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ORIGINAL ARTICLE

Mortality trends due to Paracoccidioidomycosis in Brazil - 1996 to 2020

Tendência da mortalidade por Paracoccidioidomicose no Brasil - 1996 a 2020

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KEYWORDS

Health Profile
Mortality
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ABSTRACT

Objective: To analyze the trend in mortality from paracoccidioidomycosis (PCM) and characterize the sociodemographic profile in Brazil and its geographic regions in a 25-year time series.
Methods: This is an ecological time series study. The study participants were the Brazilian population divided into age groups whose underlying cause of death was PCM. To calculate the annual percentage change (VPA) of the coefficients in the trend analysis, the Prais-Winsten regression was used. National mortality coefficients were calculated according to geographic regions, sex and age group and proportional to the other variables.
Results: According to this study, there were 2,101 deaths from PCM in Brazil. The trend over the 25 years showed stable behavior in the North and Northeast regions. In the South, Southeast, and Midwest, there was a downward trend. The average mortality in Brazil was 84.04/100,000 inhab., VPA -3.29 (95% CI -2.43; -4.14). According to the analysis of sociodemographic aspects, there was a predominance of ignored schooling (764 deaths; 36%), white race/skin color (1,109; 53%), mixed marital status: married (942; 45%) and single (640; 30%), and place of death predominantly in the hospital environment (1,852; 88%).
Conclusion: In Brazil and in the Southeast, South, and Midwest geographic regions, mortality from PCM showed a decreasing temporal trend. In the Northeast and North regions, the trend was stationary. The sociodemographic profile of the dying patients indicated males, adults, with low education, white, and married.

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PALAVRAS-CHAVE

Mortalidade
Paracoccidioidomicose
Perfil de saúde

RESUMO

Objetivo: Analisar a tendência da mortalidade por paracoccidioidomicose (PCM) e caracterizar o perfil sociodemográfico no Brasil e suas regiões geográficas numa série temporal de 25 anos.
Métodos: Trata-se de estudo ecológico de séries temporais. Considerou-se como participantes do estudo a população brasileira dividida em faixas etárias, que tiveram como causa básica do óbito a PCM. Para calcular a variação percentual anual (VPA) dos coeficientes, na análise de tendência, foi utilizada a regressão de Prais-Winsten. Os coeficientes de mortalidade foram calculados a nível nacional, segundo as regiões geográficas, sexo e faixa etária e proporcional para as demais variáveis.
Resultados: De acordo com os resultados deste estudo, ocorreram 2.101 óbitos por PCM no Brasil. A tendência ao longo dos 25 anos evidenciou um comportamento estável nas regiões Norte e Nordeste. Já no Sul, Sudeste e Centro-Oeste houve uma tendência de queda. A mortalidade média no Brasil foi de 84,04/100 mil hab., VPA -3,29 (IC 95% -2,43; -4,14). Levando em consideração a análise dos aspectos sociodemográficos, houve um predomínio de escolaridade ignorada (764; 36%), raça/ cor da pele branca (1.109; 53%), estado civil misto: casado (942; 45%) e solteiro (640; 30%), local de ocorrência do óbito predominantemente no âmbito hospitalar (1.852; 88%).
Conclusão: Tanto no Brasil como nas regiões geográficas Sudeste, Sul e Centro-Oeste a mortalidade por PCM apresentou-se com tendência temporal decrescente. Já nas regiões Nordeste e Norte a tendência foi estacionária. O perfil sociodemográfico dos pacientes que foram a óbito apontou para sexo masculino, adultos, de baixa escolaridade, brancos e casados.

INTRODUCTION

Paracoccidioidomycosis (PCM) is a disease caused by the fungus *Paracoccidioides brasiliensis*, which mainly affects the lungs and can spread to other organs[1]. This disease is endemic in Latin America, with Brazil having the highest number of registered cases. The fungus has different species that vary according to the region in which they are found[2].

