

Serious fungal diseases in Democratic Republic of Congo – Incidence and prevalence estimates

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Abstract

A literature review was conducted to assess the burden of serious fungal infections in the Democratic Republic of the Congo (DRC) (population 95,326,000). English and French publications were listed and analysed using PubMed/Medline, Google Scholar and the African Journals database. Publication dates spanning 1943–2020 were included in the scope of the review. From the analysis of published articles, we estimate a total of about 5,177,000 people (5.4%) suffer from serious fungal infections in the DRC annually. The incidence of cryptococcal meningitis, *Pneumocystis jirovecii* pneumonia in adults and invasive aspergillosis in AIDS patients was estimated at 6168, 2800 and 380 cases per year. Oral and oesophageal candidiasis represent 50,470 and 28,800 HIV-infected patients respectively. Chronic pulmonary aspergillosis post-tuberculosis incidence and prevalence was estimated to be 54,700. Fungal asthma (allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization) probably has a prevalence of 88,800 and 117,200. The estimated prevalence of recurrent vulvovaginal candidiasis and tinea capitis is 1,202,640 and 3,551,900 respectively. Further work is required to provide additional studies on opportunistic infections for improving diagnosis and the implementation of a national surveillance programme of fungal disease in the DRC.

KEYWORDS

aspergillosis, candidiasis, cryptococcosis, fungal infection, HIV/AIDS, Pneumocystis, tinea capitis, Tuberculosis

1 | INTRODUCTION

With a surface area of 2,345,000 km², DRC is the second largest country in Africa after Algeria. It has a population of around 95,326,000 inhabitants of which more than 60% live in rural areas.^{1,2} The DRC shares 9,165 kilometres of border with 9 countries (Figure 1).³ The country is currently ranks 176 out of 189 countries on the Human Development Index. In 2019, GDP per capita \$545, a 2.13% decline from 2018.⁴ With regards to health system architecture, the Ministry of Public Health is structured in the form of a 3-level pyramid. The national level has normative, regulatory and

tertiary care provision responsibility. The provincial level provides technical supervision, monitoring and translation of directives and offers secondary reference health care. The operational level includes 516 Health Zones (HZ) with 393 General Reference Hospitals and 8,504 planned Health Areas (HA) of which 8,266 have a Health Centre. The function of this level is to implement the primary health care strategy. At this level, there are 2004 health centres for the detection and treatment of tuberculosis (CSDT) and 4,587 sites for the detection and treatment of HIV (SDT). In 2019, the DRC integrated 1752 existing CSDTs into the management of HIV-TB co-infection. A HZ is a geographically limited space covering a theoretical

population of 100,000 to 150,000 inhabitants with a general reference hospital (GRH). The health system also integrates private for-profit and not-for-profit sector health facilities (health services of non-governmental organisations and faith-based organisations). The majority of GRHs lack intensive care, laboratory services (with parasitology, biochemistry, bacteriology and haematology services) and imaging X-ray, ultrasound, electrocardiogram, non stress test, Optical coherent tomography, etc). In the same way, the three University Clinics are under-equipped to serve as tertiary reference facilities. The DRC has 29 pharmaceutical industry companies, and wholesale supply and distribution is provided by 150 authorised establishments.^{5,6} There is an imbalance in the organisation of training courses and in the equitable distribution of health workers between rural and urban areas and between health structures. Health staff are concentrated in the capital Kinshasa and in the urban centres of

the provinces. Health workforce indicators are low, using the benchmark ratio of 1 doctor per 10,000 inhabitants, only three out of ten provinces have staff numbers that meet or exceed international standards.³ Communicable diseases with epidemic potential are an ongoing issue in the DRC.^{3,4} The Director General for Disease Control has placed certain infectious diseases under epidemiological surveillance, including acute flaccid paralysis, cholera, leprosy, neonatal tetanus, plague, viral haemorrhagic fever, yellow fever, monkey-pox, measles, avian flu, bloody and simple diarrhoea, meningitis, malaria, typhus, pertussis, typhoid fever, acute respiratory infections, sexually transmitted infections, several neglected tropical diseases (NTDs), AIDS and tuberculosis (TB). Despite their known association with co-infections such as HIV and TB, fungal diseases are a glaring omission from the priority list of infectious diseases being surveilled. DRC is in a phase of epidemiological transition, characterised by an

