Supplement article

Burden of serious fungal infections in Tanzania

Diana Faini,[1] Werner Maokola,[2] Hansjakob Furrer,[3] Christoph Hatz,[4,5] Manuel Battegay,[5,6] Marcel Tanner,[4,5] David W. Denning[7]* and Emilio Letang[1,4,5,8,]*

[1]Ifakara Health Institute, Dar es Salaam, Tanzania, [2]National AIDS Control Program, Dar es Salaam, Tanzania, [3]Department of Infectious Diseases, Bern University Hospital and University of Bern, Bern, Switzerland, [4]Swiss Tropical and Public Health Institute, Basel, Switzerland, [5]University of Basel, Basel, Switzerland, [6]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland, [7]The National Aspergillosis Centre, University Hospital of South Manchester, The University of Manchester and Manchester Academic Health Science Centre, Manchester, UK and [8]ISGLOBAL, Barcelona Ctr. Int. Health Res (CRESIB), Hospital Clinic – Universitat de Barcelona, Barcelona, Spain

Summary

The incidence and prevalence of fungal infections in Tanzania remains unknown. We assessed the annual burden in the general population and among populations at risk. Data were extracted from 2012 reports of the Tanzanian AIDS program, WHO, reports, Tanzanian census, and from a comprehensive PubMed search. We used modelling and HIV data to estimate the burdens of *Pneumocystis jirovecii* pneumonia (PCP), cryptococcal meningitis (CM) and candidiasis. Asthma, chronic obstructive pulmonary disease and tuberculosis data were used to estimate the burden of allergic bronchopulmonary aspergillosis (ABPA) and chronic pulmonary aspergillosis (CPA). Burdens of candidaemia and *Candida* peritonitis were derived from critical care and/ or cancer patients' data. In 2012, Tanzania's population was 43.6 million (mainland) with 1 500 000 people reported to be HIV-infected. Estimated burden of fungal infections was: 4412 CM, 9600 PCP, 81 051 and 88 509 oral and oesophageal candidiasis cases respectively. There were 10 437 estimated posttuberculosis CPA cases, whereas candidaemia and *Candida* peritonitis cases were 2181 and 327 respectively. No reliable data exist on blastomycosis, mucormycosis or fungal keratitis. Over 3% of Tanzanians suffer from serious fungal infections annually, mostly related to HIV. Cryptococcosis and PCP are major causes of mycoses-related deaths. National surveillance of fungal infections is urgently needed.

Key words: Fungal infections, Tanzania, epidemiology, HIV/AIDS, cryptococcal meningitis.

Introduction

Fungal diseases range in severity from mild superficial infections that affect a large proportion of the otherwise healthy population to life-threatening invasive diseases limited mostly to vulnerable immunosuppressed patients.[1,2]

Among the immunosuppressed population, such as people living with HIV/AIDS (PLWHA), patients with malignancies and those under intensive care, common fungal infections include cryptococcal meningitis (CM), *Pneumocystis jirovecii* pneumonia (PCP) and invasive candidiasis.[2–4] Patients with chronic respiratory illness, including cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and cavitary tuberculosis are at an increased risk for *Aspergillus* spp. infection.[5–7] Finally, a significant proportion of patients with severe asthma are sensitised to airborne fungi which may play a role as exogenous drivers of respiratory disease.[5]The general population on the other hand is

susceptible to infections such as dermatophytoses and recurrent vaginal candidiasis among women.[1,2]

Globally, over 300 million people of all ages suffer from a serious fungal infection every year, accounting for 1.35 million deaths and contributing to negative outcome of many more diseases. This figure is similar to the annual deaths from malaria and tuberculosis, which account for ~600 000 and 1.5 million fatalities per year respectively.[1,8,9]

Unfortunately, despite the life-threatening nature of many fungal infections, they have been insufficiently addressed as public health concerns. Data on incidences and prevalence of these infections are often lacking, as well as adequate diagnostic facilities, evidence-based case management protocols, optimal antifungal medications and specialists in those areas carrying a heaviest burden of disease.[1] This situation results in missed opportunities for diagnosis and effective treatment for these infections, which would result in preventable deaths.

