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Original Article

Cryptococcosis—a systematic review to inform the World Health Organization Fungal Priority Pathogens List

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Abstract

Cryptococcosis causes a high burden of disease worldwide. This systematic review summarizes the literature on *Cryptococcus neoformans* and *C. gattii* infections to inform the World Health Organization's first Fungal Priority Pathogen List. PubMed and Web of Science were used to identify studies reporting on annual incidence, mortality, morbidity, antifungal resistance, preventability, and distribution/emergence in the past 10 years. Mortality rates due to *C. neoformans* were 41%–61%. Complications included acute renal impairment, raised intracranial pressure needing shunts, and blindness. There was moderate evidence of reduced susceptibility (MIC range 16–32 mg/l) of *C. neoformans* to fluconazole, itraconazole, ketoconazole, voriconazole, and amphotericin B. *Cryptococcus gattii* infections comprised 11%–33% of all cases of invasive cryptococcosis globally. The mortality rates were 10%–23% for central nervous system (CNS) and pulmonary infections, and ~43% for bloodstream infections. Complications described included neurological sequelae (17%–27% in *C. gattii* infections) and immune reconstitution inflammatory syndrome. MICs were generally low for amphotericin B (MICs: 0.25–0.5 mg/l), 5-flucytosine (MIC range: 0.5–2 mg/l), itraconazole, posaconazole, and voriconazole (MIC range: 0.06–0.5 mg/l). There is a need for increased surveillance of disease phenotype and outcome, long-term disability, and drug susceptibility to inform robust estimates of disease burden.

Key words: *Cryptococcus neoformans*, *Cryptococcus gattii*, cryptococcosis, cryptococcal meningitis, invasive fungal infection.

Introduction

Invasive fungal infections pose a significant threat to global health. Although their burden is ill-defined, crude estimates suggest they cause over 1.6 million deaths annually.[1] The absence of strong surveillance systems results in clinicians making decisions based on limited information about local epidemiology, antimicrobial resistance, and effective treatment strategies. In response to this growing threat, the World Health Organization (WHO) developed a Fungal Priority Pathogens List (FPPL). This list, published in 2022, was created through a comprehensive international consultation process, using a survey incorporating a discrete choice experiment. The individual fungal pathogens, including *Cryptococcus neoformans* and *C. gattii*, were ranked based on the results of systematic reviews, expert opinion, and data from the discrete choice experiments.

Cryptococcosis is a life-threatening invasive fungal infection, that poses a significant global health challenge. Historically, *Cryptococcus* was described as two species: *C. neoformans* (var. *grubii* and var. *neoformans*) and *C. gattii*. More recently, phylogenetic analyses have distinguished seven clades representing species (VNI-III and VGI-IV), and there are likely

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more, with varying virulence and regional distribution.[2,3] For example, VGI is prevalent in Australia and Asia, VGII is particularly associated with the emergence in North America, VGIII is increasing among immunocompromised individuals in the United States, and VGIV is primarily found in Africa.[3–5] Notably, the terminology of two cryptococcal 'species complexes' remains common in clinical practice as it is the most practicable for management purposes.

Cryptococcosis is best documented in people living with HIV/AIDS. However, it is increasingly recognized in other immunocompromised hosts, and occurs in people with various underlying conditions and even unrecognized risk factors.[6–8] Members of the *C. neoformans* and *C. gattii* species complexes are the predominant causative agents,[9] with species-specific differences in epidemiology: for example, *C. neoformans* species complex has traditionally been observed in HIV/AIDS patients, whilst *C. gattii* species complex infection has a propensity to occur in immunocompetent patients.[10]

Innate and adaptive responses work together to combat *Cryptococcus* spp., with CD4 + T-cells particularly important for an effective adaptive response.[11,12] Symptomatic infection often indicates a compromised immune system, particularly in individuals with reduced CD4 + T-cell counts, such as people living with HIV.[13–15] Latency and dormancy are also important aspects of cryptococcal pathogenesis. The fungus can remain dormant in the host due to both immune pressure and fungal factors,[16–19] and in certain host environments, including granulomas, it can avoid immune detection.[19] Reactivation of dormant cryptococci becomes a concern when the host's immune system becomes compromised, potentially leading to invasive disease.[20] Improving our understanding of these and other factors is crucial for improving diagnostic, therapeutic, and preventive strategies.[21]

Cryptococcus neoformans and *C. gattii* species complexes are acquired via the respiratory tract, where they can cause local infection, although it is their tropism for the central nervous system (CNS) that is associated with the most serious manifestations of infection. Cryptococcal meningitis (CM) remains the most common cause of fungal meningitis worldwide with over 220 000 new cases and 180 000 deaths per annum.[22] Consequently, CM is an infection of global relevance, with most deaths seen in sub-Saharan Africa and in South and Southeast Asia.[23–25]

Treatment options for invasive cryptococcosis are limited, and development of novel anti-cryptococcal agents has been slow in recent decades.[26] Cryptococci are intrinsically resistant to echinocandins.[27] Optimal induction treatment relies on amphotericin B and 5-flucytoscine despite their substantial toxicity and limited access associated with economic and logistical constraints. Prolonged treatment with azoles is required following induction therapy.[28]

In low- and middle-income countries (LMICs) where disease burden is highest, poor access to optimal therapeutics (i.e., 5-flucytosine and amphotericin B lipid formulations) increases the clinical challenges and contributes to the observed persistent poor clinical outcomes of cryptococcosis.[29]

This systematic review evaluates *C. neoformans* and *C. gattii* species complexe infections against a set of criteria, namely: mortality, hospitalization and disability, antifungal drug resistance, preventability, yearly incidence, global distribution, and emergence, based on data published between 2011 and 2021. The purpose is to determine knowledge gaps for both *C. neoformans* and *C. gattii* species complexes in the above areas to highlight research needs and to inform the WHO FPPL.

Materials and methods

Search strategies

We conducted a comprehensive search for studies published in English using the PubMed and Web of Science databases. These databases were chosen due to their extensive coverage of medical and scientific literature. The study was conducted according to PRISMA guidelines.[30] All searches were limited to the last 10 years (from 1st January 2011 to 19th February 2021).

On PubMed, we used medical subject headings (MeSH) and/or keyword terms in the title/abstract for each pathogen and criterion.

For *C. neoformans*, the final search used (*C. neoformans*[Title] OR *C. neoformans*[Title]) combined; for *C. gattii*, the final search used (*C. gattii* [MeSH Terms]) combined, using AND term, with criteria terms including (mortality[MeSH Terms]) OR (morbidity[MeSH Terms]) OR (hospitalization[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 were used. The final search used [TI=('cryptococcus neoformans/cryptococcus gattii') OR TI=('C. neoformans') OR AB=('cryptococcus gattii')], combined using AND term with criteria terms each as topic search, including (mortality) OR (case fatality) OR (morbidity) OR (hospitalization) 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., hospitalization 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/prospective observational studies, randomized controlled trials, guidelines, epidemiology, surveillance reports, published within the last 10 years (2011–2021), reporting adults and paediatric data, including data on the fungal pathogen, and data on at least one criterion. Exclusion criteria were studies reporting on non-human data (e.g., animals, plants) or non-fungal data (e.g., bacteria), no data on relevant pathogens or criteria, case reports, conferences, abstracts, reviews, papers on drugs without marketing authorization, *in vitro* papers on resistance mechanisms, and papers published in non-English language. Identified articles underwent title and abstract screening based on the inclusion criteria. No reason was provided for exclusion during title and abstract screening. Two independent reviewers (AD and HYK) performed full text screening for the final eligible

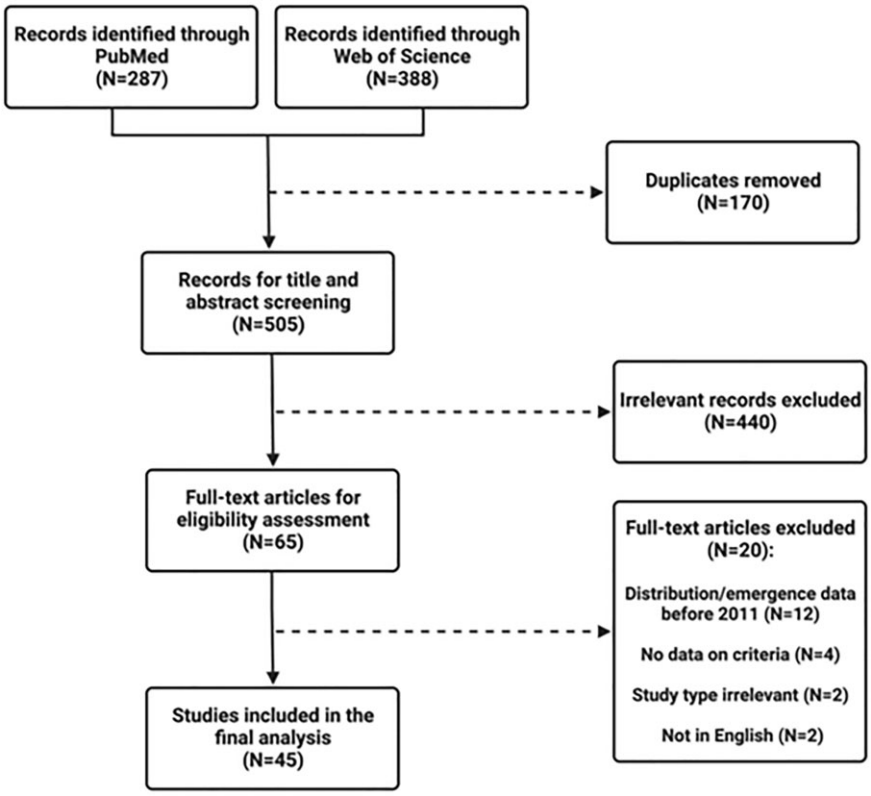

Figure 1. Flow diagram for selection of studies included in the systematic review for *C. neoformans*.

articles on Covidence®. A third reviewer resolved any discrepancies (JWA). Excluded articles were recorded with reasons when excluded during full text screening. If there were any additional articles identified from references of the included articles, these were added. The resulting articles were subject to the final analysis.