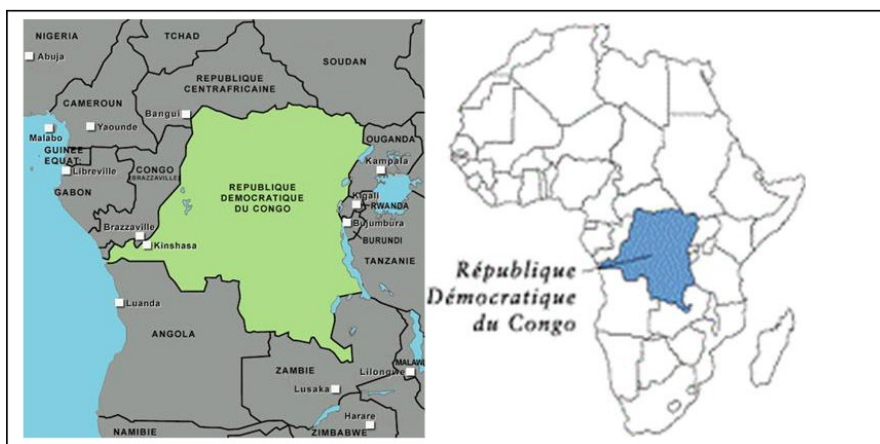


FIGURE 1 Map of the Democratic Republic of Congo with the neighbouring countries

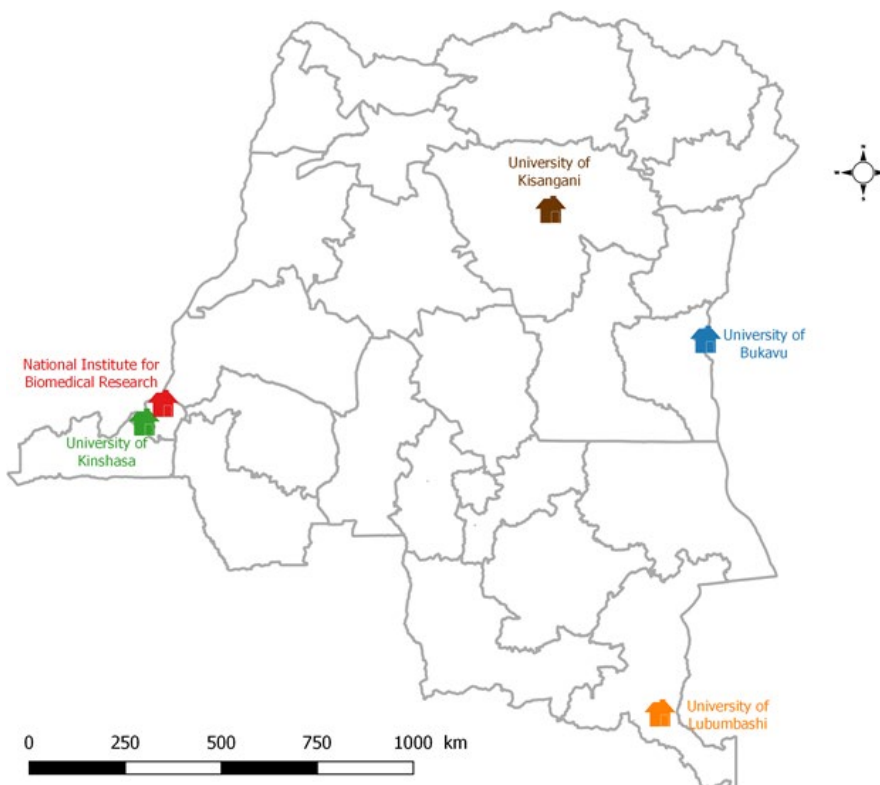


FIGURE 2 localisation of main institutions publishing articles in Democratic Republic of Congo]

increase in the incidence of non-communicable diseases such as cancer and diabetes which heighten the need to address fungal infections as a public health issue of growing significance.

There is no surveillance programme for fungal diseases in the DRC.⁶ Given the poor availability and accessibility of diagnostics in the DRC, fungal infections unfortunately remain grossly underestimated. Despite the paucity of data, some studies have been conducted in DRC which allow for baseline modelling to be carried out. The aim of this literature review is to take stock of the current incidence and prevalence of fungal infections in DRC.

