**INTRODUCTION**

In the 1980s, the global emergence of the human immunodeficiency virus (HIV) with its associated acquired immunodeficiency syndrome (AIDS), profoundly altered the epidemiology of many infectious diseases. Cryptococcosis, one of these infectious diseases, is an opportunistic invasive mycosis caused by encapsulated yeasts of the genus *Cryptococcus*, harbouring seven distinct species. This review systematically describes the clinical and biological aspects of cryptococcosis in the Democratic Republic of Congo (DRC) and estimates its 2020 burden in people living with HIV (PLHIV). Following PRISMA guidelines, we searched online databases for records of cryptococcosis/*Cryptococcus* spp. in the DRC. Meta-analysis was then performed to estimate summary statistics and the corresponding 95% confidence intervals (CI). A total of 30 studies were included. These included 1,018 cryptococcosis patients, including 80.8% with neuromeningeal cryptococcosis (NMC) and predominantly immunocompromised due to HIV/AIDS (97.6%). The NMC mean prevalence was estimated at 9.63% (95% CI: 5.99–14.07). More than one in two patients (52.7%) under treatment died. Monotherapy with fluconazole was the main treatment administered (80.6%). Furthermore, we estimate that about 9,265 (95% CI: 5,763–13,537) PLHIV had cryptococcosis in 2020, in DRC; of which about 4,883 (95% CI: 3,037–7,134) would have died in the same year. Among isolates in all included studies, 74 strains have been characterised. Of these, 82.4% concerned *Cryptococcus neoformans* sensu lato (s.l) (exclusively of serotype A and mostly of molecular types VNI and VNII) and 17.6% concerned *Cryptococcus gattii* s.l (belonging to serotype B/molecular type VGI). Cryptococcosis remains common with an unacceptably high mortality rate. A large number of PLHIV affected by and dying from cryptococcosis in 2020 demonstrates its heavy burden among the Congolese PLHIV. To mitigate this burden, it is important to improve the quality and accessibility of care for all PLHIV.

**KEYWORDS**
burden, cryptococcosis, *Cryptococcus neoformans/Cryptococcus gattii*, DRC, meta-analysis, systematic review
haploid species (Cryptococcus neoformans, Cryptococcus deneofor-
mans, Cryptococcus gattii, Cryptococcus bacillisporus, Cryptococcus
deutergattii, Cryptococcus tetragattii, and Cryptococcus decagattii) in
the Cryptococcus neoformans/Cryptococcus gattii species complexes,
and three non-pathogenic species (C. amylolentus, C. depauparatus
and C. luteus). Transmission occurs by inhalation of propagules,
after which the fungus may establish itself in the pulmonary tract.
In immunocompetent individuals, infection is often quickly resolved.
In immunosuppressed people, to the contrary, the yeast may dis-
seminate to the central nervous system, causing meningoencepha-
ritis (the so-called neuromeningeal form of the disease). HIV/AIDS
infection is considered to be the most important risk factor of cryp-
tococcosis. Other known risk factors include organ transplantation,
long-term corticosteroid therapy and some chronic illnesses, such as
autoimmune diseases. In 2014, the global incidence of cryptococcal
meningitis was estimated at 223,100, with a case-mortality rate of
over 80%, resulting in over 181,100 deaths. About three-fourths of
this burden falls on sub-Saharan Africa.

According to the 2021 United Nations Programme on AIDS
(UNAIDS) in DRC, in 2020, 74.5% of the 510,000 people living
with HIV (PLHIV) were on antiretrovirals (ARV). Despite ARV treat-
mant, 4.5% (17,000) of PLHIV yet succumbed to HIV infection.
Incomplete ARV coverage and the challenges of comprehensive HIV
management as routinely deployed in clinics, have favoured the oc-
currence of multiple opportunistic infections in the DRC. Thus, 63%
of PLHIV have suffered from at least one opportunistic infection.
Twelve per cent of PLHIV are in a bedridden state on their first visit
to a health facility. In Kinshasa, the capital city of the DRC, most
PLHIV (70%) admitted to the hospital have advanced HIV disease
with a low median CD4 count of 84 cells/μl. The resulting immuno-
compromised state increases their risk of developing opportunistic
infections.