Data collection and synthesis

Data from the final included studies were extracted for relevant criteria (AD and HYK). The extracted data were checked by the second reviewer (JWA) (initially 10% check, then expanded to 20% and more if needed, depending on the type of extent of observed errors). The extracted data on the outcome criteria were qualitatively AND/OR quantitatively synthesized, depending on the amount and nature of the data.

Risk of bias assessment

We assessed risk of bias using the risk of bias tool for randomized trials version 2 (ROB 2) tool for randomized controlled trials.[31] The risk of bias in non-randomized studies (RoBANS) tool was used to assess the non-randomized studies.[32] For the overall risk, using 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.

For the purposes of this review, we considered each criterion as an outcome of the study and assessed if any bias was expected based on the study design, data collection, and analysis methods for that outcome. Studies that were classified as having an unclear or high overall risk were still eligible for inclusion with cautious interpretation.

Results

Study selection

For *C. neoformans*, PubMed and Web of Science Core Collection databases searched between 1 January 2011 and 19 February 2021 yielded 287 and 388 articles, respectively (Fig. 1). For *C. gattii*, the search yielded 219 and 277 articles, respectively (Fig. 2). A total of 45 (*C. neoformans*) and 14 (*C. gattii*) articles were included in the final analysis.

Risk of bias

For *C. neoformans*, the overall risk of bias for each study is presented in the Table 1A. Of the included studies, 22 studies were classified as low risk of bias in all domains assessed. Twenty-three studies were classified as unclear risk of bias, mostly due to the potential selection biases caused by unclear eligibility criteria or population groups, or unclear confirmation/consideration of confounding variables.

For *C. gattii*, the overall risk of bias for each study is presented in the Table 1B. Of the 14 studies, 5 studies were classified as low risk of bias in all domains assessed. Nine studies were classified as unclear risk of bias, mostly due to the selection biases caused by unclear eligibility criteria or population groups, or unclear confirmation/consideration of confounding variables.

Mortality rates

For *C. neoformans*, 13 studies reported on mortality (Table 2). The mortality rates due to *C. neoformans* were reported to be as high as 41%–61% for patients with HIV in-

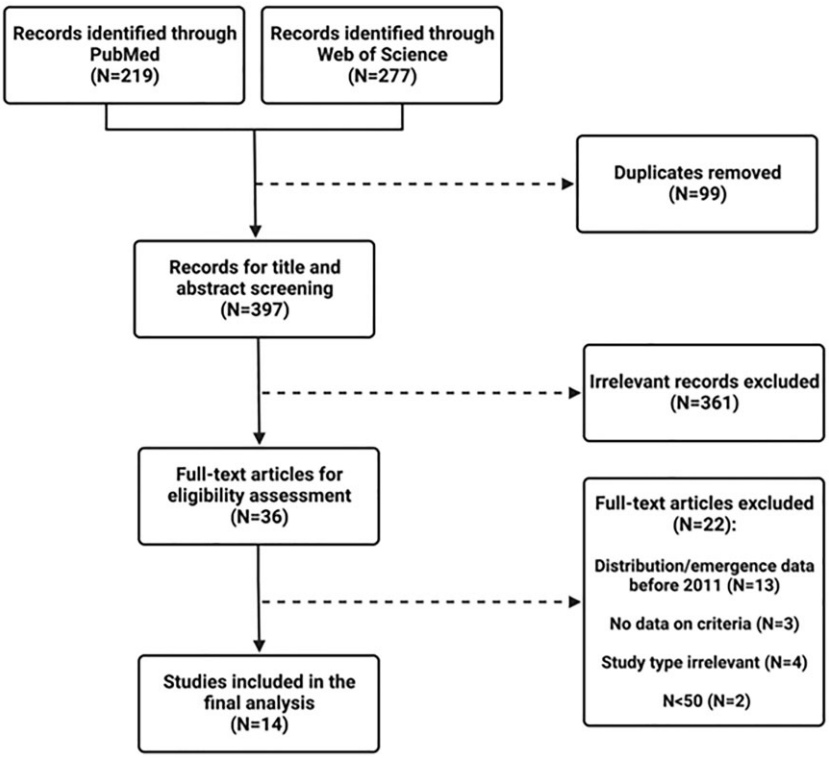

Figure 2. Flow diagram for selection of studies included in the systematic review for *C. gattii*.

fection.[37, 63, 64, 69, 73] Mortality rates specifically reported for HIV-negative patients were lower, ranging from 8% to 20%, but small patient numbers are noted ($N = 12–44$).[63,40,77]

For *C. gattii*, four studies reported on mortality (Table 2). The mortality rate due to *C. gattii*-related bloodstream infection was 43% ($N = 7$) in the study by Smith et al.[85] Other studies reported mortality rates of 10%–23.4% for CNS infections[78, 79, 84, 85] and 14.6%–21% for pulmonary infections, acknowledging the relatively small cohorts.[85,84]

Antifungal susceptibilities

In total, 33 studies reported results of antifungal susceptibility testing on *C. neoformans* isolates (Table 3), and 6 studies for *C. gattii* (Table 4); methodologies included CLSI standard, EUCAST standard, Etest, Vitek 2 YST AST, and Sensititre YeastOne assays. Details of these studies are presented in the appendix (Tables A1 and A2).

Cryptococcus neoformans susceptibility to antifungals

Before 2020, when EUCAST has provided a CBP for amphotericin B only, there were no interpretative clinical breakpoint (CBP) MICs for *C. neoformans*. It is also noteworthy that no causal relationship has been established between MIC and treatment failure.[86] Consequently, interpretive criteria applied to antifungal MIC results for *C. neoformans* in the reviewed publications were highly variable both within and between publications. Examples of interpretive criteria included utilizing *C. albicans* CBPs, or breakpoints suggested with user manuals provided with testing kits, CLSI epidemiologic cutoff values (ECVs), and values selected from previous scientific publications.

Reported susceptibility of *C. neoformans* to fluconazole was variable, with two studies reporting no 'resistance' in their tested isolates[33,42] and some others reporting higher 'resistance' rates of up to 30%.[41,75] Fluconazole MIC_{90} values were variable between studies; however, were as high as 16 to 32 mg/l based on CLSI[33,54, 75, 76] and EUCAST methods for MIC determination.[45] Chen et al. observed significantly increasing numbers of isolates with fluconazole MIC $\geq$ 8 mg/l over the study period 2001–2012 ($P < 0.001$).[41]

Limited numbers of studies reported susceptibility to isavuconazole. Geometric mean MIC values from these studies ranged from 0.011 to 0.065 mg/l[55, 56, 70, 72] and MIC_{90} values ranged from 0.031 to 0.063 mg/l.[56, 70, 72] Reduced susceptibility to itraconazole (0.03–2 mg/l) was uncommon, ranging from 0% to 22%,[42,54] with $\leq$ 1% non-wild type (non-WT) rates.[45,48,51] 'Resistance' rates were lower for ketoconazole (0%–7%)[33,54] and voriconazole (0%).[33,42] For posaconazole and voriconazole, non-WT rates of 1.3%–5.7% were reported.[45,48,51]

For amphotericin B, Andrade-Silva et al. reported a resistance rate of 11% based on 95 isolates from HIV/AIDS patients in Brazil,[33] in contrast to Tewari et al. reporting < 2% resistance rate in their Indian population (80% without HIV infection).[76]

Susceptibility to 5-flucytosine was only reported as non-WT rates of 1%–2%,[45,51] and MIC_{90} values were highly variable between studies but were as high as 8–16 mg/l.[45,70,72,51,38] Selb et al. observed a lower MIC90 of 1 mg/l for serotype A (genotype VNI) compared with MIC90 of 8 mg/l for serotype D (genotype VNIV).[74]

Cryptococcus gattii susceptibility to antifungals

For *C. gattii*, all studies reported MIC values without interpretive CBP MICs.

Studies by Espinel-Ingroff et al. and Lockhart et al. were conducted on large number of isolates (~300) from multiple

Table 1. The risk of bias for each study of *C. neoformans*.

