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Misdiagnosis of leprosy in Brazil in the period 2003 - 2017: spatial pattern and associated factors

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ABSTRACT

Background: Leprosy causes a range of symptoms, and most diagnoses are established based on the clinical picture. Therefore, false negative and positive diagnoses are relatively common. We analyzed the spatial pattern of leprosy misdiagnosis and associated factors in Brazil.
Method: Exploratory analyses of Kernel density of the new case detection rate (NCDR) and proportion of misdiagnosis in Brazil, 2003–2017. Factors associated with misdiagnosis were identified by logistic regression at the 5% significance level.
Result: A total of 574,181 new leprosy cases were recorded in Brazil within the study period, of which 7,477 (1.3%) were misdiagnoses. No spatial correlation was observed between the proportion of misdiagnoses and the NCDR. The likelihood of misdiagnosis was elevated for females [OR: 1.58 (1.51–1.66)], children [OR: 1.49 (1.36–1.64)]; paucibacillary [OR: 1.08 (1.02–1.13)], indeterminate clinical forms [OR: 2.37 (2.15–2.62)], for cases diagnosed in the frame of mass screenings [OR: 3.36 (3.09– 3.73)] and contact examination [OR: 2.30 (2.13–2.49)] and for cases with affected nerves but no skin lesions [OR: 2.47 (2.19–2.77)] when compared with those presenting both skin lesion and affected nerves.
Conclusion: Misdiagnosis of leprosy is not correlated with the endemicity level in Brazil but rather with personal, diagnosis-related and disease characteristics.

Introduction

The diagnosis of leprosy is mainly based on clinical signs and symptoms. A positive diagnosis is established when the untreated person presents one of the following cardinal signs*: definite loss of sensation in a pale (hypopigmented) or reddish skin patch and a thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve* (World Health Organization, 1998).

Most leprosy diagnoses therefore do not require major technical equipment, but it does require patient cooperation and professional skills and experience when facing a variety of subtle clinical manifestations (Scollard and Gillis, 2020). Some patients may present more rare or atypical symptoms, and the varied clinical manifestations of leprosy resembling other diseases, in addition to its tendency for chronic disease courses, are factors that often lead to delayed diagnosis and misdiagnosis (Scollard and Gillis, 2020; Hsieh and Wu, 2014; Fernandes et al., 2014; Ura and Barreto, 2004).

Other diseases also manifest with skin lesions similar to leprosy, such as granuloma annulare, localized scleroderma, syphilis, lupus erythematosus, rheumatoid arthritis, eczematid, achromic nevus and others (Fernandes et al., 2014; Hsieh and Wu, 2014; Scollard and Gillis, 2020). Moreover, certain symptoms such as fatigue, paresthesia and musculoskeletal complaints may be associated with dermatological lesions, especially in connective tissue diseases (Scollard and Gillis, 2020; Hsieh

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and Wu, 2014; Fernandes et al., 2014).

Different clinical manifestations of leprosy reflect the range of possible immune responses against its causative agent, *Mycobacterium leprae*. Clinically, the disease ranges from tuberculoid leprosy (one or few skin lesions, predominant cellular immune response and limited bacilli) to the lepromatous type (disseminated lesions, prevailing humoral response and a high bacillary load). In early stages, known as indeterminate leprosy, there are few hypopigmented macules without bacilli. The operational classification proposed by the World Health Organization is governed by the number of skin lesions: paucibacillary or PB (up to five patches), and multibacillary or MB (more than five patches), (Ridley and Jopling, 1966; Britton and Lockwood, 2004).

The presence of acid-fast bacilli in smears is the third cardinal sign of leprosy. Testing them is recommended by WHO (World Health Organization, 1998) as a laboratory tool for the diagnosis of the disease. When available, smears are considered a great resource for confirmation of MB cases, but are usually negative in PB cases (Ridley and Jopling, 1966; Ura and Barreto, 2004; Britton and Lockwood, 2004; Brasil. Ministério da Saúde, 2017). Also, the laboratory and training requirements mean that smears are not usually done in routine services and are often not available at all (Brasil. Ministério da Saúde, 2017). Histopathological examination, another complementary tool for leprosy diagnosis, often will show inconclusive results, especially in early stages of the disease (Fine et al., 1986).

