Original article

Spatial study of leprosy in Bahia, Brazil, 2001-2012: an approach based on the local empirical Bayesian model

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Abstract

Objective: to compare the temporal evolution and spatial distribution of epidemiological indicators of leprosy, both crude and also corrected using the empirical Bayesian model, Bahia, Brazil, 2001-2012. **Methods:** this was an ecological study using data from the Notifiable Diseases Information System; all 417 municipalities in Bahia were included and the following indicators per 100,000 inhabitants were analyzed – detection rate of new cases in the general population, in those <15 years old, and in those with grade 2 physical disability –; the local empirical Bayesian model was used to smoothen the indicators, and Student's t-test was used to compare means. **Results:** indicators estimated by the model were higher than crude indicators; estimated detection rates in the general population and in those <15 years old were higher than crude rates in 253 (60.7%) and 209 (50.1%) municipalities, respectively; areas of greatest risk were concentrated in the northwestern and southern regions of the state. **Conclusion:** spatial distribution of the disease was heterogeneous and there was possible underreporting of cases.

Keywords: Leprosy; Spatial Analysis; Information Systems; Ecological Studies.

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Introduction

Leprosy is a neglected tropical disease (NTD), caused by *Mycobacterium leprae*. It is an Acid-Fast Bacillum (AFB) with predilection for skin cells and peripheral nerves, resulting in lesions of a dermatoneurological nature, and therefore able to cause significant physical, functional and psychological impairments in affected individuals.[1-3]

Since the implementation of multidrug therapy in the early 1980s, the occurrence of leprosy has been progressively reduced worldwide. Despite all the efforts undertaken, however, the disease affected more than 214,000 people in 2016 alone, including more than 18,000 children. Among these new cases, more than 12,000 people had permanent physical disabilities.

Brazil is the only country in the world where it has not been possible to achieve the elimination target rate for the disease, i.e., prevalence of less than 1 case per 10,000 inhabitants.[3] Although the number of people with leprosy has decreased in recent years, in 2016 Brazil was still in first place in the global ranking of the new case detection rate and in second place in the absolute number of cases diagnosed, second only to India.[4-7]

Between 2012 and 2016, according to Ministry of Health data, 151,764 new cases of leprosy were reported, with a new case detection rate equal to 14.97 / 100,000 inhabitants, which classified the country as having high endemicity. In that same period, the new case detection rate in the population aged 0-14 years was equal to 4.5/100,000 inhab., also classifying the country as having high endemicity in this age range.[6]

> *In Northeastern Brazil, leprosy distribution is not homogeneous. The state of Bahia has occupied an intermediate position, being thirteenth in the ranking of the Brazilian states and sixth among the Northeastern states.*

In Northeastern Brazil, leprosy distribution is not homogeneous. Whereas in 2016 the state of Rio Grande do Norte recorded an average of 5.7 new cases per 100,000 inhab., the state of Maranhão registered 47.3/100,000 inhab. The state of Bahia has occupied an intermediate position, being thirteenth in the ranking of the Brazilian states and sixth among the Northeastern states, based on the detection rate of new cases registered in 2015. With regard to absolute number of cases, Bahia was in second place regarding the general population (2,077 cases) and in third place in relation to the population aged 0-14 years (116 cases).[7]

The spatial study approach to leprosy has contributed to the understanding of its transmission dynamics, identification of factors associated with its occurrence, as well as priority areas for intervention.[8-11] Standing out among the tools used in these studies is empirical Bayesian modeling, the purpose of which is to reduce the random fluctuation of data by producing corrected and therefore more stable rates.[12,13]

The objective of this study was to compare the temporal evolution and spatial distribution of epidemiological indicators of leprosy, both crude and also corrected using the empirical Bayesian model, in Bahia, Brazil, 2001-2012, thus contributing to the understanding of the dynamics of the disease in that state.

Methods

This was an ecological study having the state of Bahia as its territorial basis for analysis. Bahia is comprised of 417 municipalities and has a population of 14,016,906 inhabitants according to the 2010 demographic census.[14]

The data regarding new leprosy cases diagnosed and notified between 2001 and 2012 were obtained from the Notifiable Diseases Information System (SINAN), via the database of the Brazilian National Health System Information Technology Department (DATASUS): http://www2.datasus.gov.br.[15] Only new cases were included. Cases closed because of incorrect diagnosis were excluded, as were duplicated cases. The population data used, also resulting from the 2010 census, were provided by the Brazilian Institute of Geography and Statistics (IBGE),[16] as well as intercensal projections for the remaining years studied.

