








Disparities in leprosy relapse from 2001 to 2022 in Brazil: a nationwide register-based study

Disparidades na recidiva da hanseníase entre 2001 e 2022 no Brasil: um estudo nacional baseado em registros

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Abstract

Objective: to evaluate disparities in leprosy relapse in Brazil from 2001 to 2022. **Methods:** an ecological time series study was conducted. The ratio of leprosy relapses and new cases was obtained per 10,000, and it was adjusted secondarily according to region, sex, age group, operational classification, and smear microscopy outcomes. The temporal trends were estimated using Prais-Winsten regression analysis, and the comparisons were carried out using Negative Binomial regression. The significance level was adjusted at 5%. **Results:** the ratio of leprosy relapses per 10,000 new cases was approximately 424, considering 33,198 relapses and 783,704 new cases. The temporal trends were increasing across all Brazilian regions, sexes, operational classifications, and among individuals aged 15 years or older (all p-values <0.05). Stationarity trends were observed among individuals under 15 years (p-value = 0.422) and among smear microscopy outcomes (positive or negative, p-value = 0.147 and 0.156, respectively). Considering the comparison of ratios, significantly higher values were observed in the South region compared to the national estimate, as well as among males, individuals aged 15 years or older, multibacillary cases, and individuals with positive smear microscopy in relation to their respective counterparts (all p-value <0.001). In addition, a significantly lower value was observed in the Central-West region compared to the national estimate (p-value <0.001). **Conclusion:** in relation to new cases, there was an increase in leprosy relapses from 2001 to 2022 in Brazil, in addition to significant sociodemographic and clinical disparities.

Keywords: public health; neglected diseases; leprosy; epidemiology; recurrence.

Resumo

Objetivo: avaliar as disparidades nos casos de recidiva da hanseníase no Brasil de 2001 a 2022. **Métodos:** foi realizado um estudo ecológico do tipo série temporal. A razão entre recidivas e casos novos de hanseníase foi obtida a cada 10.000, além de ajustada secundariamente de acordo com a região, o sexo, a faixa etária, a classificação operacional e os resultados de baciloscopia. As tendências temporais foram estimadas por meio da análise de regressão de Prais-Winsten, e as comparações foram realizadas utilizando-se a regressão binomial negativa. O nível de significância foi ajustado em 5%. **Resultados:** a razão de recidivas de hanseníase por 10.000 casos novos foi de, aproximadamente, 424, considerando 33.198 recidivas e 783.704 casos novos. As tendências temporais foram crescentes em todas as regiões brasileiras, os sexos, as classificações operacionais e entre indivíduos com 15 anos ou mais (p-valor <0,05). Tendências de estacionariedade foram observadas entre indivíduos com menos de 15 anos (p-valor = 0,422) e nos resultados da baciloscopia (positiva ou negativa, p-valor = 0,147 e 0,156, respectivamente). Na comparação das razões, valores significativamente maiores foram observados na região Sul, em relação à estimativa nacional, bem como entre homens, indivíduos com 15 anos ou mais, casos multibacilares e indivíduos com baciloscopia positiva em relação aos seus respectivos pares (p-valor <0,001). Além disso, foi observado um valor significativamente menor na região Centro-Oeste em comparação com a estimativa nacional (p-valor <0,001). **Conclusão:** em relação aos casos novos, houve um aumento nas recidivas de hanseníase entre 2001 e 2022 no Brasil, além de disparidades sociodemográficas e clínicas significativas.

Palavras-chave: saúde pública; doenças negligenciadas; hanseníase; epidemiologia; iniquidades em saúde.

INTRODUCTION

Despite considerable advances in leprosy treatment, including the implementation and improvement of multidrug therapy (MDT), relapses still pose significant challenges to public health¹. The relapse of leprosy can be defined as the manifestation of new signs and symptoms of the disease in an individual who has been discharged after completing standard MDT regimens². Indeed, the implementation of MDT has acted as a crucial factor in improving the epidemiological context of leprosy in recent

decades, including the reduction of relapse cases. However, it is not uncommon to observe high relapse rates worldwide and local contexts of high endemicity, which underscores the necessity for continuous investigations on the determinants of these events^{1,2}.

Various factors intricately linked to leprosy relapses emerge prominently, notably errors in the operational classification of

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individuals. These errors suggest an inadequate duration of MDT and therapeutic shortcomings, particularly evident when multibacillary (MB) leprosy cases are erroneously identified and treated as paucibacillary (PB)³. Furthermore, within MB leprosy cases, completing a 24-month MDT regimen and attaining negative outcomes in smear microscopy is also associated with a lower relapse rate⁴. It underscores the significance of leprosy control endeavors, particularly emphasizing treatment adherence while considering the health inequalities prevalent in each country. Such adherence directly mirrors the efficacy of policies and services enacted⁵.

