the present analysis.

observed between the smoothed NCDR on the one hand and the percentage of non-white individuals, the mean number of inhabitants per PPH, the percentage of PPHs without income and that of PPHs without bathroom on the other. A negative correlation was found with respect to literacy rate among individuals aged ≥five years, mean monthly nominal income per PPH and percentage of PPHs with sanitary sewage service. Due to multicollinearity, the variable percentage of non-white individuals was not considered for further statistical modelling *(Supplementary Materials, file no. 2*). In the classical OLS model, the smoothed NCDR was negatively associated with the literacy rate among individuals aged five years and older and the mean monthly nominal income per PPH (adjusted R^2=0.199) (Table 2). The regression diagnosis of the OLS model is summarized in *Supplementary Materials, file no. 3.* As the smoothed NCDR presented a certain degree of spatial autocorrelation (*I*=0.1812, p=0.001), we tested global and local spatial modelling. SLM and SEM presented similar results as the OLS modelling, both in terms of coefficients, adjusted R^2 and AIC (Table 2). On the other hand, the GWR model explained more than 30% of the total model variation (adjusted R^2=0.305) and had a lower AIC value (*i.e.* 242.85). Therefore, this model was selected as the most appropriate option.

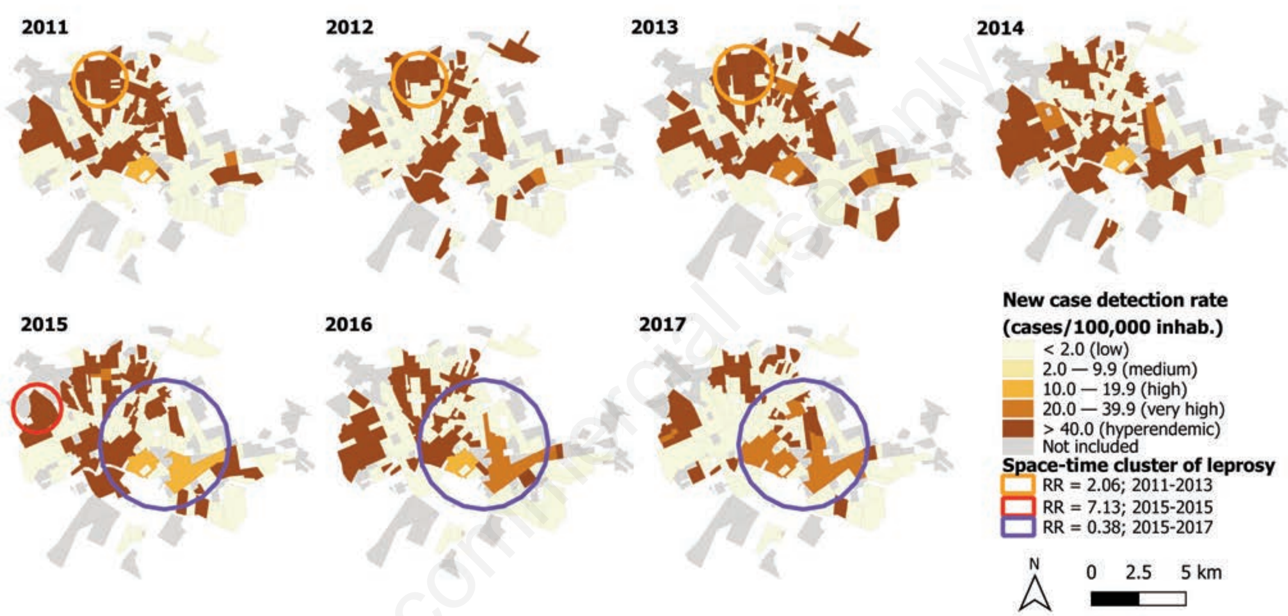

Figure 3. Spatiotemporal distribution of the crude new case detection rates (NCDR) of leprosy at the neighbourhood level in the municipality of Rondonópolis, Mato Grosso, Brazil (2011-2017). Circles represent significant spatiotemporal clusters for the disease detected by spatial scan statistics. Limits represent urban neighbourhoods. The grey areas were not included in the present analysis. In the legends, the upper bounds are included within the intervals. Class intervals were defined using the criteria of the Brazilian Ministry of Health to classify leprosy endemicity based on the annual NCDR (MoH, 2016).

