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General review

Estimates of serious fungal infection burden in Côte d'Ivoire and country health profile

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ABSTRACT

Due to limited access to more powerful diagnostic tools, there are few data on the burden of fungal infections in Côte d'Ivoire, despite a high HIV and TB burden and many cutaneous diseases. Here we estimate the burden of serious fungal infections in this sub-Saharan country with a health profiling description. National demographics were used and PubMed searches to retrieve all published articles on fungal infections in Côte d'Ivoire and other bordering countries in West Africa. When no data existed, risk populations were used to estimate frequencies of fungal infections, using previously described methodology by LIFE (www.LIFE-Worldwide.org). The population of Côte d'Ivoire is around 25 million; 37% are children (≤14 years), and 9% are > 65 years. Tinea capitis in children is common, measured at 13.9% in 2013. Considering the prevalence of HIV infection (2.6% of the population, a total of ~500,000) and a hospital incidence of 12.7% of cryptococcosis, it is estimated that 4590 patients per year develop cryptococcosis. For pneumocystosis, it is suggested that 2640 new cases occur each year with the prevalence of 11% of newly diagnosed HIV adults, and 33% of children with HIV/AIDS. Disseminated histoplasmosis is estimated a 1.4% of advanced HIV disease – 513 cases. An estimated 6568 news cases of chronic pulmonary aspergillosis (CPA) occur after pulmonary tuberculosis (a 5-year prevalence of 6568 cases [26/100,000]). Allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) were estimated in 104/100,000 and 151/100,000 respectively, in 1,152,178 adult asthmatics. Vulvovaginal candidiasis (VVC) is common and recurrent VVC affects ~6% of women in their fertile years – 421,936 women. An unknown number develop candidaemia and invasive aspergillosis. The annual incidence of fungal keratitis is estimated at 3350. No cases of sporotrichosis, mucormycosis and chromoblastomycosis are described, although some cases of mycetoma and *Conidiobolus* infection have been reported. This study indicates that around to 7.25% (1.8 million) of the population is affected by a serious fungal infection, predominently tinea capitis in children and rVVC in women. These data should be used to inform epidemiological studies, diagnostic needs and therapeutic strategies in Côte d'Ivoire.

Contents

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Introduction

Invasive fungal disease has a high attributable mortality unless diagnosed and treated promptly and appropriately. Nearly 2 million people die from invasive fungal infections each year in the world [1]. Over 90% of fungal infection-related deaths are due to species that belong to one of these four genera: *Cryptococcus, Candida, Aspergillus* or *Pneumocystis*. Epidemiological data for fungal infections are poor because many are misdiagnosed and statistics are extrapolated from few (mostly geographically localized) studies.

Côte d'Ivoire (or Ivory Coast) is located in West Africa south of the Sahara between 10 degree North latitude, 4 and 8 degree West longitude. It has an area of 322,462 km^2 and is bounded to the west by Liberia and Guinea-Conakry, to the north by Mali and Burkina Faso, to the east by Ghana and to the south by the Gulf of Guinea.

The population of Côte d'Ivoire is characterized by a growth rate of 2.6% per year and by the high proportion of its youth (41.5%) [2]. The health status of the population is marked by high maternal and infant-juvenile mortality, partly due to inadequate health services. The epidemiological profile is dominated by a high prevalence of HIV among those over 15 years of age as well as a high incidence of malaria among children under 5 and tuberculosis in the population, respectively 2.6% [3], 189.9 per 1000 (Annual Report on the Health Situation 2018) and 85 per 100,000 inhabitants (Annual TB notification case 2018) [4]. The national health priorities are these three diseases (HIV, TB and malaria) and recently the novel coronavirus disease 2019 (COVID-19) absorbing all the funds allocated to the health system and hiding the urgency of opportunistic infections such as severe fungal diseases (SFIs).

