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Review article

Histoplasma capsulatum var *duboisii* infection: A global review, 1950–2021

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ABSTRACT

Background: Most of the study reviews on *Histoplasma capsulatum* var *duboisii* (Hcd) infection have been limited to case reports from few African countries despite having cases reported outside Africa. We aimed at providing an update on the global epidemiology of histoplasmosis caused by Hcd, its diagnostic challenges and recommendations for improved diagnosis.

Materials and methods: We conducted a retrospective review of case reports and case series on Hcd infection published "between 1st January 1950 to 31st December 2021" using PubMed, Google Scholar and African Journals Online. The following search terms: "African histoplasmosis" and "*Histoplasma duboisii*" AND/OR "diagnosis of African histoplasmosis" were used. Publications on histoplasmosis caused by *H. capsulatum* var. *capsulatum* (Hcc) were excluded. Data extracted from each case included: age, gender, disease type (single organ vs. disseminated disease), sites of infection, clinical features, HIV status, diagnostic tests, treatment, and patient outcome.

Results: We identified 415 cases of Hcd infection reported globally (1950 – 2021); 359 (86.5%) cases from Africa, while 56 (13.5%) were from other geographical regions. Hcd infection was misdiagnosed as other clinical entities including tuberculosis, malignancies, osteomyelitis, neurofibromatosis, and cystic lesions. Out of the 415 cases, diagnostic modality was specified in 307 (74%) cases, with histopathology (n=270, 87.9%) as the predominant diagnostic method followed by culture (n=59, 19.2%).

Conclusion: Like classical histoplasmosis, the clinical presentation of Hcd infection mimics other diseases, hence a high index of suspicion by the attending clinician would be invaluable in making a prompt diagnosis and invariably improve clinical outcomes. In addition, there is a need to build capacity in molecular diagnostics and antigen assay specific for detecting Hcd infection as classical diagnostic methods have been proven to be inadequate.

Introduction

Histoplasmosis is a serious fungal disease that occurs worldwide. It is caused by the dimorphic fungus, *Histoplasma capsulatum.* The two varieties pathogenic to humans are *H. capsulatum* var. *capsulatum* (Hcc) and *H. capsulatum* var. *duboisii* (Hcd) [1]. Histoplasmosis cause by Hcd is endemic in Africa. Case reports of Hcd infection have also been documented outside Africa usually attributed to travelling or visits to sub–Saharan Africa [2,3]. It

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is commonly called African histoplasmosis which is a misnomer as both varieties (Hcc and Hcd) have been described in Africa [1]. The pathogenesis of Hcd infection is yet unclear. It can be acquired via inhalation of microconidia or by direct inoculation. Hcd infection commonly presents with papules, nodules, ulcers, lymph node enlargement, eczematoid or psoriasiform skin lesions [2,3]. Subcutaneous abscesses may also develop with discharging sinuses containing yeast cells of the fungus. Although it is generally believed to be acquired through inhalation, the lungs are usually spared. Disseminated forms are usually characterized by the involvement of bones and other organs including the gastrointestinal tract [1–3]. As a result of limited availability of diagnostics, data on its prevalence and epidemiology are sparse in literature. Most of the review studies on histoplasmosis caused by Hcd have been on reported cases documented in selected African countries, despite cases reported from other regions of the globe [3-5]. Data on the occurrence of Hcd infection outside Africa is rarely described. In addition, the review studies on Hcd infection from Africa documented the detection of Hcd mainly by histopathology, which is unreliable in making a proven diagnosis [6]. This can lead to false negatives with eventual misdiagnosis and poor clinical outcomes [6]. Our review aims to address these gaps with an update on the current global epidemiology of Hcd infection using reported cases and case series documented around the globe over the past seven decades. We also highlight challenges impeding the diagnosis of Hcd infection and make recommendations on the way forward.

Methods

Study design

We conducted a retrospective review of cases and case series on Hcd infection published "between 1st January 1950 and 31st December 2021".

Data collection

The following search terms: "African histoplasmosis" and "*Histoplasma duboisii*" AND/OR "diagnosis of African histoplasmosis" was used to identify publications on African histoplasmosis using PubMed, Google Scholar and African Journals Online data bases. Data extracted from each case included: age, gender, disease type (single organ vs. disseminated disease), sites of infection, clinical features, HIV status, diagnostic tests, treatment, and patient outcome.

Inclusion criteria

Publications on histoplasmosis caused by Hcd.

Exclusion criteria

1.Publications on histoplasmosis caused by Hcc. 2. Publications on studies involving histoplasmosis in non-humans. 3.Publications without location of diagnosis.

Statistical analysis

The relationship between positive HIV status and fatal outcomes was analysed using the $\chi 2$ test. A p value of <0.5 was considered statistically significant.