Three indicators were selected for analysis, in accordance with the provisions of Ministry of Health Ordinance GM/MS No. 149, dated February 3, 2016:[17]

Indicator 1 - Detection rate of new cases of leprosy in the general population per 100,000 inhabitants;

Indicator 2 - Detection rate of new cases of leprosy in children under 15 years old per 100,000 inhabitants; and

Indicator 3 - Rate of new cases of leprosy with grade 2 physical disability at the time of diagnosis per 100,000 inhabitants.

Case interpretation parameter categories were defined for each indicator, as per Brazilian Ministry of Health guidelines,[17] as described below.

a) Detection rate of new cases of leprosy in the general population:
- low, <2.00 per 100,000 inhabitants;
- medium, 2.00 to 9.99 per 100,000 inhabitants;
- high, 10.00 to 19.99 per 100,000 inhabitants;
- very high, 20.00 to 39.99 per 100,000 inhabitants; and
- hyperendemic, ≥ 40.00 per 100,000 inhabitants.

b) Detection rate of new cases of leprosy in the population aged 0-14 years:
- low, <0.50 per 100,000 inhabitants;
- medium, 0.50 to 2.49 per 100,000 inhabitants;
- high, 2.50 to 4.99 per 100,000 inhabitants;
- very high, 5.00 to 9.99 per 100,000 inhabitants; and
- hyperendemic, ≥10.00 per 100,000 inhabitants.

c) As there are no parameters defined by the Ministry of Health for rates of new cases of leprosy with grade 2 physical disability, we adopted the same parameters used for the analysis of the detection rate in children under 15 years old.

A database was built to calculate the indicators. Initially, the calculation was performed for the whole period (2001 to 2012), followed by stratification in five time periods (2001-2005, 2003-2007, 2005-2009, 2007-2011 and 2009-2012); the moving average principle was used with the aim of reducing time series noise, according to which the periods overlap.[18] The following formula was used to calculate the indicators for the periods: average number of cases in the period/ population in the middle of the period x 100,000.

In the next step, we applied the local empirical Bayesian model[12,13,19] for all three indicators analyzed, with the purpose of softening the rates for each municipality/period. The objective of this model is to identify *a posteriori* distribution (unobserved quantities of a given phenomenon), based on the application of Bayes' theorem, involving sample data (likelihood function), and the application of a set of observed data (a priori distribution).[9,10] This procedure was performed using the Terra View software, version 4.2.2, provided by the National Institute for Space Research (INPE).

Subsequently, vector difference was calculated (observed rate less estimated rate), to enable the construction of a thematic map of the differences, whereby the areas were classified as "neutral", "negative" or "positive". When the difference between the rates was situated between -1 and +1, the areas were classified as "neutral" (rates observed do not differ from estimated rates); when the difference was less than -1, the areas were classified as "negative" (estimated rates higher than those observed); and when the difference was greater than +1, the areas were classified as "positive" (observed rates greater than estimated rates). Areas classified as negative may suggest the existence of underreporting of leprosy, while positive areas may suggest improved surveillance of the disease.

In order to analyze whether the means of the observed and estimated indicators were different, we applied the paired Student's t-test, using the Statistical Package for Social Sciences (SPSS) version 22.0. We calculated the standard deviation of the means. We adopted a significance level of 5%.

The final thematic maps were constructed using QGis free software version 2.14.11, provided by the Open Source Geospatial Foundation (OSGeo). The spatial mesh for the state of Bahia was obtained from IBGE, in shapefile (shp) format.

The study was approved by the Federal University of Alagoas Research Ethics Committee: Certification of submission for ethical appraisal (CAAE) No. 70943617.5.0000.5013 and Opinion No. 2,212.723, dated 10 August 2017.

Results

In the period from 2001 to 2012, 35,176 new leprosy cases were reported in the state of Bahia. Of this total, 2,868 (8.15%) were recorded in children under 15 years old and 1,612 (4.58%) had grade 2 of disability at the time of diagnosis.

