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ORIGINAL ARTICLE

Current burden of serious fungal infections in Republic of Congo

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Abstract

Background: The Republic of Congo (RoC) is characterised by a high prevalence of tuberculosis and HIV/AIDS, which largely drive the epidemiology of serious fungal infections.

Objective: We aimed to estimate the current burden of serious fungal infections in RoC.

Material and Methods: Using local, regional or global data and estimates of population and at-risk population groups, deterministic modelling was employed to estimate national incidence or prevalence of the most serious fungal infections.

Results: Our study revealed that about 5.4% of the Congolese population (283 450) suffer from serious fungal infections yearly. The incidence of cryptococcal meningitis, *Pneumocystis jirovecii* pneumonia and disseminated histoplasmosis in AIDS patients was estimated at 560, 830 and 120 cases per year. Oral and oesophageal candidiasis collectively affects 12 320 HIV-infected patients. Chronic pulmonary aspergillosis, 67% post-tuberculosis, probably has a prevalence of 3420. Fungal asthma (allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitisation) probably has a prevalence of 3640 and 4800, although some overlap due to disease definition is likely. The estimated prevalence of recurrent vulvovaginal candidiasis and tinea capitis is 85 440 and 178 400 respectively. Mostly related to agricultural activity, fungal keratitis affects an estimated 700 Congolese yearly.

Conclusion: These data underline the urgent need for an intensified awareness towards Congolese physicians to fungal infections and for increased efforts to improve diagnosis and management of fungal infections in the RoC.

KEYWORDS

chronic pulmonary aspergillosis, cryptococcosis, fungal infection, fungal sensitisation, HIV/AIDS, Republic of Congo, TB

1 | INTRODUCTION

The Republic of Congo (RoC), mostly known as Congo-Brazzaville, is located in the Gulf of Guinea in the central-western part of sub-Saharan Africa. It lays along the equator between latitudes 4°N and 5°S, and longitude 11° W and 19°E, with a total surface of 342 000 km^2 (Figure 1).[1] The RoC has a significant hydrographic network, organised around Congo and Kouilou-Niari rivers. The country is subdivided into 3 climatic areas which are as follows: equatorial in the North, subequatorial in the central part of the country and tropical

in the South-East. The climate is characterised by a long rainy season (October to May), and a dry season (June to September). The average day temperature is 25°C.

In the RoC, the lack of strategy for developing human resources for health (HRH) combined with suspension of recruitment in the public health service for nearly 20 years has led to declining health worker numbers. The country has 0.28 physicians, and 1.91 nurses and midwives per 10 000 population. Inpatient health facilities are located within 6 general hospitals, including one university hospital centre, and 23 basic hospitals. The overall capacity of the public sector was estimated at 1945 beds in 2012. The health sector workforce is also ageing. Other challenges include an inequitable geographic distribution, with 66% of physicians, 42% of allied health professionals and 28% of hospital beds located in Brazzaville, where 56.5% of the population lives. The northern rural areas of the country have the fewest health workers, particularly physicians (1.1%-2.6%). Therefore, to face all these challenges, the RoC's government has developed a draft HRH strategic plan (2011-2020), the overall objectives of which are to improve the numbers in training, the recruitment and personnel management of health workers. The plan is meant to improve globally the national healthcare system by strengthening capacities building of 12 hospitals in the country's 12 departments (Figure 1), as well as enhancing the of training of human resources and putting in place mechanisms for intersectoral coordination at both central and decentralised levels.

