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ORIGINAL ARTICLE

# Trends and patterns of mortality arising from fungal infections in Brazil in a period of 11 years

# Tendências e padrões de mortalidade em decorrência de infecções fúngicas no Brasil, em um período de 11 anos

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## Abstract

**Objective**: To investigate the mortality attributed to fungal infections, in Brazil between 2003 and 2013. **Methods**: This ecological study relied on official data collected from the Sistema de Informação Sobre Mortalidade – Mortality Information System database. The mycoses were identified by the 10th revision of the International Classification of Diseases, which included categories B35–B49 in its first chapter. **Results:** Overall, 11,991,935 deaths were reported in the aforementioned period. The deaths of 4,192 individuals were primarily attributed to mycoses. High annual mortality rates were observed in all Brazilian regions, except in the Northeast. The main recorded mycoses were paracoccidioidomycosis (35.6%) and cryptococcosis (24.1%). There was a downward trend in the number of deaths due to paracoccidioidomycosis. In addition, 10,925 death certificates listed mycoses as an associated cause of death. Cryptococcosis (89.7%) and histoplasmosis (89.4%) were the most common mycoses associated with deaths in HIV patients. **Conclusions**: There was a downward trend in the number of deaths stemming from invasive fungal infections. However, opportunistic mycoses follow been a significant cause of death, especially in HIV patients.

**Keywords:** Mycoses; Invasive Fungal Infections; Mortality; Paracoccidioidomycosis; Cryptococcosis.

## Resumo

**Objetivo:** Investigar a mortalidade atribuída para as infecções fúngicas, no Brasil, entre 2003 e 2013. **Métodos**: Trata-se de um estudo ecológico, em que os dados foram obtidos do Sistema de Informação sobre Mortalidade (SIM), disponíveis na plataforma do DATASUS. As micoses foram identificadas por meio da 10ª revisão da Classificação Internacional de Doenças (CID-10), a qual incluiu as categorias B35-B49 no primeiro capítulo da CID-10. **Resultados**: No total, 11.991.935 óbitos foram notificados no período do estudo. Os óbitos de 4,192 indivíduos foram atribuídos às micoses. Foram observadas elevadas taxas de mortalidade em todas as regiões brasileiras, com exceção do Nordeste. As principais micoses registradas foram paracoccidioidomicose (35,6%) e criptococose (24,1%). Houve uma tendência na redução do número de óbitos em relação à paracoccidioidomicose. Além disso, em 10.925 declarações de óbitos informavam que as micoses foram causas associadas ao óbito. Criptococose (89,7%) e Histoplasmose (89,4%) foram as micoses mais comumente associadas ao óbito, principalmente em pacientes HIV positivos. **Conclusões**: Houve uma tendencia na diminuição dos óbitos por infecções fúngicas invasivas. Entretanto, micoses oportunistas continuam sendo importantes causas de morte, especialmente em indivíduos HIV positivos.

**Palavras-chave:** Micoses; Infecções Fúngicas Invasivas; Mortalidade; Paracoccidioidomicose; Criptococose.

## INTRODUCTION

Globally, the mortality rates attributed to invasive fungal infection are high and often exceed 50%, despite the availability of antifungal therapies. *Cryptococcus, Candida, Aspergillus*, and *Pneumocystis* infections account for more than 90% of all fungal-infection-related deaths reported worldwide[1]. The burden of cryptococcal meningitis has been estimated to reach nearly 1 million cases worldwide, with more than 620,000 deaths in sub-Saharan Africa. Notwithstanding treatment efforts, mortality rates are still high in developed countries like the USA, with even higher rates in Latin America and sub-Saharan Africa in HIV-positive patients[1].

The global burden of paracoccidioidomycosis (PCM) has been estimated to reach 4,000 cases/year in Brazil, with a mortality rate of 5-27%[1]. In 2011, estimated incidence rates per every 1,000 hospitalizations caused by PCM, coccidioidomycosis, and histoplasmosis were 7.99, 7.12, and 2.19, respectively, in Brazil. In hospitalized patients, the incidence of candidemia was 249 cases/100,000 individuals[2]. The overall mortality rate associated with PCM and cryptococcosis (as an underlying cause of death) in Brazil ranges from 0.8 to $1.1/10^6$ and from 0.45 to $0.48/10^6$ inhabitants, respectively[3]. It is estimated that 300,000 cases of disseminated histoplasmosis are diagnosed each year, with an

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associated average of 10,000 deaths[4].

Our goal was to investigate the mortality attributed to systemic and deep mycoses, based on the information available on death certificates (DC) issued in Brazil between 2003 and 2013.

## METHODS

This ecological study relied on official data collected from the Sistema de Informação Sobre Mortalidade – Mortality Information System (SIM) database, which is sponsored by the Ministério da Saúde do Brasil – Brazil's Ministry of Health[5]. The SIM was created in 1976 to standardize the DCs issued in Brazil. Such documents contain a section where the primary cause of death is described, with other sections where additional causes of death may be listed.

We selected DC from the period of 2003 to 2013. Only records listing mycoses as the primary cause of death (or as an associated cause of death) were selected from the SIM. The mycoses were identified by the 10th revision of the International Classification of Diseases (ICD-10), which included categories B35–B49 in its first chapter. Included fungal infections were candidiasis (B37), coccidioidomycosis (B38), histoplasmosis (B39), blastomycosis (B40), paracoccidioidomycosis (B41), sporotrichosis (B42), chromoblastomycosis (B43), aspergillosis (B44), cryptococcosis (B45), zygomycosis (B46), mycetoma (B47), one unclassified mycosis (B48), and one unspecified mycosis (B49). Pneumocystosis is classified as a parasitic disease in the ICD-10 (B59) and thus was not included. Codes B40 and B41 were grouped as PCM because the term "South American blastomycosis" is used in Latin America. Codes B48 and B49 were also grouped as "unspecified mycoses." For Brazilian populational and territorial data, the official figures from the Instituto Brasileiro de Geografia e Estatística – Brazilian Institute of Geography and Statistics were used[6]. The Brazilian population, as estimated on July 1 of 2006, 2010, and 2013, was used as the standardized mortality indicator reference.

