Temporal Evolution and Spatial Distribution of Leprosy Reaction, 2001-2022

Evolução Temporal e Distribuição Espacial da Reação Hansênica, 2001-2022

Evolución Temporal y Distribución Espacial de la Reacción Hansénica, 2001-2022

RESUMO

Objetivo: Analisar a distribuição espacial e temporal dos episódios reacionais da hanseníase. **Método:** Estudo ecológico, com dados do sistema de informação de agravos de notificação referentes a 2001–2022. As variáveis sociodemográficas foram analisadas no *software* SPSS. A distribuição espacial utilizou técnicas de georreferenciamento, Getis-Ord General G e Getis-OrdGi, enquanto a análise temporal empregou o método Prais-Winsten e a decomposição sazonal e de tendência por Loess. **Resultados:** Entre 26.298 casos de hanseníase notificados, 15.911 apresentaram episódios reacionais, predominando em homens, pessoas brancas, com ≥60 anos, baixa escolaridade e residentes em áreas urbanas/periurbanas. Identificaram-se aglomerados espaciais em todas as macrorregiões, com maior concentração nas regiões Norte e Oeste. **Conclusão:** A taxa de detecção manteve-se estacionária, evidenciando padrões regionais que subsidiam ações de vigilância e manejo direcionadas às áreas de maior risco.

DESCRITORES: Hanseníase; Reações hansênicas; Análise espacial; Estudos de séries temporais; Vigilância em saúde pública.

ABSTRACT

Objective: To analyze the spatial and temporal distribution of leprosy reaction episodes. **Method:** Ecological study using data from the Notifiable Diseases Information System for the period 2001–2022. Sociodemographic variables were analyzed using SPSS software. Spatial distribution employed georeferencing, Getis-Ord General G, and Getis-OrdGi techniques, while temporal analysis used the Prais-Winsten method and Seasonal and Trend Decomposition using Loess. **Results:** Among 26,298 reported leprosy cases, 15,911 presented reaction episodes, predominantly in men, white individuals, those aged ≥60 years, with <8 years of education, and residents of urban/periurban areas. Spatial clusters were identified in all health macroregions, with higher concentrations in the North and West regions. **Conclusion:** The detection rate remained stationary, revealing regional patterns that support surveillance and management actions targeted at higher-risk areas.

DESCRIPTORS: Leprosy; Leprosy reactions; Spatial analysis; Time series studies; Public health surveillance.

RESUMEN

Objetivo: Analizar la distribución espacial y temporal de los episodios reaccionales de la lepra. **Método:** Estudio ecológico con datos del Sistema de Información de Enfermedades de Notificación correspondientes al período 2001–2022. Las variables sociodemográficas se analizaron mediante el software SPSS. La distribución espacial empleó técnicas de georreferenciación, Getis-Ord General G y Getis-OrdGi, mientras que el análisis temporal utilizó el método Prais-Winsten y la descomposición estacional y de tendencia mediante Loess. **Resultados:** Entre 26.298 casos de lepra notificados, 15.911 presentaron episodios reaccionales, predominando en hombres, personas blancas, de ≥60 años, con baja escolaridad y residentes en áreas urbanas/periurbanas. Se identificaron conglomerados espaciales en todas las macrorregiones de salud, con mayor concentración en las regiones Norte y Oeste. **Conclusión:** La tasa de detección se mantuvo estacionaria, revelando patrones regionales útiles para orientar acciones de vigilancia y manejo en áreas de mayor riesgo.

DESCRIPTORES: Lepra; Reacciones hansénicas; Análisis espacial; Estudios de Series Temporales; Vigilancia en salud pública.