Precise estimates of fungal disease rates are lacking in many African countries, including Tanzania. In the absence of population- and hospital-based surveys as standard epidemiological data,[10,11] we sought to provide estimates by modelling of available data on fungal infections in Tanzania and using assumptions from the medical literature. This estimation of serious fungal infections in Tanzania will set up a frame and base for future studies as well as serve as reference for policy makers.

Methods

Sources of data

The burden of serious fungal infections was estimated for the general healthy population and for those population groups at risk, including PLWHA, patients with asthma, COPD, cancer, posttuberculosis and postsurgical patients, as well as those under intensive care. We consulted the Tanzania National Bureau of Statistics 2012 Population and Housing Census report[12] to obtain denominators for different age groups. Data on the HIV population were extracted from the Joint United Nations Programme on HIV/AIDS (UNAIDS) 2013 Global report[13] and where necessary, local reports for HIV treatment and care services were used.[14] The World Health Organization (WHO) tuberculosis report[15] was consulted to obtain data on tuberculosis patients. Assumptions from other published reports were used to identify the most accurate denominators as explained in detail for each fungal infection below.

We conducted a comprehensive literature review for published prevalence and/or incidence rates of fungal infections in Tanzania and applied these rates to the populations at risk. Where no available data were found in the literature, authors were sought for local unpublished data and government personnel contacted for national reports available. In the absence of local data, published estimates from neighbouring countries were used. Due to the lack of similarity between the populations studied and used in our model, conventional methods for addressing heterogeneity in systematic reviews were not applicable. Therefore, a narrative approach was taken to report the findings of the studies included. Our estimates assumed the lowest incidence rates reported and focused only on well-defined risk populations.

Results

Country's profile

In 2012, the Tanzanian total population was estimated to be 43.6 million, with 51.3% of females. In 2013, the Gross Domestic Product was estimated to be $695 per person. Of the general population, 43.9% were younger than 15 years and 5.6% above 60 years of age.[12] According to the UNAIDS 2013 report, 1 500 000 Tanzanians were estimated to be HIV-infected, 1 200 000 of those being adults. There were 83 000 new infections and 80 000-related deaths in 2012. Of all people living with HIV in 2012, 29% were already receiving antiretroviral therapy (ART). There were 580 000 patients eligible for ART initiation (CD4 counts <350 cells per µl according to WHO 2010 guidelines[16]) but only 399 886 of these were receiving therapy.[13] Assuming that 50% of these patients will have CD4 counts <200 cells per µl we estimated 90 057 patients being severely immunosuppressed with AIDS and therefore at a higher risk of fungal infections (Table 1).

Cryptococcal meningitis
Cryptococcus neoformans is the most common cause of meningitis among adults with severe immunosuppression due to HIV.[17–20] The early diagnosis of invasive cryptococcosis prior to CM in this population is possible through testing for cryptococcal antigenaemia, which can detect cryptococcal infection weeks before the onset of neurological symptoms.[21] Studies in Tanzania have reported a prevalence of cryptococcal antigenaemia ranging from 3% to 7.1% in severely immunosuppressed HIV population[22–25] (Table 2),

Table 1 Country's profile. Populations and rates required to calculate burden of serious fungal infections.

Demographic data	Total population (Mainland) = 43 625 354	Source: Tanzania 2012 population
	% of children (<15 years) = 43.9	and housing census[12]
	Total number of adults = 22 754 122	
	% women over 60 = 2.9%	
	Primary school age population 2012 = 8 341 701	
	Net primary school enrolment 2011 = 94%	
HIV/AIDS	Estimated number of people living with HIV in 2012 = 1 500 000	Source: UNAIDS 2013 report[13]
	New infections in 2012 = 83 000	
	Estimated HIV prevalence – adult (ages 15–49) = 5.1%	
	Proportion of diagnosed cases on ARVs = 0.29	
	Adults living with HIV in 2012 = 1 200 000	
	AIDS-related deaths in 2012 = 80 000	
	Estimated number of HIV patients with	
	CD4 <200 cells per ml = 90 057	
Tuberculosis	Tuberculosis case notifications in 2012 (total new cases) = 61 417	Source: WHO Global Tuberculosis
	Extra pulmonary tuberculosis cases = 14 657	report 2013[15]
	Pulmonary tuberculosis cases in 2012 = 41 389 (<10% death)	
Adults with asthma	Prevalence of asthma in adults = 3.12%	Source: To *et al.*[37]
	Asthma numbers in adults = 759 500	
COPD	COPD prevalence (all GOLD stages) = 12.6%	Source: Mfinanga *et al.*[58]
Patients with leukaemia	AML population frequency = 0.22%	Source: Kersten *et al.*[59]
Number of critical care patients	Estimated number of critical care beds = 3000	Source: World Bank, country Indicator:
	(10% of hospital beds in Tanzania)	Number of hospital beds [60]
	Hospital beds (per 1000 people) in Tanzania = 0.7	