Frequency measurements for descriptive analysis were performed using the variables studied. Parametric tests were performed using the software STATA 13.0 (StataCorp LP, College Station, Texas, USA), by means of the Chi-squared test or Fisher's exact test if any value in the cells of the contingency table was less than five. For all statistical analyses, we used a significance level of 5% ($p < 0.05$). Mortality indicators were calculated as follows:

a) Proportional mortality = number of cases of mycosis as the primary cause of death or associated cause of death x 100 / total number of deaths by infectious diseases

b) Overall mortality density = number of cases of mycosis as the primary cause of death x 10,000 / Area (km²)

c) Mortality rate = number of mycosis deaths per period (as the primary or associated cause of death) x 1,000,000 / population of that period.

The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2000. However, no ethical approval was required as this article is based on public data available in open access health sites from Brazil.

## RESULTS

Mycoses as the primary cause of death

Overall, 11,991,935 deaths were reported in the aforementioned period, with 525,650 of these being associated with infectious diseases. The mortality rate associated with infectious diseases was 4.38%. The deaths of 4,192 individuals were primarily attributed to mycoses. The proportional mortality rates ranged between 0.4% and 1.2% across the Brazilian regions. The Midwestern region had the highest proportional mortality rate. However, the most notable overall mortality density was in the Southeast region, with 22.5 cases/10,000 km². High annual mortality rates were observed in all Brazilian regions, except in the Northeast, which had a rate lower than 1.0 deaths/$10^6$ inhabitants (Table 1).

**Table 1.** Mortality of mycoses as the primary cause of deaths in Brazil, 2003-2013.

| Regions | Population (2013) | Area - km2 | Deaths by infectious diseases | Deaths by mycosis | PM* (%) | OMD† ($10^4$ km²) | AMD‡ | AMR§ |
|---|---|---|---|---|---|---|---|---|
| Brazil | 201,032,714 | 8,515,766.30 | 525,650 | 4,192 | 0.8 | 4.9 | 381.1 | 1.9 |
| North | 16,983,484 | 3,853,676.90 | 37,877 | 380 | 1.0 | 1.0 | 34.5 | 2.0 |
| Northeast | 55,794,707 | 1,554,291.60 | 137,567 | 519 | 0.4 | 3.3 | 47.2 | 0.8 |
| Southeast | 84,465,570 | 924,620.00 | 243,596 | 2,084 | 0.9 | 22.5 | 189.5 | 2.2 |
| South | 28,795,762 | 576,774.30 | 70,170 | 760 | 1.1 | 13.2 | 69.1 | 2.4 |
| Midwest | 14,993,191 | 1,606,403.50 | 36,440 | 449 | 1.2 | 2.8 | 40.8 | 2.7 |

*Proportional mortality.
†Overall mortality density.
‡Annual mean of death.
§Annual mortality rate.

Mycoses-related deaths occurred mainly during 2003-2006 (37.5%), followed by 2007-2010 (35.2%) and 2011-2013 (27.3%). Men were more affected (69.8%) than women (30.2%). Deaths were observed in all age ranges: 0-14 years (10.1%), 15-19 years (1.6%), 20-29 years (6.3%), 30-59 years (45.8%), and >59 years (36.2%).

The main recorded mycoses were PCM (n=1,493; 35.6%) and cryptococcosis (n=1,009; 24.1%). Deaths resulting from PCM were more frequent in all regions of Brazil, except for the Northeast, where deaths stemming from candidiasis and cryptococcosis were predominant. The states of São Paulo (n=420; 28.1%), Minas Gerais (n=201; 13.5%), and Paraná (n=196; 13.1%) had the highest reported number of deaths resulting from PCM. Nevertheless, the highest mortality rate was verified in the states of Rondônia and Mato Grosso in all periods (Table 2). Cryptococcosis-related deaths occurred mostly in São Paulo (n=263; 26.0%), Rio de Janeiro (n=100; 9.9%), and Minas Gerais (n=89; 8.8%). However, mortality rates were lower than 2.0 cases/$10^6$ inhabitants in all Brazilian states (Table 2).

