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ORIGINAL ARTICLE / *ARTIGO ORIGINAL*

Temporal trends of leprosy in a Brazilian state capital in Northeast Brazil: epidemiology and analysis by joinpoints, 2001 to 2012

Tendência temporal da hanseníase em uma capital do Nordeste do Brasil: epidemiologia e análise por pontos de inflexão, 2001 a 2012

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ABSTRACT: The objective of this study was to characterize epidemiological and temporal trends of leprosy in the city of Fortaleza, Ceará, Brazil, from 2001 to 2012. A total of 9,658 new cases were reported. Their temporal trend was analyzed by the jointpoint regression model. The overall detection rate showed a declining trend, with annual percent change (APC) of -4.0 and 95% confidence interval (95%CI) -5.6 – -2.3. The detection rate in children under 15 years of age (APC = -1.4; 95%CI -5.4 – 2.8) and the detection rate of disability grade 2 (APC = -0.8; 95%CI -4.5 – 3.1) were stable. The proportion of female patients was descending (APC = -1,5; 95%CI -2.3 – -0.8). The proportion of multibacillary cases from 2005 to 2012 (APC = 1.4; 95%CI 0.6 – 2.3) and among them, lepromatous cases from 2004 to 2012 (APC = 6.0; 95%CI 3.4 – 8.6) were increasing. There was stability in the proportion of cases with grade 1 (APC = 1.4; 95%CI -0.9 – 3.7) and grade 2 disability (APC = 3.7; 95%CI -0.1 – 7.8). Despite the trend towards a reduction in detection, the disease transmission persists in the city. The data also suggest late diagnosis.

Keywords: Brazil. Epidemiology. Leprosy. Communicable diseases. Neglected diseases. Incidence.

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RESUMO: O objetivo deste estudo foi caracterizar aspectos epidemiológicos e tendência temporal da hanseníase, no município de Fortaleza, Ceará, de 2001 a 2012. Foram registrados 9.658 casos novos cuja tendência foi analisada pelo modelo de regressão do *joinpoint*. O coeficiente de detecção geral apresentou tendência decrescente, com *annual percent change* (APC) de -4,0 e intervalo de confiança de 95% (IC95%) -5,6 – -2,3. O coeficiente de detecção em menores de 15 anos de idade (APC = -1,4; IC95% -5,4 – 2,8) e o coeficiente de detecção de grau 2 de incapacidade (APC = -0,8; IC95% -4,5 – 3,1) foram estáveis. A proporção do sexo feminino foi decrescente (APC = -1,5; IC95% -2,3 – -0,8). As proporções de casos multibacilares a partir de 2005 até 2012 (APC = 1,4; IC95% 0,6 – 2,3) e, dentre eles, de casos virchowianos a partir de 2004 até 2012 (APC = 6,0; IC95% 3,4 – 8,6) foram crescentes. Houve estabilidade na proporção de casos com grau 1 (APC = 1,4; IC95% -0,9 – 3,7) e grau 2 de incapacidade (APC = 3,7; IC95% -0,1 – 7,8). Apesar da tendência à redução na detecção geral, mantém-se a dinâmica de transmissão no município, além de sinalizar para diagnóstico tardio.

Palavras-chave: Brasil. Epidemiologia. Hanseníase. Doenças transmissíveis. Doenças negligenciadas. Incidência.

INTRODUCTION

Although there was some development in the control of leprosy in endemic countries throughout the last three decades, the continuous detection of new cases has been one of the greatest challenges to decrease disease burden as a public health problem[1]. Data from the World Health Organization (WHO) in 2013 highlight India and Brazil as the countries that registered the highest number of cases in the world, with 126,913 and 31,044 new cases, respectively. Brazil presented an overall detection rate of 15.44 cases per a 100,000 inhabitants for that same year, which is considered high, as compared with the other countries in the world[2]. The country has the highest number of leprosy cases in the Americas, with 93.8% of the reported cases on the continent[1,2]. Brazilian's Northeast region has the third highest overall detection rate (23.8/100 thousand residents), with a value which is considered of high endemicity for leprosy. In this region, Ceará State is noticeable, since it reported 2,069 new cases with a detection rate of 24/100,000 residents in 2013[3].

Fortaleza, the capital of Ceará State, is considered a priority for control leprosy in the country[3,4]. It is the city with the highest demographic density in the country with significant social inequalities. The analysis epidemiological characteristics of leprosy, which is strongly associated with social vulnerability[4,5], is relevant. Thus, this study aimed to characterize the epidemiological aspects and time trends of leprosy in the city of Fortaleza from 2001 to 2012.