Table 1 shows the distribution of new leprosy case detection rates in the general population, the new leprosy case detection rate in the population aged 0-14 years and the rate of new leprosy cases with grade 2 physical disability at the time of diagnosis. Both observed cases and cases estimated by the local empirical Bayesian model are shown. The estimated values for the three indicators were higher than those observed. Statistical significance was found in all periods for new case detection rates in the general population and also in the population aged 0-14 years. Statistical significance was found in the periods 2001-2005 (p=0.002) and 2001-2012 (p=0.029) for the

rate of new cases with grade 2 physical disability at the time of diagnosis.

It should be stressed that while the case detection rates in the general population and in the population aged 0-14 years declined over the period evaluated, the opposite occurred with the rate of new cases with grade 2 physical disability at the time of diagnosis, which increased from 1.8/100,000 to 3.1/100,000 in the observed data and from 2.9/100,000 to 3.5/100,000 in the estimated model (Table 1).

Analysis of the new case detection rate in the general population, between 2001 and 2012 lead to endemicity being classified as low in 11.3% of the municipalities (n=47), medium in 45.1% (n=188), high in 19.7% (n=82), very high in 13.6% (n=57) and hyperendemic in 8.4% (n=35). In 1.9% (n=8) of the municipalities no cases were registered in the period. When the local empirical Bayesian model was applied, the number of municipalities classified as having high endemicity doubled, increasing to 39.3% (n=164). An increase was also found in the hyperendemic category, with the proportion of municipalities rising to 10.3% (n=43). In the other categories there was a reduction after the model was applied: low=2.2% (n=9); medium=37.4% (n=156); and very high=10.8% (n=45). The municipalities with greater disease burden were concentrated in the state's northwestern and southern regions (Figure 1).

Analysis of the new case detection rate between 2001 and 2012 in the population aged 0-14 years showed that 43.6% (n=182) of the municipalities did not diagnose any cases in the period and none of the municipalities were considered to have low endemicity; endemicity was classified as medium in 23.0% (n=96); high in 13.9% (n=58); very high in 10.6% (n=44); and hyperendemic in 8.9% (n=37). There was an increase in the number of municipalities in all categories: low=5.8% (n=24); medium=44.4% (185); high=22.5% (94); very high=15.3% (64); and hyperendemic =12.0% (n=50). The highest rates were concentrated in the northwestern and southern regions of the state (Figure 1).

Table 1 – Monitoring indicators of the leprosy elimination process, observed and estimated values, Bahia 2001-2012

Indicator	Period	Observed Mean± SD[a]	Estimated Mean± SD[a]
Detection rate of new cases in the general population/100,000 inhabitants	2001-2005	17.7±46.3	19.9±44.9[b]
	2003-2007	19.9±44.9	22.0±43.1[b]
	2005-2009	17.4±27.1	19.5±24.5[b]
	2007-2011	14.5±19.1	16.9±17.0[b]
	2009-2012	14.3±18.7	16.7±16.6[b]
	2001-2012	16.5±28.4	18.8±26.6[b]
Detection rate of new cases in the population aged 0-14 years/100,000 inhab.	2001-2005	4.6±19.9	5.4±18.3[b]
	2003-2007	5.0±19.0	5.8±16.9[b]
	2005-2009	4.5±11.6	5.4±8.1[b]
	2007-2011	3.1±6.3	4.4±4.9[b]
	2009-2012	3.0±6.0	4.5±5.1[b]
	2001-2012	3.9±11.5	4.8±9.5[b]
Rate of new leprosy cases with grade 2 physical disability at the time of diagnosis/100,000 inhab.	2001-2005	1.8±3.8	2.3±2.5[b]
	2003-2007	2.5±5.0	2.9±3.1
	2005-2009	3.1±5.6	3.6±3.5
	2007-2011	3.3±6.1	3.7±3.4
	2009-2012	3.1±6.5	3.5±3.3
	2001-2012	2.5±4.0	2.9±2.5[b]

a) SD: standard deviation.
b) Significant Student's t-test.

As to the rate of new cases of leprosy with grade 2 physical disability at the time of diagnosis, 37.8% (n=158) of the municipalities did not diagnose any patients with this type of disability; in 26.6% (n=111), the rate was between 0.5 and 2.4/100,000 (medium endemicity); in 21.6% (n=90), the rate ranged between 2.5 and 4.9/100,000 (high endemicity); in 10.6% (n=44), it ranged between 5 and 9.9/100,000 (very high); and in only 3.4% (n=14), the rate was equal to or greater than 10/100,000 (hyperendemic). After the model was applied, we found an increase in the number of municipalities in the first three categories, in particular the proportion of municipalities classified as having medium endemicity was 50.4% (n=210), low=5.3% (n=22), high=33.1% (n=138), very high=8.6% (n=36) and hyperendemic=2.6% (n=11) (Figure 2). It is also important to highlight that the most critical areas, i.e. those having the highest rates, are located in the northwestern and southern regions of the state.