**Table 2.** Mortality rate by PCM and cryptococcosis as the primary cause of deaths in Brazil, 2003 to 2013.

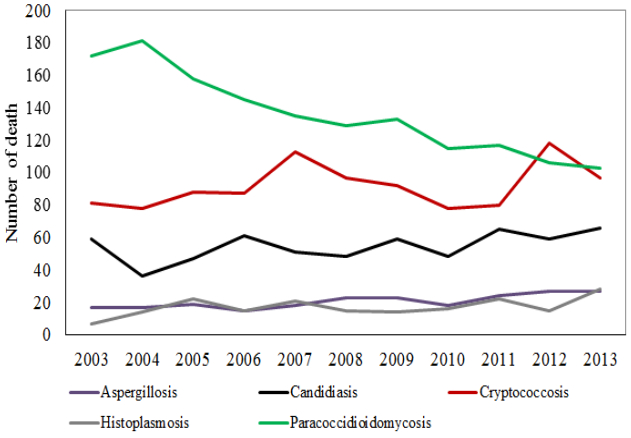
| | Population | | | 2003-2006 | | | | 2007-2010 | | | | 2011-2013 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | PCM* | | CRY† | | PCM* | | CRY† | | PCM* | | CRY† | |
| Regions/States | 2006 | 2010 | 2013 | Nº | MR‡ | Nº | MR‡ | Nº | MR‡ | Nº | MR‡ | Nº | MR‡ | Nº | MR‡ |
| Brazil | 186,770,562 | 190,747,855 | 201,032,714 | 549 | 0.8 | 302 | 0.0 | 464 | 0.6 | 328 | 0.4 | 305 | 0.4 | 260 | 0.3 |
| North | 15,022,060 | 15,880,839 | 16,983,484 | 80 | 1.3 | 33 | 0.5 | 62 | 1.0 | 46 | 0.7 | 39 | 0.8 | 32 | 0.6 |
| Rondônia | 1,562,417 | 1,560,501 | 1,728,214 | 35 | 5.6 | 2 | 0.3 | 28 | 4.5 | 3 | 0.5 | 18 | 3.5 | 3 | 0.6 |
| Acre | 686,52 | 732,793 | 776,463 | 8 | 2.9 | 0 | 0.0 | 2 | 0.7 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Amazonas | 3,311,026 | 3,480,937 | 3,807,921 | 1 | 0.1 | 9 | 0.7 | 3 | 0.2 | 11 | 0.8 | 2 | 0.2 | 7 | 0.6 |
| Roraima | 403,344 | 451,227 | 488,072 | 3 | 1.9 | 1 | 0.6 | 3 | 1.7 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Pará | 7,110,465 | 7,603,239 | 7,969,654 | 21 | 0.7 | 20 | 0.7 | 15 | 0.5 | 26 | 0.9 | 14 | 0.6 | 22 | 0.9 |
| AM | 615,715 | 668,689 | 734,996 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 1.1 | 0 | 0.0 | 0 | 0.0 |
| Tocantins | 1,332,441 | 1,383,453 | 1,478,164 | 12 | 2.3 | 1 | 0.2 | 11 | 2.0 | 3 | 0.5 | 5 | 1.1 | 0 | 0.0 |
| Northeast | 51,609,027 | 53,078,137 | 55,794,707 | 27 | 0.1 | 43 | 0.2 | 16 | 0.1 | 54 | 0.3 | 12 | 0.1 | 49 | 0.3 |
| Maranhão | 6,184,538 | 6,569,683 | 6,794,301 | 13 | 0.5 | 8 | 0.3 | 10 | 0.4 | 8 | 0.3 | 1 | 0.0 | 2 | 0.1 |
| Piauí | 3,036,290 | 3,119,015 | 3,184,166 | 3 | 0.2 | 5 | 0.4 | 1 | 0.1 | 7 | 0.6 | 2 | 0.2 | 5 | 0.5 |
| Ceará | 8,217,085 | 8,448,055 | 8,778,576 | 0 | 0.0 | 7 | 0.2 | 1 | 0.0 | 8 | 0.2 | 0 | 0.0 | 18 | 0.7 |
| Rio Grande do Norte | 3,043,760 | 3,168,133 | 3,373,959 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Paraíba | 3,623,215 | 3,766,834 | 3,914,421 | 1 | 0.1 | 2 | 0.1 | 1 | 0.1 | 2 | 0.1 | 0 | 0.0 | 2 | 0.2 |
| Pernambuco | 8,502,603 | 8,796,032 | 9,208,550 | 2 | 0.1 | 9 | 0.3 | 0 | 0.0 | 6 | 0.2 | 1 | 0.0 | 9 | 0.3 |
| Alagoas | 3,050,652 | 3,120,922 | 3,300,935 | 1 | 0.1 | 1 | 0.1 | 1 | 0.1 | 3 | 0.2 | 2 | 0.2 | 6 | 0.6 |
| Sergipe | 2,000,738 | 2,068,031 | 2,195,662 | 0 | 0.0 | 1 | 0.1 | 0 | 0.0 | 2 | 0.2 | 1 | 0.2 | 1 | 0.2 |
| Bahia | 13,950,146 | 14,021,432 | 15,044,137 | 6 | 0.1 | 10 | 0.2 | 2 | 0.0 | 17 | 0.3 | 5 | 0.1 | 6 | 0.1 |
| Southeast | 79,561,095 | 80,353,724 | 84,465,570 | 321 | 1.0 | 176 | 0.6 | 236 | 0.7 | 153 | 0.5 | 169 | 0.7 | 135 | 0.5 |
| Minas Gerais | 19,479,356 | 19,595,309 | 20,593,356 | 91 | 1.2 | 23 | 0.3 | 65 | 0.8 | 38 | 0.5 | 45 | 0.7 | 28 | 0.5 |
| Espírito Santo | 3,464,285 | 3,512,672 | 3,839,366 | 12 | 0.9 | 7 | 0.5 | 8 | 0.6 | 4 | 0.3 | 10 | 0.9 | 1 | 0.1 |
| Rio de Janeiro | 15,561,720 | 15,993,583 | 16,369,179 | 33 | 0.5 | 45 | 0.7 | 22 | 0.3 | 28 | 0.4 | 20 | 0.4 | 27 | 0.5 |
| São Paulo | 41,055,734 | 41,252,160 | 43,663,669 | 185 | 1.1 | 101 | 0.6 | 141 | 0.9 | 83 | 0.5 | 94 | 0.7 | 79 | 0.6 |
| South | 27,308,863 | 27,384,815 | 28,795,762 | 145 | 1.3 | 50 | 0.5 | 24 | 1.1 | 75 | 0.7 | 54 | 0.6 | 49 | 0.6 |
| Paraná | 10,387,378 | 10,439,601 | 10,997,465 | 86 | 2.1 | 18 | 0.4 | 76 | 1.8 | 23 | 0.6 | 34 | 1.0 | 14 | 0.4 |
| Santa Catarina | 5,958,266 | 6,249,682 | 6,634,254 | 11 | 0.5 | 5 | 0.2 | 13 | 0.5 | 21 | 0.8 | 9 | 0.5 | 15 | 0.8 |
| Rio Grande do Sul | 10,963,219 | 10,695,532 | 11,164,043 | 48 | 1.1 | 27 | 0.6 | 35 | 0.8 | 31 | 0.7 | 11 | 0.3 | 20 | 0.6 |
| Midweast | 13,269,517 | 14,050,340 | 14,993,191 | 83 | 1.6 | 32 | 0.6 | 74 | 1.3 | 52 | 0.9 | 51 | 1.1 | 30 | 0.7 |
| Mato Grosso do Sul | 2,297,981 | 2,449,341 | 2,587,269 | 13 | 1.4 | 6 | 0.7 | 11 | 1.1 | 9 | 0.9 | 9 | 1.2 | 4 | 0.5 |
| Mato Grosso | 2,856,999 | 3,033,991 | 3,182,113 | 50 | 4.4 | 11 | 1.0 | 45 | 3.7 | 8 | 0.7 | 33 | 3.5 | 14 | 1.5 |
| Goiás | 5,730,753 | 6,004,045 | 6,434,048 | 17 | 0.7 | 12 | 0.5 | 17 | 0.7 | 13 | 0.5 | 9 | 0.5 | 9 | 0.5 |
| Distrito Federal | 2,383,784 | 2,562,963 | 2,789,761 | 3 | 0.3 | 3 | 0.3 | 1 | 0.1 | 22 | 2.1 | 0 | 0.0 | 3 | 0.4 |

