

Epidemiological trends of leprosy in an endemic state

Tendência de indicadores epidemiológicos da hanseníase em um estado endêmico

Kleane Maria da Fonseca Azevedo Araújo¹, Heloisy Alves de Medeiros Leano¹, Rayssa Nogueira Rodrigues¹, Isabela de Caux Bueno¹, Francisco Carlos Félix Lana¹

Objective: to analyze the epidemiological trends of leprosy in an endemic state. **Methods:** ecological study of temporal trends. The data were taken from the National Disease Notification System and analyzed through a generalized linear regression using the Prais *Winsten method.* **Results:** a total of 12,134 new cases of leprosy were analyzed. There was a downward trend of -4.8% in the overall detection rate and of -6.7% in the detection rate in children under 15 years of age. The proportion of new cases of leprosy with grade 2 physical disability at diagnosis showed a stationary trend of 2.7%. It is noteworthy that the trends of epidemiological indicators of leprosy are heterogeneous among the macro-regions of the health system. **Conclusion:** the incidence of leprosy declined in the general population, in children under 15 years of age, and the proportion of grade 2 disability showed stability. Despite the decline, it is evident that diagnoses occur late and the transmission remains active. **Descriptors:** Leprosy; Epidemiology; Primary Health Care.

Objetivo: analisar a tendência de indicadores epidemiológicos da hanseníase em um estado endêmico. **Métodos:** estudo ecológico de tendência temporal. Os dados foram retirados do Sistema de Informação de Agravos de Notificação e a análise realizada por regressão linear generalizada pelo método de *Prais Winsten*. **Resultados:** foram analisados 12.134 casos novos de hanseníase. Observou-se tendência decrescente para taxa de detecção geral de -4,8% e para taxa de detecção em menores de 15 anos de -6,7%. A proporção de casos novos de hanseníase com grau 2 de incapacidade física no diagnóstico apresentou tendência estacionária de 2,7%. Ressalta-se que a tendência dos indicadores de hanseníase é heterogênea entre as macrorregiões de saúde. **Conclusão:** a incidência da hanseníase apresentou-se em decréscimo na população geral, em menores de 15 anos e estabilidade na proporção de grau 2 de incapacidade. Embora apresente declínio, evidencia-se que diagnósticos ocorrem tardiamente e a transmissão permanece ativa.

Descritores: Hanseníase; Epidemiologia; Atenção Primária à Saúde.

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¹Universidade Federal de Minas Gerais. Belo Horizonte, MG, Brazil.

Introduction

Although leprosy is a millennial disease, it persists as a serious modern public health problem⁽¹⁾. It affects the skin, mucous membranes and the peripheral nervous system of individuals, implying in extensive axonal losses, that if not treated at early stages, can progress to deficiencies, deformities and physical disabilities, factors that complicate the morbidity⁽²⁾ and cause limitations in social life and psychological suffering⁽³⁾.

The prevalence of leprosy has declined in the world, but the detection of new cases remains high in some regions of the world. In the year 2016, 214,783 new cases of leprosy were reported in 143 countries, with India accounting for 135,485 (63.1%), Brazil for 25,218 (11.7%) and Indonesia for 16,826 (7.8%) cases⁽¹⁾.

After three decades of the introduction of polychemotherapy and programmatic strategies and actions for the control of leprosy, a slow but decreasing tendency has been observed in the incidence of this disease in India⁽⁴⁾, Zambia (Africa)⁽⁵⁾ and Brazil⁽⁶⁾.

In Brazil, studies have shown a decrease in the overall detection rate of leprosy in conurbations located in hyperendemic states⁽⁷⁾. Despite the decline, the lack of advances in new technologies for prevention, diagnosis and treatment⁽⁸⁾ and the frailties present in health services favor the continuous transmission chain and make it difficult to control the disease in different geographic spaces.

Paraíba, for example, has a high endemicity according to the parameters of the Ministry of Health⁽⁹⁾. In 2016, 459 new cases of the disease were reported, 6.5% in children under 15 years of age and 7.6% in individuals with grade 2 physical disability at diagnosis⁽¹⁰⁾. Because leprosy has a long incubation period, the fact that the disease has been diagnosed in children under 15 years of age indicates active transmission, that is, the presence of undiagnosed and/or untreated adults living with and transmitting the disease to children and teenagers⁽¹¹⁾.

