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Emerging Problems in Infectious Diseases

Estimated burden of fungal infections in Kenya

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Abstract

Introduction: Kenya is a developing country with a high rate of tuberculosis (TB) and a moderate HIV infection burden. No estimate of the burden of fungal diseases in Kenya is published.

Methodology: We used specific populations at risk and fungal infection frequencies from the literature to estimate national incidence or prevalence of serious fungal infections. Used sources were: 2010 WHO TB statistics, Kenya Acquired Immunodeficiency Syndrome (AIDS) Epidemic Update 2012, Kenya Facts and figures 2012, Kenya Demographic and Health Survey 2008-2009.

Results: Of Kenya's population of ~40 million, 43% are under 15 years old and approximately 594,660 Kenyan women get >4 episodes *Candida* vulvovaginitis annually (2,988/100,000). The HIV/AIDS population at risk of opportunistic infections (OI) is 480,000 and the OI estimates include 306,000 patients with oral thrush (768/100,000), 114,000 with oesophageal candidiasis (286/100,000), 11,900 with cryptococcal meningitis (29/100,000) and 17,000 patients with *Pneumocystis* pneumonia (42/100,000). Chronic pulmonary aspergillosis following TB has a prevalence of 10,848 cases (32/100,000). The adult asthma prevalence is 3.1% and assuming 2.5% have allergic bronchopulmonary aspergillosis then 17,696 (44/100,000) are affected. Invasive aspergillosis, candidaemia and *Candida* peritonitis are probably uncommon. Tinea capitis infects 9.6% of children in Kenya, while fungal keratitis and otomycoses are difficult to estimate.

Conclusion: At any one time, about 7% of the Kenyan population suffers from a significant fungal infection, with recurrent vaginitis and tinea capitis accounting for 82% of the infections. These estimates require further epidemiological studies for validation.

Key words: *Aspergillus*; *Cryptococcus*; *Trichophyton;* AIDS; asthma; tuberculosis.

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Introduction

Kenya is a developing East African country with a high rate of tuberculosis (TB) and a moderate HIV infection burden. These two diseases predispose patients to the development of opportunistic fungal infections. Sub-Saharan Africa being the epicenter of HIV/AIDS burden, the main likely fungal infections are respiratory, eye, dermatological, and cryptococcal meningitis [1-6]. Evidence shows that fungal infections are often hidden killers causing a substantial morbidity and mortality in susceptible individuals. However, their impact is not widely acknowledged or appreciated as compared to other diseases. A great disparity of access to fungal diagnostic and treatment services in resource-constrained countries is apparent particularly in sub-Saharan Africa. Moreover, despite efficient diagnostic tests and safe effective drugs, research on fungal infections in comparison to other pathogens is somewhat neglected [1].

Limited technical and infrastructural capabilities for diagnosis and research, and inaccessible treatment is a big challenge in the management of fungal infections. On the other hand, infections mimic and accompany existing conditions such as HIV, TB and other bacterial infections, particularly in patients receiving immunosuppressive medications, making diagnosis difficult. As part of the efforts to improve the situation, we have been estimating the burden of serious fungal infections in many countries, using a similar methodology. Here we estimate the burden in Kenya's population of ~40 million of whom 43% are under 15 years old.

Methods

A full literature search was done to identify all epidemiology papers reporting fungal infection rates from Kenya. We used specific populations at risk and fungal infection frequencies in the population to

estimate national incidence or prevalence. The WHO population statistics of 2010 [2], antiretroviral therapy (ART) rates in 2012 [3], Kenya AIDS Epidemic Update 2012 [4], Kenya Facts and figures 2012 [5], 2008-2009 Kenya Demographic and Health Survey [6], WHO 2013 TB statistics [7], To *et al.* estimate of adult asthma prevalence [8], WHO HIV Epidemic update [9] and prevalence of cryptococcal and HIV infections [10, 11] were the data sources used in review.

Results

Fungal infections complicating HIV/AIDS

The total estimated population with HIV infection was 1,400,000 in 2012 [8,9,] with 548,588 (43%) on ART and with 680,000 (1.7% of the population) thought to be eligible for ART using the 2010 WHO ART guidelines, but not receiving it [8]. The population at risk for opportunistic fungal infection is therefore approximately 340,000 with CD4+ T-lymphocytes counts under 200×10^6/L [8]. It is estimated that there were 57,000 AIDS-related deaths in 2012 [8].