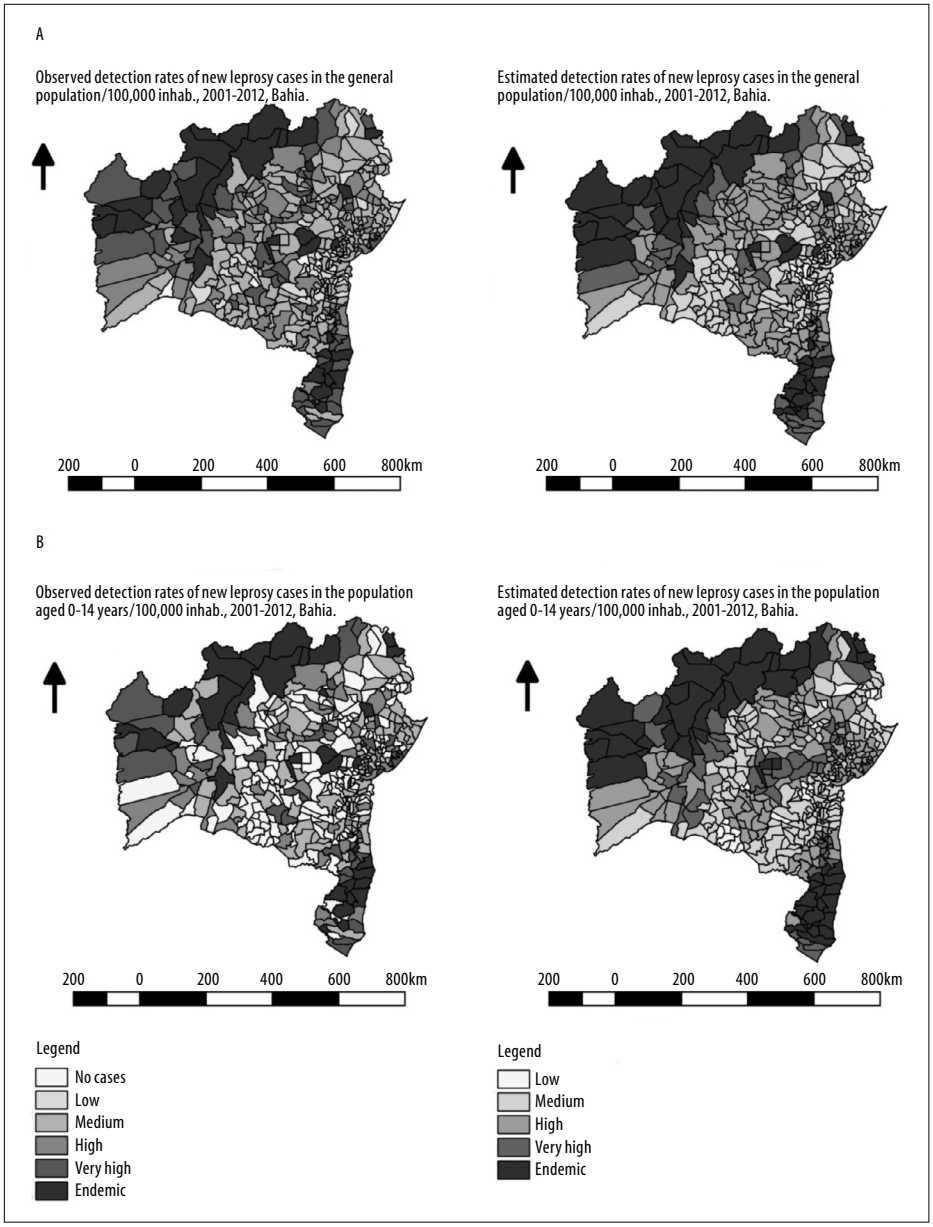

Figure 1 – Spatial distribution of new leprosy case detection coefficients in the general population (A) and in the population aged 0-14 years old (B), observed and estimated values, Bahia, 2001-2012

Following this, we sought to analyze the temporal and spatial dynamics of leprosy in the state of Bahia, based on the three indicators selected for analysis. With regard to the detection rate in the general population, there was a small proportion of municipalities classified as having low endemicity, varying between 0.9 and 2.1% (n=4 and n=9). In turn, the number of municipalities classified as having medium and high endemicity increased over the period studied. In the first period of the series (2001-2005), 74.1% of municipalities (n=309) were classified as having medium or high endemicity, while in the latter period, this percentage increased to 76.7% (n=320). The proportion of municipalities classified as hyperendemic fell throughout the series, from 12.5% (n=52), in the 2001-2005, period to 10.3% (n=43) in the period 2009-2012 (Figure 3).

