MICROBIOLOGY ARCHIVES
Review Article | ISSN: 3041-590X
Journal homepage: https://microjournal.researchfloor.org/

Burden of Invasive Fungal Diseases and Antifungal Resistance in Sub-Saharan Africa: A Review

Robinson, V. K.*[1], Aleruchi, O[1]., Alfred, J. U[2], and Okpokiri, M.[1]

[1]*Department of Microbiology, Rivers State University, Nkpolu Oroworukwo, Port Harcourt, Nigeria*
[2]*Department of Horticulture and Landscape Technology, Akanu Ibiam Federal Polytechnic Unwana, Afikpo, Ebonyi State, Nigeria*

ARTICLE INFO

Citation: Robinson, V. K., Aleruchi, O., Alfred, J. U, and Okpokiri, M. (2026). Burden of Invasive Fungal Diseases and Antifungal Resistance in Sub-Saharan Africa: A Review. *Microbiology Archives, an International Journal.*
DOI: https://doi.org/10.51470/MA.2026.8.2.38

Received 16 April 2026
Revised 18 May 2026
Accepted 20 June 2026
Available Online July 17, 2026

Corresponding Author: **Robinson, V. K.**
E-Mail: **victor.robinson3@ust.edu.ng**

ABSTRACT

Invasive fungal diseases (IFDs) are increasingly recognized as a major public health challenge in sub-Saharan Africa, particularly among immunocompromised populations. Their diagnosis and management remain difficult because their clinical manifestations are often non-specific and overlap with those of more prevalent conditions such as HIV/AIDS, tuberculosis, opportunistic infections, and malignancies. This review examines the epidemiology, disease burden, and emerging antifungal resistance associated with invasive fungal diseases in sub-Saharan Africa, with the aim of improving understanding and identifying priorities for research and public health interventions. Evidence from published literature indicates that cryptococcosis remains the leading invasive fungal disease in the region and is responsible for a substantial proportion of HIV-related mortality. Invasive aspergillosis is increasingly reported but remains underdiagnosed and is frequently misdiagnosed as pulmonary tuberculosis, particularly among individuals living with HIV. Histoplasmosis is also an important opportunistic infection, especially in West Africa, where it commonly occurs among patients with advanced HIV infection and those initially presumed to have tuberculosis. Although the prevalence of Pneumocystis pneumonia has declined due to expanded access to antiretroviral therapy, other invasive fungal diseases, including mucormycosis, talaromycosis, emergomycosis, blastomycosis, and coccidioidomycosis, continue to be reported across the region. Furthermore, the emergence of resistance to commonly used antifungal agents poses a growing threat to effective treatment and patient outcomes. Overall, invasive fungal diseases remain under-recognized but contribute significantly to morbidity and mortality in sub-Saharan Africa. Strengthening surveillance systems, expanding access to accurate diagnostic tools, improving antifungal stewardship, and increasing investment in research are essential to reducing the burden of these infections and addressing the growing challenge of antifungal resistance.

Keywords: *Invasive fungal diseases, antifungal resistance, sub-Saharan Africa, cryptococcosis, aspergillosis, histoplasmosis, HIV/AIDS, disease burden.*

Introduction

Fungal infections constitute a major global public health concern and pose a serious threat to immunocompromised individuals [1]. Fungi are capable of colonizing various anatomical sites in humans, including the gastrointestinal tract, respiratory tract, bloodstream, and female genital tract [2]; [3]. More than 300 fungal species have been identified as causes of human disease, affecting predominantly immunocompromised individuals, although immunocompetent persons with chronic respiratory diseases, diabetes mellitus, malignancies, or other underlying medical conditions are also at risk [4]. Over the past few decades, the burden of fungal diseases has increased substantially, posing significant threats to human, animal, and plant health worldwide [5]. It is estimated that approximately one billion fungal infections of varying severity occur globally each year [6]; [7].

Sub-Saharan Africa bears a disproportionate burden of fungal diseases owing to the high prevalence of human immunodeficiency virus (HIV) infection and tuberculosis (TB), widespread poverty, inadequate healthcare infrastructure, and the increasing prevalence of non-communicable diseases such as cancer, asthma, chronic respiratory diseases, and diabetes mellitus [8]. The region accounts for over 25 million people living with HIV, representing approximately 70% of the estimated 37.9 million people living with HIV worldwide [7]. Consequently, the incidence of opportunistic fungal infections remains considerably higher in sub-Saharan Africa than in many other regions. Invasive fungal diseases (IFDs) are among the leading causes of morbidity and mortality in immunocompromised populations, including individuals living with HIV/AIDS, patients with hematological malignancies, organ transplant recipients, and those receiving prolonged immunosuppressive therapy [9]; [10].

These infections occur when fungal pathogens invade deep tissues or normally sterile body sites and are confirmed through histopathological examination, culture, or other laboratory diagnostic methods using tissue biopsies or needle aspirates [11]. Delayed diagnosis and treatment frequently result in poor clinical outcomes and high case-fatality rates.

Despite the substantial health burden associated with fungal diseases in sub-Saharan Africa, they continue to receive considerably less attention than bacterial and viral infections [5]. This neglect is attributable to limited awareness among healthcare professionals, inadequate laboratory diagnostic capacity, poor surveillance systems, restricted access to essential antifungal medicines, and insufficient investment in fungal disease research [12]. Furthermore, the emergence and spread of antifungal resistance have complicated the management of invasive fungal diseases, reduced treatment effectiveness and increasing morbidity, mortality, and healthcare costs [3]. The growing population at risk for fungal infections, coupled with the global emergence of multidrug-resistant fungal pathogens, shows the urgent need for improved surveillance, enhanced diagnostic capacity, and antifungal stewardship in the region [11].