There exists notable experience in DRC with the various mi-
crobiological and clinical presentations of Cryptococcus spp. and
cryptococcal disease, both classical and atypical. Indeed, while the
Cryptococcus neoformans spherical shape by microscopy was con-
sidered as the only morphology reference, the first observations
of elongated cryptococcal yeasts in DRC led to a better description
of the Cryptococcus neoformans variety gattii species. This was fol-
lowed by the description of the Cryptococcus neoformans variety gat-
tii meningitis in Congolese PLHIV whilst this species had exclusively
infected only immunocompetent patients at that time.

In many countries, data on the distribution of Cryptococcus spe-
cies and antifungal susceptibility profiles are available and regularly
updated, both in clinical and environmental settings. In the DRC,
epidemiological surveillance is still underdeveloped, despite the
growing magnitude of the HIV pandemic, the increasing number of
a socio-economically vulnerable population, and the precariousness
of the healthcare system. Therefore, this systematic review is con-
ducted to collect and analyse available clinical and biological data on
cryptococcosis in DRC, and to estimate its burden in the high-risk
HIV population. Doing so will help to understand the need, from a

2 | MATERIALS AND METHODS

This review was conducted following the Preferred Reporting
Items for Systematic Reviews and Meta-Analysis guide-
lines (PRISMA) and analysed published papers on human
cryptococcosis/Cryptococcus spp. from 1953 to 2021 in DRC (previ-
ously called Zaire).

2.1 | Search strategy

We searched Google Scholar, PubMed and African Online (from the
oldest paper to the last online search date, 30 September 2021) and
grey literature without any language restrictions using the terms
"Cryptococcus OR Cryptococcus neoformans OR Cryptococcus gattii
OR cryptococcosis OR torulopsis OR torulosis"; “Democratic
Republic of Congo OR Zaire OR Zairean OR Congolese OR Kinshasa
OR Lubumbashi OR Bukavu OR Kimpese.”

2.2 | Inclusion and exclusion criteria

Research articles and case reports were included if they involved
Congolese (Zairian) subjects or isolates. Reviews articles were not
included.

2.3 | Study selection and data extraction

Three authors (BZB, RNY and TTY) independently reviewed the studi-
es and selected them for consideration in this review. The hierarchi-
cal approach based on title, abstract and full text was used to assess
the relevance of reports. Additional results were obtained from arti-
cle references identified during the searches. Cryptococcosis preva-
ience, epidemiological and clinical (demographic characteristics, sex,
age, marital status and clinical signs), biological and therapeutic data,
as well as isolates characterisation, were then extracted from each
study as available.

2.4 | Data analysis

Data were collated in a Microsoft Excel sheet (Microsoft, Redmond,
MA, USA). Meta-analysis was performed using SPSS 26.0 software
(IBM, Armonk, NY, USA), to estimate the pooled summary statistics
and the corresponding 95% confidence intervals (CI). Descriptive
statistics, such as simple counts, ranges and percentages were used
to describe data.
2.5 Estimates of the 2020 annual burden of the neuromeningeal cryptococcosis (NMC) among PLHIV in the DRC

The category of PLHIV who are at high risk to develop NMC are deduced from the UNAIDS 2020 DRC estimates and are adapted to local data. More specifically this category includes adults (over 15 years of age) with HIV (430,000) who know their HIV status (75%) and have an LT CD4 count of fewer than 200 cells/µl (58.9% average) and were not under ARV (25%). In addition, we considered cohorts of those on ARV in treatment failure (21.6% average) and the lost to follow-up patients proportion (12.6%).