As regards the detection rate of new cases in the population aged 0-14 years, the proportional increase in municipalities classified as hyperendemic is noteworthy. In the period 2001-2005, 10.8% (n=45) were hyperendemic, while in the period 2009-2012 this proportion was 12.9% (n=54). As occurred with the general population detection rate, the greater part of the municipalities were classified as having medium or high endemicity: 61.2% (n=255), in 2001-2005, and 60.9% (n=254) in 2009-2012 (Figure 3).

When we analyzed the rate of grade 2 physical disability at the time of diagnosis, we found an increase in municipalities classified as having high, very high and hyperendemic endemicity. The proportion of municipalities classified as having high endemicity rose from 20.6% (n=86) in the period 2000-2005 to 40.8% (n=170) in the period 2009-2012; the proportion of municipalities classified as having very high endemicity increased from 8.2% (n=34) to 11.5% (n=48), while hyperendemic municipalities increased from 1.9% (n=08) to 4.6% (n=19) (Figure 3). According to these three indicators, the evolution of the disease was found to be concentrated in the northern, western and southern regions of the state.

We also drew up thematic maps of the differences between the observed indicators and the estimated indicators (Figure 4). With respect to the detection rate of new cases in the general population, 60.7% (n=253) of the municipalities had a negative difference

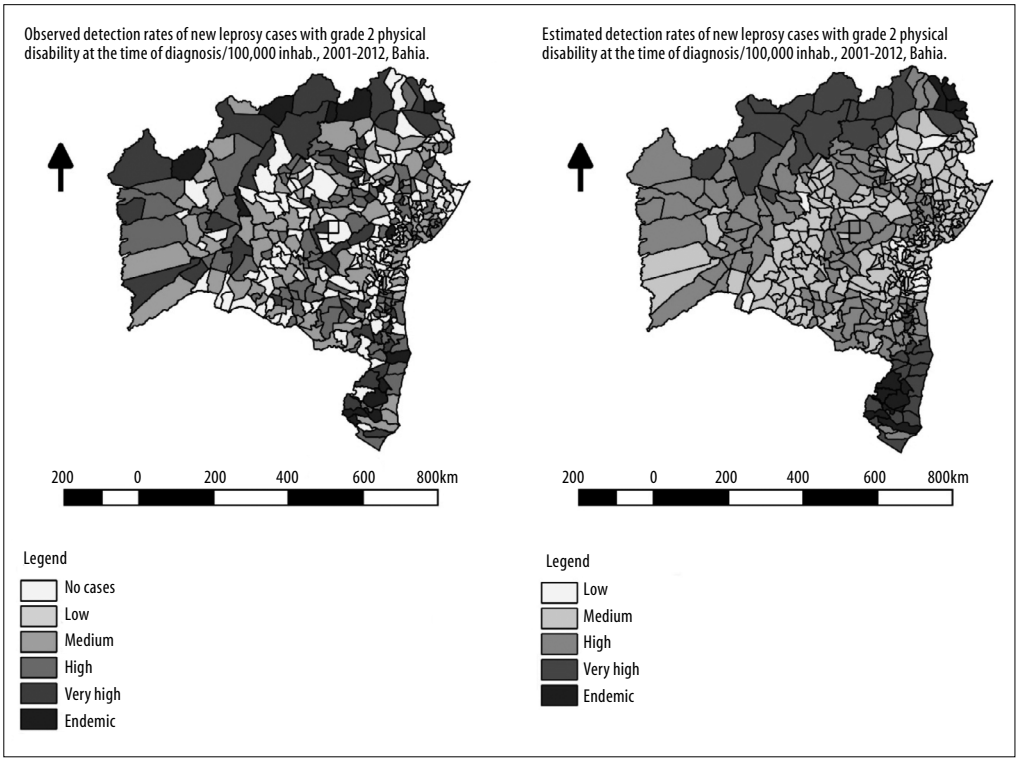

Figure 2 – Spatial distribution of the rate of new leprosy cases with grade 2 physical disability at the time of diagnosis, observed and estimated, Bahia, 2001-2012