METHODS

STUDY AREA

Fortaleza is located in Northeast Brazil. In 2013, Fortaleza had an estimated population of 2.5 million, with 314,930 km^2 of extension, and a demographic density of 7,786.44 residents/km^2. The city comprised of 119 neighborhoods[6].

STUDY POPULATION AND DESIGN

This is an ecological study analyzing time trends. All new leprosy cases notified in the city of Fortaleza in the period from 2001 to 2012, totaling 9,658 cases, were included in the study.

DATA SOURCES

Data were collected from the *Sistema Nacional de Agravos de Notificação* (SINAN) database of the city of Fortaleza. New leprosy cases reported at the moment of diganosis in Fortaleza from January 1, 2001, to December 31, 2012 were included. This information was formally obtained from the *Coordenação Geral de Hanseníase e Doenças em Eliminação do Ministério da Saúde* (CGHDEMS).

Population data for calculation of epidemiological indicators were obtained from the *Instituto Brasileiro de Geografia e Estatística* (IBGE), based on a census population (2010), and population estimates for the intercensus years (2001–2012).

DATA ANALYSIS

The epidemiological characterization was based on monitoring indicators for leprosy during the study period. The indicators selected were those established by the Brazilian Department of Health (Health Surveillance Secretariat), according to the Ministry Decree 3.025 from 2010 to evaluate and monitor leprosy: overall detection rate per 100,000 inhabitants (indicates magnitude of the disease); detection rate in < 15 year-olds per 100,000 inhabitants (indicates active transmission); rate of new cases with grade 2 physical disability per 100,000 inhabitants (indicates late diagnosis); proportion of female cases; and proportion of multibacillary (MB) cases (indicates endemic expansion).

For the comparison between proportions, we applied Pearson's χ^2 test using Stata software 11.2 (Stata Corporation, College Station, USA). Furthermore, the prevalence ratio (PR) and the 95% confidence interval (95%CI) were calculated.

For trend analysis, we identified the regression equation that best described the relation between the independent (year) and the dependent (indicators) variables. This analysis was performed using Stata software 11.2. The trends were considered statistically significant when the models presented a p-value <0.05 and higher determination rate (R^2). We calculated the annual percent change (APC) of the indicators, from 2001 to 2012, based on the model of regression by joinpoint regression, using the Joinpoint Regression Program, version 4.1[7].

The APC analysis uses joinpoints based on an algorithm that determines if a line of multiple segments is significantly higher than a straight line or a line with less segments. The joinpoint regression analysis gathers a series of straight lines in a

logarithmic scale in order to find the trend of the yearly value of the indicator. The analysis began with the minimum number of joinpoints (straight line) and was tested to evaluate if one or more joinpoints were significant and if they should be added to the model. Each joinpoint (if any) indicates a statistically significant alteration in the line inclination[7].

ETHICAL ASPECTS

This study used secondary data without identification of the participants, and was approved by the Research Ethics Committee of *Universidade Federal do Ceará*, under protocol number 782.142 from July 4, 2014.

RESULTS

From 2001 to 2012, a total of 9,658 new leprosy cases were registered in Fortaleza, Brazil. Among them, 677 (7%) were children < 15 years. The proportion of new male cases was 50.6% (n = 4,890). The results indicate a decreasing trend of the overall detection rate ($R^2 = 0.77856$; $p < 0.001$) (Figure 1). There was stability for the detection rate in children <15 years ($R^2 = 0.06052$; $p = 0.686$) and for the detection rate of grade 2 physical disability cases ($R^2 = 0.0104$; $p = 0.662$; Figure 1).

The proportion of females presented a decreasing trend ($R^2 = 0.72859$; $p < 0.001$; Figure 2). On the other hand, the proportion of cases with multibacillary leprosy remained stable ($R^2 = 0.00924$; $p = 0.945$), which is seen in Figure 3. This, however, showed a