COPD, chronic obstructive pulmonary disease; ARV, Anti-retroviral therapy.

Table 2 Prevalence rates previously reported used to estimate the burden of serious fungal infections.

Disease	Population	Prevalence	Reference
Cryptococcal Infection	Cryptococcal antigenaemia among HIV ART naïve adults with CD4 <150 cells per μl	4.3%	Letang *et al.*[24]
	Cryptococcal antigenaemia among HIV-infected adult hospitalised. Median CD4 count was 68 cells per μl (IQR 41–87, range 1–102 cells per μl)	5.1%	Wajanga *et al.*[22]
	HIV-infected outpatients with CD4 counts <200 cells per μl, both ART naive or on ART for <6 months	3%	Rugemalila *et al.*[23]
	Asymptomatic cryptococcal antigenaemia among HIV ART naïve patients with CD4 counts <200 cells per μl	7.1%	Magambo *et al.*[25]
Pneumocystis jirovecii pneumonia	Adult HIV-infected patients presenting with cough	10.4%	Mwita *et al.*[30]
	HIV-infected patients with pulmonary infections	7.5%	Kibiki *et al.*[61]
	Tuberculosis patients with or without HIV and their healthy contacts	0.3%	Jensen *et al.*[62]
Oral candidiasis	HIV-infected patients ART naïve with CD4 <200 cells per μl	90%	Fabian *et al.*[63]
Oesophageal candidiasis	AIDS patients in Denmark. 20% of patients with HIV not on ARVs and 5% of those on ARVs	20% ART naïve and 5% of those on ART	Smith *et al.*[32]
ABPA	Adult asthmatics	2.5%	Denning *et al.*[5]
CPA	PTB is responsible for 80% of all CPA in Tanzania. 22–33% of tuberculosis patients have residual cavities posttreatment	22% in tuberculosis cavity and 2% with no cavities	Denning *et al.*[2]
SAFS	Severe asthmatics (adults) 10% of Asthmatics have severe asthma	33%	Denning *et al.*[5]
rVVC	Adult women	6%	Sobel *et al.*[41], Foxman *et al.*[64]
Tinea capitis	Primary school children	5.4%	Ferie *et al.*[45]
Histoplasmosis	Admitted patient with febrile illness	0.9%	Lofgren *et al.*[46]

ART, antiretroviral therapy; ABPA, allergic bronchopulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; SAFS, severe asthma with fungal sensitisation; rVVC, recurrent attacks of vulvovaginal candidiasis; IQR, interquartile range; TB, Tuberculosis.

including a recent cross-sectional study reporting a 7.1% of cryptococcal antigenaemia among ART naïve HIV patients with CD4 <200 cells per μl[25] (Table 2).

We estimated the prevalence and incidence of CM in 2012 by first applying the 7.1% rate of cryptococcal antigenaemia among the 90 057 pre-ART HIV patients estimated to have CD4 <200 cells per μl in 2012 and calculated 6394 cases of cryptococcosis (14.66 cases per 100 000 person years) (Table 3). According to a study by Jarvis et al. [26], 69% of patients with cryptococcal antigenaemia develop CM. Using this assumption, we therefore estimated 4412 cases of CM in 2012 among ART naive HIV patients with advanced immunosuppression at rate of 10 cases per 100 000 person per years.