(less than -1), i.e., the estimated rate was higher than the observed rate. In turn, in 25.9% (n=108) of the municipalities, the difference was positive (greater than +1), i.e., the estimated rate was lower than the observed rate. In the remaining 13.4% (n=56) of municipalities in Bahia, the difference was situated between -1 and +1 and was considered to be neutral. As to the rate of new cases in the population aged 0-14 years, the proportion of municipalities with a negative difference was 50.1% (n=209); in 31.2% of municipalities (n=130), the difference was between -1 and +1; and in 18.7% of municipalities (n=78), the difference was positive. When the rate of new cases with grade 2 physical disability at the time of diagnosis was analyzed, 42.0% (n=175) of the municipalities had a negative difference, in 35.7% (n=149) the difference was neutral and in 22.3% (n=93) it was positive (Figure 4).

Discussion

The use of spatial analysis in the field of Public Health has lead to important advances in the understanding of the natural history of diseases, the identification of risk or silent areas and in assessing the impact of public policies on the burden of certain health problems, as is the case of leprosy.[12-13,19]

The time series analyzed in this study showed that the magnitude of leprosy has declined in the state of Bahia, both in the general population and also in the population aged 0-14 years old. Even though the rates have reduced in the state of Bahia, they are still much higher than the global patterns of leprosy. Globally, in 2014, the detection rate in the general population was 3 new cases/100,000 inhabitants, i.e., 4.7 times lower than the rate found in the most recent time series analyzed in our study (2009-2012).[4]

