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Supplement article

Cryptococcal disease and the burden of other fungal diseases in Uganda; Where are the knowledge gaps and how can we fill them?

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Summary

The HIV epidemic in Uganda has highlighted *Cryptococcus* and *Candida* infections as important opportunistic fungal infections. However, the burden of other fungal diseases is not well described. We aimed to estimate the burden of fungal infections in Uganda. All epidemiological papers of fungal diseases in Uganda were reviewed. Where there is no Ugandan data, global or East African data were used. Recurrent vaginal candidiasis is estimated to occur in 375 540 Uganda women per year; *Candida* in pregnant women affects up to 651 600 women per year. There are around 45 000 HIV-related oral and oesophageal candidosis cases per year. There are up to 3000 cases per year of post-TB chronic pulmonary aspergillosis. There are an estimated 40 392 people with asthma-related fungal conditions. An estimated 1 300 000 cases of tinea capitis occur in school children yearly in Uganda. There are approximately 800 HIV-positive adults with *Pneumocystis jirovecii* pneumonia (PJP) annually and up to 42 000 children with PJP per year. There are an estimated 4000 cryptococcal cases annually. There are an estimated 2.5 million fungal infections per year in Uganda. *Cryptococcus* and PJP cause around 28 000 deaths in adults and children per year. We propose replicating the model of research around cryptococcal disease to investigate and development management strategies for other fungal diseases in Uganda.

Key words: Uganda, fungal infection, *Cryptococcus*, aspergillosis, *Candida*, HIV.

Introduction

Historically infectious diseases have been the main cause of mortality in resource-limited settings. For the last 20 years, the HIV epidemic in Uganda, as elsewhere in Sub-Saharan Africa, has led to a focus research priorities on HIV and related opportunistic infections.[1] Other infectious diseases are often understudied, which has led to recent interest in 'neglected tropical diseases' which have traditionally had minimal funding, but contribute to a large burden of morbidity, as well as mortality.[2] In addition, whilst the prevalence of non-communicable diseases including respiratory conditions and malignancies is growing,[3] these conditions are relatively unstudied, and there is a paucity of information related to their epidemiology and treatment. Whilst fungal diseases fall into the category of understudied disease they often co-exist and are interdependent with other diseases. Conditions which lead to immunosuppression such as HIV, diabetes and cancers requiring immunosuppressive drugs often provide the setting to facilitate fungal infections in humans. As the HIV epidemic has led to a large body of research in HIV-related opportunistic infections in

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Sub-Saharan African settings (such as Uganda) consequently research into fungal infections has been mainly limited to HIV-related infections.

The discrepancies between available information on HIV-related fungal opportunistic infections and other fungal infections were markedly evident during the preparation of this manuscript. For example, a PubMed search on 'cryptococcal' and 'Uganda' revealed 71 articles including original articles, whereas 'aspergillosis' and 'Uganda' returned only two case reports and one case series. From this we would submit that the research work undertaken on cryptococcal disease in Uganda could serve as a template to generate evidence and interest in diagnosis and management of other fungal infections in our setting.

In this study, we present a review of the epidemiology of fungal disease in Uganda, with estimates based on available data. For Uganda it was possible to estimate HIV-related fungal infections based in information from local Uganda-specific research. However, there was very little data available to estimate the burden of non-HIV-related fungal infections and information from other African or global data were used. We also explore how research into *Cryptococcus* has developed in Uganda, which in turn has led to changes in policy and clinical practice within Uganda and beyond, and how future researchers and interested clinicians might use this experience to populate the knowledge gaps in other fungal diseases.

Methods

National statistics were used for the population demographics, including the Uganda National Surveillance Report 2011.[4] A PubMed search was performed for fungal disease using the terms; Fungal, fungal infection, fungal epidemiology, fungal burden, HIV, Uganda, Kenya, Tanzania, Africa, and variations thereof. A second search included the same searches using the following diseases; *Cryptococcus*/cryptococcal, *Candida*/thrush, *Asperillus*/aspergillosis, histoplasmosis, asthma, leukaemia, chronic obstructive pulmonary disease (COPD), Pneumocystis pneumonia/*Pneumocystis jiroveci* pneumonia (PJP)/*Pneumocystis carinii* pneumonia, chronic pulmonary aspergillosis (CPA), aspergilloma, allergic bronchopulmonary aspergillosis (ABPA), severe asthma with fungal sensitisation (SAFS), tinea/ringworm. National or local information on these conditions was used wherever available, and if not available, data were used in the following preferential order; East African (Kenya, Tanzania, Rwanda, Burundi), Sub-Saharan Africa, rest of the world.