We estimate that there are approximately 11,900 cases of cryptococcal meningitis in Kenya (Table 1) (29/100,000). Estimates of cryptococcal meningitis in Kenya indicate an incidence of 6.2-11% cryptococcal antigen positivity in those with CD4+ T-lymphocytes counts $<100\times10^6$/L [15,16]. The vast majority of these patients progress to meningitis, if they don't have meningitis when tested. We have assumed a conservative rate of 7% in those with CD4+ cell counts $<100\times10^6$/L [15,16]. In Uganda it was 1.1% of all HIV patients [17] and 12% in all HIV Sub Saharan Africa [18-20]. There is evidence that earlier screening and prophylactictreatment with fluconazole prevents cryptococcal meningitis infections in HIV patients [17] and is a less expensive therapy option [21-23]. However, fluconazole resistance could reduce the efficacy of this strategy [3].

Fungal pneumonia, especially *Pneumocystis jirovecii* pneumonia (PCP), is commonly associated with AIDS epidemic. Studies reveal the rate of PCP to be ~10% of patients not treated with ART [1,2,24] and 13% in children with severe pneumonia [2]. A study conducted in Kenya in 2003, found 37.2% with PCP infections among HIV positive patients and a mortality rate of 31% [1]. Assuming a rate of 10% amongst those with a CD4+ T-lymphocyte count $<200\times10^6$/L, we anticipate 17,000 new cases annually (42/100,000). This may be an underestimation of the total cases as many patients go undiagnosed due to diagnostic challenges.

Oral and oesophageal candidiasis is common in HIV infection. Assuming 45% of patients with CD4+ T-lymphocytes counts $<350\times10^6$/L develop oral candidiasis during 12 months [25,26] this equates to 306,000 patients with infection (768/100,000) and probably many more episodes as it tends to be recurrent. Oesophageal candidiasis may accompany oral candidiasis, but is often separate and even more debilitating. It affects ~20% of HIV/AIDS patients [25]

Table 1. Estimated incidence or prevalence of serious fungal infection associated with different underlying conditions.

Infection	Number of infections per underlying disorder per year					Total burden	Rate /100K
	No underlying disease	HIV/ AIDS	Respiratory	Cancer/ Tx	ICU		
Oral candidiasis		306,000				306,000	769
Oesophageal candidiasis		114,000				114,000	286
Candidaemia				1,393	597	1,990	5
Recurrent vaginal candidiasis (4x/year +)	594,660					594,660	2,988*
ABPA			17,696			17,696	44
SAFS			23,359			23,359	58
Chronic pulmonary aspergillosis			12,927			12,927	32
Invasive aspergillosis				239		239	0.6
Cryptococcal meningitis		11,900				11,900	29
Pneumocystis pneumonia		17,000				17,000	43
Fungal keratitis	ND						
Tinea capitis	1,712,676					1,712,676	4,302
Mucormycosis				80		80	0.2
Candida peritonitis					239	239	0.6
Total burden estimated	**2,307,336**	**822,900**	**53,982**	**1,712**	**836**	**3,186,766**	

* females only. HIV = human immunodeficiency virus infected people, AIDS = acquired immunodeficiency syndrome, Tx = transplant recipient, ICU = intensive care unit, ABPA = allergic bronchopulmonary aspergillosis, SAFS = severe asthma with fungal sensitization, ND = no data.

without ART and ~0.5% patients on ART [27]. In Kenya there may be as many as 114,000 (286/100,000) patients affected with oesophageal candidiasis each year. These estimates ignore all the other episodes of oral, vaginal and oesophageal candidiasis in other patient groups such as asthmatics, patients with cancer, neonates and the elderly patients with dentures.

Disseminated histoplasmosis occurs in Africa, having been documented initially in 1957 [28]. More recently cases have been recognized in HIV patients [12]. It is not possible to estimate the caseload with current data, but could be much more common than it is published. In northern Tanzania on the border with Kenya, a rate of 0.9% of disseminated histoplasmosis using antigen testing was documented in new hospital admissions with fever, 67% of whom were HIV infected [13].