PCM transmission occurs by inhaling fungal spores present in soil or plant material. The infection can be asymptomatic or cause respiratory symptoms, fever, weight loss, and skin and mucous membrane lesions. The disease can become chronic and compromise the quality of life of patients, in addition to increasing the risk of death. The diagnosis is made by identifying the fungus in biological samples or by serological tests. Treatment is based on oral or intravenous antifungals[3,4,9].

PCM is a public health problem that mainly affects working-age people and has high social and economic costs. In addition, the disease has a heterogeneous distribution, depending on the environmental and climatic conditions that favor the growth of the fungus. PCM can also be confused with other fungal or nonfungal diseases with similar clinical manifestations[5,6].

The disease is more common in workers or former rural workers exposed to intense and continuous contact with the soil. Epidemiological pressure associated with the predominance of the disease among male rural workers can also influence the distribution of cases by sex[3,7,8]. The absence of an epidemiological bulletin made available by the Ministry of Health makes it challenging to monitor the disease in the country and implement prevention and control measures. PCM is considered a neglected disease, mainly affecting poor and vulnerable populations with low access to health services [9].

Despite the importance of PCM, there are few studies on the temporal trend and sociodemographic profile of mortality from this disease in Brazil. Furthermore, PCM is not a notifiable disease in the country, making epidemiological monitoring and creating public policies for its control and prevention complex[9].

In this context, this study aimed to analyze the trend in mortality from PCM and characterize the sociodemographic profile of deaths from this disease in Brazil and its geographic regions over a 25-year time series. It is hoped that the results of this study can contribute to the knowledge of the epidemiological situation of PCM in the country and support health actions aimed at reducing morbidity and mortality from this disease.

METHODS

Study Design

This is an ecological study of time series. In ecological studies, the occurrence of diseases or conditions related to health and the level of exposure among groups of people (for example, inhabitants of countries, regions or municipalities) are compared to verify whether there is a potential correlation between them[10]. To understand the profile of PCM in Brazil and its regions, the following research question was formalized: In which regions of Brazil are deaths from PCM more frequent? Do the sociodemographic characteristics of deaths facilitate the implementation of public policies aimed at early diagnosis and better understanding of the disease cycle and its hosts?

Study location

The Brazilian territory has 8,515,758.7 km^2, is divided into 27 Federation Units, 26 States, and the Federal District, and is organized into five major geopolitical regions considered for territory planning and management: North, Northeast, Southeast, South, and Midwest. States are subdivided into municipalities organized into microregions, which are then organized into mesoregions[11].

Participants

The study participants were the Brazilian population divided into age groups (<1 year; 1 to 19 years; 20 to 59 years; 60 years or more) whose underlying cause of death was PCM (code B41), according to the International Classification of Diseases and Related Health Problems (ICD-10). The information was obtained from the official mortality statistics of the Mortality Information System of the Ministry of Health (SIM/MS).

Data collection procedure

To construct the results, the data were obtained through a computerized query on the website of the Department of Informatics of the Brazilian Unified Health System (DATASUS), option ACCESS TO INFORMATION, then TABNET, after which information was extracted from two different sections: VITAL, DEMOGRAPHIC AND SOCIOECONOMIC STATISTICS.

- VITAL STATISTICS: subtopics: MORTALITY - SINCE 1996 BY ICD-10 and GENERAL MORTALITY. Geographic coverage: BRAZIL BY REGION AND FEDERATION UNIT. Soon after, the years and other variables were selected based on the number of deaths by place of residence.
- DEMOGRAPHIC AND SOCIOECONOMIC: subtopic: RESIDENT POPULATION and then CENSUS (1980, 1991, 2000 AND 2010), COUNTS (1996) AND INTERCENSUS PROJECTIONS (1981 TO 2012), ACCORDING TO AGE GROUP, GENDER AND DOMICILE SITUATION, and ESTIMATES OF 1992 TO 2021 USED BY TCU TO DETERMINE FPM QUOTES (WITHOUT Gender AND AGE GROUP). Geographic coverage: BRAZIL BY REGIONS AND UNIT OF THE FEDERATION, then the years were selected, respectively, from the resident population and estimated population.