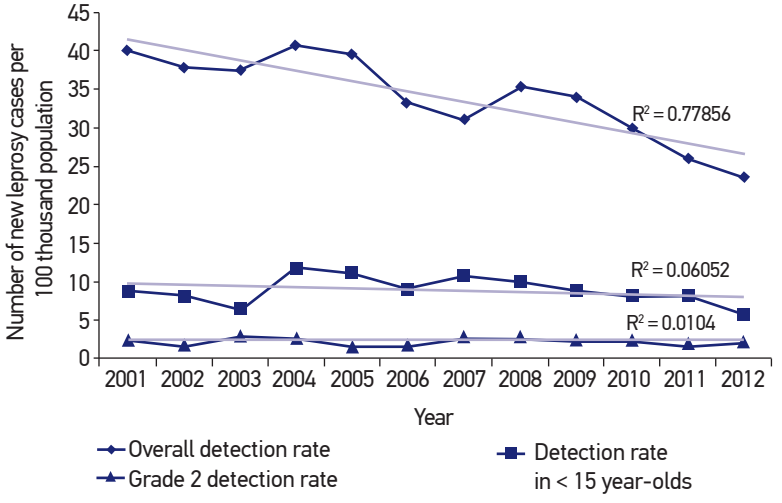

Figure 1. Trend of new leprosy cases detection in the city of Fortaleza, Brazil, 2001–2012.

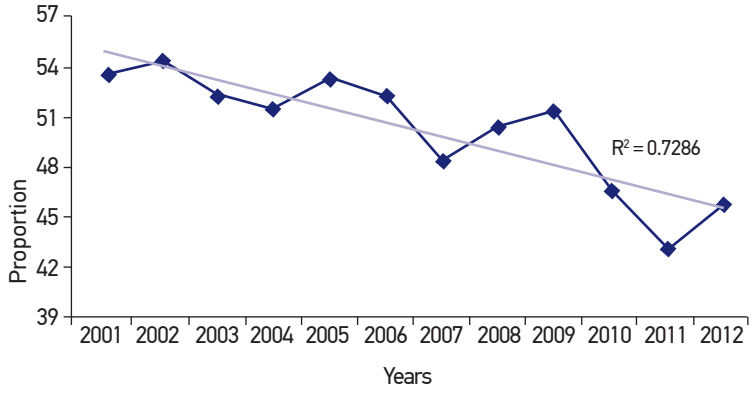

Figure 2. Trend of new leprosy cases classified as the female gender in the city of Fortaleza, Brazil, 2001–2012.

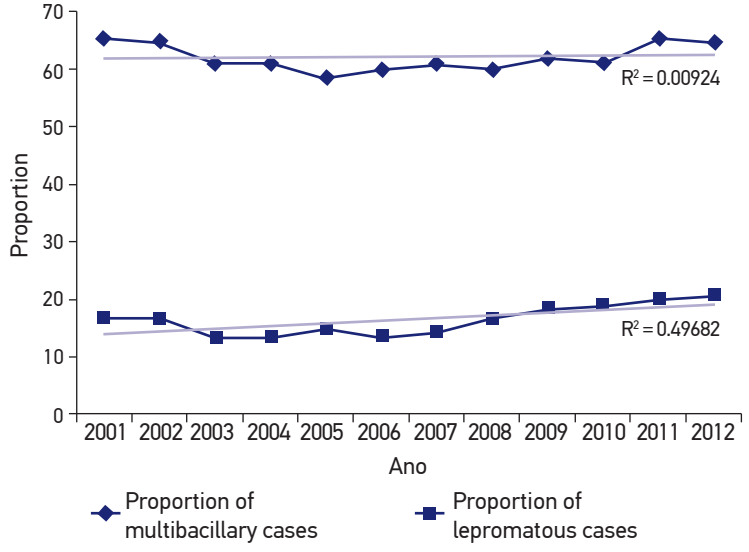

Figure 3. Trend of new leprosy cases classified as multibacillary and lepromatous cases in the city of Fortaleza, Brazil, 2001–2012.

joinpoint throughout the period with a significant decreasing trend from 2001 to 2005 (APC = 2.8; 95%CI 4.5 – 1.0) and significant increasing trend from 2005 to 2012 (APC = 1.4; 95%CI: 0.6 – 2.3; Table 1).

The proportion of the indeterminate clinical form seemed stable ($R^2 = 0.341$; p = 0.154). However, for the joinpoint regression, it showed a significant increasing trend throughout the entire period (APC = 3.6; 95%CI 0.3 – 7.0).

Table 1. Trend of epidemiological and operational leprosy indicators according to the joinpoint model, Fortaleza, Brazil, 2001–2012.