As in most of tropical countries, and while noncommunicable diseases such as hypertension, cancer, asthma and diabetes are gaining importance, infectious diseases represent a huge public health problem in RoC. Indeed, the health epidemiological profile is characterised by the predominance of infectious diseases, mainly malaria, pulmonary tuberculosis (TB) and HIV/AIDS infection. Malaria is the predominant endemic infectious disease in Congo; the latest estimations from the National Malaria Control Programme indicate that clinical malaria accounts for 47.9% of all outpatient consultations in public hospitals, 64.8% of hospital admissions and 18.4% of deaths.[2] The RoC is also considered a 'high burden' country for TB and HIV/AIDS infection by the World Health Organization (WHO).[3,4] With an incidence of 376 cases per 100 000 inhabitants, Congo belongs to the 30 countries most affected by tuberculosis according to the World Health Organisation (WHO).[5] While TB incidence is slightly decreasing since 2015, there is paradoxically an increase in the mortality rate due to TB that reached 63/100 000 inhabitants in 2017. According to the UNAIDS 2018 report, 89 000 people were estimated to be HIV/AIDS infected in RoC.[6] Of all people living with HIV in 2018, only 34.8% (n = 31 000) of individuals were receiving anti-retroviral therapy (ART). Of note, among the patients suffering TB knowing their HIV serologic status, 28% are HIV-positive so that about 99 patients per 100 000 inhabitants are co-infected with TB and HIV.[5] Without ART, it is well known that in countries with limited healthcare services HIV/AIDS infection is characterised by frequent of opportunistic infections. Among those infections, oral and oesophageal candidiasis, *Pneumocystis jirovecii* pneumonia (PjP), cryptococcal meningoencephalitis and histoplasmosis are common. Those infections can reveal the underlying viral infection and are life-threatening in the absence of specific treatment. In addition, TB is the most common predisposing factor for the development of chronic pulmonary aspergillosis (CPA). The clinical and radiological presentation of CPA, histoplasmosis and to a lesser extent cryptococcosis and PjP can mimic pulmonary TB. Considering the limited availability of diagnostic tests in low-income countries such as the RoC, these infections are often diagnosed very late or not at all, leading to an underestimation of the incidence and prevalence of most fungal diseases.[7]

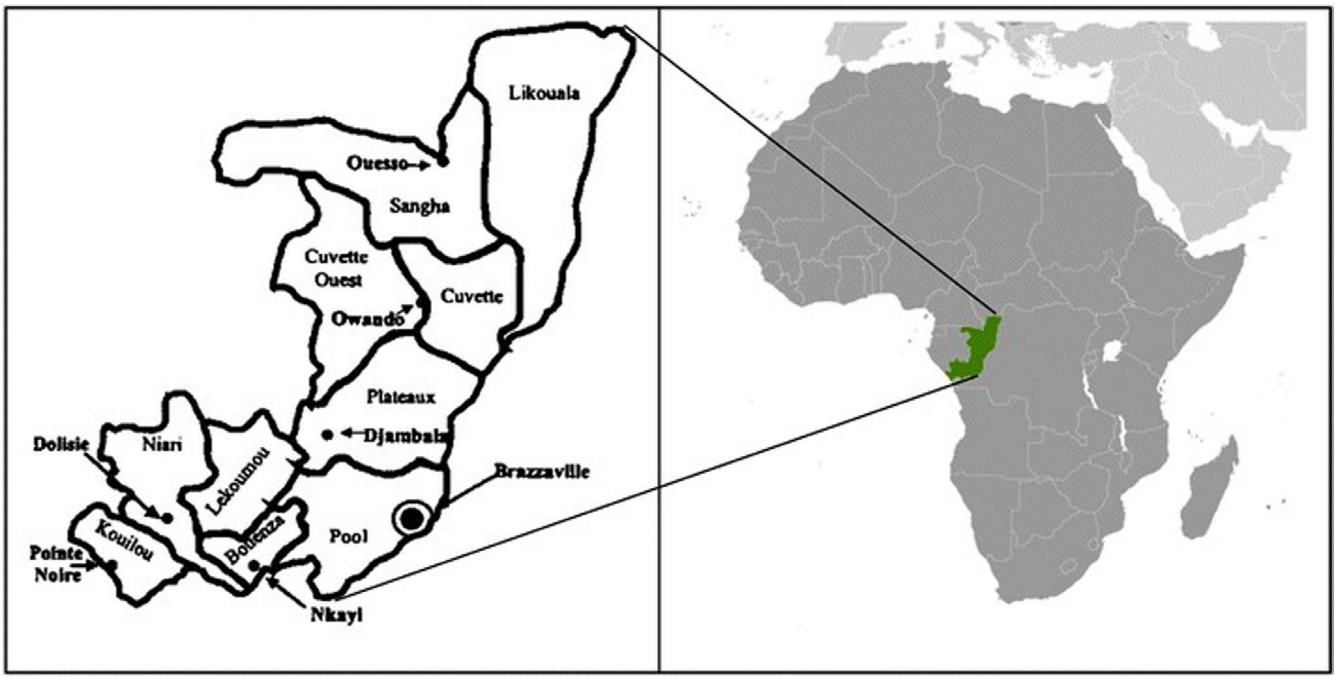

FIGURE 1 Map of the Republic of Congo with its 12 departments[81]