2 | MATERIALS AND METHODS

This literature review was based on articles about fungal infections using the Google Scholar and PubMed/Medline search engines, African newspapers, health reports, epidemiological journals in DRC and WHO reports (Figure 2). The articles searched were mostly in English. The keywords searched were: fungal infection, opportunistic disease, HIV/AIDS, tuberculosis, chronic pulmonary, cryptococcosis, histoplasma, all associated with DRC. The oldest article retrieved was from 1943 and the most recent was from 2020. There are few studies on fungal diseases in the DRC and many of them are more than a decade old so we extended our searches to studies in border countries that have already estimated the burden of some fungal infections. We first considered Central African Countries and then, other sub-Saharan African countries. The countries chosen were those that are close to the four major universities in the DRC that use published articles. Where no article was found from the DRC or neighbouring countries, we used data from other countries within Africa and if this was not available, then data from other countries outside the African region. The socio-demographic data were taken from the National Health Development Plan 2016-2020 reports and the 2017 reports of the National Statistics Institute (Table 1). The HIV prevalence and deaths were taken from the 2019 UNAIDS report. To evaluate the incidence of children and adults at risk of developing the OIs, we have assessed different factors impacting on OI incidence in the literature.⁷ Considering that people living with HIV infection (PLWHIV) who are not on ART generally develop profound immunodeficiency over 7 years for adults and 5 years for children and that the rate failure of ART is 11%, we estimated the population of PLWHIV at risk.⁸ TB rates were taken from the WHO Global report 2019, and we derived the pulmonary TB survivors. Asthma prevalence in adults living in Kinshasa was assumed to apply to the whole country.⁹ Chronic obstructive pulmonary disease (COPD) prevalence was taken from the Cameroon¹⁰ and it was assumed that 10.5% were admitted to hospital each year, as in Algeria.¹¹ Lung cancer was taken from Global cancer observatory (Globocan)¹² and acute myeloid leukaemia from the WHO expert committee.¹³ No stem cell or organ transplantation procedures are done in the DRC. We used the various populations and denominators and estimated prevalence or incidence of different fungal diseases using

information from multiple sources, all described in Table 2. The assumptions used to compute annual incidence or prevalence are also shown.

3 | RESULTS

3.1 | Country's profile

In the DRC, endemic diseases have a high mortality: malaria is the leading cause of death with a prevalence of 23%. HIV/AIDS and TB are also common. The DRC is among 30 countries with the highest burden of TB ranking 11th in the world and 3rd in Africa. It is also one of 13 countries facing the dual challenge of HIV-TB co-infection and drug resistance at the same time.^{3,14} Although HIV prevalence is declining in the DRC, at 0.8%, its epidemiology is complex. It is higher among women in some provinces and four times higher in urban areas. Apart from HIV and TB co-infection, which are well supported and documented, the prevalence and incidence of other opportunistic infections is not known due to the lack of any diagnostic capability in most health facilities.

3.2 | Review of serious fungal infections

The scarcity of articles on fungal infections has prompted us to use prevalence or incidence from other countries to estimate the burden in the DRC. The summary shown in Table 2 and 3 is derived from the various populations at risk and the rate per 100,000 inhabitants. Each year in DR Congo approximately 5,079,278 people are affected by fungal diseases, 5.32% of the whole population.

3.2.1 | Fungal skin infections: Tinea capitis and neglected tropical diseases

In children, tinea capitis is the most common superficial fungal infection. Our estimation is 3,551,862 children have tinea capitis, a rate of 3,726 per 100,000. An old study (1959) gave a disparate prevalence of tinea capitis by region, the lowest prevalence was 2.9% in the middle part of the DRC and the high was 20% in the East part.^{42,43} No recent study is published, but it is a common problem. Neglected tropical skin fungal diseases have not been reported recently. An old study from the Belgian Congo (currently DRC) found 9 cases of mycetoma in 1954.⁴⁴ A strain of *Catenulostroma chromoblastomycosum* is deposited with the information that it is from a case of chromoblastomycosis from Zaire (currently DRC).⁴⁵ *Sporothrix schenckii* is a ubiquitous fungus, causing mostly non-life-threatening localised infections of the skin and subcutaneous tissues - only one case is reported from DRC in an HIV patient.⁴⁶ No data was found for *basidiobolomycosis*, *chromoblastomycosis*, *rhinoporioidiosis* or *Conidiobolus* or *Emergomyces* infections. They are probably rare.