Research and development are ongoing for diagnostic tests based on serology and polymerase chain reaction (PCR). However, these tests have generally low sensitivity, especially for PB cases. *In vitro* stimulation of T cells using *M. leprae* specific antigens has also been evaluated as a complementary diagnostic tool (Geluk and Ottenhoff, 2006). However, it has not yet been possible to develop a gold standard biomedical test for the diagnosis of leprosy, nor one that can distinguish asymptomatic infection from the disease (Hsieh and Wu, 2014; World Health Organization, 1998; Scollard and Gillis, 2020).

Accurate diagnosis is an important factor for the control and elimination of diseases. As a relatively rare disease with a wide range of symptoms, misdiagnosis with both false negative and false positive evaluations may be a big problem for leprosy control. Undiagnosed cases contribute to transmission and are associated with a risk of progression to more severe clinical forms. Conversely, false positive diagnosis may result in inadequate treatment, emotional and physical harm and increased health care costs (Ridley and Jopling, 1966; Ura and Barreto, 2004; Britton and Lockwood, 2004; Fine et al., 1986; Brasil. Ministério da Saúde, 2017; Geluk and Ottenhoff, 2006).

This study aimed to analyze misdiagnosis of new leprosy cases in Brazil in the period 2003–2017 with regard to their spatial and temporal pattern and associated factors. The focus is on false positive cases: patients who were initially diagnosed as leprosy cases but after starting treatment with multi-drug therapy (MDT) were recognized as not having the disease.

Materials and methods

Study design

Exploratory spatio-temporal analysis of leprosy cases diagnosed in Brazil in the period 2003 - 2017, with special consideration of cases whose treatment with MDT ended due to “misdiagnosis” as reported in the national surveillance system.

Population and data sources

Data on new leprosy diagnoses and misdiagnosis were obtained from the National Information System of Notifiable Diseases (SINAN) https://sinan.saude.gov.br/sinan/login/login of the Ministry of Health of Brazil through the electronic citizen information service (e-SIC) via a formal request over the platform https://esic.cgu.gov.br/sistema/site/index.aspx.

All new leprosy diagnoses, retreatments and relapses are registered in SINAN. The original data are provided by the health center where a patient is diagnosed, and updated through a weekly bulletin in paper format to the health department of each municipality where data are entered into the system. As a chronic disease, the leprosy database also includes variables related to the clinical course of the patient. Misdiagnosis is a standard option for the compulsory variable related to the closing of the case report of a leprosy case that started treatment.

Population data by municipality was obtained from the Brazilian Institute of Geography and Statistics (IBGE), based on the census conducted in 2010 and population estimates for the years between 2001-2009 and 2011-2017. All new leprosy cases recorded in Brazil from 2003 to 2017 were selected.

Data analysis

New case detection rates (NCDR) and the proportion of patients released from treatment due to misdiagnosis were calculated based on the official records. The annual NCDR is the number of new leprosy cases per year across Brazil divided by the national resident population in the same year, and expressed per 100,000 population. The annual proportion of misdiagnoses was calculated by dividing the number of cases recognized as misdiagnoses by the total number of new cases in the same year, and is expressed per 1,000 cases.

We also calculated the same indicators for three periods, i.e. 2003-2007, 2008-2012, and 2013-2017. The average NCDR per municipality was calculated by dividing the sum of the new cases diagnosed in a municipality over a certain period by the duration of the period expressed in years, and then dividing the result by the resident population of the year mid-period, and expressed per 100,000 population. The average proportion of leprosy patients released due to misdiagnosis was calculated by dividing the number of cases classified as misdiagnosed per municipality and period by the five-year average of new cases for the site, and expressed per 1,000 cases. The descriptive analysis of the study population includes the average and median time of treatment for PB and MB cases until release due to misdiagnosis.