Thus, the number of PLHIV at cryptococcosis risk was estimated as follows: [Adults living with HIV (430,000) X proportion with known serostatus (0.75) X proportion with CD4 < 200 cells/µl (0.589) X proportion of untreated patients (0.25) + proportion of patients on ARV who are in treatment failure (0.216) + proportion of patients lost to follow-up (0.126)]. This procedure for estimating the at-risk HIV population and the cryptococcosis burden was adapted from earlier literature.

Moreover, mean NMC prevalence and the mortality rate as estimated in this manuscript were considered to estimate the cryptococcosis burden among PLHIV in DRC.

3 RESULTS

A total of 57 papers were retrieved (46 from database search and 11 from grey literature). After deduplication, 54 were retained for abstract review. Twenty-three studies were excluded due to the lack of specific data on cryptococcosis in DRC (Zaire). Out of 31 full-text articles examined, one additional study was excluded as it was a review article. Of 30 studies that were included in the present systematic review (Figure 1), 25 studies were conducted in the clinical setting, and four studies specifically focused on the laboratory characterisation of Congolese isolates. The basic characteristics of the clinical studies are summarised in Table 1.

From 1953 to 2021, 1,018 cryptococcosis patients have been reported from DRC (Zaire), including 823 (80.84%) with neuromeningeal forms, 125 (12.28%) with bloodstream forms, 47 (4.62%) with ocular forms, 19 (1.87%) with neuromeningeal and cutaneous-associated forms, three (0.29%) with neuromeningeal and bone-associated forms and one (0.09%) with the digestive form. HIV infection was the underlying risk factor in 97.6% of the cases (994 of 1,018 included patients). The remaining cases concerned patients whose HIV status was undetermined (because these cryptococcal infection occurred before the first characterisation of HIV/AIDS in the 1980s; this concerned 23 of 1,018 patients) and one HIV-negative and apparently immunocompetent patient (1 of 1,018). Based on the included prevalence studies, mean neuromeningeal cryptococcosis (NMC) prevalence was found to be 9.63% (95% CI: 5.99–14.07) among PLHIV, while the bloodstream cryptococcosis mean prevalence was 14.75% (95% CI: 12.2–17.3) in the same population.

All published data on cryptococcosis originated from medical centres in DRC provinces sharing borders with neighbouring countries (hence having higher border trade activities). The provincial cities concerned are as follows: (1) Kinshasa (10.47% prevalence, 95% CI: 6.27–16.17), (2) Lubumbashi (7.65% prevalence, 95% CI: 2.5–17.29), (3) Bukavu (10.9% prevalence) and (4) Kimpese (11.3% prevalence) as illustrated in Figure 2.

The patients included in this review were mostly women (51.7%, 213 out of 412), with a median age of 35 (28–41) years old and married (52%, 13 out of 25). Overall, the clinical presentation was mainly marked by headache (71.5%, 261 of 365), fever (69.9%, 255 of 365) and meningeal signs (36.9%, 135 of 365; Table 2). The intestinal cryptococcosis was characterised by chronic diarrhoea. Ocular involvement caused by Cryptococcus spp. was characterised by visual field defects, abnormal saccades, abnormal eye pursuits, ocular motor paralysis, papilledema and optic atrophy.

Biologically, the median LT CD4 count was 161.8 (98.0–499.6) cells/µl, with a wide distribution ranging from 79 to 610 cells/µl. The cerebral spinal fluid (CSF) was mostly clear (18/30), exhibiting elevated protein levels and lowered glucose levels in 96.5% (111/115) and 93% (107/115) of cases, respectively. The median CSF white cell
<table>
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<tr>
<th>No</th>
<th>Authors</th>
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<th>Publication year</th>
<th>Type of study</th>
<th>City</th>
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<th>General population (n)</th>
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<td>47</td>
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<td>J. Kivukuto Mutendela et al</td>
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<td>2013</td>
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<td>Bukavu</td>
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<td>24</td>
<td>Georges Yumba Numbi</td>
<td>2019</td>
<td>2020</td>
<td>Case report</td>
<td>Lubumbashi</td>
<td>IC$^b$</td>
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<td>1</td>
<td>NMC</td>
<td>-</td>
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<td>25</td>
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<td>2019</td>
<td>2021</td>
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<td>Kinshasa</td>
<td>HIV</td>
<td>94</td>
<td>NMC</td>
<td>-</td>
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</tbody>
</table>

$^a$Not defined.

