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Review

The occurrence of histoplasmosis in Brazil: A systematic review

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ABSTRACT

Background: Histoplasmosis is a systemic disease caused by the dimorphic fungus *Histoplasma capsulatum*. Diagnosis is often delayed, or it is misdiagnosed as tuberculosis. In Brazil, the infection is common and cases of histoplasmosis have been described in all regions of the country; however, the real problem is underestimated since notification of histoplasmosis is not mandatory.
Methods: Human histoplasmosis cases diagnosed in Brazil and published up to December 2018 were identified through a search conducted in the PubMed/MEDLINE, SciELO, and Web of Science databases. Moreover, the isolation of *H. capsulatum* from animals or environmental sources in Brazil was also evaluated.
Results: A total of 207 articles fulfilled the inclusion criteria and were evaluated, involving a total of 3530 patients with a diagnosis of histoplasmosis during the period studied. Of these patients, 78.3% were male, giving a male-to-female ratio of approximately 4:1. Histoplasmosis presented a higher frequency in individuals between the fourth and fifth decades of life. Disseminated disease was the most common form of histoplasmosis. Isolation of *H. capsulatum* on culture media and histopathology using staining methods were the diagnostic methods with the best efficiency. The best results in the identification of the *H. capsulatum* were achieved for samples from mononuclear phagocyte system components, skin and mucosa, and hematological samples. Regarding predisposing factors for histoplasmosis, HIV infection was the most common underlying condition. The overall mortality rate was 33.1%.
Conclusions: This study represents the first available systematic review demonstrating Brazilian cases of histoplasmosis in the literature and highlights that the disease is more widespread in the Brazilian territory than has previously been thought.

Contents

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Introduction

Histoplasmosis is a systemic disease caused by the dimorphic fungus *Histoplasma capsulatum*. This disease has a worldwide distribution, with major areas of high endemicity located in the Ohio and Mississippi river valleys in the USA and in a large part of Latin America (Couppié et al., 2006; Colombo et al., 2011). In Brazil, cases of histoplasmosis have been described throughout the country, particularly from the Midwest, Northeastern, and Southeast regions (Guimarães et al., 2006; Damasceno et al., 2013).

The infection is acquired by the inhalation of fungal infectious propagules usually present in the context of acid and moist nitrogen-rich soils containing excrement from poultry and bats (Colombo et al., 2011). Therefore, occupational exposure to the fungus can occur during construction, renovation, demolition, excavation, and caving activities, as well as recreational ecotourism practices (Cottle et al., 2013; Gundacker et al., 2017).

The clinical spectrum of this illness ranges from an asymptomatic, self-limited illness to a progressive disseminated disease. The primary focus of this fungal infection is the lung, and the disease prognosis depends on the host immune response, the fungal inoculum size inhaled, and the fungal virulence (Deepe and Buesing, 2012). Immunocompromised subjects, especially individuals with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), patients undergoing corticosteroid or other forms of immunosuppressive therapy, and those undergoing cytotoxic chemotherapy, can develop more severe forms of the disease, due to fungal dissemination to several organs (Damasceno et al., 2013; Kauffman, 2007).

Demonstration of the yeast-like *H. capsulatum* cells on microscopic examination of fluids and tissues using specific staining techniques and the isolation of the fungus in culture of clinical specimens constitute the gold standard method for the diagnosis of histoplasmosis. However, these methodologies may require invasive medical procedures to obtain clinical specimens, and the culture test is time-consuming, requiring up to 8 weeks to reveal fungal growth, and conversion to the yeast form is essential. However, this phenomenon is strain-dependent. As a result, alternative methods have been used as complementary diagnostic tools to detect anti-*Histoplasma* antibodies or *Histoplasma* antigens. These are in fact less invasive methodologies and have great sensitivity depending on the clinical form of histoplasmosis. Molecular methods with improved sensitivity are currently under development, although they are not yet validated for widespread application in most clinical laboratories (Azar and Hage, 2017).

Several studies have been published since the description of the first case of histoplasmosis reported in Brazil (Almeida and Lacaz, 1939). However, the real problem of histoplasmosis in Brazil is underestimated, as the available information on this disease comes from case reports, case series, or reviews published in the literature, and due to the fact that the notification of histoplasmosis is mandatory in only one of the 26 Brazilian states.

In this study, histoplasmosis occurrences diagnosed in Brazil and reported in the scientific literature were analyzed retrospectively. The distribution of cases, epidemiological data, and diagnostic methods are described through an analysis of all reports retrieved using the search strategy described below. Moreover, isolations of *H. capsulatum* from animals and environmental sources in Brazil were also evaluated.

Methods

Search strategy

A computerized search was conducted in the PubMed/MEDLINE, Scientific Electronic Library Online (SciELO), and Web of Science databases for articles published up to December 2018, with the last access performed on January 2, 2019. The search terms included a combination of specific keywords: *Histoplasma* [AND] Brazil or histoplasmosis [AND] Brazil. Publications describing non-human studies, non-*Histoplasma* studies, non-Brazilian cases, African histoplasmosis case reports, histoplasmosis case reports with diagnosis based solely on intradermal tests, review or research articles, non-English or non-Portuguese articles, and duplicate results were excluded from this review. Additional human case reports and cases series missed in the initial search strategy were carefully identified from the reference lists of the articles initially retrieved (Figure 1).

As a contribution to the determination of the geographical distribution of histoplasmosis in Brazil, those studies that reported the isolation of *H. capsulatum* from soil samples or from domestic and wild animals were evaluated in parallel, and epidemiological surveys using the skin test were also included.

Case definition

The histoplasmosis case definitions were outlined according to the consensus statement of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group – EORTC/MSG (De Pauw et al., 2008), with minor modifications. Proven histoplasmosis included cases in which the diagnosis was performed by identification of *H. capsulatum* yeast-like cells in culture, direct examination, or histopathological analyses. A positive antibody test combined with clinical and radiological findings were required for the classification of probable disease. Possible histoplasmosis included cases with clinical and radiological findings compatible with this disease and an epidemiological history associated with histoplasmosis, such as environmental exposure to at-risk areas, e.g. caves infested with bats.

Classification into the distinct clinical presentations of histoplasmosis followed previously reported recommendations (Guimarães et al., 2010).

Data analysis

Abstracts were independently assessed by two examiners and were included for full-text review if they were related to the proposed topic of this review. Disagreements on the inclusion of articles in the study were resolved by discussion and examiner consensus. Data supplied in the included studies were checked for missing data and internal data consistency. This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009).

During the analysis, exhaustive efforts were made to collect all available information on the following topics: language and year of publication, geographical distribution of histoplasmosis in Brazil, age and sex of patients, HIV status, co-infection with tuberculosis, proof of diagnosis, and patient clinical outcomes.