Table 1. Correlation coefficients between the smoothed new case detection rate of leprosy and investigated variables characterizing the urban neighbourhoods of the municipality of Rondonópolis, Mato Grosso, Brazil (2011-2017).

Variable	r	p
% of non-white individuals[a] (% of)	0.3181	<0.001*
Mean number of inhabitants per PPH	0.1687	0.022*
Literacy rate among individuals aged five years and older (%)	-0.4314	<0.001*
Mean monthly nominal income per PPH (in Brazilian minimum wages)[b]	-0.3965	<0.001*
PPHs without income (% of)	0.1069	0.150
PPHs without bathroom (% of)	0.1884	0.011*
PPHs with public electricity supply (% of)	-0.0610	0.412
PPHs with public water supply (% of)	0.0362	0.626
PPHs with public garbage collection (% of)	-0.040	0.583
PPHs with sanitary sewage service (% of)	-0.2535	<0.001*

PPH: private permanent household; [a]Black, mixed and indigenous; [b]Brazilian minimum wage (2010) = US$ 154.4 (R$ 510); *Significant at p<0.05.

The spatial distribution of the variables associated with the smoothed NCDR as well as their respective GWR coefficients are depicted in Figure 4. For a better visualization, we superimposed these results with the identified spatial clusters. The GWR coefficients were estimated at each location for each predictor. They reveal that the influence of the predictor on the model varied considerably across the study area. In general, literacy rate and mean monthly nominal income per PPH appeared as protective factors for leprosy. Neighbourhoods within the low-risk area presented a high literacy rate and high mean monthly nominal income per PPH, whereas those located within high-risk areas had the lowest indicators (Figure 4A and Figure 4B). Low literacy rates had a strong negative impact on the NCDR, the highest among the northern and western neighbourhoods and lower towards the central and southern areas (Figure 4C). The mean monthly nominal income per PPH showed a negative relationship with the NCDR in all evaluated areas but this was more pronounced in the western areas (Figure 4D).

Discussion

This study demonstrated that Rondonópolis remains as a priority area for leprosy control in central-western Brazil. Although the NCDR decreased in the last three years of the period (2011-2017) evaluated, the municipality was still classified as very high endemic for leprosy according to the stratification criteria (MoH, 2016). This reduction should be interpreted with caution, as it may be linked to operational challenges of health services in detecting new cases, as already suggested in other Brazilian endemic areas (Souza *et al*., 2020). Thus, spatial analysis may be a useful tool to improve leprosy surveillance and control as argued by Silva *et al*., 2017a. Although the new cases of leprosy were widely spread throughout the urban area, we observed a certain degree of spatial heterogeneity when using GIS-based methods to evaluate the spatial patterns of the NCDR. As modelled by GWR, this spatial heterogeneity seems to have been shaped by intra-urban differences related to poverty.

In line with our findings, a spatial heterogeneity of leprosy distribution has been demonstrated in endemic areas for the disease worldwide using different spatial scales (Bulstra *et al*., 2021; Machado *et al*., 2022; Monteiro *et al*., 2015). In Rondonópolis, Marciano *et al*. (2018) also reported high-risk clusters for leprosy in the northern and western periphery in a previous timeframe (2000-2010). It is likely that the rapid population growth recently experienced by the municipality has led to an unplanned urbanization process in the peripheral regions (Luz *et al*., 2021). Taken together, these events increased social inequalities and intra-urban differences with the formation of highly vulnerable areas, especially in the periphery, as already discussed for other Brazilian municipalities (Kerr-Pontes *et al*. 2004; Monteiro *et al*., 2015; Ramos *et al*., 2020). In peripheral neighbourhoods, unfavourable socioeconomic conditions may have favoured the idea that local transmission chain of many infectious diseases, including leprosy, are mainly due to an inadequate housing system, lack of hygiene, crowding, and nutritional deficit of the population (Kerr-Pontes *et al*. 2004). In fact, hotspots for other infectious diseases have already been described in the northern and western outskirts of Rondonópolis (Carvalho *et al*., 2018; Luz *et al*., 2021). In contrast, the remarkably better socioeconomic conditions of central and southern neighbourhoods supposedly play a protective role with respect to new cases of leprosy.