Data	Number	Reference	Comments
Population	95 326 400	²	2019
HIV infection	520 000	¹⁵	Prevalence 2019
Pulmonary tuberculosis	233 520	¹⁶	Annual incidence 2019
Asthma numbers in adults	3 551 860	²	With 2019 population
Acute myeloid leukaemia	380	¹⁷	Annual incidence

TABLE 1 The basic demographics of the country

Abbreviation: HIV, Human Immunodeficiency Virus.

TABLE 2 Assumptions underlying the assessment of serious fungal diseases burden

Fungal disease	Underlying condition	Assumptions made	References
Cryptococcal meningitis	HIV/AIDS	12.2% of AIDS patients	¹⁸
<i>Pneumocystis pneumonia</i>	HIV/AIDS	10% PCP as newly diagnosed HIV/AIDS adults over 2 years	¹⁹
Disseminated histoplasmosis	HIV/AIDS	1.5% of advanced HIV disease	^{20,21}
Invasive aspergillosis	HIV/AIDS; COPD; Leukaemia; lung cancer	10% of AML patients develop IA. Rate in non-AML same as in AML. 1.3% of admitted COPD patients, 2.6% of lung cancer patients and 4 per 1000 HIV/AIDS patients develop IA	²²⁻²⁶
Chronic pulmonary aspergillosis (CPA)	Tuberculosis, COPD	22% of TB survivors with cavities, 2% of those without cavities and assumed pulmonary TB is the underlying diagnosis in 80% of all CPA cases	²⁷⁻²⁹
Allergic Broncho pulmonary aspergillosis (ABPA)	Asthma	2.5% of adult asthmatics	³⁰ ³¹
Severe asthma with fungal sensitisation (SAFS)	Severe asthma	33% of worst 10% of adult asthmatics.	³²
Candidaemia		5/100,000 (mean of 2-11/100,000) with 30% in ICU (critical care and post-surgical patients) and 70% in cancer and other immunocompromised patients	³³
<i>Candida peritonitis</i>	Pancreatitis, major abdominal surgery	1 patient with hospital-acquired (almost all post-operative) <i>Candida peritonitis</i> for every 2 patients with candidaemia, in ICU	³⁴
Oral candidiasis	HIV/AIDS	90% of untreated HIV patients	^{35,36}
Oesophageal candidiasis	HIV/AIDS	20% of patients not on ARVs and 0.5% of those on ARVs	^{37,38}
Recurrent candida vaginitis ($\geq 4x/year$)		6% of adult women	³⁹
Mucormycosis		Affects 2 per million of the population based on data from Europe	⁴⁰
Tinea capitis		7.38% of school-age children	⁴¹

Abbreviations: AML, Acute myeloid leukaemia; ARV, antiretroviral; COPD, Chronic obstructive pulmonary disease; HIV/AIDS, Human Immunodeficiency Virus/ Acquired ImmunoDeficiency Syndrome; IA, invasive aspergillosis; ICU, Intensive Care Unit; PCP, *Pneumocystis pneumonia*; TB, Tuberculosis.

3.2.2 | *Candida* diseases

No data on recurrent vulvovaginal candidiasis (rVVC), candidaemia and *Candida peritonitis* were found. The prevalence of rVVC is thought to be 2523/100 000, using a 6% proportion of women aged between 15 and 54, or to affect about 1.2 million women.³⁹

Other data from Cameroon found 34.8% of women had vaginal candidiasis, suggesting this problem is more frequent than in Europe and the USA, and likely to be underestimated by our estimate.⁴⁷ Although blood culture is fairly widespread in DRC, there are no data on the frequency of candidaemia. Using a low average country incidence, of 5/100 000,⁴⁸ we estimate ~4,770 patients annually. In France, the ratio of candidaemia to intra-abdominal candidiasis