The kernel distribution calculated from the density estimate made it possible to visualize for all Brazilian regions the areas with the highest density of events by five-year periods. The kernel map represents the result of the interpolation of the events (NCDR, proportion of patients released due to misdiagnosis) considered in the analysis, namely the point intensity of their occurrence in the Brazilian territory. We used the centroids (geographic center) of the residence municipalities. Kernel maps were generated to identify areas with the highest concentration of events (NCDR and proportion of release due to misdiagnosis) showing the “hot spots” based on the following parameters: 4,121 columns and 3,854 grid lines over the area of Brazil, with quartic function algorithm and adaptive radius. Data analysis considered the distribution of areas by nuclei of case densities, classified from low to high (Brasil. Ministério da Saúde, 2017).

The spatial regression analysis was performed using the program GeoDa 1.14 (Anselin, 2005). It included as dependent variable the proportion of patients released from treatment due to misdiagnosis, and as independent variable the leprosy NCDR of the Brazilian municipalities. A neighborhood matrix was defined to evaluate the spatial weights in order to verify the similarity of values among a spatial unit of analysis (municipality and states) and its neighbors. The defined matrix used the contiguity criterion. The first step of the analysis was to estimate a classic model, which used Ordinary Least Squares (OLS), and did not take into account the spatial autocorrelation of events. In addition to the frequency distribution, the following explanatory variables were selected: gender, age group (<15; 15–>60 years), operational leprosy classification, clinical type of leprosy, detection mode, and cardinal signs categorized into: cases without skin lesions and without neural involvement; cases with skin lesions but no neural involvement; cases

without skin lesions but with neural involvement; and cases with skin lesions and neural involvement. The outcome variable was defined as "misdiagnosis".

To analyze the association between the explanatory variables and the outcome, a multivariate logistic model was developed. A significance level of 20% for the inclusion of variables in the stepwise models was defined. Crude and adjusted odds ratio (OR) estimates and their respective 95% confidence interval (CI) were calculated for the variables in the final explanatory model. SPSS Windows software (22) was used, and the kernel maps were generated using the ArcGis 10.5 software.

Ethical Considerations

This study is part of a doctoral dissertation. The underlying project was approved by the Ethics Committee of the Julio Muller University Hospital in Cuiabá - Mato Grosso, Brazil, Opinion number 2.761.449.

Results

From 2003 to 2017, a total of 574,181 leprosy cases were recorded in Brazil, among which 7,477 (1.3%) cases were later classified as "misdiagnosis". Although leprosy detection rates declined over these 15 years from 29.0 to 12.8 per 100,000 inhabitants, the proportion of cases released due to misdiagnosis remained stable, with small increases in 2004, 2008 and 2014 (Fig. 1).

The average treatment duration until release due to "misdiagnosis" was 4 months for PB cases and 7 months for MB patients. The median was 4 months for both groups. Of the 7,477 cases of misdiagnosis, 3,150 (42%) were male and 58% female; 5,340 (71%) were 15 to 59 years old; and 1,168 (15.6%) presented both skin lesions as well affected nerves, 5,072 (67.8%) had only skin lesions, 410 (5.5%) presented thickened nerves, while 827 (11.1%) did not presented skin lesions or affected nerves.

The kernel maps (Fig. 2) show that the areas with the highest NCDR density (A) do not coincide with the areas with the highest proportion of misdiagnosis (B). An exception is the Northeast region where both high detection rates and a high proportion of misdiagnoses overlap. The spatial correlation coefficient was not statistically significant for both municipalities and states as spatial units, indicating the absence of spatial dependence of events. Consequently, the later decision stages of the spatial regression model (lag or error) are disregarded (Brasil. Ministério da Saúde, 2017).

The highest NCDR density areas followed the same spatial patterns in all five-year periods (column A). Areas of very high density were identified in the North, Northeast and Midwest Regions, with an emphasis in the states of Pará, Maranhão, Piaui, Pernambuco, Goiás, Tocantins, and Mato Grosso. The density decreased from high to medium in the last five years in some parts of the North and Midwest, mirroring the decrease of the annual NCDRs in the same period.

Regarding the proportion of patients released due to misdiagnosis, the most important concentrations were identified in the Northeast, Southeast and South of the country. In the second quinquennium, the density of this indicator declined from high to medium and even low in Northeast and Midwest states. In the third quinquennium a change in the spatial pattern was observed, with increasing density in the states of São Paulo and Minas Gerais, belonging to the Southeast region. Northeastern States had areas with relatively high density of misdiagnosis across all three periods.