Currently, evaluating the epidemiological landscape of leprosy, including relapse cases, in countries like Brazil is of utmost importance. Brazil is the second country in the world in terms of the number of new leprosy cases and concentrates more than 90% of leprosy cases in the Americas⁶. In recent years, significant efforts have led to a decrease in the disease's incidence. However, despite progress, various disparities persist, including regional differences and a high number of cases diagnosed with some grade of physical disability^{7,8}.

Nonetheless, there remains a need to reinforce health surveillance systems, strengthening active screening and follow-up actions for individuals, particularly in high-endemicity territories where leprosy control efforts have not been effective⁸⁻¹⁰. Moreover, it is recognized that persistent hyperendemic areas may encounter additional barriers to overcoming the disease, such as low cure rates and high discontinuation of MDT, perpetuating inadequate treatment and sustaining high endemicity, alongside a rise in leprosy relapses^{2,11}.

In some epidemiological approaches, leprosy relapses are assessed using person-year methodologies, such as incidence of relapses or recurrence rate, and linking them to the demographic features of each area (e.g., 100 leprosy relapses per 100,000 inhabitants)^{4,5}. Hence, two different areas with similar population density and number of leprosy relapses might exhibit similar recurrence rates. However, similar estimations of leprosy relapses may have occurred within different incidences (e.g., 100 relapses per 1,000 or 10,000 new cases). Considering these factors, it is reasonable that a high ratio of leprosy relapses per new case, beyond the person-year incidence, could serve as an estimate of leprosy control actions, including treatment availability and adherence, drug resistance, follow-up deficiencies, and challenges within leprosy care networks. Therefore, this study investigated disparities in leprosy relapse in Brazil from 2001 to 2022, addressing the ratio of relapses and new cases.

METHODS

Study design

An ecological time-series study was conducted using all leprosy relapses and new cases in Brazil notified to the Notifiable

Diseases Information System (SINAN, Sistema de Informação de Agravos de Notificação)¹². The SINAN is a de-identified national public domain database established by the Brazilian Ministry of Health for the surveillance of notifiable diseases, including leprosy. Leprosy notifications are compulsory, and SINAN receives notifications from all public and private health centers in Brazil^{13,14}. The timeframe was delimited between 2001 and 2022, comprising a 22-year analysis. The area spanned Brazil, covering all five regions.

Ethics

Considering a register-based study through a de-identified data source, it was not necessary to obtain institutional review board approval or informed consent in accordance with current legislation in Brazil¹⁵.

Outcomes

The primary outcome of the study was the ratio between leprosy relapses and new leprosy cases, normalized per 10,000 new leprosy cases. Additionally, this primary outcome was further analyzed across various stratifications, including Brazilian regions (North, Northeast, Southeast, South, and Central-West), sex (male and female), age groups (<15 years and 15 or older), World Health Organization (WHO) operational classification (PB or MB leprosy), and smear microscopy outcomes (positive or negative).

Data analysis

Data on leprosy was obtained from SINAN in February 2024, similar to previous approaches^{16,17}. The significance level was adjusted to 5% ($\alpha = 0.05$), considering all p-values <0.05 as a statistically significant outcome. The JAMOMI software (version 2.3.15, Sydney, Australia) was used for correlations (using the Spearman's rank correlation matrix and rho coefficient - ρ) and comparisons (using generalized linear models, considering a quasi-Poisson distribution with robust variance, as well as employing Negative Binomial regression and maximum likelihood estimator in the logarithmic link-function)^{18,19}.

Moreover, the PAST software (version 4.03, Oslo, Norway) was used to estimate trends over time, employing the Prais-Winsten regression to obtain the value of the angular coefficient (β_1 slope) and coefficient of determination (R^2). In this analysis, the ratio of leprosy relapses per new case was subjected to logarithmic transformation (\log_{10}), and the temporal variation was quantified as the Annual Percent Change (APC). The trend classification (stationary, increasing, or decreasing) considered both the statistical outcome and the sign of the slope (positive or negative)^{20,21}.