$^b$Immunocompetent patient.
The count was 80 cells/µL (range 42.5–291.9) with neutrophil predominance in 67.9% of cases (19/28).

Although more than one diagnostic test was used for NMC diagnosis, direct India ink staining was the reference test used in most studies (264/357), followed by the cryptococcal antigen test (210/357) and culture (116/357).

Among the patients with severe cryptococcosis (including the neuromeningeal form, the ocular form, the neuromeningeal and cutaneous-associated form, the neuromeningeal and bone-associated form and the digestive form), 319 (out of 893) were reported to have been treated with antifungal drugs. This consisted of fluconazole monotherapy in 80.6% (257/319) of cases. Overall, the death rate in this category of patients was close to half the number of cases (49.3%). Of note, in the cohort with neuromeningeal cryptococcosis death rate was slightly higher (52.7%).

Furthermore, 74 Cryptococcus neoformans sensu lato (s.l) and C gattii s.l isolates were identified and reported in the DRC over the period covered by this systematic review. Among these isolates, 20.3% were recovered from environmental surveys, potentially implying that the DRC environment contains Cryptococcus spp.10 In clinical and environmental samples, biovar characterisation allowed identification of 13 isolates of C gattii s.l isolates (out of 74; 17.6%) and 61 isolates of C neoformans s.l (of 74; 82.4%). These isolates were serotyped as follows: 11 of serotype A (out of 15; 73.3%) and 4 of serotype B (out of 15; 26.7%). In all reports included in this review, only 16 isolates underwent molecular characterisation. Among these isolates, eight were characterised as molecular type VNI (50.0%), one as VNII (6.25%), and four of VGI (25.0%). In each study, molecular characterisation was performed according to molecular typing methods established by the International Society of Human and Animal Mycology (ISHAM) Cryptococcus neoformans/C gattii complexes working group. On

**TABLE 2 Clinical data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
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<tr>
<td>Female sex, n = 412</td>
<td>213 (51.7)</td>
</tr>
<tr>
<td>Median age (P25–P75) (year)</td>
<td>35 (28–41)</td>
</tr>
<tr>
<td>Marital status, n = 25</td>
<td></td>
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<tr>
<td>Single</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Married</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Divorced</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Widower</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Clinical signs, n = 365</td>
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</tr>
<tr>
<td>Headaches</td>
<td>261 (71.5)</td>
</tr>
<tr>
<td>Fever</td>
<td>255 (69.8)</td>
</tr>
<tr>
<td>Coma</td>
<td>52 (14.2)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>47 (12.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>22 (6.0)</td>
</tr>
<tr>
<td>Convulsions</td>
<td>42 (11.5)</td>
</tr>
<tr>
<td>Confusions</td>
<td>32 (8.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>54 (14.8)</td>
</tr>
<tr>
<td>Meningeal signs</td>
<td>135 (36.9)</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>16 (4.4)</td>
</tr>
<tr>
<td>Facial paralysis</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Visual disorders</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>Skin abscess</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Motor deficit</td>
<td>37 (10.1)</td>
</tr>
<tr>
<td>Clear CSF appearance, n = 30</td>
<td>18 (60)</td>
</tr>
</tbody>
</table>

*aBased on available data for each parameter.*
the contrary, one of each of the recognised DNA fingerprints patterns were identified using the DNA probe UT-4p: pattern II, V and VI (6.25% for each; Figure 3).41-44

Based on available published data meeting our inclusion criteria, and considering the DRC mean NMC prevalence as calculated and previously presented in this manuscript (9.63%), as well as the number of PLHIV at greatest risk of NMC (approximately calculated at 96,211), we estimate that 9,265 (95% CI: 5,763–13,537) PLHIV suffered from cryptococcosis in 2020. We also estimate that 4,883 (95% CI: 3037–7134) of these patients died the same year.

