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Review

Histoplasmosis: A systematic review to inform the World Health Organization of a fungal priority pathogens list

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Abstract

Histoplasmosis, a significant mycosis primarily prevalent in Africa, North and South America, with emerging reports globally, poses notable health challenges, particularly in immunocompromised individuals such as people living with HIV/AIDS and organ transplant recipients. This systematic review, aimed at informing the World Health Organization's Fungal Priority Pathogens List, critically examines literature from 2011 to 2021 using PubMed and Web of Science, focusing on the incidence, mortality, morbidity, antifungal resistance, preventability, and distribution of *Histoplasma*. We also found a high prevalence (22%–44%) in people living with HIV, with mortality rates ranging from 21% to 53%. Despite limited data, the prevalence of histoplasmosis seems stable, with lower estimates in Europe. Complications such as central nervous system disease, pulmonary issues, and lymphoedema due to granuloma or sclerosis are noted, though their burden remains uncertain. Antifungal susceptibility varies, particularly against fluconazole (MIC: ≥32 mg/l) and caspofungin (MICs: 4–32 mg/l), while resistance to amphotericin B (MIC: 0.125–0.16 mg/l), itraconazole (MICs: 0.004–0.125 mg/l), and voriconazole (MICs: 0.004–0.125 mg/l) remains low. This review identifies critical knowledge gaps, underlining the need for robust, globally representative surveillance systems to better understand and combat this fungal threat.

Key words: *Histoplasma*, histoplasmosis, invasive fungal infection, antifungal resistance, clinical mycology.

Introduction

Histoplasmosis, a common but often underdiagnosed mycosis in Africa, North and South America, is caused by dimorphic fungi in the genus *Histoplasma*. While two varieties of the type species *Histoplasma capsulatum* (i.e., var. *capsulatum* and var. *duboisii*) are reported in the literature, these are not supported by phylogenetic analysis.[1–4] *Histoplasma capsulatum* thrives in damp soil rich in bird excreta or bat guano.[5] Infection

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occurs through inhalation of aerosolized microconidia, especially during activities that disrupt these environments.[3] Both general populations and specific occupational groups in endemic areas are at risk, with increased vulnerability in those with compromised immune systems.[6,7]

Following spore inhalation, the fungus can cause acute pulmonary histoplasmosis.[7,8] For immunocompetent patients, acute pulmonary histoplasmosis typically results in no symptoms or only mild effects, with rare instances of fatal infections.[9] Conversely, this infection can become severe and disseminate in immunocompromised people, notably those with HIV/AIDS,[10] solid organ transplant recipients, or those on immune suppressive drugs such as corticosteroids or TNF-inhibitors, increasing the risk of serious complications.[11–14]

In the United States, between 2002 and 2017, the mortality rate for people living with HIV was about 37%.[1] Studies in Guatemala showed variable mortality rates in newly diagnosed people with HIV.[2] Chronic pulmonary histoplasmosis, which can be confused with tuberculosis, is particularly concerning in HIV/AIDS co-endemic regions, often leading to misdiagnosis, co-infections, and untreated chronic conditions.[9,15–17]

In about 10% of cases, *Histoplasma* can invade the central nervous system (CNS), potentially leading to fatal outcomes if not treated.[18] Diagnosing CNS histoplasmosis is challenging due to subtle symptoms and low sensitivity in fungal cultures of cerebral spinal fluid (CSF). Antigen and antibody tests, when available, aid in diagnosis. However, delayed or inaccurate diagnosis can adversely affect treatment and prognosis. Other rare complications, such as mediastinal fibrosis and lymphadenitis, can cause significant disability.[9]

Diagnosis of histoplasmosis can be challenging, involving fungal culture or tissue histology, processes that are time-consuming and often insensitive.[16,17,19] Antigen detection is a quicker method and particularly useful for disseminated histoplasmosis in people living with HIV. However, access to antigen testing is not fully adequate in all endemic regions. Antibody detection aids in identifying chronic pulmonary histoplasmosis but may be less sensitive in immunocompromised individuals.[20,21]

Treatment options for histoplasmosis are limited and complex. Fluconazole is generally not recommended due to lack of *in vitro* potency and higher failure rates.[22] The preferred treatment for severe cases is a combination of amphotericin B and itraconazole. Amphotericin B is recommended for initial therapy of moderately severe to severe disseminated histoplasmosis, while itraconazole alone can be used in mild cases or patients without HIV.[23,24]

The treatment process is further complicated by the interactions between antifungal and antiretroviral medications, especially in patients with HIV.[24] Itraconazole prophylaxis, coupled with effective antiretroviral therapy (ART), is advised for people with HIV with low CD4 cell counts to reduce the incidence of histoplasmosis in hyper-endemic regions.[25] However, primary prophylaxis is not always feasible in most high-HIV-prevalence regions. Amphotericin B is recommended for initial therapy in moderate-to-severe histoplasmosis in people living with HIV/AIDS.[24] Despite that, the toxicity of amphotericin B (particularly the deoxycholate formulation) and the prolonged duration of treatments that affect patient adherence are still significant clinical challenges.[26–29]

This systematic review summarizes mortality, complications, drug resistance, preventability, incidence, distribution, and emergence of histoplasmosis from 2011 to 2021. The purpose was to inform the World Health Organization Fungal Priority Pathogens List[30] and determine knowledge gaps to guide research efforts.