RESULTS

A total of 33,198 leprosy relapses and 783,704 leprosy new cases were recorded in Brazil between 2001 and 2022,

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amounting to 424 leprosy relapses per 10,000 new cases. There was no significant correlation between the annual numbers of leprosy relapses and new cases from 2001 to 2022 in Brazil (p -value = 0.336), indicating different patterns of temporal variation. Table 1 shows the distribution of leprosy relapses and its ratio per 10,000 new cases by sociodemographic and clinical

characteristics. The ratio was notably higher among individuals residing in the South region (801 per 10,000 new cases), males (499 per 10,000 new cases), aged 15 or older (449 per 10,000 new cases), diagnosed with MB leprosy (595 per 10,000 new cases), and those with positive smear microscopy (825 per 10,000 new cases).

Table 1. Distribution of leprosy relapses and its proportion per 10,000 new cases by sociodemographic and clinical characteristics in Brazil, from 2001 to 2022 (2024).

Variables	n	%	Proportion (relapses/new cases)
Region			
North	6,360	19.2	407/10,000
Northeast	13,579	40.9	430/10,000
Southeast	6,481	19.5	457/10,000
South	2,472	7.4	801/10,000
Central-West	4,306	13.0	310/10,000
Sex			
Female	11,732	35.3	332/10,000
Male	21,461	64.7	499/10,000
Age group (year)			
0-14	516	1.6	92/10,000
15 or older	32,677	98.4	449/10,000
Operational classification			
Multibacillary	28,463	85.9	595/10,000
Paucibacillary	4,662	14.1	153/10,000
Smear microscopy			
Positive	7,729	59.5	825/10,000
Negative	5,267	40.5	383/10,000

n: absolute frequency of leprosy relapse cases. %: relative frequency.

Table 2 shows the temporal trend of the ratio of leprosy relapses per 10,000 new cases. There was an increasing temporal trend in all five Brazilian regions over the period assessed, and the highest APC was observed in Central-West (APC = 5.7%, p -value <0.001), North (APC = 5.2%, p -value <0.001) and Southeast region (APC = 5.0%, p -value <0.001). There was also an increased temporal trend between males (APC = 4.2%, p -value <0.001), females (APC = 3.8%, p -value <0.001), individuals aged 15 or older (APC = 4.2%, p -value <0.001), MB cases (APC = 3.0%, p -value <0.001) and PB cases (APC = 3.0%, p -value <0.001).

Table 3 shows the comparison of the ratio of leprosy relapses per 10,000 new cases across demographic and clinical characteristics. When considering regions, it was observed that the North, Northeast, and Southeast regions closely aligned with the national estimate, while the South surpassed it, and the Central-West fell below. Regarding sex, the incidence was

notably higher in males compared to females. Across age groups, there was a marked increase in individuals aged 15 years or older compared to those under 15. In terms of operational classification, there was a significant elevation among MB cases compared to PB cases. Concerning smear microscopy outcomes, there was a substantial increase in positive results compared to negative ones.

A progressive escalation in the ratio of leprosy relapses per 10,000 new cases has been observed in Brazil from 2001 to 2022. This ratio surged from 271 per 10,000 in 2001 to 667 per 10,000 in 2022, marking a substantial 146% increase. Notably, this increasing temporal trend stems from the interplay of two factors: the sustained occurrence of leprosy relapses, which rose from 1,222 reports in 2001 to 1,344 reports in 2022, juxtaposed with the decline of leprosy new cases, which decreased from 45,102 reports in 2001 to 20,158 reports in 2022 (Figure 1).

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Table 2. Temporal trend of the proportion of leprosy relapses per 10,000 new cases in Brazil, from 2001 to 2022 (2024).