Moreover, the detection of cases in grade 2 physical disability point out to late diagnosis⁽¹⁾, favors the delimitation of risk areas for infection, and aggravates the problem for the health system and for the affected people.

A previous study analyzed the trend of leprosy in Paraíba using two indicators in a descriptive and predictive way⁽¹²⁾. However, no study was found in the literature that presented an analytical approach to monitoring indicators of the disease among the macro-regions of the health system.

It should be emphasized that the situation of high endemicity all for investigations in order to point out difficulties and strategies to be adopted by health professionals⁽³⁾. Nurses play a strategic role in the implementation of leprosy control actions, both in the direct care and in the coordination of the work process, health education activities and professional training, for which the results of the present study can be useful.

Considering that leprosy is a highly transcendent disease due to the physical disabilities resulting from lack of treatment and because there are plots in the territory that house expressive population segments exposed to different situations, it is relevant to carry out this study. The results can influence the decision making, the development and targeting of control strategies, and the identification of training priorities, helping to reduce the incidence of the disease.

In view of the above, the objective of the present study is to analyze the epidemiological trends of leprosy in an endemic state.

Methods

This is an ecological study of temporal trends. The state of Paraíba and its four macro-regions in the health system were used as unit of analysis. Paraíba is located in the northeastern region of Brazil, with 223 municipalities and an estimated population of 3,999,415 inhabitants in 2016⁽¹³⁾.

Within the health care organization, the state

is divided into four macro-regions that are formed according to the demographic, socioeconomic, geographical, health, epidemiological and service characteristics. The first macro-region is made up of 65 municipalities, the second macro-region has 70 municipalities, the third macro-region has 48, and the fourth has 40⁽¹⁴⁾.

The population of the study consisted of cases of leprosy reported from 2001 to 2016. The data were taken from the National Disease Notification System, provided by the Paraíba State Department of Health in April 2017. This period was chosen due to the availability of data in the National Disease Notification System from 2001 onwards, as well as for being a time that corresponds to the launching of coping plans and strategies to reduce the leprosy burden.

The annual estimates of the general population and of age groups (individuals aged <15 years) used to calculate the indicators were obtained from the Brazilian Institute of Geography and Statistics and the Department of Informatics of the Unified Health System, respectively.

Data processing and analysis took place between May and June 2017. A consistency analysis was performed using the Office Excel 2010. Among the 13,603 registered cases of leprosy, new cases were included in the study as input, and diagnostic errors were excluded, as well as cases residing in other states or countries, and those reported out of the study period, totaling 12,134 new cases of leprosy.

The following data per year were selected for descriptive analysis: number of new cases in the general population, number of new cases in children under 15 years of age, and number of new cases in those who presented grade 2 physical disability at diagnosis. Grade 2 physical disability refers to the number of cases that showed any signs of loss of protective sensitivity and complications, such as: trophic ulcers, claws, muscular atrophy, bone resorption in the hands and/or feet, varied ocular lesions(9).

The indicators recommended by the Ministry of Health for the evaluation and monitoring of leprosy⁽⁹⁾; the rate of detection of new cases of leprosy in the general population/100,000 inhabitants (measures the extent of morbidity, magnitude and trend of the endemic disease); rate of detection of new cases of leprosy in children under 15 years of age/100,000 inhabitants (measures the extent of recent transmissions and their trends); and proportion of new cases of leprosy with grade 2 physical disability at diagnosis (evaluates the effectiveness of early disease detection activities).

Data referring to the year 2007 were excluded from the calculation of the proportion of grade 2 physical disability at diagnosis due to the change that occurred in the information system of this indicator, which could cause inconsistency in the results⁽⁷⁾.

The trend analysis was performed in the program Stata, version 12. A generalized linear regression using the Prais Winsten procedure was applied because this is indicated to correct serial autocorrelation and it allowed the analysis of time series over nine years of study(15). Indicators of evaluation and monitoring of leprosy were treated as dependent variables (y) and the year as the independent variable (x) (2001 to 2016).

For the application of the method, the values were log transformed and then the autoregressive model of Prais-Winsten was applied in order to estimate the b_1 coefficients of the dependent variables. Subsequently, the b_1 coefficients corresponding to each of the rates were applied to the following formula: Annual Percent Change (APC): APC= -1+10 [b1] *100%.