TABLE 3 Estimate of serious fungal infections in Republic Democratic of Congo

Serious Fungal Infection	Estimate	No underlying disease	HIV/AIDS	Respiratory disease	Cancer +immunocompromised	Critical care +surgery	Rate/100,000	Total Burden
Cryptococcal meningitis	I	-	6168	-	-	-	6.5	6168
Pneumocystis pneumonia adult	I	-	2800	-	-	-	2.9	2800
Pneumocystis pneumonia children	I	-	595	-	-	-	0.6	595
Pneumocystis pneumonia total	I	-	3016	-	-	-	3.2	3016
Invasive aspergillosis	I	-	380	2560	123	-	3.2	3063
CPA post TB	I	-	-	11,580	-	-	12.1	11,580
CPA post TB	P	-	-	36,500	-	-	38.3	36,500
CPA - all	P	-	-	54,700	-	-	57.4	54,700
ABPA	P	-	-	88,800	-	-	93.2	88,800
SAFS	P	-	-	117,200	-	-	123	117,200
Candidaemia	I	-	-	-	3340	1430	5.0	4770
Candida peritonitis	I	-	-	-	-	715	0.8	715
Oral candidiasis	I	-	50,470	-	-	-	52.9	50,470
Oesophageal candidiasis	I	-	28,800	-	-	-	30.2	28,800
Recurrent Candida vaginitis (>4x/year)		1,202,640	-	-	-	-	2523	1,202,640
Mucormycosis	I	-	-	-	190	-	0.2	190
Histoplasmosis	I	-	-	840	-	-	0.9	840
Fungal keratitis	I	12,680	-	-	-	-	13.3	12,680
Tinea capitis	P	3,551,900	-	-	-	-	3726	3,551,900
Total burden		4,767,220	92,229	312 180	3653	2145		5,177,427

Abbreviations: ABPA, Allergic bronchopulmonary aspergillosis; CPA, Chronic pulmonary aspergillosis; I, incidence; P, prevalence; SAFS, Severe asthma with fungal sensitisation; TB, tuberculosis.

is 2:1, in intensive care.⁴⁹ On this basis, we anticipate on 715 cases (0.8/100,000), but this could be erroneous as there are few intensive care beds, but conversely many patients present with severe acute abdominal emergencies.

Oral candidiasis and oesophageal candidiasis as opportunistic infections in HIV are common. We estimated an annual incidence of 52.9/100 000 and 30.2/100,000 respectively. This equates to over 50,000 oral candidiasis patients in those with CD4 <200/ μ l^{35,50} and 28,800 oesophageal candidiasis cases.³⁷ In addition, a local cross-sectional report from 1988 found 24% of HIV patients to have oral candidiasis.⁵¹

3.2.3 | HIV-associated infection fungal disease

In 2019, 258,610 of 520,000 people living with HIV/AIDS (PLWHIV) are on ART, that is ~50%, with 15,000 deaths, 9,600 in adults.¹⁵

There were an estimated 56,074 at risk of acquiring an opportunistic infection, based on a 7 year decline in CD4 counts to <200 μ l in those not on ART, and assuming an 11% ART failure rate in those on ART (an the literature many opportunistic fungal infections are described in PLWHIV in those not on ART and immunocompromised. In the DRC, none of these infections are well documented. Considering *Pneumocystis pneumonia* (PCP) occurred an annual rate of 5% in at risk PLWHIV,¹⁹ we estimate ~2804 episodes in adults and 595 in children, a total of 3,400 or 3.6 per 100,000. Cryptococcal meningitis (CM) was estimated at a rate of 11% in at risk PLWHIV, based on a study in the east of the DRC⁵² an annual incidence 6168 or 6.5 per 100 000. The related species *Histoplasma capsulatum* have two variety: *capsulatum* and *duboisii* cause important deep mycoses and have been reported in PLWHIV. In the DRC mainly *duboisii* variety infections are reported. One study mentioned five cases.⁵³ So, we tentatively estimate 840 annual cases or 0.9 per 100 000 people.

3.2.4 | Fungal asthma and aspergillosis

There are approximately 3,551,860 adults with asthma in the DRC, 6.9% of the adult population in 2019.^{9,54} According to the only African study on allergic bronchopulmonary aspergillosis (ABPA) from South Africa, we estimated that 2.5% (88,800 people) of these asthmatics developed ABPA.³⁰ Severe asthma with fungal sensitisation (SAFS) prevalence is estimated at 117,211 adults.²⁷ The incidence of TB in the DRC in 2019 was 278,000 with 233,520 with pulmonary disease. Only 30,000 people developed TB with HIV. Given a 12.8% mortality, there were 180,920 PTB.¹⁶ After pulmonary TB, we estimate a prevalence of chronic pulmonary aspergillosis (CPA) over five years of 36,500 people (a rate of 38.3 per 100 000) and annual incidence was 11,579 (a rate of 12.1 per 100 000). Assuming that pulmonary TB comprises 67% of the cases, the total prevalence estimate for CPA is 54,700. To estimate invasive aspergillosis (IA), we started with a likely annual incidence of 380 (22%) acute myeloid leukaemia (AML) patients per year of a total of 1723 leukaemia excluding myelodysplastic syndrome.¹⁷ In this group of patients 76 IA patients are a conservative estimate.^{26,55} Globocan estimate 1811 lung cancer cases in the DRC,¹² of which a 2.6% are thought to develop IA (47 patients). No transplant programmes (solid organ and haematopoietic cell) are ongoing in the country. We also estimated that 4% of the 9,600 HIV deaths are linked to IA, a total of 380 patients. For chronic obstructive pulmonary disease (COPD) there are 193,007 admissions to hospital per year (10.5% of the total COPD population) and 1.3% develop IA, a total of 2,510 patients.⁵⁶ Overall, IA annual incidence is estimated at 3.2 per 100 000 (3016 people). Mucormycosis was estimated 0.2 per 100,000 patients. So, 190 people were affected.

