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Hansen's disease in children under 15 years old in the state of Tocantins, Brazil, 2001–2012: epidemiological patterns and temporal trends

Hanseníase em menores de 15 anos no estado do Tocantins, Brasil, 2001–2012: padrão epidemiológico e tendência temporal

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ABSTRACT: ***Introduction*:** Tocantins is the most hyperendemic state for leprosy in Brazil. ***Objective:*** To describe the epidemiological characteristics and temporal trends of leprosy indicators in children under 15 years old in Tocantins between the years of 2001 and 2012. ***Methodology*:** Data analysis of the Notification of Injury Information System (SINAN). New cases under the age of 15 have been included in the state. The indicators were calculated and the temporal trends were analyzed through the join-point regression. ***Results*:** There were 1,225 cases in children, mean age of 10.8 years, and male predominated (52%). The mode of detection by spontaneous demand prevailed (55.8%) and more than 9% had some physical disability. Detection in < 15 years was significantly increased between 2001 and 2008 (*anual percent change* — APC = 3.8%; confidence interval of 95% — 95%CI 0.1 – 7.6), and showed significant decline between 2008 and 2012 (APC = -9.4%; 95%CI -17.2 – -0.8). There was stability for the detection of grade 2 cases (APC = 4.2%; 95%CI -6.7 – 16.3), proportion of grade 2 cases (APC = 4.1%; 95%CI 6.7 – 16.3), proportion of grade 1 cases (APC = 1.3%; 95%CI -6.2 – 9.3), multibacillary ratio (APC = 2.9%; 95%CI -1.7 – 7.7), and proportion of paucibacillary (APC = 2.9%; 95%CI -1.7 – 7.7). ***Conclusion*:** Leprosy remains an important public health problem in Tocantins, with active transmission and persistence of transmission foci. The stability of the indicators points out the permanence of the late diagnosis and the repressed demands.

Keywords: Leprosy. Neglected diseases. Epidemiology. Children. Time series studies.

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RESUMO: ***Introdução*:** O Tocantins é o estado mais hiperendêmico para hanseníase no Brasil. ***Objetivo:*** Descrever as características epidemiológicas e tendências temporais dos indicadores da hanseníase em menores de 15 anos de idade no Tocantins entre 2001–2012. ***Metodologia*:** Análise de dados do Sistema de Informação de Agravos de Notificação (SINAN). Incluíram-se casos novos de menores de 15 anos residentes no estado. Calcularam-se os indicadores e analisaram-se as tendências temporais por meio da regressão *joinpoint*. ***Resultados*:** Houve registro de 1.225 casos em crianças, a média de idade foi de 10,8 anos, e o sexo masculino predominou (52%). O modo de detecção por demanda espontânea prevaleceu (55,8%) e mais de 9% tinha alguma incapacidade física. A detecção em < de 15 anos foi significativamente crescente entre 2001 a 2008 (*anual percent change* — APC = 3,8%; intervalo de confiança de 95% — IC95% 0,1 – 7,6) e apresentou declínio significativo entre 2008 e 2012 (APC = -9,4%; IC95%: -17,2 – -0,8). Houve estabilidade para a detecção de casos com grau 2 (APC = 4,2%; IC95% -6,7 – 16,3), proporção de casos com grau 2 (APC = 4,1%; IC95% -6,7 – 16,3), proporção de casos com grau 1 (APC = 1,3%; IC95% -6,2 – 9,3), proporção de multibacilares (APC = 2,9%; IC95% -1,7 – 7,7) e proporção de paucibacilares (APC = 2,9%; IC95% -1,7 – 7,7). ***Conclusão*:** A hanseníase permanece como um importante problema de saúde pública no Tocantins, com transmissão ativa e persistência de focos de transmissão. A estabilidade dos indicadores aponta a permanência do diagnóstico tardio e as demandas represadas.

Palavras-chave: Hanseníase. Doenças tropicais negligenciadas. Epidemiologia. Crianças. Estudos de séries temporais.