RECEIVED: 11/02/2025 **APROVADO EM:** 11/18/2025

How to cite this article: Luquini VC, Scholze AR, Arcoverde MAM, Gonçalves LC, Marques JO, Souza ABF, Sakai AM, Pieri FM. Temporal Evolution and Spatial Distribution of Leprosy Reaction, 2001-2022. Saúde Coletiva (Brazilian Edition) [Internet]. 2025 [cited year month day];16(103):18664-18679. Available from: DOI: 10.36489/saudecoletiva.2025v16i103p18664-18679

DOI: https://doi.org/10.36489/saudecoletiva.2025v16i103p18664-18679

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INTRODUCTION

Leprosy remains a significant public health challenge in Brazil, which ranks among those with the highest burden of the disease in the world. [1] Caused by the bacterium Mycobacterium leprae, it is a chronic infectious disease that primarily affects the peripheral nerves and skin. [2]

In 2024, 172,717 new cases of leprosy were registered worldwide, representing a 5.5% reduction compared to 2023. In Brazil, 22,129 new cases were reported, corresponding to a 2.8% decrease compared to the previous year. Despite this decrease, the country remains the second with the highest absolute number of cases, behind only India, which recorded 100,957 new cases. [3]

According to the Interministerial Committee for the Elimination of Socially Determined Diseases (CIEDDS), people's health status is directly influenced by the environmental, social, and economic factors in which they live, which contributes to the persistence of leprosy. [1,4] Late diagnosis, physical disabilities (PD), and a lack of awareness among the population and healthcare professionals contribute to social exclusion and stigma related to the disease. [5]

Leprosy reactions, also called reactional episodes of leprosy, are immune-mediated manifestations that can occur before, during, or after treatment, frequently associated with the interruption of multidrug therapy and the onset of physical disabilities, with a negative impact on quality of life and social vulnerability. They are classified into two main types: type 1 or reversal reaction (RR), predominant in dimorphic forms and characterized by the exacerbation of skin lesions and painful neuritis; and type 2, erythema nodosum leprosum (ENL), which affects multibacillary cases, especially in lepromatous and dimorphic forms with a high bacillary load, manifesting with fever, painful nodules, arthralgia, and inflammation of nerves and other organs. [2]

The distribution of infectious diseases often exhibits spatial patterns resulting from interactions between pathogen, host, and environment in specific geographic and temporal contexts. These interactions reflect how populations appropriate and occupy territories, influencing the occurrence and persistence of certain diseases. [6]

Over the past two years, there has been an increase in the detection of new cases, raising the country's endemicity level to "high" in 2023, in addition to a higher proportion of records classified as "other re-entries," which may reflect the return of patients who had abandoned treatment. This fact maintains the disease as a significant public health problem. [1,2] Paraná stands out as the state in southern Brazil with the highest detection rate (3.99/100,000 inhabitants), corre-

DOI: https://doi.org/10.36489/saudecoletiva.2025v16i103p18664-18679

sponding to 463 new diagnoses in 2023. [1]

Given this scenario, the question arises: how does the spatial distribution and temporal trend of leprosy reactional episodes occur during the treatment of cases in the state of Paraná? Studies that identify spatial clusters and assess the temporal dynamics of reactional episodes are essential to understanding the social and ecological space of the disease. Such analyses support the planning and evaluation of health service actions and guide specific surveillance and control strategies.

Thus, this study aims to analyze the spatial and temporal distribution of leprosy reactional episodes.

METHOD

This is an ecological time series and spatial analysis study, developed from data on leprosy reaction episodes reported in the state of Paraná, from 2001 to 2022.

The data were obtained from the Notifiable Diseases Information System (SINAN), made available by the Paraná State Health Department (SESA/PR) in February 2023. Paraná is located in the Southern macro-region of Brazil, with a territorial area of 199,298.981 km², an estimated population of 11,890,517 inhabitants, and administrative subdivision into 399 municipalities and four health macro-regions (east, west, north, and northwest), being the 15th largest state in territorial extension and the 5th in population. [7]

The study population consisted of leprosy cases reported between 2001 and 2022 in individuals aged ≥ 18 years, residing in Paraná, and with the "reactional episode" field duly completed in the notification form. Cases classified as "diagnostic error" and those with the "reactional episode" field blank were excluded. Cases with missing or inconsistent data were considered losses and discarded.