One of the best documented examples of underfunding for fungal diseases is cryptococcosis. This disease is currently responsible for 15–20% of deaths in individuals with AIDS, and yet in 2015 it received 1% of the funding allocated to tuberculosis [5]. Remedying this situation requires more advocacies by the infectious disease community as well as more studies documenting the local, national and global burden of fungal diseases and their impact on human health.

Several studies documenting fungal disease in Côte d'Ivoire are published. Oral *Candida* infections were reported in paediatrics and adult patients [6]. Reports on *Aspergillus* [7,8] and *Pneumocystis* pneumonia (PCP) infections are limited to few cases [9,10]. Asthma is the most common chronic respiratory disease with hospitalisation rate of 5% [11] and allergic rhinitis (which may be partly fungal in aetiology) was the most common allergic disease [12].

Estimates of the impact of diseases on public health, generally referred to as burden of disease, are valuable inputs for public health authorities, developing appropriate surveillance of fungal diseases and setting policy priorities. Many estimates of the burden of serious fungal diseases are now published for over 60 countries with populations $>$ 1 million [13]. Disease burden should be considered as the underlying basis for health care prioritisation in Côte d'Ivoire.

Here we report on the burden of fungal disease in Côte d'Ivoire focusing in particular on prevalence data and the reliability of current estimates. These data will contribute to the global SFIs estimation project and awareness campaign, help reframe health policy by bringing a numerical estimate for expanded advocacy, increased research, and improved laboratory diagnostic capacity for the fighting of fungal infection.

Methods

The methodology adopted is that previously described [14–16]. Initially, we performed a PubMed search using the Medical Subject Headings terms. Keywords were combined using the Boolean operator AND and OR. Search details are: ("mycoses" [MeSH Terms] or "mycoses" [all fields] or ("fungal" [all fields] and "infection" [all fields]) or "fungal infection" [all fields]) and ("Côte d'Ivoire" [MeSH terms] or ("cote" [all fields] and "d'Ivoire" [All Fields]) or "Côte d'Ivoire" [all fields] or ("ivory" [all fields] and "coast" [all fields]) or "ivory coast" [all fields]).

Demographic data were obtained from the "Institut National de la Statistique-Côte d'Ivoire" based on the 2014 Housing and Population Census [2]. For many estimations, we used specific populations at risk (HIV/AIDS patients [3], patients with pulmonary TB [PTB] [4], asthma [17], cancer [18], burn patients [4], and patients receiving critical care) to derive national incidence or prevalence estimates of SFIs, using validated data from the country or others nearby, if available. The incidence of chronic superficial mycoses as obtained from those reported in the PubMed-retrieved papers. Cryptococcal meningitis (CM) was estimated in adults only (it rarely occurs in children) at a rate of 12.7% among adult HIV/AIDS patients with CD4 less than 200/μL [19]. PCP frequency was estimated by assuming 11% of newly diagnosed HIV/AIDS adults (risk spread over 2 years) and 33% HIV/AIDS children at risk (25% of those not on antiretroviral therapy) [20,21]. Disseminated histoplasmosis was estimated from an autopsy study published in 1994 [22], and assumed to relate to all advanced HIV cases in the country ($\sim$80,000) over a 2 year risk period.

Regarding invasive fungal infections associated with hospital care (notably candidiasis and aspergillosis), we considered hematology malignancies [23], lung cancer [18], chronic obstructive pulmonary disease (COPD) [24], ICU and assumed peritonitis surgical patients based on neighbouring country data [25]. No transplantation procedures are currently done in Côte d'Ivoire. For chronic infections, mainly chronic pulmonary aspergillosis (CPA), we used the annual incidence of TB to calculate a annual incidence, as described previously [14–16]. This was then used to compute a five-year prevalence assuming a 15% annual mortality or surgical cure rate. We also assumed that 67% of all CPA cases had prior TB as the underlying disease. Invasive aspergillosis (IA), CPA and allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS) were estimated in adults only. Adult asthma data came from To et al. as part of the World Health Survey on asthma [17]. We assumed that 2.5% of adult asthmatics had ABPA [26] and 30% of the worst 10% of asthmatics had SAFS, supported by a recent review on asthma in Africa [27].