Materials and methods

Search strategies

We conducted a comprehensive search for studies using the databases of PubMed and Web of Science, covering data from 1 January 2011 to 19 February 2021. Reference lists of included publications were also screened for potentially eligible studies. The resulting publications were subject to the final analysis. Only English-language publications were included. The study was conducted according to PRISMA guidelines.[31]

For PubMed, we used medical subject headings (MeSH) and/or keyword terms in the title/abstract for the pathogen and criterion. The final search used (histoplasma [MeSH terms]) combined using AND term, with criteria terms including (mortality [MeSH terms]) OR (morbidity [MeSH terms]) OR (hospitalisation [MeSH terms]) OR (disability [all fields]) OR (drug resistance, fungal [MeSH terms]) OR (prevention and control [MeSH subheading]) OR (disease transmission, infectious [MeSH terms]) OR (diagnostic [title/abstract]) OR (antifungal agents [MeSH terms]) OR (epidemiology [MeSH terms]) OR (surveillance [title/abstract]).

On Web of Science, MeSH terms are not available, and therefore topic search (TS), title (TI), or abstract (AB) search are used. The final search used [TI=(histoplasma) OR AB=(histoplasma)], combined, using AND term, with criteria terms each as topic search, including (mortality) OR (case fatality) OR (morbidity) OR (hospitali∗ation) OR (disability) OR (drug resistance) OR (prevention and control) OR (disease transmission) OR (diagnostic) OR (antifungal agents) OR (epidemiology) OR (surveillance). Symbol ∗ allows a truncation search for variations of the term (e.g., hospitalisation or hospitalization).

Study selection

We imported search results from each database into the online systematic review software Covidence (Veritas Health Innovation, Australia) and removed duplicates. The inclusion criteria were retrospective and prospective observational studies, randomized controlled trials, epidemiology, and surveillance reports, published from 2011 to 2021, reporting adult and paediatric data, including data on the fungal pathogen, and data on at least one criterion. Guidelines were also reviewed as possible sources of primary studies. Exclusion criteria were studies reporting on non-human data (e.g., animals and plants), no data on relevant pathogens or criteria, case reports, conference abstracts, reviews, information about drugs without marketing authorization, and *in vitro* papers on resistance mechanism. The remaining articles underwent title and abstract screening based on the inclusion criteria. Two independent reviewers (A.D. and H.Y.K.) performed title and abstract screening as well as full text screening for the final eligible articles on Covidence. A third reviewer (J.W.A.) resolved any discrepancies. Excluded articles were recorded with reasons when excluded during full text screening.