The final step of the modeling consisted of the calculation of the 95% confidence intervals (CI 95%) of the measurements using the following formula: 95%CI = [-1+10^{bminimal}]*100%; [-1+10^{bmaximal}]*100%.

Based on the annual increase rates, 95% confidence intervals and p-values (significance level of 5%), the trends of the rates were classified as: increasing (significant p-value, positive annual growth rates), stable (non-significant p-value) and decreasing (significant p-value, negative annual growth rates).

The study complied with the formal require-

ments contained in the national and international regulatory standards for research involving human beings.

Results

In the period from 2001 to 2016, there were 12,134 new cases of leprosy in the state of Paraíba. Of these, 867 (7.1%) were reported in children under 15 years of age.

Figure 1 shows that the detection rate in the general population and in individuals younger than 15 years decreased in the studied period. However, in the periods from 2001 to 2005 and from 2001 to 2003, an upward curve was obtained followed by a decrease in the rate of detection in the general population and in children under 15 years of age, respectively.

The Figure 2 shows that the curve of grade 2 physical disability presents a cyclical variation, with the highest peak in 2011 and a slight decrease until the year 2013, and another increase in 2015.

In Table 1, the results indicate a decrease in the detection rate in the general population in Paraíba and in the 1st and 4th macro-regions, while a stationary trend was observed in the 2nd and 3rd macro-regions.

As for the detection rate in children under 15 years of age, there was a decreasing trend in Paraíba and in the 4th macro-region. The other macro-regions - the 1st, 2nd and 3rd - showed a stationary trend.

As for the proportion of new cases of leprosy with grade 2 physical disability at diagnosis, there was a stationary trend in Paraíba and in the 1st and 4th macro-regions. Only the 3rd macro-region presented a decreasing trend and the 2nd macro-region, a gro-

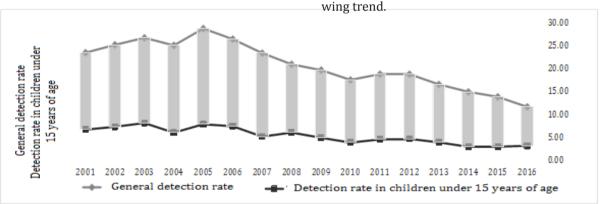


Figure 1 - Detection rates of leprosy in the general population and in children under 15 years of age

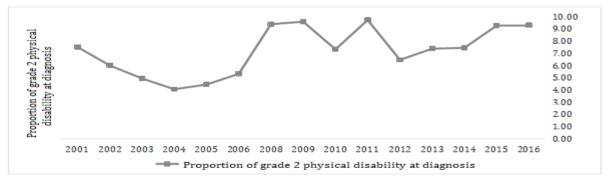


Figure 2 - Proportion of grade 2 physical disability assessed in the diagnosis of leprosy

Table 1 - Epidemiological trends of leprosy in the state of Paraíba and macro-regions of the health system

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Indicator/Macro-regions	Annual change (%)	CI 95%	p	Trend
General detection rate				
Paraíba	-4.8	(-6.8; -2.8)	0.001^{*}	Decreasing
1st	-2.3	(-4.1; -0.6)	0.013	Decreasing
2nd	-0.7	(-4.0; 2.8)	0.677	Stationary
3rd	-2.1	(-5.9; 1.8)	0.265	Stationary
4th	-6.5	(-8.0; -4.9)	0.001^{*}	Decreasing
Detection rate in children under 15 years of age				
Paraíba	-6.7	(-8.3; -5.0)	0.001^{*}	Decreasing
1st	-2.0	(-5.6; 1.9)	0.261	Stationary
2nd	-2.5	(-8.6; 4.0)	0.413	Stationary
3rd	-4.5	(-16.0; 8.6)	0.265	Stationary
4th	-8.5	(-16.1; -0.3)	0.046	Decreasing
Proportion of new cases with graphysical disability at diagnosis	ade 2			
Paraíba	2.8	(-1.4; 7.1)	0.185	Stationary
1st	4.5	(-0.4; 9.7)	0.072	Stationary
2nd	7.6	(0.5; 15.3)	0.041	Increasing
3rd	-14.6	(-23.4; -4.8)	0.009	Decreasing
4th	-4.0	(-11.3; 4.0)	0.303	Stationary

^{*} Significantly different from zero (p<0.05); CI = Confidence Interval

Discussion

Among the limitations of the study was the use of data from a secondary source, which may present inconsistencies in quality and quantity of information. This occurs due to possible underreporting, errors in the completion of notification forms and in the entry of data in the information system. Another limitation was the change in the information system of grade 2 physical disability in the year 2007. Despite these limitations, the data were treated with methodological rigor and are representative of the epidemiological situation of leprosy in the period studied.