The proportion of leprosy misdiagnoses per 1,000 new leprosy cases did not follow the NCDR by region in the three five-year periods. With the exception of the Northeast and Midwest regions, which in addition to presenting high NCDR figures, also presented a relatively higher proportion of releases due to misdiagnosis (Table 1).

According to the logistic regression model (Table 2), the likelihood of misdiagnosis was 58% higher for females compared to males (OR: 1.58, 95% CI: 1.51-1.66) while children and adults were more likely to be released from treatment due to misdiagnosis than the elderly. The chance of diagnostic error was greater for PB compared to MB patients (OR: 1.08; 95% CI: 1.02-1.13), as well as for cases with a clinical type classified as "ignored" and "indeterminate" when compared with lepromatous patients; and significantly higher for cases detected by means of mass screening (OR: 3.36; 95% CI: 3.05-3.68) and contact examination (OR: 2.30; 95% CI: 2.12-2.49) compared to patients diagnosed after referral. Patients who had only skin lesions had a reduced likelihood of release due to misdiagnosis (OR: 0.90; 95% CI: 0.84–0.96) while those diagnosed with affected nerves only but no skin lesions had a higher risk of misdiagnosis (OR: 2.47; 95% CI: 2.19–2.77) when compared with those presenting both skin lesions and affected nerves.

Discussion

This is the first study characterizing the epidemiological profile, spatial pattern and associated factors of leprosy patients released from treatment due to misdiagnosis in Brazil. Currently, primary health care physicians perform most leprosy diagnoses, as stipulated by the concept for decentralization of leprosy care in Brazil implemented in recent years (Spedo et al., 2009). The largest number of health facilities offering leprosy treatment is located in the most endemic areas while low endemic areas are served by far fewer facilities. Coverage for diagnosis and treatment of leprosy is 70.6% in the Midwest region while it is only 3.8% in the South region (World Health Assembly, 2017). These differences may explain why misdiagnosis was found to be lower in regions

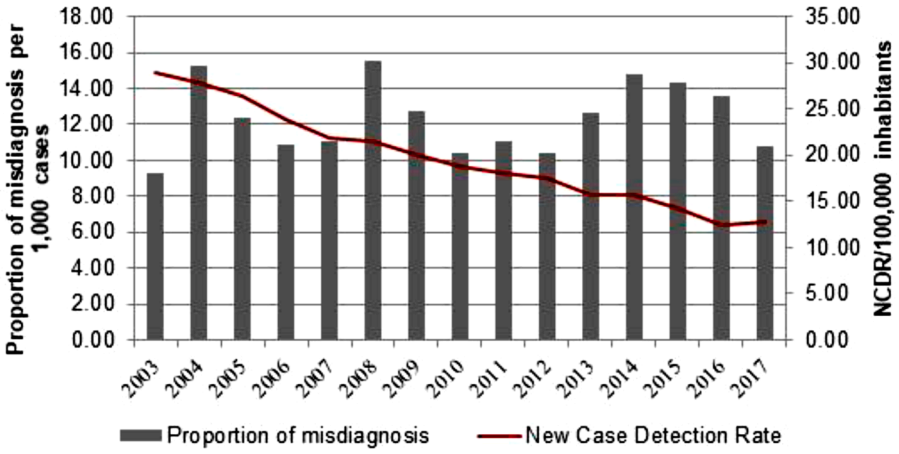

Fig. 1. Annual leprosy NCDR per 100,000 inhabitants and proportion of leprosy cases released from treatment due to misdiagnosis per 1,000 new cases, Brazil, 2003 - 2017.