Author	Publication year	Risk of bias (low, high, and unclear)	Reference
A			
Andrade-Silva et al.	2013	Unclear	33
Andrade-Silva et al.	2018	Unclear	34
Ashton et al.	2019	Unclear	35
Bariao et al.	2020	Low	36
Beale et al.	2015	Low	37
Bertout et al.	2012	Unclear	38
Cao et al.	2019	Low	39
Chan et al.	2014	Low	40
Chen et al.	2015	Low	41
Chen et al.	2018	Low	42
Chowdhary et al.	2011	Unclear	43
Cogliati et al.	2018	Unclear	44
Córdoba et al.	2016	Low	45
de Oliveira et al.	2017	Low	46
Desnos-Ollivier et al.	2015	Unclear	47
Espinel-Ingroff et al.	2012	Unclear	48
Espinel-Ingroff et al.	2012	Unclear	49
Espinel-Ingroff et al.	2015	Unclear	50
Fan et al.	2016	Low	51
Gonzalez et al.	2016	Low	52
Govender et al.	2011	Unclear	53
Gutch et al.	2015	Unclear	54
Hagen et al.	2016	Unclear	55
Herkert et al.	2018	Unclear	56
Hurtado et al.	2019	Low	57
Kassi et al.	2016	Low	58
Lahiri et al.	2020	Unclear	59
Lin et al.	2015	Unclear	60
Mahabeer et al.	2014	Low	61
Mahabeer et al.	2014	Low	62
Martins et al.	2011	Low	63
Mdodo et al.	2011	Unclear	64
Miglia et al.	2011	Unclear	65
Naicker et al.	2020	Unclear	66
Nascimento et al.	2017	Low	67
Nishikawa et al.	2019	Low	68
Nyazika et al.	2016	Low	69
Pan et al.	2012	Unclear	70
Pfaller et al.	2011	Unclear	71
Prakash et al.	2020	Low	72
Rakotoarivelo et al.	2020	Unclear	73
Selb et al.	2019	Low	74
Smith et al.	2015	Low	75
Tewari et al.	2012	Unclear	76
Yoon et al.	2020	Low	77
B. The risk of bias for each study of *C. gattii*			
Chen et al.	2012	Low	78
Chen et al.	2013	Low	79
Espinel-Ingroff et al.	2012	Unclear	48
Espinel-Ingroff et al.	2012	Unclear	49
Espinel-Ingroff et al.	2015	Unclear	50
Firacative et al.	2016	Unclear	80
Harris et al.	2011	Low	81
Hurtado et al.	2019	Unclear	57
Kassi et al.	2016	Unclear	58
Lahiri et al.	2020	Unclear	59
Lee et al.	2019	Unclear	82
Lockhart et al.	2012	Unclear	83
Phillips et al.	2015	Low	84
Smith et al.	2014	Low	85

Table 2. The mortality rates due to *C. neoformans* and *C. gattii* infections.

Author	Study period	Pathogen species	Country	Study design	Level of care	Population description	Patients (*N*=)	Mortality type, N/N, %
Desnos-Ollivier et al. [47]	1997 to 2001	*Cryptococcus neoformans*	France	Qualitative data and lab surveillance study (MC)	ND	Patients enrolled during the CryptoA/D study or the nationwide survey on cryptococcosis in France	181	% Patients who died within 90 days after diagnosis/total Serotype A: 21/82 (26%) Serotype D: 7/22 (32%) Serotype AD: 7/25 (28%)
Chan et al. [40]	1999 to 2007	*Cryptococcus neoformans*	Singapore	RCS (SC)	Tertiary	HIV with CD4 counts < 200 cells/mm3	62	HIV+ 15/45 (33%) HIV- 1/12 (8%) OR (95% CI) 5.5 (0.65–46.69) *P*-value = 0.118 HIV+ Deaths at less or equal to 30 days = 9/46 (20%) HIV- Deaths at less or equal to 30 days = 1/12 (8%) OR (95% CI) 2.68 (0.30–127.77) *P*-value = 0.670
Nascimento et al. [67]	2000 to 2011	*Cryptococcus neoformans*	Brazil	LSS (SC)	Tertiary	Patients with CM	61	6/61 (10%) deaths (*C. neoformans* var. *grubii*) in AIDS patients
Govender et al. [53]	2002 to 2008	*Cryptococcus neoformans*	South Africa	PBS (MC)	Tertiary	Patients who had been diagnosed with the first episode of laboratory-confirmed cryptococcosis. Only 1033 out of 8439 met the selection criteria.	1033	Case fatality (non-30-day mortality) 2002–2003: 62/238 (26%) 2007–2008: 84/249 (36%)
Yoon et al. [77]	2005 to 2017	*Cryptococcus neoformans*	United States	RCS (SC)	Tertiary	All patients ≥ 18 years old with the diagnosis of cryptococcosis at Montefiore Medical Centre	126	30-day mortality: HIV+ 4/68 (6%) HIV- 9/44 (20%) 1-year mortality HIV+ 7/55 (13%) HIV- 10/42 (24%) Cause of death due to cryptococcosis HIV + 3/7 (43%) HIV- 6/10 (60%)
Naicker et al. [66]	2007 to 2008 and 2017	*Cryptococcus neoformans*	South Africa	Prospective cohort study (MC)	ND	Patients with the first episode of culture-confirmed cryptococcal disease at 37 South African hospitals	249 and 204	In-hospital deaths 2007–2008: 84/249 (34%) 2017: 62/204 (30%)
Mdodo et al. [64]	2008 to 2009	*Cryptococcus neoformans*	Kenya	LSS (MC)	Tertiary	HIV-positive patients from Kenyatta National Hospital and Mbagathi District Hospital in Nairobi Kenya	67	In-hospital mortality 38/62 (61%)

Table 2. Continued

Author	Study period	Pathogen species	Country	Study design	Level of care	Population description	Patients (*N*=)	Mortality type, N/N, %
Martins et al. [63]	2008 to 2010	*Cryptococcus neoformans*	Brazil	LSS (SC)	Tertiary	Patients diagnosed with mycological CM	63	Deaths occurred in 49% of the cases HIV+ 18/37 (49%) HIV- 13/26 (50%) The number is higher for patients infected by *C. neoformans* VNI genotype. *Cryptococcus neoformans* VNI predominated in HIV + patients
Smith et al. [75]	2010 to 2014	*Cryptococcus neoformans*	Uganda	LSS (MC)	Tertiary	HIV infected and was presenting with his or her first episode of CM.	198	Day 60 deaths: FLU susceptible: 29/58, 50% FLU dose-dependent: 11/27, 41% FLU resistant: 1/5, 20% AMB susceptible 41/89, 46% AMB resistant 0/1
Nyazika et al. [69]	2013 to 2014	*Cryptococcus neoformans*	Zimbabwe	LSS (MC)	ND	HIV-infected adult inpatients from Parirenyatwa Group of Hospitals presenting signs and symptoms of meningitis.	100	Overall mortality rate 56% (30/54) AFLPI/VNI genotype 22/39 (56%) AFLPIA/VNB/VNII genotype 5/8 (63%) AFLPIB/VNII 3/7 genotype (43%)
Hurtado et al. [57]	2013 to 2015	*Cryptococcus neoformans*	Brazil	Autopsy study (MC)	Tertiary	284 deceased patients; Cause of death assigned to a cryptococcal infection	284	Seventeen died from fatal cryptococcal infections. 7/17 patients (41%) died within the first 72 hours of admission.
Rakotoarivelo et al. [73]	2014 to 2016	*Cryptococcus neoformans*	Madagascar	CSS (MC)	Tertiary	Consecutive HIV-infected adults presenting with CD4 cell counts ≤ 200/µl	129	90-day mortality: 30/129 (23%) 90-day mortality with CM: 8/14 (57%) 90-day mortality without CM: 22/115 (19%)
Beale et al. [37]	2005 to 2010	*Cryptococcus neoformans*	South Africa	RCS (MC)	ND	HIV infected individuals prior to the initiation of antifungal treatment	230	The overall mortality of 27% at 10 weeks, 41% at one year
Phillips et al. [84]	1999 to 2007	*Cryptococcus gattii*	British Columbia	RCS (MC)	ND	Patients with *C. gattii* infection, reported to BC Centre for Disease Control	152	Death due to *C. gattii* or where *C. gattii* contributed 11/47 (23.4%) (patients with CNS disease), 13/89 (14.6%) (with lung infection only)

Table 2. Continued

Author	Study period	Pathogen species	Country	Study design	Level of care	Population description	Patients (*N*=)	Mortality type, N/N, %
Chen et al. [79,78]	2000 to 2007	*Cryptococcus gattii*	Australia	RCS (MC)	Tertiary	Adults with *C. gattii* infection	86	11/85 (13%) (10 from *C. gattii*): within 4 months of diagnosis, 10/73 (13.6%) in CNS infection, 11% in CNS + lung infection, 17% in CNS infection only, (7/24) immunocompromised vs. (3/62) healthy hosts, 6/31 (19%) death at 12 months, patients with raised ICP
Smith et al. [85]	2004 to 2011	*Cryptococcus gattii*	United States Pacific Northwest (PNW)	RCS (MC)	ND	Patients with invasive *C. gattii* infection reported to CDC	70	3-month mortality in patients 13/70 (19%) in all patients, 3/7 (43%) in bloodstream infections, 7/33 (21%) pulmonary infections, 3/30 (10%) CNS infections
Harris et al. [81]	2004 to 2011	*Cryptococcus gattii*	United States	RCS (MC)	Tertiary	Patients with *C. gattii* reported to the CDC, US	76	Died of or with infection 19/57 (33%)

CSS = Cross sectional study; LSS = Lab surveillance study; MC = Multi-centre; ND = Not determined; PBS = Population-based surveillance; RSC = Retrospective cohort study; SC = Single centre

Table 3. Antifungal susceptibility of *C. neoformans*.

