BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023420
Article Type:	Research
Date Submitted by the Author:	08-Apr-2018
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Keywords:	Leprosy, Children, Epidemiology < INFECTIOUS DISEASES, Spatial analysis

Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in Endemic Area of Northeast Brazil

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ABSTRACT

Objective: This study aimed to analyze the clinical and epidemiological indicators and the spatial distribution of leprosy in patients under 15 years old in an endemic area of Northeast Brazil.

Design: Regional surveillance study of all reported cases.

Setting: State of Sergipe, endemic area of Northeast Brazil.

Methods: An ecological and time series study was conducted, based on secondary data reported by the Brazilian Information System on Notifiable Diseases (SINAN) for leprosy cases diagnosed in Sergipe state (2002-2015). We performed spatial analysis by Kernel estimator and Moran index.

Results: The incidence rate was reduced from 6.29 to 3.78 cases per 100,000 inhabitants in 2002 and 2015, respectively. However, Sergipe was still classified as highly endemicity in 2015. The mean number of household contacts (HHC) examined was significantly lower than those registered. Clinical data indicated that 21.4% of the patients developed leprosy reactions, and 31.3% presented with some physical disability in the multibacillary (MB) groups. Patients diagnosed by exam within the HHC presented better indicators, such as lower percentage of leprosy reaction and physical disability. Spatial analysis showed the most risk areas distributed on the northeast and cities around the capital, Aracaju.

Conclusion: The data indicate that there is a persistence of active *M. leprae* transmission and a delay in disease detection, following a pattern of high endemicity in many municipalities. The early detection by household contacts examination is important not only to stop transmission but also to detect the cases in a less severe state.

Keywords: Leprosy; Children; Epidemiology; Spatial analysis.

Strengths and limitations of this study

- It is a regional surveillance study including all notified cases. It was conducted using secondary data reported by SINAN and this source of date can present under notification cases and datasets missing.
- This is the first summary of leprosy cases in patients under 15 years old in Sergipe state, Northeast Brazil.
- Our study also addresses the distribution of the disease in the territory. We mapped areas of higher prevalence of leprosy in the general population, in children under 15 years and of physical disability using geoprocessing tools.
- We compared also the leprosy patient detection mode and how it affects the *M. leprae* transmission, the disease severity and the occurrence of leprosy reactions and physical disabilities.

INTRODUCTION

Leprosy is a chronic infectious disease caused by infection with *Mycobacterium leprae* [1]. This pathogen exhibits tissue tropism for phagocytes in the skin and Schwann cells within peripheral nerves and it presents a long incubation time (from 2 to 7 years) [2,3]. The disease can manifest across a broad spectrum of symptoms and the diagnosis is made based on the clinical signs (cutaneous lesions with altered sensitivity and neurological lesions). Patients are then classified as multibacillary (MB) and paucibacillary (PB) for treatment purposes, according to criteria accepted by Brazilian Ministry of Health (BMH) and International Leprosy Association (ILA) [1,2,4–7].

Despite control efforts including the widespread use of multidrug therapy (MDT), and the stabilization of the reported new case detection rate in the last few years, leprosy remains endemic in many developing countries [3–6,8–11]. In 2014, the World Health Organization (WHO) reported 213.899 new leprosy cases in 121 countries or territories [4]. Brazil ranks as the second most burdened country in the world concerning number of new cases (31,064 in 2014) and has by far the highest number of cases reported in Americas [4,12,13]. Within Brazil, the highest prevalence has been reported in the North, Northeast and Midwest regions [8,9]. In 2013, 2,439 new cases were diagnosed in children under 15 years old in Brazil, yielding a detection rate of 5.03 per 100,000 inhabitants [4].

Studies have demonstrated that leprosy presents higher incidence in population with: low educational degree, precarious health services and domiciliary infrastructure settlements, and reduced investment in prevention and control [14–16]. Moreover,

the high incidence rate in children under 15 years is important to indicate there is early exposure of the population to the bacillus, that is associated to elevated prevalence in general population, being a good indicator of a high transmission and bad quality of the control programs [10,12,17–20].

Recently, studies mapping the occurrence of infectious diseases according to their spatial distribution using "Geographic Information Systems (GIS)" have provided important information for public health programs, revealing areas of priority for interventions programs to more efficiently plan and implement control measures [2,9,16,21–23]. The use of GIS in leprosy may allow the identification of spatial-temporal distributions and profile of incidence in defined geographical areas, this potentially contributing to the effectiveness of interventions.

Despite breakthroughs in the epidemiological of leprosy, further improvements in understanding of the disease dynamics in different regions is important for the support of health services as a means for leprosy control. Spatial analyzes studies can provide important understanding of the transmission patterns of *M. leprae* and allow the identification of risk factors [21,23]. The aim of this study was to describe the various clinical and epidemiological indicators, as well as to analyze the spatial distribution, of leprosy cases in patients under 15 years old in an endemic area of Northeast Brazil.

METHODS

Patient and Public Involvement and Study Design

An ecological and time series epidemiological study was conducted, based on data reported by SINAN (Information System on Notifiable Diseases), database of the Secretariat of Health, Sergipe. Sergipe is located on the coast of Northeast Brazil. The State has 75 municipalities and the capital is Aracaju. It has a population of 2,068,017 inhabitants and an area of 21,910,354km², equivalent to 0.26% of the national territory [16]. Population data were obtained from the IBGE (Brazilian Institute of Geography and Statistics), based on population estimates for the intercensus years (2002 - 2015). The historical (from 2002 to 2015) reporting of leprosy cases in children under 15 years old was analyzed. The incidence of leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8].

The clinical and epidemiologic indicators collected by Investigation and Notification Form, as recommended by SINAN, were: gender, age, ethnicity, operational classification (PB and MB), clinical form [according to the more refined Ridley-Jopling classification [24,25], based on histopathological analyses: indeterminate leprosy (IL), true tuberculoid (TT), borderline leprosy (BL) and lepromatous leprosy (LL)], leprosy reaction (LR), number of affected nerves, degree of physical disabilities, number of household contacts (HHC) registered and examined, and the patient detection mode.

The parameters adopted by BMH and ILA were followed for interpreting the incidence rate of leprosy in patients under 15 years old. As such, this is classified as: low (<0.50

cases per 100,000 inhabitants); medium (0.50 to 2.49); high (2.50 to 4.99); very high (5.00 to 9.99) and hyperendemic (≥10.00) [4].

Spatial analysis

Thematic maps were constructed in each municipality for the period examined according to the leprosy incidence rate in patients under 15 years old and in general population, and for patients presenting with physical disability (incapacity degree 1 or 2). The kernel intensity estimator was used by smoothing the statistically generated surface density for the visual detection of hot spots, indicating cases agglomeration in a spatial distribution and a continuous surface from point data [16,21].

We performed either spatial autocorrelation analysis between disease detection rates for each group. The Moran Global Index (MGI)[26] was calculated to identify clusters with risks for disease occurrence. We construct a spatial proximity matrix obtained by the contiguity of autocorrelation. The MGI was calculated as follows:

(Moran Global Index Mathematical Equation 1)

$$I = \frac{[(n \sum_i^n \sum_j^n \omega_{ij} (y_i - \bar{y}) (y_j - \bar{y})]}{[\sum_i^n (y_i - \bar{y})^2 \sum_i^n \sum_j^n \omega_{ij}]} \quad (1)$$

ωij is a contiguity matrix element (ω); Yi is the incidence rate of municipality i; Yj is the incidence rate of municipality j; $\bar{Y}$ is the mean of sample and the symbol n represents the total number of municipalities [26].

The MGI provides a general grouping measure and it is possible to know if there are significant differences between the analyzed areas. However, it does not indicate the

clusters localization. To do that, we performed the Moran Local Index diagram [26] to build maps and identify the areas with spatial dependence (Local Index of Spatial Association - LISA) of the annual detection means, as follows:

(Local Index of Spatial Association Mathematical Equation 2)

$$I = \frac{n[(Z_i \Sigma_j^n \omega_{ij} Z_j)}{(\Sigma_j^n Z_j^2)}$$

Zi = yi - ȳ; Zi = yi - ȳ; Ωij is a contiguous matrix element ω; Yi is the incidence rate of municipality i; Yi is the incidence rate of municipality j; Ȳ is the sample mean and the symbol n represents the total number of cities [26]. The Moran Map was used to indicate the clusters and their relation with the neighbors. This analysis verifies the existence of spatial dependence and risk patterns: Q1 (high/high) and Q2 (Low/Low), which indicate municipalities with similar values between their neighbors and Q3 (high/low) and Q4 (low/high) for municipalities with different values between their neighbors and no spatial association [26]. Both Moran Index and Kernel maps were constructed using TerraView software 4.2.2.

Statistical analysis

Demographic and clinical data were compared across the different subgroups and according to operational classification and the patient detection mode. Percentage, mean and standard deviation of the groups were calculated. D'Agostino and Pearson tests were applied to analyze the normal distribution of data. Statistical differences between the groups were determined by Mann-Whitney and Kruskall-Wallis tests. All analysis was performed using SPSS Statistics, version 24.0. We assessed also the

tendency analyze by linear regression, where y (leprosy annual detection) = α + β_1(year). Results were considered statistically different when *p*-values < 0.05 were obtained.

Ethical Considerations

For conducting this study, authorization was previously requested from Coordination of Epidemiological Surveillance, Sergipe state. This project involved research on human subjects and was approved by the Ethics and Research Committee of the Federal University of Sergipe, CAAE 0152.0.107.000-07.

RESULTS

Trends in reported leprosy incidence among children

The leprosy incidence rate in the general population of Sergipe decreased from 23.08 cases to 16.99 per 100,000 inhabitants between 2002 and 2015 (**Figure 1A**). The occurrence of degree 2 physical disability, however, increased in this period (0.76 in 2002 to 1.2 in 2015, respectively). The incidence of leprosy in children under 15 years old fluctuated, increasing from 2002 (6.29 cases per 100,000 inhabitants) to 2005 (9.82) but then showing a decline to 3.78 in 2015. There was an overall decrease in leprosy incidence in the less than 15 year old group from 2002 to 2015 (*p*-value = 0.002; **Figure 1B**). The composition of leprosy cases according to the operational classification (PB and MB) was relatively stable across this period, with the majority of cases presenting as PB (**Figure 2A**). We also observed the mean number of HHC

registered (4.65 ± 2.79) was slightly, but significantly, higher than the number examined (3.66 ± 3.14; *p*-value < 0.0001; **Figure 2B**).

Demographics of childhood leprosy cases

Next, we evaluated the association among clinical and epidemiological variables according to the leprosy operational classification (patients presenting as PB and MB). Patients presenting as MB or PB were in similar age to (10.5 ± 2.81 and 10.07 ± 3.38, respectively). Despite the extended incubation period of *M. leprae*/leprosy, six cases (1.11%) were reported in children less than one year of age. Of the 538 leprosy cases identified among children under 15 years old the majority were PB [407 (75.7%) PB and 131 (24.3%) MB; **Table 1**]. When stratified on gender, however, the proportion of boys presenting with MB (63.4%) was significantly higher than presenting with PB (48.4%; *p*-value = 0.003). An interesting difference was observed when we calculated the ratio (PM/MB) according the ethnic groups. Among those identified as black, the ratio (43/24) was 1.79. Conversely, the ratio of white was higher 4.88 (88/18; *p*-value = 0.02).

As expected, the occurrence of leprosy reactions was significantly higher in MB (21.4%) than PB (4.9%; *p*-value < 0.0001) patients. The occurrence of degree 2 of physical disability was also higher in MB (4.6%), than in PB patients (0.74%; *p*-value = 0.0001). Consistent with this, we observed that the mean of number of affected nerves was higher in MB (0.5 ± 1.03), than PB (0.19 ± 0.54; *p*-value = 0.04).

Impact of case detection methods on leprosy presentation

We also performed analysis of association among clinical and epidemiological variables according to the leprosy patient detection mode. The patients were grouped in: spontaneous demand (SDem: patients that looked for medical assistance by themselves); forwarded (FW: patients that were forwarded from a primary clinic to a leprosy reference center); examined HHC; and other. We observed that patients detected by the examined HHC method presented lower mean age (9.6 ± 3.38) than those detected by either the SDem (10.54 ± 3.28) or FW methods (10.02 ± 3.15; *p*-value = 0.04; **Table 2**). Interestingly, the percentage of leprosy reaction among the examined HHC group (2.9%; *p*-value = 0.02) was lower than that observed among SDem (7.3%) and FW (13.3%). In addition, degree 2 of physical disability was not observed among patients detected in examined HHC group, while SDem and FW presented 0.43% and 3.8%, respectively (*p*-value = 0.04). Furthermore, patients identified among examined HHC presented with lower numbers of lesions (2.04 ± 2.96; *p*-value = 0.04) than SDem (3.64 ± 6.25) and FW (4.09 ± 8.68). Taken together, these data reinforce the importance of HHC examination for the detection of leprosy patients before advancement to more severe symptoms.

Spatial analyze data

Next, we performed the spatial analysis of leprosy cases in the general population, in patients under 15 years old, and in patients presenting with physical disability (both degree 1 and 2). Moran maps have showed higher risk clusters (Q1 - in red; **Figure 3A-C**) in similar areas when comparing the maps regarding leprosy cases in children under 15 years old, in general population, and patients presenting some physical disability (degree 1 and 2). The higher risk clusters (Q1) were localized in Sergipe state center

and in the metropolitan area around the capital of State. The municipalities with no spatial association (Q3 - in blue) were localized in the Semiarid region, in the northwest area and in the south region.

Similarly, The Kernel estimator, through data interpolation, showed densities (hot spots) of the highest incidence rates located at the northeast and east center regions and in the counties around the state capital (Aracaju city; **Figure 3D-F**). Lower intensity was observed on the western region. Municipalities with intermediate to high incidence values are seen in yellow and red tones of each subfigure. Low incidence areas were reported on west coast municipalities, mostly in smaller counties with small populations.

DISCUSSION

Previous studies have demonstrated that the high leprosy cases detection in patients under 15 years old is a bad parameter for leprosy control program, because it indicates early bacillus transmission from undiagnosed cases [18]. Some authors have speculated either about the risk of vertical/transplacental transmission or through breastfeeding [12].

In Brazil, the highest leprosy incidence rate in children was reported in the North area (11.91 cases per 100,000 inhabitants), followed by Northeast (8.12) [12]. We observed the leprosy incidence rate was reduced in children under 15 years old from 2002 to 2015 in Sergipe state, however considering the parameters adopted by BMH, the state was classified as very high endemicity in 2002, and still as high endemicity in 2015. It

remains also with elevated incidence rate and stationary tendency of degree 2 of physical disability. Those data reinforce either that the transmission is intense at early age, there is lack of an effective public health and the disease control is focused in the MDT [12,18]. A similar study performed at Fortaleza city (Brazil), reported also that although a decreasing has been observed on overall detection rate, the number of new cases in those under 15 years old remains stable [13].

Leprosy reactions and physical disability are the most severe leprosy clinical complications [8,27,28]. In addition, the increase or stability of the prevalence of degree 2 of physical disability indicates persisting late diagnosis [13,28]. The early diagnosis of leprosy is essential to the prevention of deformities, whose repercussions are still more catastrophic in children and adolescents [27]. Our data reported 21.4% children with leprosy reaction (LR) and 31.3% with some physical disability in the MB groups. Furthermore, MB patients presented higher mean of affected nerves. Generally, patients under 15 years old do not use to present LR, but studies have reported a low frequency of LR, varying between 1.36% and 8.33% [27]. Those data reinforce that, although there is a decreasing incidence in leprosy, patients have been exposed to bacillus early in life and diagnosed belatedly and hence they have been also developing into some clinical complications.

We have observed either that the mean of HHC examined was significantly lower than those registered by SINAN. Moreover, leprosy patients detected by exam in HHC presented lower mean of age, affected nerves, number of lesions, occurrence of LR and no physical disability, when compared with those identified by spontaneous

demand or forwarded by others. On the other hand, mostly of patients presenting as degree 2 of physical disability were identified into those forwarded to a leprosy reference center, probably because they started presenting some physical disability. HHC and neighbors are the most important *M. leprae* active sources. The risk of a person developing leprosy is nine times greater among HHC and up to four times greater among contacts with neighbors [12]. Therefore, our data reinforce the importance of leprosy early diagnosis by exam in patients and their household contacts. Besides that, the treatment and the home visits by public health programs, and an efficient health program in schools could represent important actions for the early diagnosis and the reduction of leprosy clinical complications, especially in children.

Spatial analysis of health events aim to identify geographical patterns by maps of risk and to point out areas of higher severity and to facilitate the planning of public health interventions [9]. The Kernel maps showed the spatial dynamic of leprosy, with a heterogeneous geographical pattern and the highest risk areas for leprosy infection. The highest incidence on counties around the Capital can be due there was a leprosarium at the Nossa Senhora do Socorro (a city of the metropolitan area of Aracaju), that has presented elevated detection rate in mostly evaluated years. Moreover, that area presents reference center to leprosy diagnosis and treatment and hence they have several patients forwarded to these leprosy clinics. It can be also associated with weather featuring such as humidity, considering either that counties near to São Francisco River presented also elevated incidence. In the Malawian Karonga district, a positive relationship between the proximity of water and leprosy

incidence was previously reported [5]. Some authors have hypothesized that *M. leprae* survives longer outside of human body in humid compared to dry atmospheres [9,13].