Data analysis was performed in two stages: (1) descriptive analysis and (2) spatial and temporal analysis. In the descriptive analysis, the IBM Statistical Package for the Social Sciences® (SPSS®) software, version 29.0 for Windows, was used. The variables were expressed in absolute and relative frequencies. The dependent variable was the occurrence of the reactional episode (type 1, type 2, type 1 and 2 associated, or absence of reaction). The independent variables included: sex (male and female), race/color (white and non-white), age group (18–59 and ≥ 60 years), education (< 8 and ≥ 8 years of schooling), and place of residence (urban, peri-urban, and rural).

In the spatial analysis, georeferencing and spatial aggregation techniques were used to identify distribution patterns and clustering of reactional episodes. This approach is indicated for estimating the incidence of infectious diseases and identifying socio-environmental risk factors associated with their geographic distribution. [8]

Initially, leprosy cases and detection rates were georeferenced according to the type of reactional episode, using latitude and longitude information per municipality obtained via Google Earth®. The shapefile was constructed based on the municipalities of Paraná. The municipal detection rate was calculated by dividing the number of reactional episode cases by the municipal population ≥ 18 years (2010 Census), multiplied by 100,000 inhabitants [1], and adjusted for the 22 years of observation.

To assess spatial aggregation, the Getis-Ord General G and Getis-Ord-Gi* statistics were applied. The General G index tests the null hypothesis of the absence of spatial clustering: significant p-values and z-scores ≥ ±3 indicate a 99% confidence level, with positive z suggesting a concentration of high values (hotspots) and negative z, of low values (coldspots). The Getis-OrdGi* technique identifies local clusters, considering neighborhood relationships between municipalities. The z-score and p-value values classify the areas into three significance levels (99%, 95%, and 90%), with values close to zero representing the absence of statistical significance. Spatial analyses and map creation were performed using ArcGIS Pro® software. [9]

Na análise temporal, a série foi construída com base no mês de notificação. As taxas mensais de detecção foram calculadas considerando o total de episódios reacionais (tipo 1, tipo 2, tipo 1 e 2 associados e sem reação) no numerador e a população municipal ≥ 18 anos no denominador. [1]

The temporal trend was evaluated using the Prais-Winsten regression method, which corrects for first-order autocorrelation in time series. [9,10] The annual (APC) and monthly (MPC) percentage change in rates were estimated, with 95% confidence intervals (95% CI). A significance level of 5% was adopted, classifying the trends as increasing, decreasing, or stationary. The analyses were conducted using STATA® software, version 14.

Additionally, the robust Seasonal and Trend Decomposition using Loess (STL) method was applied. [11] This technique is based on locally weighted regression (Loess) and allows the time series to be separated into three components: trend, seasonality, and noise. While Prais-Winsten evaluates the overall trend of the period, the STL method makes it possible to observe point variations and seasonal fluctuations over time, allowing the identification of periods of increase, decrease, or stability. This analysis was conducted using RStudio® software, with the Forecast package. [11,12]

The study adhered to the ethical principles of Resolution No.

DOI: https://doi.org/10.36489/saudecoletiva.2025v16i103p18664-18679

466/2012 of the National Health Council, and was approved by the Research Ethics Committee of the State University of Londrina (CEP/UEL), under opinion number 7.915.571 and CAAE 92592625.0.0000.5231.

RESULTS

Between 2001 and 2022, 26,298 cases of leprosy were reported, of which 15,911 were included in this study. Inclusion criteria were: age ≥18 years, residents of the state of Paraná, and with a reactional episode of type 1, 2, or 1 and 2, or absence of reaction, during treatment. Among the cases analyzed, 2,072 (13.0%) presented a type 1 reaction; 938 (5.9%) manifested a type 2 reaction; 347 (2.2%) evolved with a type 1 and 2 reaction simultaneously, while 12,554 cases (78.9%) did not register any reactional episodes (Table 1).