Author	MIC methods	Fluconazole	Isavuconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole	Amphotericin B	Flucytosine
Andrade-Silva et al. [33]	CLSI M27-A3	MIC GM 9.7 MIC range 2–32 MIC_{50} 8 MIC_{90} 16 %R 0% 97.9% MIC ≤ ECV 16	NA	MIC GM 0.30 MIC range 0.06–2 MIC_{50} 0.5 MIC_{90} 1 %R 22% (21/95) 100% MIC ≤ ECV 1	MIC GM 0.16 MIC range 0.03–0.5 MIC_{50} 0.12 MIC_{90} 0.5 %R 0% 100% MIC ≤ ECV 0.5	NA	MIC GM 0.11 MIC range 0.06–0.25 MIC_{50} 0.12 MIC_{90} 0.25 %R 0% 97.9% ≤ ECV 1	MIC GM 0.69 MIC range 0.12–4 MIC_{50} 1 MIC_{90} 2 %R 11% (10/95) 97.9% ≤ ECV 2	NA
Bariao et al. [36]	CLSI M27-A3	MIC GM 1.369 MIC range 0.25–16 MIC_{50} 1 MIC_{90} 4	NA	MIC GM 0.092 MIC range 0.031–0.25 MIC_{50} 0.125 MIC_{90} 0.125	NA	NA	MIC GM 0.089 MIC range 0.031–1 MIC_{50} 0.062 MIC_{90} 0.25	MIC GM 0.107 MIC range 0.031–1 MIC_{50} 0.125 MIC_{90} 0.25	MIC GM 1.079 MIC range 0.125–4 MIC_{50} 1 MIC_{90} 2
Bertout et al. [38]	Sensititre YeastOne	MIC GM 3.22 MIC range 0.5–32 MIC_{50} 2 MIC_{90} 16	NA	MIC GM 0.05 MIC range < 0.008–0.12 MIC_{50} 0.015 MIC_{90} 0.12	MIC GM 0.08 MIC range < 0.008–0.25 MIC_{50} 0.015 MIC_{90} 0.12	MIC GM 0.10 MIC range 0.008–0.5 MIC_{50} 0.06 MIC_{90} 0.5	MIC GM 0.06 MIC range < 0.008–0.12 MIC_{50} 0.015 MIC_{90} 0.12	MIC GM 0.31 MIC range 0.06–1 MIC_{50} 0.06 MIC_{90} 0.5	MIC GM 2.76 MIC range 0.5–16 MIC_{50} 2 MIC_{90} 8
Chen et al. [41]	CLSI M27-A3	MIC range 2–64 30/89 (34%) fluconazole MIC ≥ 8	NA	NA	NA	NA	NA	NA	NA
Chen et al. [42]	ATB™ FUNGUS-3 kit	No isolates with MIC ≥ 16 MIC range 1–8	NA	No isolates with MIC ≥ 1 MIC range 0.125–0.5	NA	NA	No isolates with MIC ≥ 1 MIC range 0.06–0.25	No isolates with MIC ≥ 2 MIC range < 0.5–1	No isolates with MIC ≥ 32 MIC range < 4–4
Chowdhary et al. [43]	CLSI M27-A3	MIC GM 2.190 MIC range 0.5–8 MIC_{50} 2 MIC_{90} 4	NA	MIC GM 0.099 MIC range 0.031–0.250 MIC_{50} 0.125 MIC_{90} 0.250	NA	NA	MIC GM 0.053 MIC range 0.015–0.125 MIC_{50} 0.062 MIC_{90} 0.125	MIC GM 0.235 MIC range 0.031–1 MIC_{50} 0.250 MIC_{90} 0.5	MIC GM 1.450 MIC range 0.031–64 MIC_{50} 2 MIC_{90} 4
Cogliati et al. [44]	Yeast nitrogen base (YNB) broth microdilution method	MIC GM 1.962 MIC range 0.12–16 MIC mode 4 98.6% MIC ≤ ECV 8	NA	MIC GM 0.096 MIC range 0.03–1 MIC mode 0.03 or 0.06 99.7% MIC ≤ ECV 0.5	NA	NA	MIC GM 0.049 MIC range 0.03–0.5 MIC mode 0.03 96.9% MIC ≤ ECV 0.12	NA	MIC GM 0.297 MIC range 0.12–64 MIC mode 0.25 MIC mean 0.297 97.8% MIC ≤ ECV 1
Córdoba et al. [45]	EUCAST	MIC range 0.13–128 MIC_{50} 8 MIC_{90} 32 MIC mode 8 ECV_{95} 32 (2.2% non-WT) ECV_{99} 64 (0.7% non-WT)	NA	MIC range 0.015–1 MIC_{50} 0.03 MIC_{90} 0.25 MIC mode 0.015 ECV_{95} 0.5 (0.6% non-WT) ECV_{99} 0.5 (0.6% non-WT)	NA	MIC range 0.015–0.13 MIC_{50} 0.015 MIC_{90} 0.06 MIC mode 0.015 ECV_{95} 0.06 (1.3% non-WT) ECV_{99} 0.13 (0% non-WT)	MIC range 0.015–2 MIC_{50} 0.13 MIC_{90} 0.25 MIC mode 0.13 ECV_{95} 0.5 (1.9% non-WT) ECV_{99} 1 (0.3% non-WT)	MIC range 0.015–1 MIC_{50} 0.25 MIC_{90} 0.5 MIC mode 0.25 ECV_{95} 0.5 (3.8% non-WT) ECV_{99} 1 (0% non-WT)	MIC range 0.13–128 MIC_{50}8 MIC_{90} 16 MIC mode 4 ECV_{95} 32 (2.4% non-WT) ECV_{99} 128 (0% non-WT)

Table 3. Continued

Author	MIC methods	Fluconazole	Isavuconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole	Amphotericin B	Flucytosine
de Oliveira et al. [46]	EUCAST	NA	NA	NA	NA	NA	NA	MIC GM 0.4 MIC range 0.12–1 MIC mode 0.5 $MIC_{50/90}$ 0.5	NA
Espinel-Ingroff et al. [48]	CLSI M27-A3	MIC range ≤ 0.12–≥ 64 MIC mode 4–8 98.3% MIC ≤ ECV 16	NA	MIC range ≤ 0.008–≥ 4 MIC mode 0.12 98.9% MIC ≤ ECV 0.5	NA	MIC range ≤ 0.008–≥ 2 MIC mode 0.12 94.3% MIC ≤ ECV 0.25	MIC range ≤ 0.008–≥ 4 MIC mode 0.06 96.5% MIC ≤ ECV 0.25	NA	NA
Espinel-Ingroff et al. [49]	CLSI M27-A3, Etest	NA	NA	NA	NA	NA	NA	MIC range ≤ 0.03–4 MIC mode 0.25 ECV_{95} 1 ECV_{99} 2	MIC range 0.06–to ≥ 64 MIC mode 4 ECV_{95} = 16 ECV_{99} = 32
Espinel-Ingroff et al. [50]	CLSI M27-A3	NA	MIC range 0.008–0.5 MIC mode 0.03 ECV_{95} 0.06–0.12 $ECV_{97.5}$ 0.12	NA	NA	NA	NA	NA	NA
Fan et al. [51]	Sensititre YeastOne	MIC GM 4.28 MIC range 0.5–64 MIC_{50} 4 MIC_{90} 8 WT 92.4% Non-WT 7.6%	NA	MIC GM 0.057 MIC range 0.015–0.5 MIC_{50} 0.06 MIC_{90} 0.12 WT 99% Non-WT 1%	NA	MIC GM 0.084 MIC range 0.008–0.5 MIC_{50} 0.06 MIC_{90} 0.25 WT 97.7% Non-WT 2.3%	MIC GM 0.034 MIC range 0.008–0.5 MIC_{50} 0.03 MIC_{90} 0.12 WT 98.3% Non-WT 1.7%	MIC GM 0.60 MIC range 0.25–1.0 MIC_{50} 0.5 MIC_{90} 1.0 WT 100% Non-WT 0%	MIC GM 3.42 MIC range 0.06–16 MIC_{50} 4 MIC_{90} 8 WT 98.7% Non-WT 1.3%
Gonzalez et al. [52]	CLSI M27-A3	MIC GM 1.335 MIC range 0.5–4 MIC_{50} 2 MIC_{90} 2	NA	NA	NA	NA	MIC GM 0.061 MIC range 0.03–0.125 MIC_{50} 0.06 MIC_{90} 0.125	MIC GM 0.343 MIC range 0.125–1 MIC_{50} 0.25 MIC_{90} 1	NA
Govender et al. [53]	CLSI M27-A3	2002–2003 MIC range 0.5–16 MIC_{50} 1 MIC_{90} 2 2007–2008 MIC range 0.25–8 MIC_{50} 1 MIC_{90} 2	NA	2002–2003 MIC range 0.03–1 MIC_{50} 0.12 MIC_{90} 0.25 2007–2008 MIC range 0.015–0.5 MIC_{50} 0.06 MIC_{90} 0.12	NA	2002–2003 MIC range 0.03–0.5 MIC_{50} 0.12 MIC_{90} 0.25 2007–2008 MIC range 0.03–1 MIC_{50} 0.06 MIC_{90} 0.12	2002–2003 MIC range 0.008–0.25 MIC_{50} 0.015 MIC_{90} 0.06 2007–2008 MIC range 0.008–0.25 MIC_{50} 0.015 MIC_{90} 0.03	2002–2003 MIC range 0.012–0.38 MIC_{50} 0.094 MIC_{90} 0.19 2007–2008 MIC range 0.008–0.94 MIC_{50} 0.094 MIC_{90} 0.19	2002–2003 MIC range 0.25–16 MIC_{50} 1 MIC_{90} 4 2007–2008 MIC range 0.05–8 MIC_{50} 1 MIC_{90} 2