The incidence of fungal infections is greatly increased in those who are immunosuppressed, and with an HIV prevalence of 6.4% in Uganda,[4] this has a corresponding significant effect on the fungal disease epidemiology estimates. We therefore separated our analyses into HIV-related and non-HIV-related fungal infections. In 2013 the population of Uganda was estimated to be 39 234 256.[5] There are an estimated 1 600 000 infected with HIV in Uganda.[6] There are around 50 intensive care unit beds in the country, and there are two centres providing chemotherapy nationally. There are an estimated 7 345 000 women in Uganda aged 15–45 years. There are 1 448 000[7] pregnancies per year and an estimated 1 086 000 women are pregnant at any one time. These data were used as baseline denominators.

For the non-HIV-related estimates, most of the methods follow the methodology of colleagues estimating fungal disease in other parts of the world.[8–10] Deviation from these methods has only occurred where there has been good Ugandan data to enrich the estimates. For *Candida* vulvo-vaginal candidiasis (VVC), the methods have been well described for recurrent disease[11,12] especially in USA/Europe, however, due to strong data on the large number of pregnant women in Uganda,[13] and local published data on the prevalence of *Candida* in pregnant women, an adjustment was made for VVC in pregnancy. The number of pregnant women per year[13] was multiplied by the prevalence of *Candida* in pregnancy was taken from cross-sectional studies.[14] For CPA previously published methods were used,[15] and country-specific data for pulmonary tuberculosis (PTB) was used.[16] For invasive aspergillosis (IA), ABPA, SAFS and dermatophyte infections estimates have been derived using regional data for underlying condition rates (e.g. cancer, asthma, COPD)[17–20] as well as estimates for fungal disease in these conditions in the nearest geographical region.[9,21–23]

For HIV-related fungal infections, there is more locally available evidence. For cryptococcal disease previously documented methodology was followed,[24] but an adjustment was made due to more specific information around CD4 counts. We were able to use locally available data on rates of cryptococcal disease and oral and oesophageal candidiasis in populations on and off anti-retroviral therapy (ART), as well as with CD4 counts <200 or >200 cells per μl.[25] This allowed a detailed adjustment based on current Uganda data for patients receiving ART and in different CD4 count categories[13] and a similar methodology was used for HIV-related *Candida* infections. However, due to lack of published data around PJP in Uganda, especially in children, we have used two different methods for estimation to validate our estimations.

In all conditions, mortality was based on taking the estimated number of cases and then multiplying by local, regional or globally available case fatality rates.

Results

Non-HIV-related fungal disease burden

Vulvo-vaginal Candida (VVC)

Sixty percentage of pregnant women have *Candida* colonisation or infection of the vagina at any time,[14] which may be associated with premature labour.[26] There are an estimated 1 448 000 pregnancies per year, which is an estimate of 651 600 pregnant women with *Candida* each year. The estimated rates of recurrent (≥4× year)[11] VVC is 6% of adult women.[12,27] The number of non-pregnant women per year were calculated as (7 345 000 of reproductive age − 1 086 000 pregnant women) 6 259 000 women. We calculated a rate of 6%, which is in between the projected rates of 5%[11] and discounted from the survey data of 9% by Foxman *et al.*[12], which is likely to include other vaginal infections such as bacterial vaginosis. This would be approximately 375 540 women with recurrent VVC per year. Therefore, the total estimated number of women affected with recurrent VVC or *Candida* in pregnancy is approximately 1 027 140.