Study variables

The variable studied was the PCM-specific mortality coefficient (B41). In addition, the following variables were analyzed: place of residence (Brazil and regions); gender (male, female); age range (young: from less than 1 year to 19 years old, adult: from 20 to 59 years old, elderly: 60 years old or older); color/race (white, black, yellow, brown, indigenous, unknown color/race); marital status (single, married, widowed, legally separated, other, marital status unknown); schooling (none, 1 to 3 years, 4 to 7 years, 8 to 11 years, 12 years and more, schooling unknown) and place of death (hospital, other health facilities, home, public road, other, place of instance ignored).

Data analysis

To calculate the specific crude mortality rate due to PCM, the number of deaths of residents due to PCM (B41) was considered the numerator and the resident population the denominator, multiplied by 100,000. Mortality coefficients were calculated nationally according to geographic regions, sex and age groups, and proportional to other variables.

The research period was 25 years, from 1996 to 2020, with a total of 25 points. When analyzing a series, it is not recommended to use less than 7 points because trends tend to be insignificant due to the low statistical power of the regression analysis[12,13].

To calculate the annual percentage change (APC) of the coefficients in the trend analysis, the Prais-Winsten[3] regression was used. This standard recommends correction of the first-order autocorrelation. The dependent variable was the logarithm of the mortality coefficients, and the independent variable was the number of years in the historical series.

Quantitative estimation of the trend was calculated using the following expression: APC = [- 1 + 10 ^{b}] *100%. For the calculation of confidence intervals (CI): CI 95%= [- 1 + $10^{b \pm t^{*}se}$] * 100%, where "*b*" corresponds to the annual growth rate. The "*b*" and standard error (*se)* values were extracted from regression analysis[12,13].

The series was considered increasing when the rate was positive, decreasing when negative, and stationary when there was no significant difference between its value and zero ($p > 0.05$)[12]. This analysis was performed using STATA 17.0 software, licensed under registration 301709072489.

Descriptive statistics were used for the other variables, and the total and percentage values were tabulated and displayed using absolute and relative frequencies, which were represented using tables and figures.

Ethical and legal aspects

This study was based on official secondary data from the Ministry of Health; therefore, the opinion of the Research Ethics Committee was not necessary.

RESULTS

There were 2,101 deaths from PCM in Brazil, corresponding to 84.04/100,000 inhab. During this period, the average number of deaths was 35.4/100,000 inhab. in the Southeast region, 25.28/100,000 inhab. in the South, 10.84/100,000 inhab. in the Midwest, 3.5/100,000 inhab. in the Northeast, and 9.16/100,000 inhab. in the Northern region (Table 1).

The North and Northeast regions expressed a stationary trend, respectively: (APC: -0.67; 95% CI: 1.37; -2.67) and (APC: -0.24; CI 95 %: 2.86; -3.24). The other regions, southeast (APC: -2.20; 95% CI: -1.19; -3.21), south (APC: -6.00; 95% CI: -4.60; -7.38) and Midwest (APC: -3.86; 95% CI: -2.43; -4.14) showed a decreasing trend (Table 1).

According to Figure 1, a stable distribution of deaths was noted in the North, Northeast, and Midwest regions concerning the trend over the 25 years of the study. In the South and Southeast regions, the deaths showed varying periods of increase and decrease, but with a decreasing trend. In Brazil, a sharp downward

trend was observed in the death curve. In general, a moderate reduction in absolute values was evident when comparing the deaths that occurred in the initial period of 1996 (103) and the end of 2020 (57).