*Paracoccidioidomycosis. †Cryptococcosis. ‡Mortality rate.

The less frequently reported mycoses were candidiasis (n=599; 14.3%), aspergillosis (n=228; 5.4%), histoplasmosis (n=189; 4.5%), zygomycosis (n=44; 1%), coccidioidomycosis (n=26; 0.6%), mycetoma (n=23; 0.5%), chromoblastomycosis (n=21; 0.5%), and sporotrichosis (n=15; 0.4%). Unspecified mycoses were registered in 545 cases (13%). Candidiasis was registered in all states of Brazil, but mainly in São Paulo (30.2%), Rio de Janeiro (12.5%), and Bahia (11.3%). Aspergillosis was reported mainly in São Paulo (36%), Rio Grande do Sul (12.3%), and Minas Gerais (11.8%), while histoplasmosis was mainly reported in São Paulo (22.7%), Rio Grande do Sul (11.1%), and Goiás (10%) (Supplementary Figure S1). However, the mortality rates were lower than 1.0 cases/$10^6$ inhabitants in all periods.

HIV infection as an associated cause of death was notified in only five DC. Cryptococcosis occurred in four individuals and mycetoma in one HIV-positive patient. There was a downward trend in the number of deaths and of the mortality rate due to PCM. However, in other mycoses such as aspergillosis, candidiasis, cryptococcosis, and histoplasmosis, a slight increase was observed over the years (Figure 1).

**Figure 1.** Temporal trend of deaths by mycoses as the primary cause of death, 2003-2013, Brazil.




## Mycoses as the associated cause of death

In the study period, 10,925 DC listed mycoses as an associated cause of death, with a mortality density of 12.8 deaths/10,000 km$^2$ . Most cases occurred in the period of 2007-2010 (37.6%), followed by 2003-2006 (34.2%) and 2011-2013 (28.2%). Men were more affected (66%) than women (34%). Deaths were observed in all age ranges: 0-14 years (5.6%), 15-19 years (1.9%), 20-29 years (12.6%), 30-59 years (61%), and >59 years (18.9%).

Deaths were more frequent in the Southeast (493 cases/ year; 58.7 deaths/10,000 km$^2$ ) and South (220 cases/year; 41.9 deaths/10,000 km$^2$ ) regions, followed by the Northeast (122 cases/year; 8.7 deaths/10,000 km$^2$), Midwest (98 cases/ year; 6.7 deaths/10,000 km$^2$), and North (59 cases/year; 1.7 deaths/10, 000 km$^2$ ). The majority of deaths were notified in São Paulo (289 cases/year), Rio Grande do Sul (107 cases/ year), and Rio de Janeiro (104 cases/year).

With regard to annual mortality rates, the following figures were yielded: 7.6 deaths/$10^6$ inhabitants in the Southern region, 6.5 deaths/$10^6$ inhabitants in the Midwest, 5.8 deaths/$10^6$ inhabitants in the Southeast, 3.5 deaths/$10^6$ inhabitants in the North, and 2.2 deaths/$10^6$ inhabitants in the Northeast.

The most reported mycoses were cryptococcosis (40.4%), candidiasis (23.9%), histoplasmosis (9.7%), PCM (7.2%), aspergillosis (5.9%), zygomycosis (0.6%), chromoblastomycosis (0.3%), mycetoma (0.3%), coccidioidomycosis (0.2%), and sporotrichosis (0.2%). Unspecified mycoses were notified in 11.4% of cases. Cryptococcosis occurred mostly in the South, Southeast, and Midwest regions. The states of Rio Grande do Sul and Santa Catarina showed the highest mortality rates for cryptococcosis during the entire study period, particularly in the 4 years during 2007-2010. Nevertheless, insome states, mortality rates either remained stable or showed a slight increase, as observed in Rio de Janeiro, Goiás, Distrito Federal, Pará, and Piauí (Table 3).