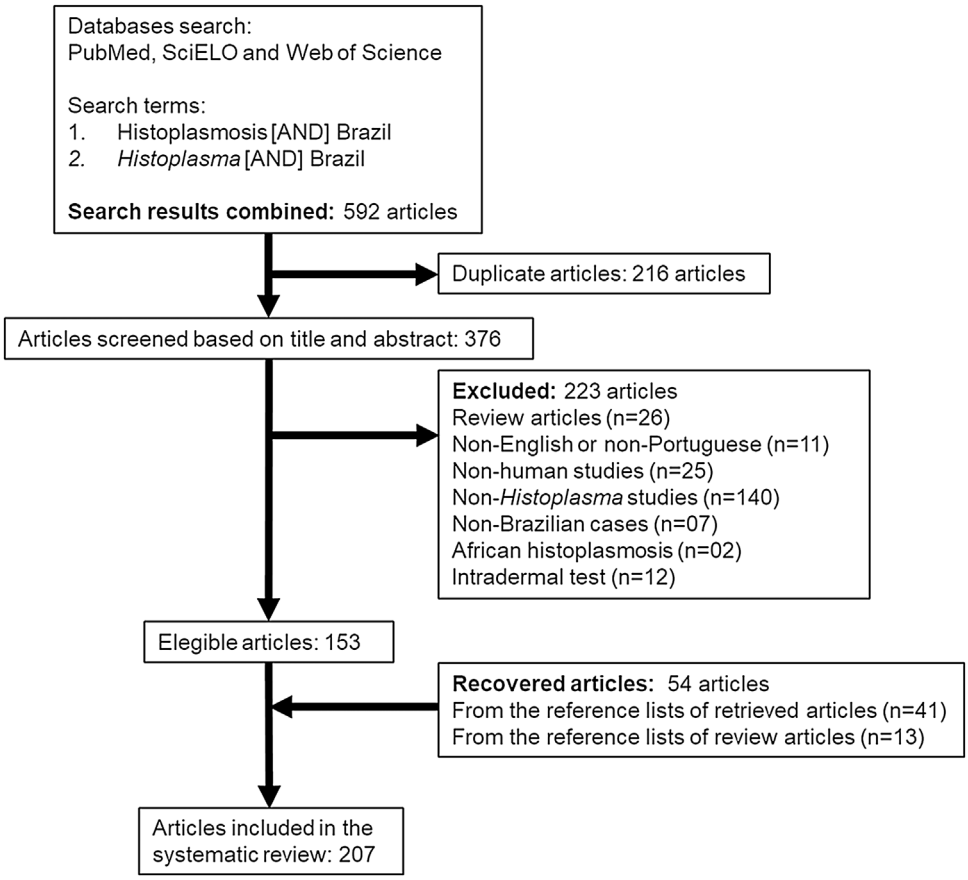

Figure 1. Flowchart demonstrating the systematic review process of human cases included in this study.

This study was registered in the PROSPERO database (number 124523).

Statistical analysis

Descriptive statistics were calculated with GraphPad Prism 7.0.

Results

Identification of studies

The initial search identified 592 studies related to a combination of specific keywords; 216 articles were excluded due to duplication. After the assessment of titles and abstracts, 223 studies were excluded because they did not fulfill the inclusion criteria and 153 studies were selected for full-text assessment.

In order not to miss information on the real disease frequency in Brazil, 54 additional studies were included: 41 articles were retrieved from the reference lists of the initially eligible articles and 13 articles were recovered from the reference lists of excluded review articles.

Finally, 207 articles fulfilled the inclusion criteria and were further evaluated in this systematic review (Figure 1).

Human histoplasmosis in Brazil

Of the 207 studies evaluated, all were published between the years of 1939 and 2018. Regarding the language, 68.6% were published in English and 31.4% in Portuguese. The number of patients described in these publications ranged from 1 to 279, for a total of 3530 patients with a diagnosis of histoplasmosis during this period in Brazil. Figure 2 shows the distribution of publications and number of cases over time.

Histoplasmosis is endemic in all Brazilian regions, with emphasis on the Northeast, Central-West, Southeast, and South regions. Cases of human histoplasmosis were reported in 19 of the 26 Brazilian states, as well as in the Federal District (Figure 3).

Of the 3530 histoplasmosis cases analyzed in this review, information regarding patient sex was retrieved in 3013 cases. Of these, 78.3% (95% confidence interval (CI) 76.79–79.73%) were male and 21.7% (95% CI 20.27–23.21%) were female, leading to a male-to-female ratio of approximately 4:1. The age of the patients ranged from 3 days to 88 years, with a greater incidence in persons between the fourth and fifth decades of life. Age was not reported for 517 patients.

According to the consensus statement of EORTC/MSG, 85.3% of the cases in this study were classified as proven, 11.0% as probable, and 2.6% as possible. Regarding the clinical form of the disease, histoplasmosis patients were clinically classified into four clinical forms; however, 1.1% of cases could not be classified due to insufficient data in the reports. A predominance of disseminated histoplasmosis was found ($n = 2882$, 81.65%; 95% CI 80.32–82.91%), followed by acute pulmonary histoplasmosis ($n = 529$, 14.99%; 95% CI 13.83–16.23%), chronic pulmonary histoplasmosis ($n = 103$, 2.92%; 95% CI 2.41–3.54%), and mediastinal histoplasmosis ($n = 16$, 0.44%; 95% CI 0.26–0.73%).

The diagnosis of histoplasmosis was confirmed by a positive culture for *H. capsulatum* in 570 cases. Histological findings of *H. capsulatum* cells comprised the diagnostic method in 523 cases,

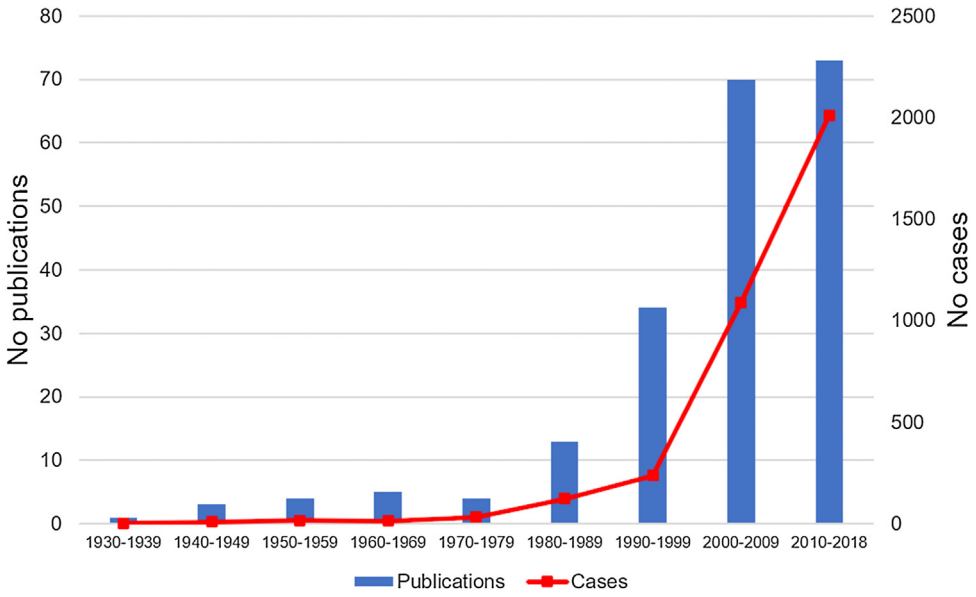

Figure 2. The number of publications (bars) and number of cases (line) related to a diagnosis of histoplasmosis in Brazil, 1939–2018.

and direct demonstration in clinical samples was positive in 142 cases. Serological tests for antibody detection by double immunodiffusion or Western blot was the prime diagnostic indicator of histoplasmosis in 408 cases. In the other reported cases, it was not possible to accurately state the methodology used for the diagnosis of histoplasmosis. In these studies, diagnoses by means of two or more different methods were described, or the tests used were not specified. Detailed information is presented in Figure 4.