Regarding the trend in mortality from PCM according to gender and age group, it was noticed that all variables showed a decreasing trend: male (VPA: -3.29; 95% CI: -2.37; -4.21), female gender (VPA: -2.29; 95% CI: -0.72; -3.83), young age group (VPA: -0.22; 95% CI: 2.34; -2.71), adult (VPA: -4.03; 95% CI: -3.13; -4.93), and elderly (VPA: -5.81; 95% CI: -4.79; -6.82). The average number of deaths was 72.64/100,000 inhab. in males, 11.4/100,000 inhab. among females, 3.24/100,000 inhab. in the young age group, 49.6/100,000 inhab. for adults, and 31.2/100,000 inhab. in the elderly (Table 2).

Considering the sociodemographic aspects, there was a predominance of ignored educational status (764 deaths; 36%), white race/skin color (1,109; 53%), mixed marital status: married (942; 45%) and single (640; 30%), and place of death predominantly in the hospital environment (1,852; 88%) (Table 3).

Table 1 — Relative and absolute frequencies, mean number of deaths per 100,000 inhabitants, and trends in mortality due to Paracoccidioidomycosis in Brazil and its regions, 1996 to 2020.

Brazil/Regions	Frequencies		Average of deaths*	Prais -Winston		95% CI§		Trend Interpretation
	Absolute	Relative		p-value	VPA‡	Lower	Higher	
North	229	11%	9.16	0.500†	-0.67	1.37	-2.67	Stationary
North East	84	4%	3.5	0.874†	-0.24	2.86	-3.24	Stationary
Southeast	885	42%	35.4	0.000	-2.20	-1.19	-3.21	Descending
South	632	30%	25.28	0.000	-6.00	-4.60	-7.38	Descending
Midwest	271	13%	10.84	0.001	-3.86	-1.84	-5.83	Descending
Brazil	2,101	100%	84.04	0.000	-3.29	-2.43	-4.14	Descending

*Average of deaths per 100,000 inhab.; † not significant; ‡ VPA: annual percentage change; § 95% confidence interval (lower and upper).

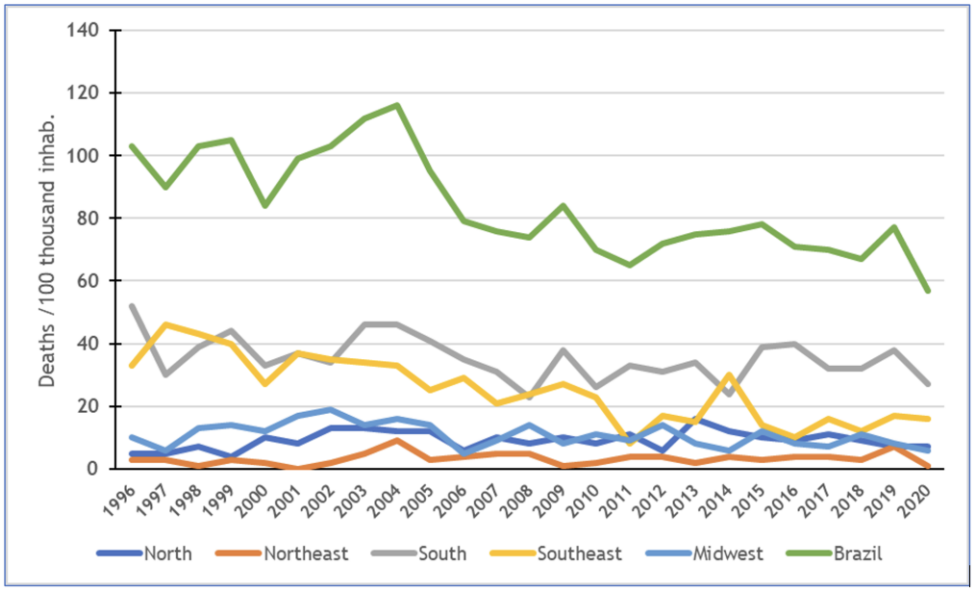

Figure 1 — Trend in mortality from Paracoccidioidomycosis in Brazil and its regions, 1996 to 2020.