Tinea capitis prevalence was estimated based on a local study in school children [28]. Fungal keratitis annual incidence was extrapolated from East Africa [29].

Results and discussion

Population profile

The total population of Côte d'Ivoire was 22,671,331 inhabitants according to the results of the General Population and Housing Census (RGPH) of 2014. In 2018, it is estimated at 25,195,140 inhabitants (the basis of our estimates). About 48.4% are females and ~48% of population live below the poverty line. Poverty is unequally distributed among the regions of Côte d'Ivoire. The level of poverty varies from 22.7% in urban areas to 71.7% in rural areas [30]. Moreover, with the scarcity of public resources, investments in basic social services (health, education, infrastructure, etc.) have fallen considerably, leading to a decrease in the supply of these services. In terms of health resources, Côte d'Ivoire had 2023 primary health care institutions (PHCI), 82 general hospitals and 17 regional hospitals, i.e. one PHCI for 12,006 inhabitants and one reference hospital for 173,490 inhabitants [31].

Overall disease profile

In 2016, the incidence of endemic diseases (malaria, acute respiratory diseases, HIV/AIDS, tuberculosis) has declined, with the exception of diarrhea and sexually transmitted infections, which are on the rise. The WHO estimated the number of malaria cases at 7,890,000 (5,720,000–10,740,000) in 2016. Since 1995, a National Tuberculosis Program has been established to organize the fight against TB on a national scale. The tuberculosis notification rate in 2016 was 89 notifications per 100,000 inhabitants, compared to 98 per 100,000 inhabitants in 2015. Of 21,299 tuberculosis cases, 4608 (21.6%) were found to be HIV-positive [31].

The total prevalence of HIV infection in 2018 was 2.6% [3]. At the level of care for HIV patients, 44% (1013 sites) of health facilities offered antiretroviral (ARV) care and treatment services. There were 252,125 patients on ARVs including 12,347 children (4.9%) and 239,778 adults.

With regard to cancer in Côte d'Ivoire, 15,000 new cases are expected each year. Among these cancers, it is estimated that 271 cases of lung cancer (5-year prevalence) are diagnosed each year, or 1.09% of all cancers [18,32].

Healthcare facility profile and human resources

Côte d'Ivoire registered 6732 functioning hospital beds in 2018. The estimated number of critical care beds in 2018 was 673 (assuming 10% of hospital beds are occupied by critically ill patients). Transplant singular programs (solid organ and hematopoietic stem cell) do not exist in Côte d'Ivoire and there is no nationwide registry of surgeries undertaken.

In terms of the technical platform and existing health equipment (shown in Table 1), there were a total number of 99 operating theatre, 253 public medical biology laboratories, 85 radiology units, 629 ambulances and 162 blood transfusion centers in public health establishments in 2018 compared to 2017. However, it should be noted that at the level of health districts: 8.1% register at least one non-functional medical device in their public biology laboratory, 18.6% do not have an operating theatre, 26.7% do not have any radiology service and 2.3% do not have a blood transfusion center [4]. Only a few (9) centres undertake bronchoscopy with 40% belonging to the private sector and almost all are based in Abidjan.

Table 1
HealthTechnical plateform and equipment available in the country (RASS 2018).

Technical plateform and equipment	2017	2018
Public lab of medical biology	231	253
Operating theatre	89	99
Ambulance	536	629
Blood transfusion centers	162	162
Radiology department	84	85

Also in 2018, the Ministry of Health and Hygiene recorded a ratio of physicians providing healthcare in the public sector of 1.4 physicians per 10,000 inhabitants. The ratio of nurses to health care providers in the public sector is 2.3 nurses per 5000 inhabitants and the ratio of midwives to health care providers in the public sector is 2.7 midwives per 3000 women of reproductive age (WRA). The WHO minimum standards for human resources in health (1 doctor per 10,000 inhabitants, 1 nurse per 5,000 inhabitants and 1 midwife for 3,000 WRA) were reached in 2018 [31].