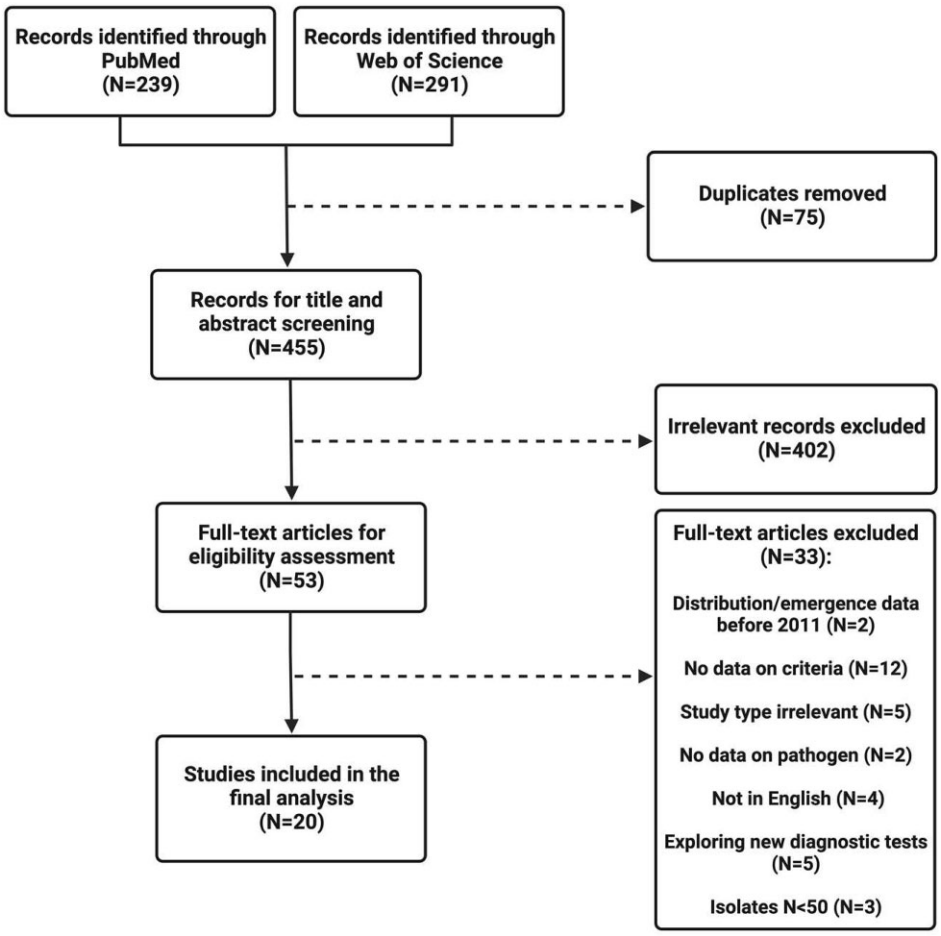


Figure 1. PRISMA flow diagram for selection of studies included in the systematic review.

Data collection and synthesis

The extracted data on the outcome criteria were quantitatively or qualitatively synthesized, depending on the amount and nature of the data. Data from the final included studies were extracted for relevant criteria. The extracted data were checked by another reviewer (initially a 10% check, then expanded to 20% if needed depending on the type of extent of accounted errors).

Risk of bias assessment

We assessed risk of bias for included articles based on relevant bias criteria, depending on the type of data extracted. For randomized trials, we used the risk of bias tool version 2 (ROB 2) to assess the randomized controlled trials.[32] The risk of bias in non-randomized studies (RoBANS) tool was used to assess the non-randomized studies.[33] For the overall risk, using the ROB 2 tool, the studies were rated 'low', 'high', or 'some' concerns. Using the RoBANS tool, the studies were rated as 'low', 'high', or 'unclear' risk. We used each criterion as an outcome of the study and assessed if any bias was expected based on the study design, data collection, or analysis in that study. Studies classified as 'unclear' or 'high' overall risk were still considered for analysis, with due caution and appropriate warnings about the risk and nature of the bias identified. The risk of bias was assessed independently by two reviewers (A.D. and H.Y.K.).

Results

Study selection

PubMed and Web of Science Core Collection databases yielded 239 and 291 articles, respectively. After removing duplicate references, 455 articles underwent title/abstract screening, 53 articles underwent full text screening, and 20 studies were included in the final analysis (Fig. 1).

Risk of bias

Of the included studies, 12 were classified as low risk of bias in all assessed domains; 7 studies were classified as unclear risk of bias, primarily due to selection biases caused by unclear eligibility criteria or population groups or unclear confirmation/consideration of confounding variables; and 1 study was classified as a high risk due to potential bias in the patient population selection (Table 1).

Mortality rates

A total of 15 studies reported mortality rates due to *Histoplasma* infections (Table 2). Mortality rates were predominantly reported for people with HIV/AIDS with histoplasmosis and ranged from 21% to 53%.[34–48] One study involving immunosuppressed patients, including those living with HIV, transplant recipients or patients treated with TNF-α inhibitors, reported a lower mortality rate of 9%.[41] The mortality rate was 11% in solid organ transplant recipients with

Table 1. The risk of bias for each study of *Histoplasma*.

Author	Publication year	Risk of bias
Armstrong et al.	2018	Unclear
Assi et al.	2013	Unclear
Benedict et al.	2020	Unclear
Brilhante et al.	2012	Low
Brilhante et al.	2018	Low
Charalambous et al.	2018	Low
Damasceno-Escoura et al.	2020	High
Faiolla et al.	2013	Low
Falci et al.	2019	Low
Kwizera et al.	2020	Unclear
Luckett et al.	2015	Low
Ouellette et al.	2019	Low
Ozenci et al.	2019	Low
Peigne et al.	2011	Unclear
Putot et al.	2015	Low
Ramos et al.	2018	Low
Rodrigues et al.	2020	Unclear
Samayoa et al.	2017	Low
Vergidis et al.	2015	Low
Wheat et al.	2018	Unclear

histoplasmosis, and the majority (72%) of deaths occurred in the first month after the diagnosis.[35] CNS histoplasmosis mortality was estimated to be 20%–44%.[48] Moreover, patients treated with deoxycholate (81.2%; 13 out of 16) or liposomal amphotericin B (80.8%; 21 out of 26) had a higher 1-year survival rate compared to those treated with amphotericin B lipid complex (56.2%; 9 out of 16).[48] Studies involving various patients with histoplasmosis, including immunocompetent patients, reported mortality rates of 5%–7%.[34,39] One study reported a mortality rate of 2.7% among children with histoplasmosis ($n = 73$).[42]