The results of the multivariate spatial modelling support the aforementioned assumptions. The GWR model was selected as the most appropriate option to describe the heterogeneous relationship between leprosy occurrence and urban characteristics. This suggests that spatial non-stationarity should be taken into account when analyzing leprosy distribution (Brunsdon *et al*., 1996). Given the existence of intra-urban differences and spatial correlation, local models may better reflect reality (Duarte-Cunha *et al*., 2016). We found that socioeconomic indicators of disadvantage (namely, lower literacy rates and lower mean income) were locally associated with a higher smoothed NCDR of leprosy, especially in the high-risk western and northern neighbourhoods. These variables are related to deprivation and poor living conditions, which reaffirms leprosy as a neglected tropical disease (Souza *et al*., 2018; WHO, 2020b). Notably, in the univariate analysis, significant and plausible correlations were also found among the NCDR and other variables proxy of poverty (*e.g.*, percentage of non-white individuals, crowding and sanitary sewage coverage). In particular, studies have demonstrated the role of literacy/education and income as risk factors for leprosy at both individual (Nery *et al*., 2019) and ecological (Ramos *et al*., 2020) levels. Low education may impact leprosy risk by decreasing better work conditions, health knowledge and health behaviours (Pescarini *et al*., 2018). Low income is frequently linked to social vulnerability and less access to health services (Monteiro *et al*., 2017; Leano *et al*., 2019). Consequently, early diagnosis of leprosy followed by treatment becomes more difficult among the poorest populations (Leano *et al*., 2019) as

Table 2. Modelling of the natural logarithm of the smoothed new case detection rate of leprosy in urban neighbourhoods of the municipality of Rondonópolis, Mato Grosso, Brazil (2011-2017).

Variable	Classical OLS			SLM			SEM		
	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
Mean monthly nominal income per PPH (log)	-0.250	0.111	<0.001*	-0.240	0.112	0.032*	-0.251	0.110	0.023*
Literacy rate among individuals aged ≥five years	-3.507	1.029	<0.001*	-3.493	1.020	<0.001*	3.509	1.020	<0.001*
Intercept	9.104	0.743	0.026*	8.876	0.910	<0.001*	9.111	0.736	<0.001*
Rho		-			0.034			-	
Lambda		-			-			-0.005	
Adjusted R^2		0.199			0.237			0.237	
AIC		263.69			265.56			265.69	

OLS, ordinary least squares; SLM, spatial lag model; SEM, spatial error model; PPH, private permanent household; SE, standard error; Rho, spatial autoregressive parameter; Lambda, spatial error coefficient; AIC, Akaike information criterion; *Significant at p<0.05.

already demonstrated in Brazil (Andrade *et al*., 2019).

Given the geographic and temporal persistence of high-risk areas for leprosy in the northern and western outskirts of Rondonópolis, public health authorities and decision-makers should urgently target these areas for interventions. Strengthening of primary health care teams is highly recommended, as these professionals are crucial for the active screening of new cases in the community, patient follow-up, and contact tracing. To increase coverage and effectiveness, these actions can be integrated with those already adopted for other endemic diseases in the area, such as cutaneous leishmaniasis (Carvalho *et al*., 2021a). In addition, health education activities focused on awareness and reduction of leprosy-related stigma, as well as early disease suspicion should be performed within the community, particularly involving knowledge multipliers (*e.g*., local community leaders and school children).