We used the 7.1% rate of cryptococcal antigenaemia in our estimation due to the fact that the study population used in this literature fits the definition of severe immunosuppression due to HIV used in our model (patients with CD4 counts <200 cells per μl). This rate is

Table 3 Estimated annual case load of serious fungal infections in Tanzania.

Fungal infection	Predominant groups at risk	Rate per 100 000	Estimated number of cases
Cryptococcosis	AIDS	14.66	6394
Pneumocystis jirovecii pneumonia	AIDS	22	9600
Oral candidiasis	HIV/AIDS	186	81 051
Osephageal candidiasis	HIV/AIDS	203	88 509
ABPA	Asthma patients	44	18 987[1]
CPA	Tuberculosis patients	24	10 437
IA	Haematological malignancy	0.05	20
SAFS	Asthma patients	57	25 063[1]
Recurrent vaginal candidiasis	Adult women	3482	759 500
Candidaemia	Immunocompromised patients	5	2181
Candida peritonitis	Immunocompromised patients	0.75	327
Tinea capitis	Poor hygiene	963	420 000
Histoplasmosis	None	0.31	135
Total burden estimated			1 422 204

ABPA, allergic bronchopulmonary aspergillosis; IA, invasive aspergillosis; SAFS, severe asthma with fungal sensitisation; CPA, chronic pulmonary aspergillosis.

[1]There is probably some duplication as some ABPA patients have severe asthma and many SAFS patients are sensitised to Aspergillus.

consistent with rates observed in neighbouring countries. Even though other studies in Tanzania have reported a lower prevalence of cryptococcal antigenaemia (Table 2), none of these rates could be generalised to the HIV/AIDS population at risk.

Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii pneumonia, like CM, is a life-threatening condition affecting patients with severe immunosuppression.[4,27] However, with early diagnosis and treatment, survival outcomes have been reported at 70% in Africa and in well-resourced settings may be as high as 90%.[28,29]

In Tanzania, all patients with advanced immunosuppression due to HIV are recommended to receive co-trimoxazole prophylaxis for prevention of PCP. A study by Mwita et al. in 2012 reported a prevalence of 10.4% of PCP among HIV patients presenting with cough for more than 2 weeks not attributed to chronic disease or a cardiac condition attending a HIV care and treatment centre, irrespective of their ART status or use of co-trimoxazole prophylaxis[30] (Table 2). The prevalence of cough for more than 2 weeks at the same site had been reported in another study to be 8%.[31]

We therefore estimated a total of 9600 cases of PCP in 2012 (22 cases per 100 000 person years) assuming that 8% of all 1 200 000 adults living with HIV in 2012 will present with cough and that, out of these, 10.4% will have PCP (Table 3). Due to the lack of data, we were not able to make a reliable estimate of the number of children with PCP among the 300 000 children infected with HIV.

Oral candidiasis

Oral candidiasis is among the most common clinical presentations of ART naive immunosuppressed HIV patients. About 50% of newly presenting symptomatic HIV-infected patients have oral candidiasis.[3,43] Over the course of a year this rate rises to about 90% of those HIV patients not taking but in need of ART[44] (Table 2).

We estimated oral candidiasis to affect 81 051 Tanzanian at a rate of 186 per 100 000 person-years (Table 3). This burden was estimated by assuming that 90% of all patients with advanced HIV annual new AIDS cases with CD4 <200 cells per μl (90 057 cases) will develop oral candidiasis (Table 1).

Oesophageal candidiasis

Oesophageal candidiasis is another AIDS defining illness occurring among patients with advanced HIV, especially but not limited to those ART-naïve.

Oesophageal candidiasis cases were estimated to be 88 509 at a rate of 203/100 000 person-years (Table 3) under the assumptions that 20% of AIDS patients not on ART, and 0.5% of those on ART develop oesophageal candidiasis[32,33] (Table 2).

Serious fungal respiratory infections

Allergic bronchopulmonary aspergillosis (ABPA)

Allergic bronchopulmonary aspergillosis is a common complication of bronchial asthma and CF, and serves as a predisposing factor for chronic pulmonary aspergillosis (CPA).[34–36] A previously described model by Denning *et al.* on the burden of ABPA, including one study from South Africa reported a 2.5% prevalence of ABPA among adults with asthma[5] (Table 2).