Antifungal susceptibilities

Only two studies reported on antifungal drug susceptibility data with a sufficient number ($N \geq 50$) of isolates (Table 3). Both studies were single-centre retrospective cohort studies at the tertiary level of care, focusing on people co-infected with HIV and histoplasmosis in Brazil.[37,49] Due to the lack of established clinical breakpoints, studies reported MIC results without calculating resistance rates. The isolates were collected from various body sites. The Clinical and Laboratory Standard Institute (CLSI) broth microdilution method was used to determine the MICs. The mean and modal MICs to fluconazole were high (≥32 mg/l) in both studies.[37,49] The mean or modal MIC for caspofungin was 4 mg/l, with individual isolates up to 32 mg/l. The MICs to itraconazole and voriconazole were low, with mean or mode MICs of 0.0039–0.097 mg/l. For amphotericin B, modal MIC was reported to be 0.125 mg/l.[49]

Annual incidence and global distribution

The annual incidence of *Histoplasma* infections was reported in two studies conducted in the United States and Sweden (Table 4). In the United States, the annual incidence rates were variable between the states, ranging from 0 to 4.3 cases per 100 000 people.[34] The annual incidence rate for Sweden was reported to be 0.01 cases per 100 000 people.[50]

The prevalence of *Histoplasma* spp. as the cause of the disease was mainly available from studies conducted in the United States and Brazil. The prevalence of confirmed *Histoplasma* infection in people living with HIV presenting with infectious symptoms was 22% and 44% in Brazil and the United States, respectively[36,40]; 6% of all fungal meningitis cases were caused by *Histoplasma* spp. in a study from the United States.[51]

Inpatient care and the length of stay in hospital

Three studies in the United States reported on the hospital length of stay (Table 5). A median length of stay of 5 and 7 days was reported in children and adults with histoplasmosis, respectively.[34,42] There was a large variability (IQR 4–138 days) for patients.[34] The average length of stay in the first year of diagnosis was 39 days in patients with *Histoplasma* meningitis.[51]

Complications, sequelae, and disabilities

No data on the prevalence and impact of disability in histoplasmosis was found in the included studies.

Preventability

In eight studies, various risk factors for histoplasmosis were determined (Table 6). Among recipients of solid organ transplants (SOTs), a notable 34% of histoplasmosis cases were diagnosed within the first year post-transplant.[35] Advanced HIV infection with diminished CD4 cell count (≤50–75 cells/μl) and untreated (not only ART-naïve but also interrupted ART) HIV infection are contributing risk factors.[40,45,46]

Demographically, patients with histoplasmosis tend to be younger, male, and have a weakened immune system.[36] A Brazilian study later revealed that acute pulmonary histoplasmosis was more prevalent among younger individuals aged 13–39 years, while chronic pulmonary histoplasmosis was more common in an older demographic of 50–55 years, particularly among smokers and alcohol consumers.[39] Additional risk factors for severe disease included the use of mycophenolate, and the simultaneous use of corticosteroids with TNF-α inhibitors.[47] Despite some studies recommending preventive strategies, there remains a lack of data on their efficacy.

Trends and distribution

Three studies reported on the trends for *Histoplasma* infections in the last decade (Table 7). A stable trend was reported in the United States based on the state-dependent incidence rates of 0–4.3 cases/100 000 between 2011 and 2014,[34] and prevalence rates of 6%–7% over 2000–2012 in patients with fungal meningitis.[51] One retrospective study looking at histology reports in Uganda reported a stable incidence from 0.04/100 000 persons in 2000–2009 to 0.02/100 000 persons in 2010–2019.[52]

Discussion

This systematic review highlights gaps in understanding histoplasmosis, a complex and potentially severe fungal infection. The geographical variability in incidence and potential for adverse outcomes underscores the need for collaborative efforts between stakeholders to expand surveillance and create a comprehensive global picture. Standardizing testing approaches could enhance clinical management and guide therapeutic development.

Table 2. The mortality rates due to *Histoplasma* infections.