INTRODUCTION

Despite the significant improvements achieved in leprosy control in recent decades, the disease remains a public health issue in many countries worldwide, including Brazil[1]. The detection coefficient of new cases in children under 15 years of age is used to monitor the active transmission of the disease. In this regard, reducing cases in children is a priority to the national control program, considering that cases detected in this age group indicate recent transmission foci in humans[1,2]. In 2016, approximately 211 thousand new leprosy cases were reported in the world. About 15% of all cases occurred in the Americas, with Brazil being responsible for 92% of them. The overall detection in the country was 12.2 new cases per 100 thousand inhabitants[1]. Leprosy detection coefficients are hyperendemic in many states of the North and Midwest regions[3,4].

In 2016, the state of Tocantins – located in the North Region of the country – held the first place among Brazilian states in new cases of the disease in the general population (88.6/100 thousand inhabitants) and children under 15 years of age (21.7/100 thousand inhabitants)[5]. This scenario shows the magnitude and strength of leprosy transmission in Tocantins. Some studies have contributed to improving the understanding of the epidemiology of leprosy in that territory[6-8]. A recent study revealed that the raw detection coefficient in children under 15 years of age was hyperendemic (10.0 to 19.9 cases/100 thousand inhabitants) in 65.4% (91/139) of the cities of Tocantins. The Bayesian analysis showed that this hyperendemicity was even more extensive in the cities – 85.6% (119/139)[4].

The fact that Tocantins has the highest detection coefficient of new cases in children in the country indicates early exposure to *Mycobacterium leprae* and recent and autochthonous transmission from undiagnosed bacillary sources. Thus, the objective of this study was to describe the epidemiological characteristics and time trends of leprosy indicators in children under 15 years of age from the Tocantins.

METHODS

This study is part of a project from Universidade Federal do Ceará called Integrahans - North/Northeast.

STUDY AREA

Tocantins is located in the North Region of Brazil (Figure 1). Newest state of the country, it is part of the Brazilian Amazon, with cerrado as its predominant vegetation. Its territorial extension is 277,622 km^2, with an estimated population of 1.5 million people in 2016. The state has 139 cities, divided into eight health regions, according to city, population, and demographic density to offer a minimum of services and actions in each territory.

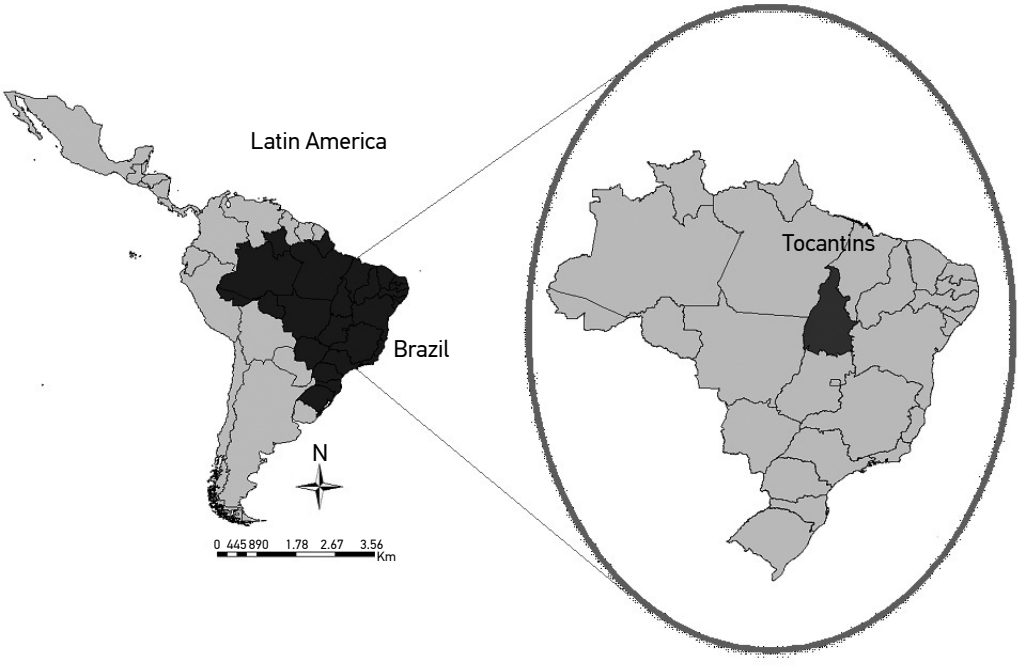

Figure 1. Location of the state of Tocantins in Brazil and the Americas.