4 | DISCUSSION

About 1,018 cryptococcosis cases have been reported in the DRC from 1953 to 2021. The neumomenigeal form was the main clinical presentation. About half of the patients died from this infection. Although the global number of patients newly infected with HIV has decreased from 2.1 million PLHIV in 2015 to 1.5 million in 2020, and the access to ARV has significantly improved from 23.3 million PLHIV in 2018 to 27.5 million in 2020, the HIV epidemiological situation in the clinics remains worrisome, mainly in the advanced HIV management clinics.45-47 In Kinshasa (DRC), at the Centre Hospitalier Kabinda (CHK), about 70% of PLHIV hospitalised for the first time for AIDS complications exhibit a CD4 counts below 200 cells/µl. Among these hospitalised PLHIV, a monthly average of 12% suffer from the cryptococcal disease.8 Although these are data from a single hospital, it is likely that other institutions hospitalising PLHIV for AIDS-associated complications are dealing with similar or even higher figures. This suggests that the incidence data obtained in this study may yet be underestimated. Nevertheless, this review can serve as a starting point for larger epidemiological studies and development of a much-needed surveillance system.

Overall, cryptococcosis was mainly detected in females with an average of 32.6 ± 10.6 years old. Without being too disproportionate to the men infected proportion, the predominantly female distribution was in line with the general HIV sex distribution in the word as well as in the DRC (310,000 versus 120,000, HIV-positive women and men, respectively). Also in DRC, it appears that the HIV-positive men proportion who die each year (5.4%, 6500/120,000) is currently higher than the HIV-positive women proportion who succumb (3.1%, 9800/310,000), further increasing the HIV-positive women number at high risk of cryptococcosis.7,46 Paradoxically, in vitro studies suggest that macrophages offer better protection against Cryptococcus species in the presence of oestrogen, potentially explaining a decreased susceptibility for cryptococcal infections in females.48 On the contrary, in the mouse model of disseminated cryptococcosis, describes by Lortholary et al, it is shown that the expression of all cytokines in plasma and of tumour necrosis factor-α and interferon-γ in the spleen are significantly increased in female mice compared with male mice, but survival and fungal load were quite similar in both sex-groups.49 Interestingly, exposure to Cryptococcus ecological niches, once thought to be more pronounced in males than females, is outdated in the African context, especially in rural areas where field and other activities are no longer considered the preserve of males. Here, we observed that females living with HIV could still be the main group affected by cryptococcosis. This warrants further epidemiological and biological investigations. For example, a comparative study of the occurrence of cryptococcosis in each sex-proportion, in a single population controlled for confounding factors, could improve knowledge about the clinical presentation of this deadly disease. The interplay of possible oestrogen-mediated protection, with immunological aspects of HIV infection, would also need to be taken into consideration; especially since most of the above-mentioned experiments were not conducted in an environment of permanent HIV-Cryptococcus co-infection.

Cryptococcosis develops mainly in the T-cell immunosuppression context, which may be caused by HIV/AIDS or other risk factors such as solid organ transplantation, long-term corticosteroid therapy, malignancy, diabetes and cirrhosis. It can also occur in patients without identified immunosuppression, whose confirmation is highly dependent on the capacity of the available diagnostic equipment.50