Interestingly, higher risk clusters were identified in similar areas when we analyzed the occurrence of leprosy cases in children, in general population and patients presenting physical disability. It corroborates the hypothesis that the early transmission of *M. leprae* and the occurrence of leprosy in children under 15 years old is directly related to the late diagnosis, which explains the occurrence of patients with degree 2 of physical disability in the same geographic distribution [27].

In summary, our study demonstrated that the leprosy incidence rate has decreased in Sergipe state. However, it is still classified as high endemicity considering the WHO proposed ratios for children under 15 years. Patients detected by exam in collectivity or HHC presented better indicators. Altogether, the epidemiological data and spatial analysis indicate that there is persistence of active transmission of *M. leprae* and later case detection in Sergipe state, increasing the risk of transmission in children. In addition, the spatial analysis brings new advantages to comprehend the leprosy dynamic, and reinforce the superimposed regions of high occurrence areas of patients presenting degree 2 of physical disability and cases in children lower than 15 years, and highlights the need to strengthen effective disease control measures, mainly in primary health care.

Acknowledgments The authors would like to thank the Manager of the Nucleus of endemic/Division of Epidemiological Surveillance - [Divisão de Vigilância Epidemiológica (DIVEP)]/ Secretariat of Health of the Sergipe state (SES) for providing information.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Contributors The project was suggested by MS, AS and AJ. The manuscript was written by MS. All authors contributed to refining the idea, analyzing the data, revising the manuscript and have agreed the final version.

Competing interests The authors declare that they have no conflicts of interest.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Table 1. Association of demographic and clinical data according to the operational classification of leprosy (PB and MB) in children under 15 years in Sergipe state, Brazil (2002-2015).

Variables	Operational Classification		
	PB (n = 407)	MB (n = 131)	*p*-value
Age mean ± SD	10.07 ± 3.38	10.5 ± 2.81	*0.46
Gender n (%)			
Male	197 (48.4)	83 (63.4)	+0.003
Ethnicity n (%)			
White	88 (21.6)	18 (13.7)	#0.02
Black	43 (10.5)	24 (18.3)	
Brown	251 (61.7)	78 (59.5)	
Indian	4 (0.9)	3 (2.3)	
Leprosy reaction n (%)	20 (4.9)	28 (21.4)	+<0.0001
Physical Disability Degree n (%)			
0	337 (82.8)	90 (68.7)	#0.0001
1	26 (6.4)	18 (13.7)	
2	3 (0.74)	6 (4.6)	
Number of affected nerves (mean ± SD)	0.19 ± 0.54	0.5 ± 1.03	*0.04
Number of Lesions (mean ± SD)	1.61 ± 1.14	9.92 ± 12.03	*<0.0001
HHC registered (mean ± SD)	4.6 ± 2.71	4.85 ± 3.04	*0.14
HHC examined (mean ± SD)	3.54 ± 3.04	4.05 ± 3.44	

*Mann-Whitney test; +Fisher's exact test; #Chi-square test. SD = Standard Deviation. We missed data in some variables.

Table 2. Demographic and clinical aspects accordingly to the detection mode of leprosy cases in children under 15 years in Sergipe state, Brazil (2002-2015).

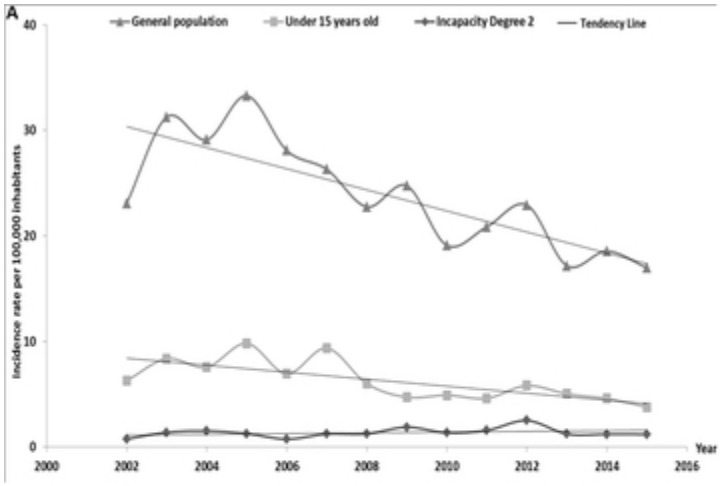
Variables	Patient detection mode				
	Spontaneous demand (n = 234)	Forwarding (n = 210)	Examined HHC (n = 69)	Other (n = 25)	*p*-value
Age mean ± SD	10.54 ± 3.28	10.02 ± 3.15	9.6 ± 3.38	9.6 ± 3.22	*0.04
Gender n (%)					
Male	123 (52.6)	110 (52.4)	38 (55.1)	09 (36)	#0.41
Leprosy reaction n (%)	17 (7.3)	28 (13.3)	2 (2.9)	1 (4.0)	#0.02
Physical disability degree n (%)					
0	199 (85.1)	150 (71.4)	55 (79.7)	18 (72)	#0.04
1	17 (7.3)	21 (10)	5 (7.2)	1 (4.0)	
2	1 (0.43)	08 (3.8)	0 (0.0)	0 (0.0)	
Number of affected nerves (mean ± SD)	0.24 ± 0.67	0.34 ± 0.81	0.06 ± 0.25	0.25 ± 0.5	*0.48
Number of lesion (mean ± SD)	3.64 ± 6.25	4.09 ± 8.68	2.04 ± 2.96	4 ± 5.2	*0.04
HHC registered (mean ± SD)	4.57 ± 2.53	4.59 ± 2.74	5.57 ± 3.81	3.45 ± 1.96	*0.04
HHC examined (mean ± SD)	3.71 ± 3.02	3.02 ± 2.98	4.64 ± 4.06	2.04 ± 1.77	*0.01

*Kruskal-Wallis test; #Chi-square test. SD = Standard Deviation. We missed data in some variables.

Figure 1. Leprosy incidence rates in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (▲), in patients under 15 years old (■), degree 2 of physical disability (♦) and the tendency line. B) Tendency analyzes description. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Proportion of leprosy cases according to the clinical operational classification (Paucibacilary - PB (■) and Multibacilary – MB (♦) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. * Mann-Whitney test.

Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).



B

General Population

Regression Model	R^2	Tendency	*p* value	CI (95%)
y = -0.999x + 2030	0.648	Decreasing	*0.0005	[-1.46 to -0.53]

Under 15 Years Old

Regression Model	R^2	Tendency	*p* value	CI (95%)
y = -0.332x + 673.6	0.539	Decreasing	*0.002	[-0.52 to -0.13]

Incapacity Degree 2

Regression Model	R^2	Tendency	*p* value	CI (95%)
y = 0.033x - 65.29	0.1	Stationary	0.27	[-0.02 to 0.09]

Figure 1. Leprosy incidence rates in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (☐), in patients under 15 years old (☐), degree 2 of physical disability (☐) and the tendency line. B) Tendency analyzes description. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

30x32mm (300 x 300 DPI)

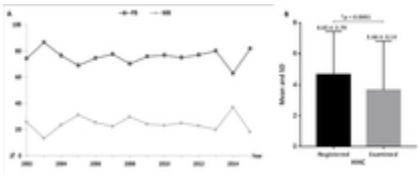


Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Proportion of leprosy cases according to the clinical operational classification (Paucibacilary - PB (☐) and Multibacilary – MB (☐) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. * Mann-Whitney test.

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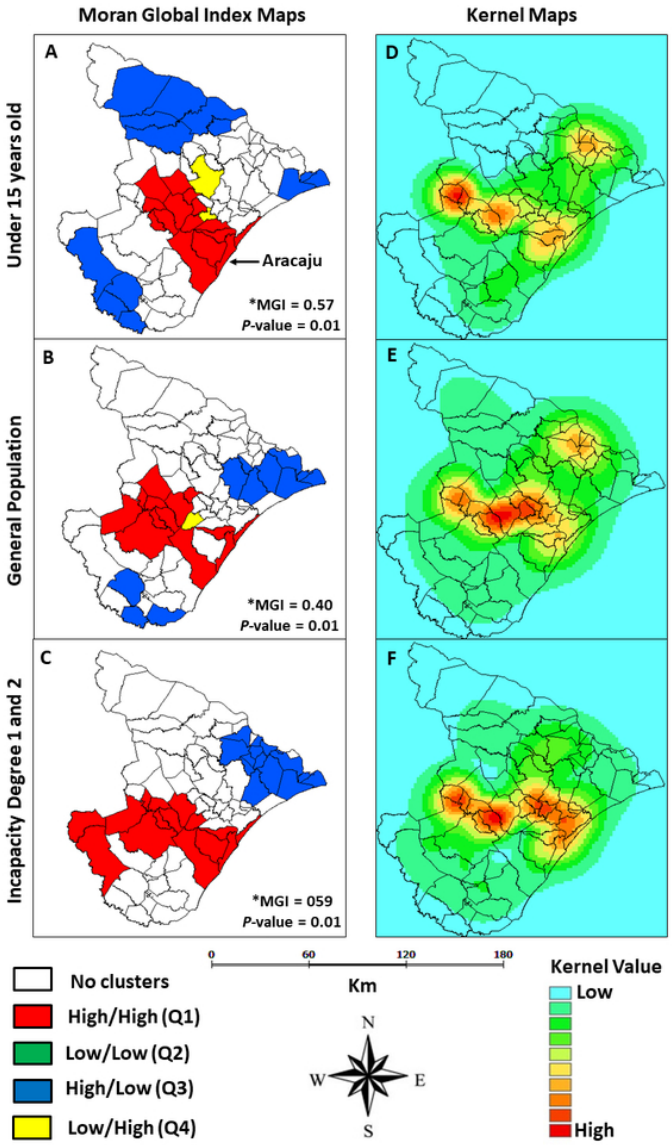

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64x85mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	01
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	02
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	04-05
Objectives	3	State specific objectives, including any prespecified hypotheses	05
Methods			
Study design	4	Present key elements of study design early in the paper	06
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	06
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	06
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	06
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	06-07
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	06
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	06-08
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	08-09
		(*b*) Describe any methods used to examine subgroups and interactions	08-09
		(*c*) Explain how missing data were addressed	08-09
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	08-09
		(*e*) Describe any sensitivity analyses	08-09
Results			08-09

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	09
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	09-10
		(b) Indicate number of participants with missing data for each variable of interest	--
Outcome data	15*	Report numbers of outcome events or summary measures	09-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	--
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	09-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023420.R1
Article Type:	Research
Date Submitted by the Author:	06-Feb-2019
Complete List of Authors:	Santos, Márcio; Universidade Federal de Sergipe, Health Education; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Santos, Allan; Universidade Federal de Sergipe, Nursing Barreto, Aline; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Souza, Mariana; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Goes, Marco; Universidade Federal de Sergipe, Medicine Barreto Alves, Jose Antonio; Universidade Federal de Sergipe, Nursing Barreto, Ikaro; Universidade Federal Rural de Pernambuco, Programa de Pos-Graduacao em Biometria e Estatistica Aplicada Silva, José-Rodrigo; Universidade Federal de Sergipe, Statistics and Actuarial Sciences Oliveira, Daniela; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Araújo, Karina; Universidade Federal de Sergipe, Morphology Duthie, Malcolm; Infectious Diseases Research Institute Jesus, Amélia; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology; Universidade Federal de Sergipe, Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Public health
Keywords:	Leprosy, Children, Epidemiology < INFECTIOUS DISEASES, Spatial analysis

Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

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ABSTRACT

Objective: This study aimed to analyze the clinical and epidemiological indicators, temporal trends and the spatial distribution of leprosy in patients under 15 years old in an endemic area of Northeast Brazil.

Design: Regional surveillance study of all reported cases.

Setting: State of Sergipe, endemic area of Northeast Brazil.

Methods: An ecological and time series study was conducted, based on secondary data reported by the Brazilian Information System on Notifiable Diseases (SINAN) for leprosy cases diagnosed in Sergipe state (2002-2015). The analysis of temporal trends was performed using the Joinpoint Regression Program through Poisson regression. We performed spatial analysis by Kernel estimator and Moran index.

Results: The incidence rate was reduced from 6.29 to 3.78 cases per 100,000 inhabitants in 2002 and 2015, respectively. However, Sergipe was still classified as highly endemicity in 2015. The mean number of household contacts (HHC) examined was significantly lower than those registered. Clinical data indicated that 21.4% of the patients developed leprosy reactions, and 31.3% presented with some physical disability in the multibacillary (MB) groups. Patients diagnosed by exam within the HHC presented better indicators, such as lower percentage of leprosy reaction and physical disability. Spatial analysis showed the most risk areas distributed on the northeast and cities around the capital, Aracaju.

Conclusion: The data indicate that there is a persistence of active *M. leprae* transmission and a delay in disease detection, following a pattern of high endemicity in many municipalities. The early detection by household contacts examination is

important not only to stop transmission but also to detect the cases in a less severe state.

Keywords: Leprosy; Children; Epidemiology; Spatial analysis.

Strengths and limitations of this study

- This is a surveillance study that includes all notified cases of leprosy, in a State of Brazil with moderate prevalence of the disease.
- This is the first summary of leprosy cases in patients under 15 years old in Sergipe state, Northeast Brazil.
- This study was conducted using secondary data reported by SINAN and this source of data may have datasets missing.
- We also mapped the leprosy cases and physical disability in children under 15 years in areas of higher prevalence of leprosy in the general population, using geoprocessing tools.
- We compared the leprosy patient detection mode and how it affects the disease severity at diagnosis and the occurrence of leprosy reactions and physical disabilities.

INTRODUCTION

Leprosy is a chronic infectious disease caused by infection with *Mycobacterium leprae* [1]. This pathogen exhibits tissue tropism for phagocytes in the skin and Schwann cells within peripheral nerves and it presents a long incubation time (from 2 to 7 years) [2,3]. The disease can manifest across a broad spectrum of symptoms and the diagnosis is made based on the clinical signs (cutaneous lesions with altered sensitivity and neurological lesions). Patients are then classified as multibacillary (MB) and paucibacillary (PB) for treatment purposes, according to criteria accepted by Brazilian Ministry of Health (BMH) and International Leprosy Association (ILA) [1,2,4–7].

Despite control efforts including the widespread use of multidrug therapy (MDT), and the stabilization of the reported new case detection rate in the last few years, leprosy remains endemic in many developing countries [3–6,8–11]. In 2014, the World Health Organization (WHO) reported 213,899 new leprosy cases in 121 countries or territories [4]. Brazil ranks as the second most burdened country in the world concerning number of new cases (31,064 in 2014) and has by far the highest number of cases reported in Americas [4,12,13]. Within Brazil, the highest prevalence has been reported in the North, Northeast and Midwest regions [8,9]. The incidence of leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8]. In 2013, 2,439 new cases were diagnosed in children under 15 years old in Brazil, yielding a detection rate of 5.03 per 100,000 inhabitants [4].

Studies have demonstrated that leprosy presents higher incidence in population with: low educational degree, precarious health services and domiciliary infrastructure

settlements, and reduced investment in prevention and control [14–16]. Moreover, the high incidence rate in children under 15 years is important to indicate there is early exposure of the population to the bacillus, that is associated to elevated prevalence in general population, being a good indicator of a high transmission and bad quality of the control programs [10,12,17–20]. There is no study reporting the incidence of leprosy in children under 15 years in Sergipe state.

Recently, studies mapping the occurrence of infectious diseases according to their spatial distribution using "Geographic Information Systems (GIS)" have provided important information for public health programs, revealing areas of priority for interventions programs to more efficiently plan and implement control measures [2,9,16,21–23]. The use of GIS in leprosy may allow the identification of spatial-temporal distributions and profile of incidence in defined geographical areas, this potentially contributing to the effectiveness of interventions.

Despite breakthroughs in the epidemiological of leprosy, further improvements in understanding of the disease dynamics in different regions is important for the support of health services as a means for leprosy control. Spatial analyzes studies can provide important understanding of the transmission patterns of *M. leprae* and allow the identification of risk factors [21,23]. The aim of this study was to describe the 1) various clinical and epidemiological indicators of leprosy; to analyze 2) temporal trends and 3) the spatial distribution of leprosy cases in patients under 15 years old in an endemic area of Northeast Brazil.