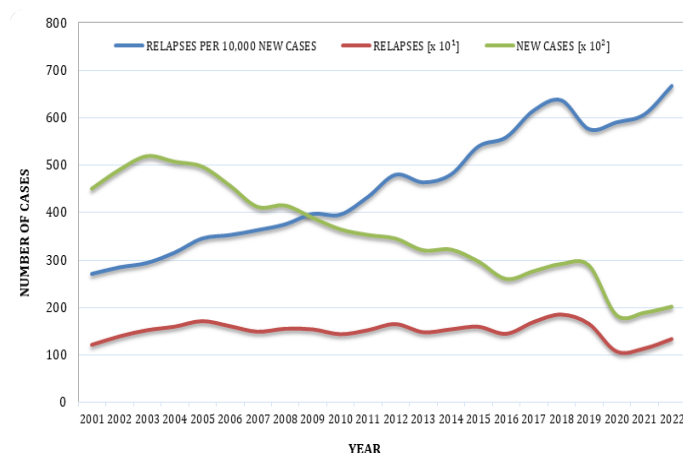
Variables	β_1	R ²	<i>p</i> -value	Trend	APC (%)
Region					
Brazil	0.018 [0.017-0.020]	0.969	<0.001*	Increasing	4.2 [4.0-4.7]
North	0.022 [0.017-0.024]	0.874	<0.001*	Increasing	5.2 [4.0-5.7]
Northeast	0.016 [0.014-0.019]	0.884	<0.001*	Increasing	3.8 [3.3-4.5]
Southeast	0.021 [0.019-0.025]	0.858	<0.001*	Increasing	5.0 [4.5-5.9]
South	0.011 [0.005-0.017]	0.429	0.002*	Increasing	2.6 [1.2-4.0]
Central-West	0.024 [0.017-0.030]	0.781	<0.001*	Increasing	5.7 [4.0-7.2]
Sex					
Female	0.016 [0.014-0.018]	0.942	<0.001*	Increasing	3.8 [3.3-4.2]
Male	0.018 [0.016-0.021]	0.955	<0.001*	Increasing	4.2 [3.8-4.9]
Age group (years)					
0-14	-0.003 [-0.011-0.006]	0.318	0.422	Stationary	N/A
15 or older	0.018 [0.016-0.020]	0.962	<0.001*	Increasing	4.2 [3.8-4.7]
Operational classification					
Multibacillary	0.013 [0.009-0.016]	0.878	<0.001*	Increasing	3.0 [2.1-3.8]
Paucibacillary	0.013 [0.007-0.017]	0.674	<0.001*	Increasing	3.0 [1.6-4.0]
Smear microscopy					
Positive	0.005 [-0.002-0.011]	0.099	0.147	Stationary	N/A
Negative	0.009 [-0.004-0.024]	0.097	0.156	Stationary	N/A

β_1 : angular coefficient (slope). R²: coefficient of determination. APC: Annual Percent Change (%). N/A: not applicable. *: *p*-value <0.05 (statistically significant outcome). []: 95% confidence interval.

Table 3. Comparison of the proportion of leprosy relapses per 10,000 new cases across demographic and clinical characteristics (2024).

Variables	Ratio	Limits		p-value
		Lower	Upper	
Region				
Intercept	493	467	520	<0.001*
Brazil	ref			
North	0.989	0.821	1.191	0.903
Northeast	0.993	0.824	1.196	0.940
Southeast	1.182	0.982	1.424	0.078
South	1.907	1.584	2.296	<0.001*
Central-West	0.721	0.598	0.869	<0.001*
Sex				
Intercept	437	405	473	<0.001*
Female	0.662	0.565	0.775	<0.001*
Male	ref			
Age group (years)				
Intercept	210	193	229	<0.001*
0-14	ref			
15 or older	5.26	4.45	6.23	<0.001*
Operational classification				
Intercept	320	301	341	<0.001*
Multibacillary	ref			
Paucibacillary	0.279	0.247	0.315	<0.001*
Smear microscopy				
Intercept	522	477	573	<0.001*
Positive	ref			
Negative	0.457	0.380	0.551	<0.001*

ref: reference level for comparison (ratio = 1). *: p-value <0.05 (statistically significant outcome).

Figure 1. Leprosy relapses and new cases from 2001 to 2022 in Brazil.

DISCUSSION

This study analyzed disparities in leprosy relapses in Brazil from 2001 to 2022, addressing the ratio of relapses per new case. These outcomes depict sociodemographic and clinical disparities in the ratio of relapses by new cases in Brazil over the last 22 years, along with an increasing trend of this ratio among most variables, as well as in the national estimate.

A notable disparity was observed in the ratio of leprosy relapses compared to new cases between the South and Central-West regions of Brazil, diverging from the national average. Surprisingly, the South region exhibited a higher ratio, while the Central-West region demonstrated a lower ratio. This finding contrasts with existing literature, which typically associates the Central-West region with adverse outcomes in leprosy control efforts, including elevated incidence and age-standardized mortality rates in recent years. Conversely, the South region consistently presents significantly lower values in both variables⁹.

The initial hypothesis to rationalize these findings posits that the Central-West region may experience a significantly higher number of new cases of leprosy, leading to a lower ratio relative to relapses, whereas the South region may encounter a lower number of new cases of leprosy, resulting in a higher ratio of relapses. This proposition finds support in a prior investigation designating the Central-West as a high-risk area for leprosy from 2011 to 2021, while categorizing the South region as low-risk for this disease²². However, despite the comparatively favorable epidemiological landscape in the South region, the escalating frequency of leprosy relapses warrants attention, comprising 3.9% of new cases and 7.4% of relapses nationwide. In contrast, the Central-West region accounts for 17.7% of new cases and 13% of relapses, reflecting a different epidemiological dynamic.