**FIGURE 3** Percentage of Cryptococcus neoformans s.l and C gattii s.l isolates (n = 74) identified in the DRC at species or biovar (a) and molecular type level (b)
Nineteen of the 23 cases described in this manuscript without any specification of underlying risk factors occurred in the HIV/AIDS era (1995a). We assume that they would have been developed in HIV patients but this would just not have been mentioned in the paper. The remaining four cases were described before the 1980s. Interestingly, Numbi et al described a seemingly immunocompetent patient (610 CD4 cells per μl) who developed Cryptococcus neoformans s.i. meningitis, based on the diagnostic tools available in the region. However, it cannot be excluded that in similar cases there may be other underlying factors, not necessarily related to HIV/AIDS, which may similarly undermine immunity against infection by these yeasts. For example, the presence of auto-antibodies against GM-CSF (granulocyte-macrophage colony-stimulating factor) was reported to predispose otherwise immunocompetent patients to infections caused by certain species of Cryptococcus spp. These observations invite further research in factors that may predispose to infection by each of the various Cryptococcus species. Within the Cryptococcus gattii species complex, for example, C. gattii sensu stricto and C. deuterogattii are major cause of infections encountered among immunocompetent patients, whereas C. bacillisporus, C. tetragattii and C. decagattii are commonly associated with immunocompromised subjects. This tropism is also described for the C. neoformans species complex. To clear it up, some studies have compared virulence factors of C. gattii species complex to those found in other cryptococcal species, such as C. neoformans s.l. Indeed, while C. neoformans s.l mutants who lack the calcineurin gene (a gene involved in yeast resistance to high-temperatures conditions) become avirulent, Cryptococcus deuterogattii (VGIIa) strains remain viable at high temperatures, suggesting the involvement of other important thermal regulatory gene factors. In addition, the enzymatic activity of laccases in melanin production was found to be higher in serotype AD hybrids, followed by C. neoformans, C. bacillisporus, C. deuterogattii, C. deneiformans and C. gattii. On the contrary, isolates of serotype AD hybrids had the thinnest capsules compared with C. gattii, followed by C. neoformans, C. deneiformans, C. bacillisporus and C. deuterogattii which were thicker. The aforementioned case report of an immunocompetent individual infection could harbour features that have not been elucidated.

The occurrence of CSF increased leukocyte counts with neutrophil predominance is another interesting observation that calls for further studies. A bacterial aetiology of meningitis may be part of the differential diagnosis of meningitis in PLHIV. Therefore, to understand the phenomenon of neutrophil predominance in cryptococcal meningitis, studies would be needed that systematically exclude the phenomenon of neutrophil predominance or co-infection. Moussa Togola et al described a similar profile in the hospital setting in Togo.

In the DRC context, the diagnosis of cryptococcal meningitis was mainly based on direct microscopic analysis of CSF after India ink staining. However, CSF direct microscopic analysis has been poorly rated than cryptococcal antigen tests and culture. Treatment regimens consisted mainly of monotherapy with fluconazole. Worryingly, in recent years, the efficacy of this azole has been decreasing due to rising drug resistance. This may have contributed to the stark case-fatality ratio of cryptococcal infections observed in this study, which approximates 50%.

Of the 30 included studies, only 4 were conducted before 1980, which is considered the year marking the dramatic worldwide spread of HIV/AIDS to reach pandemic status or the quick rise of identified cases in the world. Although PLHIV already existed as early as 1920 in DRC, the later rise of AIDS cases in the world, particularly in western parts of the world, certainly raised the attention toward opportunistic infections in PLHIV such as cryptococcosis, which has already been described in DRC. We believe that this may explain the quick post-1980 rise of reports and data related to this opportunistic fungal disease in the world, particularly in the DRC where HIV is believed to have originated.

Additionally, it is believed that an increase in the vulnerable population, due to the HIV/AIDS pandemic in the 1980s, had a major influence on epidemiological changes in the prevalence of Cryptococcus species globally. Before 1969, most isolates in DRC were of the gattii biovar, known to thrive in immunocompetent hosts. The post-1970s period, which saw the dramatic spread of HIV/AIDS, also saw the emergence of the neoformans biovar. Evidence suggests that the emergence of the neoformans biovar was the result of the HIV/AIDS pandemic. Although other immunocompromising factors, not necessarily related to HIV, could be influencing host susceptibility to C. gattii, epidemiological evidence supports the existence of a link between AIDS-related immune status and Cryptococcus species in patients. Despite the heterogeneity in cryptococcal species distribution in DRC at that time, molecular characterisation of isolates has not been completed with new characterisation methods, let alone for newly isolated strains.