METHODS

Study Design

The source of all data from this study was the leprosy cases and the information of each individual case notified by the health centers of the municipalities to the SINAN (Information System on Notifiable Diseases) from the State of Sergipe, Brazil. This is an important database of the Secretariat of Health of all States of Brazil, to report information about sociodemographic, clinical features and the address of notifiable diseases. Leprosy is a notifiable disease in Brazil, and as a legislative requirement, all leprosy cases have to be notified to the SINAN, including information about social and demographic features, clinical forms and follow-up of each patient. Sergipe is located on the coast of Northeast Brazil. The State has 75 municipalities and the capital is Aracaju. It has a population of 2,068,017 inhabitants and an area of 21,910,354km², equivalent to 0.26% of the national territory. The median population per county was 27,573.56 in 2015 [16]. Population data were obtained from the IBGE (Brazilian Institute of Geography and Statistics), based on population estimates for the intercensus years (2002 - 2015). An ecological and time series epidemiological study was conducted, based on the leprosy cases reported by SINAN. The historical (from 2002 to 2015) reporting of leprosy cases in children under 15 years old was analyzed. We also compared those data with data in all ages and with the occurrence of physical disability. The incidence of leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8].

The clinical and epidemiologic indicators collected by Investigation and Notification Form from SINAN, were: gender, age, ethnicity, address, operational classification (PB

and MB), clinical form [according to the more refined Ridley-Jopling classification [24,25], based on histopathological analyses: indeterminate leprosy (IL), true tuberculoid (TT), borderline leprosy (BL) and lepromatous leprosy (LL)], leprosy reaction (LR), number of affected nerves, degree of physical disabilities, number of household contacts (HHC) registered and examined, and the patient detection mode.

The parameters adopted by BMH and ILA were followed for interpreting the incidence rate of leprosy in patients under 15 years old. As such, this is classified as: low (<0.50 cases per 100,000 inhabitants); medium (0.50 to 2.49); high (2.50 to 4.99); very high (5.00 to 9.99) and hyperendemic (≥10.00) [4].

Spatial analysis

Thematic maps were constructed in each municipality for the period examined according to the leprosy incidence rate in patients under 15 years old and in general population, and for patients presenting with physical disability (incapacity degree 1 or 2). The kernel technique was applied to identify the intensity of the distribution of leprosy cases in the state of Sergipe. This technique shows the statistically generated surface density for the visual detection of hot spots, that indicates agglomeration of cases in a spatial distribution. This is an appropriate data interpolation for application in point location data. The point distribution was transformed into a smoothed surface and presented as a continuous map, representing different levels of case intensity. The amount of smoothing, that is, the width of the radius of influence was defined as 3,000 meters, since this value generated an adequate representation of the distribution of

the leprosy cases in the municipalities, minimizing the overlapping bias or the occurrence of sub distribution patterns smoothed [16,21].

We performed either spatial autocorrelation analysis between disease detection rates for each group. The Moran Global Index (MGI)[26] was calculated to identify clusters with risks for disease occurrence. We construct a spatial proximity matrix obtained by the contiguity of spatial correlation. The MGI was calculated as follows:

(Moran Global Index Mathematical Equation 1)

$$I = \frac{[(n\Sigma^{n}_{i}\Sigma^{n}_{j}\omega_{ij}(\gamma_i - \check{y})(\gamma_j - \check{y})]}{[\Sigma^{n}_{i}(\gamma_i - \check{y})^2\Sigma^{n}_{i}\Sigma^{n}_{j}\omega_{ij}]}$$

ωij is a contiguity matrix element (ω); yi is the incidence rate of municipality i; yj is the incidence rate of municipality j; ȳ is the mean of sample and the symbol n represents the total number of municipalities [26].

The MGI provides a general grouping measure and it is possible to know if there are significant differences between the analyzed areas. However, it does not indicate the clusters localization. To do that, we performed the Moran Local Index diagram [26] to build maps and identify the areas with spatial dependence (Local Index of Spatial Association - LISA) of the annual detection means, as follows:

(Local Index of Spatial Association Mathematical Equation 2)

$$I = \frac{n[(Z_i\Sigma^{n}_{j}\omega_{ij}Z_j)]}{(\Sigma^{n}_{j}Z^{2}_{j})}$$

Zi = yi - ȳ; Zi = yi - ȳ; Ωij is a contiguous matrix element ω; yi is the incidence rate of municipality i; yj is the incidence rate of municipality j; ȳ is the sample mean and the symbol n represents the total number of cities [26]. The Moran Map was used to indicate the clusters and their relationship with the neighbors. This analysis verifies the existence of spatial dependence and risk patterns: Q1 (high/high) and Q2 (Low/Low), which indicate municipalities with similar values between their neighbors and Q3 (high/low) and Q4 (low/high) for municipalities with different values between their neighbors and no spatial association. A spatial proximity matrix obtained by the contiguity criterion was adopted. The level of significance was 5% and the Moran Global Index (I) varying between -1 and +1, representing the spatial autocorrelation of leprosy detection rate in the geographic space analyzed to identify spatial clusters and risk areas. Values between 0 and +1 indicate positive spatial autocorrelation (Q1 and Q2) and between -1 and 0 negative spatial autocorrelation (Q3 and Q4) [26,27]. Both Moran Index and Kernel maps were constructed using TerraView software 4.2.2.

Statistical analysis

Demographic and clinical data were compared across the different subgroups and according to operational classification and the patient detection mode. Percentage, mean and standard deviation of the groups were calculated. For groups' comparison, we first analyze if the data followed normal distribution by the D'Agostino and Pearson normality test, and statistical differences between the groups were determined by Mann-Whitney and Kruskall-Wallis tests. All analysis was performed using SPSS

Statistics, version 24.0. Results were considered statistically different when *p*-values < 0.05 were obtained.

In order to enable trend analysis, annual incidence of leprosy was calculated as dependent variables (y), and the years of the study period as the independent variables (x). Initially, trend analysis was performed with the Joinpoint program, version 4.0.4 (Surveillance Research, National Cancer Institute, USA). This program estimates the Annual Percentage Change (APC) of a segmented linear regression (Jointpont regression) and identifies inflection points. Each inflection point reflects changes in the increase or decline of le rates [27]. Poisson regression is used to determine the number of segments required to adequately explain the relationship between two variables [27]. We considered the points of trend change that presented p-value < 0.05.

Ethical Considerations

For conducting this study, authorization was previously requested from Coordination of Epidemiological Surveillance, Sergipe state. This project involved research on human subjects and was approved by the Ethics and Research Committee of the Federal University of Sergipe, CAAE 0152.0.107.000-07.

Patient and Public Involvement statement

There was no patient and public involvement in this study. The study was based on secondary data.

RESULTS

Trends in reported leprosy incidence among children

The incidence of leprosy in children under 15 years old fluctuated, increasing from 2002 (6.29 cases per 100,000 inhabitants) to 2005 (9.82) but then showing a decline to 3.78 in 2015. There was an overall decrease trend in leprosy incidence in children from 2002 to 2015, by Joinpoint regression analyzes (APC = -5.3 and *p*-value < 0.05; **Figure 1A and B**). Similarly, the leprosy incidence rate in the general population of Sergipe decreased from 23.08 cases to 16.99 per 100,000 inhabitants between 2002 and 2015 (**Figure 1A and C**). The occurrence of degree 2 physical disability, however, increased in this period (0.76 in 2002 to 1.2 in 2015, respectively), however there is no significant reduction (APC = 2.6 and *p*-value = 0.20; **Figure 1A and D**). The composition of leprosy cases according to the operational classification (PB and MB) was relatively stable across this period, with majority of cases presenting as PB (**Figure 2A**). We also observed the mean number of HHC registered (4.65 ± 2.79) was slightly, but significantly, higher than the number examined (3.66 ± 3.14; *p*-value < 0.0001; **Figure 2B**).

Demographics of childhood leprosy cases

Next, we evaluated the association among clinical and epidemiological variables according to the leprosy operational classification (patients presenting as PB and MB). Patients presenting as MB or PB were in similar age to (10.5 ± 2.81 and 10.07 ± 3.38, respectively). Despite the extended incubation period of *M. leprae*/leprosy, six cases (1.11%) were reported in children less than one year of age. Of the 538 leprosy cases identified among children under 15 years old the majority were PB [407 (75.7%) PB

and 131 (24.3%) MB; **Table 1**]. When stratified on gender, however, the proportion of boys presenting with MB (63.4%) was significantly higher than presenting with PB (48.4%; *p*-value = 0.003). An interesting difference was observed when we calculated the ratio (PB/MB) according the ethnic groups. Among those identified as black, the ratio (43/24) was 1.79. Conversely, the ratio of white was higher 4.88 (88/18; *p*-value = 0.02).

As expected, the occurrence of leprosy reactions was significantly higher in MB (21.4%) than PB (4.9%; *p*-value < 0.0001) patients. The occurrence of degree 2 of physical disability was also higher in MB (4.6%), than in PB patients (0.74%; *p*-value = 0.0001). Consistent with this, we observed that the mean of number of affected nerves was higher in MB (0.5 ± 1.03), than PB (0.19 ± 0.54; *p*-value = 0.04).

Impact of case detection methods on leprosy presentation

We also performed analysis of association among clinical and epidemiological variables according to the leprosy patient detection mode. The patients were grouped in: spontaneous demand (SDem: patients that looked for medical assistance by themselves); forwarded (FW: patients that were forwarded from a primary clinic to a leprosy reference center); examined HHC; and other. We observed that patients detected by the examined HHC method presented lower mean age (9.6 ± 3.38) than those detected by either the SDem (10.54 ± 3.28) or FW methods (10.02 ± 3.15; *p*-value = 0.04; **Table 2**). Interestingly, the percentage of leprosy reaction among the examined HHC group (2.9%; *p*-value = 0.02) was lower than that observed among SDem (7.3%) and FW (13.3%). In addition, degree 2 of physical disability was not

observed among patients detected in examined HHC group, while SDem and FW presented 0.43% and 3.8%, respectively (*p*-value = 0.04). Furthermore, patients identified among examined HHC presented with lower numbers of lesions (2.04 ± 2.96; *p*-value = 0.04) than SDem (3.64 ± 6.25) and FW (4.09 ± 8.68). Taken together, these data reinforce the importance of HHC examination for the detection of leprosy patients before advancement to more severe symptoms.

Spatial analyze data

Next, we performed the spatial analysis of leprosy cases in the general population, in patients under 15 years old, and in patients presenting with physical disability (both degree 1 and 2). Moran maps have showed higher risk clusters (Q1 - in red; **Figure 3A-C**) in similar areas when comparing the maps regarding leprosy cases in children under 15 years old, in general population, and patients presenting some physical disability (degree 1 and 2). The higher risk clusters (Q1) were localized in Sergipe state center and in the metropolitan area around the capital of State. The municipalities with no spatial association (Q3 - in blue) were localized in the Semiarid region, in the northwest area and in the south region.

Similarly, The Kernel estimator, through data interpolation, showed densities (hot spots) of the highest incidence rates located at the northeast and east center regions and in the counties around the state capital (Aracaju city; **Figure 3D-F**). Lower intensity was observed on the western region. Municipalities with intermediate to high incidence values are seen in yellow and red tones of each subfigure. Low incidence

areas were reported on west coast municipalities, mostly in smaller counties with small populations.

DISCUSSION

Previous studies have demonstrated that the high leprosy cases detection in patients under 15 years old is a bad parameter for leprosy control program, because it indicates early bacillus transmission from undiagnosed cases [18]. Some authors have speculated either about the risk of vertical/transplacental transmission or through breastfeeding [12].

In Brazil, the highest leprosy incidence rate in children was reported in the North area (11.91 cases per 100,000 inhabitants), followed by Northeast (8.12) [12]. We observed the leprosy incidence rate was reduced in children under 15 years old from 2002 to 2015 in Sergipe state, however considering the parameters adopted by BMH, the state was classified as very high endemicity in 2002, and still as high endemicity in 2015. It remains also with elevated incidence rate and stationary tendency of degree 2 of physical disability. Those data reinforce either that the transmission is intense at early age, there is lack of an effective public health and the disease control is focused in the MDT [12,18]. A similar study performed at Fortaleza city (Brazil), reported also that although a decreasing has been observed on overall detection rate, the number of new cases in those under 15 years old remains stable [13].

Leprosy reactions and physical disability are the most severe leprosy clinical complications [8,28,29]. In addition, the increase or stability of the prevalence of

degree 2 of physical disability indicates persisting late diagnosis [13,29]. The early diagnosis of leprosy is essential to the prevention of deformities, whose repercussions are still more catastrophic in children and adolescents [28]. Our data reported 21.4% children with leprosy reaction (LR) and 31.3% with some physical disability in the MB groups. Furthermore, MB patients presented higher mean of affected nerves. Generally, patients under 15 years old do not use to present LR, but studies have reported a low frequency of LR, varying between 1.36% and 8.33% [28]. Those data reinforce that, although there is a decreasing incidence in leprosy, patients have been exposed to bacillus early in life and diagnosed belatedly and hence they have been also developing into some clinical complications.

We have observed either that the mean of HHC examined was significantly lower than those registered by SINAN. Moreover, leprosy patients detected by exam in HHC presented lower mean of age, affected nerves, number of lesions, occurrence of LR and no physical disability, when compared with those identified by spontaneous demand or forwarded by others. On the other hand, mostly of patients presenting as degree 2 of physical disability were identified into those forwarded to a leprosy reference center, probably because they started presenting some physical disability. HHC and neighbors are the most important *M. leprae* active sources. The risk of a person developing leprosy is nine times greater among HHC and up to four times greater among contacts with neighbors [12]. Therefore, our data reinforce the importance of leprosy early diagnosis by exam in patients and their household contacts. Besides that, the treatment and the home visits by public health programs, and an efficient health program in schools could represent important actions for the

early diagnosis and the reduction of leprosy clinical complications, especially in children.

Spatial analysis of health events aim to identify geographical patterns by maps of risk and to point out areas of higher severity and to facilitate the planning of public health interventions [9]. The Kernel maps showed the spatial dynamic of leprosy, with a heterogeneous geographical pattern and the highest risk areas for leprosy infection. The highest incidence on counties around the Capital can be due there was a leprosarium at the Nossa Senhora do Socorro (a city of the metropolitan area of Aracaju), that has presented elevated detection rate in mostly evaluated years. Moreover, that area presents reference center to leprosy diagnosis and treatment and hence they have several patients forwarded to these leprosy clinics. It can be also associated with weather featuring such as humidity, considering either that counties near to São Francisco River presented also elevated incidence. In the Malawian Karonga district, a positive relationship between the proximity of water and leprosy incidence was previously reported [5]. Some authors have hypothesized that *M. leprae* survives longer outside of human body in humid compared to dry atmospheres [9,13].

Interestingly, higher risk clusters were identified in similar areas when we analyzed the occurrence of leprosy cases in children, in general population and patients presenting physical disability. It corroborates the hypothesis that the early transmission of *M. leprae* and the occurrence of leprosy in children under 15 years old is directly related to the late diagnosis, which explains the occurrence of patients with degree 2 of physical disability in the same geographic distribution [28]. The maps present certain

disagreements regarding the occurrence of leprosy cases in the state of Sergipe because they use distinct techniques of spatial analysis. The Kernel estimator produces a continuous surface, with densities calculated at all locations, based on total number of cases and no considering the geographical boundaries of the municipalities [27,30,31]. The Kernel technique presents greater advantages to the quick visualization of areas that deserve attention, besides not being affected by political-administrative division, while the Moran technique, constructs maps considering the political-administrative divisions of the state and the clusters are based on the number of cases by the municipalities population rates [27,30].

Our study had some limitations, particularly because it was conducted using secondary data reported by SINAN. This source of date can present numbers under notification and datasets missing. However, in Brazil we have a specific normative that is an obligation to notify several diseases to SINAN, and leprosy is one of them. SINAN is an important database of the Secretariat of Health of all States of Brazil, to report information about sociodemographic, clinical features and the address of each diagnosed case. This source of data can present under notification because Leprosy is an asymptomatic disease and the active search would be important to detect more cases, but all diagnosed cases are reported to SINAN. The limitation mentioned about missing data is not very important in the case of the disease prevalence, but the complete information about the cases follow-up, such as degree of neurological disability at the end of treatment, leprosy reactions and treatment details, because it is a secondary database that depends on other doctors or nurses from the health care centers to fulfill the information. Despite this, those data reported high endemicity of

leprosy cases in patients under 15 years old, and this study do not focus on patient follow-up.

In summary, our study demonstrated that the leprosy incidence rate has decreased in Sergipe state. However, it is still classified as high endemicity considering the WHO proposed ratios for children under 15 years. Patients detected by exam in collectivity or HHC presented better indicators. Altogether, the epidemiological data and spatial analysis indicate that there is persistence of active transmission of *M. leprae* and later case detection in Sergipe state, increasing the risk of transmission in children. In addition, the spatial analysis brings new advantages to comprehend the leprosy dynamic, and reinforce the superimposed regions of high occurrence areas of patients presenting degree 2 of physical disability and cases in children lower than 15 years, and highlights the need to strengthen effective disease control measures, mainly in primary health care.

Acknowledgments The authors would like to thank the Manager of the Nucleus of endemic/Division of Epidemiological Surveillance - [Divisão de Vigilância Epidemiológica (DIVEP)]/ Secretariat of Health of the Sergipe state (SES) for providing information.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Contributors The project was suggested by MB-S, MA, JB and AS. The statistical analyzes was performed by MB-S, IB, JS and AJ. The spatial analyzes was performed by MS, AS, AB and KA. The manuscript was written by MB-S, AB, DO, MD and AJ. All

authors contributed to refining the idea, revising the manuscript and have agreed the final version.