Table 1 - Sociodemographic characteristics of reported leprosy cases according to reactional episodes type 1, type 2, type 1 and 2, and no reaction. Paraná, Brazil, 2001 to 2022 (n= 15,911).

Variables (n)*	Reactional episode of leprosy							
	Type 1		Type 2		Type 1 and 2		No Reaction	
	n.	%	n.	%	n.	%	n.	%
Sex* (n=15907)								
Male	1237	13,2	607	6,5	237	2,5	7298	77,8
Female	835	12,8	331	5,1	109	1,7	5253	80,5
Race/Color* (n=15482)								
White	1494	13,3	614	5,5	237	2,1	8899	79,1
Not White	527	12,4	301	7,1	97	2,3	3313	78,2
Age Group* (n=15911)								
≥ 60 years	1427	13,2	679	6,3	263	2,4	8469	78,1
18 to 59 years	645	12,7	259	5,1	84	1,7	4085	80,5
Years of instruction* (n=14335)								
< 8 years	1471	13,2	675	6,1	243	2,2	8738	78,5
≥ 8 years	390	12,2	163	5,1	68	2,1	2587	80,6
Residential Zone* (n=14809)								
Urban + Peri-urban	1641	13,1	733	5,9	271	2,2	9863	78,9
Rural	297	12,9	123	5,3	53	2,3	1828	79,4

Source: Authors.
*Valid values.

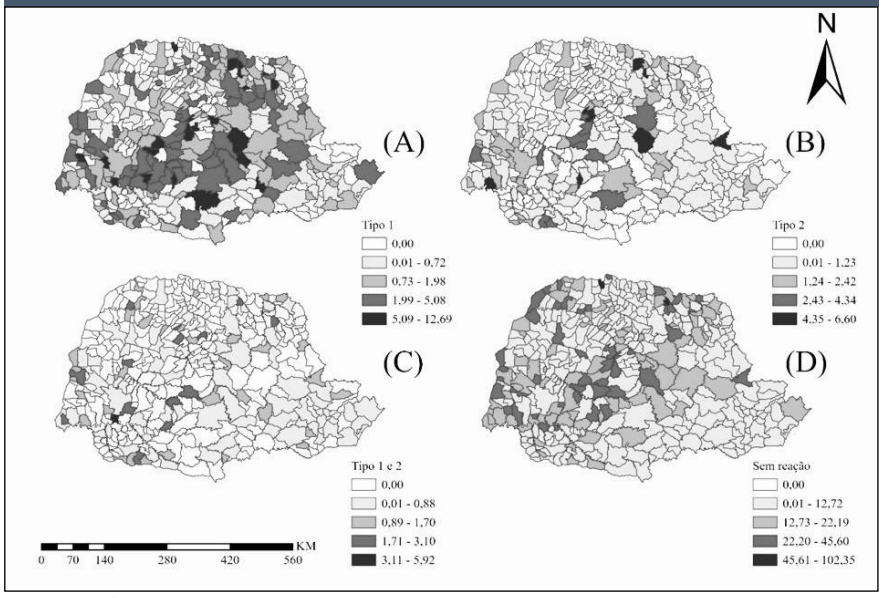
When analyzing the spatial distribution of the detection rate of leprosy reactional episodes (Figure 1), heterogeneity was observed in the distribution of different reaction types among the macro-regions of Paraná. The highest rates of type 1 reactions were concentrated in the North and West macro-regions, particularly in municipalities such as Londrina and Foz do Iguaçu, followed by specific areas in the East and Northwest regions.

The type 2 reaction showed a similar pattern, although with less territorial amplitude, mainly concentrated in municipalities in the West and East macro-regions. In contrast, type 1 and 2 reactions combined showed restricted foci in the West, while cases without reaction exhibited wide dispersion, with higher detection rates in the North and Northwest macro-regions.