Author	Year	Study design		Study period	Country	Level of care	Population description	Number of patients	Mortality type, *N/N*, %
Armstrong et al.[34]	2018	RCS	MC	2011–2014	United States	Various	Patients with histoplasmosis (immunocompromised and immunocompetent) reported from 12 states	3409	76/1142 (6.7%) patients from eight states
Assi et al.[35]	2013	RCS	MC	January 2003–December 2010	United States	Tertiary	Histoplasmosis after solid organ transplant (SOT)	152	17/152 (11%) (72% deaths in the first month after diagnosis)
Benedict et al.[36]	2020	RCS	MC	2012–2014	United States	A range of health services (on the database of insurance claims)	Medical records of patients with probable or suspected *histoplasma*	1935 patients (943 probable, 922 suspected)	In-hospital mortality: 50/1935 (2.6%)
Brilhante et al.[37]	2012	RCS	SC	January 2006–December 2010	Brazil	Tertiary	AIDS patients with histoplasmosis	208	88/208 (42.3%) (69/88, 78.4% of these patients were treated with amphotericin B and 19/88, 21.6% without antifungal therapy)
Damasceno-Escoura et al.[38]	2020	RCS	SC	2005–2018	Brazil	Tertiary	Respective medical and necropsy records of HIV-infected patients with histoplasmosis	36	19/36 (52.8%) patients in total (13 who received antifungal therapy, 6 prior to therapy)
Faiolla et al.[39]	2013	RCS	SC	1970–2012	Brazil	Tertiary	Immunocompetent patients with histoplasmosis	95	5/95 (5.3%) patients with active histoplasmosis
Falci et al.[40]	2019	PCS	MC	October 2016–February 2018	Brazil	Tertiary	Patients with HIV/AIDS with *Histoplasma* urine antigen detection and symptoms	570 (123 histoplasmosis)	30-day mortality: 27/123 (22%)
Luckett et al.[41]	2015	RCS	SC	July 1999–June 2012	United States	Tertiary	Patients with active histoplasmosis and HIV infection, a history of transplantation, or tumour necrosis factor (TNF)-α inhibitor use	90	90-day mortality: 8/90 (9%) in all groups (no significant differences between initial treatment)
Ouellette et al.[42]	2019	RCS	SC	April 2008–April 2014	United States	Tertiary	Children (age 0–18) with histoplasmosis (22% immunocompromised)	73	2/73 (2.7%)
Peigne et al.[43]	2011	RCS	MC	1985–1994 (pre-HAART) & 1997–2006 (HAART era)	France	Various	Adult patients with AIDS-related *H. capsulatum* infections	40 (1985–1994), 64 (1997–2006)	Mortality during HAART era (1997–2006): 22%
Putot et al.[44]	2015	RCS	SC	May 2002–May 2012	French Guiana	Tertiary	HIV patients with disseminated histoplasmosis (DH)	82	Within 1 month of treatment: 10/82 (13%) 1-year mortality: 17/82 (25%)

Table 2. Continued

Author	Year	Study design		Study period	Country	Level of care	Population description	Number of patients	Mortality type, *N/N*, %
Ramos et al.[45]	2018	PCS	SC	January 2006–January 2007	Brazil	Tertiary	Hospitalized AIDS patients with presumptive disseminated histoplasmosis (DH)	117 (48 patients with *H. capsulatum*)	In-hospital mortality in patients with DH: 10/48 (20.8%)
Samayoa et al.[46]	2017	PCS	SC	January 2005–March 2009	Guatemala	Tertiary	HIV/AIDS patients with histoplasmosis	101	Crude overall mortality: 44/101 (44%), 30-day mortality: 25/101 (25%)
Vergidis et al.[47]	2015	RCS	MC	January 2000–June 2011	United States	Tertiary	Patients who developed histoplasmosis as a complication of TNF-α blocker therapy.	98	Mortality at 32 months follow up: 3/95 (3.2%)
Wheat et al.[48]	2018	RCS	MC	1997–2010	United States	Tertiary	Patients with CNS histoplasmosis	77	1-year survival in patients treated with deoxycholate: 13/16 (81.2%), or AMB-L 21/26 (80.8%) vs. amphotericin B lipid complex 9/16 (56.2%), P= .20

MC, multi-centre; PCS, prospective cohort study; RSC, retrospective cohort study; SC, single centre.

Table 3. Drug susceptibility.