Fungal infections complicating cancer and other immunosuppressive conditions

We have estimated the total annual incidence rate for candidemia based on a population basis only, in the absence of data from Kenya and East Africa. Using a low international rate of 5 per 100,000 population per year [31], we estimate there to be ~1,990 cases annually. The actual number could be much higher or lower: higher because procedures for infection control are lax and antibiotic management is unrestrained and lower because there is less intensive/high dependency medicine practiced. Candidaemia is found in approximately 40% of cases of invasive candidiasis [32,33], including intra-abdominal candidiasis so candidaemia rates substantially underestimate the total population of invasive candidiasis.

Invasive aspergillosis (IA) is probably uncommon in most of sub Saharan Africa because of the general lack of high intensity cancer treatments, transplantation and less aggressive immunomodulatory treatment for immunological disorders, with the one exception of corticosteroids. We have however assumed that the rates of infection are similar in acute myeloid leukaemia as elsewhere (10%) and that an equal number of cases of IA occur in those with other haematological disorders [34]. This estimate provides an estimate of approximately 239 cases (0.6/100,000), which ignores HIV-associated and chronic obstructive pulmonary disease (COPD) cases, as well as other corticosteroid treatment risk. It is likely that mucormycosis and other opportunistic infections occur, but it is not possible to estimate their frequency.

Chronic pulmonary aspergillosis after TB

Chronic pulmonary aspergillosis (CPA) is a complication of pulmonary TB that is often diagnosed late. It may be confused with TB relapse/reinfection or multi-drug resistant pulmonary tuberculosis as its clinical features are similar [6,35]. Pulmonary TB survivors in 2013 were estimated to be 67,788 of which 42% are in HIV positive patients [12]. Using identical assumptions as previously described [36] (i.e 22% CPA rate in those with residual cavities following TB and 2% in those without residual cavities) the incidence of new cases of CPA was estimated at 3,281 (8.2/100,000) cases. With a 15% annual mortality or surgical resection rate, CPA prevalence after TB is estimated at 10,341 (26/100,000) cases. As TB is only one of the underlying diseases associated with CPA [37], but recognizing that there are very few Kenyans older than 60 years, the majority of the CPA cases will be attributable to TB, probably 80%. Therefore the total CPA prevalence estimate for Kenya is 12,927 (44/100,000) cases. Currently relapsed or non-responding TB is a common scenario facing clinicians and without *Aspergillus* IgG serology is not a diagnosable disease in Kenya currently [38].

Fungal allergy complicating asthma

Fungal allergy exacerbates asthma, especially in adults. The prevalence of asthma in adults in Kenya is 3.12% based on the World Health Survey developed and implemented by the WHO [13]. The prevalence of allergic bronchopulmonary aspergillosis (ABPA) in adult asthmatics is taken to be 2.5% [39-41] and therefore totals 17,796 cases in Kenya in those with underlying asthma. One of these estimates of ABPA prevalence is from Africa [39] and all are in referred populations to secondary care. Therefore, the rate could be overestimated (rate only in referred patients) or underestimated (some patients never referred). Severe asthma with fungal sensitization (SAFS) prevalence is about 0.33% of the worst 10% adult asthmatics (70,700), thus 3% of asthma patients have SAFS [42-44], approximately 23,359 cases in Kenya (58/100,000). Like ABPA, SAFS is responsive to oral itraconazole therapy, improving quality of life [43]. Increasing numbers of fungal spores in the air may contribute to respiratory diseases particularly near garbage damping sites which provide a suitable substrate for fungal proliferation and a predisposing factor for asthma [14, 46].