POPULATION AND STUDY DESIGN

This study is based on data from the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* – SINAN). We included all new leprosy cases in children under 15 years of age living in Tocantins from 2001 to 2012.

DATA SOURCE

Data were collected from compulsory notification forms of SINAN, Ministry of Health. These forms are a standardized instrument with sociodemographic and clinical information filled by health professionals. The database with all national notifications was obtained from the General Coordination of Leprosy and Diseases Targeted for Elimination (*Coordenação Geral de Hanseníase e Doenças em Eliminação* – CGHDE) of the Ministry of Health. We excluded records with diagnostic error, duplicates, ignored city, and patients living in other states. Population data were collected from the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* – IBGE) based on information from state population censuses (2010) and intercensal population estimates (2001–2009 and 2011–2012)[9].

DATA ANALYSIS

Variables for the descriptive analysis were selected according to cases notified per year. We described the sociodemographic, clinical, and epidemiological characteristics of cases reported in the study period according to the variables: gender, years of schooling, area of residence, ethnicity, detection method, number of skin lesions, number of damaged nerves, operational classification, clinical classification, bacilloscopy, and reactive episodes. We selected indicators recommended by the national program to assess and monitor leprosy: detection coefficient in children under 15 years of age (indicates the active transmission of the disease); proportion of multibacillary cases (points to late diagnosis); proportion of paucibacillary cases (reveals early diagnosis), and proportion of new disability grade 1 and 2 cases among all new cases detected during the year, which we used to evaluate the delay in diagnosis as an indicator of the quality of detection actions[1,10].

Detection coefficients for the trend analysis of leprosy in children under 15 years of age were calculated based on population estimates from IBGE for the study period. The geographical unit of analysis was the state of Tocantins. Time trends for 12 years of observation were analyzed using the joinpoint regression model. This analysis aimed to identify significant changes in the linear trend (in log scale) during the study period[11]. We considered the year of detection as the independent variable and the selected leprosy indicators as

dependent ones. The analysis began with the minimum number of joinpoints (for instance, 0 joinpoint; which is a straight line); next, we tested one or more joinpoints to check if they were significant and, depending on the result, whether we should include them in the model. This test reached 1 joinpoint. Each significant joinpoint – that indicated a slope change – was retained in the final model.

We calculated the annual percentage change (APC) for each of these trends to describe the linear trends per period, using an adjusted regression line for the natural logarithm of the indicators. When we identified more than one slope, we calculated the average annual percentage change (AAPC) over the entire period (when available), based on an underlying joinpoint model. AAPC was estimated as the weighted geometric mean of the APCs, with weights equal to the length of each segment in the time interval[11,12]. Growth trend with a minimum confidence interval greater than 0 pointed to increasing indicators. Conversely, declining trends with a maximum confidence interval below 0 represented a decrease. Stability was determined when the confidence interval included 0. Joinpoint regression analyses were conducted on the Joinpoint Regression Program, version 4.1.0 (US National Cancer Institute, Bethesda, MD, USA). We calculated indicators and elaborated tables and figures using Microsoft Excel spreadsheets.

ETHICAL ASPECTS

The Research Ethics Committee (REC) of Universidade Federal do Ceará approved this study, protocol number: 544,962 (02/28/2014).