Table 2 — Relative and absolute frequencies, mean number of deaths per 100,000 inhabitants, and trends in mortality from Paracoccidioidomycosis in Brazil according to sex and age group, 1996 to 2020.

Gender and age group	Frequencies		Average of deaths*	Prais -Winston		95% CI§		Trend Interpretation
	Absolute	Relative		p-value	VPA‡	Lower	Higher	
Masculine	1,816	86%	72.64	0.000	-3.29	-2.37	-4.21	Descending
Feminine	285	14%	11.4	0.006	-2.29	-0.72	-3.83	Descending
Young	81	4%	3.24	0.860 †	-0.22	2.34	-2.71	Descending
Adult	1,240	59%	49.6	0.000	-4.03	-3.13	-4.93	Descending
Elderly	780	37%	31.2	0.000	-5.81	-4.79	-6.82	Descending

*Average of deaths per 100,000 inhabitants; † not significant ; ‡ VPA: annual percentage change; § 95% confidence interval (lower and higher).

Table 3 — Relative and absolute frequencies of mortality from Paracoccidioidomycosis in Brazil according to education, race/skin color, marital status, and place of death, 1996 to 2020.

Sociodemographic Variables	n (%)
Education	
None	262 (12)
1 to 3 years	452 (22)
4 to 7 years	412 (20)
8 to 11 years	173 (8)
12 years and over	38 (2)
schooling ignored	764 (36)
color/race	
White	1,109 (53)
black	160 (8)
Yellow	13 (1)
brown	512 (24)
Indigenous	14 (1)
color/race unknown	293 (14)
marital status	
Single	640 (30)
Married	942 (45)
Widower	183 (9)
legally separated	144 (7)
Other	52 (2)
marital status unknown	140 (7)
Local	
Hospital	1,852 (88)
Other health establishments	44 (2)
Residence	153 (7)
Public highway	14 (1)
Others	13 (1)
Occurrence location ignored	25 (1)

DISCUSSION

Considering the relative frequency of deaths, the Southeast, South, and Midwest regions led the ranking, representing 42%, 30%, and 13% of reported cases, respectively. Together, these three areas account for 85% of all deaths. According to the series, from 1980 to 1995, in the Southeast region, there were 1,707 deaths (53.66% of the total), compared with 875 (27.51%) in the South. The two regions together accounted for 2,593 deaths (81.52%). The Midwest registered 318 deaths (10.00%), and the North and Northeast regions recorded 281 deaths (8.83%)[5].

Leite et al. reported that the highest incidence of PCM cases in the Southeast region was found in the states of São Paulo and Minas Gerais. However, even with the characteristic of a stationary trend in the North and Northeast regions, there was an appearance of hyperendemic disease in the state of Rondônia and a significant number of new cases in Maranhão and Ceará[14].

The distribution of cases in these areas leads us to two questions. The first considers the ideal conditions for the proliferation of this fungus, which in turn essentially needs an ecosystem of tropical or subtropical humid forests, with temperatures ranging between 10 and 28 °C and soils that are almost always acidic[15,16].

In this case, the number of deaths in the southernmost regions of the country would be slightly related to the environmental conditions conducive to the appearance of this fungus, considering that the temperature is milder in these areas; alternatively, in the North and Northeast states, the temperature rarely drops close to 10 °C. However, the other environmental variables are very similar throughout the national territory[17].

The second important factor to consider regarding the discrepancy in cases between Brazilian regions concerns underreporting, as the Ministry of Health pointed out through the Department of Epidemiological Surveillance (2022). Because PCM is not a compulsorily notifiable disease, underreporting is a potential problem, as most cases are raised through unofficial data[9,17].

However, issues related to the environmental patterns of case distribution and underreporting problems must be carefully investigated before drawing a definitive overview of the occurrence of the disease in a national context.