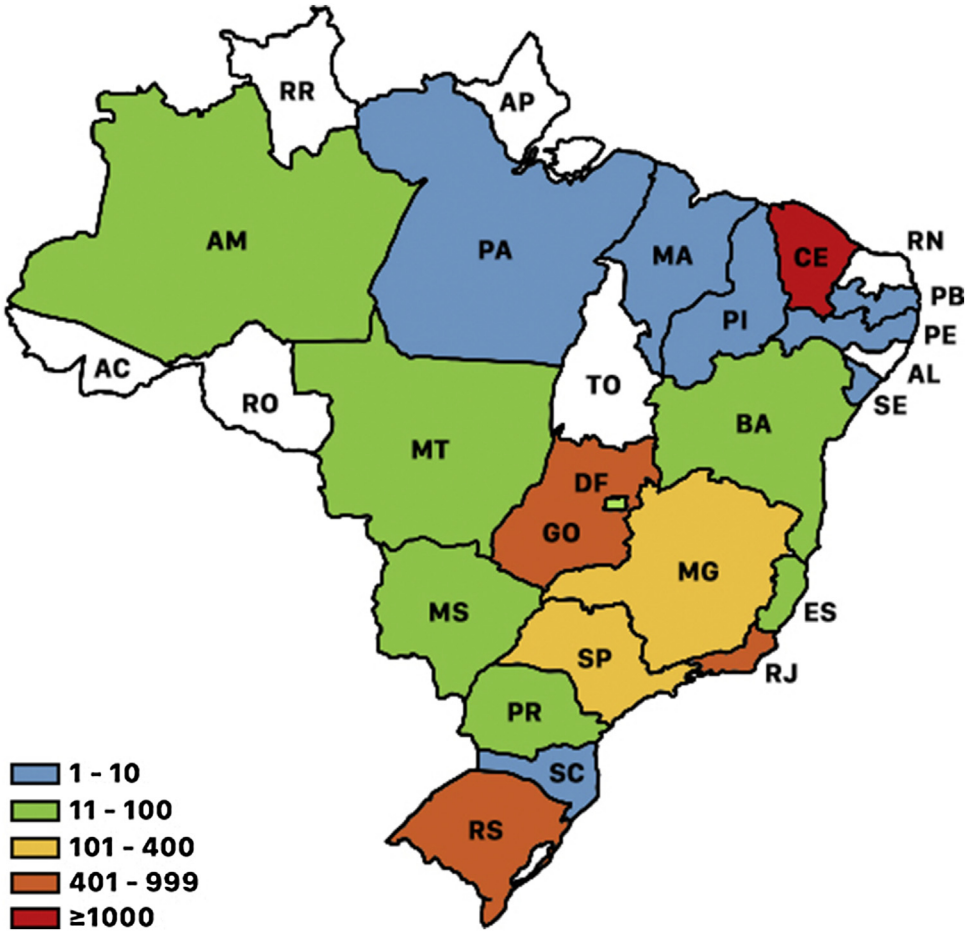

Figure 3. Geographic distribution of the number of histoplasmosis cases reported in Brazil (1939–2018).

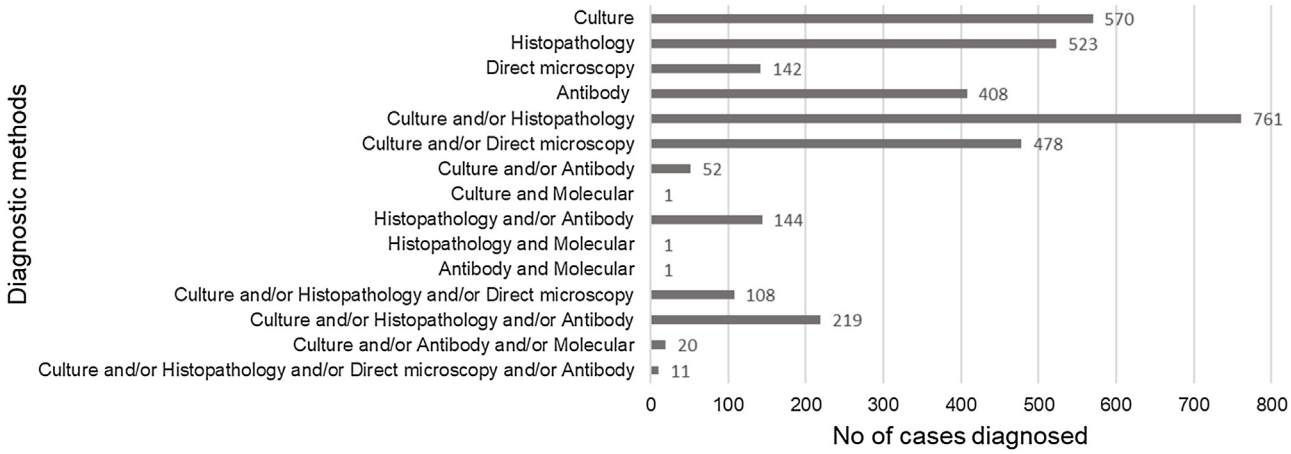

Figure 4. Diagnostic methods employed for the diagnosis of histoplasmosis in Brazil during the period 1939–2018.

Identification of the agent in proven histoplasmosis cases was most often achieved in samples obtained from mononuclear phagocyte system components ($n = 611$), skin and mucosa ($n = 503$), and hematological samples ($n = 464$). Further data on the clinical specimens in which the demonstration of *H. capsulatum* was performed are shown in Table 1.

Regarding the underlying disease and predisposing factors for histoplasmosis, 2143 patients (56.66%, 95% CI 55.02–58.28%) had a history of immunosuppression. Among the reasons for immunosuppression, infection with HIV was the most common underlying condition, accounting for 97.20% (95% CI 96.38–97.84%) of immunocompromised cases. The other causes of immunosuppression consisted of patients receiving a solid-organ transplant with immunosuppressive therapy (1.20%; 95% CI 0.80–1.79%), long-term corticosteroid therapy (0.5%; 95% CI 0.26–0.93%), patients at the extremes of age (0.2%; 95% CI < 0.01–0.39%), and other factors (0.9%; 95% CI 0.56–1.43%).

Due to the difficulties in the clinical differentiation between histoplasmosis and tuberculosis, 1167 patients were tested for both of these infections; tuberculosis was concomitantly diagnosed in 10.37% (95% CI 8.74–12.25%) of the patients with a diagnosis of histoplasmosis.