Otherwise, the budget granted by the State of Côte d'Ivoire to the Ministry of Health and Public Hygiene fell from USD $665,138,840 in 2017 to $650,292,813 in 2018, a decrease of $14.8 million (−2.22%). This budget represents 5.3% of the general State budget in 2018. This is lower than the commitments made by the State of Côte d'Ivoire at the Abuja (Nigeria) summit in 2001 which is to devote 15% of the general state health budget [31].

Mycology diagnostics

Only a few laboratories (5) are capable of doing diagnostic tests for fungal infection with conventional methods (culture, direct examination), antifungal susceptibility testing and/or innovative technical detection or for identification (PCR, MALDI-TOF). India ink microscopy in cerebrospinal fluid is the principal means of making the diagnosis of cryptococcal meningitis. Recent years have seen the introduction of cryptococcal, *Histoplasma* and *Aspergillus* antigen lateral flow assays, as well as Elisa based assays. Only the first is available in Côte d'Ivoire and is not extensively used. An *Aspergillus* antibody point of care assay with excellent sensitivity and specificity [33] has also been launched in the last 2 years and is not yet available. All of these tests are WHO essential diagnostics.

A solution of choice for the early diagnosis of PCP in health facilities without fiberoptic bronchoscopy is the examination of expectorated sputum or induced by inhalation of a hypertonic solute [34]. Detection of *Pneumocystis jirovecii* in sputum or bronchoalveolar lavage fluid can be by direct microscopy using Gomori Methenamine Silver (GMS) or calcofluor white stain, immunoflurescence or PCR. *Pneumocystis* PCR is the most sensitive technique, is now a WHO essential diagnostic and is the only means of diagnosing pneumocystosis in children [35]. None of these techniques are currently used in Côte d'Ivoire.

Table 2
Estimated incidence and prevalence of most serious fungal diseases in Côte d'Ivoire.

Infection	Number of infection per underlying disorder per year					Total burden	Rate/100K
	None	HIV/AIDS	Respiratory	Cancer	ICU		
Esophageal candidiasis	–	4665	–	–	–	4665	19
Oral candidiasis	–	17,280	–	–	–	17,280	69
Candida peritonitis	–	–	–	–	189	189	0.75
Candidaemia	–	–	–	882	378	1260	5
Recurrent *candida* vaginitis (4×/year)	421,936	–	–	–	–	421,936	1675
ABPA	–	–	28,804	–	–	28,804	114
SAFS	–	–	38,022	–	–	38,022	151
CPA	–	–	6568	–	–	6568	26
Invasive aspergillosis	–	640	852	58	–	1550	6.15
Cryptococcal meningitis	–	4590	–	–	–	4590	1.822
Pneumocystis pneumonia	–	2640	–	–	–	2640	1.048
Histoplasmosis	–	513	–	–	–	513	2.04
Tinea capitis	1,295,786	–	–	–	–	1,295,786	5143
Fungal keratitis	3350	–	–	–	–	3350	13.3
Total burden estimated	1,721,072	30,328	74,246	940	567	1,827,204	–

ABPA: allergic bronchopulmonary aspergillosis; SAFS: severe asthma with fungal sensitisation; CPA: chronic pulmonary aspergillosis; ICU: intensive care unit.

Incidence and prevalence of serious fungal infections

About 7.25% (1,827,204) Ivorians were estimated to be affected by SFIs. Table 2 shows the estimated total burden of fungal infections, the number of infections classified according to the main risk factors as well as the rate for 100,000 inhabitants.