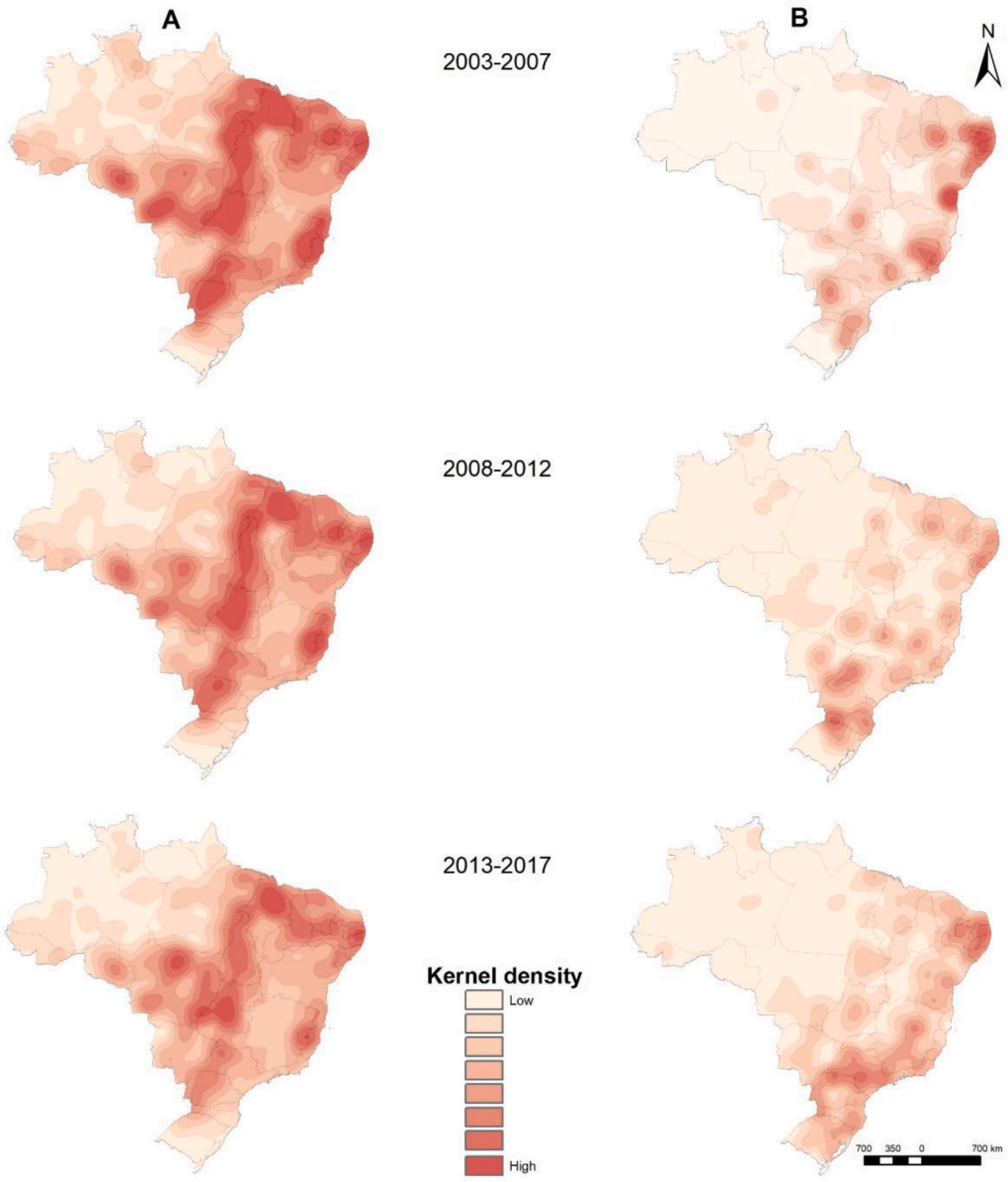

Fig. 2. Kernel density distribution of the leprosy NCDR (A) and the proportion of leprosy patients released from treatment due to misdiagnosis (B) by municipality; Brazil, 2003 - 2017.

with high NCDR, such as the Midwest Region, and the inverse result was observed in the South Region where lower NCDRs were associated with a higher proportion of misdiagnoses. The relatively small number of cases requires fewer professionals involved with the disease and leads to a relative centralization of care. As a result, access to diagnosis and treatment is limited. Patients in non-endemic areas may thus face greater difficulties in obtaining a correct diagnosis (Ura and Barreto, 2004; Obadia et al., 2011). In this context, it is important to consider the situation observed in the Northeast Region, where both the NCDR and the proportion of misdiagnoses were constantly high. This may reflect the poor economic and health care infrastructure of this region, which may translate into reduced investments in training and supervision (de Souza et al., 2019).