Chronic pulmonary aspergillosis (CPA)

There were 47 650 cases of TB identified in 2014 in Uganda, which is an estimated 76.8% of the 62 000 (range 56–73 000) estimated incidence. Of these 80% (38 294) are new PTB cases per year. There are an estimated 11 300 deaths from TB per year, and if 80% (9040) of these have pulmonary TB this will result in approximately 29 300 estimated new PTB survivors per year based on locally available Ugandan data.[16] To estimate CPA we have calculated the number of people developing cavities and the risk of CPA with and without post-PTB cavitation as shown in Fig. 1. Worldwide estimates suggest percentage of people developing cavities after PTB is 7–35%, which gives an estimated 2 050–10 260 new people in Uganda with cavities each year.[15] This translates to an estimated number of CPA cases between 246 and 2257 (12–22%). In addition, there are an estimated to 19 040–27 250 new cases without cavities which gives a CPA estimate of 190–1090 (1–4%).[15] Therefore, the overall estimate of CPA incidence is 436–3347. Using recent data in post-TB patients from Uganda the rate of CPA with symptoms is 7%, an additional 1.5% have an aspergilloma.[28] (A further 1.7% had detectable Aspergillus IgG antibodies with cavitation, but no symptoms; which could represent 'incubating' CPA and develop symptoms, a fungal ball or further asymptomatic lung destruction over time, or have successfully resolved their infection). Therefore, using 8.5% with the number of alive ex-PTB cases last year (29 300), this method estimates 2490 cases, which is in the upper middle of the estimates.

With a mortality of 15% the estimated CPA mortality is up to 500 deaths per year. It is difficult to estimate the ongoing prevalence, due to high yearly mortality, but if the average life expectance in this group is 6 years, there will be an estimated 15 000–18 000 people living with CPA.

Invasive aspergillosis (IA)

Recent estimates suggest an incidence of leukaemia of between 3.5/100 000 and 3.8/100 000 in Uganda.[20,29] Using 3.7% (1443 people) as an estimate incidence of haematological malignancies, at an estimate of 7% there would be up to an estimated 100 cases of IA per year.[21,30] The other group of patients

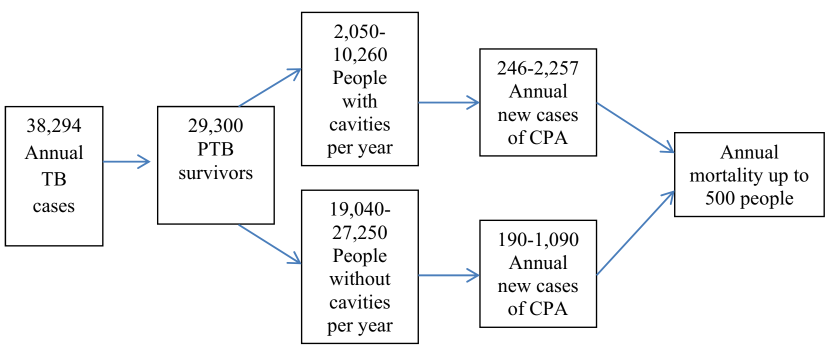

Figure 1 Estimation of post-TB aspergillosis in Uganda.

who develop IA is those with COPD, however, there is no estimate of COPD prevalence available in Uganda. Therefore, using data from South Africa showing rates of around 20% of COPD in those over 40 (20% × 1 500 000 over 40 years we estimate 318 000 patients with COPD in Uganda.[17] Assuming 5–7% get admitted to hospital annually[31] = 22 260, and of these 1.3% are estimated to have IA.[32] This gives an estimated 289 patients with COPD-related IA, with 100% mortality if untreated,[33,34] (which is likely to be the case in Uganda due to lack of diagnostics and treatment options).

ABPA and SAFS

Asthma rates in Uganda are 4.4% using the GINA data.[19] The number of adults in Uganda is 17 000 000 and therefore, adult asthma affects approximately 748 000 adults. Asthma deaths occur in Uganda;[18] there are few systematic data in children, but most deaths related to severe asthma occur in adults, for whom there is no data. The estimated rate of ABPA is 2.5% in adult asthmatics, equalling a prevalence of 18 700.[22] SAFS affects an estimated 3.3% in adult asthmatics, which gives a Ugandan estimate of 24 684. There is likely to be some duplication between ABPA and SAFS because some ABPA patients are both sensitised to *Aspergillus* and have severe asthma.

Dermatophyte infections

There is no data on tinea capitis in Uganda, but tinea capitis affects 10% of all Kenya school children.[23] If also true in Uganda, those with tinea capitis would comprise 1 300 000 of all Ugandan school children. Dermatophyte infections are therefore a serious but neglected health problem in Uganda.