RESULTS

Among the 14,532 new leprosy cases registered in Tocantins between 2001 and 2012, 1,225 (8.4%) affected children under 15 years of age. The mean age of patients younger than 15 years was 10.8 years, ranging from 2.2 to 14.9 years, with a median of 11.32 and a standard deviation of ± 2.9. Most of them were males (52%). Children with 5 to 8 years of schooling (44.5%) and living in urban areas (82.4%) were more prevalent. The walk-in detection method (55.8%) and paucibacillary cases (75.8%) had a higher incidence. More than 9% of the sample had some kind of physical disability (Table 1).

In the time trend analysis, the detection coefficient in children under 15 years of age showed a significant increase of 3.8% between 2001 and 2008, while from 2008 to 2012, it significantly decreased by 9.4%. The total period (2001-2012) presented a stable trend. The other indicators evaluated remained stable in the evaluation period of the historical series (Table 2; Figure 2).

Table 1. Sociodemographic, clinical, and epidemiological characterization of new leprosy cases in children under 15 years of age from the state of Tocantins, Brazil, 2001–2012.

Variables	N (1,225)	%
Gender		
Male	637	52.0
Female	588	48.0
Age group (years)		
< 4	19	1.6
4	29	2.4
5	45	3.7
6	52	4.2
7	82	6.7
8	93	7.6
9	109	8.9
10	114	9.3
11	136	11.1
12	144	11.8
13	174	14.2
14	228	18.6
Ethnicity		
Multiracial	794	64.8
White	207	16.9
Black	174	14.2
Asian	19	1.5
Indigenous	13	1.1
Not informed	18	1.5
Area of residence		
Urban	1,009	82.4
Rural	176	14.4
Not informed	40	3.3

Continue...

Table 1. Continuation.

Variables	N (1,225)	%
Detection method		
Referral	288	23.5
Walk-in	684	55.8
Collective examination	25	2.0
Contact examination	217	17.8
Other	11	0.9
Operational classification		
Paucibacillary	929	75.8
Multibacillary	296	24.2
Clinical classification		
Undetermined	608	49.6
Tuberculoid	317	25.9
Borderline	210	17.2
Lepromatous	64	5.2
Not informed/Not classified	26	2.1
Leprosy reactive episodes*		
No	739	60.3
Yes	62	5.1
Not informed	424	34.6
Damaged nerves*		
≤ 1	52	4.2
≥ 2	73	5.9
Skin lesions*		
≤ 5	925	75.5
≥ 5	233	19.0
Disability grade at diagnosis		
Grade 0	932	76.1
Grade 1	97	7.9
Grade 2	20	1.6
Not assessed	176	14.4

*Data unavailable for all cases.

DISCUSSION

In this study, the detection coefficients for children under 15 years of age showed that the disease persisted with active and continuous transmission in state of hyperendemicity in Tocantins. Clinical data about late diagnosis, multibacillary cases, reactive episodes, and physical disabilities reveal late diagnosis in children.

Table 2. Trend in leprosy indicators in children under 15 years of age according to the joinpoint regression analysis in the state of Tocantins, Brazil, 2001–2012.

Indicator	Annual percentage change (APC)			Average annual percentage change (AAPC)		
Tocantins	Period	APC	95%CI	Total period	AAPC	95%CI
Detection in < 15 years/100 thousand inhabitants	2001–2008	3.8*	0.1 – 7.6	2001–2012	-1.2	-1.2 – -4.4
	2008–2012	-9.4*	-17.2 – -0.8			
% Multibacillary	2001–2012	2.9	-1.7 – 7.7	2001–2012	2.9	-1.7 – 7.7
% Paucibacillary	2001–2012	-1.1	-2.4 – 0.2	2001–2012	-1.1	-2.4 – 0.2
% Grade 1	2001–2012	1.3	-6.2 – 9.3	2001–2012	1.3	-6.2 – 9.3
% Grade 2	2001–2012	4.1	-6.7 – 16.3	2001–2012	4.1	-6.7 – 16.3
Grade 2/100 thousand inhabitants	2001–2012	4.2	-6.7 – 16.3	2001–2012	4.2	-6.7 – 16.3

95%CI: 95% confidence interval; *significant p-value.