As in other low and middle-income countries, absence of diagnostic tools and antifungal drugs coupled with insufficient training of healthcare professionals (regarding fungal diseases) ensures that the mortality and morbidity of fungal infection remain unacceptably high. Furthermore, public health and research institutions in RoC have showed insufficient interest in the topic, probably due to ignorance or lack of awareness. There are no surveillance programmes on fungal diseases in RoC. Fungal infections currently represent a secondary priority for RoC's government.

Including fungal disease as a differential diagnosis followed by a precise diagnosis on confirmatory testing is crucial to initiate appropriate therapy for fungal infection. Indeed, across the world deaths due to fungal infections are similar to the number of people dying from TB (www.LIFE-worldwide.org). Access to data on the medical burden of diseases is critical for public health actions. Therefore, in the recent years, many countries have estimated the burden of fungal diseases.[8,9]

Knowledge of the local epidemiology of invasive and serious fungal infections, as well as risk factors for infection, is essential for effective infection control programmes and treatment approaches. The epidemiology of fungal infections in RoC is largely unknown. Hence, the present study aimed to estimate the current burden of serious fungal infections in RoC in order to guide local medical institutions and authorities towards economic investment in diagnosis and therapeutic management of fungal infections. Our estimates should also stimulate collaborative studies to better depict the landscape of fungal infections in the Republic of Congo.

2 | MATERIAL AND METHODS

Published epidemiology papers reporting fungal infection rates in RoC were identified using Medline, PubMed, Google Scholar. The following terms were used to identify specific disease conditions, included "Fungal infections" and "Congo," "Candidosis" and "Congo," "*Tinea*" and "Congo," "*Aspergillosis*" and "Congo," "Cryptococcosis" and "Congo," "Histoplasmosis" and "Congo," and "Fungal keratitis" and "Congo". We have also added the following terms, "Africa" or "sub-Saharan Africa" to expand research. When data were lacking, we used epidemiological data reported from nearby countries from the Central Africa region, notably Cameroon, and even from other African countries that have already estimated the burden of serious fungal infections in their respective country.[8,9]

We used population at-risk groups for particular infections and deterministic modelling to derive national incidence and prevalence estimates for the most serious fungal diseases. We contrasted these with diseases entities for which data are available. The demographic dynamics of RoC population were obtained from the United Nations Economic Commission for Africa (2017),[10] based on the National Statistical Institute 2016 reports.[10] HIV/AIDS and tuberculosis prevalence were sourced, respectively, from UNAIDS country factsheets[6] and the World Health Organization (WHO, 2017) (https://www.who.int/tb/country/data/profiles/en/). The assumptions made in estimating burden are shown in Table 1, with the pertinent references. All estimates are rounded to the nearest 10 cases.

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required.

3 | RESULTS

3.1 | Country's profile

The RoC population was estimated to be 5 244 000 inhabitants in 2018 (the basis of our estimates).[11] Predominantly, the population is urban (62.2%), and 56.5% of the total population live in Brazzaville, the capital and largest city. Pointe-Noire, the second city of the country, is an important economic centre. 38.4% of the Congo population is under 15 years, and only 2.9% are over 65 years old. The life expectancy at birth has increased from 54.6 years in 2005 to 64.1 years in 2015.[10]

3.2 | Serious fungal infections

Our online search for epidemiological reports focused on fungal infections in the RoC only retrieved a few studies conducted in AIDS patients in the 90 seconds.[12-14] So, most of the estimates were inferred from Congolese population data and estimates from other countries. Sensitivity analyses were thus not added, and more precise local estimates are desirable before more sophisticated modelling can be done.