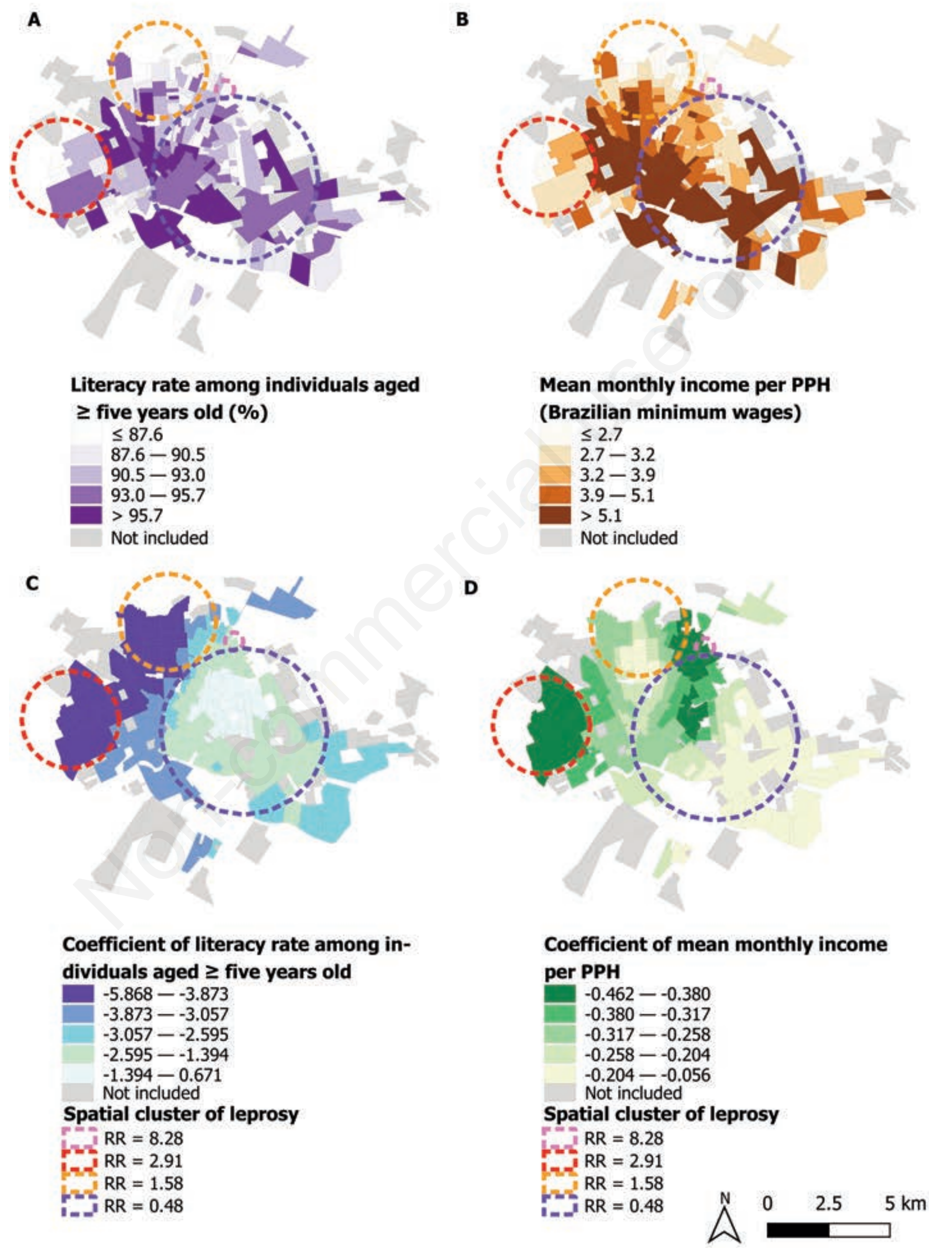

Figure 4. Socioeconomic variables associated with leprosy spatial distribution at the neighbourhood level in the municipality of Rondonópolis, Mato Grosso, Brazil (2011-2017). A) Literacy rate among individuals aged five years and older; B) Mean monthly nominal income per private permanent household (PPH); C) and D) Geographic weighted regression model and β parameters for smoothed new case detection rates of leprosy and covariates. All results were superimposed with significant spatial clusters for the disease (dotted circles) detected by spatial scan statistics. Limits represent urban neighbourhoods. The grey areas were not included in the present analysis. In the legends, the upper bounds are included within the class intervals that were defined using the quintile distribution of the variables.

In addition to classical diagnostic and curative measures, our findings strongly reinforce that leprosy control programs should also address social determinants and integrative public policies aimed at reducing social inequalities in endemic areas (Leano *et al*., 2019; Pescarini *et al*., 2018). This may be achieved by improving living conditions, social inclusion, wealth distribution, work and study opportunities, and wide access to health services (Freitas *et al*., 2017; Ramos *et al*., 2020). Indeed, the positive impact of cash transfer programmes (Nery *et al*., 2014) and strengthening of health services (Barbieri *et al*., 2016) on reducing the NCDR of leprosy is already evident.