Competing interests The authors declare that they have no conflicts of interest.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Table 1. Association of demographic and clinical data according to the operational classification of leprosy (PB and MB) in children under 15 years in Sergipe state, Brazil (2002-2015).

Variables	Operational Classification		
	PB (n = 407)	MB (n = 131)	*p*-value
Age mean ± SD	10.07 ± 3.38	10.5 ± 2.81	*0.46
Gender n (%)			
Male	197 (48.4)	83 (63.4)	+0.003
Ethnicity n (%)			
White	88 (21.6)	18 (13.7)	#0.02
Black	43 (10.5)	24 (18.3)	
Brown	251 (61.7)	78 (59.5)	
Indian	4 (0.9)	3 (2.3)	
Leprosy reaction n (%)	20 (4.9)	28 (21.4)	+<0.0001
Physical Disability Degree n (%)			
0	337 (82.8)	90 (68.7)	#0.0001
1	26 (6.4)	18 (13.7)	
2	3 (0.74)	6 (4.6)	
Number of affected nerves (mean ± SD)	0.19 ± 0.54	0.5 ± 1.03	*0.04
Number of Lesions (mean ±	1.61 ± 1.14	9.92 ± 12.03	*<0.0001

SD)			
HHC registered (mean ± SD)	4.6 ± 2.71	4.85 ± 3.04	*0.14
HHC examined (mean ± SD)	3.54 ± 3.04	4.05 ± 3.44	

*Mann-Whitney test; ⁺Fisher's exact test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household contacts; SD = Standard Deviation. We missed data in some variables.

Table 2. Demographic and clinical aspects accordingly to the detection mode of leprosy cases in children under 15 years in Sergipe state, Brazil (2002-2015).

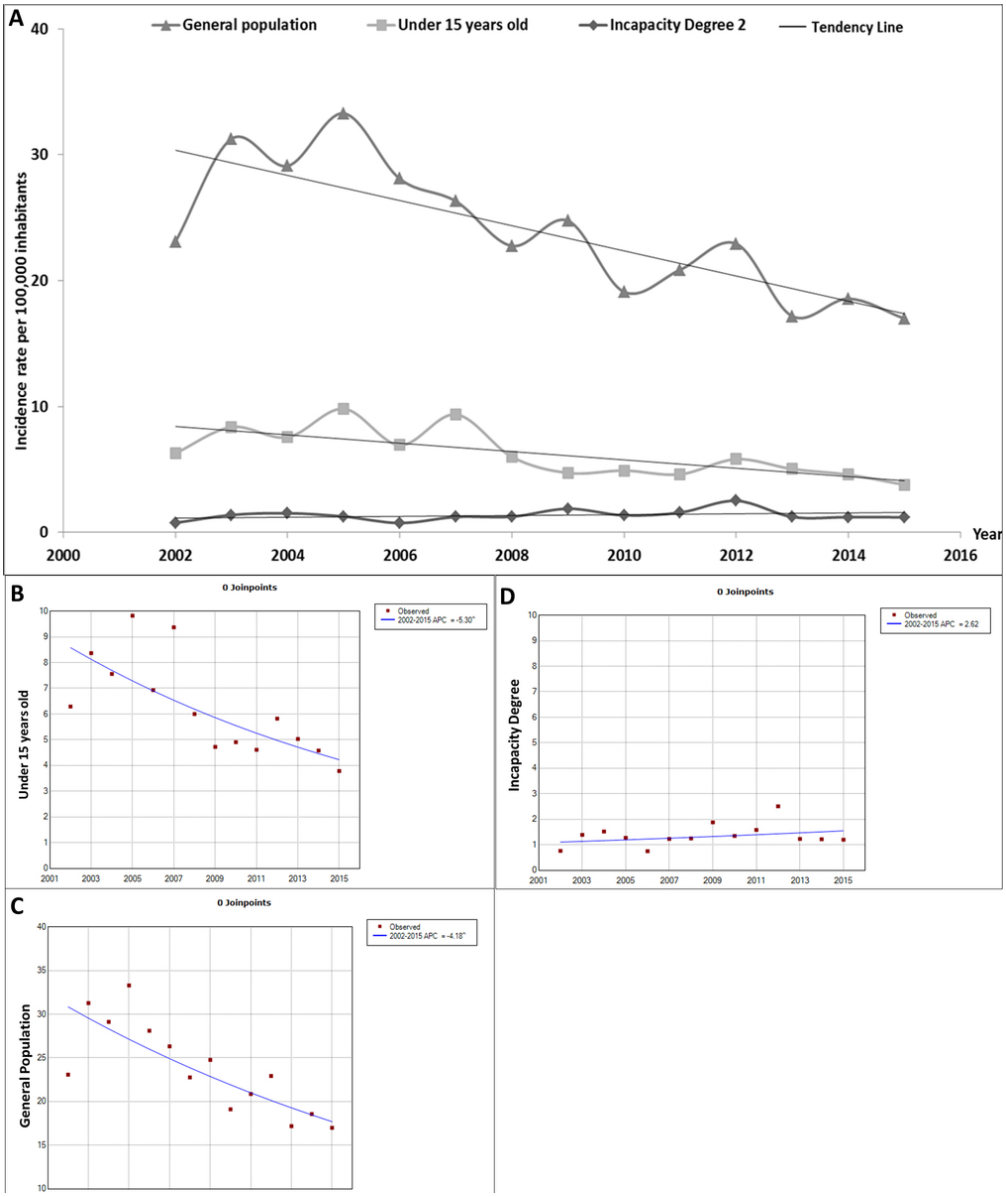
Variables	Patient detection mode				
	Spontaneous demand (n = 234)	Forwarding (n = 210)	Examined HHC (n = 69)	Other (n = 25)	*p*-value
Age mean ± SD	10.54 ± 3.28	10.02 ± 3.15	9.6 ± 3.38	9.6 ± 3.22	*0.04
Gender n (%)					
Male	123 (52.6)	110 (52.4)	38 (55.1)	09 (36)	#0.41
Leprosy reaction n (%)	17 (7.3)	28 (13.3)	2 (2.9)	1 (4.0)	#0.02
Physical disability degree n (%)					
0	199 (85.1)	150 (71.4)	55 (79.7)	18 (72)	#0.04
1	17 (7.3)	21 (10)	5 (7.2)	1 (4.0)	
2	1 (0.43)	08 (3.8)	0 (0.0)	0 (0.0)	
Number of affected nerves (mean ± SD)	0.24 ± 0.67	0.34 ± 0.81	0.06 ± 0.25	0.25 ± 0.5	*0.48
Number of lesion (mean ± SD)	3.64 ± 6.25	4.09 ± 8.68	2.04 ± 2.96	4 ± 5.2	*0.04
HHC registered (mean ± SD)	4.57 ± 2.53	4.59 ± 2.74	5.57 ± 3.81	3.45 ± 1.96	*0.04
HHC examined (mean ± SD)	3.71 ± 3.02	3.02 ± 2.98	4.64 ± 4.06	2.04 ± 1.77	*0.01

*Kruskal-Wallis test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household contacts; SD = Standard Deviation. We missed data in some variables.

Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (▲), in patients under 15 years old (■), degree 2 of physical disability (♦) and the tendency line. Temporal trend of standardized incidence rates by Joinpoint Regression for B) patients under 15 years old, C) General population and D) incapacity degree. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Number of leprosy cases according to the clinical operational classification (Paucibacilary - PB (■) and Multibacilary – MB (■) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. * Mann-Whitney test.

Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).



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85x101mm (300 x 300 DPI)

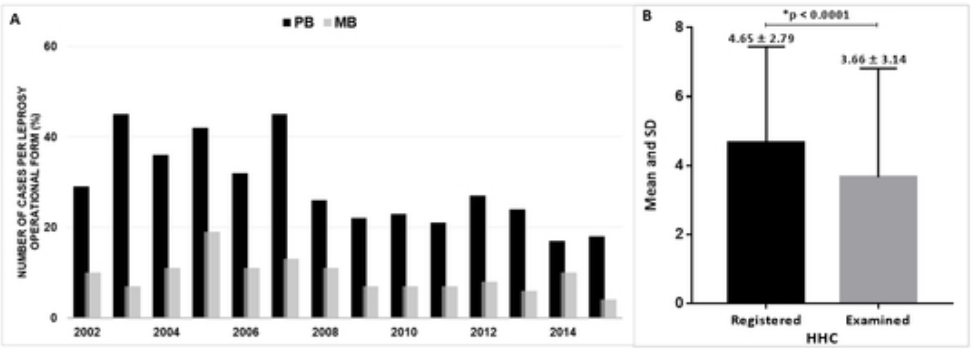
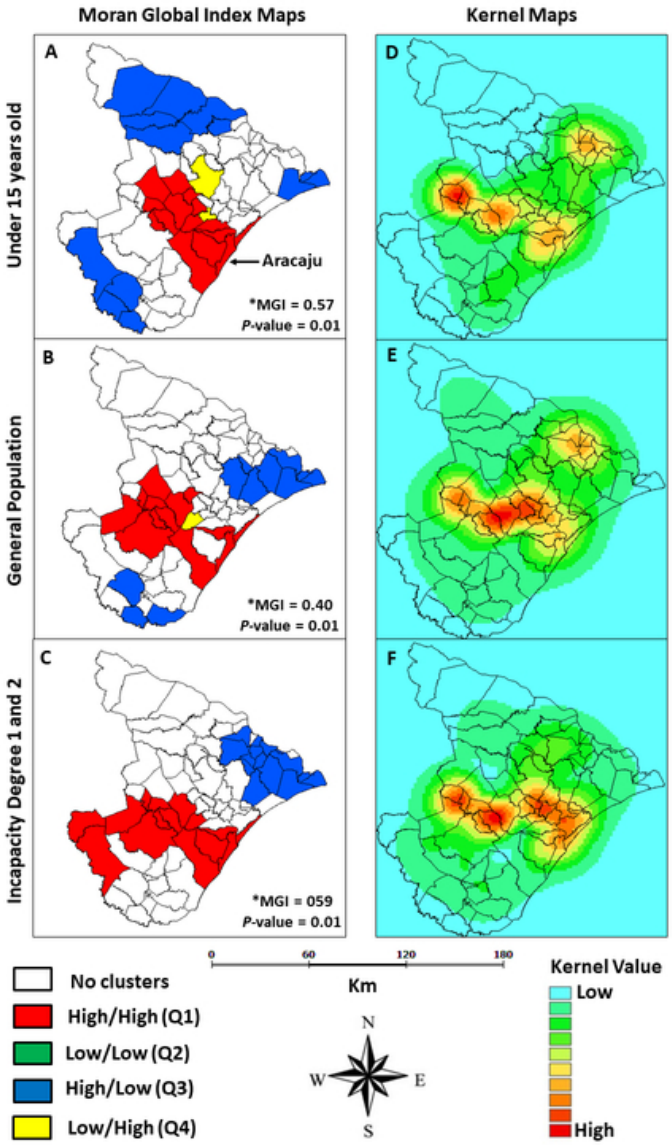


Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Number of leprosy cases according to the clinical operational classification (Paucibacilary - PB (☐) and Multibacilary – MB (☐) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. * Mann-Whitney test.

46x17mm (300 x 300 DPI)



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48x64mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	01
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	02
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	04-05
Objectives	3	State specific objectives, including any prespecified hypotheses	05
Methods			
Study design	4	Present key elements of study design early in the paper	06
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	06
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	06
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	06
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	06-07
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	06
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	06-08
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	08-09
		(*b*) Describe any methods used to examine subgroups and interactions	08-09
		(*c*) Explain how missing data were addressed	08-09
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	08-09
		(*e*) Describe any sensitivity analyses	08-09
Results			08-09

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	09
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	09-10
		(b) Indicate number of participants with missing data for each variable of interest	--
Outcome data	15*	Report numbers of outcome events or summary measures	09-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	--
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	09-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023420.R2
Article Type:	Research
Date Submitted by the Author:	20-Mar-2019
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Public health
Keywords:	Leprosy, Children, Epidemiology < INFECTIOUS DISEASES, Spatial analysis

Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

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ABSTRACT

Objective: This study aimed to analyze the clinical and epidemiological indicators, temporal trends and the spatial distribution of leprosy in patients under 15 years old in an endemic area of Northeast Brazil.

Design: Regional surveillance study of all reported cases.

Setting: State of Sergipe, endemic area of Northeast Brazil.

Methods: An ecological and time series study was conducted, based on secondary data reported by the Brazilian Information System on Notifiable Diseases (SINAN) for leprosy cases diagnosed in Sergipe state (2002-2015). The analysis of temporal trends was performed using the Joinpoint Regression Program through Poisson regression. We performed spatial analysis by Kernel estimator and Moran index.

Results: The incidence rate was reduced from 6.29 to 3.78 cases per 100,000 inhabitants in 2002 and 2015, respectively. However, Sergipe was still classified as highly endemicity in 2015. The mean number of household contacts (HHC) examined was significantly lower than those registered. Clinical data indicated that 21.4% of the patients developed leprosy reactions, and 31.3% presented with some physical disability in the multibacillary (MB) groups. Patients diagnosed by exam within the HHC presented better indicators, such as lower percentage of leprosy reaction and physical disability. Spatial analysis showed the most risk areas distributed on the northeast and cities around the capital, Aracaju.

Conclusion: The data indicate that there is a persistence of active *M. leprae* transmission and a delay in disease detection, following a pattern of high endemicity in many municipalities. The early detection by household contacts examination is important not only to stop transmission but also to detect the cases in a less severe state.

Keywords: Leprosy; Children; Epidemiology; Spatial analysis.

Strengths and limitations of this study

- This is a surveillance study that includes all notified cases of leprosy, in a State of Brazil with moderate prevalence of the disease.
- This is the first summary of leprosy cases in patients under 15 years old in Sergipe state, Northeast Brazil.
- This study was conducted using secondary data reported by SINAN and this source of data may have datasets missing.
- We also mapped the leprosy cases and physical disability in children under 15 years in areas of higher prevalence of leprosy in the general population, using geoprocessing tools.
- We compared the leprosy patient detection mode and how it affects the disease severity at diagnosis and the occurrence of leprosy reactions and physical disabilities.

INTRODUCTION

Leprosy is a chronic infectious disease caused by infection with *Mycobacterium leprae* [1]. This pathogen exhibits tissue tropism for phagocytes in the skin and Schwann cells within peripheral nerves and it presents a long incubation time (from 2 to 7 years) [2,3]. The disease can manifest across a broad spectrum of symptoms and the diagnosis is made based on the clinical signs (cutaneous lesions with altered sensitivity and neurological lesions). Patients are then classified as multibacillary (MB) and paucibacillary (PB) for treatment purposes, according to criteria accepted by Brazilian Ministry of Health (BMH) and International Leprosy Association (ILA) [1,2,4–7].

Despite control efforts including the widespread use of multidrug therapy (MDT), and the stabilization of the reported new case detection rate in the last few years, leprosy remains endemic in many developing countries [3–6,8–11]. In 2014, the World Health Organization (WHO) reported 213,899 new leprosy cases in 121 countries or territories [4]. Brazil ranks as the second most burdened country in the world concerning number of new cases (31,064 in 2014) and has by far the highest number of cases reported in Americas [4,12,13]. Within Brazil, the highest prevalence has been reported in the North, Northeast and Midwest regions [8,9]. The incidence of leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8]. In 2013, 2,439 new cases were diagnosed in children under 15 years old in Brazil, yielding a detection rate of 5.03 per 100,000 inhabitants [4].

Studies have demonstrated that leprosy presents higher incidence in population with: low educational degree, precarious health services and domiciliary infrastructure

settlements, and reduced investment in prevention and control [14–16]. Moreover, the high incidence rate in children under 15 years is important to indicate there is early exposure of the population to the bacillus, that is associated to elevated prevalence in general population, being a good indicator of a high transmission and bad quality of the control programs [10,12,17–20]. There is no study reporting the incidence of leprosy in children under 15 years in Sergipe state.

Recently, studies mapping the occurrence of infectious diseases according to their spatial distribution using "Geographic Information Systems (GIS)" have provided important information for public health programs, revealing areas of priority for interventions programs to more efficiently plan and implement control measures [2,9,16,21–23]. The use of GIS in leprosy may allow the identification of spatial-temporal distributions and profile of incidence in defined geographical areas, this potentially contributing to the effectiveness of interventions.

Despite breakthroughs in the epidemiological of leprosy, further improvements in understanding of the disease dynamics in different regions is important for the support of health services as a means for leprosy control. Spatial analyzes studies can provide important understanding of the transmission patterns of *M. leprae* and allow the identification of risk factors [21,23]. The aim of this study was to describe the 1) various clinical and epidemiological indicators of leprosy; to analyze 2) temporal trends and 3) the spatial distribution of leprosy cases in patients under 15 years old in an endemic area of Northeast Brazil.