Results

Our extensive literature search identified 415 cases of Hcd infection documented globally. Of the 415, 359 (86.5%) cases were from Africa while 56 (13.5%) cases were from other geographical regions including Europe and the Americas. Figure 1 summarises various locations around the globe were Hcd infection has been reported with the highest number of cases reported from Nigeria (n=117, 28.2%). Mapping was based on the number of Hcd infection diagnosed in various locations and does not necessarily imply where Hcd histoplasmosis exists in nature as most of the reported cases were deemed to be imported from Africa. Full list of references for all 415 case reports represented in the map are as documented in Appendix (1).

Of the 415, only 307 (74%) were included in the analyses of cases in this review. The remainder were excluded as the full texts were not available. Of the 307 cases, gender was specified in only 237 (77.2%), with males consisting 62% (n=147). We could not calculate the median age as age was not stated in 12 case reports. Besides some were case series with age represented as a range. 78 (25.4%) were HIV positive. No statistically significant relationship was observed when comparing the relationship between positive HIV status and fatal outcomes ($p > 0.05$, $\chi 2$ test).

The affected sites were skin (n = 178, 58.0%), lymph nodes (n = 57, 18.6%), bones (n = 100, 32.6%), subcutaneous tissues (n = 23, 7.5%), liver (n = 11, 3.6%), spleen (n = 11, 3.6%), lungs (n = 10, 3.3%), central nervous system (n = 6, 2.0%), mucosa (n = 15, 4.9%), ganglions (n = 3, 1.0%), colon (n = 1, 0.3%), tongue (n = 1, 0.3%), adrenal gland (n = 1, 0.3%), eyes (n = 4, 1.3%), tonsils (n =

1, 0.3%), peritoneum (n = 1, 0.3%) and pericardium (n = 1, 0.3%).

Diagnosis was done by histopathology (n=270, 87.9%), culture (n=59, 19.2%), microscopy/direct examination (n=27, 8.8%), serology (n = 7, 2.3%), cytology (n = 1, 0.3%), polymerase chain reaction (n = 43, 14.1%) and immunohistochemistry (n = 12, 3.9%). The clinical features and diagnosis of the included 307 cases are summarized in supplementary table 1.

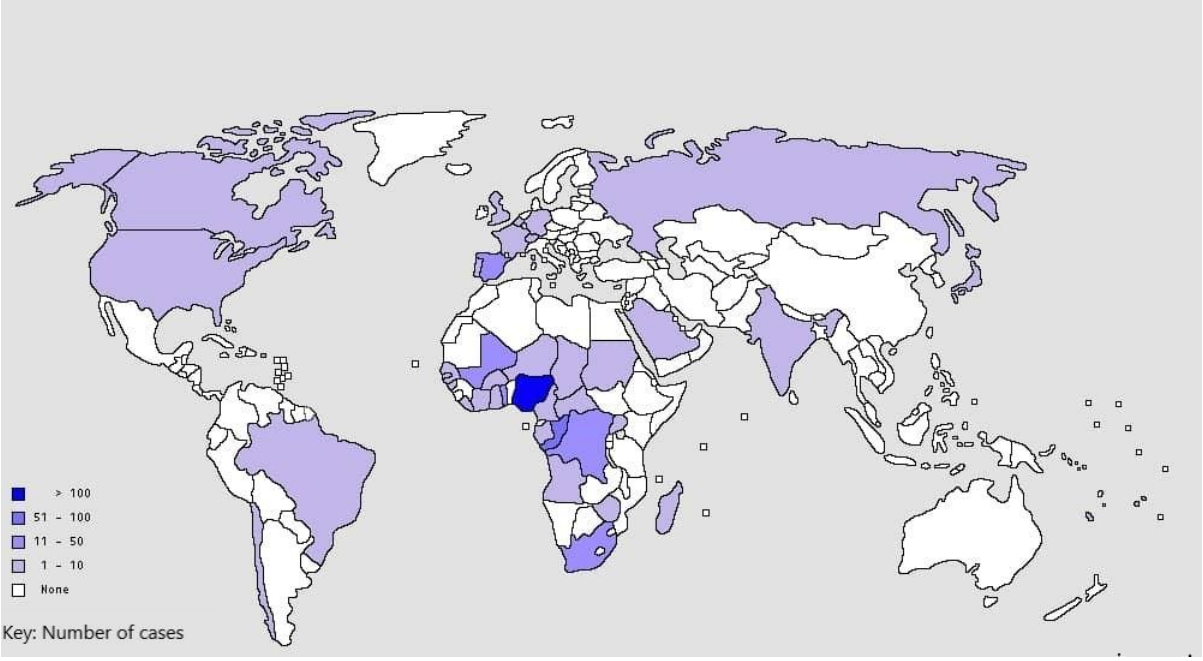
Of the 307 case reports, treatment modality was stated in 129 (42.1%) and were antifungal therapy (n = 123) and surgery (n = 15). Other less common methods included the use of iodine (n = 1), and sulfamethoxazole and trimethoprim (n = 2). Amphotericin B (n = 75) was predominantly used, followed by itraconazole (n = 42) and ketoconazole (n = 31). Others were fluconazole (n = 7) and econazole (n = 1). 94 (72.9%) had favourable outcomes, 19 (14.7%) died, 2 (1.6%) were lost to follow up, 7 (5.4%) relapsed and outcome unclear in the remainder. Of the 94 with favourable outcomes, eighteen (19.1%) received combination therapy with amphotericin B and azoles, 1 (1.06%) received liposomal amphotericin B and azoles, 30 (31.9%) received azole monotherapy, 30 (31.9%) received amphotericin B alone, 2 (2.1%) received sulfamethoxazole and trimethoprim, 1 (1.06%) received terbinafine, 3 (3.2%) had surgeries alone, while 6 (6.4%) had surgeries and also received azole therapy (Table 1).