Fungal infections in women and children

Kenya's population was about 40 million people in 2009 [11] with 43% under 15 years of age and 4% over the age of 60 [10]. Across the world, approximately 9% of women report 4 episodes or more of *Candida* vulvovaginitis (VVC) per year [47] which we have reduced arbitrarily to 6% because of over self-diagnosis. In Kenya, this equates to approximately 594,660 patients aged 15-50 affected annually (2,988/100,000 females). This estimate excludes women on hormone replacement therapy, and is an annual prevalence estimate, not a lifetime experience estimate which is considerably higher [47]. Recurrent VVC is an unpleasant problem for women with many psychological consequences as well as being costly in terms of medical consultation time and treatment cost. There are some data consistent with pre-term premature membrane rupture related to vaginal *Candida* colonization in women during late pregnancy [48-50]. Some fluconazole resistance among *Candida* spp isolated from women with VVC have been identified by recent studies [51].

A published estimate of tinea capitis in children indicates 9.6% affected in Kenya [52,53]. Assuming that 10% of all children up to age 15 have tinea capitis, a total of 1,712,267 (4,302/100,000) cases are estimated. Similar surveys in Nigeria showed 9.4% [54] and Ethiopia 23-32% of children to have tinea capitis [55].

Fungal keratitis

Fungal keratitis is responsible for human blindness, unless diagnosed and treated early. There are no reports from Kenya regarding fungal keratitis. Many fungal eye infections occur in HIV patients [56-58]. A study at the Kilimanjaro Christian Medical Centre, Moshi, Tanzania showed that 50% of the referred patients with an ocular problem had microbial keratitis and concluded that fungal keratitis is more prevalent in the tropics than in temperate climates. It concluded that lack of diagnostic and treatment capability hinders prevention efforts thus resulting in human blindness [59]. In Uganda, keratitis is responsible for 25% of children with impaired vision [60]. Timely access to diagnostics and treatment services could reverse this trend. Hence improving patients' quality of life with the introduction of measures aimed at improving treatment outcomes.

The Kenya national laboratory diagnostic survey of 2010 by the Ministry of Health shows a limited utilization of fungal diagnostic tests (M. Mwau personal communication, August 23, 2013 unpublished policy survey). The lack of routine mycological investigation coupled with lack of trained laboratory technologists capable of supporting a fungal treatment service is a challenge in most public hospitals. Limited data and a poor diagnostic capacity may be linked to apparent low prevalence rates and missed opportunities for reducing mortality caused by fungal infections. Epidemiological studies are needed to ascertain the actual burden of this disease and give the accurate data on the incidence rates; ensuring accurate diagnosis and hence timely treatment preventing the eye complications that could result to total blindness.

Discussion

The true burden of fungal infections is unknown in Kenya because of limited research studies and lack of systematic diagnosis and data collection. To truly measure the burden and impact of fungal diseases in different patient groups and clinical settings requires more epidemiological studies. Health impact assessment studies are needed to estimate the economic and disability caused. We acknowledge that our estimates are crude at best and require confirmation or modification to develop a true picture of the current situation. Several important fungal infections are omitted, including fungal sinus disease, all skin and nail infections, many episodes of oral thrush, fungal keratitis and rare invasive infections such as mucormycosis.

Cohen has pointed out the important role the 'New World of Global Health' which he considers a revolution that has made the case for increasing funding for battling diseases in poor countries [61]. In his view the substantial funds provided have been instrumental in reducing the burden of disease and improving the overall economy of many poor countries. Therefore, there is considerable benefit for global organizations to direct more efforts and implement ambitious programs in poor countries which would make diagnostics and treatment generally accessible especially where most needed. The medical mycology community might borrow from examples of other infections by working with local organizations and patients to raise awareness and advocate for resources to reduce morbidity and mortality linked to fungal diseases among policy makers and political leaders.

Similarly, Cohen [61] and others have observed that funding in HIV/AIDS dwarfs that of any other infectious diseases including tuberculosis - and we add fungal infections. A recent summary of epidemiological data and medical needs, estimated over 1.5 million deaths from invasive fungal infections [6,62]. This

estimate serves to bring to the attention of the local public health organizations and health practitioners that fungal infections are also in the league of 'great killers' that need much greater allocation of resources. We propose that new efforts drive forward local programs to evaluate the actual burden of CPA, cryptococcal meningitis, PCP and fungal keratitis; the current state of knowledge is scanty and there are limited infrastructures to diagnose and treat these serious problems, which is not acceptable. Cohen citing UNAIDS "the three ones" principle offers a solution to major neglected diseases where each country should create one national coordinating committee, one national monitoring and another evaluation system that has been harmonized to provide local and international agencies necessary epidemiological and performance information in low limited resource countries to fight major problems including the HIV/AIDS epidemic [61].