In addition to the risk factors for histoplasmosis related to immunosuppression described above, a description of risk behaviors was provided for 465 patients: 313 of the patients (67.31%; 95% CI 62.92–71.42%) had known exposure to chicken houses, birds, or bats; 88 patients (18.92%; 95% CI 15.62–22.74%) were involved in agricultural work or resided in a rural area, where exposure to contaminated soil would have been a possibility; and 64 patients (13.76%; 95% CI 10.91–17.21%) had a documented exposure to caves.

Final outcome data were available for 2421 cases. The overall mortality rate was 33.09% (95% CI 31.24–34.99%), and 66.91% (95% CI 65.01–68.76%) reported improvement or cure. In 149 cases (18.60% of fatal cases; 95% CI 16.05–21.45%), the diagnosis of histoplasmosis was only made post-mortem by histopathological examination using specific stains.

Table 1
Rates of direct examination, culture, and histopathology positive results in patients with histoplasmosis ($N = 3274$).[a]

Site	*n*	%	95% CI
Mononuclear phagocyte system	611		
Bone marrow	363	59.41%	55.47–63.23
Liver	135	22.09%	18.98–25.56
Lymph nodes	103	16.86%	14.09–20.04
Spleen	10	1.64%	0.85–3.03
Skin and mucosa	503		
Skin	268	53.28%	48.91–57.60
Mucosa	133	26.44%	22.77–30.47
Skin and mucosa	102	20.28%	16.99–24.02
Hematological samples	464		
Blood	461	99.35%	98.02–99.87
Dialysis fluid	3	0.65%	0.12–1.98
Respiratory samples	92		
Sputum	50	54.35%	44.20–64.15
Bronchoalveolar lavage	21	22.83%	15.38–32.46
Respiratory secretions	20	21.74%	14.46–31.28
Sinus aspirate	1	1.09%	<0.01–6.49
Digestive system	42		
Organ not specified	32	76.19%	61.30–86.69
Intestine	6	14.29%	6.33–28.22
Pancreas	4	9.52%	3.21–22.62
Central nervous system	38		
Sample not specified	31	81.58%	66.27–91.09
Brain biopsy	4	10.53%	3.59–24.71
Cerebrospinal fluid	3	7.89%	2.00–21.52
Endocrine glands	29		
Supra-renal	25	86.21%	68.82–95.12
Thyroid	4	13.79%	4.88–31.18
Urinary system	20		
Kidney	7	35.00%	17.99–56.84
Urine	3	15.00%	4.39–36.88
Testicle	2	10.00%	1.57–31.32
Other samples	8	40.00%	21.83–61.40
Osteoarticular system	4		
Joints	2	50.00%	15.00–85.00
Synovial fluid	1	25.00%	3.41–71.09
Bone	1	25.00%	3.41–71.09
Other samples	2		
Heart	1	50.00%	9.45–90.55
Cornea	1	50.00%	9.45–90.55
Not specified	1469		

CI, confidence interval.
[a] More than one specimen was obtained from some patients.

Histoplasmin skin test reactivity in Brazil

The search strategy of this systematic review revealed 77 publications reporting histoplasmin skin test reactivity. Eight Brazilian states (29.6%) did not present studies on this subject during the period studied. A high degree of positivity was observed in published results on the reactivity of the histoplasmin skin test among individuals from the remaining 19 Brazilian states and the Federal District. Among the states that presented positive results, the four states with highest average positivity in the histoplasmin skin test were Amapá, Ceará, Mato Grosso, and Pará (Figure 5).

The overall positive reactivity in the histoplasmin skin test across all publications identified was 19.3% (95% CI 18.9–19.7%). The study of

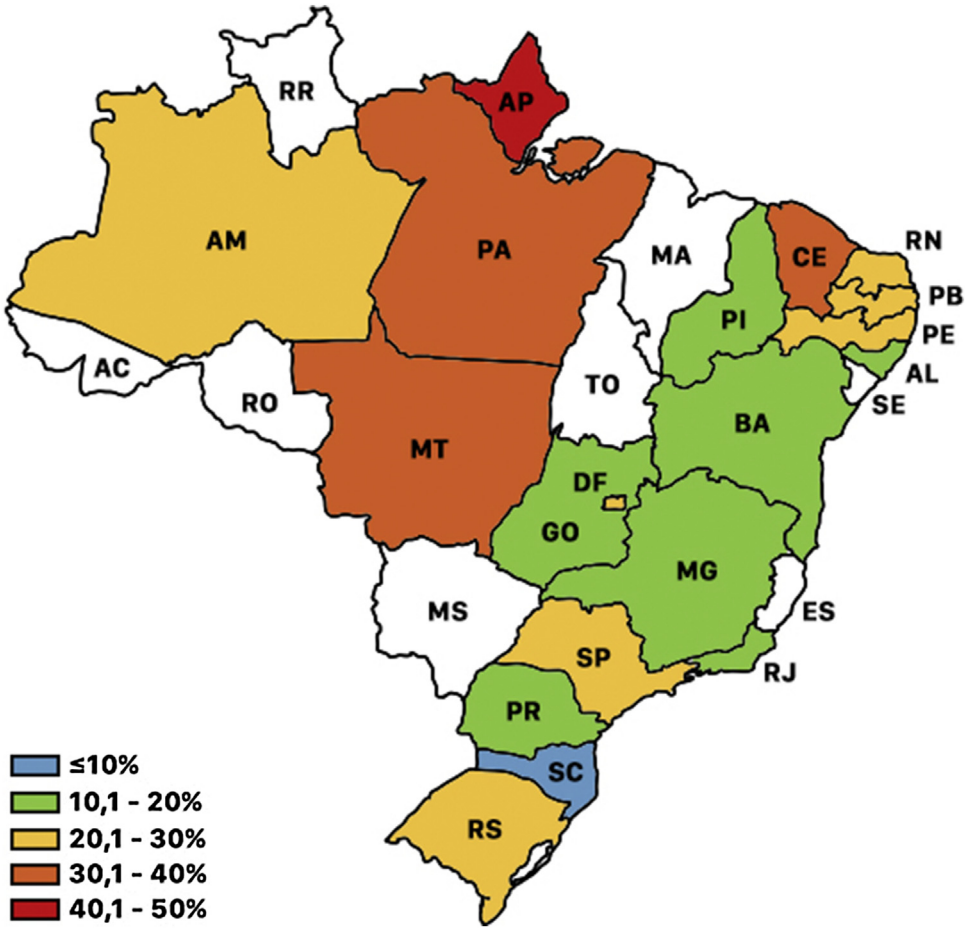

Figure 5. Mean rates of *Histoplasma* infection determined by histoplasmin skin test positivity.

Wanke (1985) presented more than 90% positivity in histoplasmin skin tests in Rio de Janeiro state; this is the highest positivity index found among the published data. The state of Rio de Janeiro also presented the lowest positivity index (3.3%), described approximately 30 years before (Douat and Diaz, 1953). The data showing the number of individuals tested and the skin test positivity index are shown in the Supplementary Material (Table S1).