To estimate the burden of ABPA, we initially sought data on asthma and CF in Tanzania. However, no reliable published data exist on prevalence of neither CF nor adult asthma. We thus used published prevalence of adult asthma from a neighbouring country, Kenya (3.12%) to estimate the number of adults with asthma in Tanzania[37] (Table 1). Of note, the rates we used from Kenya are comparable to previous reports from Tanzania (2.2–5%).[38]

Using the 3.12% adult asthma prevalence (759 500 adults) and the estimated 2.5% ABPA prevalence among asthmatic adults previously described by Denning *et al.* [5]. 18 987 adults were estimated to have ABPA in 2012 (Table 3). We used asthma prevalence among adults, as the relative frequency of asthma is much higher in children and ABPA correspondingly lower, whereas CPA is exclusively an adult disease.[5,39]

Chronic pulmonary aspergillosis (CPA)

Chronic pulmonary aspergillosis occurs commonly as a sequel of several lung inflammatory conditions.[36] Treated pulmonary tuberculosis can lead to CPA as a long-term sequel.[2] In sub-Saharan Africa, lack of diagnosis of *Aspergillus fumigatus* causing CPA, may lead to under diagnosis and mismanagement with most of these patients treated as cases of sputum smear-negative tuberculosis.[40] CPA presents with different radiological features such as a simple aspergilloma, chronic cavitary pulmonary aspergillosis and chronic fibrosing pulmonary aspergillosis. Consequently, in tuberculosis endemic areas such as Tanzania, misdiagnosis is common.[2]

We calculated the incidences and prevalence of CPA using data on tuberculosis and applying the model described by Denning *et al.* in Bull WHO 2011[2] (Table 2). In 2012, pulmonary tuberculosis was reported in 41 389 Individuals[15] (Table 1). According to Denning *et al.*, the rate of CPA is 22% among the 22–35% pulmonary tuberculosis cases who develop cavities, and 2% in those without visible cavities (Table 2). Assuming that pulmonary tuberculosis is responsible for 80% of all CPA cases in Tanzania, we estimated 10 437 cases of all stages CPA at a rate of 24 cases per 100 000 person per years (Table 3).

Severe asthma with fungal sensitisation (SAFS)

We estimated the burden of SAFS in Tanzania from the adult asthmatic population. Severe asthma occurs in 10% of the asthmatic population. Out of these, 33% have been reported to be sensitised to one or other fungus[5] (Table 2). We calculated from these assumptions that SAFS affects 25 063 Tanzanians annually at a rate of 57 cases per 100 000 person years (Table 3).

Invasive aspergillosis (IA)

We estimated 20 cases of IA in 2012 occurring at a rate of 0.05 per 100 000 person years (Table 3). We calculated this from severely immunosuppressed patients with leukaemia, assuming that 10% of leukaemic patients will develop IA[2]

Candida infections

Recurrent vulvovaginal candidiasis

Recurrent vulvovaginal candidiasis is defined as four or more episodes per year.[41] The infection is usually caused by *Candida albicans*, less often by other species, notably *C. glabrata* which is fluconazole resistant. An estimated 70–75% of women suffer from vulvovaginal candidiasis at least once in their lives, often during pregnancy.[41]

Recurrent attacks of vulvovaginal candidiasis (rVVC) have been estimated to affect 5–9% women annually based on a global epidemiological review by Sobel *et al.*, and on more recent data from Foxman *et al.*[64] (Table 2). There has been controversy about these data. However, there are no better estimates for rVVC, and there are intrinsic difficulties in conducting a study to reliably estimate the incidence and prevalence of rVVC among women.[11] There are no reports of rVVC from Tanzania or East Africa, but a study published by Amouri *et al.* found a similar prevalence of 6.1% in Tunisia.[42]

We estimated recurrent vulvovaginal candidiasis among adult women in the general healthy population to affect 759 500 women in 2012 at a rate of 3482 women per 100 000 person-years (Table 3). We

calculated this assuming that 6% of all adult women in Tanzania have recurrent infections per year, unrelated to HIV infection.

