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Review Article

A Review of Antifungal Resistance in West Africa

Abraham Bwalhuma Muhindo [1,2,3*]
Adamu Almustapha Aliero [4]
Festo Mwebaze Syalhasha [5]
Ibrahim Ntulume [2]
Emmanuel Eilu [2]
Martin Odoki [2]
Joe Mutebi [6]

[1] Department of Medical Laboratory Sciences, Mbarara University of Science and Technology, Mbarara, Mbarara District, Uganda
[2] Department of Microbiology and Immunology, Kampala International University, Ishaka, Bushenyi District, Uganda
[3] Department of Microbiology, Premium Medical Services, Freetown, Western Area Urban District, Sierra Leone
[4] Department of Microbiology, Kebbi State University of Science and Technology, Aliero, Kebbi State, Nigeria
[5] Institute of Public Health and Management, Clarke International University, Kampala, Kampala District, Uganda
[6] Department of Computing, Kampala International University, Ishaka, Bushenyi District, Uganda

*email: abrahambwalhuma@gmail.com; phone: +256485421373

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Abstract

Knowledge of local and regional antimicrobial resistance (AMR) is important for clinical decision-making. However, surveillance capacity for fungal infections let alone antifungal resistance is lacking throughout West Africa, and current antifungal resistance data are sparse. We sought to address this gap by summarizing all available high-quality data on antifungal resistance in West Africa. We searched the PubMed database, African Journals Online archives, and free web searches in October and December 2023 using the terms "antifungal resistance" and "West Africa" to find articles published from 2010 onwards. Only 11 articles were included in our analysis most of which were cross-sectional and descriptive in design; relatively high levels of antifungal resistance (AFR) to commonly used antifungals were reported including (24-75%) resistance to fluconazole and ketoconazole, two of the most frequently-prescribed antifungals in this region. There is a high level of resistance to griseofulvin, ketoconazole, cotrimoxazole, and fluconazole among dermatophyte infections (80-100%) with 100% resistance to amphotericin B, ketoconazole, and fluconazole reported by the invasive fungal disease-causing pathogen *Cryptococcus neoformans*. Resistance to commonly used anti-fungal drugs is prevalent; raising concern that these drugs may no longer be useful for treating moderate or severe fungal infections in West Africa hence calling for countries to promote acceptance of antimicrobial stewardship as a programmatic strategy not just focused on bacterial resistance but also fungal resistance including pharmacy management, laboratory complete mycological investigations and dissemination of standard fungal susceptibility profiles.

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INTRODUCTION

"*Emerging from the shadows of the bacterial antimicrobial resistance pandemic, fungal infections are growing, and are ever more resistant to treatments, becoming a public health concern worldwide*," said Dr Hanan Balkhy, WHO Assistant Director-General, Antimicrobial Resistance (AMR)[1]. Approximately 1 million individuals have invasive fungal infections (Candida, Cryptococcus, Aspergillus, and Pneumocystis) worldwide, resulting in the death of 1.7 million people annually[2,3]. While the benefits of appropriate antifungal usage to treat fungal infections are well established, all antifungal use carries a risk of

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inducing antifungal resistance (AFR). The emergence of resistant or even multi-resistant strains is of concern, because of the limited antifungal arsenal[4]. The emerging global health threat of fungal diseases is compounded by the rapid emergence of antifungal resistance and, in many settings, limited access to quality diagnostics and treatment[5-7].

There are four major classes of antifungal medicines (azoles, echinocandins, pyrimidines, and polyenes) mostly used in clinical practice, and only a few others are under development[8-11]. With the growing prevalence of human fungal infections, especially in immunocompromised patients, these diseases have become a worldwide public health issue[12]. The immune system status of the host determines the outcome of the disease and therefore infections may progress or range from limited cutaneous or subcutaneous to invasive, disseminated, and life-threatening infections[13]. Invasive Fungal infections (IFI) have been observed to increase in the last decades due to an increased number of immunosuppressed patients or persons resulting in increased use of systemic antifungal drugs to treat these infections eg echinocandins, polyenes, triazoles, and flucytosine[14]. Overuse and misuse especially prophylactically have resulted in stronger selective pressure on fungi[15].