Table 1. Summary of treatment and outcomes.

Treatment	Number of cases	Outcome					References
		F	R	L	D	NS	
AmB + Azoles	28	18	1	-	7	2	2,4,7-19
AmB alone	38	30	1	-	5	2	2,4,14,20-36
[a]LAmB + Azoles	3	1	2	-	-	-	37-38
AmB + Terbinafine	1	-	-	-	-	1	39
Terbinafine	1	1	-	-	-	-	40
ABLC	1	1	-	-	-	-	2
Surgery + Azoles	8	6	-	-	2	-	41-44
Surgery + Azole + AmB	2	1	-	-	1		45-46
Surgery alone	3	3	-	-	-	-	30, 47,48
Azole monotherapy	39	30	3	-	4	2	2,8,10,17,30,36,49-71
Iodine	1	-	-	1	-	-	7
Septrin	2	2	-	-	-	-	72
AmB + Rifampin	2	1	-	1	-	-	73
Total	129	94	7	2	19	7	

F; Favourable, R; Relapsed, L; Lost to follow up, D; Death, NS; Not stated, AmB; Amphotericin B, LAmB; Liposomal Amphotericin B, ABLC; Amphotericin B lipid complex. [a] of the three, two also had surgeries.

Figure 1. Locations around the globe with documented cases of Hcd infection.



Discussion

Although the occurrence of Hcd infection is largely attributed to Africa, several cases have been reported outside Africa including indigenous case reports [69,74,75]. This is corroborated in an earlier review by Antinori et al. and Develoux et al. which also confirmed significant number of Hcd infection cases reported outside Africa [74,75]. Our review demonstrates the occurrence of Hcd infection as a worldwide disease entity contrary to the previous opinion that all cases are contracted from Africa. In addition, some of the patients who developed histoplasmosis after returning from travel to Africa presented with symptoms several decades after leaving the endemic area [61-65]. Although, this may be due to the reactivation of latent infections due to immunocompromise from underlying conditions, it does not fully explain why these cases were said to be contracted from Africa because a significant proportion of them were not reported to be immunocompromised. Further study is required to ascertain whether these cases were imported from Africa or autochthonous cases in areas previously considered to be non-endemic.

As documented in previous reviews, the clinical presentation of Hcd infection in the cases highlighted in this review were predominantly cutaneous [supplementary table 1]. However, like classical histoplasmosis, Hcd infection also mimics several clinical entities including tuberculosis and malignancies [11,25,26]. Osteolytic lesions from Hcd infection may compress the spinal cord, resulting in paraplegia, which is a typical presentation of Pott's disease [76]. In addition, the clinical and radiological findings due to bone involvement in Hcd infection can also mimic neoplasms. Patients commonly present with tender painful swelling, osteoarthritis, generalized lymphadenopathy and the involvement of internal organs. The awareness of this possibility from the outset is very important in determining the clinical outcome of an index patient [25,26,76]. This is further buttressed by the cases reported by Mace, Akinyoola et al. and Shoroye et al. whose patients were initially thought to be cases of malignancies but later revealed by further investigations to be histoplasmosis caused by Hcd [25,26,77]. Coinfection with Hcd and *Mycobacterium tuberculosis* (TB) has also been reported [11]. The need for a thorough investigation of suspected TB patients for other close mimics such as histoplasmosis caused by Hcd is advised [78,79]. Goncalves et al. reported a 12-year-old boy with a 2-year history of multiple nodular formations in cervical, axillary, and inguinal regions associated

with cutaneous fistulas previously managed as a case of lymphoma. Subsequent investigations were TB (gastric aspirate PCR and culture) positive and Hcd infection established on cervical nodular biopsy. The patient was started on a 6-month course of anti-tuberculous therapy and also received antifungal therapy with favourable outcome [11].

The diagnosis of African histoplasmosis remains a challenge for several reasons: (1) it has several, very common differential diagnoses as already stated; (2) inadequate awareness by healthcare practitioners leading to underdiagnoses as it may not be suspected; (3) insufficient access to laboratory diagnostics.