Between 2003 and 2006, histoplasmosis was documented mostly in Goiás and Ceará. However, the highest mortality rates associated with histoplasmosis were observed during 2007-2010, in Goiás (3.4 cases/$10^6$ inhabitant), Ceará (2.4 cases/$10^6$ inhabitant), Rondônia (1.9 cases/$10^6$ inhabitant), and Roraima (1.7 cases/$10^6$ inhabitants). In the following period, it was observed that Goiás and Ceará continued to report many cases, and a relevant increase in histoplasmosis was observed in Rondônia (Table 3).

Candidiasis occurred mostly in the Southeast (125 deaths/year), followed by the Northeast (48.1 deaths/year), South (38.6 deaths/year), North (13.3 deaths/year), and Midwest (12.5 deaths/year). São Paulo and Rio de Janeiro were the states with the highest number of cases. Furthermore, the states of Rio de Janeiro (2.5 cases/$10^6$ inhabitant), Rio Grande do Sul (1.8 cases/$10^6$ inhabitant), Alagoas (1.7 cases/$10^6$ inhabitant), and Espírito Santo (1.5 cases/$10^6$ inhabitant) reported the highest overall mortality rates. In other states, mortality rates were lower than 1.5 cases/$10^6$ inhabitant.

HIV infection was the primary cause of death in 59% of death-associated fungal infections.

Other primary causes of death were neoplasia (15%), respiratory diseases (4.6%), other infectious diseases (4.2%), cardiovascular diseases (3.9%), gastrointestinal disorders (2.6%), metabolic disorders (2.5%), hematologic diseases (2.2%), urologic diseases (1.9%), and other conditions (4.5%).

Cryptococcosis (89.7%) and histoplasmosis (89.4%) were the most common mycoses associated with HIV deaths. During the period between 2003 and 2013 occurred 128,733 deaths due to HIV infection in Brazil. The incidence of cryptococcosis/HIV co-infection was 30.8 cases for every 1,000 HIV-related deaths, followed by 9.6 for candidiasis/HIV and 7.4 for histoplasmosis/ HIV (Table 4).

**Table 3.** Mortality rate resulting from cryptococcosis and histoplasmosis as an associated cause to deaths in Brazil, 2003 to 2013.