Table 2 shows the estimates of the total burden of serious fungal infections and the number of infections classified according to the major at-risk groups as well as the rate per 100 000 inhabitants. In total, we estimated the occurrence of 293 918 new cases of serious fungal infections in RoC each year (Table 2). This amounts to 5.6% of the population affected by a serious fungal infection.

3.2.1 | Respiratory diseases conditions

It is considered that 77% of the 10 706 new cases or relapses of TB present with pulmonary infection (WHO) (https://www.who.int/tb/country/data/profiles/en/). Considering the mortality rate of TB at 63/100 000, it is estimated that 720 patients develop chronic pulmonary aspergillosis (CPA) each year due to past TB, leading to a cumulative of a 5-year period prevalence of 2290. Assuming that pulmonary tuberculosis is the underlying condition of 67% of CPA Congolese patients, a total prevalence of 3420 CPA cases is likely (43.5/100 000 inhabitants).

There is currently no reliable diagnostic tool for invasive aspergillosis (IA) in the RoC. Based on previous estimations,[15] we assumed that patients with one of following conditions may develop IA: HIV/AIDS (4% of deaths [n = 4000]), 2.6% of lung cancer patients

TABLE 1 Assumptions made in assessing burden

Disease	Underlying Disease(s)	Incidence/Prevalence Used to Estimate Burden	Comments	Reference
Cryptococcal meningitis	HIV/AIDS	6.7% in patients with CD4 counts <200 × 10^6/mL	Country dependant	Rajasingham et al[25] Dzoyem et al[74]
Pneumocystis pneumonia	HIV/AIDS	10% in patients with CD4 counts <200 × 10^6/mL	Relatively rare in HIV/AIDS patients	Carme et al[14]
Disseminated histoplasmosis	HIV/AIDS	1.5% in patients with CD4 counts <200 × 10^6/mL	Probably an underestimate	Oladele et al[33]
Invasive aspergillosis	HIV/AIDS, leukaemia, lung cancer, COPD admissions to hospital	4% of deaths from HIV/AIDS 10% rate in AML, Number in non-AML same as AML patients. 2.6% of lung cancer patients 1.3% of the 10.5% of COPD patients admitted to hospital		Lortholary et al[75]
Chronic pulmonary aspergillosis (CPA) post-TB	Tuberculosis (TB), COPD, prior pneumothorax, lung cancer	Number of annual PTB survivors with cavities (22%) × incidence of CPA in cavities (22%) + 2% of the 78% without cavities,		Perkhofer et al[76]
Chronic pulmonary aspergillosis post-TB		Conversion from annual incidence to 5 y period prevalence	From Denning et al, Bull WHO 2011	Denning et al[77]
Chronic pulmonary aspergillosis—all		TB is the underlying diseases in 67%	Assumes TB prevalence of the underlying cause which may need correction	
Allergic bronchopulmonary aspergillosis (ABPA)[a]	Asthma and CF	2.5% of adult asthmatics		Keen et al[18]
Severe asthma with fungal sensitisation (SAFS)[a]	Asthma	33% of worst 10% of adult asthmatics		Kwizera et al[20]
Candidaemia	Hospitalised patients	5/100 000 (mean of 2-11/100 000)		Arendrup et al[38]
Candida peritonitis	Postsurgical, pancreatitis	50% annual incidence of candidaemia in ICU, itself assumed to be 33% of all candidaemia		
Oral candidiasis	HIV/AIDS	90% of untreated HIV patients, with CD4 <200 × 10^6/mL		Matee et al[78]
Oesophageal candidiasis	HIV/AIDS	20% of patients not on ARVs and CD4 <200 × 10^6/mL, and 0.5% of those on ARVs		Smith et al[79] Buchacz et al[80]
Recurrent Candida vaginitis (≥4x/year)	Premenopausal women	6% of adult women. Literature estimate is 5%-8%		Sobel et al[34]
Mucormycosis	Diabetes, leukaemia	2 per million population		Petrikkos et al[16]
Fungal keratitis	Injury	13.3/100000		Lottie et al[45]
Tinea capitis	None	8.1% of children <15 y of age		Kechia et al[46]

Abbreviations: AML, acute myeloid leukaemia; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease, ARVs, anti-retroviral therapy; ICU, intensive care unit; PTB, post-tuberculosis.