The WHO Fungal Priority Pathogens List[1] represents the first global response to identify and prioritize fungal pathogens and their impact on global public health and to consider the unmet research and development needs grouped the priority fungal pathogens into those of critical, high, and medium priority. Global warming, increased international travel, lack of globally affordable diagnostic platforms, and increasing resistance have increased the incidence of mycoses yet the prevention and control of fungal diseases remains a major challenge, especially in resource-poor countries, despite their likely large burden[16]. Although such reports are concerning, the burden of Antifungal Resistance (AFR) in the West Africa region is not well published. Additionally, knowledge of the situation in many parts of the world further complicates the problem[17].

Better knowledge of the burden and proportion of infections caused by drug-resistant fungi in low-resource settings would raise awareness of the need to prevent the rise and spread of drug resistance[18]. Understanding current levels of AFR throughout West Africa could improve clinical practice by guiding empirical antifungal choice. Toward this end, we reviewed the available evidence on the burden of AFR among fungal pathogens in West Africa to ascertain the common antifungal pathogens isolated in West Africa, summarize the antifungal sensitivity profiles of common fungal pathogens to available antifungal agents, and to critically analyze current clinical and diagnostic practices and future research interventions to address antifungal resistance.

SEARCH STRATEGY AND SELECTION CRITERIA

A comprehensive literature search was conducted in October and December 2023 to identify relevant studies on antifungal resistance (AFR) in West Africa (**Figure 1**). We searched the PubMed database (www.ncbi.nlm.nih.gov/pubmed/), African Journals Online archives (https://www.ajol.info/index.php/ajol), Google Scholar (https://scholar.google.com/), and ScienceDirect (https://www.sciencedirect.com/). The search terms "antifungal resistance" and "West Africa" were used to identify articles published from 2010 onwards. Only English language articles were included.

Inclusion criteria for full-text articles were reported the proportion of AFR among clinical fungal isolates obtained from human subjects or environmental samples in any West African country (including Cameroon, Ghana, Nigeria, Ivory Coast, Sierra Leone, Guinea, Central African Republic, Mali, Liberia, Niger, and others), as well as described the studied patient population, isolated organisms, specific laboratory methods used for antifungal susceptibility testing, and interpretation methods for minimum inhibitory concentration breakpoints or zone diameters of inhibition as outlined by the Clinical and Laboratory Standards Institute (CLSI)[19,20]. To ensure the inclusion of contemporary and relevant AFR data, only studies published from 2010 onwards were considered. Data extraction focused on fungal species isolated, the number of isolates tested for AFR, specific antifungals tested, and the percentage of organisms resistant to each antifungal agent.

Our initial search strategy identified 413 articles: 257 from PubMed, 133 from AJOL, and 23 from other free web sources. After screening, 100 articles were deemed relevant for further evaluation. Of these, 33 full-text articles were accessible. We excluded 22 articles for the following reasons: three lacked data on fungal resistance, six reported antifungal resistance by a specific antifungal group, and 13 lacked information on isolate identity or specific laboratory methods employed. The remaining 11 articles were included in this review (**Table I**). These studies investigated patterns of antifungal resistance (AFR) in various African countries: five focused on Cameroon[21-23,28,31], four on Nigeria[24,26,27,29], one on Ivory Coast[30], and one

on Ghana[25]. A total of 2,721 subjects were included across the selected studies. Notably, Cameroon contributed the highest number of studies (45%).