3.2.5 | Other fungal diseases and immunocompromised status

Fungal keratitis was not recorded in any publication. However corneal disease and opacities are relatively frequent, some due to parasites such as in onchocerciasis. In one study of 750 people in an area hyperendemic for onchocerciasis, visual loss was found in 8.5%, of which 2.2% had monocular blindness with a corneal scar found in nearly 10% of patients.⁵⁷ Many of these cases are likely to be due to unrecognised fungal keratitis. We have estimated an annual incidence of 13/100,000 from data from other parts of Africa and 12,678 people are affected.⁵⁸ There is no nationwide registry of surgeries but 75 abdominal surgeries annually were reported in a local university hospital in Southeastern DRC.⁵⁹

4 | DISCUSSION

This study is the first to comprehensively estimate the burden of fungal diseases in the DRC. Our burden estimate of 5,177,427 people affected by serious fungal disease (>5.5% of the population) indicates significant morbidity and probably mortality in the DRC.

Extended on both sides of the Equator, the DRC has four microclimates, including a hot and humid equatorial climate in the centre, a tropical climate in the South and North, an oceanic climate at the mouth of the Congo River and a temperate climate in the east. Rainfall varies from 800 mm on the shores of Lake Tanganyika to over 2,500 mm in the mountainous regions west of Lake Kivu. The hydrographic network is dense, with a large river running through the whole country. Surface water resources (river, streams and lakes) represent 52% of the continent's reserves, covering 86,080 Km² or 3.8% of the country's surface area. Most of the lakes are in the East: Tanganyika, Kivu, Albert, Moero and Edouard and Upemba (in the middle of Katanga).³ This climate is conducive to the sustainability of several endemic diseases: Malaria, enteric diseases, TB, cholera and a diverse population of mostly unknown and undiagnosed endemic and opportunistic fungal pathogens.⁴² Fungal infections are frequent opportunists in HIV infection and observed clinically in the DRC.⁶⁰ The most common are oral and oesophageal candidiasis, PCP, cryptococcal meningoencephalitis and histoplasmosis. In addition, TB is the most common predisposing factor for the development of CPA. The clinical presentation of PCP, histoplasmosis and CPA is similar to TB and often mistaken. Among those who die, there is currently no indication of any fungal aetiologies, because it is not looked for and autopsy is rarely done.¹⁵

From 2016, current policy is to "test and treat" HIV care in order to achieve the 90-90-90 targets, reducing transmission and progression to advanced HIV disease and death. These targets were to ensure that by 2020, 90% of people living with HIV know their HIV status, 90% of these people are on antiretroviral treatment (ART) and 90% of people on ART have an undetectable viral load. In 2020, all these targets are missed.^{61,62}

Oesophageal candidiasis is common with HIV and was frequently reported with oral candidiasis. Our estimates place it as the most common opportunistic infectious disease in HIV after oral candidiasis, but we have not estimated the prevalence of cutaneous dermatophyte infections which are also common in HIV. The prevalence of HIV-associated oesophageal candidiasis in sub-Saharan Africa was 12%, with a range from 1% to 52% across individual studies.⁴¹ However, oesophageal candidiasis can also be diagnosed in otherwise healthy people such as those receiving antibiotic therapy which promotes the overgrowth of *Candida*.⁶³