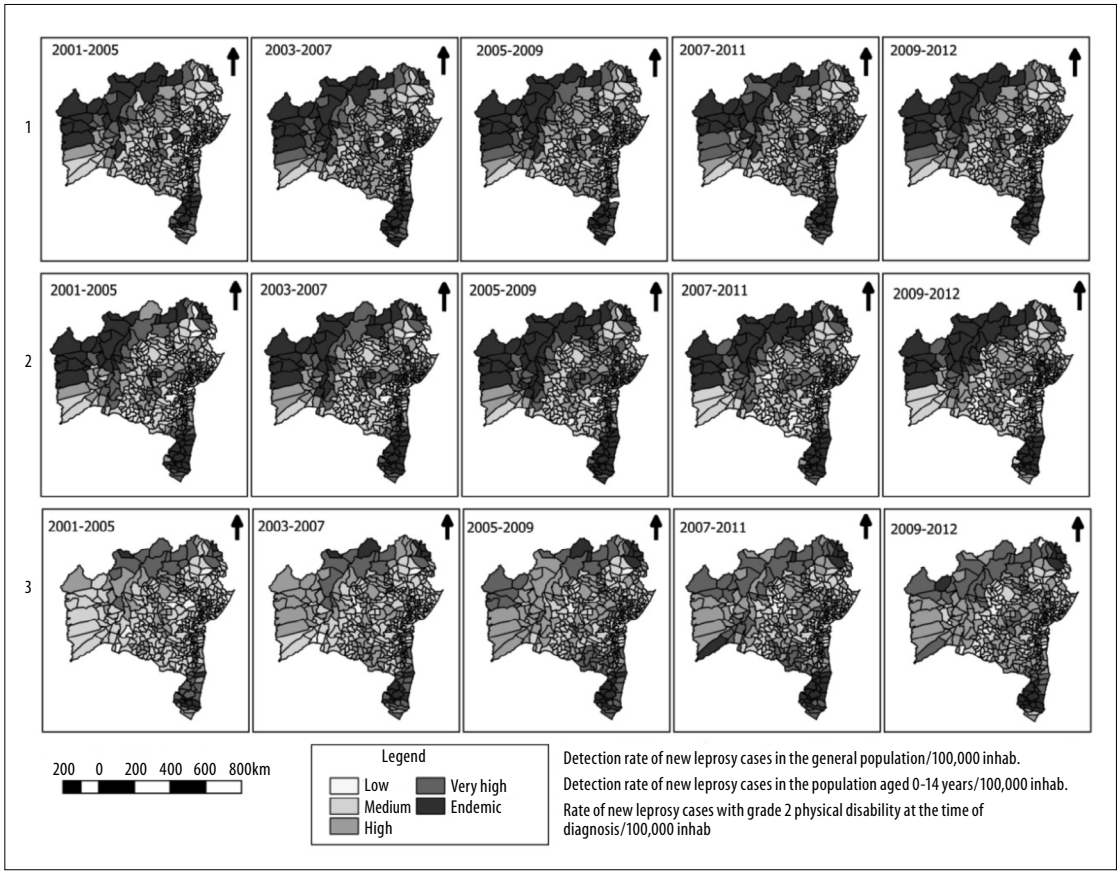

Figure 3 – Spatial-temporal dynamics of the detection rate in the general population, in the population aged 0-14 years old and in the population with grade 2 disability at the time of diagnosis, estimated by local empirical Bayesian modeling, Bahia, 2001-2012

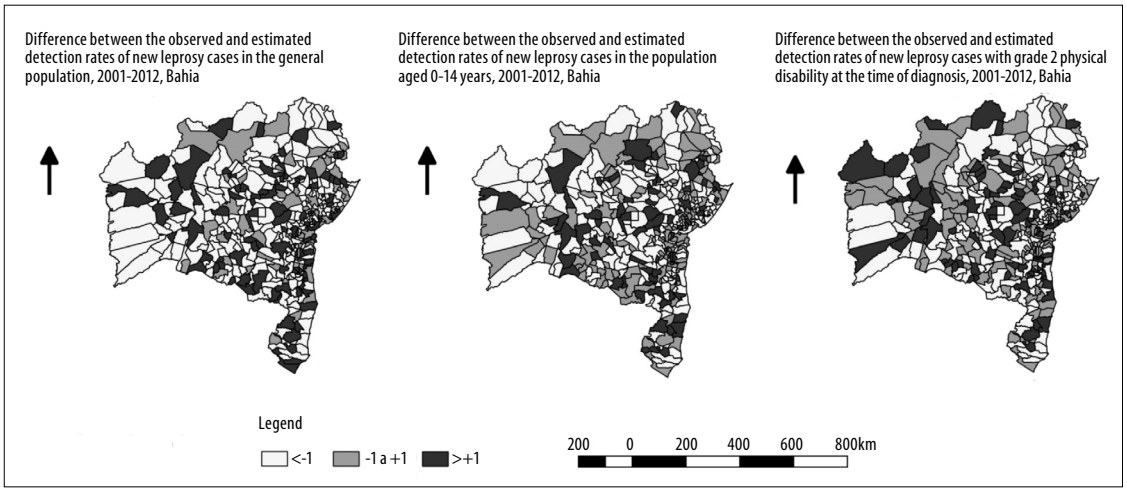

Figure 4 – Spatial distribution of the differences between observed indicators and indictors estimated by local empirical Bayesian modeling, Bahia, 2001-2012

The scenario found in the population aged under 15 years old is similar to that found in the general population. Although a reduction in the rate of new cases was found, leprosy still affects an important contingent of individuals aged 0-14 years old, classifying the state of Bahia as having high endemicity for this subgroup: between 2.5 and 4.99 cases per 100,000 inhabitants.[17] The proportion found in this study in this age group is lower than the global proportion: in 2014, according to World Health Organization (WHO) data, 8.8% of the total number of cases registered worldwide related to children.[4] The number of leprosy cases in Brazil has been questioned by a large number of researchers, who defend that there are many more people with leprosy than those who are in fact included on in official information systems.[13,14]

Although the detection rate in the general population has declined in Bahia, it must be emphasized that the number of municipalities classified as having medium, high and very high endemicity and as being hyperendemic rose considerably, reaching 76.7% (n=320) of the total number of municipalities in the final period of the time series studied (2009-2012). A similar pattern occurred with the detection rate in the pediatric population. One explanation for these findings may be based on the expansion of the primary health care network all over Brazil in recent years.[9,20,21] A study conducted by Nery et al.[20] which analyzed 1,358 Brazilian municipalities, showed that the then Family Health Program (FHP) – now referred to as the Family Health Strategy (FHS) – made progress in increasing the detection of new cases of leprosy. Moreover, the existence of decentralized health centers was also associated with increased detection of the disease. It is assumed that new cases become identified when new health centers are deployed in endemic areas.