| | | | | 2003-2006 | | | | 2007-2010 | | | | 2011-2013 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Population | | | CRY* | | HIS † | | CRY* | | HIS † | | CRY* | | HIS † | |
| Regions/ States | 2006 | 2010 | 2013 | Nº | MR‡ | Nº | MR‡ | Nº | MR‡ | Nº | MR‡ | Nº | MR‡ | Nº | MR‡ |
| Brazil | 186,770,562 | 190,747,855 | 201,032,714 | 1,621 | 2.2 | 316 | 0.4 | 1,641 | 2.2 | 417 | 0.5 | 1,152 | 1.9 | 331 | 0.5 |
| North | 15,022,060 | 15,880,839 | 16,983,484 | 49 | 0.8 | 23 | 0.4 | 89 | 1.4 | 50 | 0.8 | 85 | 1.7 | 46 | 0.9 |
| Rondônia | 1,562,417 | 1,560,501 | 1,728,214 | 1 | 0.2 | 1 | 0.2 | 7 | 1.1 | 12 | 1.9 | 11 | 2.1 | 21 | 4.1 |
| Acre | 686.,52 | 732,793 | 776,463 | 0 | 0.0 | 0 | 0.0 | 2 | 0.7 | 0 | 0.0 | 2 | 0.9 | 0 | 0.0 |
| Amazonas | 3,311,026 | 3,480,937 | 3,807,921 | 6 | 0.5 | 6 | 0.5 | 23 | 1.7 | 10 | 0.7 | 34 | 3.0 | 6 | 0.5 |
| Roraima | 403,344 | 451,227 | 488,072 | 5 | 3.1 | 1 | 0.6 | 1 | 0.6 | 3 | 1.7 | 1 | 0.7 | 0 | 0.0 |
| Pará | 7,110,465 | 7,603,239 | 7,969,654 | 31 | 1.1 | 10 | 0.4 | 50 | 1.6 | 21 | 0.7 | 34 | 1.4 | 18 | 0.8 |
| Amapá | 615,715 | 668,689 | 734,996 | 2 | 0.8 | 2 | 0.8 | 0 | 0.0 | 2 | 0.7 | 0 | 0.0 | 1 | 0.5 |
| Tocantins | 1,332,441 | 1,383,453 | 1,478,164 | 4 | 0.8 | 3 | 0.6 | 6 | 1.1 | 1 | 0.2 | 3 | 0.7 | 0 | 0.0 |
| Northeast | 51,609,027 | 53,078,137 | 55,794,707 | 81 | 0.4 | 72 | 0.3 | 97 | 0.5 | 113 | 0.5 | 105 | 0.6 | 85 | 0.5 |
| Maranhão | 6,184,538 | 6,569,683 | 6,794,301 | 8 | 0.3 | 3 | 0.1 | 6 | 0.2 | 2 | 0.1 | 10 | 0.5 | 4 | 0.2 |
| Piauí | 3,036,290 | 3,119,015 | 3,184,166 | 0 | 0.0 | 0 | 0.0 | 6 | 0.5 | 1 | 0.1 | 11 | 1.2 | 1 | 0.1 |
| Ceará | 8,217,085 | 8,448,055 | 8,778,576 | 16 | 0.5 | 63 | 1.9 | 18 | 0.5 | 80 | 2.4 | 19 | 0.7 | 50 | 1.9 |
| Rio Grande do Norte | 3,043,760 | 3,168,133 | 3,373,959 | 2 | 0.2 | 0 | 0.0 | 0 | 0.0 | 5 | 0.4 | 1 | 0.1 | 6 | 0.6 |
| Paraíba | 3,623,215 | 3,766,834 | 3,914,421 | 1 | 0.1 | 1 | 0.1 | 3 | 0.2 | 2 | 0.1 | 5 | 0.4 | 0 | 0.0 |
| Pernambuco | 8,502,603 | 8,796,032 | 9,208,550 | 21 | 0.6 | 1 | 0.0 | 28 | 0.8 | 2 | 0.1 | 19 | 0.7 | 3 | 0.1 |
| Alagoas | 3,050,652 | 3,120,922 | 3,300,935 | 3 | 0.2 | 0 | 0.0 | 7 | 0.6 | 0 | 0.0 | 9 | 0.9 | 0 | 0.0 |
| Sergipe | 2,000,738 | 2,068,031 | 2,195,662 | 5 | 0.6 | 0 | 0.0 | 6 | 0.7 | 2 | 0.2 | 6 | 0.9 | 0 | 0.0 |
| Bahia | 13,950,146 | 14,021,432 | 15,044,137 | 25 | 0.4 | 4 | 0.1 | 23 | 0.4 | 17 | 0.3 | 25 | 0.6 | 21 | 0.5 |
| Southeast | 79,561,095 | 80,353,724 | 84,465,570 | 884 | 2.8 | 103 | 0.3 | 777 | 2.4 | 102 | 0.3 | 490 | 1.9 | 87 | 0.3 |
| Minas Gerais | 19,479,356 | 19,595,309 | 20,593,356 | 127 | 1.6 | 26 | 0.3 | 130 | 1.7 | 28 | 0.4 | 84 | 1.4 | 20 | 0.3 |
| Espírito Santo | 3,464,285 | 3,512,672 | 3,839,366 | 29 | 2.1 | 5 | 0.4 | 40 | 2.8 | 5 | 0.4 | 14 | 1.2 | 1 | 0.1 |
| Rio de Janeiro | 15,561,720 | 15,993,583 | 16,369,179 | 159 | 2.6 | 15 | 0.2 | 166 | 2.6 | 17 | 0.3 | 130 | 2.6 | 18 | 0.4 |
| São Paulo | 41,055,734 | 41,252,160 | 43,663,669 | 569 | 3.5 | 57 | 0.3 | 441 | 2.7 | 52 | 0.3 | 289 | 2.2 | 48 | 0.4 |
| South | 27,308,863 | 27,384,815 | 28,795,762 | 460 | 4.2 | 39 | 0.4 | 536 | 4.9 | 41 | 0.4 | 346 | 4.0 | 35 | 0.4 |
| Paraná | 10,387,378 | 10,439,601 | 10,997,465 | 116 | 2.8 | 6 | 0.1 | 95 | 2.3 | 7 | 0.2 | 91 | 2.8 | 7 | 0.2 |
| Santa Catarina | 5,958,266 | 6,249,682 | 6,634,254 | 101 | 4.2 | 13 | 0.5 | 189 | 7.6 | 8 | 0.3 | 89 | 4.5 | 10 | 0.5 |
| Rio Grande do Sul | 10,963,219 | 10,695,532 | 11,164,043 | 243 | 5.5 | 20 | 0.5 | 252 | 5.9 | 26 | 0.6 | 166 | 5.0 | 18 | 0.5 |
| Midwest | 13,269,517 | 14,050,340 | 14,993,191 | 147 | 2.8 | 79 | 1.5 | 142 | 2.5 | 111 | 2.0 | 126 | 2.8 | 78 | 1.7 |
| Mato Grosso do Sul | 2,297,981 | 2,449,341 | 2,587,269 | 35 | 3.8 | 5 | 0.5 | 44 | 4.5 | 14 | 1.4 | 20 | 2.6 | 4 | 0.5 |
| Mato Grosso | 2,856,999 | 3,033,991 | 3,182,113 | 13 | 1.1 | 4 | 0.4 | 12 | 1.0 | 5 | 0.4 | 17 | 1.8 | 9 | 0.9 |
| Goiás | 5,730,753 | 6,004,045 | 6,434,048 | 78 | 3.4 | 67 | 2.9 | 70 | 2.9 | 91 | 3.8 | 72 | 3.7 | 64 | 3.3 |
| Distrito Federal | 2,383,784 | 2,562,963 | 2,789,761 | 15 | 1.6 | 3 | 0.3 | 16 | 1.6 | 1 | 0.1 | 17 | 2.0 | 1 | 0.1 |

*Cryptococcosis. †Histoplasmosis ‡Mortality rate.

**Table 4.** Mycoses associated with HIV-deaths in Brazil, 2003 to 2013.

| Mycoses | HIV Negative (n=4,452) | % | HIV Positive (n=6,498) | % | OR (CI 95%) | Mycoses incidence (1,000 HIV-deaths) |
|---|---|---|---|---|---|---|
| Aspergillosis (n=652) | 616 | 94.5 | 36 | 5.5 | 0.03 (0.02-0.04) | 0.3 |
| Candidiasis (n=2,616) | 1,377 | 52.6 | 1,239 | 47.4 | 0.52 (0.48-0.57) | 9.6 |
| Coccidioidomycosis (n=27) | 16 | 59.3 | 11 | 40.7 | 0.47 (0.21-1.01) | 0.1 |
| Cryptococcosis (n=4,413) | 451 | 10.2 | 3,962 | 89.7 | 13.86 (12.42-15.46) | 30.8 |