The analysis revealed a statistically significant reduction in detection rates in the general population and in children under 15 years, and a stationary trend in the proportion of cases with grade 2 physical disability at diagnosis. Although the disease has declined in Paraíba, this occurred in different ways in the macro-regions of the state.

Actions to control leprosy, timely detection of

new cases, treatment with the polychemotherapy scheme, contact surveillance, prevention of disabilities and rehabilitation are decentralized in the Primary Health Care in Brazil⁽⁹⁾.

Thus, the increase in the detection rate of leprosy in the general population in the period from 2001 to 2005 and the subsequent decline may be a reflection of the implantation of Family Health Teams in the state. These teams facilitate the integration of leprosy control actions in the services as they made it possible to bring the necessary assistance close to the people affected by the disease.

Studies carried out in Brazil have shown that greater coverage of Primary Health Care services initially resulted in an increase in the rate of detection of new cases of leprosy, but a reduction took place in later periods⁽⁶⁻¹⁶⁾. In Ethiopia⁽¹⁷⁾, leprosy control actions were decentralized in basic health services with the aim of bringing the population closer to early diagnosis, timely treatment and follow-up, and positive results have already been reported.

As for the detection rate of leprosy in children under 15 years of age, despite the decline in the state, the fact that there are cases diagnosed in children points to the circulation of the bacillus and active transmissibility, as well as lack of control of the disease by the health system⁽¹¹⁾.

The discrete increase in this indicator in 2016 in relation to 2014 may be a reflection of control actions developed by state services, such as training of the family health teams and greater articulation with the School Health Program which contributed to the realization of educational activities on signs and symptoms of the disease, active search among schoolchildren, and improvement of the examination of contacts in this age group.

As for the comparison between the detection rate in the general population and the rate in children under 15 years of age, there was a similar decreasing trend, with a greater annual percentage variation in the incidence in children under 15 years of age. This result is consistent with the hypothesis that this may reflect, in fact, a decrease in the incidence of leprosy in the state.

A study that analyzed this endemic disease in India showed a decline in the detection rate of leprosy with differences between the regions of the country⁽⁴⁾. In Zambia (Africa), a reduction was detected in both adults and children⁽⁵⁾.

Although Paraíba shows a decreasing trend in the detection rate in the general population and in children under 15 years of age, this occurs in a differentiated way among the state macro-regions. The trend of the detection rate in the general population in the 1st and 4th macro-regions was decreasing, while in the others was stationary. As for the detection rate in children under 15 years of age, the trend was decreasing only in the 4th macro-region, what may be a reflection not only of improved access to health services, but also of the intensification of detection activities, since these two macro-regions have the municipalities with the highest number of cases.

A study carried out in Tocantins, a hyper endemic state, also presented a decreasing trend in the general detection rate of leprosy, with differentiated patterns among the regions of the state. One of the rasons attributed to this result was the coverage of actions and health services in some municipalities and regions to the detriment of others that do not have services yet consolidated⁽¹⁸⁾.

The detection rate of leprosy is limited by the ability of professionals to perform early diagnosis. Thus, the differences in the behavior of the disease among the macro-regions found in this study may be due to both the coverage of family health teams and operational factors, mainly those related to the ability of health professionals to make the diagnosis and timely treatment.

The reduction in the detection rate of leprosy in the general population observed in Paraíba is similar to the results of studies conducted in Pará, Maranhão, Rondônia, and Tocantins⁽⁷⁻¹⁸⁾. In children under 15 years of age, the downward trend is similar to that found

in Pará and Maranhão⁽⁷⁾ and Mato Grosso⁽¹⁹⁾.

Another aspect that may have impacted the decrease in leprosy indicators is the improvement in the socioeconomic conditions of the population. A study conducted in Brazil showed that government programs for income transference have had a positive impact on the epidemiological indicators of leprosy⁽¹⁶⁾.

Although the results point to a decline of the endemic in Paraíba, the proportion of cases with grade 2 disability at diagnosis showed an increasing curve from 2012 onwards; a stationary trend in the state, in the 1st and 4th macro-regions; and an increasing trend in the 2nd macro-region.