Kenya as a country needs a public–private partnership to address limited resources and access to fungal infection care as per the suggestions of Buse and Walt [63]. As a nation, it needs help to establish structures for a national program for fungal diagnostics and treatment services with high quality standards of care. We suggest that such a national program should have the power to conduct health promotion and advocacy including a monitoring and evaluation program to track public health programs and disseminate information. Such monitoring would help global agencies participate and contribute to in country efforts to fight fungal disease. The timely access to local data helps organizations make quick and real time decisions on clinical practices for those with fungal and other infections. Getting to Zero, the current target of the national and international AIDS program is not achievable without much improved diagnosis and therapy for fungal disease. As Table 2 indicates, even implementation of antiretroviral therapy still leaves many patients dying in the first year of cryptococcal meningitis and undefined sepsis, as well as tuberculosis. Infectious disease programs should include personnel strengthening, quality assurance and regulation components to help standardize service delivery [63]. Low income countries such as Kenya are struggling to fight preventable, treatable illnesses which continue to cause massive suffering and premature deaths [61].

One major limitation that is likely to undermine improved outcomes from fungal disease in Kenya is access to fungal drugs which are either unaffordable to the patients or not locally available because of limited resources. Current availability and pricing of generic antifungal agents is shown graphically for Kenya and most other countries [62,68]. Reports from other countries on HIV/AIDS access to treatment programs show that making treatment accessible has a great impact on the quality of life of patients, in the first year of therapy [69,70], although poor adherence and ARV resistance reduces this impact thereafter. Kenya can learn from other's experience [71] by developing a benchmark for its own fungal disease prevention and control strategy effectively taking into account that "individuals who can access effective care are the most likely to get HIV tests" [71]. Provision of more comprehensive care of HIV/AIDS, including curative antifungal therapy, will likely encourage greater engagement with health services. Our opinion is informed partly by lessons learned from HIV epidemic in which Castro and Farmer suggest that "the last 2 decades have taught us a great deal about failure and how it is best measured; new HIV infections and AIDS deaths are grim yardsticks. A lack of decent medical care and effective prevention strategies (including the absence of a vaccine and inadequate women-controlled barrier methods) frustrates public health efforts" [71].

Conclusion

Our estimate from local data and literature on the incidence or prevalence of fungal infections indicates

Table 2. The outcome in the first year of antiretroviral therapy in 4 published studies from Africa.

Country	Ref. No	Deaths in first year of ARV therapy (%)					Years
		Total	Cryptococcal meningitis	PCP	TB	Undiagnosed infections	
Senegal	66	47/404 (12)	5/47 (11)	unknown	8/47 (16)	9/47 (18)	1998-2002
Morocco	67	57/1243 (4.6)	7/57 (12)	unknown	20/57 (35)	unknown	1999-2010
Zimbabwe + Uganda	68	179/3316 (5.4)	20/179 (11)	1/179 (1)	14/179 (8)	33/179 (18)	2003-2004
Malawi	69	190/1584 (12)	7/190 (4)	2/190 (1)	10/190 (5)	35/190 (18)	2003-2005

ARV = antiretroviral therapy, PCP = pneumocystis pneumonia, TB = tuberculosis.

that nearly 7% of the Kenyan population suffers from serious fungal infections each year. Recurrent VVC and tinea capitis account for 85% of the infections. While these data certainly underestimate the total problem of fungal infection, the neglect that mycology has suffered in Africa cannot be overemphasized. Lack of technical and infrastructural capabilities for diagnosis and treatment, and limited research on fungal infections significantly underscores the importance of fungi as agents of public health importance in Kenya. The significance of fungal burden is important in the context of controlling opportunistic infections in HIV/AIDS and not inappropriately treating apparent relapsed TB or MDR TB, which are actually chronic fungal disease. Private and public health stakeholders must consider investing and facilitating approaches that would bridge the gap and disparities associated with clinical fungal disease care provision.

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