Definitive diagnosis involves the laboratory demonstration of evidence of the fungi. The commonest laboratory approach relied on for the detection of Hcd infection remains via histopathology [75]. However, the morphological appearance of the yeast cells resembles other endemic mycoses such as blastomycosis and emergomycosis. In addition, recent advances in molecular diagnosis of African histoplasmosis have shown this classical identification method to have significant flaws [6]. In a retrospective study from Spain involving thirteen patients, the fungus was detected by histopathological examination in only 36% (4/11) of tested cases, which were all positive by qPCR [6]. Authors opined that classical identification methods based on measurement of yeast size may not be sufficient in distinguishing between Hcd and Hcc [6]. Molecular analysis plays a major role in confidently discriminating between the two species [6].

Culture remains the gold-standard but is only occasionally positive and largely unavailable in many African countries [80]. This raises concerns about classifying some cases as possible or probable. Additionally, despite the evolution of antigen testing in classical histoplasmosis, the pattern is yet to be realized in Hcd infection. The role of the previously evaluated and recommended *Histoplasma* antigen detection assays and the newly introduced ones are yet to be extensively deployed in the diagnosis of Hcd infection. Moreover, the current antigen detection assays are not specie-specific and in Africa where both Hcc and Hcd abound, it is possible for one to be misdiagnosed as the other. It is thus possible that some cases of Hcd infection included in the present study may have been classical histoplasmosis or other endemic mycosis. This is because diagnosis had relied on histopathology or antigen detection which have questionable specificity [1,4,6,81].

To better appreciate the burden of Hcd infection on a continent, high-performing species-specific biomarkers are required in the form of rapid diagnostic tests [82]. This is particularly important because, many cases are reported among people dwelling in rural areas, where this point of care test kits can easily be employed. It is important to note that, although sporadic use of contemporary testing procedures such as galactomannan testing have been reported, prospective evaluation studies are presently lacking [83].

The Infectious Diseases Society of America (IDSA) recommends the lipid formulation of amphotericin B followed by itraconazole for the treatment of severe or disseminated forms of histoplasmosis [84]. The deoxycholate formulation (94.7%, 71/75) was predominantly used for treatment contrary to the IDSA guidelines which recommends it as an alternative to its lipid formulation in patients at low risk for nephrotoxicity, (Table 1). This is not unconnected with the poor availability and accessibility to appropriate antifungal drugs and the high cost of these medications in Africa and other resource-limited settings. The preponderance of favourable outcomes with azole monotherapy suggests a likelihood of mild to moderate clinical presentation in most of the cases highlighted, (Supplementary table 1). In addition, it further emphasizes the importance of the use of azoles in the management of patients who fail standard therapy [11,84]. The factors associated with fatal outcomes included sepsis, delayed presentation and diagnosis, non-compliance with HAART regimen and complications from HIV infection. This is yet indicative of the various challenges limiting the successful management of invasive fungal infections globally and in Africa in particular. Clinical outcomes can be improved by taking steps to address these problems.

Conclusion

Besides cases reported in Africa, autochthonous cases of Hcd infections have been reported from other geographical regions. In addition, some of the patients with a travel history presented with symptoms several decades after leaving the endemic area. Further study is required to ascertain whether these cases were imported from Africa or autochthonous cases in areas previously believed to be non-endemic. African histoplasmosis

also mimics other clinical entities including TB and neoplasms. More awareness and a high index of suspicion on the part of clinicians will lead to early diagnosis and invariably improve clinical outcomes. As per diagnosis, although culture is the gold standard for diagnosis, histopathology is the commonest method used due to the previously narrated reasons. This is of great concern because diagnosis of Hcd infection using histopathology has been shown to have significant false negative outcomes which can lead to misdiagnosis or underdiagnosis of Hcd infections and poor clinical outcomes. There is a dire need to build capacity and infrastructure towards improved diagnosis especially by antigen assay and molecular detection. Treatment with a combination of amphotericin B and azoles or azole monotherapy in mild to moderate infections give good clinical outcomes.

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

B.E.E.; Conceptualization, Data curation, Formal analysis, Methodology, Resources, Validation, and Writing—original draft, review, and editing. A.A.D.; Data curation, Resources, and Writing—review and editing. B.K.O.; Resources, and Writing—review and editing. N.R.H.S.; Resources, and Writing—review and editing. R.O.O.; Conceptualization, Resources, and Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Supplementary Table 1: Clinical summary and demographics of 307 cases of Hcd infection (1950–2021).