| Mycoses | HIV Negative (n=4,452) | % | HIV Positive (n=6,498) | % | OR (CI 95%) | Mycoses incidence (1,000 HIV-deaths) |
|---|---|---|---|---|---|---|
| Chromoblastomycosis (n=29) | 23 | 79.3 | 6 | 20.7 | 0.17 (0.07-0.43) | 0.0 |
| Sporotrichosis (n=25) | 10 | 40.0 | 15 | 60.0 | 1.02 (0.46-2.29) | 0.1 |
| Histoplasmosis (n=1,064) | 113 | 10.6 | 951 | 89.4 | 6.58 (5.39-8.03) | 7.4 |
| Mycetoma (n=30) | 26 | 86.7 | 4 | 13.3 | 0.10 (0.03-0.30) | 0.0 |
| Paracoccidioidomycosis (n=788) | 702 | 89.0 | 86 | 11.0 | 0.07 (0.05-0.08) | 0.7 |
| Zygomycosis (n=62) | 60 | 96.8 | 2 | 2.8 | 0.02 (0.00-0.09) | 0.0 |

## DISCUSSION

Mycoses have contributed to a large number of deaths due to infectious diseases in Brazil. The mortality density observed in this study demonstrated several cases of fungal infections, mostly in Southeastern and Southern Brazil. PCM was found to be the most frequent primary cause of death. However, a downward trend in mortality rates has been noted, mainly in hyperendemic areas such as the North of Brazil. In addition, opportunistic mycoses like cryptococcosis and histoplasmosis were the most frequent fungal infections recorded in patients with HIV.

Systemic mycoses are considered to be neglected diseases worldwide, with their actual prevalence and incidence figures being unknown. Epidemiologic surveillance for mycosis is performed in few public health agencies, such as the Centers for Disease Control and Prevention (CDC) in the USA. In addition, the World Health Organization does not yet sponsor a program focused specifically on fungal infections[1]. In Brazil, these infections are not broadly reported diseases. Only PCM, histoplasmosis and sporotrichosis are compulsorily reported diseases at a local scale in Rondônia, Goiás, and Rio de Janeiro, respectively. This can contribute to an underestimated incidence and mortality rate owing to invasive fungal infections in the country. Moreover, many fungal infections are often misdiagnosed due to similarities with other infectious diseases such as tuberculosis.

Brazil is the most important endemic PCM area in the world, with more than 80% of cases occurring in the Southeast, South, and Midwest regions[7]. The estimated incidence in Brazil is 1 to 3 cases/100,000 people. In some specific states, such as Rondônia (North of Brazil), the incidence of PCM is very high (9.4 cases/105 people), although it has decreased over the years[8].

Among mycoses as the primary cause of death, PCM was associated with the highest mortality rate in Brazil. From 1980 to 1995, PCM mortality rate in Brazil was 1.45/$10^6$ inhabitants. The states with the highest mortality rates in this study were Mato Grosso do Sul (4.39/$10^6$ inhabitants) and Rondônia (3.65/$10^6$ inhabitants)[9]. The annual mortality rates showed a sharp downward trend, with an overall reduction of 37% in the South and 31% in the Southeast[9]. In another study carried out in São Paulo, the mortality rate of PCM as the primary cause of death also decreased from 2.28 to 0.92 for every 1,000,000 inhabitants, during the period between 1985 and 2005[10].

Prado et al.[3] revealed that PCM was the most commonly reported mycosis as the primary cause of death between 1996 and 2006. Mortality rates decreased in the South and Southeast regions but increased in the North[3]. In 1999, Rondônia became the state with the highest mortality rate in Brazil, with Mato Grosso ranked second. Rondônia (8.2/$10^6$ inhabitants) and Acre (5.6/$10^6$ inhabitants), in the Northern region, had a greater number of fatal PCM cases, mainly in the period between 2002 and 2004[3]. Vieira et al.[8] reported a mean mortality rate of 5.6/$10^6$ inhabitants in Rondônia from 1997 to 2012, likewise demonstrating a downward trend in the number of occurrences.

Our findings also intended to demonstrate the high mortality rates in those states and the low mortality rates in the Northeast of Brazil. In reality, there have been decreases in the mortality rates in all regions and states of Brazil. We believe that this could be the result of improvements in disease control and prevention and decreases in exposure to fungus micro-niches in rural populations due to migration towards urban areas seen in recent decades.

PCM associated-deaths occurred in a few cases with a small number of cases related to PCM/HIV co-infection, a finding also observed by others[11-13]. It is already well known that PCM does not behave as an opportunistic infection in immunocompromised individuals; however, due to the increase in the number of cases involving HIV individuals older than 50 years of age over the last 10 years, PCM should be considered in this population[8].

Cryptococcosis ranked second among the most frequent mycoses reported as a primary cause of death, affecting predominantly Southeastern and Southern Brazil. However, low mortality rates by cryptococcosis were observed in the majority of the states. In Distrito Federal (2.5/$10^6$ inhabitants) however, from 2007 to 2010, and in Mato Grosso (1.5/$10^6$ inhabitants) between 2011 and 2013, elevated mortality rates were noted. It should be noted that HIV infection was verified as the secondary cause of death from cryptococcosis in only three cases.

Cryptococcosis, caused mainly by *Cryptococcus neoformans*, affects a broad number of immunocompromised individuals. However, this mycosis can also affect patients without immunologic defects in up to 20% of cases[14,15]. In Mato Grosso do Sul, a study including 123 cases of hospitalization due to cryptococcosis identified that 84.5% of the patients had HIV infection, 10.6% were normal hosts, and 4.9% had other predisposing conditions[15]. Conversely, *C. gattii* affects predominantly immunocompetent hosts, including children and young adults in Northern and Northeastern Brazil[14]. Lomes et al.[16] published a series of 29 cases of cryptococcosis in non-HIV and non-transplant patients, in which the mortality rate population was 20.6%. *C. gattii* was the most prevalent species in this study.