These results highlight persistent foci of transmission and the occurrence of immunological complications, indicating regional inequality and the need for focused surveillance and health care actions in territories with the highest disease burden.

DOI: https://doi.org/10.36489/saudecoletiva.2025v16i103p18664-18679

Figure 1 - Spatial distribution of leprosy detection rate according to type of leprosy reaction. Paraná, Brazil, 2001 to 2022.



Source: Authors.

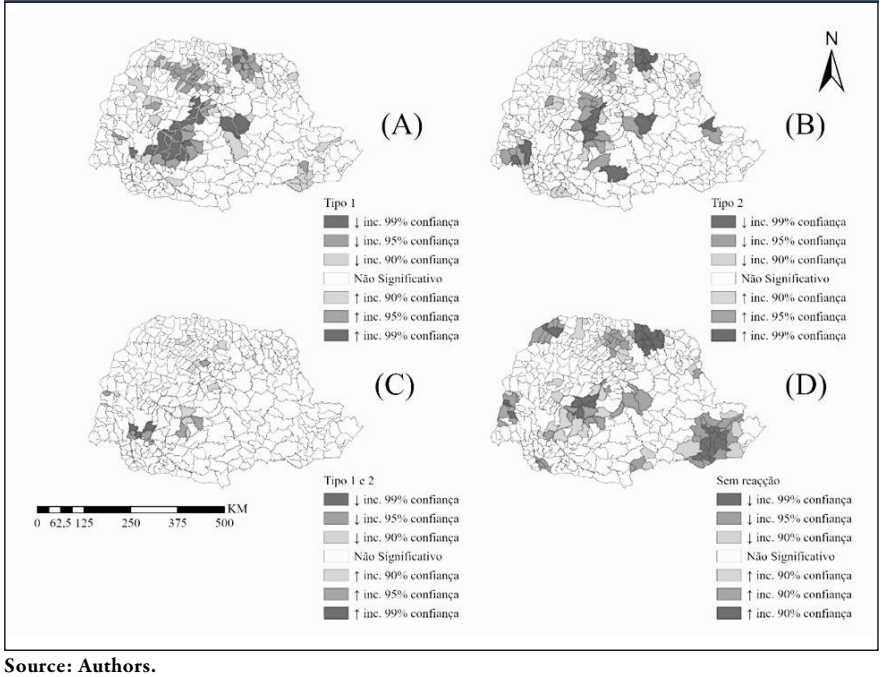
Figure 2 shows the significant areas of spatial clustering of leprosy reactional episodes. In Figure 2A, hot spots are observed distributed across all macro-regions, with a higher concentration in the East and West regions, especially in the central part of the state. Cold spots, indicative of protection zones, are concentrated in the East and Northwest macro-regions (General G = 0.003; z = 3.258; p = 0.001).

In Figure 2/B, referring to type 2 reactions, hot areas are also observed scattered among the macro-regions, although with less intensity, and cold zones predominate in the North and Northwest (General G = 0.003; p = 0.569).

Figure 2/C shows hot clusters in the East, West, and North regions, and cold clusters in the North and Northwest, with no statistical significance (p = 0.526). Finally, Figure 2/D shows significant spatial clusters related to the absence of leprosy reactions, distributed across all macro-regions, with warm areas in the West and North regions and cold areas in the East and Northwest (General G = 0.003; z = 6.698; p < 0.001).

These patterns reinforce the spatial heterogeneity of leprosy and highlight areas of greater vulnerability, especially in the western and northern macro-regions of Paraná.

Figura 2 - Áreas de aglomerado de reação tipo 1 (A), tipo 2 (B), tipo 1 e 2 (C) e sem reação (D), de acordo com a taxa de detecção. Paraná, Brasil, 2001 a 2022.