This study highlighted relevant aspects related to the occurrence of leprosy at the neighbourhood level, which could not be revealed by investigating individual attributes. Our findings can be useful to guide surveillance and control measures focused on reducing the occurrence of leprosy in Brazilian municipalities with high endemicity for the disease, as Rondonópolis shares similar demographic characteristics with other urban areas in the country (Assis *et al*., 2020; Ramos *et al*., 2020). Given the instability of resources provision for the control of leprosy already reported in Brazil (Souza *et al.*, 2017), high-risk areas should be targeted as a strategy to enhance the effectiveness of measures aimed at active case detection, accessibility to health services, and decentralization of care. In particular, the decentralization of leprosy care plays a crucial role in timely case detection and management, as it reduces the transmission and disease-related disabilities (Lanza & Lana, 2011). In Brazil, this can be achieved with the Family Health Strategy, which is a national program based on prevention, promotion, and person-centred health care through integration of a multidisciplinary team (Carvalho *et al*., 2021b). In parallel, policies to reduce socioeconomic inequalities and to improve living conditions in Brazilian municipalities should be prioritized to decrease intra-urban differences and, consequently, the occurrence of leprosy.

The main limitation of our study is related to the use of secondary surveillance data, which may be influenced by non-completeness and unavailability of information. In addition, the neighbourhood population count used to calculate the NCDRs was assumed to be constant over the years. It is likely that fluctuations may have occurred due to the accelerated urbanization process of Rondonópolis. Also, the size and shape of the neighbourhoods vary. It is also noteworthy that ecological studies are prone to ecological fallacy, *i.e.* associations for aggregated data may not be extrapolated to the individual level. Hence, future studies addressing individual risk factors for leprosy are encouraged.

Conclusions

In conclusion, leprosy presented a heterogeneous spatial distribution at the neighbourhood level in the study area, with peripheral neighbourhoods considerably more affected by the disease. This distribution seems to have been shaped by intra-urban differences related to deprivation and poor living conditions. This information should be considered by decision-makers while implementing surveillance measures aimed at leprosy control.

References

Andrade KVF, Silva Nery J, Moreira Pescarini J, Ramond A, de Souza Teles Santos CA, Ichihara MY, Fernandes Penna ML, Brickley EB, Rodrigues LC, Smeeth L, Barreto ML, Martins Pereira S, Oliveira Penna G, 2019. Geographic and socioeconomic factors associated with leprosy treatment default: An analysis from the 100 Million Brazilian Cohort. PLoS Negl Trop Dis 13:e0007714.

Anselin L, Arribas-Bel D, 2013. Spatial fixed effects and spatial dependence in a single cross-section. Pap Reg Sci 92:3-17.

Anselin L, Ibnu S, Youngihn K, 2006. GeoDa: An Introduction to Spatial Data Analysis. Geogr Anal 38:5-22.

Assis IS, Berra TZ, Alves LS, Ramos ACV, Arroyo LH, Dos Santos DT, Arcoverde MAM, Alves JD, de Almeida Crispim J, Pieri FM, Frade MAC, Pinto IC, Nunes C, Arcêncio RA, 2020. Leprosy in urban space, areas of risk for disability and worsening of this health condition in Foz Do Iguaçu, the border region between Brazil, Paraguay and Argentina. BMC Public Health 20:119.

Barbieri RR, Sales AM, Hacker MA, Nery JA, Duppre NC, Machado AM, Moraes MO, Sarno EN, 2016. Impact of a Reference Center on Leprosy Control under a Decentralized Public Health Care Policy in Brazil. PLoS Negl TropDis 10:e0005059.

Barreto ML, Teixeira MG, Bastos FI, Ximenes RA, Barata RB, Rodrigues LC, 2011. Successes and failures in the control of infectious diseases in Brazil: social and environmental context, policies, interventions, and research needs. Lancet 377:1877-1889.