In 2002, the Family Health Program had been implemented in 183 municipalities in Bahia, representing statewide coverage below 30%, and had almost four thousand community health agents (CHA);[22] in 2012, coverage had reached 63.57%, with 2,851 health teams and 26,230 CHA in operation.[23]

It is evident that health service expansion, by itself, does not mean that the population has more access to services. Other elements must be considered, such as availability of human resources, physical structure, health center performance, health team technical capacity and sensitivity, definition of work flows and processes.

If, on the one hand, the drop in these two observed rates shows that the state is not indifferent or inert in the face of the challenge to eliminate the disease as a public health problem, on the other hand, the temporal and spatial patterns of the rates estimated by the Bayesian modeling indicate that the real magnitude of leprosy is higher than that found in the data. When applying the model to the general detection rate, for example, the number of municipalities in the state of Bahia classified as having high endemicity

(10.00-19.99 cases/100,000 inhab.) doubled. This finding indicates the existence of pockets of case underreporting, identified as negative areas.

Many reasons can be indicated as causing underreporting. Among them, (i) low capacity of health care services in identifying new cases of the disease, (ii) operational deficiency of leprosy programs, (iii) lack of municipal policies and plans for controlling the disease, (iv) low sensitivity of health service managers regarding the issue and (v) fragile integration between health surveillance and primary health care, in addition to (vi) weak epidemiology and data recording services, especially in smaller municipalities.[24-26]

Apart from case underreporting, late diagnosis as a problem found in the state of Bahia needs to be highlighted. The main argument confirming this hypothesis is the rate of new cases with grade 2 physical disability at the time of diagnosis. This indicator points to the efficiency of early detection of leprosy in a given population.[4] In our study, we found a progressive increase in this indicator, which was even bigger when estimated by the Bayesian model.

The finding in question shows that health care services are currently not capable of identifying all new cases of leprosy existing in the state of Bahia in a timely manner. This suggests the existence of a high hidden prevalence of the disease.[27,28] The difference between the rates estimated by the model and the rates observed indicates the gap in diagnosis on the part of public health services.

Hidden high prevalence has been reported in various studies.[24-26,28] According to Ribeiro et al.,[28] between 2006 and 2010, 72 cases should have been diagnosed in the Diamantina microregion of the state of Minas Gerais beyond the 91 cases actually recorded, which would imply a 79.1% increase in leprosy prevalence in that microregion. In our study, 42.0% (n=175) of the Bahia municipalities had negative differences between observed and estimated rates, indicating that these areas should have more individuals with grade 2 disability at the time of diagnosis than found on the official records.

The three indicators estimated by the local empirical Bayesian model allowed a spatial understanding of the dynamics of leprosy in the state of Bahia: random fluctuation of data resulting from the population size was reduced, resulting in smoothed thematic maps which enabled understanding not only of the magnitude of underreporting of cases, but also the identification of areas of high risk of transmission. In our study, these areas are represented by those municipalities with positive differences between observed and estimated values, i.e., fewer cases were expected in these places.

Despite the robustness of the statistical procedures used, it is important to highlight four limitations of this study: (i) the use of secondary data from information systems may not fully reflect reality;[29] (ii) given the disease's long incubation period, place of residence at the time of diagnosis may not be the location where infection occurred; (iii) instability associated with the use of crude rates, especially in locations with very small populations, which is why we opted to smoothen the indicators by using the Bayesian model to reduce random fluctuation;[13] and (iv) the use of the rate of new cases with grade 2 disability, since this can only be considered viable for analysis when the assessment proportion is greater than 75%.[17] In the period analyzed, the assessment proportion in the state of Bahia remained above the minimum, thus enabling the inclusion of this indicator in the analysis.

The heterogeneous spatial distribution found demonstrated two equally important scenarios: on the one hand, the existence of municipalities with high risk of leprosy transmission; and on the other hand, a contingent of silent municipalities, presumably inert in the face of the presence of leprosy. In addition, the growth in the rate of new cases with grade 2 physical disability at the time of diagnosis emphasizes the existence of negligence and the high social value - transcendence - of leprosy as a public health problem.

Authors' contributions

Souza CDF participated in the conception and design of the study, analysis and interpretation of the results, writing and critical review of the manuscript. Santos FGB, Sales-Marques C, Leal TC, Paiva JPS and Araújo EMCF contributed to data analysis and interpretation, writing and critical review of the manuscript. All the authors have approved the final version and declared themselves to be responsible for all aspects of the study, ensuring its accuracy and integrity.

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