Author	MIC determination method	Strains tested (*n*)	Fluconazole	Itraconazole	Voriconazole	Caspofungin	Amphotericin B
Brilhante et al.[37]	CLSI broth microdilution	Filamentous ($n = 68$)	GM: 36.36 Range: 3.9–125	GM: 0.0073 Range: 0.001–0.0312	GM: 0.097 Range: 0.0078–0.5	GM: 3.65 Range: 0.016–32	GM: 0.12 Range: 0.0078–0.5
	CLSI broth microdilution	Yeast ($n = 8$)	GM: 5.52 Range: 3.9–7.8	GM: 0.016 Range: 0.039–0.03	GM: 0.010 Range: 0.002–0.03	GM: 2.0 Range: 1–4	GM: 0.16 Range: 0.06–0.5
Brilhante et al.[49]	CLSI broth microdilution	Filamentous ($n = 138$)	GM: 32 Range: 2 to ≥256)	GM: 0.0039 Range: 0.0005–0.0625	GM: 0.0625 Range: 0.0078–1	GM: 4 Range: 0.0156 to ≤32	GM: 0.125 Range: 0.0078–1
	CLSI broth microdilution	Yeast ($n = 20$)	GM: 8 Range: 1–32	GM: 0.0156 Range: 0.0020–0.0313	GM: 0.0313 Range: 0.0020–0.0625	GM: 2 Range: 0.5–8	GM: 0.125 Range: 0.0156–0.5
Kathuria et al.[63]	CLSI broth microdilution	Filamentous ($n = 23$)	GM: 7.05 Range: 2–32	GM: 0.043 Range: <0.03–0.125	GM: 0.102 Range: <0.03–0.25	GM: 0.097 Range: 0.015–0.5	GM: 0.11 Range: 0.03–0.25
	CLSI broth microdilution	Yeast ($n = 23$)	GM: 4.56 Range: 2–8	GM: 0.051 Range: 0.0.03–0.25	GM: 0.17 Range: 0.03–0.5	GM: 0.17 Range: 0.03–1	GM: 0.13 Range: 0.03–0.5

Note: Susceptibility values are expressed as minimum inhibitory concentrations (MICs) in mg/ml (CLSI). GM, geometric mean. Data are given as provided in source documents.

Table 4. Annual incidence.

Author	Publication year	Study design		Study period	Country	Population description	Number of patients	*N* cases/*N* population
Armstrong et al.[34]	2018	RCS	MC	2011–2014	United States	Patients with histoplasmosis reported from 12 states	3409	Range from 0 to 4.3 cases/100 000 population between the states
Ozenci et al.[50]	2019	RCS	ND	2016	Sweden	Swedish population	9995 153 inhabitants	0.01/100 000 persons

MC, multi-centre; ND, not determined; RSC, retrospective cohort study; SC, single centre.

Table 5. Length of stay.

Author	Publication year	Study design		Study period	Country	Level of care	Population description	Number of patients	Length of stay
Armstrong et al.[34]	2018	RCS	MC	2011–2014	United States	Mixed	Patients with histoplasmosis reported from 12 states	3409	median 7 (IQR 4–138) days ($n = 548$ patients)
Charalambous et al.[51]	2018	RCS	MC	2000–2012	United States	Mixed	Patients diagnosed with fungal meningitis	1927 total (115 histoplasmosis)	Average annual length of stay peaked in the first diagnosis year (39.3 days)
Ouellette et al.[42]	2019	RCS	SC	April 2008–April 2014	United States	Tertiary	Children (age 0–18) with histoplasmosis	73	median 5 (IQR 2–11) days

MC, multi-centre; RSC, retrospective cohort study; SC, single centre.

Table 6. Risk factors for *Histoplasma* infections.

Author	Publication year	Study design		Study period	Country	Level of care	Population description	Number of patients	Risk factors
Assi et al.[35]	2013	RCS	MC	January 2003–December 2010	United States	Tertiary	Solid organ transplant (SOT) recipients with histoplasmosis	152	The first year after SOT: 34% diagnosed in the first year after transplant. Factors for severe disease: mycophenolate: OR 9.41 (95% CI 1.27–66.1)
Benedict et al.[36]	2020	RCS	MC	2012–2014	United States	A range of health services (on the database of insurance claims)	Patients with probable or suspected histoplasmosis	1935 patients (943 probable, 922 suspect)	Probable patients were more likely than suspect patients to be male (51% vs. 45%, $P = .009$), younger (median 55 vs. 58 years, $P < .0001$), and immunocompromised (24% vs. 13%, $P < .0001$)
Faiolla et al.[39]	2013	RCS	SC	1970–2012	Brazil	Tertiary	Immuno-competent patients with histoplasmosis	95	Acute disease more reported in children/younger subjects. Chronic disease more reported in older subjects, smoking, and alcoholism: The average age for acute disease 13–38.5 years old. The average age for chronic disease 50–54.5 years. 79%–85% of patients with chronic disease smoke. 61%–83% of patients with chronic disease drink alcohol.
Falci et al.[40]	2019	PCS	MC	October 2016–February 2018	Brazil	Tertiary	Patients with HIV/AIDS with infectious symptoms	570 (123 histoplasmosis)	Independent risk factors for probable/proven histoplasmosis: CD4+ <50 cells/mm^3 (OR 2.45; 95% CI 1.60–3.78) and being enrolled in a city in the Northeast region of Brazil (OR 2.61; 95% CI 1.53–4.40) Use of antiretroviral at study entry: (OR 0.54; 95% CI 0.34–0.83)