METHODS

Study Design

The source of all data from this study was the leprosy cases and the information of each individual case notified by the health centers of the municipalities to the SINAN (Information System on Notifiable Diseases) from the State of Sergipe, Brazil. This is an important database of the Secretariat of Health of all States of Brazil, to report information about sociodemographic, clinical features and the address of notifiable diseases. Leprosy is a notifiable disease in Brazil, and as a legislative requirement, all leprosy cases have to be notified to the SINAN, including information about social and demographic features, clinical forms and follow-up of each patient. Sergipe is located on the coast of Northeast Brazil. The State has 75 municipalities and the capital is Aracaju. It has a population of 2,068,017 inhabitants and an area of 21,910,354km², equivalent to 0.26% of the national territory. The median population per county was 27,573.56 in 2015 [16]. Population data were obtained from the IBGE (Brazilian Institute of Geography and Statistics), based on population estimates for the intercensus years (2002 - 2015). An ecological and time series epidemiological study was conducted, based on the leprosy cases reported by SINAN. The historical (from 2002 to 2015) reporting of leprosy cases in children under 15 years old was analyzed. We also compared those data with data in all ages and with the occurrence of physical disability. The incidence of leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8].

The clinical and epidemiologic indicators collected by Investigation and Notification Form from SINAN, were: gender, age, ethnicity, address, operational classification (PB

and MB), clinical form [according to the more refined Ridley-Jopling classification [24,25], based on histopathological analyses: indeterminate leprosy (IL), true tuberculoid (TT), borderline leprosy (BL) and lepromatous leprosy (LL)], leprosy reaction (LR), number of affected nerves, degree of physical disabilities, number of household contacts (HHC) registered and examined, and the patient detection mode.

The parameters adopted by BMH and ILA were followed for interpreting the incidence rate of leprosy in patients under 15 years old. As such, this is classified as: low (<0.50 cases per 100,000 inhabitants); medium (0.50 to 2.49); high (2.50 to 4.99); very high (5.00 to 9.99) and hyperendemic (≥10.00) [4].

Spatial analysis

Thematic maps were constructed in each municipality for the period examined according to the leprosy incidence rate in patients under 15 years old and in general population, and for patients presenting with physical disability (incapacity degree 1 or 2). The kernel technique was applied to identify the intensity of the distribution of leprosy cases in the state of Sergipe. This technique shows the statistically generated surface density for the visual detection of hot spots, that indicates agglomeration of cases in a spatial distribution. This is an appropriate data interpolation for application in point location data. The point distribution was transformed into a smoothed surface and presented as a continuous map, representing different levels of case intensity. The amount of smoothing, that is, the width of the radius of influence was defined as 3,000 meters, since this value generated an adequate representation of the distribution of the

leprosy cases in the municipalities, minimizing the overlapping bias or the occurrence of sub distribution patterns smoothed [16,21].

We performed either spatial autocorrelation analysis between disease detection rates for each group. The Moran Global Index (MGI)[26] was calculated to identify clusters with risks for disease occurrence. We construct a spatial proximity matrix obtained by the contiguity of spatial correlation. The MGI was calculated as follows:

(Moran Global Index Mathematical Equation 1)

$$I = \frac{[(n\Sigma^{n}_{i}\Sigma^{n}_{j}\omega_{ij}(\gamma_i - \check{y})(\gamma_j - \check{y})]}{[\Sigma^{n}_{i}(\gamma_i - \check{y})^2\Sigma^{n}_{i}\Sigma^{n}_{j}\omega_{ij}]}$$

ω_{ij} is a contiguity matrix element (ω); γ_i is the incidence rate of municipality $_i$; γ_j is the incidence rate of municipality $_j$; $\check{y}$ is the mean of sample and the symbol n represents the total number of municipalities [26].

The MGI provides a general grouping measure and it is possible to know if there are significant differences between the analyzed areas. However, it does not indicate the clusters localization. To do that, we performed the Moran Local Index diagram [26] to build maps and identify the areas with spatial dependence (Local Index of Spatial Association - LISA) of the annual detection means, as follows:

(Local Index of Spatial Association Mathematical Equation 2)

$$I = \frac{n[(Z_i\Sigma^{n}_{j}\omega_{ij}Z_j)]}{(\Sigma^{n}_{j}Z^{2}_{j})}$$

$Z_i = yi - \bar{y}$; $Zj = yj - \bar{y}$; ω_{ij} is a contiguous matrix element ω; yi is the incidence rate of municipality i; yj is the incidence rate of municipality j; $\bar{y}$ is the sample mean and the symbol n represents the total number of cities [26]. The Moran Map was used to indicate the clusters and their relationship with the neighbors. This analysis verifies the existence of spatial dependence and risk patterns: Q1 (high/high) and Q2 (Low/Low), which indicate municipalities with similar values between their neighbors and Q3 (high/low) and Q4 (low/high) for municipalities with different values between their neighbors and no spatial association. A spatial proximity matrix obtained by the contiguity criterion was adopted. The level of significance was 5% and the Moran Global Index (I) varying between -1 and +1, representing the spatial autocorrelation of leprosy detection rate in the geographic space analyzed to identify spatial clusters and risk areas. Values between 0 and +1 indicate positive spatial autocorrelation (Q1 and Q2) and between -1 and 0 negative spatial autocorrelation (Q3 and Q4) [26,27]. Both Moran Index and Kernel maps were constructed using TerraView software 4.2.2.

Statistical analysis

The annual incidence rates were calculated for the general population, according to the population data from IBGE. For patients younger than 15 years the annual rates were age-standardised, and the standard population used was the population under 15 years from IBGE. Demographic and clinical data were compared across the different subgroups and according to operational classification and the patient detection mode. Percentage, mean and standard deviation of the groups were calculated. For groups'

comparison, we first analyze if the data followed normal distribution by the D'Agostino and Pearson normality test, and statistical differences between the groups were determined by Mann-Whitney and Kruskall-Wallis tests. All analysis was performed using SPSS Statistics, version 24.0. Results were considered statistically different when *p*-values < 0.05 were obtained.

In order to enable trend analysis, annual incidence rate of leprosy was calculated as dependent variables (y), and the years of the study period as the independent variables (x). Initially, trend analysis was performed with the Joinpoint program, version 4.0.4 (Surveillance Research, National Cancer Institute, USA). This program estimates the Annual Percentage Change (APC) of a segmented linear regression (Jointpont regression) and identifies inflection points. Each inflection point reflects changes in the increase or decline of leprosy rates [27]. The joinpoint regression provided the adjustment of a series of lines as well as their inflection points on a logarithmic scale by means of the annual trend test. To obtain the adjustment based on the best line of each analyzed segment, the Monte Carlo permutation method was used as a test of significance. From the definition of the follow-ups, the annual percentage change (APC) and the average annual percentage change (AAPC), with their respective 95% confidence intervals, were estimated and tested. If the occurrence of an inflection point with inverted direction was verified, the study periods were analyzed separately. The number of inflections used in the analysis was the result of models defined by the program itself, in order to allow the best representation of the trend, with the lowest number of inflection points. The result showed growth (positive APC values), reduction (APC negative values) or maintenance (APC value equal to zero) of the trend throughout the historical series

analyzed (2006-2014). Poisson regression is used to determine the number of segments required to adequately explain the relationship between two variables [27]. We considered the points of trend change that presented p-value < 0.05.

Ethical Considerations

For conducting this study, authorization was previously requested from Coordination of Epidemiological Surveillance, Sergipe state. This project involved research on human subjects and was approved by the Ethics and Research Committee of the Federal University of Sergipe, CAAE 0152.0.107.000-07.

Patient and Public Involvement statement

There was no patient and public involvement in this study. The study was based on secondary data.

RESULTS

Trends in reported leprosy incidence among children

The incidence of leprosy in children under 15 years has declined from 6.29 cases per 100,000 inhabitants in 2002, to 3.78 in 2015, confirmed by Joinpoint regression analyzes (APC = -5.3 and *p*-value < 0.05; **Figure 1A and B**). Similarly, the leprosy incidence rate in the general population of Sergipe decreased from 23.08 cases to 16.99 per 100,000 inhabitants between 2002 and 2015 (**Figure 1A and C**). The occurrence of degree 2 physical disability, however, increased in this period (0.76 in 2002 to 1.2 in 2015, respectively), however it is a non-significant increasing trend (APC = 2.6 and *p*-value = 0.20; **Figure 1A and D**). The composition of leprosy cases according to the operational

classification (PB and MB) was relatively stable across this period, with majority of cases presenting as PB (**Figure 2A**). We also observed the mean number of HHC registered (4.65 ± 2.79) was slightly, but significantly, higher than the number examined (3.66 ± 3.14; *p*-value < 0.0001; **Figure 2B**).

Demographics of childhood leprosy cases

Next, we evaluated the association among clinical and epidemiological variables according to the leprosy operational classification (patients presenting as PB and MB). Patients presenting as MB or PB were in similar age to (10.5 ± 2.81 and 10.07 ± 3.38, respectively). Despite the extended incubation period of *M. leprae*/leprosy, six cases (1.11%) were reported in children less than one year of age. Of the 538 leprosy cases identified among children under 15 years old the majority were PB [407 (75.7%) PB and 131 (24.3%) MB; **Table 1**]. When stratified on gender, however, the proportion of boys presenting with MB (63.4%) was significantly higher than presenting with PB (48.4%; *p*-value = 0.003). An interesting difference was observed when we calculated the ratio (PB/MB) according the ethnic groups. Among those identified as black, the ratio (43/24) was 1.79. Conversely, the ratio of white was higher 4.88 (88/18; *p*-value = 0.02).

As expected, the occurrence of leprosy reactions was significantly higher in MB (21.4%) than PB (4.9%; *p*-value < 0.0001) patients. The occurrence of degree 2 of physical disability was also higher in MB (4.6%), than in PB patients (0.74%; *p*-value = 0.0001). Consistent with this, we observed that the mean of number of affected nerves was higher in MB (0.5 ± 1.03), than PB (0.19 ± 0.54; *p*-value = 0.04).

Impact of case detection methods on leprosy presentation

We also performed analysis of association among clinical and epidemiological variables according to the leprosy patient detection mode. The patients were grouped in: spontaneous demand (SDem: patients that looked for medical assistance by themselves); forwarded (FW: patients that were forwarded from a primary clinic to a leprosy reference center); examined HHC; and other. We observed that patients detected by the examined HHC method presented lower mean age (9.6 ± 3.38) than those detected by either the SDem (10.54 ± 3.28) or FW methods (10.02 ± 3.15; *p*-value = 0.04; **Table 2**). Interestingly, the percentage of leprosy reaction among the examined HHC group (2.9%; *p*-value = 0.02) was lower than that observed among SDem (7.3%) and FW (13.3%). In addition, degree 2 of physical disability was not observed among patients detected in examined HHC group, while SDem and FW presented 0.43% and 3.8%, respectively (*p*-value = 0.04). Furthermore, patients identified among examined HHC presented with lower numbers of lesions (2.04 ± 2.96; *p*-value = 0.04) than SDem (3.64 ± 6.25) and FW (4.09 ± 8.68). Taken together, these data reinforce the importance of HHC examination for the detection of leprosy patients before advancement to more severe symptoms.

Spatial analyze data

Next, we performed the spatial analysis of leprosy cases in the general population, in patients under 15 years old, and in patients presenting with physical disability (both degree 1 and 2). Moran maps have showed higher risk clusters (Q1 - in red; **Figure 3A-C**) in similar areas when comparing the maps regarding leprosy cases in children under 15 years old, in general population, and patients presenting some physical disability

(degree 1 and 2). The higher risk clusters (Q1) were localized in Sergipe state center and in the metropolitan area around the capital of State. The municipalities with no spatial association (Q3 - in blue) were localized in the Semiarid region, in the northwest area and in the south region.

Similarly, The Kernel estimator, through data interpolation, showed densities (hot spots) of the highest incidence rates located at the northeast and east center regions and in the counties around the state capital (Aracaju city; **Figure 3D-F**). Lower intensity was observed on the western region. Municipalities with intermediate to high incidence values are seen in yellow and red tones of each subfigure. Low incidence areas were reported on west coast municipalities, mostly in smaller counties with small populations.

DISCUSSION

Previous studies have demonstrated that the high leprosy cases detection in patients under 15 years old is a bad parameter for leprosy control program, because it indicates early bacillus transmission from undiagnosed cases [18]. Some authors have speculated either about the risk of vertical/transplacental transmission or through breastfeeding [12].

In Brazil, the highest leprosy incidence rate in children was reported in the North area (11.91 cases per 100,000 inhabitants), followed by Northeast (8.12) [12]. We observed the leprosy incidence rate was reduced in children under 15 years old from 2002 to 2015 in Sergipe state, however considering the parameters adopted by BMH, the state was

classified as very high endemicity in 2002, and still as high endemicity in 2015. It remains also with elevated incidence rate and stationary tendency of degree 2 of physical disability. Those data reinforce either that the transmission is intense at early age, there is lack of an effective public health and the disease control is focused in the MDT [12,18]. A similar study performed at Fortaleza city (Brazil), reported also that although a decreasing has been observed on overall detection rate, the number of new cases in those under 15 years old remains stable [13].

Leprosy reactions and physical disability are the most severe leprosy clinical complications [8,28,29]. In addition, the increase or stability of the prevalence of degree 2 of physical disability indicates persisting late diagnosis [13,29]. The early diagnosis of leprosy is essential to the prevention of deformities, whose repercussions are still more catastrophic in children and adolescents [28]. Our data reported 21.4% children with leprosy reaction (LR) and 31.3% with some physical disability in the MB groups. Furthermore, MB patients presented higher mean of affected nerves. Generally, patients under 15 years old do not use to present LR, but studies have reported a low frequency of LR, varying between 1.36% and 8.33% [28]. Those data reinforce that, although there is a decreasing incidence in leprosy, patients have been exposed to bacillus early in life and diagnosed belatedly and hence they have been also developing into some clinical complications.

We have observed either that the mean of HHC examined was significantly lower than those registered by SINAN. Moreover, leprosy patients detected by exam in HHC presented lower mean of age, affected nerves, number of lesions, occurrence of LR and

no physical disability, when compared with those identified by spontaneous demand or forwarded by others. On the other hand, mostly of patients presenting as degree 2 of physical disability were identified into those forwarded to a leprosy reference center, probably because they started presenting some physical disability. HHC and neighbors are the most important *M. leprae* active sources. The risk of a person developing leprosy is nine times greater among HHC and up to four times greater among contacts with neighbors [12]. Therefore, our data reinforce the importance of leprosy early diagnosis by exam in patients and their household contacts. Besides that, the treatment and the home visits by public health programs, and an efficient health program in schools could represent important actions for the early diagnosis and the reduction of leprosy clinical complications, especially in children.

Spatial analysis of health events aim to identify geographical patterns by maps of risk and to point out areas of higher severity and to facilitate the planning of public health interventions [9]. The Kernel maps showed the spatial dynamic of leprosy, with a heterogeneous geographical pattern and the highest risk areas for leprosy infection. The highest incidence on counties around the Capital can be due there was a leprosarium at the Nossa Senhora do Socorro (a city of the metropolitan area of Aracaju), that has presented elevated detection rate in mostly evaluated years. Moreover, that area presents reference center to leprosy diagnosis and treatment and hence they have several patients forwarded to these leprosy clinics. It can be also associated with weather featuring such as humidity, considering either that counties near to São Francisco River presented also elevated incidence. In the Malawian Karonga district, a positive relationship between the proximity of water and leprosy incidence was

previously reported [5]. Some authors have hypothesized that *M. leprae* survives longer outside of human body in humid compared to dry atmospheres [9,13].

Interestingly, higher risk clusters were identified in similar areas when we analyzed the occurrence of leprosy cases in children, in general population and patients presenting physical disability. It corroborates the hypothesis that the early transmission of *M. leprae* and the occurrence of leprosy in children under 15 years old is directly related to the late diagnosis, which explains the occurrence of patients with degree 2 of physical disability in the same geographic distribution [28]. The maps present certain disagreements regarding the occurrence of leprosy cases in the state of Sergipe because they use distinct techniques of spatial analysis. The Kernel estimator produces a continuous surface, with densities calculated at all locations, based on total number of cases and no considering the geographical boundaries of the municipalities [27,30,31]. The Kernel technique presents greater advantages to the quick visualization of areas that deserve attention, besides not being affected by political-administrative division, while the Moran technique, constructs maps considering the political-administrative divisions of the state and the clusters are based on the number of cases divided by the municipalities [27,30].

Our study had some limitations, particularly because it was conducted using secondary data reported by SINAN. This source of date can present numbers under notification and datasets missing. However, in Brazil we have a specific normative that is an obligation to notify several diseases to SINAN, and leprosy is one of them. SINAN is an important database of the Secretariat of Health of all States of Brazil, to report information about

sociodemographic, clinical features and the address of each diagnosed case. This source of data can present under notification because Leprosy is an asymptomatic disease and the active search would be important to detect more cases, but all diagnosed cases are reported to SINAN. The limitation mentioned about missing data is not very important in the case of the disease prevalence, but the complete information about the cases follow-up, such as degree of neurological disability at the end of treatment, leprosy reactions and treatment details, because it is a secondary database that depends on other doctors or nurses from the health care centers to fulfill the information. Despite this, those data reported high endemicity of leprosy cases in patients under 15 years old, and this study do not focus on patient follow-up.