[a]Collectively called 'fungal asthma'.

(n = 66), 1.3% of the 10.5% of COPD patients admitted to hospital (n = 13 215) and 10% of acute myeloid leukaemia (AML) (n = 131) as well as other haematological conditions and lymphomas. The total annual caseload of IA was therefore estimated at 360 cases, not including those treated with corticosteroids or in critical care. We also estimated at 10 the number of cases of mucormycosis annually at a rate of 0.2/100 000.[16]

Asthma prevalence in the RoC has been previously estimated.[17] So, it is anticipated that 145 690 (4.79%) adults suffer with clinical asthma in the RoC. We assumed that 2.5% of these people developed allergic bronchopulmonary aspergillosis (ABPA), based on a study from South Africa,[18] corresponding to about 3642 Congolese people. ABPA is rare in children notably because cystic fibrosis (CF) has not been reported in RoC. We also estimated

TABLE 2 Estimate of serious fungal infections in Republic 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	-	560	-	-	-	10.7	560
Pneumocystis pneumonia	I	-	830	-	-	-	15.8	830
Disseminated histoplasmosis	I	-	120	-	-	-	2.3	120
Invasive aspergillosis	I	-	160	-	30	170	6.9	360
CPA—post-TB	I	-	-	724	-	-	13.8	724
CPA—post-TB	P	-	-	2282	-	-	43.5	2282
CPA—all	P	-	-	3422	-	-	65.3	3422
ABPA in adults asthmatics	P	-	-	3642	-	-	69.4	3642
SAFS in adults	P	-	-	4808	-	-	91.7	4808
Candidaemia	I	-	-	-	180	80	5.00	260
Candida peritonitis	I	-	-	-	-	40	0.76	40
Oral candidiasis	I	-	7460	-	-	-	142	7460
Oesophageal candidiasis	I	-	4860	-	-	-	93	4860
Recurrent Candida vaginitis (≥4x/year)	P	85 440	-	-	-	-	1629	85 440[a]
Mucormycosis	I	-	-	-	10	-	0.2	10
Fungal keratitis	I	700	-	-	-	-	13.3	700
Tinea capitis	P	178 400	-	-	-	-	3402	178 400
Total serious fungal infection burden		264 540	13 990	14 878	220	290	-	293 918

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; I, incidence; P, prevalence; SAFS, severe asthma with fungal sensitisation.

[a]Females only.

that severe asthma with fungal sensitisation (SAFS) is present in 3.3% of asthmatic adults, affecting thus 4810 people in the RoC. Recently, the hospital prevalence of asthma has been estimated at 3.5% in children.[19] This is in accordance with a recent survey of fungal asthma from Africa,[20] which shows an increase in morbidity and mortality due to asthma in African adults with a prevalence of 4%. There is probably some overlap between ABPA and SAFS.

3.2.2 | HIV/AIDS-defining opportunistic fungal infections

Considering the AIDS epidemics in the RoC and the still high prevalence of untreated patients, opportunistic fungal infections have a huge morbidity and mortality impact on the population. Oral candidiasis and/or oesophageal candidiasis are among the most frequent opportunistic infections in this condition.[21,22] Indeed in 1986 and 1987, 36% of oral pharyngeal candidiasis cases have been reported in HIV/AIDS patients.[23] Also, from 1995 to 2001, 14.6% of pharyngeal candidiasis have been reported in HIV patients.[24] It is expected that 7460 cases of oral candidiasis occur annually in the RoC, while oesophageal candidiasis cases should be 4860.

Cryptococcal meningitis (CM) caused by *Cryptococcus neoformans* is also a common fungal infection in AIDS and among other severely immunocompromised patients.[25,26] It has the highest incidence and mortality rates among subjects with advanced HIV disease with CD4 counts < 100×10^6/mL, and its global burden has recently been re-estimated in AIDS.[25] Considering that only 34.8% of HIV-infected patients benefit from anti-retroviral therapy, it is expected that 8286 patients may have a CD4 cells count below 200×10^6/mL. A recently published study of the global burden of disease of HIV-associated cryptococcal meningitis[25] utilised a 6.7% incidence of CM in RoC. We thus estimated the number of cases at 560 per year in the RoC.