Candidaemia and candida peritonitis was estimated to affect 2181 and 327 patients, respectively, at rates of 5 and 0.75 per 100 000 person-years respectively (Table 3). These incidences were estimated among patients with cancer, postsurgical patients and those on intensive care (Table 1). We calculated this under the assumption that candidaemia occurs at a population rate of 5 cases/100 000 and candida peritonitis at a ratio of 1 patient with hospital-acquired (almost all postoperative) case for every two patients with candidaemia.[2]

Other fungal infections

Tinea capitis affects 5.4% of primary school children in Tanzania[45] (Table 2), a lower rate than other sub-Saharan African countries. According to the national population census, there are 8 341 701 primary school aged children in Tanzania and the country's net primary school enrolment is 94%[12] (Table 1). We estimated from these reports that 420 000 school children suffer from tinea capitis each year at a rate of 963 per 100 000 person-years (Table 3).

Histoplasmosis cases have been reported in a study done at a referral hospital in northern Tanzania at a prevalence of 0.9% among patients admitted with febrile illness[46] (Table 2). Assuming that 50% of all admitted patients in Tanzania have febrile illness, we estimated 135 cases of histoplasmosis in 2012 at a rate of 0.31 per 100 000 person-years (Table 3). Apart from case reports, no reliable epidemiological data exist for IA blastomycosis, mucormycosis or fungal keratitis in Tanzania and in sub-Saharan Africa.[40,47–49]

Estimated number of deaths due to fungal infections in Tanzania

Based on our estimations, 5777–15 541 Tanzanians die of fungal opportunistic infections each year mainly cryptococcosis, PCP and CPA. In Tanzania, cryptococcosis (with or without meningitis) has been reported to have a 92% fatality rate (within the first year) when no antifungal treatment is given versus 50% fatality at any dose of antifungal given upon physician discretion.[24] We estimated that in 2012, out of 6394 patients with cryptococcosis between 3197 and 5882 patients died, contributing up to 55% of all annual deaths due to fungal infections in the country (Fig. 1).

In turn, the fatality rate of PCP in Africa ranges from 16% to 68%[29] and therefore estimated to cause between 1536 and 6528 deaths annually in Tanzania. CPA fatality rate has been reported to be 10–30%,[5,28] which estimates to be responsible for 1044–3131 deaths annually. HIV/AIDS remains the leading cause of premature death and years of life lost in Tanzania,[50] and CM and PCP make a major contribution to this high loss of life.

No deaths are expected to be associated with ABPA, recurrent vaginitis or tinea capitis. In 2013, 500 000 asthma deaths were estimated to occur worldwide.[50] As SAFS is not uncommon among this group, some of these are probably attributable to SAFS.

Discussion

This is the first attempt to estimate the burden of serious fungal infections in Tanzania. Overall, about 3% of Tanzanians suffer from fungal infections yearly. HIV fungal opportunistic infections contribute to 18% of the total and account for 80% (79.9–81.9%) of all deaths due to fungal infections in the country. Cryptococcosis and PCP are the major causes of mycoses-related deaths contributing up to 55% and 42% respectively.

Our estimates show that most fungal infections in Tanzania affect PLWHA. Besides biological plausibility explaining this finding, this is also influenced by the fact that more data are available on the HIV population in Tanzania than on other groups of patients with immunosuppressive conditions.

Nevertheless, out of all severely immunosuppressed HIV patients at high risk of fungal opportunistic infections, nearly 30% are not on antiretroviral therapy. Fortunately the current national guidelines recommend a higher CD4 threshold of 350 cells per μl for ART initiation as compared to previous values of CD4 <200 cells per μl.[51] Moreover, this threshold is likely to increase to 500 cells per μl in Tanzania following the adoption of the latest WHO guidelines.[52] This strategy was established on the basis of evidence showing a delay in HIV progression and secondary transmission associated with earlier initiation, and is expected to reduce the number of PLWHA at risk of highly fatal fungal opportunistic infections such as CM and PCP. In addition, early diagnosis and linkage to care are paramount as most people living with HIV in Tanzania are not aware of their HIV status, and present late in the course of HIV disease. Of note, in 2011, 66.4% of all baseline patients presenting for care in HIV clinics in Tanzania had CD4 <200 cells per μl.[14]