Bratschi MW, Steinmann P, Wickenden A, Gillis TP, 2015. Current knowledge on *Mycobacterium leprae* transmission: a systematic literature review. Lepr Rev 86:142-155.

Breusch TS, Pagan AR, 1979. A simple test for heteroscedasticity and random coefficient variation. Econometrica 47:1287-1294.

Brunsdon C, Fotheringham AS, Charlton ME, 1996. Geographically Weighted Regression: A Method for Exploring Spatial Nonstationarity. Geogr Anal 28:281-298.

Bulstra CA, Blok DJ, Alam K, Butlin CR, Roy JC, Bowers B, Nicholls P, de Vlas SJ, Richardus JH, 2021. Geospatial epidemiology of leprosy in northwest Bangladesh: a 20-year retrospective observational study. Infect Dis Poverty 10:36.

Câmara G, Carvalho MS, Cruz OG, Correa V, 2014. Análise Espacial de Áreas, in: Druck S, Carvalho MS, Câmara G, Monteiro, AVM (Eds), Análise Espacial de Dados Geográficos. Embrapa, 1-44 pp.

Carvalho AG, Alves I, Borges LM, Spessatto LB, Castro LS, Luz JGG, 2021b. Basic knowledge about visceral leishmaniasis before and after educational intervention among primary health care professionals in Midwestern Brazil. Rev Inst Med Trop Sao Paulo 63:e56.

Carvalho AG, Luz JGG, Dias JVL, Tiwari A, Steinmann P, Ignotti E, 2020. Hyperendemicity, heterogeneity and spatial overlap of leprosy and cutaneous leishmaniasis in the southern Amazon region of Brazil. Geospat Health 15:293-301.

Carvalho AG, Luz JGG, Rodrigues LD, Dias JVL, Fontes CJF, 2018.High seroprevalence and peripheral spatial distribution of visceral leishmaniasis among domestic dogs in an emerging urban focus in Central Brazil: a cross-sectional study. Pathog Glob Health 112:29-36.