Table 3. Continued

Author	MIC methods	Fluconazole	Isavuconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole	Amphotericin B	Flucytosine
Tewari et al. [76]	Vitek 2, Etest, CLSI M27-A3	CLSI MIC range 0.25–32 MIC_{90} 16 Etest MIC range 1– >256 MIC_{90} 16 Vitek 2 MIC range < 1–>64 MIC_{90} 8 80%–90% of isolates MIC ≤ 8	NA	NA	NA	NA	NA	CLSI MIC range 0.06–5 MIC_{90} 0.5 Etest MIC range 0.047–0.38 MIC_{90} 0.25 Vitek 2 MIC range < 0.25–2 MIC_{90} 1 98%–100% of isolates MIC < 1	NA
Gutch et al. [54]	CLSI M27-A	MIC range 0.063–64 MIC_{50} 8 MIC_{90} 32 Mean 6.93 MIC ≥ 64, 8.6% MIC 16–32, 31.1% MIC ≤ 8, 60.3%	NA	MIC range 0.03–1 MIC_{50} 0.125 MIC_{90} 0.5 Mean 0.124 MIC ≥ 1, 5.2% MIC 0.25–0.5, 24.1% MIC ≤ 0.125, 70.7%	MIC range 0.03–0.25 MIC_{50}0.064 MIC_{90} 0.064 Mean 0.051 MIC ≥ 0.125, 6.9% MIC 0.0625, 55.2% MIC < 0.0625 37.9%	NA	NA	NA	NA
Hagen et al. [55]	EUCAST	MIC GM 8.96 MIC range 0.5–> 32 MIC_{50} 4	MIC GM 0.065 MIC range < 0.03–0.25 MIC_{50} 0.06	NA	NA	NA	MIC GM 0.104 MIC range < 0.03–0.5 MIC_{50} 0.06	MIC GM 0.180 MIC range < 0.03–1 MIC_{50} 0.125	MIC GM 8.80 MIC range 1–> 32 MIC_{50} 8
Herkert et al. [56]	CLSI M27-A3	MIC GM 0.516 MIC range 0.125–8 MIC_{50} 0.5 MIC_{90} 0.5	MIC GM 0.011 MIC range < 0.016–0.063 MIC_{50} < 0.016 MIC_{90} 0.031	MIC GM 0.027 MIC range < 0.016–0.25 MIC_{50} 0.031 MIC_{90} 0.063	NA	MIC GM 0.027 MIC range < 0.016–0.125 MIC_{50} 0.031 MIC_{90} 0.063	MIC GM 0.021 MIC range < 0.016–0.125 MIC_{50} 0.031 MIC_{90} 0.031	MIC GM 0.098 MIC range < 0.016–0.125 MIC_{50} 0.125 MIC_{90} 0.125	MIC GM 2.42 MIC range 0.25–8 MIC_{50} 2 MIC_{90} 4
Hurtado et al. [57]	Sensititre YeastOne	MIC range 4–16	NA	MIC range 0.03–0.12	NA	MIC range 0.06–0.25	MIC range 0.06–0.25	MIC range 0.5–1	MIC range 1–16
Kassi et al. [58]	CLSI M27-A3	MIC range 0.125–8	NA	NA	NA	NA	NA	MIC range 0.125–1	MIC range 0.5–16
Mahabeer et al. [61]	CLSI M27-A3, Etest, Vitek 2	CLSI MIC range 0.25–4 MIC_{50} 1 MIC_{90} 2 Etest MIC range 0.25–4 MIC_{50} 1 MIC_{90} 2 Vitek 2 MIC range ≤ 1–16 MIC_{50} ≤ 1 MIC_{90} 2	NA	NA	NA	NA	CLSI MIC range ≤ 0.002–0.064 MIC_{50} 0.004 MIC_{90} 0.016 Etest MIC range ≤ 0.002–0.064 MIC_{50}0.008 MIC_{90} 0.016	CLSI MIC range ≤ 0.008–1 MIC_{50} 0.125 MIC_{90} 0.25 Etest MIC range ≤ 0.008–0.25 MIC_{50} 0.06 MIC_{90} 0.125 Vitek 2 MIC range ≤ 0.25–0.5 MIC_{50} ≤ 0.25 MIC_{90} 0.5	CLSI MIC range ≤ 0.125–4 MIC50 1 MIC_{90} 2 Etest MIC range ≤ 1–8 MIC_{50} ≤ 1 MIC_{90} 2

Table 3. Continued

Author	MIC methods	Fluconazole	Isavuconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole	Amphotericin B	Flucytosine
Mahabeer et al. [62]	CLSI M27-A3, Etest, Vitek-2	CLSI MIC range 0.25–4 MIC_{50} 1 MIC_{90} 2 Etest MIC_{50} 1 MIC_{90} 2 MIC range 0.06–4 Vitek-2 MIC range ≤ 1–16 MIC_{50} ≤ 1 MIC_{90} 2	NA	NA	NA	NA	CLSI MIC range ≤ 0.002–0.064 MIC_{50} 0.004 MIC_{90} 0.016 Etest MIC range ≤ 0.002–0.064 MIC_{50} 0.008 MIC_{90} 0.016	CLSI MIC range ≤ 0.008–1 MIC_{50} 0.125 MIC_{90} 0.25 Etest MIC range ≤ 0.008–0.25 MIC_{50} 0.06 MIC_{90} 0.125 Vitek-2 MIC range ≤ 0.25–0.5 MIC_{50} ≤ 0.25 MIC_{90} 0.5	CLSI MIC range ≤ 0.125–4 MIC_{50} 1 MIC_{90} 2 Vitek-2 MIC range ≤ 1–8 MIC_{50} ≤ 1 MIC_{90} 2
Mdodo et al. [64]	CLSI M27-A3	MIC range 0.25–16 MIC_{50} 4 MIC_{90} 8	NA	NA	NA	NA	MIC range 0.015–0.25 MIC_{50} 0.06 MIC_{90} 0.25	MIC range 0.5–1 MIC_{50} 1 MIC_{90} 1	MIC range 1–16 MIC_{50} 2 MIC_{90} 4
Naicker et al. [66]	CLSI M27-A3	2007–2008 MIC GM: 2.08 MIC range 0.25–8 MIC_{50} 1 MIC_{90} 2 2017 MIC GM: 4.11 MIC range 0.5–64 MIC_{50} 4 MIC_{90} 8	NA	NA	NA	NA	NA	NA	NA
Nascimento et al. [67]	CLSI M27-A2, E–test	CLSI MIC GM 0.30 MIC range 1–16 MIC_{50} 0.25 MIC_{90} 0.5 Etest MIC GM 0.20 MIC range 0.047–0.5 MIC_{50} 0.19 MIC_{90} 0.38	NA	CLSI MIC GM 0.13 MIC range 0.03–1.0 MIC_{50} 0.06 MIC_{90} 0.25 Etest MIC GM 0.44 MIC range 0.016–2.0 MIC_{50} 0.38 MIC_{90} 0.75	NA	NA	CLSI MIC GM 0.27 MIC range 0.03–0.5 MIC_{50} 0.25 Broth MIC_{90} 0.50 Etest MIC GM 0.14 MIC range 0.016–0.75 MIC_{50} 0.094 MIC_{90} 0.25	CLSI MIC GM 0.30 MIC range 0.13–0.5 MIC_{50} 0.25 Broth MIC_{90} 0.50 Etest MIC GM 0.20 MIC range 0.047–0.5 MIC_{50} 0.19 MIC_{90} 0.38	NA

Table 3. Continued

Author	MIC methods	Fluconazole	Isavuconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole	Amphotericin B	Flucytosine
Nishikawa et al. [68]	CLSI M27-A3, Etest, Vitek 2	CLSI MIC range 2–8 MIC_{50} 4 MIC_{90} 4 MIC mode 4 Etest MIC range 2–32 MIC_{50} 4 MIC_{90} 16 MIC mode 8 Vitek 2 MIC range ≤ 1–2 MIC_{50} 1 MIC_{90} 2 MIC mode 2	NA	CLSI MIC range 0.06–0.5 MIC_{50} 0.125 MIC_{90} 0.125 MIC mode 0.125 Etest MIC range 0.032–1 MIC_{50} 0.125 MIC_{90} 0.75 MIC mode 0.125	NA	NA	CLSI MIC range 0.015–0.25 MIC_{50} 0.06 MIC_{90} 0.06 MIC mode 0.06 Etest MIC range 0.016–0.38 MIC_{50} 0.047 MIC_{90} 0.094 MIC mode 0.06 Vitek 2 MIC range ≤ 0.125 MIC_{50} ≤ 0.125 MIC_{90} ≤ 0.125 MIC mode ≤ 0.125	CLSI MIC range 0.5–2 MIC_{50} 1 MIC_{90} 1 MIC mode 1 Etest MIC range 0.012–0.25 MIC_{50} 0.094 MIC_{90} 0.125 MIC mode 0.094 or 0.125 Vitek 2 MIC range 1–2 MIC_{50} 1 MIC_{90} 1 MIC mode 1	CLSI MIC range 1–8 MIC_{50} 2 MIC_{90} 4 MIC mode 2, 4 Etest MIC range 0.125–>32 MIC_{50} 4 MIC_{90} 8 MIC mode 4 Vitek 2 MIC range ≤ 1–2 MIC_{50} ≤ 1 MIC_{90} 2 MIC mode ≤ 1
Pan et al. [70]	CLSI M27-A3	MIC GM 2.294 MIC range 0.125–32 MIC_{50} 2 MIC_{90} 4	MIC GM 0.027 MIC range < 0.016–0.125 MIC_{50} 0.031 MIC_{90} 0.063	MIC GM 0.063 MIC range < 0.016–0.5 MIC_{50} 0.063 MIC_{90} 0.25	NA	MIC GM 0.061 MIC range < 0.016–0.5 MIC_{50} 0.063 MIC_{90} 0.125	MIC GM 0.049 MIC range < 0.016–0.5 MIC_{50} 0.063 MIC_{90} 0.125	MIC GM 0.251 MIC range 0.063–1 MIC_{50} 0.25 MIC_{90} 0.5	MIC GM 3.483 MIC range < 0.063–>64 MIC_{50} 4 MIC_{90} 8
Pfaller et al. [71]	CLSI M27-A3	MIC range 0.25–32 Mode 4 ECV 8 96.9% MIC ≤ ECV 8	NA	NA	NA	MIC range 0.03–0.5 Mode 0.12 ECV 0.25 96.5% MIC ≤ ECV 0.25	MIC range 0.008–0.5 Mode 0.06 ECV 0.12 95.1% MIC ≤ ECV 0.12	NA	NA
Prakash et al. [72]	CLSI M27-A3	MIC GM 3.575 MIC range 0.06–64 MIC_{50} 4 MIC_{90} 8	MIC GM 0.03136 MIC range 0.016–0.25 MIC_{50} 0.03 MIC_{90} 0.063	MIC GM 0.517 MIC range 0.016–0.5 MIC_{50} 0.06 MIC_{90} 0.125	NA	MIC GM 0.06658 MIC range 0.016–0.5 MIC_{50} 0.06 MIC_{90} 0.125	MIC GM 0.051 MIC range 0.016–1 MIC_{50} 0.06 MIC_{90} 0.125	MIC GM 0.228 MIC range 0.03–4 MIC_{50} 0.25 MIC_{90} 0.5	MIC GM 4.660 MIC range 0.25–64 MIC_{50} 4 MIC_{90} 16
Rakotoarivelo et al. [73]	Etest	MIC range 0.5–>256 MIC mode 12 ECV 32	NA	NA	NA	NA	MIC range 0.004–0.5 MIC mode 0.047 ECV 0.5	MIC range 0.032–0.5 MIC mode 0.250 ECV 1	MIC range 4–>32 MIC mode > 32 ECV 16