Annual estimates of number of cases and deaths associated with the most relevant fungal infections in Tanzania.
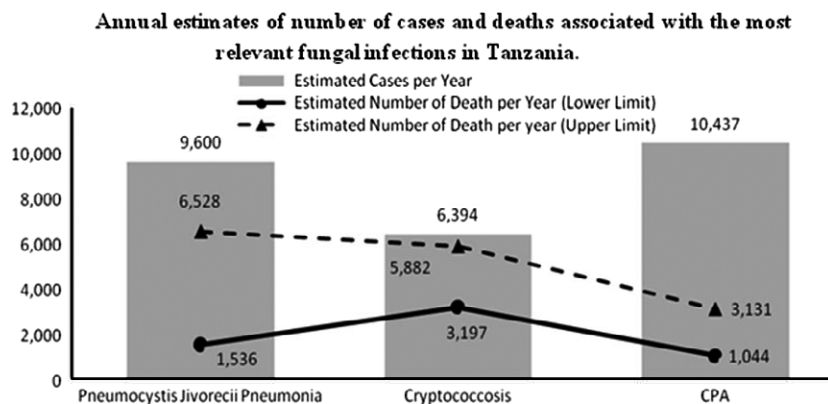

Figure 1 Annual estimates of number of cases and deaths associated with the most relevant fungal infections in Tanzania. CPA, chronic pulmonary aspergillosis.

In 2012, there were 80 000 deaths due to HIV/AIDS in Tanzania. Assuming that 10–20% of these occur due to CM,[17] we would expect 8000–16 000 deaths in 2012 due to this infection, many more than our estimate of a total of 4412 patients. The assumptions used in our model may have underestimated the prevalence of CM. We believe this underestimation may be explained by the low awareness among clinicians as well as the lack of widely available confirmatory tests. A study by Wajanga *et al.* showed a 1–2 weeks delay of cryptococcal infection diagnosis in a referral centre in north Tanzania.[22] Given the burden in Tanzania, the rollout of CD4 targeted screening for invasive cryptococcosis using cryptococcal antigen lateral flow assay, as recommended by the WHO [53], is urgently needed. This cost-effective strategy would facilitate early detection of cases and consequently reduce mortality.[24] Furthermore, increasing the availability of first-line antifungals, such as amphotericin B and flucytosine, would be an effective measure towards reducing mortality dramatically.[54] Additional measures to reduce mortality include ensuring a wider availability of lumbar puncture equipments to reduce intracranial pressure, and increased awareness and uptake of the most recent recommendations. Importantly, the long-term prognosis is excellent for patients who survive CM and are initiated on ART.[55]

We estimated 9600 annual cases of PCP from a study diagnosing PCP using bronchoalveolar lavage, and toludine staining in sputum.[30] In this study, half of the patients were on ART and co-trimoxazole. Our estimates may have been higher than expected as our denominator did not account for number of patients on co-trimoxazole prophylaxis. In routine HIV care provided in Tanzanian clinics as well as other African settings, PCP is diagnosed clinically as presence of cough and low oxygen saturation,[56] and microscopy diagnosis is only performed in research settings. The

current treatment guidelines in Tanzania have increased the cut-off point for co-trimoxazole prophylaxis initiation among all HIV patients from CD4 <200 cells per μl to CD4 <350 cells per μl,[51] but drug stock outs are frequent in the country. This leads to patients being often recommended to buy the co-trimoxazole themselves, which seldom happens due to the economic constraints of many patients. This worrisome scenario may result in an increased incidence rate of PCP among other associated conditions prevented by co-trimoxazole prophylaxis, including toxoplasmosis, malaria and respiratory and enteric infections. Also our model did not include non-HIV immunocompromised patients such as malnourished patients and those with haematological malignancies who are also at risk of developing PCP.