Candida *infections*

There are no studies published on candidaemia or invasive candidiasis in Côte d'Ivoire, so we have estimated a general rate of 5/100,000 or 1260 cases of candidaemia annually [36]. Burned patients are more likely to develop candidemia and other fungal systemic lesions, as are HIV-positive patients [37]. Candidemia occurs in 2.5 to 7% of patients in intensive care units for burns [38]. In Côte d'Ivoire, the Abidjan center for burn victims receives about 500 burn patients a year. So nearly 25 will develop candidemia [39]. We have assumed that 30% of candidaemia cases occur in intensive care.

For surgical ICU patients *Candida* peritonitis may develop in association with recurrent gastrointestinal perforations or anastomotic leakage after surgical intervention. *Candida* species are isolated between 70–90% of all patients with peritonitis [40]. Acute peritonitis is a very common pathology. It occupies third place in acute surgical abdomens after appendicitis and intestinal occlusions. Its frequency is estimated, compared to all acute surgical abdomens, to be 3% in France [41] and 20% in Mali [25]. If as in France we assume that the number of patients with intra-abdominal candidiasis is 50% of those with candidaemia [42], we estimate 189 such cases, but this may be a substantial underestimate.

Esophageal candidasis occurs frequently in HIV-infected patients. We estimate 4665 cases based on 20% of new HIV-infected patients and 0.5% of those on ARVs [43]. HIV/AIDS adds nearly 2 million cases of oral thrush and > 500,000 cases of oesophageal fungal infections annually in the world [44]. Oral fungal infections are also common in babies, denture wearers, individuals using inhaled steroids for asthma, leukemia and transplant patients and people receiving radiotherapy for head and neck cancers, but we have been unable to estimate incidence of these cases.

rVVC is defined as four or more episodes of vulvovaginal candidiasis per year. This is a surprisingly common health problem in sexually active women. rVVC is relatively common in Côte d'Ivoire with *C. albicans* as the main causative agent. In Côte d'Ivoire, a cross-sectional study of 400 women attending an STD clinic found – 40% had evidence of VVC [45]. This same cohort was later re-analysed for rVVC and 23.5% of adult women were apparently affected by rVVC [46]. This is however a select population and so the denominator will be larger than 400, but it is not clear how large. Considering the actual adult female population size, our estimate of rVVC prevalence is 421,936 cases of rVVC at a rate of 1675 females per 100,000 person-years, but the real figure may be higher than this (and we have used 6% in our estimate [Table 2]). About one in four women with VVC developed rVVC, a significantly higher proportion than that reported in the literature, which ranges from 6 to 9% in European and North American women [47,48]. This relatively high rate seems to corroborate previous studies suggesting an association of rVVCs with the black people [47,49,50], suggesting that genetic factors related to being black are responsible for the high susceptibility of women of this racial group to rVVC [50,51]. However, these putative genetic factors may not explain alone this relatively high rate of rVVC. Host-related and behavioural factors could also be associated with the occurrence of these recurrences.

Fungal related respiratory diseases

Respiratory diseases including TB and asthma are major causes of morbidity and hospital admissions in Côte d'Ivoire. Exacerbations of asthma are common and may be driven by fungi, especially *Aspergillus* spp, which is common in the environment and colonise the airways. ABPA, CPA and SAFS frequencies are thus anticipated to be high. We calculated that SAFS affects 38,022 Ivorian adults annually. ABPA and SAFS are collectively known as "fungal asthma" which is responsive to antifungal therapy, and over 40,000 adults probably suffer from this, as there is probably some duplication between ABPA and SAFS prevalence. The long-term natural history of fungal allergy is not well documented. Some people have allergic fungal infection that comes and goes in severity, usually for unclear reasons. Mucus production and mucosal swelling in the airways, nose and sinuses is the hallmark of fungal allergy.

CPA is particularly common after pulmonary TB, and we estimate an annual incidence of 1567 cases. However as this is a chronic condition, the overall prevalence will be higher, an estimated 6,568, of which 75% of cases are TB related and the remainder to other pulmonary conditions such as sarcoidosis and previous pneumothorax. Some patients have no underlying condition at all, are usually misdiagnosed and TB. The key test *Aspergillus* IgG antibody (or precipitins) is not available in Côte d'Ivoire.