Addressing this epidemiological landscape, and despite a lower incidence, a previous study demonstrated that the South region showed a higher incidence of new leprosy cases with some degree of physical disability, significantly higher than the North, Northeast, and Central-West between 2008 and 2018⁹. Concurrently, another study showed that the South region performed fewer smear microscopies compared to Brazil (national estimate) between 2013 and 2022¹⁷. In 2015, evaluating a specific service for leprosy, another study demonstrated an average delay in diagnosis of over two years, along with a high frequency of physical disabilities at the time of diagnosis and treatment-related complications, such as drug side effects, co-infections, and comorbidities²³.

Therefore, drawing from this evidence and the outcomes of this study, it is imperative to highlight that a decrease in leprosy incidence within an area does not necessarily correlate directly with a reduction in relapses. Furthermore, it is crucial to acknowledge that a lower incidence may not fully reflect the effectiveness of leprosy control actions and their impact within

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an area, as the epidemiological landscape may still grapple with significant other challenges, such as relapses, even amidst a smaller number of new cases^{9,17,23}. Moreover, this scenario underscores the importance of analyzing the ratio of leprosy relapses to new cases to enhance our understanding of the epidemiological landscape, providing a more comprehensive insight into spatio-temporal dynamics.

The increasing temporal trends observed in the ratio of relapses per new case could potentially be linked to the significant decrease in leprosy detection coefficients in recent years. A study revealed an APC of -5.20% in Brazil between 2001 and 2020, ranging from -3.81% to -8.13% across regions. Furthermore, this decreasing trend remained consistent regardless of sex. Interestingly, a stationary temporal trend was noted in the ratio of cured cases in the South region from 2001 to 2018²⁴, suggesting a potential correlation with relapses.

A study conducted at a leprosy reference center in Brazil found that approximately 11.9% of cases were relapses, with a median relapse interval of 10 years, predominantly involving MB cases (approximately 96%). Additionally, there was a slight male predominance, with the average age at relapse diagnosis at 49.5 years old². Another investigation indicated that patients aged 40 years or older faced a heightened risk of leprosy relapse, with an average relapse interval of around 9 years and an average patient age of 41.5 years³. In a study conducted in a state in the Northeast region of Brazil, a higher prevalence of leprosy relapses was observed among male patients, MB cases, and individuals aged 15 years or older. Moreover, a higher prevalence was noted among individuals with positive smear microscopy results²⁵.

Therefore, this nationwide study substantiated, at a national level, the local evidence regarding leprosy relapse in Brazil. Nevertheless, it is necessary to consider that the ratio of relapses per new case unfolds within a multifaceted landscape intertwined with surveillance and healthcare dynamics in Brazil.

Over recent years, numerous transformations have occurred in leprosy diagnosis and treatment, alongside intrinsic changes within the Brazilian public health system. Consequently, the sociodemographic and clinical variations outlined herein can be perceived as outcomes of leprosy care and control efforts in each region. It is crucial not to confine our interpretation solely to the findings presented here, as numerous other pertinent issues beyond the scope of this study merit consideration²⁶⁻²⁷, as well as COVID-19-related impacts and Brazil's macro-regional disparities^{28,29}. However, assessing this ratio provides insight into distinct dynamics across Brazil, including regional disparities, and has facilitated the identification of discrepancies while considering leprosy incidence.

These findings should be interpreted with caution. Given its register-based approach, it is important to acknowledge potential misreporting and minor discrepancies in case numbers, as they are continually updated based on notifications. Additionally, classifying cases as relapses, a task that can be challenging, is not influenced by researchers. Future studies could delve into the factors linked with leprosy relapses in Brazil, seeking to comprehend their effects on epidemiological indicators and patient outcomes. Ultimately, there is a pressing need to investigate and propose interventions aimed at diminishing leprosy relapses in the country.

CONCLUSION

Brazil has witnessed a rise in the ratio of leprosy relapses per new case from 2001 to 2022. This trend was predominantly driven by the persistent occurrence of relapses alongside a decrease in new cases during this timeframe, resulting in an increasing ratio. Furthermore, this ratio was notably higher among individuals residing in the South region, males aged 15 years or older diagnosed with multibacillary (MB) leprosy, and those with positive smear microscopy results. These findings highlight significant sociodemographic and clinical disparities within the epidemiological landscape of leprosy.

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