In summary, our study demonstrated that the leprosy incidence rate has decreased in Sergipe state. However, it is still classified as high endemicity considering the WHO proposed ratios for children under 15 years. Patients detected by exam in collectivity or HHC presented better indicators. Altogether, the epidemiological data and spatial analysis indicate that there is persistence of active transmission of *M. leprae* and later case detection in Sergipe state, increasing the risk of transmission in children. In addition, the spatial analysis brings new advantages to comprehend the leprosy dynamic, and reinforce the superimposed regions of high occurrence areas of patients presenting degree 2 of physical disability and cases in children lower than 15 years, and highlights the need to strengthen effective disease control measures, mainly in primary health care.

Acknowledgments The authors would like to thank the Manager of the Nucleus of endemic/Division of Epidemiological Surveillance - [Divisão de Vigilância

Epidemiológica (DIVEP)]/ Secretariat of Health of the Sergipe state (SES) for providing information.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Contributors The project was suggested by MB-S, MA, JB and AS. The statistical analyzes was performed by MB-S, IB, JS and AJ. The spatial analyzes was performed by MS, AS, AB and KA. The manuscript was written by MB-S, AB, DO, MD and AJ. All authors contributed to refining the idea, revising the manuscript and have agreed the final version.

Competing interests The authors declare that they have no conflicts of interest.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Table 1. Association of demographic and clinical data according to the operational classification of leprosy (PB and MB) in children under 15 years in Sergipe state, Brazil (2002-2015).

Variables	Operational Classification		
	PB (n = 407)	MB (n = 131)	*p*-value
Age mean ± SD	10.07 ± 3.38	10.5 ± 2.81	*0.46
Gender n (%)			
Male	197 (48.4)	83 (63.4)	+0.003
Ethnicity n (%)			
White	88 (21.6)	18 (13.7)	#0.02
Black	43 (10.5)	24 (18.3)	
Brown	251 (61.7)	78 (59.5)	
Indian	4 (0.9)	3 (2.3)	
Leprosy reaction n (%)	20 (4.9)	28 (21.4)	+<0.0001
Physical Disability Degree n (%)			
0	337 (82.8)	90 (68.7)	#0.0001
1	26 (6.4)	18 (13.7)	
2	3 (0.74)	6 (4.6)	
Number of affected nerves (mean ± SD)	0.19 ± 0.54	0.5 ± 1.03	*0.04
Number of Lesions (mean ± SD)	1.61 ± 1.14	9.92 ± 12.03	*<0.0001
HHC registered (mean ± SD)	4.6 ± 2.71	4.85 ± 3.04	*0.14
HHC examined (mean ± SD)	3.54 ± 3.04	4.05 ± 3.44	

*Mann-Whitney test; +Fisher's exact test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household contacts; SD = Standard Deviation. We missed data in some variables.

Table 2. Demographic and clinical aspects accordingly to the detection mode of leprosy cases in children under 15 years in Sergipe state, Brazil (2002-2015).

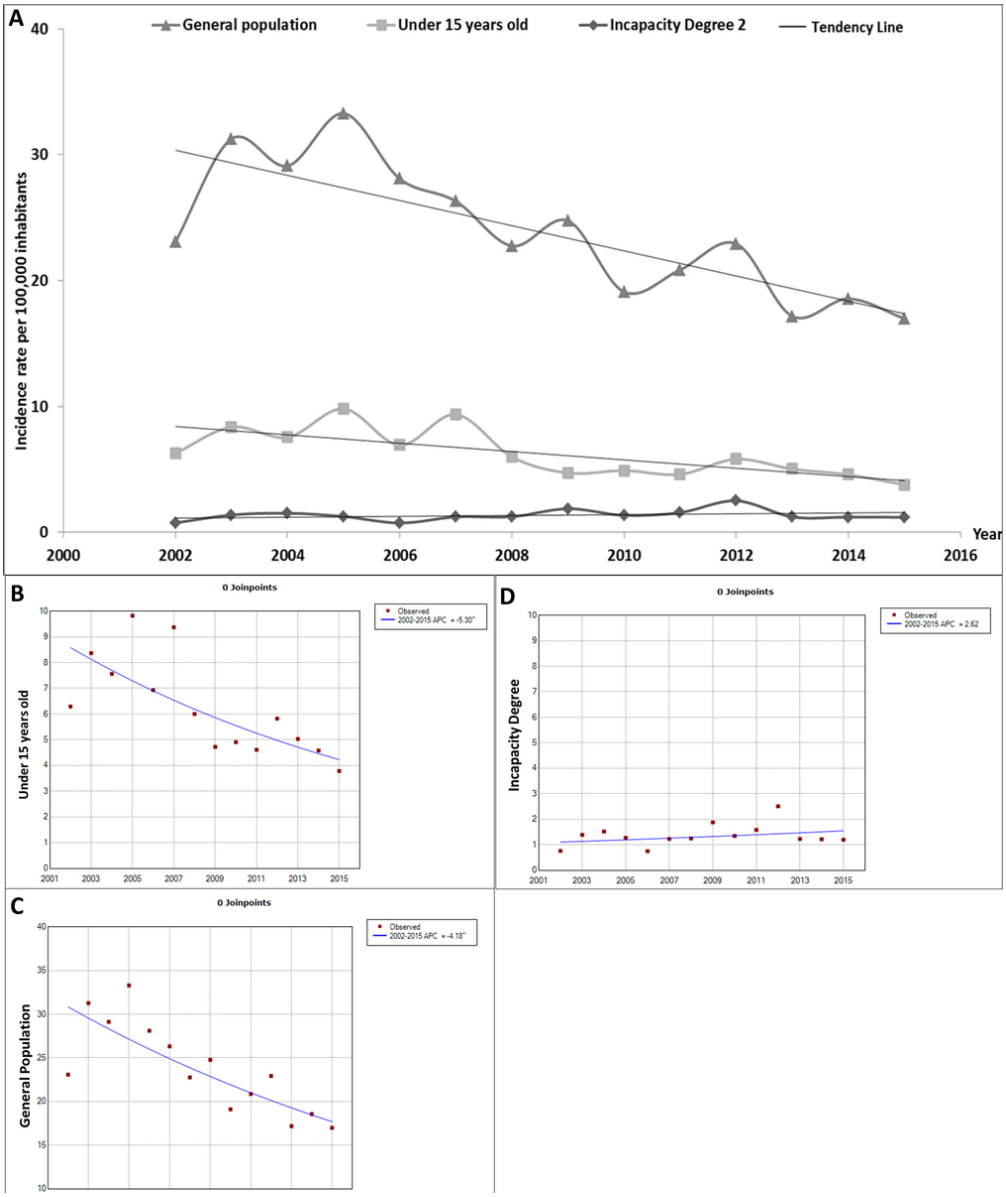
Variables	Patient detection mode				
	Spontaneous demand (n = 234)	Forwarding (n = 210)	Examined HHC (n = 69)	Other (n = 25)	*p*-value
Age mean ± SD	10.54 ± 3.28	10.02 ± 3.15	9.6 ± 3.38	9.6 ± 3.22	*0.04
Gender n (%)					
Male	123 (52.6)	110 (52.4)	38 (55.1)	09 (36)	#0.41
Leprosy reaction n (%)	17 (7.3)	28 (13.3)	2 (2.9)	1 (4.0)	#0.02
Physical disability degree n (%)					
0	199 (85.1)	150 (71.4)	55 (79.7)	18 (72)	#0.04
1	17 (7.3)	21 (10)	5 (7.2)	1 (4.0)	
2	1 (0.43)	08 (3.8)	0 (0.0)	0 (0.0)	
Number of affected nerves (mean ± SD)	0.24 ± 0.67	0.34 ± 0.81	0.06 ± 0.25	0.25 ± 0.5	*0.48
Number of lesion (mean ± SD)	3.64 ± 6.25	4.09 ± 8.68	2.04 ± 2.96	4 ± 5.2	*0.04
HHC registered (mean ± SD)	4.57 ± 2.53	4.59 ± 2.74	5.57 ± 3.81	3.45 ± 1.96	*0.04
HHC examined (mean ± SD)	3.71 ± 3.02	3.02 ± 2.98	4.64 ± 4.06	2.04 ± 1.77	*0.01

*Kruskal-Wallis test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household contacts; SD = Standard Deviation. We missed data in some variables.

Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (▲), in patients under 15 years old (■), degree 2 of physical disability (♦) and the tendency line. Temporal trend of standardized incidence rates by Joinpoint Regression for B) patients under 15 years old, C) General population and D) incapacity degree. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Number of leprosy cases according to the clinical operational classification (Paucibacilary - PB (■) and Multibacilary – MB (■) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. * Mann-Whitney test.

Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).



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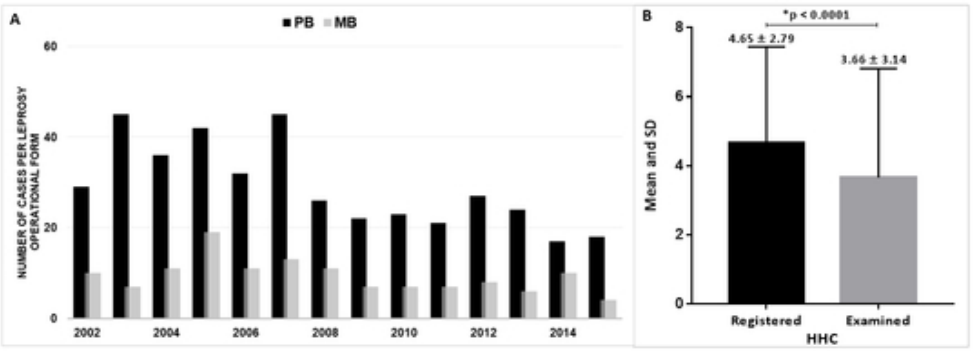

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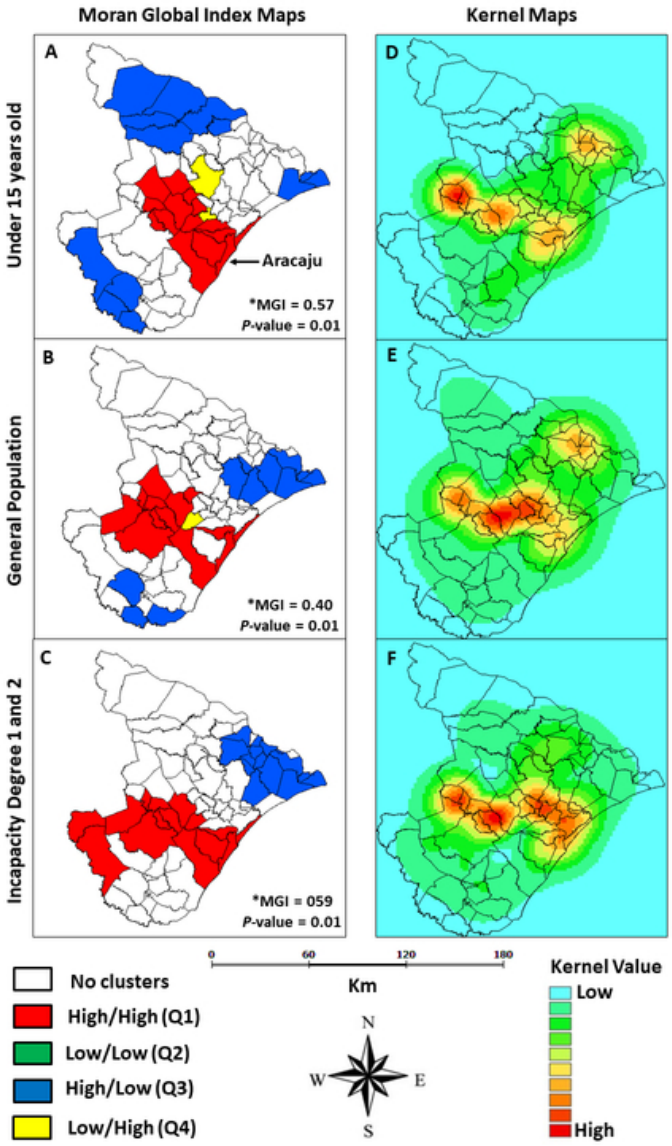

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48x64mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	01
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	02
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	04-05
Objectives	3	State specific objectives, including any prespecified hypotheses	05
Methods			
Study design	4	Present key elements of study design early in the paper	06
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	06
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	06
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	06
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	06-07
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	06
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	06-08
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	08-09
		(*b*) Describe any methods used to examine subgroups and interactions	08-09
		(*c*) Explain how missing data were addressed	08-09
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	08-09
		(*e*) Describe any sensitivity analyses	08-09
Results			08-09

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	09
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	09-10
		(b) Indicate number of participants with missing data for each variable of interest	--
Outcome data	15*	Report numbers of outcome events or summary measures	09-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	--
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	09-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023420.R3
Article Type:	Research
Date Submitted by the Author:	27-May-2019
Complete List of Authors:	Santos, Márcio; Universidade Federal de Sergipe, Health Education; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Santos, Allan; Universidade Federal de Sergipe, Nursing Barreto, Aline; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Souza, Mariana; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Goes, Marco; Universidade Federal de Sergipe, Medicine Barreto Alves, Jose Antonio; Universidade Federal de Sergipe, Nursing Barreto, Ikaro; Universidade Federal Rural de Pernambuco, Programa de Pos-Graduacao em Biometria e Estatistica Aplicada Silva, José-Rodrigo; Universidade Federal de Sergipe, Statistics and Actuarial Sciences Oliveira, Daniela; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology Araújo, Karina; Universidade Federal de Sergipe, Morphology Duthie, Malcolm; Infectious Diseases Research Institute Jesus, Amélia; Universidade Federal de Sergipe, Laboratory of Immunology and Molecular Biology; Universidade Federal de Sergipe, Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Infectious diseases, Public health
Keywords:	Leprosy, Children, Epidemiology < INFECTIOUS DISEASES, Spatial analysis

Clinical and Epidemiological Indicators and Spatial Analysis of Leprosy Cases in Patients Under 15 Years Old in an Endemic Area of Northeast Brazil: an ecological and time series study

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ABSTRACT

Objective: This study aimed to analyze the clinical and epidemiological indicators, temporal trends and the spatial distribution of leprosy in patients under 15 years old in an endemic area of Northeast Brazil.

Design: Regional surveillance study of all reported cases.

Setting: State of Sergipe, endemic area of Northeast Brazil.

Methods: An ecological and time series study was conducted, based on secondary data reported by the Brazilian Information System on Notifiable Diseases (SINAN) for leprosy cases diagnosed in Sergipe state (2002-2015). The analysis of temporal trends was performed using the Joinpoint Regression Program through Poisson regression. We performed spatial analysis by Kernel estimator and Moran index.

Results: The incidence rate was reduced from 6.29 to 3.78 cases per 100,000 inhabitants in 2002 and 2015, respectively. However, Sergipe was still classified as highly endemicity in 2015. The mean number of household contacts (HHC) examined was significantly lower than those registered. Clinical data indicated that 21.4% of the patients developed leprosy reactions, and 31.3% presented with some physical disability in the multibacillary (MB) groups. Patients diagnosed by exam within the HHC presented better indicators, such as lower percentage of leprosy reaction and physical disability. Spatial analysis showed the most risk areas distributed on the northeast and cities around the capital, Aracaju.

Conclusion: The data indicate that there is a persistence of active *M. leprae* transmission and a delay in disease detection, following a pattern of high endemicity in many municipalities. The early detection by household contacts examination is important not only to stop transmission but also to detect the cases in a less severe state.

Keywords: Leprosy; Children; Epidemiology; Spatial analysis.

Strengths and limitations of this study

- This is a surveillance study that includes all notified cases of leprosy, in a State of Brazil with moderate prevalence of the disease.
- This is the first summary of leprosy cases in patients under 15 years old in Sergipe state, Northeast Brazil.
- This study was conducted using secondary data reported by SINAN and this source of data may have datasets missing.
- We also mapped the leprosy cases and physical disability in children under 15 years in areas of higher prevalence of leprosy in the general population, using geoprocessing tools.
- We compared the leprosy patient detection mode and how it affects the disease severity at diagnosis and the occurrence of leprosy reactions and physical disabilities.

INTRODUCTION

Leprosy is a chronic infectious disease caused by infection with *Mycobacterium leprae* [1]. This pathogen exhibits tissue tropism for phagocytes in the skin and Schwann cells within peripheral nerves and it presents a long incubation time (from 2 to 7 years) [2,3]. The disease can manifest across a broad spectrum of symptoms and the diagnosis is made based on the clinical signs (cutaneous lesions with altered sensitivity and neurological lesions). Patients are then classified as multibacillary (MB) and paucibacillary (PB) for treatment purposes, according to criteria accepted by Brazilian Ministry of Health (BMH) and International Leprosy Association (ILA) [1,2,4–7].