PjP is also a life-threatening fungal infection complicating HIV/AIDS infection. It is well known as an initial presentation of AIDS. There are some reports on PjP in RoC(15,40,41)[23] but overall the disease is poorly described in the country. We considered that PjP occured exclusively in HIV-positive patients with an annual rate of 10% in HIV-positive patients with CD4 counts <200×10^6/mL.[14] So it is expected that 830 cases of PjP occur each year. We have not estimated cases of PjP in non-HIV patients.

Several cases of histoplasmosis both attributable to the *capsulatum* variety and the *duboisii* variety of *Histoplasma capsulatum* have been reported in Congolese patients.[12-13,27-32] Nevertheless, no precise incidence could be calculated. Based on African data,[33] we used an annual rate 1.5% in patients with HIV/AIDS and CD4 counts <200×10^6/mL to calculate an estimated incidence at 120 cases annually.

3.2.3 | Other fungal infections

Recurrent vulvovaginal candidiasis (rVVC) is defined by the occurrence of four or more episodes of vulvovaginal candidiasis per year.[34-36] Across the world, approximately 5-9% of women report such infections per year, although there are few data from Africa.[34] Assuming an a incidence of 6%,[37] this equals circa 85 440 women aged 15-50 affected annually with rVVC in the RoC.

Data were not found on candidaemia, *Candida* peritonitis, or other forms of invasive candidiasis, and so we have estimated the annual incidence of the first two entities at 5/100 000 and 0.75/100 000, based on data from other countries.[38,39]

Fungal keratitis is a challenging ophthalmological problem often leading to corneal blindness.[40-44] Unfortunately, as in many tropical African countries, fungal keratitis has not been recorded in RoC. We used the recent estimate from South Africa as the basis of a 13.3/100 000 rate in Congo.[45] So, 700 cases of fungal keratitis are estimated yearly.

Tinea capitis is a frequent superficial infection of the scalp hair caused by dermatophyte fungi, occurring predominantly in children.[46-48] We estimated that 178 401 schoolchildren suffer from tinea capitis, prevalence of 3402 per 100 000 children.

Onychomycosis has not yet been reported in RoC but is likely very frequent. To the best of our knowledge, there are no reliable epidemiological data for the fungal neglected tropical diseases (NTDs) such as mycetoma, chromoblastomycosis or sporotrichosis in RoC, although they are expected to occur among Congolese people. They are probably uncommon or rare.

4 | DISCUSSION

Despite continuous reinforcement in the supply of healthcare workers and improvement of the quality of care, reliable diagnostic tools are still lacking for the detection of fungal infections. This current study serves to provide an estimate of the current fungal disease burden in RoC, and the figures show a worrisome situation. The HIV/AIDS pandemic, TB, COPD, asthma and the increasing incidence of cancers are the major drivers of fungal infections notably in resource-limited countries.[49-53] Our burden estimate of 293 918 (5.6% of the population) serious fungal disease cases indicates significant morbidity and certainly mortality among the people of the RoC. Despite this huge number of cases, there are no studies or reports of on any form of aspergillosis (ABPA, CPA, invasive aspergillosis) or invasive candidiasis/candidaemia in the RoC, as clear-cut examples of missing information. Medical ignorance, lack of physician awareness and limited access to diagnostics tools are the major issues. Indeed, microscopy plus culture on non-selective media is the main diagnostic approach for fungal diagnosis in the RoC (Table 3). However, it is well known that the sensitivity of those techniques is limited and non-based culture methods have supplanted them for many fungal infections.