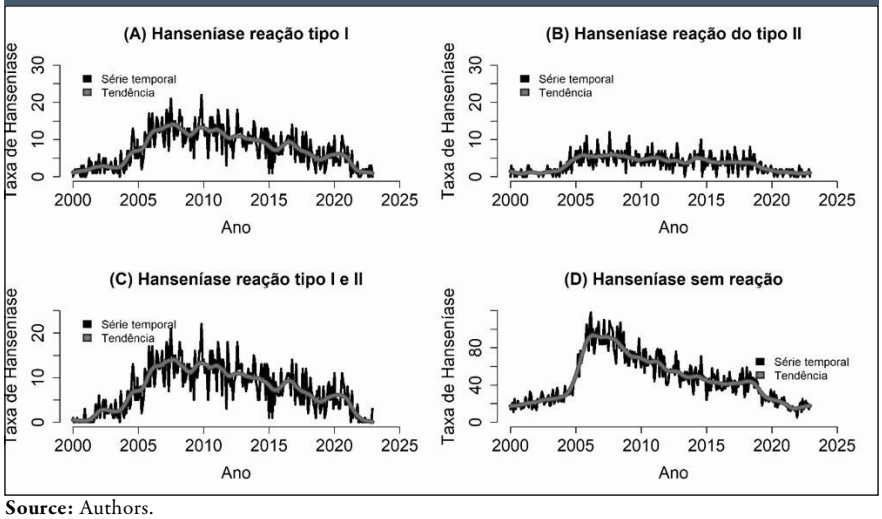


Source: Authors.

Analyzing Figure 3, it can be observed that the temporal trend of the leprosy rate shows a distinct behavior. Figures 3/A and 3/D show a decreasing trend, while Figures 3/B and 3/C indicate a stationary pattern.

DOI: https://doi.org/10.36489/saudecoletiva.2025v16i103p18664-18679

Figure 3 - Temporal trend of leprosy detection rate according to type of leprosy reaction. Paraná, Brazil, 2001 to 2022.



Source: Authors.

Table 2, which presents the temporal trend of the incidence of reactional episodes of leprosy type 1, type 2, type 1 and 2, and no reaction, using the Prais-Winsten method, shows that the trend remained stationary for all variables analyzed.

Table 2 - Temporal trend of the incidence of reactional episodes of leprosy type 1, type 2, type 1 and 2, and no reaction. Paraná, Brazil. (n=15,911), 2001 to 2022.

VARIABLE	APC (CI 95%)	MPC (CI 95%)	P-VALUE	TREND
Type 1 reaction	0,049 (-0,204 – 0,304)	0,004 (-0,017 – 0,025)	0,701	Stationary
Type 2 reaction	-0,047 (-0,372 – 0,279)	-0,003 (-0,031 – 0,023)	0,776	Stationary
Type 1 and 2 reaction	0,349 (-0,286 – 0,990)	0,029 (-0,023 – 0,082)	0,281	Stationary
No reaction	-0,096 (-0,473 – 0,278)	-0,008 (-0,039 – 0,023)	0.608	Stationary

Source: Authors.
Caption: APC - *Annual PercentChange*; MPC - *Monthly PercentChange*; CI – Confidence Interval

DISCUSSION

This study analyzed the spatial and temporal distribution of reactional episodes of leprosy in the state of Paraná. The results reinforce the relevance of integrating SINAN-Leprosy with other information systems, in order to expand the surveillance of complications associated with the disease, including reactional episodes.