PCP exists in Côte d'Ivoire as evidenced by the autopsy study of Coulibaly et al. who found in post-mortem a prevalence of 8.6% in 70 HIV-infected patients [22]. This disease is caused by the opportunistic fungus *P. jirovecii*, which is a life-threatening infection in HIV/AIDS patients. Compared with adults, HIV-positive children had a high prevalence of *P. jirovecii* pneumonia and a low prevalence of tuberculosis. Almost a third of HIV-positive children had PCP, according to Lucas et al. [10], a rate similar to that found in affected children in industralized countries but much higher than the incidence in adults in Abidjan. We can estimate 2640 cases of PCP, 990 in adults and 1650 in children. Several studies from different African countries found the incidence of PCP in HIV-positive patients to vary from 1.25–49% [52].

The relative infrequency of pneumocystosis is due to the low prevalence of *P. jirovecii* in the African environment and lack of appropriate diagnostic means, such as bronchoalveolar lavage and trans-bronchial biopsy [53]. PCP may occur in other immunosuppression contexts, including solid organ transplant patients (kidney in particular), lymphoma or in patients receiving long-term corticosteroids. In these cases the clinical picture is often more brutal and the symptoms more frequently require admission to intensive care unit. We were unable to assess the incidence of these cases in the absence of any data.

Invasive aspergillosis (IA) was estimated in leukaemia, lung malignancies, COPD and HIV/AIDS. It was assumed that 10% of acute myeloid leukaemia (and an equal number of other leukaemia and lymphoma patients), 2.6% of lung cancer patients [54] 1.3% of COPD hospital admissions (65,500) and 4% of HIV/AIDS deaths (16,000) [55] develop IA. We estimate an annual incidence of 1550 cases. Very few of these diagnoses are currently established in Côte d'Ivoire and the optimal therapy of voriconazole is unavailable. Globally over 300,000 individuals develop IA annually with mortality rates ranging between 30% and 95% despite recent advanced HIV disease is a significant risk factor for the development of IA [56,57]. We know that the diagnosis of IA can be challenging: host risk factors, clinical symptoms and radiological findings must be put into context. Demonstration of morphological features consistent with *Aspergillus* species or recovery of *Aspergillus* from a tissue sample is required to define a positive (definitive) case. Obtaining tissue samples is often problematic in these multi-morbid patients and the yield of fungi in culture is low, difficult to interpret and prior antifungal prophylaxis further reduces its sensitivity [58,59]. Detection of *Aspergillus* antigen (galactomannan) by ELISA or more recently immune-chromatographic technology (lateral flow devices) have been shown to be much more sensitive than culture [60] but which unfortunately are not yet available in the country. Just as IA cases are challenging to diagnose, so is mucormycosis and we have not estimated this life-threatening infection.

Superficial fungal infections

Approximatively 25% of the general population have superficial fungal infections of skin and nails, that are caused by dermatophytes [61]. Children constitute the most affected population, especially in playgrounds, and thus are more likely to be in closer contact with sources of fungal pathogens. Tinea capitis is very common in children of sub-Saharan countries particularly in Côte d'Ivoire. In a large epidemiology study conducted in 2013, 13.9% of 17,745 children were found to be positive, mainly with anthropophilic dermatophytes, such as *Trichophyton soudanense* and *Microsporum langeroni* [28]. We thus estimated that 1,295,786 school children suffer from tinea capitis according to this epidemiological study. A similar pattern and frequency is seen in other West Africa countries including Nigeria [62], Guinea [63] and Senegal [64].