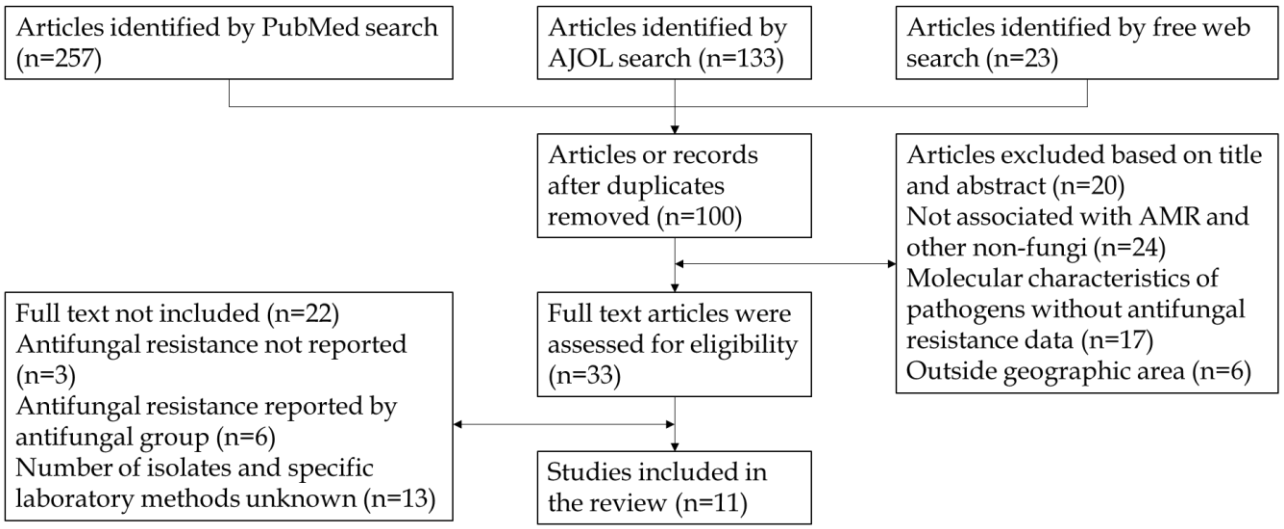

Figure 1. Selection of publications for inclusion.

Table I. Summary of studies included in the analysis.

Country	Year	Fungal group	Sample source/patient populations	Number of study participants/samples
Nigeria	2011	*Candida* spps	HIV/AIDS patients	200
Cameroon	2012	*Candida* spps	HIV/AIDS patients	304
Ghana	2012	*Candida* spps	General outpatients	528
Ivory Coast	2012	*Candida* spps	Women with leukorrhoea	150
Cameroon	2013	*Candida* spps	HIV/AIDS patients	207
Cameroon	2016	*Trichophyton* spps	Diabetic patients	152
Cameroon	2016	*Cryptococcus* spps	Environmental isolates	350
Cameroon	2020	*Candida* spps	HIV/AIDS patients	378
Nigeria	2020	*Tinea* spps	Children attending elementary school	301
Nigeria	2020	Dermatophytes	University students	119
Nigeria	2021	Dermatophytes	Children attending elementary school	32

ANTIFUNGAL RESISTANCE PATTERNS

A review of the laboratory methodologies employed within the studies included in this review revealed concerning levels of resistance among fungal pathogens to commonly used antifungals in West Africa (**Table II**). Notably, *Candida* spp., a prevalent fungal genus, exhibited resistance rates ranging from 24% to 75% for fluconazole and ketoconazole, two of the most frequently prescribed antifungal medications in the region[21-25]. Similarly, high resistance rates (80-100%) were observed for griseofulvin, ketoconazole, cotrimoxazole, and fluconazole among school children diagnosed with dermatophyte infections[26,27]. Additionally, a study investigating environmental samples reported 100% resistance to amphotericin B, ketoconazole, and fluconazole among *Cryptococcus* spp., including both *Cryptococcus gattii* and *Cryptococcus neoformans*, fungal pathogens responsible for invasive fungal diseases[28].