Table 6. Continued

Author	Publication year	Study design		Study period	Country	Level of care	Population description	Number of patients	Risk factors
Luckett et al.[41]	2015	RCS	SC	July 1999–June 2012	United States	Tertiary	Immunosuppressed patients with active histoplasmosis (HIV, transplant, on TNF-α inhibitor)	90	TNF-α inhibitors cause milder disease compared to HIV (27% vs. 2%; $P = .01$).
Ramos et al.[45]	2018	PCS	SC	January 2006–January 2007	Brazil	Tertiary	Hospitalized AIDS patients with presumptive disseminated histoplasmosis (DH)	117 (48 patients with *H. capsulatum*)	Independent risk factors for disseminated histoplasmosis in AIDS patients: hepatomegaly, CD4 count $\leq$ 75 cells/μl, LDH level $\geq 5\times$ the upper limit of normal (ULN), maculopapular/papular rash
Samayoa et al.[46]	2017	PCS	SC	January 2005–March 2009	Guatemala	Tertiary	HIV/AIDS patients with histoplasmosis	101	Lower laboratory markers in patients with histoplasmosis vs. without histoplasmosis at first visit: CD4 T-cell count, median (range): (25 cells/mm^3 (10–57) vs. 45 (18–98); $P = .02$. White blood cell counts (4280 cells/μl vs. 5360; $P = .01$). Platelet count (181 $\times$ 103 cells/μl vs. 284; $P \leq .001$). Haemoglobin levels (9.0 g/dl vs. 10.0; $P = .003$). Haematocrit levels (27.7% vs. 29.2%; $P = .003$).
Vergidis et al.[47]	2015	RCS	MC	January 2000–June 2011	United States	Tertiary	Patients who developed histoplasmosis as a complication of TNF-α blocker therapy.	98	Independent predictors of disease severity: concomitant corticosteroid: OR 3.94 (95% CI 1.06–14.60) Higher urine antigen: 1.14 (1.03–1.25)

MC, multi-centre; PCS, prospective cohort study; RSC, retrospective cohort study; SC, single centre.

Table 7. Distribution and trends.

Author	Publication year	Study design		Study period	Country	Level of care	Population description	Number of patients	Prevalence	Trends
Armstrong et al.[34]	2018	RCS	MC	2011–2014	United States	ND	Patients with histoplasmosis reported from 12 states	3409	ND	Stable (2011–2014)
Benedict et al.[36]	2020	RCS	MC	2012–2014	United States	A range of health services (on the database of insurance claims)	Patients with probable or suspected histoplasma	1935 patients (943 probable, 922 suspect)	855/1935 (44%) resided in the East North Central Census Division	ND
Charalambous et al.[51]	2018	RCS	MC	2000–2012	United States	ND	Patients diagnosed with fungal meningitis	1927 total (115 histoplasmosis)	6% histoplasmosis over the study period (6.9% in 2012)	Stable (2000–2012)
Falci et al.[40]	2019	PCS	MC	October 2016–February 2018	Brazil	Tertiary	Patients with HIV/AIDS with infectious symptoms.	570 (123 histoplasmosis)	123/570 (21.6%) probable/proven histoplasmosis	ND
Kwizera et al.[52]	2020	RCS	SC	January 1950–September 2019	Uganda	Tertiary	Patients with deep fungal infections	697	2010–2019: Decade incidence 0.02/100 000 persons: (based on 8 histoplasma/51 deep fungal infections)	Decreased from previous decade 2000–2009 (decade incidence 0.04/100 000 persons) (based on 12 histoplasma/138 deep fungal infections)
Rodrigues et al.[66]	2020	RCS	MC	2011–2015	Brazil	ND	Patients with histoplasmosis	ND	Brazil has nine highly diverse genetic groups of Histoplasma (LAm C, LAm B, BrHC1 most common) Emerging genotype LAm C: major lineage causing histoplasmosis in HIV patients in Brazil	ND

MC, multi-centre; ND, not determined; PCS, prospective cohort study; RSC, retrospective cohort study; SC, single centre.

The mortality rates of histoplasmosis are predominantly reported in people living with HIV (21%–53%), while lower rates (<10%) have been found for other immunosuppressed patients. Mortality in CNS histoplasmosis was 20%–44%. In a small paediatric study, the rate was 2.7%. These are consistent with non-English papers reporting 22%–23% mortality.[53,54]

Population-based incidence data were only available from the United States and Sweden. Data from endemic areas like Latin America and Africa were lacking, though histoplasmosis is likely underestimated. A recent Guatemalan study found 7.4% HIV-associated incidence, exceeding prior estimates.[15,55] Histoplasmosis appears underdiagnosed in Africa, often obscured by tuberculosis.[56,57] Antigen testing would aid in the diagnosis of disseminated HIV-associated disease in Africa, but expanding its access across the continent and simplifying the available test formats should be prioritized.[58]

Histoplasmosis is an emerging concern for solid organ transplant recipients.[13,59,60] However, data on these patients in endemic areas is limited, meaning risk factors, diagnosis, management, and outcomes require further investigations.