Considering that this indicator evaluates the effectiveness of early and/or timely detection activities⁽⁹⁾, since physical disabilities are the outcome of the progress of the untreated disease, flaws in the control of the disease become evident, that is, a difficulty of early diagnosis and treatment of the disease. On the other hand, this result also shows the lack of knowledge of the population about the first signs and symptoms of leprosy.

We find data from the state of Tocantins in Brazil that corroborate the results of the present study, on the decline in the general detection rate and a stationary trend in the proportion of grade 2 disability⁽¹⁸⁾. Notably, the apparent inconsistency in the stability of the grade 2 disability, given the decreased incidence trends, can indicate areas of high endemicity⁽⁷⁾ and provide information on the failure of services to detect the disease in early stages.

Furthermore, reflections on the effectiveness of the policies and strategies for prevention and control of this endemic disease emerge, pointing to the need for technological innovations to help in the early diagnosis of the disease. This way it will be possible to reach the goal of eliminating the incidence of disabilities in children under 15 years of age by 2020 and reducing the incidence rate to one case per million inhabitants in the general population, a goal proposed by the Global Leprosy Strategy 2016-2020⁽²⁰⁾.

Although in decline, the persistence of the bur-

den of leprosy in Paraíba was confirmed in the present study. This is due to the detection of cases in children under 15 years of age, and the diagnoses in late stages of the disease, a fact that contributes to the creation of transmission foci, as well as installation of complications such as disabilities and deformities. Therefore, there is a need to review control strategies and perform other studies to understand the magnitude of leprosy at the municipal level.

We highlight the contribution of this study on epidemiological trends of leprosy for its relevance to guide actions in the effort to control and prevent the maintenance of the transmission chain in different regions, as well as to provide evidence that contributes to public policies geared at eliminating the disease.

Conclusion

The incidence of leprosy declined in the general population, in children under 15 years of age, and the proportion of grade 2 disability showed stability. Despite the decline, it is evident that diagnoses occur late and the transmission remains active.

Collaborations

Araújo KMFA contributed to the drafting and design of the project, analysis and interpretation of data, article writing, critical review of the intellectual content, and final approval of the version to be published. Leano HAM, Rodrigues RN and Bueno IC contributed to the data analysis and article writing. Lana FCF contributed to the drafting and design of the project, relevant critical revision of the intellectual content, and final approval of the version to be published.

References

1. World Health Organization. Global leprosy update, 2016: accelerating reduction of disease burden. Wkly Epidemiol Rec [Internet]. 2017 [cited 2017 Oct 24]; 35:501-19. Available from: http://apps. who.int/iris/bitstream/10665/258841/1/ WER9235.pdf?ua=1

- 2. Garbino JA, Marques Júnior WA. Neuropatia da hanseníase. In: Alves ED, Ferreira IA, Ferreira TL. Hanseníase: avancos e desafios [Internet]. 2014 [citado 2017 jun. 20]; 215-27. Disponível em: http://www.morhan.org.br/views/upload/ hanseniaseavancoes.pdf
- Sousa GC, Vieira FS, Oliveira DEP, Costa ES, Moura MES. Clinical-epidemiological characterization of leprosy cases with physical disabilities. Rev Rene. 2017; 18(1):99-105. doi: http://dx.doi. org/10.15253/2175-6783.2017000100014
- 4. Brook CE, Beauclair R, Ngwenya O, Worden L, Ndeffo-Mbah M, Lietman TM, et al. Spatial heterogeneity in projected leprosy trends in India. Parasit Vectors. 2015; 8:542. doi: http://dx.doi. org/10.1186/s13071-015-1124-7
- 5. Kapata N, Chanda-Kapata P, Grobusch MP, O'Grady I, Bates M, Mwaba P, et al. Leprosy trends in Zambia 1991-2009. Trop. med. int. health. 2012; 17(10): 1289-93. doi: http://doi.org/10.1111/ j.1365-3156.2012.03050.x
- 6. Penna MLF, Grossi MAF, Penna, GO. Country profile: leprosy in Brazil. Lepr Rev [Internet]. 2013 [cited 2017 June 02]; 84(4):308-15. Available from: https://www.ncbi.nlm.nih.gov/ pubmed/?term=PMID%3A+24745130
- Freitas LRS, Duarte EC, Garcia LP. Trends of main indicators of leprosy in Brazilian municipalities with high risk of leprosy transmission, 2001-2012. BMC Infect Dis. 2016; 16(1):472. doi: http:// dx.doi.org/10.1186/s12879-016-1798-2
- 8. Ferreira IN. A hanseníase no contexto das doenças negligenciadas. In: Alves ED, Ferreira IA, Ferreira TL. Hanseníase: avanços e desafios. [Internet]. 2014 [citado 2017 jun. 20]; 41-3. Disponível em: http://www.morhan.org.br/views/upload/ hanseniaseavancoes.pdf
- Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Diretrizes para vigilância, atenção e eliminação da hanseníase com problema de saúde pública. Manual técnico-operacional [Internet]. 2016 [citado 2017 jun. 20]. Disponível em: http://www.saude.pr.gov.br/arquivos/File/ retrizesdoManuaTcnicoOperacionaldeHansenase. pdf