Isolation of H. capsulatum *from animals and soil: the One Health concept of histoplasmosis in Brazil*

Reports of animal and/or soil isolation of *H. capsulatum* were found in 12 Brazilian states. Infection in domestic animals (dogs, cats, bovines, equines, and sheep) was reported in seven states, and descriptions about histoplasmosis in wild animals (rodents, marsupials, primates, felines, and xenarthra) were also observed in seven states. The isolation of *H. capsulatum* from bats was reported in four Brazilian states and from soil in seven states. It is important to highlight that the state of São Paulo had the highest indexes of fungal isolation from animals (domestic, wild, and bats) and the state of Rio de Janeiro had the highest index of soil isolation (Figure 6).

Discussion

Histoplasmosis is endemic in several regions of the world, especially in the USA and in parts of Latin America, including Brazil (Wheat et al., 2016).

Despite the recognition of Brazil as an area endemic for histoplasmosis, where the disease has been considered the fourth most common cause of death among systemic mycoses, the real incidence in this country is unknown, since the disease is not included in the watch-list for compulsory notification (Prado et al., 2009). In fact, only the number of hospitalized histoplasmosis patients is reported to the Brazilian Ministry of Health and the overall frequency of the disease can only be estimated based on published cases (Giacomazzi et al., 2016).

In this systematic review, 207 studies were evaluated in which 3530 patients were reported until 2018. Since the first histoplasmosis case described in Brazil (Almeida and Lacaz, 1939), several others have been presented in case reports or case series published in the literature. A significant increase was observed from the 1980s onwards, after the rise in HIV/AIDS cases, mainly of the disseminated form, giving histoplasmosis a prominent place among fungal diseases seen in this country (Ferreira and Borges, 2009).

This study revealed a high incidence of histoplasmosis in middle-aged persons and a predominance of the disease among males, factors that were also observed in studies conducted in China, India, and Panama (Gutierrez et al., 2005; Pan et al., 2013; Gupta et al., 2017). The male predominance can be explained by the fact that HIV is more prevalent in males than females in Brazil (Damasceno et al., 2013). Most of the patients covered by this review were infected with HIV; however it is not possible to discount HIV infection in other patients, since this information was missing in several reports. Reports from 1939 to 1979, i.e., before

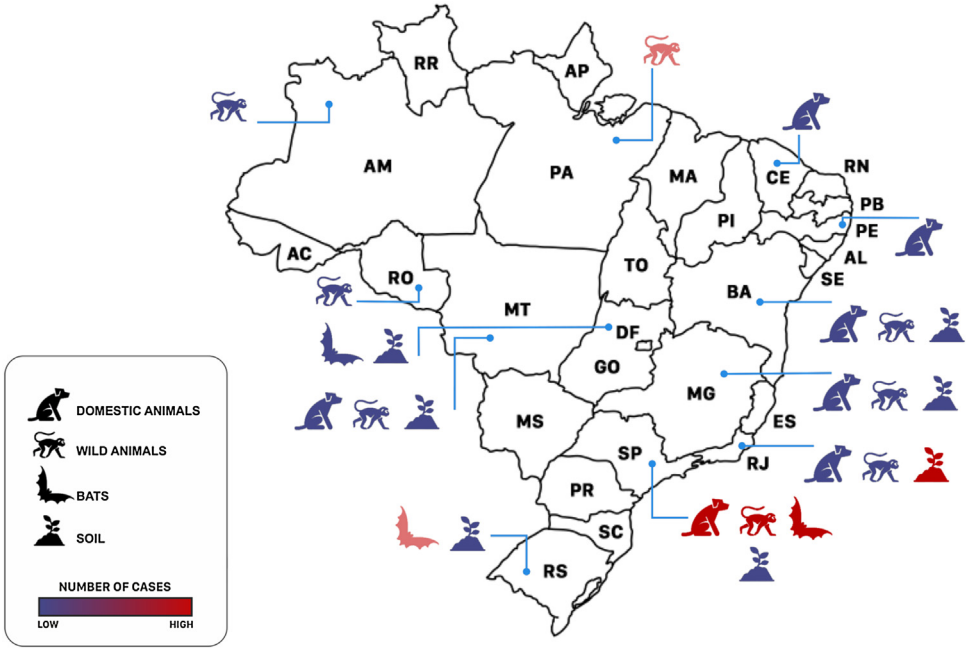

Figure 6. Brazilian sites where environmental detection (from soil and domestic and wild animals) of *Histoplasma capsulatum* has been conducted up until 2018. The overall number of cases in the studied publications is presented in heat map format on the icons representing isolations from domestic animals, wild animals, bats, and soil.

the appearance of HIV, demonstrated a male-to-female ratio of 5:1, while from the 1980s the male-to-female ratio was 4:1.

The finding that almost 80% of the patients presented disseminated forms of histoplasmosis, the most severe form of the disease, is mostly related to individuals with compromised cellular immunity (Wheat et al., 2016). Similar results were found in Colombia and China (Pan et al., 2013; Arango et al., 2011). A factor to take into account regarding the actual ratio of disseminated histoplasmosis is the reporting bias, since the scientific community tends to report the most serious and unusual cases of infectious diseases (Almeida-Silva et al., 2016; Silva-Ferreira et al., 2017). For instance, in this systematic review, several uncommon manifestations of histoplasmosis were detected, such as osteoarticular, urinary, ocular, and heart involvement (Rocha and Severo, 1994; Unis et al., 2004; Chang et al., 2007; Arcieri et al., 2007).

The high rate of HIV-infected patients found in this study is in agreement with data from other Latin American countries (Arango et al., 2011; Vantilcke et al., 2014), Asia (Gupta et al., 2017), and Europe (Antinori et al., 2006), demonstrating the strong relationship between HIV and histoplasmosis co-infection.

In endemic areas, histoplasmosis can be mistaken for tuberculosis during diagnosis, since the clinical manifestations are very similar, and it is not easy to differentiate between the two diseases, especially in patients with AIDS. Sometimes in these endemic areas, histoplasmosis is a primary consideration in HIV-infected patients with suspected tuberculosis (Adenis et al., 2014). In this study, 10.4% of patients were diagnosed with histoplasmosis–tuberculosis co-infection, a value close to that reported in a study from French Guiana in Latin America by Huber et al., which demonstrated an occurrence around 8.0% (Huber et al., 2008). This co-infection has also been described by Gutierrez and colleagues in Panama (Gutierrez et al., 2005), with higher results shown when compared to both of the studies mentioned above. Similarly, over a period of 19 years, 30 HIV-infected patients were diagnosed concomitantly with both TB and histoplasmosis at the Corporación para Investigaciones Biológicas (CIB) in Medellín, Colombia (Agudelo et al., 2012).

The overall mortality rate observed in these Brazilian reported cases, where these data were available, was 33.1%. This mortality rate is higher than those described in previous reviews from China and India (Pan et al., 2013; Gupta et al., 2017), but lower than those observed in a study conducted in French Guiana involving HIV patients (Adenis et al., 2014). It is difficult to differentiate mortality between HIV and non-HIV co-infected patients, because this information is missing for 36.5% of the publications. However, it is interesting to note that the mortality on reports before the description of HIV was 36.6%.