Indicator	Trend 1			Trend 2			Total period	
	Period	APC	95%CI	Period	APC	95%CI	AAPC	95%CI
Overall detection rate	2001 – 2012	-4.0*	-5.6 – -2.3	–	–	–	-4.0*	-5.6 – -2.3
Detection rate in children < 15 years	2001 – 2012	-1.4	-5.4 – 2.8	–	–	–	-1.4	-5.4 – 2.8
Detection rate in grade 2 cases	2001 – 2012	-0.8	-4.5 – 3.1	–	–	–	-0.8	-4.5 – 3.1
Proportion of new female cases	2001 – 2012	-1.5*	-2.3 – -0.8	–	–	–	-1.5*	-2.3 – -0.8
Ratio of new MB cases	2001 – 2005	-2.8*	-4.5 – -1.0	2005 – 2012	1.4*	0.6 – 2.3	-0.1	-0.8 – 0.6
Proportion of Indeterminate cases	2001 – 2012	3.6*	0.3–7.0	–	–	–	3.6*	0.3–7.0
Proportion of new lepromatous cases	2001 – 2004	-8.0	-18.0 – 3.3	2004 – 2012	6.0*	3.4–8.6	2.0	-1.0 – 5.1
Proportion of new grade 0 cases	2001 – 2012	-1.7*	-2.9 – -0.4	–	–	–	-1.7*	-2.9 – -0.4
Proportion of new grade 1 cases	2001 – 2012	1.4	-0.9 – 3.7	–	–	–	1.4	-0.9 – 3.7
Proportion of new Grade 2 cases	2001 – 2012	3.7	-0.1 – 7.8	–	–	–	3.7	-0.1 – 7.8

APC: annual percent change; 95%CI: 95% confidence interval; AAPC: average annual percent change; MB: multibacillary cases; *results with statistical significance.

Among the MB cases, the lepromatous clinical form presented an increasing trend ($R^2 = 0.482$; p = 0.012; Figure 3). However, this same indicator presented a joinpoint throughout the period, a nonsignificant decreasing trend from 2001 to 2004 (APC = 8.0; 95%CI 18.0 – 3.3), and a significant increasing trend from 2004 to 2012 (APC = 6.0; 95%CI 3.4 – 8.6; Table 1).

We found a decreasing trend for the proportion of new cases diagnosed with grade 0 physical disability ($R^2 = 0.526$; p = 0.008) and stability for the proportion of grade 1 cases ($R^2 = 0.285$; p = 0.222). The proportion of grade 2 disability cases was also stable ($R^2 = 0.349$; p = 0.043; Figure 4).

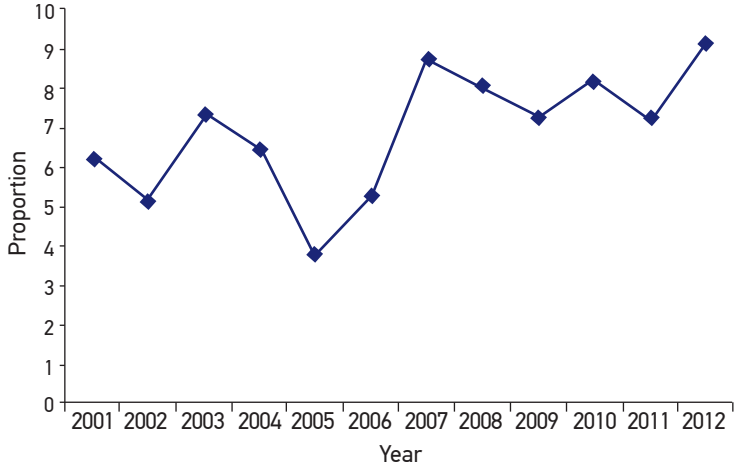

Figure 4. Trend of new leprosy cases with grade 2 disability in the city of Fortaleza, Brazil, 2001–2012.

DISCUSSION

Leprosy transmission remains an important public health issue in the city of Fortaleza, Brazil. Even though there was a decreasing trend of the overall detection rate, the number of new cases in < 15 year-olds remained stable. In addition, the stability of grade 2 physical disability rates suggests persisting late diagnosis.

The significant decrease of the detection of leprosy cases indicates that morbidity is also decreasing. Despite this apparent reduction, the mentioned indicator changed from a hyperendemicity classification (≥ 40.0/100,000 residents) in 2001 to high endemicity (20.00 to 39.99/100,000 residents) in 2012, according to the WHO standards[9].

Our results indicate a vulnerability of the study area in terms of disease control, which might be a result of continuous transmission and/or of late detection of cases. The situation is further aggravated by circulation of the bacillus and active transmission, as evidenced by the increase of MB cases and occurrence of cases in children[8,10].

Stable detection rates in < 15 year-olds indicate the current ongoing transmission, and early exposure to the bacillus[8,10]. The fact that the detection rate in children did not follow the decrease as observed for the overall detection rate, highlights areas for improvement in the surveillance and control of leprosy, considering the charactersitics of leprosy as a disease of adults, owing to its long incubation period[9,10].