- 10. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Situação epidemiológica dados [Internet]. 2017 [citado 2017 jun. 11]. Disponível em:http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/leia-mais-o-ministerio/705-secretaria-svs/vigilancia-de-a-a-z/hanseniase/11298-situacao-epidemiologica-dados
- 11. Lana FCF, Fabri ACOC, Lopes FN, Carvalho APM, Lanza FM. Deformities due to leprosy in children under fifteen years old as an indicator of quality of the Leprosy Control Programme in Brazilian Municipalities. J Trop Med. 2013; 8(12):1-6. doi: http://dx.doi.org/10.1155/2013/812793
- Brito KKG, Andrade SSC, Santana EMF, Peixoto VB, Nogueira JA, Soares MJG. Análise epidemiológica da hanseníase em um estado endêmico do nordeste brasileiro. Rev Gaúcha Enferm. 2015; 36(esp):24-30. doi: http://dx.doi.org/10.1590/1983-1447.2015.esp.55284
- 13. Instituto Brasileiro de Geografia e Estatística. Cidades [Internet]. 2017 [citado 2017 jun. 11]. Disponível em: https://cidades.ibge.gov.br/brasil/pb/panorama
- 14. Brandão ICA, Martiniano CS, Monteiro AI, Marcolino EC, Brasil SKD, Sampaio J. Análise da organização da rede de saúde da Paraíba a partir do modelo de regionalização. Rev Bras Ciênc Saúde. 2012; 16(3):357-52. doi: http://dx.doi.org/10.4034/RBCS.2012.16.03.11
- 15. Antunes JLF, Cardoso MRA. Uso da análise de séries temporais em estudos epidemiológicos. Epidemiol Serv Saúde. 2015; 24(3):565-76. doi: http://dx.doi.org/10.5123/S1679-49742015000300024

- 16. Nery JS, Pereira SM, Rasella D, Penna MLF, Aquino R, Rodrigues LC, et al. Effect of the Brazilian conditional cash transfer and Primary Health Care programs on the new case detection rate of leprosy. Plos Negl Trop Dis. 2014; 8(11):3357. doi: http://dx.doi.org/10.1371/journal.pntd.0003357
- 17. Abeje T, Negera E, Kebede E, Hailu T, Hassen I, Lema T, et al. Performance of general health workers in leprosy control activities at public health facilities in Amhara and Oromia States, Ethiopia. BMC Health Serv Res. 2016; 16:122. doi: https://doi.org/10.1186/s12913-016-1329-2
- 18. Monteiro LD, Martins-Melo FR, Brito AL, Lima MS, Alencar CH, Heukelbach J. Tendências da hanseníase no Tocantins, um estado hiperendêmico do Norte do Brasil, 2001-2012. Cad Saúde Pública. 2015; 31(5):971-80. doi: http://dx.doi.org/10.1590/0102-311X00075314
- Freitas BHBM, Cortela DCB, Ferreira SMB. Trend of leprosy in individuals under the age of 15 in Mato Grosso (Brazil), 2001-2013. Rev Saúde Pública. 2017; 51(28). doi: http://dx.doi.org/10.1590/ S1518-8787.2017051006884
- 20. Organização Mundial da Saúde. Estratégia global para hanseníase 2016–2020. Brasília: Organização Pan-Americana da Saúde [Internet]. 2016 [citado 2017 jun. 01]. Disponível em: http://apps. who.int/iris/bitstream/10665/208824/17/9789 290225201-pt.pdf