In summary, the methodologies most often employed for the diagnosis of histoplasmosis in Brazil identified in this study were culture, visualization of the fungus by direct and histopathological examination, and double immunodiffusion for antibody detection. In addition to these tests, other diagnostic methods have been developed, including Western blot, indirect ELISA, and PCR assays targeting *H. capsulatum* DNA. However, these latter assays are not commercially available and therefore cannot be included in the routine investigation of histoplasmosis by several clinical laboratories (Scheel and Gómez, 2014).

According to Hage and colleagues (Hage et al., 2011), culture is a key diagnostic investigation tool for patients with disseminated disease, providing better yields of fungal isolation from bone marrow and blood samples, which explains the high number of these clinical specimens in the present study. Additionally, skin biopsies also presented good results in the identification of *H. capsulatum*. Cutaneous histoplasmosis indeed has a higher occurrence in Brazilian patients, in contrast to US patients (Karimi et al., 2002). When it was not possible to isolate and identify the fungus in clinical specimens, the serological tests were useful for the presumptive diagnosis of histoplasmosis.

Histoplasma antigen tests are particularly useful for the diagnosis of disseminated histoplasmosis, especially in people living with HIV/AIDS whose antibody titers are low or absent (Scheel and Gómez, 2014). In Brazil, the diagnosis of histoplasmosis is usually delayed, as *Histoplasma* antigen detection is not available in the clinical routine of hospitals. However, in recent research involving 570 patients in 14 tertiary medical centers in

Brazil, histoplasmosis was identified in 21.6% of the patients. In this study, the overall mortality was 22.1% in 30 days, decreasing to 14.3% in patients with a *Histoplasma* antigen test diagnosis (Falci et al., 2019).

A study performed in Colombia showed that training physicians in the clinical, diagnostic, and epidemiological aspects of histoplasmosis associated with the availability of antigen detection tests significantly increased the number of diagnoses, demonstrating that access to this diagnostic tool could have a positive impact on the diagnosis of this mycosis worldwide (Caceres et al., 2015).

According to previous reviews on epidemiological surveys using histoplasmin skin tests, areas endemic for histoplasmosis were found in the five major regions of Brazil, but with distinct patterns (Colombo et al., 2011; Guimarães et al., 2006). The present study also showed that histoplasmosis cases were reported in the five major regions of Brazil, highlighting the Northeast, Central-West, Southeast, and South regions, with at least 400 cases described in each. The small number of cases reported in the Northern region of Brazil may be related to the lack of diagnosis or misdiagnosis of patients with other infectious diseases such as tuberculosis. In fact, individuals presenting reactivity to the histoplasmin skin test are reported in most Brazilian states, and a high incidence of histoplasmosis is also reported in neighboring countries, such as French Guiana (Vantilcke et al., 2014).

Among the seven Brazilian states for which there are no reports in the scientific literature of human histoplasmosis, five have indirect indications of the presence of *H. capsulatum*. In Alagoas, Amapá, and Rio Grande do Norte, skin tests using histoplasmin revealed 14.0%, 42.2%, and 25.7% reactivity, respectively, demonstrating that the inhabitants of these regions had already had contact with the fungus (Santos and Pedrosa, 1990; Nohmi et al., 1976; Ribeiro, 1978). In the state of Amapá, although a high index of skin test reactivity was observed, no cases of human histoplasmosis or environmental isolation were reported. In Rondônia, besides the isolation and identification by culture of *H. capsulatum* in five wild animals (Naiff et al., 1996), at least 15 persons displayed a positive serological test for histoplasmosis (double immunodiffusion) as performed by our group at the National Reference Laboratory for Systemic Mycoses. In Roraima, we have also diagnosed at least one case of probable histoplasmosis through the detection of antibodies in a serum sample (unpublished data). It is important to take into account that Brazil is a country with a large territorial area, and the lack of access to microbiology facilities in low income areas may hinder the construction of a more accurate map of the actual distribution of histoplasmosis in Brazil.

Reviewing the literature data, different levels of histoplasmin skin test reactivity were observed among individuals in the distinct Brazilian states. Positivity in the skin test with histoplasmin strongly indicates contact with *H. capsulatum*. The high levels of positive skin test found in Brazilian studies are far above the levels of studies conducted in other endemic areas, such as in Asian and African countries (Pan et al., 2013; Bahr et al., 2016; Oladele et al., 2018). However, similar results were found in regions of the USA, where percentages of between 60% and 90% were noted in areas surrounding the Ohio and Mississippi River valleys (Benedict and Mody, 2016). The skin test has been stated to be an important informative test in outbreak investigations (Luby et al., 2005). Individuals with positive results in this test need to be placed under constant observation, since these persons, including immunocompetent individuals, can occasionally present symptomatic infections (Guimarães et al., 2006).

Environmental exposure to nitrogen-rich soil, e.g. the soil of caves mixed with bat guano and exposure to chicken houses or bird roosts, has already been demonstrated to be a risk factor for histoplasmosis in the general populace (Pan et al., 2013; McKinsey et al., 1997). Moreover, residence in a rural area or a history of agriculture-related work could explain the exposure to *H. capsulatum* contaminated soils (Gupta et al., 2017). In this study, reports of soil isolation of *H. capsulatum* were scarce, except in Rio de Janeiro state where the National Reference Laboratory for Systemic Mycoses is located. This reflects the difficulty of isolating the fungus from soil or detecting its DNA in environmental samples (Macêdo et al. (2011). It is possible that with the advances in next-generation sequencing, the detection of *H. capsulatum* from environmental sources will become feasible, as has occurred with other infectious organisms (Pilotte et al., 2016).

Human health, animal health, and the state of the environment characterize the concept of One Health. Several studies have suggested the environment as a determinant source of contamination for various infectious diseases, including histoplasmosis, where individuals may acquire the disease at sites contaminated by the fungus (Dias et al., 2011).

In this review, environmental isolation of *H. capsulatum* from soil was detected in seven Brazilian states. The demonstration of naturally infected wild animals indicates, in the One Health context, the existence of an *H. capsulatum* contaminated soil niche, which points to the environmental presence of *H. capsulatum* in all Brazilian geographic regions. These findings confirm the role of the animals as sentinels of histoplasmosis and suggest that areas with infected animals need a surveillance approach for the endemic form of this disease (Zancopé-Oliveira and Wanke, 1986).

It is important to highlight the isolation of *H. capsulatum* from bats in some Brazilian states. Bats play a significant role in the eco-epidemiology of histoplasmosis, since these animals are considered as long-distance flight migratory animals, and they are therefore very important to the dispersion of the fungus (Dos Santos et al., 2018). Also, in the One Health context, the mapping of potential sources of infection, contaminated areas, and risk and recreational activities in inappropriate areas should be observed in order to reduce the number of cases of human histoplasmosis through education of prevention measures and notification of the population of areas with the presence of *H. capsulatum* (Yeh et al., 2018).