Pneumonia is one of the leading causes of mortality and morbidity in children under five years. In low and middle-income countries, poverty, poor living conditions, inadequate health services, malnutrition and HIV are the risk factors for pneumonia. The risk of death is highest in HIV-infected children with pneumonia in Sub-Saharan Africa.⁷ In the DRC, lethality is estimated at 4.9% without distinction of aetiologies.⁶⁴ PCP occurs in children and other immunocompromised persons and is a common cause of severe pneumonia in HIV children. *Pneumocystis jirovecii*, which causes PCP, was classified as a protozoan, but now is identified as a fungus. Rates of 3.6 to 11% were described for Tanzania, Congo and Ivory Coast in the first decade of the AIDS epidemic.⁶⁵⁻⁶⁷ PCP remains the most important AIDS opportunistic infection in the developed countries; by contrast

tuberculosis is the most frequent in sub-Saharan Africa countries. The incidence of PCP among 18 sub-Saharan African countries was 15.4%.⁶⁸ We have estimated a conservative incidence of 595 children with PCP and HIV infection, which is almost certainly an underestimate given 5,000 paediatric HIV deaths in 2019. Our estimate of only 2,804 adult cases of PCP is also conservative, given 9,600 AIDS deaths and only a 70% response rate for PCP in Africa,⁶⁹ if treated. Trimethoprim-sulfamethoxazole (TMP-SMX) resistance has emerged and leads to treatment failure increasing death.⁷⁰ The case fatality ranges from 10% to 27% in sub-Saharan Africa countries.⁷¹

Cryptococcal meningitis is a common problem in advanced HIV disease in the DRC, with an 11% incidence documented. This translates into over 6000 cases annually, a similar figure to a 2017 global and national estimate.⁷² With only India ink available for diagnosis (~80% sensitivity)⁷³ and fluconazole available for therapy,⁷⁴ at least 80% of these patients will die currently.

Disseminated histoplasmosis has been described in the Cameroon caused by both species of *Histoplasma*. The prevalence of histoplasmosis in advanced HIV infection in Cameroon is 13% and is documented more in HIV positive patients than negative patients.²⁰ Histoplasmosis was previously reported sporadically in the DRC.⁷⁵ Based on these limited data, we have assumed a 1.5% annual rate of disseminated histoplasmosis in the DRC in advanced HIV disease. This needs confirmation with antigen (or PCR) diagnosis.

The CPA spectrum includes aspergilloma, chronic cavitary pulmonary aspergillosis and chronic fibrosing pulmonary aspergillosis. The literature notes some of the highest burdens of CPA after TB in some African countries. Ahead is Nigeria (120,747) followed by Uganda (18,000), Kenya (12,927) and Tanzania (10,437).³³ As pulmonary TB is relatively common in the DRC, we estimate an annual incidence in cured TB patients of over 11,000 patients, and a 5 year period prevalence of ~36,500 patients. Without *Aspergillus* IgG antibody detection, most will go undiagnosed and so inappropriately treated with antibiotics and anti-TB therapy, but not antifungal therapy. The mortality of CPA in Africa has been well described, but in other countries is 50%-80% over 5 years in non-HIV patients.⁷⁶

ABPA is an uncommon complication of asthma or cystic fibrosis usually caused by *Aspergillus fumigatus*. The estimated prevalence derives from South Africa. In Africa, the highest burden is found in Algeria (310,310) followed by Nigeria (93,649), Tanzania (18,987), Uganda (18,700), Kenya (17,696) and Senegal (9976).³³

Severe asthma has a heterogeneous nature. Depending on the definition used, 5% to 15% of all patients with asthma are classified as severe and a large proportion have poorly controlled disease. The mortality due to asthma in Africa was 0.7% in 2017.³² In Africa, the diagnosis of asthma is still a challenging issue. No African country has registered yet with the International Severe Asthma Registry. Data about severe asthma deaths are scarce.^{77,78} SAFS is uncertain as this disease has been recently described, it was conservatively estimated that 30% of patients with severe asthma have or develop SAFS in the world. In Africa the highest burden was described in Egypt (176,661)

and the lowest is Kenya (23,359).³³ Antifungal therapy for SAFS is effective and mostly affordable in Africa, unlike many of the new monoclonal agents used in Europe and the USA.⁷⁹

Tinea capitis is a public health problem caused by the dermatophytes *Epidermophyton*, *Microsporum* and *Trichophyton* spp. Without a recent review of dermatophytes in DRC, studies from other countries have been used to estimate the prevalence in school-age children. Biguet's study in 1943 demonstrated that the prevalence varied from one region to another in the DRC.⁴³ Bongomin made the same observation in Tanzania where this pathology had a correlation with socio-economic conditions and in Rwanda it was demonstrated that different species of dermatophytes predominated in different regions.⁴¹ In a large epidemiological study involving 15,000 people, *M langeronii* (renamed *M audouinii*) (41.8%) and *T violaceum* (32.3%) have been reported as the main causative agents of tinea capitis in Congo, Rwanda and Burundi.⁴¹