One 'good' example of limitations in fungal diagnosis is the probable misdiagnosis of CPA as TB given the similarities of clinical symptoms and on thoracic imaging, probably leading to unnecessary presumptive antituberculosis treatment. Indeed, TB is highly endemic in the RoC and is considered as the main underlying condition

TABLE 3 Essential diagnostics and antifungal agents in Republic of Congo

WHO recommended Essential in vitro Diagnostics	WHO recommended Essential antifungal Medicines
Available	**Available**
Direct microscopy	Fluconazole
Blood culture[a]	Griseofulvin
Histopathology	Miconazole
Fungal culture[a,b]	Nystatin
Cryptococcal antigen (CrAg)[a]	Ketoconazole
Unavailable	**Unavailable**
Histoplasma antigen	Amphotericin B
Aspergillus antigen[c]	Itraconazole
Aspergillus antibody[c]	Voriconazole
Pneumocystis PCR[c]	Flucytosine
	Natamycin eye drops

[a]Only in some centres.

[b]No species identification is done.

[c]Proposed to the WHO with a decision due in 2020.

of CPA in such countries. The confusion is due both to the lack of efficient laboratory methods for diagnosis of aspergillosis including microscopy or culture on bronchoscopy or sputum samples and the detection of anti-*Aspergillus* antibodies. But there are a limited number of microbiologists with skills in medical mycology, because teaching this speciality is still considered as secondary in the RoC.

The RoC, as in many other African countries, has a high prevalence of HIV/AIDS patients—with an estimated 89 000 cases in RoC and 24.7 million cases in sub-Saharan Africa.[54,55] Opportunistic fungal infections are common in HIV-infected people, and nearly half of AIDS deaths are reportedly caused by opportunistic fungal infections.[56] The prevalence of oropharyngeal candidiasis (OPC) was up to 82% of HIV-infected patients in a review of the opportunistic infections related to HIV in sub-Saharan Africa.[54] So 7460 cases are expected yearly but no epidemiological studies have been conducted in the RoC and substantiation of our estimates is needed.

Cryptococcal meningitis (CM) is also reported with a high frequency in African HIV-infected patients.[57-59] We estimated 560 new cases of CM among adult HIV/AIDS patients yearly in the RoC. A published paper previously reported 39 cases of CM diagnosed from 1981 to 1988,[13] including 12 cases of CM out of 139 patients (8.6% of confirmed cases) reported by the same author in RoC.[23] This corresponds to a surprisingly low prevalence of rate of 4% over 2 years in patients with CD4 counts <200 × 10^6/mL. However, this cannot be generalised to the population because of the selection bias in this study such that many patients with cryptococcal infection probably died before either being tested for HIV or attending the clinic. Our estimate is approximately similar to the estimate of Rajasingham et al from 2017 of 636 cases and 540 deaths.[25] Definitive diagnosis requires either positive culture from the cerebrospinal fluid or the detection of the specific capsular antigen (CrAg). The latter can be easily achieved using lateral flow devices, with excellent sensitivity and specificity when applied either to the CSF or the serum. Indeed, cryptococcal antigenemia was shown to be 100% sensitive for predicting the development of CM in the first year of ART.[60] Unfortunately, the CrAg test is not yet routinely available for almost all patients admitted to hospital or attending HIV clinics in RoC. CM is reportedly responsible for ~15% of AIDS-related deaths.25 So, there is a real need for screening subclinical or asymptomatic infection with a serum CrAg assay in patients with advanced HIV infection, and this is cost-effective.[61,62]

Pneumocystis pneumonia occurs worldwide and is especially common in children and severely immunocompromised patients such as those with AIDS. Again, a precise incidence is not available in the RoC because this requires the common practice of bronchoalveolar lavage, which is not widely available in this country, but is described.[14,63,64] A recent study in Cameroon reported a high prevalence (82%) of anti-*P jirovecii* major surface glycoprotein (Msg) antibodies detection among healthy HIV patients,[65] while another reported that PjP was responsible for 31% of all deaths and for 48% of deaths in infants <1 year, with HIV infection in Botswana.[66]