When deaths linked to cryptococcosis were evaluated, the number of cases was much higher than those reported only as a primary cause. In addition, almost 90% of cryptococcosis cases were associated with HIV infections as the primary cause of death. Cryptococcal meningitis is the most prevalent clinical form, for both HIV-positive and HIV-negative individuals, and its mortality is seen to be extremely high in both groups[17]. Hospital-based studies have demonstrated that HIV individuals are generally more affected and that the incidence of cryptococcosis in patients with AIDS can reach 36 cases/1,000 admissions[15,18,19].

A reduction in cryptococcosis-related mortality, from above 90% in the pre-HAART to about 40% in the HAART was reported in São Paulo[17]. Here, we also observed a decreasing pattern in the number of deaths associated with cryptococcosis in São Paulo and Rio Grande do Sul; however, in other states, the mortality rate either did not change or showed a minor increase only. Unlike Prado et al.[3] we found an increase in cryptococcosis-related mortality for every 1,000 HIV deaths (23.8 to 30.8). This was probably due to delays in HIV diagnosis and consequently HAART initiation in some Brazilian regions like the North and Northeast, the lack of swift testing available for diagnosis, and the unavailability of 5-flucytosine (optimal treatment) in many centers of Brazil. Moreover, the prevalence of AIDS in Brazil has increased in the North and Northeastern regions during the past 10 years[20].

Histoplasmosis was reported to be the primary cause of death in 56 cases between 1996 and 2006[3]. In contrast, we found 189 citations of histoplasmosis as the underlying cause of death, representing three times the number of deaths. Histoplasmosis is a systemic mycosis that occurs globally and affects mainly individuals with severe immunosuppression. In Latin America, the disseminated form of histoplasmosis is the most prevalent, appearing mostly in Brazil, Mexico, and Colombia[21,22], where this fungal infection is a public health problem in endemic areas. The mortality rate is very high in some parts of the Northeast, Midwest, and South and can reach up to 40–70%2[3-25]. In contrast, in immunocompetent individuals, the mortality is unremarkable[18].

The present study, however, observed low mortality rates in the majority of the states where histoplasmosis was associated with death. The exceptions were Goiás and Ceará, which had high mortality rates in all the studied periods. In addition, high mortality rates were observed in Rondônia, beginning in 2007. HIV infection was the main primary cause of death in more than 85% of cases. There was an increase in the incidence of histoplasmosis associated with HIV deaths, when compared to a previous study[3]. A recent cohort study conducted with HIV patients in many centers of Brazil identified a high prevalence of histoplasmosis in the Northeast and Midwest regions[21]. Ceará and Goiás are the most endemic areas of histoplasmosis in Brazil, and the lack of fast assays for early diagnosis has contributed to high mortality levels in these regions. It is worth noting that AIDS detection rates increased by 4% in Ceará and 7% in Goiás between 2007 and 2017[20].

Candidiasis was the third primary cause of death among the studied fungal infections. Furthermore, the mortality rates for candidiasis were lower than for other mycoses such as PCM and cryptococcosis. Similar to Prado et al.[3], Candida infection was notified mainly in the Southeastern and Southern regions and mostly affected patients who did not have HIV. Candidiasis as an underlying cause of death affected mostly older patients (>60 years), and as an associated cause of death, was more predominant in adults older than 30 years of age (data not shown).

The incidence of invasive candidiasis in a study performed in São Paulo identified a prevalence of 8.3 cases/1,000 AIDS patient's hospitalizations during a year, with a mortality rate of 50%[18]. From 1996 to 2006, the incidence of candidiasis in patients who died from HIV was 4.17/1,000 deaths[3]. In contrast, the incidence of candidiasis in this study was considerably higher (9.6/1,000 deaths from HIV infections). Mucosal infection like oropharyngeal and esophageal candidiasis is more commonly reported in patients with AIDS, mainly in individuals with severe immunosuppression (CD4+ < 200 cells/mm$^3$)[4].

Deaths stemming from other invasive fungal infections had low frequencies. In Brazil, of the nine states with semiarid climates, only the states of Piauí and Ceará have reported considerable numbers of cases of coccidioidomycosis, which may be due to specific environmental conditions for the micro-niche of *Coccidioides* spp. or due to unrecorded cases in other areas. The lack of medical suspicion and limited access to laboratory diagnosis has limited epidemiologic data on this fungal infection. Rio de Janeiro is a well-known endemic area for sporotrichosis; however, all states with the exception of Roraima have reported hospitalizations by sporotrichosis[26]. Other implantation mycoses, such as chromoblastomycosis and mycetoma are chronic fungal infections that led to higher morbidity than mortality. Deaths due to these mycoses are occasional and can occur due to secondary bacterial infections[27,28].

Zygomycosis or mucormycosis is an emerging invasive fungal infection. Mortality rates in HIV patients are extremely high and

occur generally in their disseminated forms[29,30]. Aspergillus spp. continues to be a significant cause of life-threatening infections in immunocompromised patients, but in Brazil, its incidence and mortality are unknown[29].

In summary, although there was a downward trend in the number of deaths stemming from invasive fungal infections, opportunistic mycoses might be a significant cause of death, especially in HIV patients. The decrease in PCM mortality rates in all regions, even in hyperendemic areas, could be the result of epidemiologic surveillance, health education, early diagnosis, and/or access to appropriate treatment.

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