Superficial fungal infections are more rarely caused by non-dermatophyte moulds (NDM) attacking the skin or nails. A longitudinal analysis of clinical data in the last 10 years shown the increased prevalence of filamentous fungi involved in superficial mycosis in Côte d'Ivoire. We have recently found *Aspergillus flavus* (24.3%) *Penicillium sp* (22.9%), *Fusarium sp* (17.2%), and *Aspergillus niger* (15.7%) from clinical samples primarily of nails but also intertrigo and mucosal infections (data unpublished). This data was confirmed by a recent review of 42 epidemiological studies from Bongomin et al. [65], showed that onychomycosis due to *Aspergillus* spp. varies between < 1 and 35% of all cases of onychomycosis in the general population and higher among diabetic populations (accounting for up to 71%) and older people.

A single case of *Conidiobolus* infection of the face is described [66]. A small number of mycetoma cases are described [67]. No cases of sporotrichosis or chromoblastomycosis are described. Fungal keratitis is seen clinically but rarely confirmed. Based on a global analysis and using data from East Africa, we estimate 3,351 cases annually. Clearly, this needs confirmation and it is likely that all these eyes go blind, or have to be removed.

Table 3
Antifungal agents available in Côte d'Ivoire and whether included in the essential medecines list.

Antifungal agent	Available	On EML	Hospital use	Community pharmacy availability
Systemic agents				
Amphotericin B	Yes	Yes	Yes	Yes
Lipid amphotericin B	No	–	–	–
Fluconazole	Yes	Yes	Yes	Yes
Itraconazole	Yes	Yes	No	Yes
Ketoconazole	Yes	Yes	Yes	Yes
Terbinafine	Yes	Yes	Yes	Yes
Griseofulvin	Yes	Yes	Yes	Yes
Flucytosine	No	–	–	–
Voriconazole	No	–	–	–
Capsofungin	No	–	–	–
Micafungin	No	–	–	–
Anidulafungin	No	–	–	–
Topical agents				
Natamycin eye drops	No	–	–	–
Nystatin	Yes	–	Yes	Yes
Miconazole	Yes	Yes	Yes	Yes
Econazole	Yes	No	Yes	Yes
Cyclopiroxolamine	No	–	–	–

EML: WHO essential medicine list.

Cryptococcosis

The emergence of *Cryptococcus* infections has dramatically changed the epidemiology of cerebro-meningeal disease in sub-Saharan Africa, where 70% of HIV/AIDS infections are concentrated. Neuromeningeal cryptococcosis (NMC) is the most serious form of this infection. Death is inevitable in the absence of antifungal treatment and mortality remains high despite it. The incidence of this pathology varies from 2 to 30% in HIV-positive patients. However, epidemiological data of this pathology for Africa are limited. We estimated 4590 cases of NMC among adult HIV/AIDS patients, using a 12.7% rate from a study Osazuwa et al. [19] However, two hospital-based studies in Côte d'Ivoire [68,69] reported a surprisingly low prevalence of rate of 0.6 and 3.6 and they cannot be generalized to the population because of selection bias such that many patients with cryptococcal infection probably died before either being tested for HIV or attending the clinic and by the lack of use of cryptococcal antigenemia (CRAG) test which is not yet routinely available in hospitals. CRAG is detectable a median of 22 days before the onset of symptoms [70] and was shown to be 100% sensitive for predicting the development of NMC in the first year of ART [71], and is also associated with both NMC and mortality [72]. In view of these observations, screening for subclinical or asymptomatic infection by a serum CRAG assay in patients with advanced HIV infection, and giving antifungal therapy to those testing positive, may prevent the development of NMC.

Histoplasmosis

Histoplasmosis is one of the opportunistic infections associated with AIDS. Most diagnoses of histoplasmosis are made post-mortem, as pre-mortem confirmatory tests are unavailable. The autopsy study carried out in Côte d'Ivoire on 70 HIV-positive patients who died revealed only 1.42% histoplasmosis [73]. Otherwise, histoplasmosis in children or the immunocompetent subject are very rarely described and the clinical presentation is often misleading. But in Côte d'Ivoire two cases of histoplasmosis in immunocompetent patients are recorded: *Histoplasma capsulatum var. capsulatum* in a patient 36 years and without blemish [74] and *Histoplasma capsulatum var. duboisii* in a child [75]. We estimate 513 acute disseminated cases based on 1.42% of HIV-infected patients. Our estimate could be an underestimate with a 13% rate of histoplasmosis among HIV-positive patients with persistent fever and coughing associated with cutaneous lesions reported by Mandengue et al. in Cameroon [76] and also the fact that we have a few skilled personnel and facilities to make the diagnosis. In AIDS, 10–40% of patients present with skin lesions, which could facilitate rapid diagnosis if biopsied and examined histopathologically.