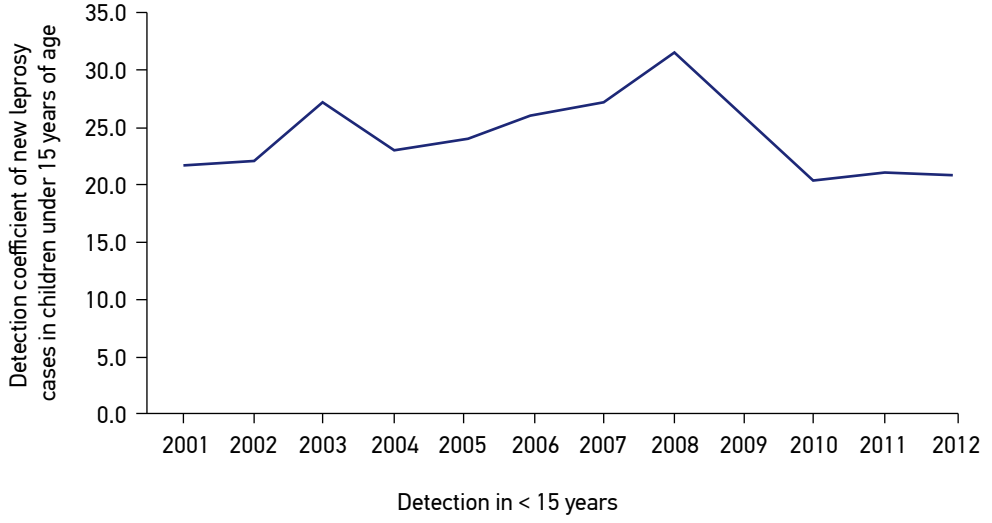

Figure 2. Trend in detection of new leprosy cases (per 100 thousand inhabitants) in children under 15 years of age from the state of Tocantins, Brazil, 2001–2012.

The predominance of males and multiracial ethnicity had similar characteristics to those of adults[13-15]. There was no significant proportional difference between genders; however, the predominance of paucibacillary cases is opposite to the profile of adults, who usually present multibacillary leprosy in epidemiological studies[15-17]. Although the disease is more common in its initial clinical classifications in children, due to the exposure and incubation periods, these children were also diagnosed with multibacillary clinical forms, evidencing the delay in diagnosis by health services, as well as in other scenarios[18,19]. The visible physical deformities presented by the children at the time of diagnosis shows the higher severity of the disease. This fact can be explained by the precarious offer of contact examination in the state during the 12 years of study evaluation (mean of 67%). Another important issue is that the detection method by contact examination had an average of only 17.6% for children in this period.

These data reveal the fragility of operational surveillance by primary care, which probably results from the lack of effective training to detect these cases promptly. Qualitative contact examination is the primary action for early detection in children.

It is important to consider that diagnosis during childhood is more difficult. Consequently, the chances of the disease progressing to complications and deformities increase. Evidence shows that family contact is responsible for 95% of illness in childhood[14]. Early leprosy diagnosis in children under 15 years of age is crucial to prevent physical deformities, whose effects are even more disastrous in this population[15,20,21].

Detection in children ≤ 6 years of age in this study should not be trivialized, as it reached almost 12% of cases, evidencing active and autochthonous *M. leprae* transmission, that is, originating from intense exposure to the agent in the household. Leprosy in children is strongly related to active bacillary foci in the community, more precisely within the family. Therefore, contact examination is the primary action to adopt[20]. The disease at such a young age also indicates flaws in the control program in timely detecting new cases through contact examination and immediate treatment, which could impact the break in the transmission chain[18,22]. The passive detection method in almost 80% of cases (walk-ins and referrals) in children points to the operational fragility of the surveillance of the disease. Approximately 20% of the children were diagnosed by active search (collective and contact examinations). This finding explains the late diagnosis in this group.