The sociodemographic characterization showed a similar pattern among the different types of reaction, with a predominance of male, white individuals with low levels of education and residing in urban and peri-urban areas. These findings corroborate national and international studies that associate leprosy and its complications with contexts of social vulnerability, especially in populations with low income, precarious housing conditions, and lower educational levels. [4,13,14]

These factors reinforce the need for early detection and timely treatment, which are fundamental to preventing disabilities and interrupting the chain of transmission. [15]

Spatial analysis revealed a concentration of reactional episodes in the North and West macro-regions of Paraná, coinciding with historically endemic areas. This pattern reflects the regional disparities observed in the country, where the North, Northeast, and Central-West regions present higher detection rates compared to the South and Southeast regions. Despite the reduction in the detection rate in Paraná—from 9.63/100,000 inhabitants in 2011 to 3.43/100,000 in 2022—pockets of risk and intra-state heterogeneity persist. [1,16]

The persistence of leprosy as a public health problem is associated with structural determinants such as poverty, social inequality, and gaps in the coverage and quality of primary health care (PHC). A global study indicates a 27.86% reduction in incidence between 1990 and 2019, but socioeconomic and geographic influences on transmission persist. Vulnerable populations face barriers to accessing diagnosis and treatment, perpetuating the cycle of exclusion and stigma. [1,17]

Literature suggests that technological and educational integration can contribute to disease control. Mobile applications developed for primary health care, such as the leprosy symptom reactivation app (RSH), have shown promise for the diagnosis and management of leprosy reactions, re-entries, and relapses. [18] However, the effectiveness of these strategies depends on the continuous training of health teams and the consolidation of coordinated care flows between primary health care and referral services.

Although the largest absolute number of cases occurs in cities with more than 100,000 inhabitants, the highest rates are observed in small municipalities, where there are greater structural difficulties in surveillance and in maintaining qualified teams. [19] The geographical distance to specialized

DOI: https://doi.org/10.36489/saudecoletiva.2025v16i103p18664-18679

services and the lack of logistical and diagnostic resources hinder access and favor late diagnosis, contributing to an increase in disabilities and reactive episodes. [1, 4, 20]

Several factors related to both the individual and the health system influence late diagnosis, and addressing this requires intersectoral actions, strengthening the care network, and increasing social awareness. [21] Although the diagnosis of leprosy is predominantly clinical, cases of pure neural leprosy and atypical manifestations require laboratory support and integration between primary health care and referral services. In this sense, it is essential to invest in continuing education and professional development for healthcare professionals, especially in areas with higher endemicity. [22]

The process of regionalizing healthcare presents another challenge, as the availability of specialized services still depends on demographic and economic factors. [23] In areas of low endemicity, actions such as active case finding and professional training have increased the number of cases detected, revealing hidden endemic diseases. [2, 24] Furthermore, low educational levels are associated with up to twice the risk of transmission and disabilities, reflecting the social vulnerability of smaller municipalities. [1, 24]

Particularly in border regions, such as between Paraná and the Argentine province, studies indicate specific epidemiological characteristics that are still poorly explored. Intensifying international health cooperation is fundamental to addressing challenges related to migratory flows, cross-border surveillance, and regional integration. [25]

CONCLUSION

Temporal analysis revealed a stationary trend in the detection rate of reactional episodes between 2001 and 2022, suggesting epidemiological stability of the disease. Even so, the presence of spatial clusters and the persistence of cases indicate that controlling leprosy requires territorial and differentiated strategies, integrating surveillance, early diagnosis, and clinical management of reactions.

It was evident that reactional episodes of leprosy are present in all macro-regions of health in Paraná, with clusters of high rates in the West and North regions and lower concentrations in the East and Northwest regions.

Among the study's limitations, the shortcomings in filling out variables in SINAN and the ecological design, which does not allow for individual inferences, stand out. Despite this, the results offer valuable support for health surveillance by identifying priority areas and temporal patterns of occurrence.

The study provides relevant support for the planning, evaluation, and strengthening of health surveillance actions aimed at controlling leprosy in Paraná. By highlighting regional inequalities and identifying areas of higher risk for reactional episodes, spatial and temporal analysis proves to be a strategic tool to guide decision-making, promote early detection of reactions, and intensify care strategies in priority territories. Such evidence contributes to the implementation of more effective public policies that are appropriate to local realities.

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