Antifungal therapy

Despite an increase in antifungal treatments over the past two decades, treatment outcomes are still disappointing. Delays in diagnosis and fungal identification greatly limit the efficacy of therapy. Restrictions in route of administration, spectrum of activity, and bioavailability of some antifungal, especially in HIV/AIDS and drug interactions hampers treatment success.

There are some antifungal agents available in Côte d'Ivoire that are included in the country's essential medicines list (Table 3), including fluconazole, itraconazole, amphotericin B [77]. Many are off patent with numerous generic formulations. Very large numbers of topical azoles are available clinically for thrush and superficial infections; but these are not covered in this report. Conventional amphotericin B treatment is largely used in the hospitalized patient for systemic infection. In Cameroon and Zimbabwe, about 100,000 days of amphotericin B therapy are estimated annually. But in Mozambique and DRC, an estimated 200,000 days of amphotericin B therapy are needed. Flucytosine is not available in Côte d'Ivoire although it has been on the WHO EML since 2013. Itraconazole is not available in Senegal, Gambia, Burundi and Eritrea, and probably some other countries. The total estimated market for itraconazole capsules in Cote d'Ivoire and other antifungals has not been estimated. Natamycin eyedrops is also not available but critically important for fungal keratitis.

The increasing incidence of antifungal drug resistance, documenting fungal disease with diagnostic evidence has several merits. First, it can establish the correct diagnosis, with both immediate and longer term implications for therapy – cryptococcal meningitis being an excellent example. Second, exclusion of a fungal diagnosis can allow stopping of therapy – a good example is discontinuing high dose (and often toxic) cotrimoxazole for PCP [78], as well as corticosteroids. Third, if a fungal diagnosis can be made, instead of a bacterial diagnosis, such as CPA instead of smear negative tuberculosis, then antibacterial therapy can be stopped, contributing to antimicrobial resistance (AMR) control [78]. Finally, increasing antifungal resistance, both acquired and intrinsic, allows optimisation of antifungal therapy, instead of blind empiricism before treatment performed.

Conclusions

In conclusion, with almost 1.8 million cases among 25 million people, severe fungal infections affect 7.25% of the population of Côte d'Ivoire. This result is comparable to that of Senegal, Ghana and Burkina Faso and other West African countries. Due to the paucity of data, we believe that the true prevalence of fungal infection may still be underestimated. As in other low and middle income countries, serious fungal infections remain neglected and underestimated in Côte d'Ivoire despite the rising trend globally [79]. Most of these infections are undiagnosed or misdiagnosed leading to no treatment or incorrect treatment. Low indices of suspicion among clinicians and gaps in the availability of diagnostics services and antifungal drugs are the identified causes. Furthermore, the government and public health agencies have paid less attention to fungal infections. Increasing awareness is a significant initial step to change the status quo.

There is a need for the national government in Cote d'Ivoire to consider the implications of this increasing disease burden and facilitate better management of health in this neglected and usually vulnerable population. The negative effects of fungal infections on human health are not widely recognized despite the fact that millions of people worldwide will contract life-threatening invasive infections.

Patient consent for publication

Not required.

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Contribution of authors

DWD, TOA and DK conceived and designed the protocol. DWD and DK drafted the manuscript with some adds of TOA. DWD, MD, IVB, FK, AM, REMN, KS and DK revised successive drafts of the manuscript. All authors approved the final version of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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