HIV-related fungal infections

The following estimates from the Ugandan National AIDS Indicator Survey[4] and most recent UNAIDs estimations[6] were used to determine national HIV characteristics; 3.5% (56 000) of those with HIV have a CD4 count <100 cells per μl, 9.2% (147 200) of those with HIV have a CD4 count <200 cells per μl. Of those eligible with a CD4 count <350 cells per μl 69.4% are receiving ART.

Pneumocystis jirovecii Pneumonia (PJP)

An estimated 2–4% of people living with HIV (PLHIV) with CD4 <200 are admitted to hospital,[25] which is approximately 1120–2240 HIV-related hospital admissions per year. Of these an estimated 36.8% have PJP, which gives 412–824 cases of PJP per year.[35–38] Of these 30% die.[39] As an alternative calculation, there are an estimated 63 000 HIV-related deaths per year[3]; 38 000 adults, and African post-mortem studies in PLHIV show that 5.3% are attributable to PJP, which equates to a higher estimate of 2014 deaths per year[46]. Post-mortem found no PJP in HIV negative adults.

In children there were 199 697 episodes of severe community acquired pneumonia in 2010[40]; and estimated 10–48.6% of HIV positive children hospitalised with pneumonia had PJP and overall 21% of children admitted.[41,42,44] This gives an estimate of 41 937 annual cases of PJP in children. In-patient mortality for pneumonia in children is 15.5% in Uganda,[43] but PJP associated mortality in South Africa is 39.5%[44] and 75% in Malawi.[45] So there will be an estimated 16 564–31 452 deaths per year. This may overestimate deaths due to a bias towards the severest cases being admitted to hospital.

An alternative calculation is derived from the number of childhood deaths per year. There were 103 000 deaths in children under 5 years in 2012, of these approximately 25% were due to HIV, which is around 25 000 children. PJP was found to be the cause of death in post-mortem studies in 11–29% of children with HIV = 2750–7250 deaths per year, as well as 2.6% of HIV negative children or 1950 children per year.[46,47] This gives an overall mortality from PJP between 4740 and 11 214 cases per year.

HIV-related Candida

In those prior to starting ART oesophageal candida occurs at a rate of 21.3/100 per year of observation (PYO)[25] (in the 30.6% not on ART with CD4 <200 μl = 45 182) which is approximately 9624 cases per year, and in those on ART, oesophageal candida is around 2.39/100 PYO[25] (in 69.4% = 102 018 people on ART) giving an estimated 2438 cases per year. From the same study rates of oral and vaginal candida were 61.4/100 PYO, which gives an estimate of 27 741 year[25] in those not on ART and on ART there are 11.6/100 PYO with an estimated 3218 cases per year. The total estimated number of cases is 43 021 per year.

Cryptococcal disease

Much of the recent work on cryptococcal disease has taken place in Sub-Saharan Africa, and this has been driven by high mortality in HIV patients in Sub-Saharan Africa from cryptococcal disease.[48] Work in asymptomatic PLHIV starting ART suggests that around 7.1% with CD4 counts <100 cells per μl[49] or 2.8% <200 cells per μl[25] have a positive serum cryptococcal antigen. From the AIDS indicator survey are 56 000 estimated PLHIV with CD4 counts <100 cells per μl (approximately 3976) or an estimated 147 300 with CD4 counts <200 cells per μl (approximately 4124). Using the mean of these gives an estimate of 4050 HIV patients developing *Cryptococcus* infection per year, in the absence of screening and pre-emptive treatment for asymptomatic cryptococcal infection.

To estimate survival, data from Kambugu *et al.*, were used with estimated 0% survival in those with cryptococcal meningitis by 6 months pre-ART and 41% 6 month survival post-ART.[50] The proportion receiving ART is 69.4% in those with CD4 counts <200 per μl which gives an estimated cryptococcal-related mortality of 1658 cases per year, and the 30.6% not on ART have 100% mortality, which equates to another 1239 deaths per year. Therefore, total overall annual HIV-related cryptococcal mortality is approximated at 2412 cases per year.

Other fungal infections including fungal keratitis

Whilst there are older publications indicating that other fungal infections have been found in Uganda, there are no data from Uganda related to the frequency of *Candida* bloodstream infection or intra-abdominal abscess, fungal keratitis, chromoblastomycosis, mycetoma,[51] histoplasmosis, blastomycosis[52–54] or mucormycosis. Histoplasmosis certainly occurs in Uganda, as evidenced by occasional case reports.[55–60] Many cases of fungal keratitis were reported from Tanzania.[61] In Uganda a remarkable 22% of cases of visual impairment in children was attributable to corneal ulceration in Uganda (trachoma was not seen)[62]; among these children, 80% were blind, indicative a substantial national problem and we would hypothesise that a proportion are fungal in origin.