We also found limited hospitalization data. The short hospital stays reported may not reflect the recommended treatment duration,[8,61,62] potentially underestimating hospitalization or early mortality. One explanation for the short duration of hospitalization is that other treatment regimens were concurrently administered. Alternatively, patients had lethal outcomes shortly after hospitalization. We also found no data quantifying histoplasmosis disability, although complications such as CNS disease can cause disability.[9,18] Therefore, it is imperative to conduct further investigations in endemic regions.

Two studies reported elevated fluconazole and caspofungin MICs but lower itraconazole/voriconazole/amphotericin B MICs.[37,49] However, treatment history was unclear, preventing assessment of prior drug exposure effects on MICs. One excluded study from India tested the antifungal susceptibility profiles of 23 *H. capsulatum* strains from pulmonary and disseminated histoplasmosis patients.[63] It showed that posaconazole and isavuconazole exhibited antifungal activity similar to voriconazole and itraconazole (also summarized in Table 3). However, no MIC data for posaconazole and isavuconazole were shown in any of the included studies. Standardized susceptibility testing is still required, especially for dimorphic fungi such as *Histoplasma*.[63,64]

Regarding preventability, immunosuppression and younger ages were associated with histoplasmosis.[6,39,40] Advanced HIV disease is an independent risk factor, so prompt diagnosis and earlier treatment may reduce mortality.[23,55] Although not captured in our search window, a double-blinded prospective randomized trial including 149 participants with advanced HIV disease showed that itraconazole significantly delayed the time to onset of histoplasmosis.[65]

This systematic review has several strengths, including duplicate searches, multiple databases, adherence to PRISMA guidelines, and risk of bias assessment. These strengths increase the reliability and quality of our findings.

However, a notable limitation in the reviewed literature is the inconsistent reporting on the distinctions between disseminated and non-disseminated histoplasmosis, as well as the specific antifungal treatments employed. This lack of detailed clinical data hampers a nuanced understanding of how disease presentation and treatment choices influence mortality risks associated with histoplasmosis. Future studies should aim for more detailed reporting on these aspects to enable a deeper analysis of the factors affecting patient outcomes.

Moreover, only literature from 2011 to 2021 was included, and the restriction to English-language publications potentially omits valuable research published in other languages, limiting the review's comprehensiveness. Also, the exclusion of grey literature, encompassing unpublished or non-peer-reviewed studies, may further constrain the scope of our findings.

Broadening the search parameters beyond the 2011–2021 timeframe could provide insights into the historical trajectory and long-term impacts of histoplasmosis. However, our search period was chosen so that our review could reflect the recent data and trends to assess the future direction. Including historical data may be beneficial in some aspects, as mentioned; however, it may not allow the accurate assessment of the current situation to guide us in decision-making for research as well as public action taken.

Nonetheless, this systematic review highlights the gaps in our understanding of histoplasmosis. Given the geographical variability of histoplasmosis and its potential for severe outcomes, there is a compelling need for collaborative efforts between researchers, clinicians, and public health authorities. It is critical to expand surveillance efforts beyond regions to create a more comprehensive picture of the global burden of histoplasmosis. Additionally, efforts to standardize antifungal susceptibility testing methods, particularly for the yeast forms of dimorphic fungi, could greatly enhance the clinical management of infections and guide the development of new therapeutic strategies.

Future research directions should also encompass a comprehensive assessment of disability and quality of life impact on individuals recovering from histoplasmosis. Additionally, the exploration of pathogen genomics, host-pathogen interactions, genetic susceptibility factors, and the dynamics of *Histoplasma* transmission in different regions could provide critical insights into disease prevention and management strategies.

Conclusions

This systematic review highlights the limited studies on histoplasmosis, emphasizing the need to determine its geographic distribution and clinical impact. Advancements in diagnostic techniques, including broader access to antigen tests with point-of-care testing, are essential for prompt diagnosis and treatment. The review identifies a significant gap in the data on antifungal susceptibility and treatment approaches. Future studies should clarify the case definition and distinguish between disseminated and non-disseminated histoplasmosis when reporting cases. There is a pressing need for research into preventive measures, especially for patients with advanced HIV disease, who are at particularly high risk. Enhancing diagnostic methods, including access to testing, developing therapeutic solutions, and exploring preventive strategies, is critical to effectively manage histoplasmosis.

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Author contributions

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Conflict of interest

The authors report no conflicts of interest.

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