FUNGAL ORGANISMS

Several studies have identified *Candida* spps. (particularly *C. albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, *C. parapsilosis*, and *C. pseudotropicalis*) as the predominant fungal isolates from immunocompromised patients[21-25,29,30]. Conversely, dermatophytes (*Trichophyton enotrephon, T. bullosum, T. simii, T. tonsurans, Microsporum audouinii, M. canis, T. concentricum, T. mentagrophytes, T. rubrum,* and *T. violaceum*) were the most prevalent isolates among school children and university students[26,27,31]. An alarming trend highlighted in the reviewed literature is the emergence of single fungal isolates exhibiting resistance to multiple antifungal drugs. This phenomenon appears to be most common among *Candida* spp. isolated from

immunocompromised patients, particularly those with HIV/AIDS[21-25]. Notably, susceptibility to nystatin remained generally good across *Candida* spp., suggesting its potential as a first-line empirical treatment for Candida infections[32]. The identification of multi-drug resistant fungi underscores the critical need for promoting appropriate antifungal usage and routine microbiological sampling of infected patients, especially in resource-limited settings[33]. The collective evidence presented here strongly suggests the existence of AMR, particularly against widely used antifungal drugs (**Table II**).

Table II. Antifungal resistance patterns from selected studies in West Africa.

Authors	Year	Country	Method	Organism	AMP	NYS	FCY	GRS	MIC	FLU	ITR	VOR	KET	ECO	CTM
Njunda *et al.*[21]	2012	Cameroon	Disc diffusion	*C. albicans* (n=175)	92	23	-	-	-	124	-	-	23	24	-
Njunda *et al.*[22]	2013	Cameroon	Broth microdilution	*C. albicans* (n=103)	5	76	11	-	9	16	10	4	2	8	-
				C. dubliniensis	0	3	0	-	0	2	0	0	0	0	-
				(n=3)	1	13	1	-	3	2	1	1	0	5	-
				C. tropicalis (n=23)	0	2	1	-	0	0	0	0	0	0	-
				C. famata (n=4)											
Abrantes *et al.*[23]	2016	Cameroon	Broth microdilution	*C. albicans* (n=92)	4	-	6	-	0	46	47	46	-	-	-
				C. dubliniensis	1	-	-	-	-	0	0	0	-	-	-
				(n=10)											
				C. glabrata (n=24)	1	-	-	-	16	1	4	1	-	-	-
				C. krusei (n=3)	1	-	-	-	0	2	0	1	-	-	-
				C. tropicalis (n=4)	2	-	-	-	0	0	0	0	-	-	-
				C. kefyr/para/lusi	1	-	-	-	-	0	0	0	-	-	-
				(n=2)											
Dongmo *et al.*[28]	2014	Cameroon	Broth microdilution	*C. neoformans*	4	4	-	-	-	64	-	-	1	-	-
Eba *et al.*[31]	2016	Cameroon	Broth microdilution	*Trichopyton* spps.	67	-	-	96	19	-	98	-	79	-	-
Nweze *et al.*[24]	2011	Nigeria	Broth microdilution	*C. albicans* (n=54)	0	-	5	-	-	9	6	1	-	-	-
				C. dubliniensis	0	-	1	-	-	3	1	0	-	-	-
				(n=9)	0	-	2	-	-	0	0	1	-	-	-
				C. tropicalis (n=22)	0	-	2	-	-	2	1	0	-	-	-
				C. parapsilopsis											
				(n=18)	0	-	0	-	-	0	1	0	-	-	-
				C. guilliermondii											
				(n=11)											
Ayodele *et al.*[29]	2020	Nigeria	Disc diffusion	*T. rubrum* (n=156)	156	-	-	-	33	156	156	-	156	-	33
				M. ferrugineum	51	-	-	-	0	51	51	-	51	-	0
				(n=51)											
				T. mentagrophytes	17	-	-	-	0	0	17	-	17	-	0
				(n=17)											
				T. verrucosum	4	-	-	-	4	4	4	-	4	-	4
				(n=4)											
David *et al.*[26]	2020	Nigeria	Broth microdilution	*M. canis* (n=6)	-	1	-	-	-	5	-	-	2	-	6
				T. concentricum	-	3	-	-	-	5	-	-	4	-	5
				(n=6)											
				T. mentagrophytes	-	4	-	-	-	12	-	-	6	-	12
				(n=12)											
				T. rubrum (n=7)	-	4	-	-	-	7	-	-	4	-	7
				T. violaceum (n=7)	-	5	-	-	-	7	-	-	5	-	7
Ungokore *et al.*[27]	2021	Nigeria	Disc diffusion	*T. eriotrephon*	1	-	-	0	-	2	-	-	4	-	-
				(n=10)	1	-	-	0	-	0	-	-	1	-	-
				T. bullosum (n=2)	1	-	-	0	-	0	-	-	5	-	-
				T. simii (n=12)	1	-	-	1	-	2	-	-	1	-	-
				T. tonsurans (n=3)	0	-	-	0	-	0	-	-	1	-	-
				M. audouinii (n=2)											
Djohan *et al.*[30]	2012	Ivory Coast	Semi-solid medium microdilution	*C. albicans* (n=45)	0	-	-	-	-	2	22	11	-	-	-
Feglo *et al.*[25]	2012	Ghana	Semi-solid medium microdilution	*C. albicans* (n=33)	9	-	3	-	-	0	2	0	-	-	-
				C. dubliniensis	0	-	4	-	-	0	0	0	-	-	-
				(n=4)	1	-	0	-	-	0	3	0	-	-	-
				C. glabrata (n=12)	2	-	1	-	-	0	0	0	-	-	-
				C. krusei (n=3)	3	-	0	-	-	0	0	0	-	-	-
				C. tropicalis (n=8)											