The Northeast and North regions had the lowest death rates during the study years, around 4% and 11%, respectively. The temporal trend in both regions was stationary but slightly declined in cases. It is also noteworthy that the low mortality due to paracoccidioidomycosis in the Northeast may be due, at least in part, to the high mortality classified as unexplained in this region, in addition to the availability and limitations of health services[5].

Regarding the trend of deaths by gender, it was evident that men were more likely to die than women. Similar results were found in a study aimed at analyzing mortality from PCM in the state of São Paulo between 1985 and 2005, where mortality was either calculated by the total number of mentions or considering Paracoccidioides infections as the underlying or related cause and was consistently higher in men[19]. Considering the above, a study conducted in Brazil between 1980 and 1995 also confirms our results, where there was a predominance of deaths in males (84.72%), and the proportion was 562 men for 100 women[5,20].

One of the factors that can be considered for a more significant number of deaths in men compared with women is that the better response of women to the fungus may be related to the higher concentration of estrogen because this hormone, in vitro, inhibits the hyphal transition into mycelium[21,22].

In terms of age group, adults have a higher mortality rate than the young and elderly. The disease most often occurs between the ages of 20 and 50, although it also occurs in children between the ages of 4 and 5. Note that cases between 3 and 102 years of age have been reported in the literature[5,22].

Analysis carried out to verify whether changes in the behavior of PCM occurred in the last three decades (1980 to 2009) in the endemic area of Mato Grosso do Sul revealed that the average age increased from the first

to the third decade of study: 41.8 ± 15.1 years in the first decade, 45.0 ± 13.3 years in the second and 49.5 ± 13.1 years in the third[19,23]. In this context, a study pointed out that in the State of Paraná there were 551 deaths due to PCM, and of the total number of deaths in men (85%), 4.4% occurred up to 29 years old compared with 65.1% from 30 to 59 years[1].

In regions with a cold climate, such as the state of São Paulo, mortality from the disease in the elderly occurs mainly in the winter months[19]. The illness is uncommon in elderly individuals; however, factors such as "Advanced age, immunosenescence, and diabetes mellitus probably contribute to the rapid evolution and atypical presentation" in this social group[24].

In terms of schooling, there were more deaths in people with low education, where only 2% of patients had more than 12 years of study. This highlights existing disparities, such as the absence or lack of access to general information, prevention or treatment for this or other diseases, and difficulty in obtaining medical assistance[25].

Regarding race/skin color, white and brown patients were more prevalent in this study. Concerning racial predisposition, it is believed that there is no pattern to be considered because what predisposes to the contagion and development of PCM that can lead to death is the exposure to *P. brasiliensis*, which is more commonly found in those who work in agriculture than in large urban centers[26].

However, an analysis of mycoses performed in the mestizo population in southern Brazil showed that black or brown patients were more likely to present with acute/subacute diffuse lesions than white. Variations in genetic makeup and differences in living conditions may be responsible for the correlation between clinical symptoms and racial characteristics of mycoses[27].

Notably, this study used data compiled from the SIM, which only registers cases after the death investigation. However, as mortality data for this disease are characterized only by case series, epidemiological reports and hospitalization data, and reporting was not mandatory until 2020, underdiagnosis may occur.

The main limitations of this study are related to the scarcity of epidemiological and sociodemographic data associated with PCM in Brazil. In this sense, most articles found are from periods before the time frame usually applied to scientific research.

CONCLUSION

Both in Brazil and in the Southeast, South and Midwest geographic regions, mortality from PCM showed a decreasing temporal trend. In the Northeast and North regions, the trend was stationary. The sociodemographic profile of the dying patients indicated males, adults, with low education, white, and married.

It is recommended that more epidemiological research be conducted and linked in a reliable, comprehensive, and systematic way to compare the different outcomes of deaths in the country's regions and consequently subsidize public policies to improve the early diagnosis and timely treatment of PCM.

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