It is noteworthy that the differential diagnosis of leprosy is still made by specialized physicians in secondary and tertiary health services (Barbieri et al., 2016; Lapa et al., 2006). In some municipalities, the correct diagnosis of leprosy in primary care may be impaired due to poor capacity to perform differential diagnosis (International Leprosy Association, 2002). Leprosy cases with complex symptomatic presentations can be difficult to diagnose when evaluated by non-specialized professionals (Barbieri et al., 2016). Often the primary care physician suspects the disease but is unable to confirm the diagnosis. Some health professionals also lack specific training, resulting in diagnostic insecurity (International Leprosy Association, 2002; Marchon et al., 2014). The lack of continuous medical education programs coupled with the high turnover of professionals in primary care contribute to this problem. Additionally, undergraduate courses do not always prepare medical doctors to accurately diagnose and treat leprosy, contributing to the neglect of the disease by the population and healthcare workers.

Decentralization facilitates access to diagnosis, and overall, most of the diagnoses are correct. Even with decentralization of leprosy services, in many places diagnosis is still confirmed by specialists while treatment and discharge are within the scope of primary care. Thus, once treatment has started, the likelihood that a false-positive diagnosis is recognized by the treating general practitioners is probably small. Of

Table 1
Leprosy NCDR and proportion of leprosy patients released due to misdiagnosis by geographic region; Brazil, 2003 - 2017.

	Region	NCDR / 100,000 hab	Proportion of misdiagnosis / 1,000 cases
2003-2007	North	67.23	9.73
	Northeast	36.27	11.27
	Midwest	58.22	13.59
	Southeast	12.53	8.20
	South	7.83	38.18
2008-2012	North	47.43	15.12
	Northeast	29.15	12.21
	Midwest	44.54	15.11
	Southeast	8.11	42.30
	South	5.63	42.30
2013-2017	North	28.04	17.67
	Northeast	20.28	13.34
	Midwest	33.00	27.06
	Southeast	2.14	19.47
	South	9.63	19.47

Source: SINAN. DATASUS / MOH, 2018.

note, in the light of the low rate of false-positive diagnoses, local events may have a disproportionate effect on overall numbers: In an endemic municipality in the Northeast, the new case detection rate was found to be higher than expected, with many false positive diagnoses later attributed to a single clinician (Campos et al., 2005). This demonstrates the impact of decentralization of leprosy services which tends to increase sensitivity but decrease specificity of diagnosis.

Only few specialized health units exist in Brazil with dermatologists, infectiologists or leprologists, and these are usually located in large urban centers. Only 9.1% of all Brazilian municipalities have dermatologists (Schmitt and Miot, 2014). While most leprosy cases can be diagnosed based on the presence of cardinal signs of the disease, up to 30% of the MB cases do not have skin lesions with loss of sensation. For such cases it is important to have access to additional laboratory tests to support the diagnosis, which would mean implementing and strengthening the slit skin smear network (Oliveira et al., 2008). Despite the broad acceptance of the current criteria for clinical diagnosis, advances in diagnostic technologies are crucial (Ignotti and Steinmann, 2020).

The evaluated database does not provide information on the differential diagnosis established at the moment the leprosy misdiagnosis was recognized. In our study, we observed that the rate of misdiagnosis was higher in people without skin lesions, either with or without nerve involvement. Although some patients may present peripheral nerve involvement without skin lesions (known as pure neural or primary neuritic leprosy) (Ura and Barreto, 2004), the prevalence of these cases is small and may be overestimated due to incomplete investigation of skin lesions, and especially when differential diagnosis is incomplete. Unfortunately, no information is available on the most common differential diagnoses for leprosy cases later re-classified as misdiagnosis. With regard to variations over time, it should be noted that in 2004, the National Leprosy Program carried out a review of the database with an emphasis on the date of release from treatment to update the prevalence estimate. In 2007, another round of review focused on the exclusion of grade 3 physical disability from the database, impacting figures in 2008. In 2014 the Ministry of Health expanded the schoolchildren leprosy screening campaign, and priority municipalities received additional financial support to increase active case detection.