S/No.	Authors	Sex	Age (Months/Years)	Country/Location	HIV Status	Affected Sites	Diagnostic Techniques
				Southern Africa			
1	Marjolet et al., 1984	-	-	S. Afr	-	Lungs	Culture
2	Marjolet et al., 1984	-	-	S. Afr	-	Skin	Histopathology
3	Murphy et al., 2015	M	36	S. Afr	+	Skin, liver, spleen, LN	Histopathology
4	Murphy et al., 2015	M	35	S. Afr	+	Skin, tongue, nasal septum	Histopathology
5	Murphy et al., 2015	M	45	S. Afr	+	LN, liver, spleen	Histopathology
6	# Khathali et al., 2021	M = 14 F = 10	36.5	S. Afr	+ (*n* = 24)	Skin (*n* = 24)	Histopathology (*n* = 24), Culture (*n* = 8), PCR (*n* = 24)
				Western Africa			
7	Khalil et al., 1999	M	9	Nigeria	-	Bones	Histopathology
8	Khalil et al., 1999	F	38	Nigeria	-	Skin	Histopathology
9	Khalil et al., 1999	M	35	Nigeria	-	Skin	Histopathology
10	Khalil et al., 1999	M	14	Nigeria	-	LN	Histopathology
11	Katchy et al., 2019	M	9	Nigeria	-	Bones	Histopathology
12	Adekeye et al., 1988	M	14	Nigeria	-	Bones	Histopathology
13	Akinosi et al., 1970	F	25	Nigeria	-	Mucosa, bones	Histopathology
14	Olurin et al., 1969	F	6	Nigeria	-	Eyes, LN	Histopathology
15	Bansal et al., 1977	M	20	Nigeria	-	Eyes	Histopathology
16	Daramola et al., 1979	F	19	Nigeria	-	Bones, mucosa	Histopathology
17	Akpuaka et al., 1998	M	6	Nigeria	-	Skin	Histopathology
18	Akpuaka et al., 1998	M	11	Nigeria	-	Skin	Histopathology
19	Onwuasoigwe et al., 1998	F	30	Nigeria	-	Bones, LN	Histopathology, Culture
20	Onwuasoigwe et al.,1999	M	10	Nigeria	-	Skin, LN	Histopathology
21	Khalil et al., 1989	F	56	Nigeria	-	Colon	Histopathology
22	¥ Mace et al., 1978	M	14	Nigeria	-	Mucosa	Histopathology
23	¥ Shoroye et al., 1982	M	13	Nigeria	-	Skin, bones, liver, spleen	Histopathology
24	¥ Akinyoola et al., 2006	F	23	Nigeria	-	Skin, bones	Histopathology

25	Ige et al., 1992	-	-	Nigeria	-	Bones	Histopathology
26	Olasoji et al., 1999	-	56	Nigeria	-	Skin	Histopathology, Culture
27	Egere et al., 1978	-	-	Nigeria	-	Skin	Culture
28	Egere et al., 1978	-	-	Nigeria	-	Skin, LN, lungs	Culture
29	Ajabor et al., 1971	F	28	Nigeria	-	Skin, subcutaneous	Histopathology
30	Ajabor et al., 1971	F	25	Nigeria	-	Skin, subcutaneous, Liver	Culture
31	Ajabor et al., 1971	F	25	Nigeria	-	Skin, subcutaneous, Liver	Histopathology, culture
32	Loulergue et al., 2007	M	30	Nigeria	+	Skin lesions, LN	Histopathology, culture
33	Loulergue et al., 2007	F	50	Nigeria	+	Skin, bones	Histopathology
34	Lucas, 1970	n=52	10 months–65 years	Nigeria	-	Skin (*n* = 36), bones (*n* = 43), subcutaneous (*n* = 17)	Histopathology (*n* = 52)
35	Adekunle et al., 1978	-	-	Nigeria	-	Jejunum	Histopathology
36	Olatoke et al., 2003	F	50	Nigeria	+	Bone	Histopathology
37	Seleye-Fubara et al 2011	M	62	Nigeria	-	Bone	Histopathology
38	Onuigbo et. al., 1976	M	11	Nigeria	-	Skin	Histopathology
39	Onuigbo et. al., 1976	F	15	Nigeria	-	Skin	Histopathology
40	Onuigbo et. al., 1976	M	12	Nigeria	-	Skin	Histopathology
41	Onuigbo et. al., 1976	M	7	Nigeria	-	Skin	Histopathology
42	Onuigbo et. al., 1976	M	44	Nigeria	-	LN	Histopathology
43	Onuigbo et. al., 1976	M	12	Nigeria	-	Bone	Histopathology
44	Iseh et al., 2003	F	44	Nigeria	-	Sinuses, Eyes	Histopathology
45	Asamoa et al., 1990	M	13	Nigeria	-	Mandible	Histopathology
46	Jacyk et al, 1981	F	35	Nigeria	-	Skin	Culture
47	Jacyk et al, 1981	M	22	Nigeria	-	Skin, bones, mucosa	Histopathology
48	Khalil et al, 1998	M	9	Nigeria	-	Bone	Histopathology
49	Khalil et al, 1998	F	38	Nigeria	-	Skin	Histopathology
50	Khalil et al, 1998	M	35	Nigeria	-	Skin	Histopathology
51	Khalil et al, 1998	M	14	Nigeria	-	LN	Histopathology
52	Loulergue et al., 2007	F	31	Cameroon	+	Bones	Histopathology, culture
53	Loulergue et al., 2007	M	29	Liberia	+	Skin	Histopathology, culture
54	Mabey et al., 1989	F	4	Gambia	-	Skin, bones	Histopathology
55	Mabey et al., 1989	F	5	Gambia	-	LN	Histopathology
56	Mabey et al., 1989	M	10	Gambia	-	Skin	Histopathology
57	Mabey et al., 1989	M	50	Gambia	-	Skin	Histopathology
58	Mabey et al., 1989	F	37	Gambia	-	Skin	Histopathology
59	Thompson et al., 1980	F	4	Gambia	-	Bones	Histopathology
60	þ Goncalves et al., 20	M	12	Guinea-Bissau	-	LN	Histopathology, culture
61	Loulergue et al., 2007	F	43	Guinea-Bissau	+	-	Histopathology
62	α Cipriano et al., 2020	M	30	Guinea-Bissau	+	Skin, LN	Histopathology
63	Moraes et al 1997	M	17	Guinea-Bissau	-	Skin, bone	Culture, direct examination
64	Moraes et al 1997	M	15	Guinea-Bissau	-	Skin, bone	Culture, direct examination
65	Giacomini et al 1993	M	61	Niger	-	Adrenal gland	Direct examination