Some limitations were found in this systematic review, since data were missing or extremely scarce for some Brazilian regions, including the North and Northeast. For instance, the state of Ceará, with the largest number of published cases of histoplasmosis, is surrounded by states with few cases or without any case of histoplasmosis described in the literature. These findings could be explained by misdiagnosis or non-published cases of histoplasmosis. The same is seen in the state of Amapá, where there are no published cases, even though it borders French Guiana, a country with a high incidence of histoplasmosis.

Another limitation of this study is the existence of some factors with data constraints, including the accuracy of the diagnostic method used, data on co-infection with tuberculosis, and the final outcome, as well as the precise determination of the area where the *Histoplasma* infection was acquired, since there has been a notable increase in international and national tourism in Brazil.

Lastly, it is highly possible that different methods and reagents used in several studies over the study period included in this review may have interfered with the results obtained. This may explain, for example, the differences in reactivities of the histoplasmin skin test observed in the studies of Wanke14 and Douat and Dias (Douat and Diaz, 1953).

In conclusion, many cases of histoplasmosis have been reported in Brazil. This infection has been demonstrated to be an endemic mycosis in all geographic regions, with emphasis on the Northeast,

Central-West, Southeast, and South regions. The disease has been reported mainly in males between the fourth and fifth decades of life presenting with some immunosuppression factor, particularly HIV infection. The usual reported clinical form of the disease is mainly disseminated, although many cases of pulmonary histoplasmosis may be missed due to asymptomatic or milder symptomatology, being unnoticed and undiagnosed or misdiagnosed. This leads to the speculation that the actual number of histoplasmosis cases is underestimated in Brazil. The histoplasmin skin test and environmental recovery of *H. capsulatum* from animals or soil could be considered as useful tools for a better understanding of the eco-epidemiology of histoplasmosis in Brazil, through knowledge of the natural habitat of *H. capsulatum*. Due to the increase in national and international tourism and outdoor recreation, histoplasmosis is a disease of interest not only to individuals in endemic areas, but also to physicians anywhere whose patients have resided in or travelled to endemic areas in Brazil. Finally, this study represents the first systematic review available to report on the Brazilian cases of histoplasmosis in the literature, and highlights that current knowledge of its distribution is restricted and the disease is more widespread than has previously been thought.

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Conflict of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.07.009.

References

Adenis A, Nacher M, Hanf M, Vantilcke V, Boukhari R, Blachet D, et al. HIV-associated histoplasmosis early mortality and incidence trends: from neglect to priority. PLoS Negl Trop Dis 2014;8:e3100.
Agudelo CA, Restrepo CA, Molina DA, Tobón AM, Kauffman CA, Murillo C, et al. Tuberculosis and histoplasmosis co-infection in AIDS patients. Am J Trop Med Hyg 2012;87(6):1094–8.
Almeida F, Lacaz CS. Cogumelos do gênero *Histoplasma* isolado de lesões de cromomicose. Associações de fungos nas lesões. Folia Clinica et Biológica 1939;11:65–9.
Almeida-Silva F, Damasceno LS, Serna MJ, Valero C, Quintella LP, Almeida-Paes R, et al. Multiple opportunistic fungal infections in an individual with severe HIV disease: a case report. Rev Iberoam Micol 2016;33:118–21.
Antinori S, Magni C, Nebuloni M, Parravicini C, Corbellino M, Sollima S, et al. Histoplasmosis among human immunodeficiency virus-infected people in Europe: report of 4 cases and review of the literature. Medicine (Baltimore) 2006;85:22–36.
Arango M, Castañeda E, Agudelo CI, De Bedout C, Agudelo CA, Tobón A, et al. Histoplasmosis: results of the Colombian national survey, 1992–2008. Biomedica 2011;31:344–56.
Arcieri ES, Rocha A, Mendonça CN, Andreo EG, Finotti IG, Furlanetto RL, et al. Infectious keratitis secondary to *Histoplasma capsulatum*: the first case reports in humans. Braz J Infect Dis 2007;11:595–7.
Azar MM, Hage CA. Laboratory diagnostics for histoplasmosis. J Clin Microbiol 2017;55:1612–20.
Bahr NC, Sarosi GA, Meya DB, Bohjanen PR, Richer SM, Swartzentruber S, et al. Seroprevalence of histoplasmosis in Kampala, Uganda. Med Mycol 2016;54:295–300.
Benedict K, Mody RK. Epidemiology of histoplasmosis outbreaks, United States, 1938–2013. Emerg Infect Dis 2016;22:370–8.
Caceres DH, Zuluaga A, Arango-Bustamante K, De Bedout C, Tobón Á, Restrepo Á, et al. Implementation of a training course increased the diagnosis of histoplasmosis in Colombia. Am J Trop Med Hyg 2015;93(3):662–7.
Chang MR, Taira CL, Paniago AM, Taira DL, Cunha RV, Wanke B. Study of 30 cases of histoplasmosis observed in the Mato Grosso do Sul State, Brazil. Rev Inst Med Trop Sao Paulo 2007;49:37–9.
Colombo AL, Tobón A, Restrepo A, Queiroz-Telles F, Nucci M. Epidemiology of endemic systemic fungal infections in Latin America. Med Mycol 2011;49:785–98.
Cottle LE, Gkrania-Klotsas E, Williams HJ, Brindle HE, Carmichael AJ, Fry G, et al. A multinational outbreak of histoplasmosis following a biology field trip in the Ugandan rainforest. J Travel Med 2013;20:83–7.
Couppié P, Aznar C, Carme B, Nacher M. American histoplasmosis in developing countries with a special focus on patients with HIV: diagnosis, treatment, and prognosis. Curr Opin Infect Dis 2006;19:443–9.
Dasmasceno L, Novaes AJ, Alencar C, Lima D, Sidrim J, Gonçalves M, et al. Disseminated histoplasmosis and aids: relapse and late mortality in endemic area in north-eastern Brazil. Mycoses 2013;56:520–6.
De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;6:1813–21.
Deepe GS, Buesing WR. Deciphering the pathways of death of *Histoplasma capsulatum*-infected macrophages: implications for the immunopathogenesis of early infection. J Immunol 2012;188:334–44.
Dias MA, Oliveira RM, Giudice MC, Netto HM, Jordão LR, Grigorio IM, et al. Isolation of *Histoplasma capsulatum* from bats in the urban area of São Paulo State, Brazil. Epidemiol Infect 2011;139:1642–4.
Dos Santos B, Langoni H, Da Silva RC, Menozzi BD, Bosco SMG, Paiz LM, et al. Molecular detection of *Histoplasma capsulatum* in insectivorous and frugivorous bats in Southeastern Brazil. Med Mycol 2018;56:937–40.
Douat NE, Diaz VM. Intradermoreações de paracoccidioidina, coccidioidina e histoplasmina: Resultados de testes em 300 indivíduos. Rev Bras Tuberculose 1953;26:663–8 [Article in Portuguese].
Falci DR, Monteiro AA, Braz Caurio CF, Magalhães TCO, Xavier MO, Basso RP, et al. Histoplasmosis, an underdiagnosed disease affecting people living with HIV/AIDS in Brazil: results of a multicenter prospective cohort study using both classical mycology tests and histoplasma urine antigen detection. Open Forum Infect Dis 2019;6(4)ofz073.
Ferreira MS, Borges AS. Histoplasmosis. Rev Soc Bras Med Trop 2009;42:192–8.
Giacomazzi J, Baethgen L, Carneiro LC, Millington MA, Denning DW, Colombo AL, et al. The burden of serious human fungal infections in Brazil. Mycoses 2016;59:145–50.
Guimarães AJ, Nosanchuk JD, Zancopé-Oliveira RM. Diagnosis of histoplasmosis. Braz J Microbiol 2006;37:1–13.
Guimarães AJ, Pizzini CV, De Abreu Almeida M, Peralta JM, Nosanchuk JD, Zancopé-Oliveira RM. Evaluation of an enzyme-linked immunosorbent assay using purified, deglycosylated histoplasmin for different clinical manifestations of histoplasmosis. Microbiol Res (Pavia) 2010;1:e2.
Gundacker ND, Rolfe RJ, Rodriguez JM. Infections associated with adventure travel: a systematic review. Travel Med Infect Dis 2017;16:3–10.
Gupta A, Ghosh A, Singh G, Xess I. A twenty-first-century perspective of disseminated histoplasmosis in India: literature review and retrospective analysis of published and unpublished cases at a tertiary care hospital in North India. Mycopathologia 2017;182:1077–93.
Gutierrez ME, Canton A, Sosa N, Puga E, Talavera L. Disseminated histoplasmosis in patients with AIDS in Panama: a review of 104 cases. Clin Infect Dis 2005;40:1199–202.
Hage CA, Ribes JA, Wengenack NL, Baddour LM, Assi M, McKinsey DS, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis 2011;53:448–54.
Huber F, Nacher M, Aznar C, Pierre-Demar M, El Guedj M, Vaz T, et al. AIDS-related *Histoplasma capsulatum* var. *capsulatum* infection: 25 years experience of French Guiana. AIDS 2008;22:1047–53.
Karimi K, Wheat LJ, Connolly P, Cloud G, Hajjeh R, Wheat E, et al. Differences in histoplasmosis in patients with acquired immunodeficiency syndrome in the United States and Brazil. J Infect Dis 2002;186:1655–60.
Kauffman C. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev 2007;20:115–32.
Luby JP, Southern PM, Haley CE, Vahle KL, Munford RS, Haley RW. Recurrent exposure to *Histoplasma capsulatum* in modern air-conditioned buildings. Clin Infect Dis 2005;41:170–6.
Macêdo RC, Rosado AS, Da Mota FF, Cavalcante MA, Eulálio KD, Filho AD, et al. Molecular identification of *Coccidioides* spp. in soil samples from Brazil. BMC Microbiol 2011;11:108.
McKinsey DS, Spiegel RA, Hutwagner L, Stanford J, Driks MR, Brewer J, et al. Prospective study of histoplasmosis in patients infected with human