The depletion of infection sources is only possible by active surveillance in the community and households. The literature recognizes that a person's risk of developing leprosy is nine times greater by household contact and up to four times higher by contact with neighbors[23]. In the same household, the incidence is higher among blood relatives of a nuclear family compared to other family members, evidencing the genetic predisposition, which has been widely reported in the literature[18,24]. Also, a study indicates that children are more susceptible to this disease than other family members[25]. On the other hand, the data showed that the illness in children increased proportionally for each year of life, corroborating the literature. This fact results from the greater

exposure to the bacillus and enough time for the incubation and clinical manifestation of the disease, which can have a domestic or community source[20,21]. We underline that, in hyperendemic areas, the prevalence of undiagnosed leprosy can be two to eight times higher than that of notified cases, consequently increasing the risk of infection for the population[20].

Recently, the diagnosis of the disease with campaigns was associated with late diagnosis in the Tocantins territory, demonstrating the importance of carrying out this strategy to search for suppressed demands, especially in extensive areas, focusing on high-risk groups and socioeconomically disadvantaged populations[8,16]. Active search is an important tool to control leprosy in hyperendemic areas. In this scenario, households should be routinely visited as an opportunity to examine members of these communities for early diagnosis, treatment, prevention of deformities, interruption of the transmission chain, and stigma of the disease[25,26].

Some studies described unequal patterns in the space-time trend of leprosy indicators for Tocantins, related to issues such as health service coverage, borders with hyperendemic states, migration, social vulnerability of the disease, and urbanization[3,6-8,27]. One of these studies identified spatial patterns to detect cases in children under 15 years of age using local empirical Bayesian analysis, which classified more than 90% of the cities of Tocantins as hyperendemic[4]. These findings corroborate our trend analysis by joinpoint regression, given the stable trend for all evaluated indicators in children under 15 years of age, reflecting the high vulnerability in areas of greater risk of the disease.

The leprosy burden in Tocantins will persist for many years due to the determinants that favor hyperendemicity[3,6,8]. The fact that the state has the highest detection burden in children reveals the severe epidemiological situation and the need to strengthen control programs. The sharp drop in the detection coefficient among children in Tocantins after 2008 does not reflect a real decrease; that is not possible for a chronic disease with a long incubation period. This decline reflects the inability of maintaining and intensifying control actions after 2008. A significant drop in the leprosy detection coefficient is only real when it occurs slowly over the years with continuous control measures[28-30].

Another study with a spatial pattern using serological data obtained from examining students in the state of Pará found that children with high serum concentration of anti-PGL-I (subclinical disease) or diagnosed with the disease were close to space-time clusters of leprosy cases, evidencing the vulnerability and need for actions in areas of greater risk[20].

In the face of the remaining challenges to control the disease in various regions of the world, the World Health Organization (WHO) recently launched the Global Leprosy Strategy 2016–2020, with the commitment to accelerate actions for a world without leprosy. One of its pillars is the special emphasis on children as a way to reduce disabilities and transmission in areas of greater risk[1].

Lastly, the interpretation of our findings should take into consideration that this study might have limitations resulting from the use of secondary data. We compared the national

SINAN database with the state SINAN database, provided by the Tocantins State Secretariat of Health, to minimize errors, gaps, and inconsistencies, strengthening the evidence base of this research as it ensures a better quality of information. We emphasize that the quality of the assessment of completeness of database information was good for all variables included in the statistical analysis. Information about ethnicity is not standardized in Brazil, and the interpretation of this variable is limited for being self-reported and with potential reporting bias.

Despite the limitations mentioned, the results showed internal consistency and coherence with existing knowledge about leprosy, in addition to being highly representative, as it included all notifications of children under 15 years of age living in Tocantins, even those reported in other states, from 2001 to 2012.

FINAL CONSIDERATIONS

Leprosy remains an important public health issue in Tocantins, with active transmission and persistent transmission foci. Indicator stability in multibacillary leprosy, the proportion of grade 2 cases, and the detection of grade 2 cases over time indicate that late diagnosis and suppressed demands continue unchanged. The state leprosy control program should concentrate on and promote sustainable monitoring actions that focus on active surveillance by contact examination, mass campaigns, and other collective examinations.

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