Respiratory fungal infections such as histoplasmosis blastomycosis and non-tuberculous mycobacterial infection may be indistinguishable from pulmonary tuberculosis. This is especially the case in a tuberculosis endemic area such as Tanzania. We noted that in 2012, there were 46% smear-negative pulmonary tuberculosis cases and that 39% of all tuberculosis patients were HIV positive. Although fungal respiratory infections have rarely been reported in Tanzania, we assume that most of these may have been misdiagnosed and treated as smear-negative tuberculosis cases.[40]

A previous large systematic review on blastomycosis from 18 African countries reported a total of 81 cases, one of which was from Tanzania[48] showing that the lack of epidemiological data does not exclude the presence of blastomycosis in Tanzania. Also, a case report from Canada reported a Tanzanian expatriate diagnosed with blastomycosis.[49] As discussed above, in this case report, the patient had been previously treated empirically for tuberculosis before being diagnosed with blastomycosis.

We estimated 10 437 cases of CPA in 2012 among posttuberculosis patients. This underlines the necessity for incorporating management of this frequently neglected tuberculosis-associated disease into national tuberculosis treatment guidelines in Tanzania. To diagnose CPA, ELISA for IgG antibodies to *Aspergillus* or an *Aspergillus* precipitin test is needed. Although these tests are widely available (total IgE, dermal tests), inexpensive and feasible also in low-income countries, they are not widely available in Tanzania. Consequently, patients are usually treated with extended course of anti-tuberculosis medication even with a negative sputum smear for *Mycobacteria*.[40]

Candidaemia is reported as the fourth most common cause of nosocomial bloodstream infection globally.[57] The incidence of invasive candidiasis in our estimates is much lower than expected. We estimated candidaemia and *Candida* peritonitis from immunocompromised patients including postsurgical patients, patients with haematological malignancy and those in intensive care units. The lack of precise data on number of patients with these conditions in Tanzania used as denominators in our model may explain our lower estimates. For instance, there are no precise data on number of ICU beds in Tanzania, we assumed that 5% of all hospital beds in Tanzania serve as 'intensive care bed' (T. Baker, personal communication). This is because ICUs are only found in tertiary and referral hospitals while in most hospitals designated patient rooms serve as 'intensive care rooms/close observation rooms' with patients receiving intensive care services.

This study has several limitations. Despite having identified all manuscripts published on fungal infections in Tanzania, some of these lack the necessary denominators and others are not updated to be incorporated in our model. Also, the estimates on the number of other groups of patients with immunosuppression in Tanzania are imprecise. The national cancer registry was started in 2010 and currently there is insufficient epidemiological data on patients with haematological conditions (A. Mwakigonja, personal communication). On the other hand, although organ transplantation is not routinely done in Tanzania, patients are referred outside the country for these services. To our knowledge there is no official registry for all patients who have had organ transplant living in Tanzania (Ministry of Health Tanzania, personal communication). Again, a centralised registry on all surgeries performed in the country is missing. We believe that the lack of data on these groups of patients may have slightly underestimated the number of some invasive fungal conditions such as candidaemia.

Finally, due to the nature of the modelling we conducted, and based on the lack of robust data from Tanzania and neighbouring countries, our estimates probably have wide confidence limits. A scenario-based modelling that also takes into account focal distributions might yield more accurate estimates and extrapolations. Despite these shortcomings, we feel that these very first country-wide assessments and extrapolations provide an acceptable ground to raise awareness of the non-addressed burden of fungal disease, and point at the need for better registries, effective use of available diagnostic tools, as well as strengthening the availability of and access to first-line antifungals in Tanzania.

Conclusion

To our knowledge, this is the first attempt to estimate the burden of serious fungal infections in Tanzania. We estimated that 3% of Tanzanians suffer from a fungal infection every year. However, the actual number of fungal infections may be higher than our estimates since most data used in the model were derived from HIV studies, given the scarcity of data from other immunocompromised populations. Our estimates form a basis for future epidemiological studies and may stimulate the development of a national survey that is currently lacking. These estimates aim to address a relevant and largely non-addressed public health concern with very important implications. In particular, our results point at the urgent need for better epidemiological surveillance within the health system, better laboratory and point-of care diagnostics, better availability of existing tests, and increased access to existing first-line antifungal drugs. The integrated implementation of these measures will help to reduce the unacceptable burden and mortality of fungal infections in Tanzania.

Acknowledgments

Conflicts of interest

DF, WM, HF, CH, MB, MT, and EL have no conflict of interest to declare. DWD holds Founder shares in F2G Ltd a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the

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