Despite control efforts including the widespread use of multidrug therapy (MDT), and the stabilization of the reported new case detection rate in the last few years, leprosy remains endemic in many developing countries [3–6,8–11]. In 2014, the World Health Organization (WHO) reported 213,899 new leprosy cases in 121 countries or territories [4]. Brazil ranks as the second most burdened country in the world concerning number of new cases (31,064 in 2014) and has by far the highest number of cases reported in Americas [4,12,13]. Within Brazil, the highest prevalence has been reported in the North, Northeast and Midwest regions [8,9]. The incidence of leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8]. In 2013, 2,439 new cases were diagnosed in children under 15 years old in Brazil, yielding a detection rate of 5.03 per 100,000 inhabitants [4].

Studies have demonstrated that leprosy presents higher incidence in population with: low educational degree, precarious health services and domiciliary infrastructure

settlements, and reduced investment in prevention and control [14–16]. Moreover, the high incidence rate in children under 15 years is important to indicate there is early exposure of the population to the bacillus, that is associated to elevated prevalence in general population, being a good indicator of a high transmission and bad quality of the control programs [10,12,17–20]. There is no study reporting the incidence of leprosy in children under 15 years in Sergipe state.

Recently, studies mapping the occurrence of infectious diseases according to their spatial distribution using "Geographic Information Systems (GIS)" have provided important information for public health programs, revealing areas of priority for interventions programs to more efficiently plan and implement control measures [2,9,16,21–23]. The use of GIS in leprosy may allow the identification of spatial-temporal distributions and profile of incidence in defined geographical areas, this potentially contributing to the effectiveness of interventions.

Despite breakthroughs in the epidemiological of leprosy, further improvements in understanding of the disease dynamics in different regions is important for the support of health services as a means for leprosy control. Spatial analyzes studies can provide important understanding of the transmission patterns of *M. leprae* and allow the identification of risk factors [21,23]. The aim of this study was to describe the 1) various clinical and epidemiological indicators of leprosy; to analyze 2) temporal trends and 3) the spatial distribution of leprosy cases in patients under 15 years old in an endemic area of Northeast Brazil.

METHODS

Study Design

The source of all data from this study was the leprosy cases and the information of each individual case notified by the health centers of the municipalities to the SINAN (Information System on Notifiable Diseases) from the State of Sergipe, Brazil. This is an important database of the Secretariat of Health of all States of Brazil, to report information about sociodemographic, clinical features and the address of notifiable diseases. Leprosy is a notifiable disease in Brazil, and as a legislative requirement, all leprosy cases have to be notified to the SINAN, including information about social and demographic features, clinical forms and follow-up of each patient. Sergipe is located on the coast of Northeast Brazil. The State has 75 municipalities and the capital is Aracaju. It has a population of 2,068,017 inhabitants and an area of 21,910,354km², equivalent to 0.26% of the national territory. The median population per county was 27,573.56 in 2015 [16]. Population data were obtained from the IBGE (Brazilian Institute of Geography and Statistics), based on population estimates for the intercensus years (2002 - 2015). An ecological and time series epidemiological study was conducted, based on the leprosy cases reported by SINAN. The historical (from 2002 to 2015) reporting of leprosy cases in children under 15 years old was analyzed. We also compared those data with data in all ages and with the occurrence of physical disability. The incidence of leprosy (referred as the new case detection rate) in Sergipe in 2010 was 18.4 per 100,000 [8].

The clinical and epidemiologic indicators collected by Investigation and Notification Form from SINAN, were: gender, age, ethnicity, address, operational classification (PB

and MB), clinical form [according to the more refined Ridley-Jopling classification [24,25], based on histopathological analyses: indeterminate leprosy (IL), true tuberculoid (TT), borderline leprosy (BL) and lepromatous leprosy (LL)], leprosy reaction (LR), number of affected nerves, degree of physical disabilities, number of household contacts (HHC) registered and examined, and the patient detection mode.

The parameters adopted by BMH and ILA were followed for interpreting the incidence rate of leprosy in patients under 15 years old. As such, this is classified as: low (<0.50 cases per 100,000 inhabitants); medium (0.50 to 2.49); high (2.50 to 4.99); very high (5.00 to 9.99) and hyperendemic (≥10.00) [4].

Spatial analysis

Thematic maps were constructed in each municipality for the period examined according to the leprosy incidence rate in patients under 15 years old and in general population, and for patients presenting with physical disability (incapacity degree 1 or 2). The kernel technique was applied to identify the intensity of the distribution of leprosy cases in the state of Sergipe. This technique shows the statistically generated surface density for the visual detection of hot spots, that indicates agglomeration of cases in a spatial distribution. This is an appropriate data interpolation for application in point location data. The point distribution was transformed into a smoothed surface and presented as a continuous map, representing different levels of case intensity. The amount of smoothing, that is, the width of the radius of influence was defined as 3,000 meters, since this value generated an adequate representation of the distribution of the

leprosy cases in the municipalities, minimizing the overlapping bias or the occurrence of sub distribution patterns smoothed [16,21].

We performed either spatial autocorrelation analysis between disease detection rates for each group. The Moran Global Index (MGI)[26] was calculated to identify clusters with risks for disease occurrence. We construct a spatial proximity matrix obtained by the contiguity of spatial correlation. The MGI was calculated as follows:

(Moran Global Index Mathematical Equation 1)

$$I = \frac{[(n\Sigma^{n}_{i}\Sigma^{n}_{j}\omega_{ij}(\gamma_i - \check{y})(\gamma_j - \check{y})]}{[\Sigma^{n}_{i}(\gamma_i - \check{y})^2\Sigma^{n}_{i}\Sigma^{n}_{j}\omega_{ij}]}$$

ω_{ij} is a contiguity matrix element (ω); γ_i is the incidence rate of municipality $_i$; γ_j is the incidence rate of municipality $_j$; $\check{y}$ is the mean of sample and the symbol n represents the total number of municipalities [26].

The MGI provides a general grouping measure and it is possible to know if there are significant differences between the analyzed areas. However, it does not indicate the clusters localization. To do that, we performed the Moran Local Index diagram [26] to build maps and identify the areas with spatial dependence (Local Index of Spatial Association - LISA) of the annual detection means, as follows:

(Local Index of Spatial Association Mathematical Equation 2)

$$I = \frac{n[(Z_i\Sigma^{n}_{j}\omega_{ij}Z_j)]}{(\Sigma^{n}_{j}Z^{2}_{j})}$$

$Z_i = yi - \bar{y}$; $Zj = yj - \bar{y}$; ω_{ij} is a contiguous matrix element ω; yi is the incidence rate of municipality i; yj is the incidence rate of municipality j; $\bar{y}$ is the sample mean and the symbol n represents the total number of cities [26]. The Moran Map was used to indicate the clusters and their relationship with the neighbors. This analysis verifies the existence of spatial dependence and risk patterns: Q1 (high/high) and Q2 (Low/Low), which indicate municipalities with similar values between their neighbors and Q3 (high/low) and Q4 (low/high) for municipalities with different values between their neighbors and no spatial association. A spatial proximity matrix obtained by the contiguity criterion was adopted. The level of significance was 5% and the Moran Global Index (I) varying between -1 and +1, representing the spatial autocorrelation of leprosy detection rate in the geographic space analyzed to identify spatial clusters and risk areas. Values between 0 and +1 indicate positive spatial autocorrelation (Q1 and Q2) and between -1 and 0 negative spatial autocorrelation (Q3 and Q4) [26,27]. Both Moran Index and Kernel maps were constructed using TerraView software 4.2.2.

Statistical analysis

The crude annual incidence rates were calculated for the general population, according to the population data from IBGE. For patients younger than 15 years the annual rates were age-standardised, and the standard population used was the population under 15 years from IBGE. Demographic and clinical data were compared across the different subgroups and according to operational classification and the patient detection mode. Percentage, mean and standard deviation of the groups were calculated. For groups'

comparison, we first analyze if the data followed normal distribution by the D'Agostino and Pearson normality test, and statistical differences between the groups were determined by Mann-Whitney and Kruskall-Wallis tests. All analysis was performed using SPSS Statistics, version 24.0. Results were considered statistically different when *p*-values < 0.05 were obtained.

In order to enable trend analysis, annual incidence rate of leprosy was calculated as dependent variables (y), and the years of the study period as the independent variables (x). Initially, trend analysis was performed with the Joinpoint program, version 4.0.4 (Surveillance Research, National Cancer Institute, USA). This program estimates the Annual Percentage Change (APC) of a segmented linear regression (Jointpont regression) and identifies inflection points. Each inflection point reflects changes in the increase or decline of leprosy rates [27]. The joinpoint regression provided the adjustment of a series of lines as well as their inflection points on a logarithmic scale by means of the annual trend test. All the models were run under the same specifications. The minimum number of observations from a joinpoint to either end of the data was 3 and the minimum number of observations between two joinpoints was 4. The maximum number of joinpoints allowed was 2. To obtain the adjustment based on the best line of each analyzed segment, the Monte Carlo permutation method was used as a test of significance. From the definition of the follow-ups, the annual percentage change (APC) and the average annual percentage change (AAPC), with their respective 95% confidence intervals, were estimated and tested. If the occurrence of an inflection point with inverted direction was verified, the study periods were analyzed separately. The number of inflections used in the analysis was the result of models defined by the program itself, in

order to allow the best representation of the trend, with the lowest number of inflection points. The result showed growth (positive APC values), reduction (APC negative values) or maintenance (APC value equal to zero) of the trend throughout the historical series analyzed (2006-2014). Poisson regression is used to determine the number of segments required to adequately explain the relationship between two variables [27]. We considered the points of trend change that presented p-value < 0.05.

Ethical Considerations

For conducting this study, authorization was previously requested from Coordination of Epidemiological Surveillance, Sergipe state. This project involved research on human subjects and was approved by the Ethics and Research Committee of the Federal University of Sergipe, CAAE 0152.0.107.000-07.

Patient and Public Involvement statement

There was no patient and public involvement in this study. The study was based on secondary data.

RESULTS

Trends in reported leprosy incidence among children

The incidence of leprosy in children under 15 years has declined from 6.29 cases per 100,000 inhabitants in 2002, to 3.78 in 2015, confirmed by Joinpoint regression analyzes (APC = -5.3 and *p*-value < 0.05; **Figure 1A and B**). Similarly, the leprosy incidence rate in the general population of Sergipe decreased from 23.08 cases to 16.99 per 100,000 inhabitants between 2002 and 2015 (**Figure 1A and C**). The occurrence of degree 2

physical disability, however, increased in this period (0.76 in 2002 to 1.2 in 2015, respectively), however it is a non-significant increasing trend (APC = 2.6 and *p*-value = 0.20; **Figure 1A and D**). The composition of leprosy cases according to the operational classification (PB and MB) was relatively stable across this period, with majority of cases presenting as PB (**Figure 2A**). We also observed the mean number of HHC registered (4.65 ± 2.79) was slightly, but significantly, higher than the number examined (3.66 ± 3.14; *p*-value < 0.0001; **Figure 2B).**

Demographics of childhood leprosy cases

Next, we evaluated the association among clinical and epidemiological variables according to the leprosy operational classification (patients presenting as PB and MB). Patients presenting as MB or PB were in similar age to (10.5 ± 2.81 and 10.07 ± 3.38, respectively). Despite the extended incubation period of *M. leprae*/leprosy, six cases (1.11%) were reported in children less than one year of age. Of the 538 leprosy cases identified among children under 15 years old the majority were PB [407 (75.7%) PB and 131 (24.3%) MB; **Table 1**]. When stratified on gender, however, the proportion of boys presenting with MB (63.4%) was significantly higher than presenting with PB (48.4%; *p*-value = 0.003). An interesting difference was observed when we calculated the ratio (PB/MB) according the ethnic groups. Among those identified as black, the ratio (43/24) was 1.79. Conversely, the ratio of white was higher 4.88 (88/18; *p*-value = 0.02).

As expected, the occurrence of leprosy reactions was significantly higher in MB (21.4%) than PB (4.9%; *p*-value < 0.0001) patients. The occurrence of degree 2 of physical disability was also higher in MB (4.6%), than in PB patients (0.74%; *p*-value = 0.0001).

Consistent with this, we observed that the mean of number of affected nerves was higher in MB (0.5 ± 1.03), than PB (0.19 ± 0.54; *p*-value = 0.04).

Impact of case detection methods on leprosy presentation

We also performed analysis of association among clinical and epidemiological variables according to the leprosy patient detection mode. The patients were grouped in: spontaneous demand (SDem: patients that looked for medical assistance by themselves); forwarded (FW: patients that were forwarded from a primary clinic to a leprosy reference center); examined HHC; and other. We observed that patients detected by the examined HHC method presented lower mean age (9.6 ± 3.38) than those detected by either the SDem (10.54 ± 3.28) or FW methods (10.02 ± 3.15; *p*-value = 0.04; **Table 2**). Interestingly, the percentage of leprosy reaction among the examined HHC group (2.9%; *p*-value = 0.02) was lower than that observed among SDem (7.3%) and FW (13.3%). In addition, degree 2 of physical disability was not observed among patients detected in examined HHC group, while SDem and FW presented 0.43% and 3.8%, respectively (*p*-value = 0.04). Furthermore, patients identified among examined HHC presented with lower numbers of lesions (2.04 ± 2.96; *p*-value = 0.04) than SDem (3.64 ± 6.25) and FW (4.09 ± 8.68). Taken together, these data reinforce the importance of HHC examination for the detection of leprosy patients before advancement to more severe symptoms.

Spatial analyze data

Next, we performed the spatial analysis of leprosy cases in the general population, in patients under 15 years old, and in patients presenting with physical disability (both

degree 1 and 2). Moran maps have showed higher risk clusters (Q1 - in red; **Figure 3A-C**) in similar areas when comparing the maps regarding leprosy cases in children under 15 years old, in general population, and patients presenting some physical disability (degree 1 and 2). The higher risk clusters (Q1) were localized in Sergipe state center and in the metropolitan area around the capital of State. The municipalities with no spatial association (Q3 - in blue) were localized in the Semiarid region, in the northwest area and in the south region.

Similarly, The Kernel estimator, through data interpolation, showed densities (hot spots) of the highest incidence rates located at the northeast and east center regions and in the counties around the state capital (Aracaju city; **Figure 3D-F**). Lower intensity was observed on the western region. Municipalities with intermediate to high incidence values are seen in yellow and red tones of each subfigure. Low incidence areas were reported on west coast municipalities, mostly in smaller counties with small populations.

DISCUSSION

Previous studies have demonstrated that the high leprosy cases detection in patients under 15 years old is a bad parameter for leprosy control program, because it indicates early bacillus transmission from undiagnosed cases [18]. Some authors have speculated either about the risk of vertical/transplacental transmission or through breastfeeding [12].

In Brazil, the highest leprosy incidence rate in children was reported in the North area (11.91 cases per 100,000 inhabitants), followed by Northeast (8.12) [12]. We observed the leprosy incidence rate was reduced in children under 15 years old from 2002 to 2015 in Sergipe state, however considering the parameters adopted by BMH, the state was classified as very high endemicity in 2002, and still as high endemicity in 2015. It remains also with elevated incidence rate and stationary tendency of degree 2 of physical disability. Those data reinforce either that the transmission is intense at early age, there is lack of an effective public health and the disease control is focused in the MDT [12,18]. A similar study performed at Fortaleza city (Brazil), reported also that although a decreasing has been observed on overall detection rate, the number of new cases in those under 15 years old remains stable [13].

Leprosy reactions and physical disability are the most severe leprosy clinical complications [8,28,29]. In addition, the increase or stability of the prevalence of degree 2 of physical disability indicates persisting late diagnosis [13,29]. The early diagnosis of leprosy is essential to the prevention of deformities, whose repercussions are still more catastrophic in children and adolescents [28]. Our data reported 21.4% children with leprosy reaction (LR) and 31.3% with some physical disability in the MB groups. Furthermore, MB patients presented higher mean of affected nerves. Generally, patients under 15 years old do not use to present LR, but studies have reported a low frequency of LR, varying between 1.36% and 8.33% [28]. Those data reinforce that, although there is a decreasing incidence in leprosy, patients have been exposed to bacillus early in life and diagnosed belatedly and hence they have been also developing into some clinical complications.

We have observed either that the mean of HHC examined was significantly lower than those registered by SINAN. Moreover, leprosy patients detected by exam in HHC presented lower mean of age, affected nerves, number of lesions, occurrence of LR and no physical disability, when compared with those identified by spontaneous demand or forwarded by others. On the other hand, mostly of patients presenting as degree 2 of physical disability were identified into those forwarded to a leprosy reference center, probably because they started presenting some physical disability. HHC and neighbors are the most important *M. leprae* active sources. The risk of a person developing leprosy is nine times greater among HHC and up to four times greater among contacts with neighbors [12]. Therefore, our data reinforce the importance of leprosy early diagnosis by exam in patients and their household contacts. Besides that, the treatment and the home visits by public health programs, and an efficient health program in schools could represent important actions for the early diagnosis and the reduction of leprosy clinical complications, especially in children.