Thickened nerves are found in an elevated proportion of new leprosy cases especially among MB patients and when the diagnosis is late. The ability of health workers to identify nerve enlargements is extremely variable and non-specific symptoms are often seen among manual workers. Thus, it is recommended to accept a thickened nerve as diagnostic for leprosy when it is associated with a typical skin lesion with

Table 2
Likelihood of release from leprosy treatment due to misdiagnosis (case) according to demographic, clinical and operational factors (gender, age group, operational classification, clinical type, mode of detection, and categories of cardinal signs) estimated by logistic regression; Brazil, 2003 - 2017.

Variables	Case	Control	OR	OR (adjusted)	CI 95%[&]
Gender[a]					
Female	4,327 (0.8%)	254,900 (44.4%)	1.68	1.58	1.51- 1.66
Male	3,150 (0.5%)	311,804 (54.3%)	1	1	-
Age Group[a]					
˂ 15	772 (0.1%)	37,298 (6.6%)	1.86	1.49	1.36 - 1.64
15–59	5,340 (0.9%)	411,501 (72.8%)	1.17	1.06	1.00–1.13
˃ 60	1,209 (0.2%)	108,862 (19.3%)	1	1	-
Operational classification[b]					
Ignored	46 (0.0%)	778 (0.1%)	4.90	3.65	2.65 - 5.03
PB	3,399 (0.6%)	232,589 (40.5%)	1.20	1.08	1.02 - 1.13
MB	4,032 (0.7%)	333,347 (58.1%)	1	1	-
Clinical type[a]					
Ignored	1,144 (0.2%)	49,763 (8.7%)	3.79	3.11	2.80- 3.45
Indetermined	1,875 (0.3%)	105,138 (18.3%)	2.93	2.37	2.15 -2.62
Tuberculoid	1,242 (0.2%)	118,198 (20.6%)	1.73	1.47	1.33 -1.63
Borderline	2,664 (0.5%)	202,635 (35.3%)	2.16	1.90	1.73 -2.08
Lepromatous	552 (0.1%)	90,970 (15.8%)	1	1	-
Detection mode[a]					
Referral	2,091 (0.4%)	243,717 (42.4%)	1	1	-
Spontaneous presentation	3,538 (0.6%)	251,615 (43.8%)	1.64	1.57	1.49–1.66
Mass screening	609 (0.1%)	18,508 (3.2%)	3.84	3.36	3.05 - 3.68
Contact examination	951 (0.2%)	40,180 (7.0%)	2.76	2.30	2.12–2.49
Other	288 (0.1%)	12,684 (2.2%)	2.65	2.38	2.09–3.69
Cardinal signs[**a]					
A	827 (0.1%)	40,901 (7.1%)	1.70	1.59	1.45 - 1.75
B	5,072 (0.9%)	413,939 (72.1%)	1.04	0.90	0.84 - 0.96
C	410 (0.1%)	12,843 (2.2%)	2.70	2.47	2.19 - 2.77
D	1,168 (0.2%)	99,021 (17.2%)	1	1	-

**A) Cases WITHOUT skin lesions and WITHOUT neural involvement; B) Cases WITH skin lesions but NO neural involvement; C) Cases WITHOUT skin lesions but WITH neural involvement; D) Cases WITH skin lesions and WITH neural involvement

[a] adjusted by all variables except operational classification [b]adjusted by all variables except clinical type

[&] p-value < 0.005

sensory loss, as well as in cases of a nerve function impairment (NFI), demonstrated particularly on the palms of the hands or soles of the feet (Brasil. Ministério da Saúde, 2017). Peripheral neuropathy from connective tissue diseases make differential diagnosis of leprosy more difficult, especially for the lepromatous type (Hsieh and Wu, 2014; Fernandes et al., 2014). Other neurological diseases may also show symptoms similar to leprosy, such as carpal tunnel syndrome; meralgia paresthetica; alcoholic neuropathy, diabetic neuropathy and repetitive strain injuries (Scollard and Gillis, 2020). The main causes of

leprosy-like multiple mononeuropathy are vasculitic neuropathies: collagenose and arteritis; and viral infectious diseases: hepatitis B and C and HIV infection (Höke, 2005).