immunodeficiency virus: incidence, risk factors, and pathophysiology. Clin Infect Dis 1997;24:1195–203.
Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
Naiff RD, Barrett TV, Naiff MF, Ferreira LC, Arias JR. New records of *Histoplasma capsulatum* from wild animals in the Brazilian Amazon. Rev Inst Med Trop Sao Paulo 1996;38:273–7.
Nohmi N, Azevedo DO, Fava-Netto C. Provas intradérmicas com paracoccidioidina e histoplasmina em Macapá, Território Federal do Amapá.12 Congresso da Sociedade Brasileira de Medicina Tropical. Belém – Pará – Brazil: Congresso da Sociedade Brasileira de Medicina Tropical; 1976.
Oladele RO, Toriello C, Ogunsola FT, Ayanlowo OO, Foden P, Fayemiwo AS, et al. Prior subclinical histoplasmosis revealed in Nigeria using histoplasmin skin testing. PLoS One 2018;13:e0196224.
Pan B, Chen M, Pan W, Liao W. Histoplasmosis: a new endemic fungal infection in China? Review and analysis of cases. Mycoses 2013;56:212–21.
Pilotte N, Papaiakovou M, Grant JR, Bierwert LA, Llewellyn S, McCarthy JS, et al. Improved PCR-based detection of soil transmitted helminth infections using a next-generation sequencing approach to assay design. PLoS Negl Trop Dis 2016;10:e0004578.
Prado M, Silva MB, Laurenti R, Travassos LR, Taborda CP. Mortality due to systemic mycoses as a primary cause of death or in association with AIDS in Brazil: a review from 1996 to 2006. Mem Inst Oswaldo Cruz 2009;104:513–21.
Ribeiro MAG. Contribuição para o estudo da histoplasmose e paracoccidioidomicose no Estado do Rio Grande do Norte. Provas intradérmicas com histoplasmina e paracoccidioidina nos municípios de São Paulo do Potengi e Macaiba. Natal – Rio Grande do Norte: Universidade Federal do Rio Grande do Norte; 1978.
Rocha MM, Severo LC. Disseminated histoplasmosis in patients with acquired immunodeficiency syndrome (AIDS). Study of 25 cases. Rev Inst Med Trop Sao Paulo 1994;36:167–70.
Santos MC, Pedrosa CM. Epidemiologic survey with histoplasmin and paracoccidioidine in Arapiraca-Alagoas. Rev Soc Bras Med Trop 1990;23:213–5.
Scheel C, Gómez B. Diagnostic methods for histoplasmosis: focus on endemic countries with variable infrastructure levels. Curr Trop Med Rep 2014;1:129–37.
Silva-Ferreira B, De Araújo Filho JA, Matos Pereira N, De Miranda Godoy L, Borges Lamounier B, Dias-Nunes E, et al. Disseminated histoplasmosis in AIDS patients: an urban disease. Experience in a metropolis in the middle east of Brasil. Infez Med 2017;25:258–62.
Unis G, Oliveira Fe M, Severo LC. Disseminated histoplasmosis in Rio Grande do Sul. Rev Soc Bras Med Trop 2004;37:463–8.
Vantilcke V, Boukhari R, Jolivet A, Vautrin C, Misslin C, Adenis A, et al. Fever in hospitalized HIV-infected patients in Western French Guiana: first think histoplasmosis. Int J STD AIDS 2014;25:656–61.
Wanke B. Histoplasmose. Estudo epidemiológico, clínico e experimental. Thesis. Rio de Janeiro: Faculdade de Medicina da Universidade Federal do Rio de Janeiro; 1985 [In Portuguese].
Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin North Am 2016;30:207–27.
Yeh HY, Chen KH, Chen KT. Environmental determinants of infectious disease transmission: a focus on one health concept. Int J Environ Res Public Health 2018;15:e1183.
Zancopé-Oliveira R, Wanke B. Isolamento do *Histoplasma capsulatum* de animais silvestres no Municipio do Rio de Janeiro. Cad Saude Publica 1986;2:42–52.