66	Sanguino et al 1996	M	46	Guinea-Bissau	-	Digestive tract	Histopathology
67	Konan et al., 2020	F	42	Ivory Coast	+	CNS	Histopathology
68	Bankolé et al., 1998	M	6	Ivory Coast	-	Skin, bones	Histopathology
69	Ahogo et al., 2009	-	-	Ivory Coast	-	Skin	Histopathology
70	Loulergue et al., 2007	M	30	Ivory Coast	+	LN	Histopathology
71	Arlet et al., 2004	M	27	Mali	-	LN	Histopathology
72	Minta et al., 2014	M	6	Mali	-	Bones, skin, mucosa, LN	Microscopy
73	Minta et al., 2014	M	40	Mali	-	Subcutaneous, bones	Culture
74	Minta et al., 2014	M	30	Mali	-	Bones	Culture
75	Minta et al., 2014	M	22	Mali	-	Bones	Culture
76	Minta et al., 2014	F	22	Mali	-	Subcutaneous, bones, lungs	Culture
77	Minta et al., 2014	F	65	Mali	-	Bones, lungs	Culture
78	Minta et al., 2014	F	35	Mali	-	Bones	Culture
79	Minta et al., 2005	M	19	Mali	-	LN	Direct examination
80	Oka et al., 2001	-	40	Mali	-	Spinal cord	Histopathology
81	Oka et al., 2001	-	47	Mali	-	Spinal cord	Histopathology
82	Darre et al., 2020	M	27	Togo	-	Skin, LN	Histopathology
83	Darre et al., 2017	M = 11, F = 6	27.2	Togo	+ (*n* = 3), - (*n* = 14)	Skin (*n* = 7), mucosa (*n* = 3), bones (*n* = 2), ganglion (*n* = 3)	Histopathology (*n* = 17), culture (*n* = 5), microscopy (*n* = 5)
84	Diadie et al., 2018	M	22	Senegal	-	Skin, LN, Liver, Spleen	Histopathology
85	Zida et al., 2015	F	22	Burkina Faso	-	Skin, LN	Culture
86	Barro/Traore et al., 2013	-	8	Burkina Faso	-	Skin, LN, bones	Histopathology
87	Delclaux et al., 1992	-	-	Burkina Faso	-	LN, Lung, Liver	Histopathology
88	Quedraogo et al.,2021	M	27	Burkina Faso	-	Skin, liver, spleen, subcutaneous lesions, LN, peritoneum, pericardium	Microscopy
89	Martin et al., 2020	F	36	Ghana	-	Skin, LN, subcutaneous nodules	Histopathology
				Central Africa			
90	Arendt et al.,1991	M	65	DRC	+	Liver, spleen, LN, Bones, lungs	Histopathology
91	Carme et al., 1992	-	26	CB	+	Skin, LN, Spleen, Liver	Histopathology
92	Tsiodras et al., 2012	M	66	DRC	-	Skin	Histopathology, PCR
93	⁎ Pakasa et al., 2018	M = 13 F = 23	20.5	DRC	- (*n* = 36)	Skin (*n* = 7), LN (*n* = 5), bones (*n* = 7)	Histopathology (*n* = 36), immunohistochemistry (*n* = 12), RT-PCR (*n* = 3)
94	Loulergue et al., 2007	M	65	DRC	+	-	Histopathology, culture
95	Loulergue et al., 2007	M	28	DRC	+	Skin, LN, bones	Histopathology, culture
96	Loulergue et al., 2007	M	38	DRC	+	LN	Histopathology, culture
97	Geffray et al 1994	F	32	DRC	-	Skin, bone	Direct examination, histopathology
98	Geffray et al., 1994	M	50	DRC	-	Skin, lymph nodes, bone, digestive tract	Direct examination, histopathology
99	Geffray et al., 1994	M	30	DRC	-	Skin	Direct examination, histopathology
100	Geffray et al., 1994	M	28	DRC	-	Skin	Direct examination, histopathology, culture
101	Garcia-Guiñon et al., 2009	F	10	Chad	-	Skin, LN	Microscopy, serology
102	N'Golet et al., 2005	M	17	CB	-	Bones	Histopathology