Discussion

This study attempts to explore the burden of fungal disease in Uganda. Whilst estimates for fungal burden in HIV are Uganda specific, the estimates for non-HIV-related fungal infections are mainly extrapolated from global or regional data. Nevertheless, as summarised in Table 1, there is a substantial burden of fungal infection in Uganda affecting up to 2.5 million people (up to 6.5% of the population), and up to 38 000 deaths per year, predominantly driven by HIV-related cryptococcal disease, post-TB aspergillosis, PJP in children and asthma associated ABPA. In 2013 it was estimated that Uganda has 63 000 deaths per year due to HIV; of these we have estimated 26 000 due to HIV-related PJP, 2000 due to cryptococcal disease and around 300 with post-PTB/HIV aspergillosis. Overall this suggests that fungal infections are contributing up to 45% of HIV-related mortality in Uganda.

However, it is important to be cautious as these data are still based on multiple estimates. In non-HIV-related fungal infections the estimates are based on previously published estimations, which often from resource rich settings. In these countries, there is likely to be both greater health seeking behaviour and hospital admissions due to greater resources, but also greater diagnostic capacity for both fungal infections and underlying predisposing conditions. Also we would like to emphasise that whilst the methodology for most of these estimations has been established in previous publications, these estimates are themselves based on estimates often from regional, not Ugandan data. For example in estimating CPA incidence and mortality rates of PTB are based on WHO estimates. Given that there is only a 78% case detection rate, an interaction between HIV and TB, that those with extra-pulmonary TB are more likely to die, and that those with HIV are less likely to develop PTB cavities, there are subtleties around these diseases that an estimated burden such as ours will not be able to predict.

Within the HIV–fungal disease burden calculations, much is based on population characteristics for HIV patients. This maybe a simplification; for example the ORCAS study team has found 4000 PLHIV with CD4 <100 per μl over 2 years at only 18 clinical sites, compared to an estimated 56 000 across over 11 000 health centres countrywide, therefore we may be underestimating the number of PLHIV with low CD4 counts. However, due to the rapid scale up of HIV treatment and recent changes in guidelines to treat at CD4 counts <500 μl^{-1}, there may actually have been a reduction in the number of people with low CD4 counts. In addition, the number being hospitalised with low CD4 counts seems low, but this is the only data we were able to find on hospital admissions in a Ugandan HIV cohort. Given that hospitalisation may not be representative of severe illness in our setting, due to lack of resources for transport or healthcare, or lack of quality services available, where possible, such as in PJP, two different methods of calculation have been used (one relying on hospital admission data and one not). These challenges highlight that full information on the burden of fungal disease in Uganda as

Table 1 Summary of estimated incidence and mortality of fungal disease in Uganda.

Infection	Special population	Incidence/rate in specific population	Estimated annual incidence	Estimated deaths from condition in Uganda
Non-HIV-Related				
Candida vaginitis (pregnancy)	Pregnant women	60%	651 600	NA
Recurrent *Candida* vaginitis (≥4 × year^{-1})	Women 15–45 years	6%	375 540	NA
CPA post-TB	With cavities	7–35%	246–2257	500
	Without cavities	1–4%	190–1090	
Invasive aspergillosis	Haematology malignancy	7%	100	389
	COPD admissions	1.3%	289	
ABPA	Adult asthmatics	2.5%	18 700	?
SAFS	Adult asthmatics	3.3%	24 684	?
Non-HIV-related childhood PJP	Children <15 years	2.6% of non-HIV pneumonia deaths	4936	1950
Tinea capitis	School children	10%	1 300 000	NA
HIV related				
HIV-related oral/vaginal candidiasis	HIV +ve pre ART <200CD4	61.4/100PYO	27 741	NA
	HIV +ve on ART <200 CD4	11.6/100PYO	3218	
HIV-related Oesophageal candidiasis	Pre ART <200CD4	21.3/100PYO	9624	NA
	On ART <200 CD4	2.39/100PYO	2438	
PJP	Adults HIV +ve & hospital admission CD4 <100	36.8%	412–824[1]	247–2014
	Children with HIV	10–49% of pneumonia admissions	41 937	16 564-31 452
Cryptococcosis	CD4 count <200 or <100	2.8–7.1%	4 050	2412
Fungal keratitis	?	?	?	NA
Histoplasmosis, mucormycosis, coccidiomycosis, paracoccidomycosis	NA	No data available	?	?
Total (approximate)			2 500 000	31 000

ABPA, allergic bronchopulmonary aspergillosis; CPA, Chronic pulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; SAFS, Severe asthma with fungal sensitisation; PJP, *Pneumocystis jirovecii* pneumonia; PYO, per year of observation.