Table 3. Continued

Author	MIC methods	Fluconazole	Isavuconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole	Amphotericin B	Flucytosine
Selb et al.[74]	CLSI M27-A3	Serotype A	NA	NA	NA	Serotype A	Serotype A	Serotype A	Serotype A
		MIC range 0.5–16				MIC range 0.03–0.5	MIC range 0.03–0.125	MIC range 0.125–0.5	MIC range
		MIC_{50} 1				MIC_{50} 0.06	MIC_{50} 0.03	MIC_{50} 0.5	0.25–>64
		MIC_{90} 2				MIC_{90} 0.125	MIC_{90} 0.03	MIC_{90} 0.5	MIC_{50} 1
		MIC mode 1				MIC mode 0.06	MIC mode 0.03	MIC mode 0.5	MIC_{90} 1
		Serotype D				Serotype D	Serotype D	Serotype D	MIC mode 1
		MIC range 0.125–0.5				MIC range	MIC range 0.03	MIC range 0.25–0.5	Serotype D
		MIC_{50} 0.5				0.03–0.125 MIC_{50}	MIC_{50} 0.03	MIC_{50} 0.5	MIC range 1–>64
		MIC_{90} 2				0.03	MIC_{90} 0.03	MIC_{90} 0.5	MIC_{50} 4
		MIC mode 0.5				MIC_{90} 0.06	MIC mode 0.03	MIC mode 0.5	MIC_{90} 8
						MIC mode 0.03			MIC mode 2
Smith et al.[75]	CLSI	MIC range 0.125–64	NA	NA	NA	NA	NA	MIC range 0.125–2	NA
		MIC mode 8						MIC mode 0.5	
		MIC_{50} 8						MIC_{50} 0.5	
		MIC_{90} 32						MIC_{90} 1	
		69% isolates MIC < 16							

Data are reported as they appear in source documents. Susceptibility is expressed as mg/l unless indicated otherwise. ECV = epidemiological cutoff value, GM = geometric mean, MIC = minimum inhibitory concentration, NA = not available, MIC_{50} = MIC required to inhibit the growth of 50% of isolates, MIC_{90} = MIC required to inhibit the growth of 90% of isolates.

countries.[48,49,50,83] Reported MICs for fluconazole were generally high (range: 0.5–32 mg/l), although variable, with isolates of molecular type VGII showing the highest modal or geometric mean MIC of > 8 mg/l compared with other molecular types (1.7–4.0 mg/l for VGI and VGIII).[48,83] Modal MICs of itraconazole, posaconazole, and voriconazole for *C. gattii* ranged from 0.06 to 0.5 mg/l for both molecular-typed and non-typed isolates.[48]

For amphotericin B, modal or geometric mean MICs ranged from 0.25 to 0.5 mg/l for both typed and non-typed isolates.[49,80,82] Susceptibility results for flucytosine were variable with modal or geometric mean MICs of 0.5–2 mg/l, and with higher values reported (> 64 mg/l) for molecular types VGI and VGII.[49,80,82] No susceptibility data were available for echinocandins, but *Cryptococcus* species, like all basidiomycetes are intrinsically resistant to this class.

Annual incidence and global distribution

Annual global incidence rates for *C. neoformans* and *C. gattii* could not be assessed due to lack of denominator from all included studies. However, at a population level, there were estimated 220 000 cases of CM globally in 2014 (about 3 in 100 000 population).[22] Chen et al. reported the annual incidence of *C. gattii* infections was 6 in 100 000 between 2000 and 2007 in Australia,[78] but higher (nearly 10-fold) annual incidence rate was reported in Aboriginal Australians.[78]

Although its proportional contribution to total cases of cryptococcal disease varies by geographic region, it was evident that *C. neoformans* was globally distributed.[87] The prevalence of *C. neoformans* among isolates causing CM was reported in three multi-centre studies from African countries[73,58,65] and one single-centre study from India (Table 5).[59] In Madagascar during 2014–2016, the proportion of cryptococcal infection caused by *C. neoformans* var. *grubii* (serotype A) in HIV-infected patients was 13.2%.[73] A multi-centre lab surveillance study conducted in South Africa during 2005–2006 reported a high prevalence (82%) of *C. neoformans* serotype A (VNI) and a lower prevalence (0%–10%) of serotype A (VNB, VNII), serotype AD (VNIII), and serotype D (VNIV) among paediatric patients with cryptococcosis.[65] Similarly, in Ivory Coast during 2012–2014, a study showed 86% of HIV-associated CM was caused by *C. neoformans* VNI genotype.[58] In India, the majority of the CNS cryptococcosis patients were from Bangalore Urban, Karnataka, which is in the southern part of India; 80% of the clinical strains were *C. neoformans* VNI and 8.75% were *C. neoformans* VNII.[59]

There was limited data available to assess the global distribution of *C. gattii,* four studies informed prevalence of *C. gattii* in patients with cryptococcal infections in different study locations, including Australia, India, Brazil, and Africa (Table 5). Overall, *C. gattii* accounted for 11%–33% of cryptococcal infections.[82,59,57] In contrast, the earlier study conducted in Ivory Coast reported only one case of *C. gattii* infection in 61 HIV-positive patients with cryptococcal infections.[58] Like *C. neoformans*, the distribution of *C. gattii* molecular types seems to vary across regions, although it was difficult to assess as few regions were represented. In Australia, genotype VGI caused the majority of the *C. gattii* cases,[82] whereas in India, VGIV was the most commonly observed genotype.[59]

Table 4. Antifungal susceptibility of *C. gattii*.

Author	Year	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole	Amphotericin B	Flucytosine
Espinel-Ingroff et al. [48]	2012	CLSI M27A-3	MIC mode Non-typed 4 VGI 4 VGII 8 VGIIa 4 VGIII 4 VGIV 8	NA	MIC mode Non-typed 0.12 VGI 0.25 VGII 0.12 VGIII 0.25 VGIV 0.5	MIC mode Non-typed 0.12 VGI 0.12	MIC mode Non-typed 0.06 VGI 0.12 VGII 0.12 VGIIa 0.12	NA	NA
Espinel-Ingroff et al. [49]	2012	CLSI M27A-3	NA	NA	NA	NA	NA	MIC mode (range) Non-typed 0.5 (0.06–1) VGI 0.25 (0.03–1) VGII 0.5 (0.125–2) VGIIa 0.25 (0.06–1)	MIC mode Non-typed 1 (0.25–8) VGI 2 (0.125–>64) VGII 2 (0.25–≥64)
Espinel-Ingroff et al. [50]	2015	CLSI	NA	MIC mode (range) 0.03 (0.008–0.5)	NA	NA	NA	NA	NA
Firacative et al. [80]	2016	Sensititre YeastOne	Clinical isolates GM MIC 5.384	NA	Clinical isolates GM MIC 0.0453	Clinical isolates GM MIC 0.06 987	Clinical isolates GM MIC 0.04421	Clinical isolates GM MIC 0.2726	Clinical isolates GM MIC 1.927
Lee et al. [82]	2019	Sensititre YeastOne	VGI GM MIC 1.46 MIC range 0.25–2	NA	VGI GM MIC 0.02 MIC range 0.015–0.06	VGI GM MIC 0.04 MIC range 0.008–0.12	VGI GM MIC 0.02 MIC range 0.008–0.06	VGI GM MIC 0.39 MIC range 0.12–1	VGI GM MIC 0.47 MIC range 0.25–2
Lockhart et al. [83]	2012	CLSI	All isolates GM MIC 5.51 MIC range 0.5–32 VGI GM MIC 1.69 MIC range 0.5–8 VGII GM MIC 8.60 MIC range 1–32 VGIII GM MIC 3.48 MIC range 1–16 VGIV GM MIC 4.79 MIC range 0.5–32	NA	All isolates GM MIC 0.30 MIC range 0.03–2 VGI GM MIC 0.19 MIC range 0.03–1 VGII GM MIC 0.36 MIC range 0.06–2 VGIII GM MIC 0.28 MIC range 0.06–0.5 VGIV GM MIC 0.30 MIC range 0.06–2	All isolates GM MIC 0.31 MIC range 0.008–1 VGI GM MIC 0.20 MIC range 0.03–1 VGII GM MIC 0.33 MIC range 0.008–1 VGIII GM MIC 0.34 MIC range 0.12–1 VGIV GM MIC 0.34 MIC range 0.12–1	All isolates GM MIC 0.10 MIC range 0.008–1 VGI GM MIC 0.03 MIC range 0.008–0.25 VGII GM MIC 0.13 MIC range 0.015–1 VGIII GM MIC 0.07 MIC range 0.03–0.25 VGIV GM MIC 0.10 MIC range 0.03–0.5	NA	NA

Data are reported as they appear in source documents. Susceptibility is expressed as mg/l unless indicated otherwise. ECV = epidemiological cutoff value, GM = geometric mean, MIC = minimum inhibitory concentration, NA = not available, MIC_{50} = MIC required to inhibit the growth of 50% of isolates, MIC_{90} = MIC required to inhibit the growth of 90% of isolates.