103	Therby et al., 2006	F	33	CB	+	Skin	Culture, Microscopy, serology
104	Ngatse-Oko et al., 2006	F	60	CB	-	Skin, Bones	Histopathology
105	Chandenier et al., 1995	M	4	CB	-	Skin, Bones, LN	Histopathology
106	Chandenier et al., 1995	F	20	CB	+	Skin	Histopathology
107	Chandenier et al., 1995	M	44	CB	+	Skin	Histopathology
108	Chandenier et al., 1995	M	45	CB	-	Skin	Histopathology
109	Chandenier et al., 1995	M	41	CB	+	Skin	Histopathology
110	Chandenier et al., 1995	M	32	CB	+	Skin, Bones	Histopathology
111	Babela et al., 2017	F	9	CB	-	Skin	Cytology
112	Babela et al., 2017	M	4	CB	-	Bones	Histopathology
113	Babela et al., 2017	M	3	CB	-	Skin	Histopathology
114	Boukassa et al., 2019	F	30	CB	-	Skin	Microscopy, histopathology
115	Boukassa et al., 2019	F	29	CB	-	Skin	Microscopy
116	Boukassa et al., 2019	M	60	CB	-	Skin, lung	Microscopy, histopathology
117	Boukassa et al., 2019	M	52	CB	-	Skin, lung	Microscopy, histopathology
118	Boukassa et al., 2019	M	34	CB	-	Skin, lung	Microscopy
119	Loulergue et al., 2007	F	20	CB	+	Skin	Histopathology
120	Loulergue et al., 2007	M	44	CB	+	Skin	Histopathology
121	Loulergue et al., 2007	M	41	CB	+	Skin, hepatomegaly, splenomegaly	Histopathology
122	Loulergue et al., 2007	M	26	CB	+	LN	Histopathology
123	Carme et al., 1993	M	44	CB	-	Skin	Histopathology
124	Carme et al., 1993	F	66	CB	-	Skin	Histopathology
125	Carme et al., 1993	M	36	CB	-	Skin, mucosa	Histopathology
126	Carme et al., 1993	F	13	CB	-	Mucosa, bone	Histopathology
127	Carme et al., 1993	M	25	CB	-	Skin	Histopathology
128	Carme et al., 1993	M	45	CB	-	Skin	Histopathology
129	Carme et al., 1993	F	26	CB	-	Skin	Histopathology
130	Carme et al., 1993	M	27	CB	-	Skin	Histopathology
131	Carme et al., 1993	F	1.5	CB	-	Skin, bone, eye	Histopathology
132	Carme et al., 1993	M	13	CB	-	Skin, bone	Histopathology
133	Carme et al., 1993	M	17	CB	-	Skin	Histopathology
134	Carme et al., 1993	M	17	CB	-	Skin, mucosa	Histopathology
135	Carme et al., 1993	M	26	CB	+	Skin	Histopathology
136	Carme et al., 1993	M	50	CB	-	Skin	Histopathology
137	Simon et al., 1994	-	28	CAR		Bones, skin, LN	Histopathology
				Eastern Africa			
138	Gumbo et al., 2011	-	-	Zimbabwe	+	Skin	Histopathology
139	§ Musoke et al., 2001	F	39	Uganda	-	Skin, Bones	Histopathology
140	Lanceley et al., 1961	M	10	Uganda	-	Skin, Bones, LN	Microscopy
141	Rakotoarivelo et al., 2010	M	39	Madagascar	-	LN	Histopathology, Microscopy, serology
				Northern Africa			
142	Gumaa' et al., 1988	-	25	Sudan	-	Skin	Histopathology, culture
				Europe			
143	[a] Cardoso et al., 2017	M	68	Portugal	-	Tonsils, LN	Culture, PCR
144	[b] Velho et al., 1998	M	45	Portugal	-	Skin	Histopathology