Carvalho AG, Tiwari A, Luz JGG, Nieboer D, Steinmann P,

Richardus JH, Ignotti E, 2021a. Leprosy and cutaneous leishmaniasis affecting the same individuals: A retrospective cohort analysis in a hyperendemic area in Brazil. PLoS Negl Trop Dis 15:e0010035.
Castro SS, Santos JP, Abreu GB, Oliveira VR, Fernandes LF, 2016. Leprosy incidence, characterization of cases and correlation with household and cases variables of the Brazilian states in 2010. An Bras Dermatol 91:28-33.
Duarte-Cunha M, Almeida AS, Cunha GM, Souza-Santos R, 2016. Geographic weighted regression: applicability to epidemiological studies of leprosy. Rev Soc Bras Med Trop 49:74-82.
Fotheringham AS, Oshan TM, 2016. Geographically weighted regression and multicollinearity: dispelling the myth. J Geogr Syst 18:303-329.
Freitas LRS, Duarte EC, Garcia LP, 2017. Análise da situação epidemiológica da hanseníase em uma área endêmica no Brasil: distribuição espacial dos períodos 2001-2003 e 2010-2012. Rev Bras Epidemiol 20:702-713.
IBGE, 2010. [Censo Demográfico.] Available from: https://sidra.ibge.gov.br/pesquisa/censo-demografico/demografico-2010/universo-caracteristicas-da-populacao-e-dos-domicilios. Accessed: July 15, 2021. [Website in Portuguese].
IBGE, 2022. [Instituto Brasileiro de Geografia e Estatística. Cidades – Panorama – Rondonópolis.] Available from: https://cidades.ibge.gov.br/brasil/mt/rondonopolis/panorama. Accessed: April 27, 2022. [Website in Portuguese].
Jarduli LR, Alves HV, de Souza-Santana FC, Marcos EVC, Pereira AC, Dias-Baptista IMF, Fava VM, Mira MT, Moraes MO, Virmond MCL, Visentainer JEL, 2014. Influence of KIR genes and their HLA ligands in the pathogenesis of leprosy in a hyperendemic population of Rondonópolis, Southern Brazil. BMC Infect Dis 14:438.
Kerr-Pontes LR, Montenegro AC, Barreto ML, Werneck GL, Feldmeier H, 2004. Inequality and leprosy in Northeast Brazil: an ecological study. Int J Epidemiol 33:262-269.
Kulldorff M, Nagarwalla N, 1995. Spatial disease clusters: detection and inference. Stat Med 14:799-810.
Kulldorff M. and Information Management Services, Inc, 2021. SaTScan™ v10.0: Software for the spatial and space-time scan statistics. Available from: www.satscan.org.
Lanza FM, Lana FC, 2011. Decentralization of leprosy control actions in the micro-region of Almenara, State of Minas Gerais. Rev Lat Am Enfermagem 19:187-194.
Leano HAM, Araújo KMDFA, Bueno IC, Niitsuma ENA, Lana FCF, 2019. Socioeconomic factors related to leprosy: an integrative literature review. Rev Bras Enferm 72:1405-1415.
Luz JGG, Dias JVL, Carvalho AG, Piza PA, Chávez-Pavoni JH, Bulstra C, Coffeng LE, Fontes CJF, 2021. Human visceral leishmaniasis in Central-Western Brazil: Spatial patterns and its correlation with socioeconomic aspects, environmental indices and canine infection. Acta Trop 221:105965.
Machado LMG, Dos Santos ES, Cavaliero A, Steinmann P, Ignotti E, 2022. Spatio-temporal analysis of leprosy risks in a municipality in the state of Mato Grosso-Brazilian Amazon: results from the leprosy post-exposure prophylaxis program in Brazil. Infect Dis Poverty 11:21.
Marciano LHSC, Belone AFF, Rosa PS, Coelho NMB, Ghidella CC, Nardi SMT, Miranda WC, Barrozo LV, Lastória JC, 2018. Epidemiological and geographical characterization of leprosy in a Brazilian hyperendemic municipality. Cad Saude Publica 34:e00197216.
Marshall RJ, 1991. Mapping disease and mortality rates using empirical Bayes estimators. J R Stat Soc Ser C Appl Stat 40:283-94 pp.
Miguel CB, da Mota PB, Afonso BO, Agostinho F, Cazzaniga RA, de Abreu MCM, Oliveira CJF, Rodrigues WF, 2021. Leprosy morbidity and mortality in Brazil: 2008-2018. Braz J Infect Dis 25:101638.
Ministry of Health (MoH), 2016. [Diretrizes para vigilância, atenção e eliminação da Hanseníase como problema de saúde pública: manual técnico-operacional.] Available from: http://portal.saude.pe.gov.br/sites/portal.saude.pe.gov.br/files/diretrizes_para_._eliminacao_hanseniase_-_manual_-_3fev16_isbn_nucom_final_2.pdf. Accessed: April 15, 2022. [Website in Portuguese].
MoH, 2021. [BoletimEpidemiológico – Hanseníase 2021.] Available from:http://www.aids.gov.br/system/tdf/pub/2016/67493/boletim_hanseniase_internet_.pdf?file=1&type=node&id=67493&force=1. Accessed: April 15, 2021.[Website in Portuguese].
MoH, 2023. [SINAN – Sistema de Informação de Agravos de Notificação] Available from: http://portalsinan.saude.gov.br/o-sinan. Accessed: August 28, 2023. [Website in Portuguese].
Mollalo A, Vahedi B, Rivera KM, 2020. GIS-based spatial modeling of COVID-19 incidence rate in the continental United States. Sci Total Environ 728:138884.
Monteiro CN, Beenackers MA, Goldbaum M, Barros MBA, Gianini RJ, Cesar CLG, Mackenbach JP, 2017. Use, access, and equity in health care services in São Paulo, Brazil. Cad Saude Publica 33:e00078015.
Monteiro LD, Martins-Melo FR, Brito AL, Alencar CH, Heukelbach J, 2015. Spatial patterns of leprosy in a hyperendemic state in Northern Brazil, 2001-2012. Rev Saude Publica 49:84.
Nery JS, Pereira SM, Rasella D, Penna ML, Aquino R, Rodrigues LC, Barreto ML, Penna GO, 2014.Effect of the Brazilian conditional cash transfer and primary health care programs on the new case detection rate of leprosy. PLoS Negl Trop Dis 8:e3357.
Nery JS, Ramond A, Pescarini JM, Alves A, Strina A, Ichihara MY, Penna MLF, Smeeth L, Rodrigues LC, Barreto ML, Brickley EB, Penna GO, 2019. Socioeconomic determinants of leprosy new case detection in the 100 Million Brazilian Cohort: a population-based linkage study. Lancet Glob Health 7:e1226-36.
Pescarini JM, Strina A, Nery JS, Skalinski LM, Andrade KVF, Penna MLF, Brickley EB, Rodrigues LC, Barreto ML, Penna GO, 2018. Socioeconomic risk markers of leprosy in high-burden countries: A systematic review and meta-analysis. PLoS Negl Trop Dis 12:e0006622.
Pinto GF, Nicácio RAR, Oliveira FRA, Oliveira IA, Alves RJR, Santos DADS, Goulart LS, 2021. Factors associated to quality of life in patients with leprosy. Einstein (Sao Paulo) 19:eAO5936.
QGIS, 2019. Development Team. QGIS Geographic Information System. Open Source Geospatial Foundation Project. Available from: http://qgis.osgeo.org.
R Studio Team, 2021. R Studio: Integrated Development Environment for R. R Studio, PBC, Boston, MA. Available from: http://www.rstudio.com/.
Ramos ACV, Neto MS, Arroyo LH, Yamamura M, Assis IS, Alves JD, Marcos Augusto Moraes Arcoverde, Alves LS, Berra TZ, Martoreli Júnior JF, Pieri FM, Arcêncio RA, 2020. Magnitude