No recent report of fungal NTDs diseases has been published in the DRC. Some cases were reported decades ago. The lack of epidemiological data does not exclude their presence in the DRC. A systematic review of blastomycosis from 25 African countries and 5 from middle eastern countries reported a total of 172 cases with only one isolate from the DRC.⁸⁰

No data on fungal keratitis are published from the DRC, but diagnosis with routine eye examination including visual acuity testing, slit-lamp biomicroscopy and direct ophthalmoscopy can all contribute. The key tests include corneal scraping with direct microscopy and fungal culture. Adequate microbiology laboratories are only present in tertiary hospitals, some private hospitals and GRH's (Table 4). Clinical features alone may be suggestive of a fungal aetiology of corneal ulcer, but are not perfect.^{81,82}

The WHO recommended Essential in vitro Diagnostics list now includes rapid tests for *Histoplasma* antigen, *Cryptococcus* antigen, *Aspergillus* antigen, *Aspergillus* antibody and *Pneumocystis* PCR, the latter three tests being added in 2021.⁸⁴ Without access to these diagnostics, patients suffering from serious fungal infections nearly always die. A recent survey of WHO EDL in DRC revealed that only four of the recommended nine diagnostic modalities for fungal disease are available in the DRC and of those that do exist, availability and penetration are variable across the country. None of the newer recommended rapid tests are present in the country outside of the limited confines of small scale research studies. Vulnerable patients are underserved in this regard and this invariably leads to a high level of preventable mortality for a significant proportion of the population. Of the WHO recommended antifungal drugs that are critical for providing optimal treatment for fungal disease, only 30% of the required minimum set of antifungal medication is available in the DRC. For HIV patients, flucytosine and amphotericin B when used in combination with each other and coupled with an accurate diagnosis of cryptococcal meningitis and therapeutic interventions increase survival chances of the estimated 6,170 HIV patients with cryptococcal meningitis by up to 70%⁷⁴ Neither flucytosine or amphotericin B are available in DRC. For TB patients, itraconazole and

TABLE 4 Essential diagnostics and antifungal agents in Democratic Republic of Congo

WHO recommended Essential in vitro Diagnostics	WHO recommended Essential antifungal Medicines
Available	Available
Direct microscopy	Fluconazole
Blood culture ^a	Griseofulvin
Histopathology	Nystatin
Fungal culture ^{a, b}	Ketoconazole (withdrawn internationally) ⁸³
Unavailable	Unavailable
<i>Histoplasma</i> antigen	Amphotericin B
<i>Aspergillus</i> antigen	Itraconazole
<i>Aspergillus</i> antibody	Voriconazole
<i>Pneumocystis</i> PCR	Flucytosine
Cryptococcal antigen (CrAg)	Natamycin eye drops
	Capsogungin
	Micafungin
	Anidulafungin

Abbreviations: PCR, Polymerase chain reaction; WHO, World Health Organization.

its alternative, voriconazole are essential antifungal drugs currently unavailable in the DRC which, if made available, could treat an estimated 54,745 people currently living with the debilitating effects of invasive or chronic aspergillosis, and many more with fungal asthma. Natamycin, an effective treatment usually available in high-income countries could contribute significantly to saving the eyesight of 12,680 people who are at risk of blindness due to undiagnosed fungal keratitis. Without significant redress, the high numbers of people dying or living with a severely impaired quality of life from fungal disease in DRC will remain and with emerging threats such as antifungal resistance, and the rise of non-communicable diseases, could be set to increase. Efforts should be made to ensure the provision of access to essential diagnostics and treatment, underpinned by increased surveillance, research and capacity building of health professionals. The implementation of dedicated programmes to integrate fungal disease care pathways into the health system must be prioritised by public health authorities and donors.

CONFLICT OF INTEREST

No COI for the authors.

AUTHOR CONTRIBUTIONS

Guyguy Kamwiziku: Investigation (equal); Methodology (supporting); Writing-original draft (lead). **Jean Claude Makangara:** Methodology (supporting); Writing-original draft (supporting). **Emma Orefuwa:** Investigation (equal); Writing-original draft (supporting). **David Denning:** Conceptualization (lead); Methodology (lead); Writing-review & editing (lead).

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