Table 5. The incidence and global distribution of *C. neoformans* and *C. gattii*.

Study period	Pathogen	Country	Study design	Level of care	Population description	Patients (*N*=)	Incidence	References
2005 to 2006	*Cryptococcus neoformans*	South Africa	LSS (MC)	ND	Paediatric and adult patients with cryptococcosis during a 2-year period in South Africa	199	Paediatric cases Serotype A, VNI: 67/82 (82%) Serotype A, VNB: 8/82 (10%) Serotype A, VNII: 6/82 (7%) Serotype AD, VNIII: 1/82 (1%) Serotype D, VNIV: 0/82	Miglia et al. [65]
2008 to 2017	*Cryptococcus gattii*	Australia	RCS (MC)	ND	Patients with cryptococcal infections	ND	13/55 (24%) *C. gattii* complex (majority VGI (11), VGII (2) uncommon)	Lee et al. [82]
2012 to 2014	*Cryptococcus neoformans and C. gatii*	Ivory Coast	LSS (MC)	Tertiary	Patients with HIV positive, and none of them received a systemic antifungal treatment	61	High prevalence of CM (86%) due to *C. neoformans* VNI among HIV-infected patients. The results show the prevalence (95%) of serotype A in Ivory Coast. 1/61 (*C. gattii* (VGII))	Kassi et al. [58]
2013 to 2015	*Cryptococcus gattii*	Mozambique and Brazil	Autopsy study (MC)	Tertiary	Deceased patients (for diagnostic autopsies)	223 (Mozambique) and 61 (Brazil)	5/15 (33%) *C. gattii* (VGI and VGIV molecular types) out of fatal cryptococcal infections	Hurtado et al. [57]
2014 to 2016	*Cryptococcus neoformans*	Madagascar	CSS (MC)	Tertiary	Consecutive HIV-infected adults presenting with CD4 cell counts ≤ 200/µl	129	The overall prevalence of cryptococcal infection was 13.2% (17/129, 95% CI7.9-20.3), and that of CM was 10.9% (14/129, 95% CI 6.1–17.5).	Rakotoarivelo et al. [73]
ND	*Cryptococcus neoformans and C. gatii*	India	Epidemiology study (SC)	Tertiary	CNS cryptococcosis patients attending the neurological and neurosurgical services of National Institute of Mental Health and Neurosciences.	160	146/160 (91%) from Karnataka 14/160 (9%) from Tamil Nadu, Andhra Pradesh, West Bengal, Orissa, Bihar, and Pondicherry. 80% *C. neoformans* VNI, 8.75% VNII and 22.5% *C . gattii* (VGI), 8.75% *C. gattii* (VGIV).	Lahiri et al. [59]
ND	*Cryptococcus gattii*	India	PCS (SC)	Tertiary	Patients with CNS cryptococcosis	160	18/160 (11.25%) *C. gattii* (Of these, 14 (8.75%) were *C. gattii* genotype AFLP7/VGIV (serotype C), and 4 (2.5%) *C. gattii* AFLP4/VGI (serotype B).	Lahiri et al. [59]

CSS = Cross sectional study; LSS = Lab surveillance study; MC = Multi-centre; ND = Not determined; PCS = Prospective cohort study; RSC = Retrospective cohort study; SC = Single centre

Inpatient care and the length of stay in hospital

The median hospital length of stay in patients with *C. neoformans* infection ranged from 18 to 39 days,[40,69,73,39] with only Cao et al. 2019 reporting on HIV-negative patients (Table 6). Although Chan et al. reported a greater length of stay for HIV-negative patients with cryptococcosis (predominantly involving *C. neoformans* var. *grubii* VNI*)* compared with HIV positive cryptococcosis patients (31 days vs. 18.5 days), this difference was based on only 12 HIV-negative patients and was not statistically significant.[40]

Only one study reported on the hospital length of stay in patients with *C. gattii* infection (Table 6). This nationwide retrospective study conducted in Australian hospitals described average intensive care unit (ICU) stay related to *C. gattii* infection in 18 adult patients as 9.1 days with a wide range of 1–29 days.[78] It did not report overall hospital length of stay. Notably, 90% of patients in this study received amphotericin B for the first 14 days, which typically requires inpatient therapy.

Complications, sequelae, and disabilities

Both *C. neoformans* and *C. gattii* infections can lead to severe complications, sequelae, and disabilities (Table 7).

A 2017 review highlighted that neurosensorial impairment and disability are common sequelae 6 months to 1 year after diagnosis in *C. neoformans* infections. Symptoms mainly include residual headache, motor deficit, and vertigo.[88] Other common complications may include anaemia, hypokalaemia, elevated aminotransferase levels, neutropenia, hypercreatinemia, and opportunistic infections.[89]

A study ($n = 50$) described complications from *C. neoformans* infection and treatment in HIV-positive individuals (mostly infected with *C. neoformans* var. *grubii* VNI genotype), including acute renal impairment, likely associated with antifungal therapies (28% of patients), raised intracranial pressure (ICP) needing shunts (18%), and blindness (12%).[40] Cao et al. reported a higher rate of unfavourable clinical outcome (defined as death, vegetative status, or severe to moderate disability) in CM patients with pulmonary nodules compared with those without the pulmonary nodule involvement (72.5% vs. 48%, $P = 0.019$).[39]

Day et al. (2013) found that baseline fungal count and Glasgow Coma Scale (GCS) were independent predictors of 6-month survival for CM. Furthermore, the choice of therapy regimen affects the survival rate and complications. For instance, it was found that neutropenia was more frequent among patients receiving amphotericin B with fluconazole or flucytosine than patients receiving amphotericin B monotherapy. Also, fewer patients had severe anaemia and visual deficit when combined therapy of amphotericin B with fluconazole/flucytosine than amphotericin B therapy alone.[89]

Neurological sequelae at 12 months of treatment were reported in 17%–27% of patients with *C. gattii* infections, and included signs and symptoms of visual impairment, hearing loss, limb weakness or balance disturbance, and cognitive impairment.[78,84]

Immune reconstitution inflammatory syndrome (IRIS) was observed in 9.4% of patients with *C. gattii* infections from 6 weeks to as long as 12 months after the initiation of azole eradication therapy, and these patients presented with new or enlarging brain lesions.[78]

Preventability

Risk factors for *C. neoformans* infection were documented in two studies. HIV/AIDS, cell-mediated immunity-suppressive regimens without calcineurin inhibitors, and decompensated liver cirrhosis were risk factors for CM (adjusted OR of 181.4, 15.9, and 8.5, respectively) and cryptococcemia (adjusted OR of 216.3, 7.3, and 23.8, respectively).[60] Autoimmune diseases (adjusted OR = 9.3) were an additional risk factor for cryptococcemia.[60]

HIV-infected patients and immunocompromised individuals are particularly vulnerable to cryptococcal infections and CM. Although not specific to *C. neoformans*, a retrospective review of routine cerebrospinal fluid laboratory records ($N = 4702$) between 2000 and 2014 in Botswana, South Africa, determined that antiretroviral therapy access alone did not lead to a significant decrease in the incident rate of HIV-associated CM.[90] Furthermore, several systematic reviews have quantified the preventative effect of pre-emptive therapy on CM: Relative risk of 0.19 ($P < 0.0001$)[91]; incidence reduced from 21% to 5% in patients with CD4 < 100, relative risk 0.23[92]; and incidence reduced from 5% to 3% in patients with CD4 < 200, relative risk 0.6.[93]

A study by Harris et al. observed that patients with *C. gattii* outbreak strain infections had more pre-existing conditions compared with patients with non-outbreak strain infections (86% vs. 31%; $P < 0.0001$).[81] The pre-existing conditions mainly involved immunosuppression or previous use of oral corticosteroids (during the year before infection) in 50% of patients and existing lung, renal, heart disease, or diabetes in 20%–30% of patients. It was also observed that patients with outbreak strain infections were older [median (range) of 56 (2–95) vs. 45 (18–56) years, $P = 0.007$].

Discussion

Cryptococcosis is particularly common in HIV/AIDS patients. However, antiretroviral therapy (ART) access alone has not always decreased the incidence of HIV-associated CM significantly.[90] This observation may be associated with late presentation and cumulative default from care by HIV/AIDS patients, suggesting that integrated interventions beyond simply providing ART are required to prevent cryptococcosis and CM.

Cryptococcosis can lead to prolonged hospitalization. The long length of stay in hospital may be partially attributed to treatment recommendations involving 14 days induction therapy with amphotericin B for most of the study period (although current WHO treatment recommendations for HIV-associated CM now favour shorter courses of amphotericin). Amphotericin B must be administered intravenously and, in most settings, is delivered as in-patient therapy. Although CM clearly causes significant morbidity and has a long-term impact on patients, the effect is poorly quantified, and future CM studies should continue to expand the evidence on short- and longer-term disability and quality of life.

There is clear evidence that cryptococcosis is associated with high mortality. Baddley et al. stated that the all-cause mortality rates were 18.8% at 3 months and 25.5% at 12 months.[94] The rates described in this review are higher than those observed in clinical trials. For example, some studies have reported mortality rates for CM of around 20%.[95–99] In trials, patients with significant co-morbidities or very

Table 6. The hospital length of stay due to *C. neoformans* and *C. gattii* infections.