of social determinants in high risk areas of leprosy in a hyper-endemic city of northeastern Brazil: An ecological study. Lepr Rev 91:41-55.

Rodrigues RN, Leano HAM, Bueno IC, Araújo KMDFA, Lana FCF, 2020. High-risk areas of leprosy in Brazil between 2001-2015. Rev Bras Enferm 73:e20180583.

Shapiro SS, Wilk MB, 1965. An analysis of variance test for normality (complete samples). Biometrika 52:591-611.

Silva CLM, Fonseca SC, Kawa H, Palmer DOQ, 2017a. Spatial distribution of leprosy in Brazil: a literature review. Rev Soc Bras Med Trop 50:439-449.

Silva EA, Rosa PS, Belone AFF, Coelho NMB, Ura S, Tomimori J, 2017b. Serodiagnosis of leprosy and follow-up of household contacts using a commercial rapid test containing ND-O/LID-1 antigens. Lepr Rev 88:174-183.

Souza EA, Ferreira AF, Boigny RN, Alencar CH, Heukelbach J, Martins-Melo FR, Barbosa JC, Ramos AN Jr, 2018. Leprosy and gender in Brazil: trends in an endemic area of the Northeast region, 2001-2014. Rev Saude Publica 52:20.

Souza EA, Heukelbach J, Oliveira MLW, Ferreira AF, Sena Neto AS, Raposo MT, Ramos Jr NA, 2020. Low performance of operational indicators for leprosy control in the state of Bahia: spatiotemporal patterns, 2001–2014. Rev Bras Epidemiol 23:e200019.

Souza MF, Vanderlei LCM, Frias PG, 2017. Assessment of the implementation of the Leprosy Control Program in Camaragibe, Pernambuco State, Brazil. Epidemiol Serv Saude 26:817-834.

WHO, 2020a. Weekly Epidemiological Record. World Health Organization. Available from: https://apps.who.int/iris/handle/10665/334140.

WHO, 2020b. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. World Health Organization. Available from: https://apps.who.int/iris/rest/bitstreams/1326801/retrieve.

Online Supplementary Materials

File 1. Percentage distribution of the urban neighbourhoods of the municipality of Rondonópolis, Mato Grosso, Brazil, according to the magnitude of leprosy endemicity using the annual new case detection rate as recommended by the Brazilian Ministry of Health (Brasil, 2016).
File 2. Correlation matrix between the smoothed new case detection rate (NCDR) of leprosy and demographic, socioeconomic and structural characteristics of the urban neighbourhoods of the municipality of Rondonópolis, Mato Grosso, Brazil (2011-2017).
File 3. Regression diagnosis of the ordinary least squares model.