[1]Mortality numbers based on post-mortem data, incidence data based on hospital admissions; likely an underestimate.

elsewhere in Sub-Saharan Africa will only be possible with further research which specifically addresses fungal infection by disease incidence in Uganda rather than extrapolation from other diseases and other countries.

Observational data from the late 1990s showed the cryptococcal attributable mortality in Ugandan HIV patients at around 13%.[63] This was followed by more systematic analysis of cryptococcal antigen positivity associated with mortality in HIV patients.[64,65] When the huge burden of cryptococcal disease and associated mortality became clear, the first large scale randomised controlled trial (RCT) for cryptococcal prevention in Sub-Saharan Africa was started in 2004, using fluconazole in Uganda.[25] During this period other researchers were exploring treatment strategies for cryptococcal disease in Uganda, as a resource limited setting,[66,67] and the pharmaceutical company Pfizer started a fluconazole donation programme to treat all those with diagnosed cryptococcal disease in 2002. Highly active anti-retroviral treatment started to become widely available to patients at no cost in 2003, and HIV services proliferated countrywide. In the late 2000′s research work was concentrated around screening strategies,[49] investigation of treatment outcomes,[50] and further therapeutic strategies.[68,69] Following success in use of cryptococcal antigen screening as a prevention strategy in South Africa,[70] Ugandan researchers undertook operational and cost effectiveness research on screening strategies as well as exploring and validating novel point of care tests for Crag.[71–76] Other research focused on immune reconstitution inflammatory syndrome in patients with cryptococcal disease receiving ART [77–80] and this led to an RCT which explored the correct timing of ART initiation following cryptococcal diagnosis and treatment.[81] This showed that unlike TB, early initiation of ART in patients being treated for cryptococcal disease was associated with a higher mortality than a delayed ART. Work on cryptococcal disease is now building capacity in the basic science areas of immunology, mycology and clinical pharmacology.[82–85]

Importantly, this body of work is responsible for changing clinical practice, as many of the papers have a direct clinical application and have been used to develop international and national guidelines.[86,87] As a low income country (as defined by the World Bank) with a gross domestic product (GDP) of $571 per person,[88] most money for medical research comes from international funders. Research collaborations between international organisations such as University of Minnesota, University of Liverpool and Johns Hopkins which were based on cryptococcal and associated research have assisted with the development of epidemiological, clinical, operational and translational research capacity in Uganda, and in particular the Infectious Diseases Institute at Makerere University. This research infrastructure, expertise and knowledge is training the next generation of researchers to document, develop diagnostic tools and explore management strategies for other diseases in Uganda.

Conclusion

Given that fungal disease in Uganda may be affecting up to 6.5% of the population per year, with the exception of cryptococcal disease, these diseases are understudied and under diagnosed in Uganda. As the number of PLHIV in Uganda continues to rise, as well as the number of people with non-communicable diseases such as COPD and cancers treated with chemotherapy, we need to urgently address gaps in knowledge, diagnosis, and management of fungal disease in Uganda and Sub-Saharan Africa. The global health research model of cryptococcal disease in Uganda provides an example of how we might start to explore other fungal diseases, whilst continuing to build capacity for African based and relevant medical research.

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Conflict of interest

RP-R has received consultancy fees from Janssen Global Public Health for work unrelated to the manuscript. BA and RK declare no conflict of interest. AK has received consultancy fees form Abvvie and MSD for work unrelated to the manuscript. DM declares no conflict of interest. DWD holds Founder shares in F2G Ltd a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, NorthWest Lung Centre Charity, Medical Research Council, Astellas and the Fungal Infection Trust. He acts as a consultant to T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology and Pulmicort. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups. He is also President of the Global Action Fund for Fungal Infections.

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