Study period	Pathogens	Study design	Country	Level of care	Population description	Patients (*N*=)	Length of stay	References
1999 to 2007	*Cryptococcus neoformans*	RCS (SC)	Singapore	Tertiary	HIV with CD4 counts < 200 cells/mm^3	62	HIV+ 18.5 days (13–33) (median IQR) HIV- 31 days (17.5–44.5) OR (95% CI) 0.99 days (0.97–1.01), *P*-value 0.192	Chan et al. [40]
2000 to 2007	*Cryptococcus gattii*	RCS (MC)	Australia	Tertiary	Adults with *C. gattii* infection	86	mean ICU stay: 9.1 days (range 1–29) (n = 18)	Chen et al. [79,78]
2010 to 2016	*Cryptococcus neoformans*	RCS (SC)	China	Tertiary	CM patients	90	Pulmonary nodule (PN) positive: 39 days (2–180) PN negative: 37 days (5–210) *P*-value 0.768	Cao et al. [39]
2013 to 2014	*Cryptococcus neoformans*	LSS (MC)	Zimbabwe	ND	HIV-infected adult inpatients from Parirenyatwa Group of Hospitals with signs and symptoms of meningitis.	100	17.5 days of hospital stay IQR (10–22 days)	Nyazika et al. [69]
2014 to 2016	*Cryptococcus neoformans*	CSS (MC)	Madagascar	Tertiary	Consecutive HIV-infected adults presenting with CD4cell counts ≤ 200/μl	129	Hospital stay, days, median, (IQR): 22 (11.0–35.0)	Rakotoarivelo et al. [73]

CSS = Cross sectional study; LSS = Lab surveillance study; MC = Multi-centre; ND = Not determined; RSC = Retrospective cohort study; SC = Single centre

Table 7. The complications, sequelae and disabilities caused by *C. neoformans* and *C. gattii*.

Study period	Pathogens	Study design	Country	Level of care	Population description	Patients (*N*=)	Complications, sequelae, and disabilities	References
1999 to 2007	*Cryptococcus neoformans*	RCS (SC)	Singapore	Tertiary	HIV with CD4 counts < 200 cells/mm^3	62	Complications in 50 HIV+ patients: Raised ICP needing shunts (18%) of patients, blindness (12%), acute renal impairment (28%)	Chan et al. [40]
1999 to 2007	*Cryptococcus gattii*	RCS (MC)	British Columbia	ND	Patients with *C. gattii* infection, reported to BC Centre for Disease Control	152	Persistent neurological symptoms at the end of 12-month follow-up in 8/47 (17%) of CNS patients: including gait or balance disturbance ($n = 3$), partial hearing loss ($n = 2$), cognitive impairment ($n = 2$), blindness ($n = 1$), and seizure disorder ($n = 1$)	Phillips et al. [84]
2000 to 2007	*Cryptococcus gattii*	RCS (MC)	Australia	Tertiary	Adults with *C. gattii* infection	86	20/73 (27%) with neurological sequelae at 12 months, including: visual impairment ($n = 8$), deafness ($n = 3$), limb weakness ($n = 2$), dysphasia ($n = 2$), IRIS ($n = 8$) after 6 weeks to 12 months	Chen et al. [79,78]
2010 to 2016	*Cryptococcus neoformans*	RCS (SC)	China	Tertiary	CM patients	90	Unfavourable clinical outcome in pulmonary nodule (PN)-positive patients vs. PN-negative patients (72.5% vs. 48%, $P = 0.019$): Glasgow Outcome Scale score (on discharge) of 1 to 4, which indicates death, vegetative status, severe and moderate disability, was considered unfavourable clinical outcomes. [40/90 (44%) patients was PN-positive and 50/90 (56%) was PN-negative]	Cao et al. [39]

MC = Multi-centre; ND = Not determined; RSC = Retrospective cohort study; SC = Single centre

advanced disease may be excluded, and interventions and investigations follow a strict protocol. These factors may contribute to the lower mortality.[26,100] Furthermore, diagnoses such as toxoplasmosis, *Pneumocystis jirovecii* pneumonia, or other opportunistic infections may be more thoroughly screened for and managed in trial settings. This hypothesis is supported by Tenforde et al. (2020), who found that in sub-Saharan Africa, short-term mortality rate was 44% in observational studies and only 21% in randomized control trials.[101] Regardless, the mortality rate is unacceptably high, and global research to improve outcomes is needed.

A detailed summary of antifungal susceptibility data is presented in this review. We observed rising MICs to azoles (e.g., itraconazole, ketoconazole, and voriconazole), including *in vitro* 'resistance' to fluconazole in up to 30%,[41] with an increasing number of isolates with MIC ≥8 μg/ml between 2001 and 2012. However, the data are limited, and there is yet no clear association between MIC and clinical outcomes. Nonetheless, this observation calls for ongoing surveillance globally and investigation into the cause. Since *Cryptococcus* spp. are not transmitted from human to human, an environmental selection pressure for azole resistance could hypothetically be at play, as described for other fungal pathogens such as *Aspergillus*.[102] Two studies reported that in patients with HIV/AIDS, 11% of the *Cryptococcus* strains showed non-WT MICs to amphotericin B. A much lower percentage (< 2%) of the *Cryptococcus* strains showed non-WT MICs to amphotericin B in HIV-negative patients.

Cryptococcus gattii susceptibility data varied with molecular type and, in general, showed higher MICs to fluconazole compared with other azoles, including isavuconazole, itraconazole, posaconazole, and voriconazole. MICs for amphotericin B (0.25–0.5 mg/l) and 5-flucytosine (0.5–2 mg/l) were low. Therefore, future studies should continue tracking antifungal susceptibility and resistance for *C. gattii*, and their correlation with clinical outcomes.

There have been significant developments in prevention of CM over the past decade. Strong evidence has emerged for the cost-effectiveness of screening for *C. neoformans* cryptococcal antigenaemia with point-of-care antigen tests and treating positive cases, especially in low-resource settings or high-prevalence areas with high number of HIV cases.[103,104] However, there are no data on high-income countries, for *C. gattii*, or for patient groups outside of HIV/AIDS.

The systematic reviews of *C. neoformans* and *C. gattii* infections were characterized by sparse, frequently inconsistent data. For instance, there were few studies determining the incidence of infections in specific countries. However, it is known that *C. neoformans* is globally distributed, with some geographic variation between members of the species complex as the causative agent. For example, in Madagascar, 13.2% of HIV-infected patients had cryptococcal infection due to *C. neoformans* var. *grubii* (serotype A). Studies in South Africa, Ivory Coast, and India reported high prevalence of *C. neoformans* serotype A (VNI) (80%–86%) in adult and paediatric patients with cryptococcosis. *C. gattii* accounted for 11%–33% of cryptococcal infections overall in countries such as Australia, India, Brazil, and Africa.

Trends over the last 10 years for *C. neoformans* were difficult to assess due to incomplete data. However, the prevalence of *C. neoformans* serotype A VNI reported in two African countries and India was comparable and was consistently high (80%–86%) over the period of 2011–2020.[58,59,65] Apart from that, there was also a lack of country-level or global surveillance studies reporting the emergence of *C. gattii* infections in the last 10 years. The studies reporting the prevalence of *C. gattii* did not provide adequate data to assess global trends. Although studies conducted in African countries (Ivory Coast and Mozambique, respectively) showed a greater prevalence of 33% in 2019 compared with 1.6% in 2016,[58,57] these data are confounded by environmental and study population-related variables. Thus, it is not possible to make a conclusive statement about the trend in this region.

Our review has several limitations. In particular, we were unable to include non-English-language studies. We only included data from peer-reviewed and indexed publications and may therefore have missed valuable data.

Future perspectives

Future research on *C. neoformans* and *C. gattii* should focus on several key areas: (1) obtaining more robust clinical and microbiological data to support diagnosis and treatment; (2) developing new diagnostic tools and treatments; (3) understanding the genetic and molecular mechanisms of these pathogens; (4) understanding host-pathogen interactions and host's immunological response to the infection; (5) understanding the epidemiology of these pathogens in different regions and populations to identify high-risk groups and develop targeted prevention and control strategies.

Stronger surveillance systems and epidemiology studies would better inform the disease burden and the global distribution of *C. neoformans* and *C. gattii*. These may allow more rigorous identification of at-risk populations, dispersion patterns, and preventative measures. Better understanding of clinical manifestations and susceptibility profiles for different molecular types is needed and could potentially inform individualized treatment options. Conducting trials in cryptococcosis is complex because disease is rare, and it is difficult to recruit sufficient patients into clinical trials to detect impacts on clinical outcome, especially in non-HIV populations. Several groups have investigated surrogate markers of treatment effect (such as early fungicidal activity)[105,106] to allow smaller trials. Additional work in this area is needed.

Conclusion

Cryptococcus neoformans and *C. gattii* are important fungal pathogens. Both are globally distributed with significant incidence and mortality rates. Although rising MICs to antifungals have been reported, these are yet to show a clear impact on clinical outcomes. Careful ongoing systematic observations are warranted alongside detailed work to better define burden of infection in terms of both death and disability.

The knowledge gaps identified through this systematic review open avenues for future research studies to elucidate the genetic and molecular mechanisms underlying *C. neoformans* and *C. gattii* infections. Understanding host-pathogen interactions, the role of host immune responses, and the impact of specific molecular characteristics on disease outcomes can guide the development of targeted therapies and interventions. Furthermore, the observed disparities in global distribution and prevalence among different regions and populations emphasize the importance of region-specific surveillance and

tailored public health strategies. By addressing these research gaps, the disease burden of cryptococcosis can be reduced, and the health outcomes of affected individuals across the globe can be improved.

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Supplementary material

Supplementary material is available at *Medical Mycology* online.

Conflict of interest

AA-I has received personal fees for educational talks on behalf of Gilead and Pfizer.

None.

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