In Africa, both forms of histoplasmosis, due to *H capsulatum var. duboisii* (Hcd) and *H capsulatum var. capsulatum* (Hcc), respectively, co-exist.[33] This is the case in the RoC where cases of Hcd have been reported, principally in non-HIV patients.[12-13,27-32] Alternatives of PCR on sputum or nasopharyngeal aspirates are feasible, but not currently done.[67,68] A recent study by Oladele et al reports 35 cases of Hcd and 1 case of Hcc in the last six decades in RoC (1952-2017).[33] In total, 45 cases of histoplasmosis have been reported, making the RoC the country with the higher number of reported cases. Hcd infection may be easier to diagnose, as cutaneous lesions are more frequent and accessible for diagnosis. It mainly relies on the demonstration of large yeasts in the pus aspirated from chronic skin abscesses or fistulae from underlying osteomyelitis or lymph node. In contrast, Hcc infection most often mimics pulmonary TB and requires microscopy of bone marrow biopsy, antigen detection or PCR testing of blood or long-term fungal culture. So, most diagnoses of Hcc histoplasmosis are made postmortem, as premortem confirmatory tests are unavailable in low-income countries. The underdiagnosis of histoplasmosis has been stressed by colleagues from Cameroon, who showed that histoplasmosis is frequently ignored in HIV-positive patients with pulmonary symptoms as they were considered as TB infected.[69]

Mucocutaneous fungal infections are also very common in patients most often without specific underlying medical conditions, although they may be the harbinger of advanced HIV disease. They are not life-threatening, but they can greatly affect the quality of life of affected individuals. Serious mucocutaneous infections include rVVC, fungal keratitis, tinea capitis, especially with kerion, and neglected tropical diseases such as mycetoma, chromoblastomycosis and sporotrichosis. Epidemiological data on chronic and recurrent forms of vulvovaginal candidiasis that do cause significant morbidity and discomfort are nonexistent in RoC. However, a study in 2012 reported the prevalence of vulvovaginal candidiasis among Ghanaian women at 21% in a gynaecology clinic[70]

and it is likely that a similar pattern of frequency would be seen in RoC. Considering the local healthcare facilities, it is unlikely that infected women have access to dedicated medical advice for such kinds of infection. Finally, tinea capitis is very common in children from sub-Saharan countries. In a large study conducted in Ivory Coast, 13.9% of 17 745 children were found to be positive, mainly with anthropophilic dermatophytes, such as *Trichophyton soudanense* and *Microsporum langeroni*.[71]

Finally, it is well known that fungi can act as allergens and as such can induce allergic disease.[20] Many fungal species may colonise the tracheobronchial airways and induce fungal sensitisation. The immune response towards those fungal antigens can trigger or worsen asthma. Given the prevalence of asthma throughout the world, the number of cases of severe asthma with fungal sensitisation can be huge, estimated at 3.3% of adults affecting 4810 patients in the RoC. Currently, none of the diagnostic tests that should be used to diagnose allergic diseases are available in most low-income countries.

We hope this study sheds light on the almost totally ignored problem of medical mycology in the Roc. The size of the problem demands that the essential systemic antifungal drugs namely itraconazole, voriconazole, flucytosine and amphotericin B become available, which is not currently the case.[72] Currently, only fluconazole, ketoconazole (withdrawn across most of the world because of toxicity), topical miconazole, griseofulvin and nystatin are available (Table 3).[72] As in many African countries, flucytosine is also not available,[73] increasing the mortality of cryptococcal meningitis in RoC. Topical natamycin eye drops for fungal keratitis are not available. With the one exception of PjP, it can be assumed that most patients suffering invasive fungal infection will die early.

5 | CONCLUSION

Our study confirms previous reports from other countries from Central Africa showing that about 5.6% of the Congolese population suffers from fungal infections. Many of these infections are life-threatening as a result of the HIV/AIDS epidemic in this country. This worrisome data should promote public awareness of the seriousness of these infections. A national reporting system on fungal infections and a fungal surveillance system should be implemented to better depict the dynamic landscape of these infections and ascertain the impact of serious fungal infections and promote public awareness of the seriousness of these infections. Advanced laboratory diagnostic techniques are urgently needed for this and to adapt treatment based on reliable diagnosis. Indeed, the availability of more antifungal drugs will be the next challenge. Optimisation in the distribution of drugs should include central purchasing and a distribution system for the whole country as several of these infections can be managed out of the hospital.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Fructueux Modeste Amona and David W. Denning conceived the paper and wrote the manuscript. Donatien Moukassa and Christophe Hennequin wrote and revised all the manuscript. All authors read and approved the final manuscript.

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