Such characterisation could, for example, provide a better understanding of the epidemiological, clinical and biological situation, while measuring the impact of circulating cryptococcal species in the burden of this deadly disease, as well as the link with environmental strains.

Whether a biological and epidemiological link between environmental and clinical isolates exist remains speculative. Indeed, Cryptococcus spp. in the Congolese environments have been reported both in the PLHIV homes, domestic cockroaches, pigeon and chicken droppings, as well as in the air and dust. In order to determine the significance of environmental reservoirs, Zairian isolates from PLHIV were subject to DNA fingerprinting. Surprisingly, environmental isolates were shown to have different DNA fingerprints compared with isolates recovered from patients. Large-scale causality studies will be of great importance for clarifying the relationship between environmental reservoirs and strains involved in clinical infections.

In DRC, the majority (82.4%) of strains are C. neoformans s.l. exclusively from serotype A, and most of the molecular types VNI and VNII. The remaining 17.6% are C. gattii s.l, serotype B, only molecular type VGII. Notably, C. neoformans type VNI and VNII have also been isolated in the DRC neighbouring countries such as Rwanda, Burundi, Tanzania and Uganda, hence raising questions on the possibility of fungal spread through birds and wind.
multilocus sequence typing (MLST), characterisation of strains of the C. neoformans/C. gattii complexes, the only sequence type ST32 strain previously isolated in Zaire (DRC) and recorded in the MLST ISHAM Fungal Database, was also identified in Tanzania and Uganda (https://mlst.mycologylab.org/).

We estimate that 9,265 (95% CI: 5,763-13,537) PLHIV suffered from cryptococcosis and 4,883 (95% CI: 3,037-7,134) died in 2020, in DRC. The number of deaths among PLHIV due to cryptococcosis approximately represents 28.7% of all PLHIV who died in the same year (17,000). While this annual incidence is not statistically different to the DRC incident numbers previously reported, these data are slightly higher than the incident cases reported across the borders in the Republic of Congo and Uganda. These numbers are much higher than those reported in Europe and Asia. Apart from differences in HIV prevalence in different countries, disproportionate results could perhaps also be attributed to differences in the HIV population at high risk of cryptococcosis considered in each study.

To relieve this humanitarian and public health burden, a Congolese national mycosis control programme should (1) consider the identification of high-risk people to develop mycosis, (2) focus on active screening of fungal diseases among this high-risk population, (3) improve the capacity and conditions of the diagnostic and therapeutic technical platform by increasing availability of adequate tests and therapeutic resources, (4) incite local research and (5) encourage continuous training of service providers.

5 | CONCLUSIONS

Data on cryptococcosis/Cryptococcus spp. in the DRC are historically rich but outdated and incomplete. While the cryptococcosis burden has been heavy over the years, clinical and biological presentations of the disease have mostly remained classic, apart from certain atypical situations. Because of the growing scale of HIV in DRC and the burden of cryptococcosis in this population, it is important to improve the quality and accessibility of care for all PLHIV. The establishment of a national fungal disease control programme can support these efforts.

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CONFLICT OF INTEREST

The authors report nothing to disclose.

AUTHOR CONTRIBUTION

Bive Bive ZONO: Conceptualization (equal); Formal analysis (equal); Investigation (lead); Methodology (lead); Project administration (lead); Resources (equal); Software (lead); Visualization (lead); Writing – original draft (lead). Daquid Kasumba: Writing – review & editing (equal). Hippolyte Situakibanza: Supervision (equal). Ben Bepouka: Conceptualization (equal). Marc Yambayamba: Formal analysis (equal). Ruth Nsuka: Resources (equal). Thimy Tshimanga: Resources (equal). Erick Kamangu: Writing – review & editing (equal). Marie-Pierre Hayette: Funding acquisition (equal); Supervision (equal); Validation (equal); Writing – review & editing (equal). Georges Mvumbi: Funding acquisition (equal); Supervision (equal); Validation (equal); Writing – review & editing (equal).

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