The observed stability of grade 2 rate disability in new cases further indicates ongoing late diagnosis, even within the context of overall reduction of reported cases. This indicator allows assessing the effectiveness of leprosy detection. Even though it does not establish control parameters, it should be decreasing[2], which is a contrasting fact with the study results.

While available studies vary in terms of leprosy occurrence by gender, many studies point out the larger appearance in females[11,12]. Our results show a decrease in the proportion female cases that, even though it is significant, did not show great changes in the study years[12]. A possible explanation for this finding may be the observation that male cases are more commonly detected at a later stage. In fact, there is an association of the male gender with grade 2 physical disability in this population[13]. Some particularities of this population can be mentioned, such as its higher difficulty in seeking care in health service networks, besides the fear of losing the source of income owing to the stigma that involves leprosy[10,13,14].

It was possible through the joinpoint regression, to visualize the change in the endemic pattern for the proportion of MB cases (Figure 3). Although there was no significant difference of proportions from one year to the other, until 2005, there was a decreasing trend of this indicator, which could have been influenced by an operational change of the clinical management of MB cases. Indeed, the new WHO treatment scheme reducing treatment from 24 to 12 months may be responsible for this observation. Active case detection could also have happened[1,15].

However, since 2005, the proportion of MB cases has significantly increased. As this indicator is associated with male gender, we emphasize the hypothesis that the endemic situation is influenced by an increased rate of late detection in men. The increase of MB cases contributes to the maintenance of disease transmission, because they represent the main group capable of infecting nontreated subjects, thus corroborating the high levels of the disease in children < 15 years[15,16].

In addition, MB cases have a higher probability of developing physical disabilities, besides neural injuries, which is associated with late diagnosis[17-19]. These factors emphasize the need for more effective control measures in the city[18,19], as the current situation shows the existence of active disease foci and continuity of the creation of new cases.

Among the MB cases, there has been a progressive increase in the last years of lepromatous leprosy cases. It is known that this is one of the groups with highest bacillary load, which favors the spread of the bacillus[8,20]. Lepromatous cases have higher chances of developing physical disabilities owing to the disease or of strengthening them owing to the higher occurrence of reactional episodes[13,21].

The increasing trend of the indeterminate cases also indicates vulnerability of the population from Fortaleza. It is known that this clinical form indicates the initial phase of the disease and that it occurs in patient with good immune response[20]. Therefore, the predominance of indeterminate cases is another indication of leprosy extension and endemicity in the city[19,22].

Cases diagnosed with some degree of physical disability indicate late diagnosis even before the beginning of multidrug therapy[8,9]. The situation in Fortaleza becomes even worse when the proportion of cases with grades 1 and 2 physical disability

does not follow the decreasing trend of overall detection, indicating late diagnosis and probable a hidden endemic.

The proportion of grade 2 disability cases has been used more recently as an indicator for early diagnosis – in our study it presented a mean above the parameters established by WHO: high (≥ 10%); medium (5 – 9.9%); and low (< 5%)[10,23]. Notwithstanding, this endemicity pattern and its increasing trend do not indicated any improvement to be expected in the near future, given the chronic nature and natural history of leprosy.

Late diagnosis associated with leprosy reflects the inability of city health services to identify and treat all cases at early stages, contributing, therefore, to the permanence of people without treatment[8]. Furthermore, it signalizes the low sensitivity of the general population to clinical signs associated with leprosy. Low education level, unfavorable socioeconomic conditions, and delayed presentation at the health system are factors that are generally associated with late diagnosis[24-26]. A possible lack of training of the professionals who work in health services, especially in primary health care, is an addition challenge to treat leprosy cases.

Even though the coverage of the family health program in Fortaleza has doubled from 15%, in 2001, to 33%, in 2012[6,27], these services still are not sufficient to identify and diagnose cases, mainly because this coverage is restricted to some areas of the city. The training of health professionals is very important so that they become more skilled to perform diagnosis and treatment.

The interpretation of the results should consider that this study might present limitations, primarily because of the use of SINAN secondary data. These data are subject to subnotification, besides errors owing to incomplete datasets and low internal consistency. However, the analysis of these data has great relevance for the development health surveillance measures. The use of the most sensitive approach to trend analysis brings new elements to form the epidemiological analyses.

CONCLUSION

This study confirms the maintenance of leprosy burden in Fortaleza throughout the last 12 years, indicating active transmission of *Mycobacterium leprae* and late detection of cases. There is a need to strengthen effective disease control measures in the city, mainly in primary health care. Further studies are needed that explore in more detail the factors associated with maintenance of leprosy transmission in Fortaleza.

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