Notes: AMP-amphotericin B, NYS-nystatin, FCY-flucytosine, GRS-griseofulvin, MIC-micafungin, FLU-fluconazole, ITR-itraconazole, VOR-voriconazole, KET-ketoconazole, ECO- econazole, CTM-clotrimazole

This review summarizes the findings of 11 studies highlighting significant resistance across West Africa to antifungals crucial for everyday use. Notably, most Candida species exhibited limited susceptibility to fluconazole, a commonly-used first-line antifungal in the region and recommended by the WHO for managing superficial and systemic mycoses[34]. Furthermore, Cryptococcus isolates (both *C. neoformans* and *C. gatti* variants) obtained from the environment displayed concerning resistance to amphotericin B, ketoconazole, and fluconazole[35]. Cryptococcus, a globally distributed invasive

fungus, presents a substantial therapeutic challenge due to the lack of documented human-to-human transmission yet possesses established virulence mechanisms that enable infection, dissemination, and ultimately, host mortality[36].

Antifungal resistance to commonly used drugs like fluconazole, ketoconazole, cotrimoxazole, and amphotericin B appears prevalent in West Africa and could be a growing concern, particularly among immunocompromised HIV/AIDS patients. However, as highlighted in the 2022 WHO report on fungal priority pathogens[1], this resistance is likely under-reported due to limited access to diagnostic testing, inadequate microbiology support, and inconsistencies in laboratory standards. The scarcity of readily available diagnostic tools, such as rapid antigen assays, and the high costs or lack of access to polymerase chain reaction (PCR) testing significantly hinder diagnosis, leading to underreported cases[37]. These limitations in antifungal susceptibility testing often contribute to antifungal misuse and overuse, further exacerbating resistance development[38]. The limited data on antifungal resistance in West Africa could stem from several factors, including low clinician awareness of fungal infections and a shortage of healthcare personnel equipped to diagnose mycoses[39]. Even when some antifungal resistance information exists, inadequate national laboratory strategic plans, particularly regarding mycoses, might hinder proper communication to healthcare providers across the region[40].