145	Sanguino et al., 1996	-	-	Portugal	-	Mucosa	Histopathology
146	[c] Vanbreuseghem et al., 1953	-	-	Belgium	-	LN	Histopathology, microscopy, Culture
147	[d] Richaud et al., 2014	M	60	France	-	Lungs	Histopathology
148	[e] Rivron et al., 1988	F	43	UK	-	LN	Histopathology
149	[f] Duncan et al., 1958	M	63	UK		Skin	Histopathology
150	[g] Paccoud et al., 2020	M	47	France	-	CNS	Histopathology
151	[h] Régnier-Rosencher et al., 2014	F	60	France	+	Skin	Histopathology, culture
152	[i] Pellaton et al., 2009	M	32	Switzerland	+	Skin, LN	Microscopy, histopathology, PCR
153	* Eichmann et al., 1996	M	38	Switzerland	+	Skin	Culture, microscopy
154	* Hasse et al., 2003	M	30	Switzerland	+	Skin, LN, Splenomegaly	Histopathology
155	* Macowiak et al 2003	M	30	Switzerland	+	Skin, bone, LN, Splenomegaly	Histopathology
156	* Breton et al., 2006	F	20	France	+	Skin, CNS	Histopathology, culture
157	* Breton et al., 2006	M	41	France	+	Skin, LN	Histopathology, culture
158	* Breton et al., 2006	M	56	France	+	LN	Histopathology, culture
159	* Breton et al., 2006	M	34	France	+	GIT, Meninges	Histopathology
160	Loulergue et al., 2007	M	37	France	+	LN	Histopathology
161	Loulergue et al., 2007	M	41	France	+	Skin, LN	Culture
162	Loulergue et al., 2007	F	2	France	+	Skin, bones	Histopathology, Culture
163	Fritzsche et al., 2009	F	-	Germany	+	Mucosa	Histopathology, serology, PCR
164	ƹ Valero et al., 2018	M = 10 F = 3	47	Spain	+ (*n* = 10), - (*n* = 3)	Mucosa (*n* = 1), skin (*n* = 2), LN (*n* = 3)	Histopathology (*n* = 4), Culture (*n* = 7), PCR (*n* = 11), serology (*n* = 3)
				South America			
165	[j] Oddo et al., 1990	M	30	Chile	-	LN	Histopathology
166	[k] Abrucioneto et al., 1993	M	30	Brazil	-	Skin	Histopathology, culture
				North America			
167	[l] Shore et al.,1981	F	34	USA	-	Skin	Culture, Histopathology
168	[m] Nethercott et al., 1977	M	24	Canada	-	Skin, LN	Histopathology
				Asia			
169	ᏼ Ravindran et al., 2015	M	39	India	-	Skin	Histopathology, culture
170	[n] Murata et al., 2007	M	45	Japan	+	Lungs, liver, spleen, bones	Microscopy (Blood smear), PCR

¥; African histoplasmosis masquerading as malignancies, þ; Hcd and *Mycobacterium tuberculosis* coinfection, §; African histoplasmosis misdiagnosed as tuberculous spondylitis, α; African histoplasmosis misdiagnosed as disseminated tuberculosis, ᏼ; an autochthonous case, *; cases reported in Europe in indigenes of Liberia, Nigeria, Ivory Coast, Congo, French Guyana and Surinam, #; a case series with clinicopathological features of *H. duboisii* infections. All the patients were HIV positive, ⊀; a case series of Hcd histoplasmosis confirmed by histopathology, immunohistochemistry, and reverse transcription PCR. All patients were HIV negative. ƹ; a case series of African histoplasmosis reported in Spain, [a]; African histoplasmosis in an immunocompetent Portuguese host 45 years later after living 3 years in Africa, [b]; Caucasian male resident in Portugal following two years military service in Guinea Bissau, [c]; Hcd histoplasmosis reported in a Belgian who had lived 6 years in Belgian Congo, [d]; Hcd histoplasmosis reported in France in a Portuguese who visited Guinea-Bissau 40 years ago where he lived for 2 years, [e]; Hcd histoplasmosis reported in UK in a Caucasian female following a 2-month holiday in the Gambia, [f]; Hcd histoplasmosis reported in UK in an English man who had worked as a mining engineer for 6 years in Ghana, [g]; Hcd histoplasmosis reported in France in an indigene of Congo Brazzaville, [h]; Hcd histoplasmosis reported in France in a French woman 18 years after her last stay in West and Central Africa (Mali, Ivory Coast, Cameroon, Burundi and Rwanda), [i]; Hcd histoplasmosis reported in Switzerland in an indigene of Conakry, Guinea, [j]; Hcd histoplasmosis reported in Chile in a French man who had lived in Ivory Coast and west Africa, [k]; Hcd histoplasmosis reported in Brazil in an indigene of Angola, [l]; Hcd histoplasmosis reported in Maryland woman who had been in Zaire 6 years earlier, [m]; Hcd histoplasmosis reported in Canada in an immigrant 40 years after he lived in Guinea-Bissau for 2 years, [n]; Disseminated histoplasmosis in a Ghanian resident in Japan, CAR; Central African Republic, DRC; Democratic Republic of Congo, CB; Congo Brazzaville

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