Our findings indicate that men are less likely to be misdiagnosed as having leprosy than women. This might be due to relatively late diagnosis and a higher frequency of advanced disease symptoms in this group, which reduces the chance of misdiagnosis. Men are diagnosed as MB leprosy twice as often than women in different parts of the world and in all Brazilian regions (Nobre et al., 2017). A study by Monteiro et al. (2013) found a 1.7 times higher rate of physical deformities due by leprosy in men than in women, suggesting a higher proportion of late diagnosis in males. On the other hand, women and children are more likely to present localized PB types of leprosy, with more discrete lesions, which may explain the higher chances of misdiagnosis for these population groups. In the present study, an increased probability of misdiagnosis was observed for patients under the age of 15 years compared to those aged 60 or more. It has been reported that elderly people present MB leprosy twice as often as patients younger than 60 years old, in all Brazilian states and regions (Nobre et al., 2017). Some studies indicate that the age group most affected by leprosy are individuals aged 35 to 50 years, which is part of the economically active population (de Lima et al., 2015). Of note, the indeterminate clinical form of leprosy is more common in individuals under 15 years of age, and in many cases, the diagnosis is made through the examination of contacts (de Freitas et al., 2017; Chaitra and Bhat, 2013). This highlights the importance of applying the Complementary Protocol for Diagnostic Investigation of Leprosy Cases in Minors under 15, part of the Brazilian Ministry of Health's Epidemiological Surveillance Guide (Brasil. Ministério da Saúde, 2017).

For well-trained health professionals it is not difficult to classify a leprosy case according to the clinical spectrum or operational classification. Thus, an unknown clinical form of leprosy suggests a compromised diagnosis or incomplete data. Both indicate a lack of capacity or commitment by health professionals (Barbieri et al., 2016). Not surprisingly, the rate of misdiagnosis was higher among such patients.

The greater chance of misdiagnosis among patients identified in the frame of group examinations is important. Active case finding is one of the main approaches to identify disease at an early stage, which may increases the number of doubtful cases. This includes the examination of contacts and community screenings (Brasil. Ministério da Saúde, 2017). Collective exams are usually performed in joint efforts, which are attended by several health professionals, not always experienced in leprosy diagnosis, and sometimes working under unsuitable conditions (Lana et al., 2004).

Diagnoses reported via SINAN have to be taken at face value. Thus, it is unknown how many individuals with false positive diagnoses complete treatment. Although the proportion of recognized misdiagnoses remained stable over the fifteen years analyzed in this study, the percentage never exceeded 2%. This suggests a good capacity of the health system to establish a correct leprosy diagnosis, but also demonstrates the importance of continuous training of health professionals to reduce not only false leprosy diagnoses, but especially false negative cases that may maintain the chain of disease transmission. According to our study, false-positive diagnoses have little influence on new case detection rates. On the other hand, the underestimate due to false-negative diagnoses remains unknown.

Conclusions

We observed a stable spatial and temporal pattern in the proportion of false-positive misdiagnoses over the 15 years analyzed. Female subjects, children, PB cases with unknown and indeterminate clinical type, those without skin lesions - with or without affected nerves - at the time of diagnosis are more susceptible to this type of misdiagnosis. Our findings reinforce Brazilian guidelines (Brasil, 2016), which recommend that patients suspected of having leprosy with nerve impairment without skin lesion should be referred to specialized services for confirmation of their diagnosis.

Author Contributions

Karine Vila Real Nunes Neves: Conceptualization, Formal analysis, Writing, draft, Writing, revision

Maurício Lisboa Nobre: Supervision, Writing, draft, Writing, revision

Lúbia Maieles Gomes Machado: Writing, draft, Writing, revision

Peter Steinmann: Formal analysis, Supervision, Writing, draft, Writing, revision

Eliane Ignotti: Conceptualization, Supervision, Writing, draft, Writing, revision

E. Ignotti and K.V.R. Neves conceived the study; K.V.R. Neves and L. M.G. Machado collected and analyzed the data, all co-authors contributed to interpreting the results and writing the manuscript.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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