PREVENTION OF THE DEVELOPMENT AND SPREAD OF ANTIFUNGAL RESISTANCE

Antifungal resistance is likely to become an even greater challenge in West Africa and may be compounded by overuse of antifungals, the lack of antifungal prescription oversight, and the paucity of relevant local information and data on antifungal resistance[41]. To address these issues, existing antimicrobial stewardship programs should be strengthened or, where they are not yet in place, they should be developed and implemented in all regional referral hospitals in response to these challenges[42]. Based on our findings, there are variations in the incidence and prevalence of fungal conditions dependent on local clinical practice with varying antifungal resistance. Therefore, each country in the West African region needs to contextualize the fight during the design or formation of local priorities for better-targeted public health outcomes[43]. The area of particular focus should be immunocompromised patients presenting with Candida-like symptoms. Existing but limited resources should be directed equally at discovering the causes and offering appropriate treatment of infections in this population[44,45].

Additionally, there is a need to urgently scale up the training of both laboratory and pharmacy staff in antifungal/antibiotic stewardship at health facilities where laboratory investigations are available[46]. This is critical in communicating with clinicians, who are the cornerstone in the proper management of patients with infections, especially about the use of these fungal drugs. There is a need for regular antifungal resistance surveys to establish evidence-based and locally relevant resistance data that would help create guidelines to improve clinical practice[47-49].

The implementation and development of the 2022 WHO fungal priority pathogens list to guide research, development, and public health action for containment of antifungal resistance through inter-continental, regional, and sub-regional-wide surveillance programs as a health systems approach has met with several challenges[1,50]. In low- and middle-income countries, implementing the strategy has proven difficult, because the human and financial resources as well as mycological expertise are insufficient[51,52]. In addition, it is difficult to obtain appropriate sample sizes for an accurate representation of resistance patterns. Novel approaches to antimicrobial surveillance are therefore needed for low-resource settings, which include the development of surveillance programs utilizing smaller sample sizes to provide locally relevant AMR patterns and to encourage appropriate empirical antimicrobial therapy[53-55]. Also, the development of new point-of-care diagnostic tools able to detect antifungal resistance resistance cost-effectively will improve patient management and limit the emergence of drug resistance[56,57].

Lastly, of the 413 publications identified, we considered only 11 dues to the lack of standardization and quality of the methodology and reporting. This highlights the scarcity of good-quality data that could allow stakeholders to assess the real burden of antifungal resistance. The susceptibility data reported was very inconsistent and less from low mid-income countries of West Africa, perhaps due to the limited access to mycology laboratories and expertise[58,59]. Thus, better-standardized research protocols are needed to evaluate the emergence of antifungal resistance in different local settings to obtain comparable results and implement befitting interventions[60,61]. Although many papers reported susceptibility data from small ad-hoc laboratory surveillance projects, formal surveillance and data linkage to clinical outcomes were lacking[62-

[64]. Furthermore, susceptibility was reported very inconsistently, making comparisons over time or between geographic areas difficult. Susceptibility data were less common from low- and middle-income countries, likely due to limited access to medical mycology laboratories in resource-limited settings[65].

CONCLUSION

This review highlights the concerning prevalence of resistance to commonly used antifungal drugs in West Africa. The emergence of multi-drug resistance poses a significant and growing threat in the region, potentially rendering multiple antifungal therapies ineffective for treating fungal infections. Single isolates exhibiting resistance to more than one antifungal drug, including those from different classes, further complicate this challenge. To address this growing public health concern, West African countries should prioritize the implementation of comprehensive antimicrobial stewardship programs. These programs should not only focus on combating bacterial resistance but also encompass strategies to tackle the rising threat of antifungal resistance. Key areas for intervention include strengthening pharmacy management practices, implementing robust laboratory quality control measures, expanding mycological investigations, and disseminating standardized fungal susceptibility profiles.

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AUTHORS' CONTRIBUTION

Conceptualization: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero
Data curation: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi
Formal analysis: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi
Funding acquisition: -
Investigation: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi
Methodology: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero
Project administration: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi
Resources: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi
Software: -
Supervision: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi
Validation: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi
Visualization: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi
Writing - original draft: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero

Writing - review & editing: Abraham Bwalhuma Muhindo, Adamu Almustapha Aliero, Festo Mwebaze Syalhasha, Ibrahim Ntulume, Emmanuel Eilu, Martin Odoki, Joe Mutebi

DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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