Spatial analysis of health events aim to identify geographical patterns by maps of risk and to point out areas of higher severity and to facilitate the planning of public health interventions [9]. The Kernel maps showed the spatial dynamic of leprosy, with a heterogeneous geographical pattern and the highest risk areas for leprosy infection. The highest incidence on counties around the Capital can be due there was a leprosarium at the Nossa Senhora do Socorro (a city of the metropolitan area of Aracaju), that has presented elevated detection rate in mostly evaluated years. Moreover, that area presents reference center to leprosy diagnosis and treatment and hence they have

several patients forwarded to these leprosy clinics. It can be also associated with weather featuring such as humidity, considering either that counties near to São Francisco River presented also elevated incidence. In the Malawian Karonga district, a positive relationship between the proximity of water and leprosy incidence was previously reported [5]. Some authors have hypothesized that *M. leprae* survives longer outside of human body in humid compared to dry atmospheres [9,13].

Interestingly, higher risk clusters were identified in similar areas when we analyzed the occurrence of leprosy cases in children, in general population and patients presenting physical disability. It corroborates the hypothesis that the early transmission of *M. leprae* and the occurrence of leprosy in children under 15 years old is directly related to the late diagnosis, which explains the occurrence of patients with degree 2 of physical disability in the same geographic distribution [28]. The maps present certain disagreements regarding the occurrence of leprosy cases in the state of Sergipe because they use distinct techniques of spatial analysis. The Kernel estimator produces a continuous surface, with densities calculated at all locations, based on total number of cases and no considering the geographical boundaries of the municipalities [27,30,31]. The Kernel technique presents greater advantages to the quick visualization of areas that deserve attention, besides not being affected by political-administrative division, while the Moran technique, constructs maps considering the political-administrative divisions of the state and the clusters are based on the number of cases divided by the municipalities [27,30].

Our study had some limitations, particularly because it was conducted using secondary data reported by SINAN. This source of date can present numbers under notification and datasets missing. However, in Brazil we have a specific normative that is an obligation to notify several diseases to SINAN, and leprosy is one of them. SINAN is an important database of the Secretariat of Health of all States of Brazil, to report information about sociodemographic, clinical features and the address of each diagnosed case. This source of data can present under notification because Leprosy is an asymptomatic disease and the active search would be important to detect more cases, but all diagnosed cases are reported to SINAN. The limitation mentioned about missing data is not very important in the case of the disease prevalence, but the complete information about the cases follow-up, such as degree of neurological disability at the end of treatment, leprosy reactions and treatment details, because it is a secondary database that depends on other doctors or nurses from the health care centers to fulfill the information. Despite this, those data reported high endemicity of leprosy cases in patients under 15 years old, and this study do not focus on patient follow-up.

In summary, our study demonstrated that the leprosy incidence rate has decreased in Sergipe state. However, it is still classified as high endemicity considering the WHO proposed ratios for children under 15 years. Patients detected by exam in collectivity or HHC presented better indicators. Altogether, the epidemiological data and spatial analysis indicate that there is persistence of active transmission of *M. leprae* and later case detection in Sergipe state, increasing the risk of transmission in children. In addition, the spatial analysis brings new advantages to comprehend the leprosy dynamic, and reinforce the superimposed regions of high occurrence areas of patients

presenting degree 2 of physical disability and cases in children lower than 15 years, and highlights the need to strengthen effective disease control measures, mainly in primary health care.

Acknowledgments The authors would like to thank the Manager of the Nucleus of endemic/Division of Epidemiological Surveillance - [Divisão de Vigilância Epidemiológica (DIVEP)]/ Secretariat of Health of the Sergipe state (SES) for providing information.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Contributors The project was suggested by MB-S, MA, JB and AS. The statistical analyzes was performed by MB-S, IB, JS and AJ. The spatial analyzes was performed by MS, AS, AB and KA. The manuscript was written by MB-S, AB, DO, MD and AJ. All authors contributed to refining the idea, revising the manuscript and have agreed the final version.

Competing interests The authors declare that they have no conflicts of interest.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The source of all data from this study was the leprosy cases and the information of each individual case notified by the health centers of the municipalities to the SINAN (Information System on Notifiable Diseases) from the State of Sergipe, Brazil. SINAN is an important database of the Secretariat of Health of all States of Brazil, to report information about sociodemographic, clinical features and the address of notifiable diseases, such as leprosy.

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Table 1. Association of demographic and clinical data according to the operational classification of leprosy (PB and MB) in children under 15 years in Sergipe state, Brazil (2002-2015).

Variables	Operational Classification		
	PB (n = 407)	MB (n = 131)	*p*-value
Age mean ± SD	10.07 ± 3.38	10.5 ± 2.81	*0.46
Gender n (%)			
Male	197 (48.4)	83 (63.4)	+0.003
Ethnicity n (%)			
White	88 (21.6)	18 (13.7)	#0.02

Black	43 (10.5)	24 (18.3)	
Brown	251 (61.7)	78 (59.5)	
Indian	4 (0.9)	3 (2.3)	
Leprosy reaction n (%)	20 (4.9)	28 (21.4)	+<0.0001
Physical Disability			
Degree n (%)			
0	337 (82.8)	90 (68.7)	#0.0001
1	26 (6.4)	18 (13.7)	
2	3 (0.74)	6 (4.6)	
Number of affected nerves (mean ± SD)	0.19 ± 0.54	0.5 ± 1.03	*0.04
Number of Lesions (mean ± SD)	1.61 ± 1.14	9.92 ± 12.03	*<0.0001
HHC registered (mean ± SD)	4.6 ± 2.71	4.85 ± 3.04	*0.14
HHC examined (mean ± SD)	3.54 ± 3.04	4.05 ± 3.44	

*Mann-Whitney test; +Fisher's exact test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household contacts; SD = Standard Deviation. We missed data in some variables.

Table 2. Demographic and clinical aspects accordingly to the detection mode of leprosy cases in children under 15 years in Sergipe state, Brazil (2002-2015).

Variables	Patient detection mode				
	Spontaneous demand (n = 234)	Forwarding (n = 210)	Examined HHC (n = 69)	Other (n = 25)	*p*-value
Age mean ± SD	10.54 ± 3.28	10.02 ± 3.15	9.6 ± 3.38	9.6 ± 3.22	*0.04
Gender n (%)					
Male	123 (52.6)	110 (52.4)	38 (55.1)	09 (36)	#0.41
Leprosy reaction n (%)	17 (7.3)	28 (13.3)	2 (2.9)	1 (4.0)	#0.02
Physical disability degree n (%)					
0	199 (85.1)	150 (71.4)	55 (79.7)	18 (72)	#0.04
1	17 (7.3)	21 (10)	5 (7.2)	1 (4.0)	
2	1 (0.43)	08 (3.8)	0 (0.0)	0 (0.0)	
Number of affected nerves (mean ± SD)	0.24 ± 0.67	0.34 ± 0.81	0.06 ± 0.25	0.25 ± 0.5	*0.48
Number of lesion (mean ± SD)	3.64 ± 6.25	4.09 ± 8.68	2.04 ± 2.96	4 ± 5.2	*0.04
HHC registered (mean ± SD)	4.57 ± 2.53	4.59 ± 2.74	5.57 ± 3.81	3.45 ± 1.96	*0.04
HHC examined (mean ± SD)	3.71 ± 3.02	3.02 ± 2.98	4.64 ± 4.06	2.04 ± 1.77	*0.01

*Kruskal-Wallis test; #Chi-square test. PB = paucibacillary; MB = multibacillary; HHC = household contacts; SD = Standard Deviation. We missed data in some variables.

Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (▲), in patients under 15 years old (■), degree 2 of physical disability (♦) and the tendency line. Temporal trend of standardized incidence rates by Joinpoint Regression for B) patients under 15 years old, C) General population and D) incapacity degree. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Number of leprosy cases according to the clinical operational classification (Paucibacilary - PB (■) and Multibacilary – MB (■) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. * Mann-Whitney test.

Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).

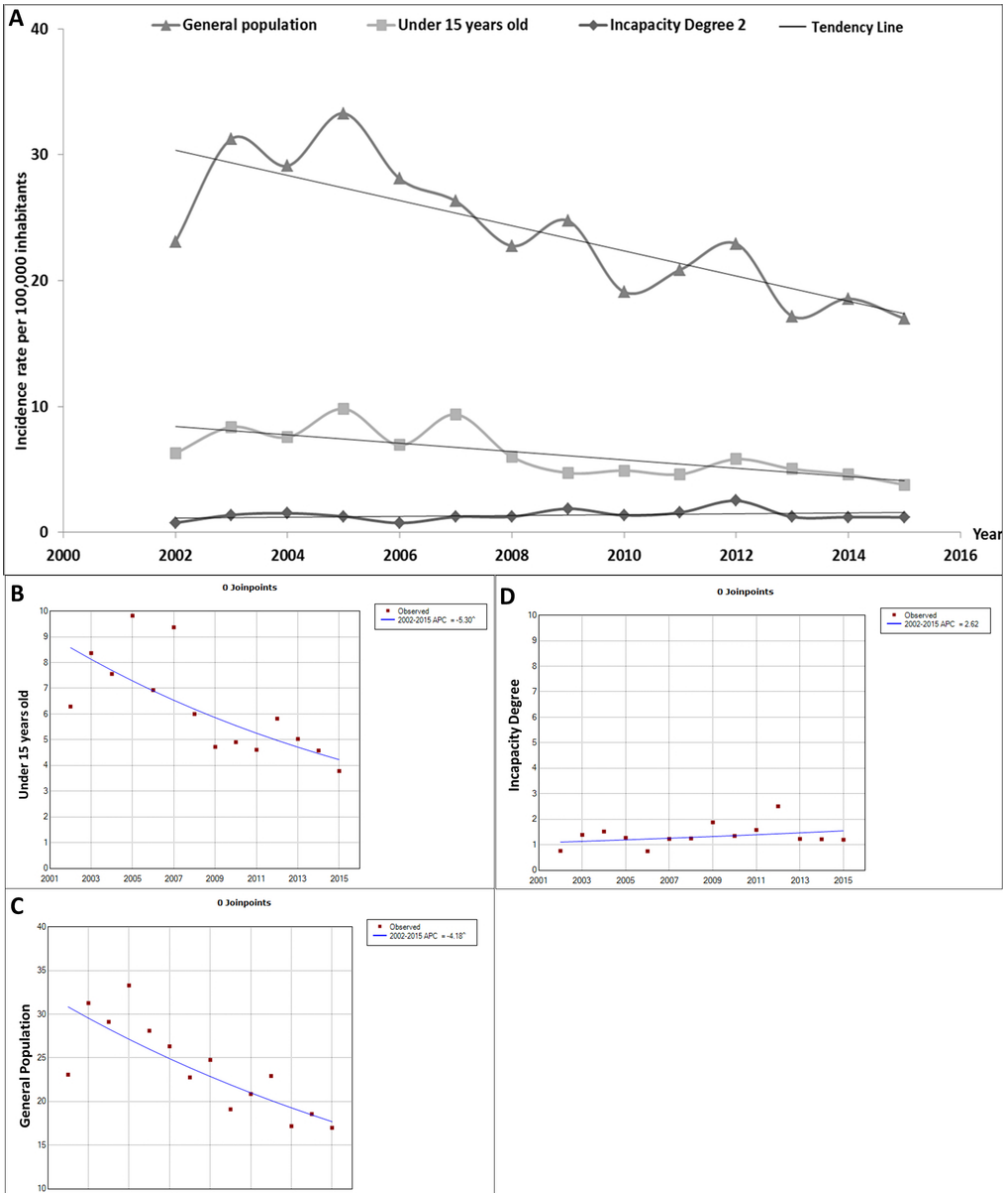

Figure 1. Leprosy incidence rates and temporal trend in state of Sergipe, Northeast Brazil, 2002-2015. A) Leprosy incidence rate (per 100,000 inhabitants) in general population (☐), in patients under 15 years old (☐), degree 2 of physical disability (☐) and the tendency line. Temporal trend of standardized incidence rates by Joinpoint Regression for B) patients under 15 years old, C) General population and D) incapacity degree. Data were considered statistically different when p-value < 0.05. CI: Confidence Interval.

85x101mm (300 x 300 DPI)

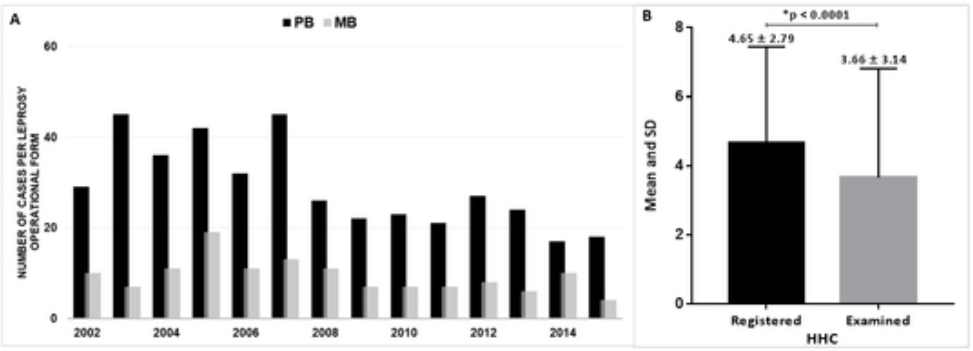

Figure 2. Epidemiological, clinical and operational indicators in leprosy patients, state of Sergipe, Brazil, 2002-2015. A) Number of leprosy cases according to the clinical operational classification (Paucibacilary - PB (☐) and Multibacilary – MB (☐) forms). B) Mean and standard deviation (mean ± SD) of the number of household contacts (HHC) that were registered and examined for leprosy diagnosis. Data were considered statistically different when p-value < 0.05. * Mann-Whitney test.

46x18mm (300 x 300 DPI)

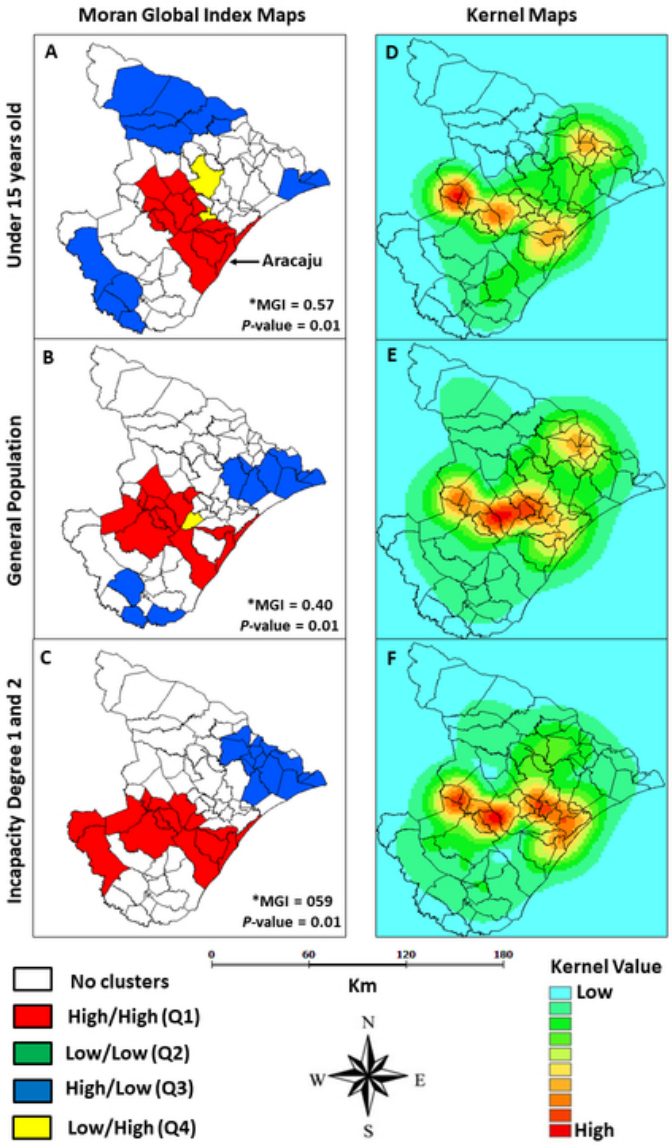

Figure 3. Spatial analysis maps. Moran Global Index maps and Kernel maps were constructed by TerraView Software 4.2.2. The Moran Global Index (*MGI) was calculated to identify the occurrence of clusters. Moran (A) and Kernel (B) maps of leprosy cases in patients under 15 years old. Moran (C) and Kernel (D) maps of leprosy cases in the general population. Moran (E) and Kernel (F) maps of occurrence of incapacity degree 1 and 2. Sergipe state, Northeast Brazil (2002 – 2015).

48x64mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	01
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	02
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	04-05
Objectives	3	State specific objectives, including any prespecified hypotheses	05
Methods			
Study design	4	Present key elements of study design early in the paper	06
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	06
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	06
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	06
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	06-07
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	06
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	06-08
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	08-09
		(*b*) Describe any methods used to examine subgroups and interactions	08-09
		(*c*) Explain how missing data were addressed	08-09
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	08-09
		(*e*) Describe any sensitivity analyses	08-09
Results			08-09

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	09
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	09-10
		(b) Indicate number of participants with missing data for each variable of interest	--
Outcome data	15*	Report numbers of outcome events or summary measures	09-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	--
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	09-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	--

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.