Although several studies have reported the occurrence of invasive fungal diseases and antifungal resistance in individual countries within sub-Saharan Africa, comprehensive information on their overall burden, epidemiological trends, and resistance patterns remains limited. Synthesizing available evidence is essential to inform healthcare policy, guide clinical practice, and identify research priorities. Therefore, this review aims to examine the burden of invasive fungal diseases and the prevalence of antifungal resistance in sub-Saharan Africa, highlighting current epidemiological trends, emerging resistance patterns, and existing knowledge gaps that require further investigation.

Methodology

Study Design

This study was conducted as a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to identify, evaluate, and synthesize evidence on the burden of invasive fungal diseases and antifungal resistance in sub-Saharan Africa.

Search Strategy

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, with Google Scholar used as an additional source to identify relevant publications. The search covered studies published between January 2016 and June 2026. Reference lists of all eligible articles were also manually searched to identify additional relevant studies.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators ("AND" and "OR"). The search terms included *"invasive fungal diseases," "invasive fungal infections," "antifungal resistance," "antifungal susceptibility," "cryptococcosis," "aspergillosis," "histoplasmosis," "candidiasis," "mucormycosis," "talaromycosis," "emergomycosis," "sub-Saharan Africa," "Africa,"* and the names of individual countries within sub-Saharan Africa.

Eligibility Criteria

Studies were included if they:

- were published between January 2016 and June 2026;
- were published in English;
- involved human participants;
- reported data on the epidemiology, prevalence, incidence, disease burden, diagnosis, treatment, or antifungal resistance of invasive fungal diseases in sub-Saharan Africa; and
- were original observational studies, including cross-sectional, cohort, case-control, surveillance, and hospital-based studies.

Studies were excluded if they:

- focused exclusively on superficial fungal infections;
- investigated environmental or veterinary fungal isolates without human clinical data;
- were conference abstracts, editorials, commentaries, letters to the editor, duplicate publications, or studies with insufficient data; or
- were published in languages other than English.

Study Selection

Records retrieved from the electronic databases were exported into reference management software, where duplicate records were removed. Titles and abstracts were screened against the eligibility criteria, after which the full texts of potentially relevant studies were assessed for inclusion. The study selection process was documented using the PRISMA 2020 flow diagram.

Data Extraction

A standardized data extraction form was used to collect information from the included studies. Data extracted included the first author's name, year of publication, country, study design, study population, sample size, fungal species investigated, diagnostic methods, prevalence or incidence of invasive fungal diseases, antifungal susceptibility profiles, resistance patterns and mechanisms, mortality outcomes, and other relevant findings.

Data Synthesis

Due to heterogeneity in study designs, populations, fungal pathogens, diagnostic methods, and reported outcomes, a meta-analysis was not performed. Instead, the findings were synthesized narratively and organised according to fungal pathogen, geographical distribution, disease burden, and antifungal resistance patterns across sub-Saharan Africa. Summary tables were used to compare the characteristics and principal findings of the included studies.

RESULT AND DISCUSSION

Burden of Invasive Fungal Diseases (IFDs) in Sub-Saharan Africa

Candidemia

One of the most prevalent blood-stream infections is candidaemia, which is defined as the presence of *Candida species* in the blood [13]. *Candida albicans*, *Candida auris*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida glabrata* are the most prevalent species that cause candidaemia [11]. *C. auris* is an emergent healthcare-associated pathogen with a significant mortality rate due to treatment options being limited by antifungal drug resistance, hospital chlorine-based disinfectants, and other hygiene and infection control measures [14]; [15]. Actually, the use of reusable skin surface temperature monitoring probes, antifungal and disinfectant resistance, and previous systemic fluconazole

exposure have all been linked to the increased nosocomial transmission of *C. auris* [16]; [15]. According to a paper by [17], in South Africa, 45 cases of *C. auris*-caused candidaemia were shown to be amenable to both amphotericin B and micafungin. However, patients treated with amphotericin B alone had a greater death rate than those treated with an echinocandin.

Furthermore, [18] reported that *C. albicans* has a greater mortality rate than *C. auris* (36% and 29%, respectively). The most recent retrospective analysis carried out in South Africa revealed an overall increase in the proportion of azole resistant candidaemia cases from 39.6% in 2016 to 69.5% in 2020, indicating a growing number of cases of antifungal resistance by *Candida species* [19]. However, only 0.2% and 0.3% of *C. albicans* isolates and 0.9% and 6.6% of isolates that were not albicans were resistant to echinocandin and amphotericin B, respectively [19].

Also, according to another South African paper that used laboratory-based surveillance, neonates were the most afflicted age group (49%), followed by babies (27%). In the study, the most common causes of single species candidaemia were *Candida albicans* (36%) and *Candida parapsilosis* (42%) [20]. Furthermore, neonates (43%) and adolescents (43%) had the highest 30-day in-hospital death rates [20]. In another study carried out in Egypt, patients between the ages of six months and fifteen years had a somewhat reduced mortality rate (16.7%) from candidaemia [11]. Also, 55% of participants in five-year retrospective descriptive research carried out in South Africa by [13] died from candidaemia and its consequences, indicating a significant overall mortality linked to the condition.

Additionally, according to surveillance investigations conducted in South Africa, Algeria, and Kenya, the most frequently isolated species were *C. parapsilosis*, *C. tropicalis*, and *C. auris*, respectively [18]; [21]; [20]. *C. albicans* was reported to be the most common cause of candidaemia in other surveillance-based studies carried out in South Africa in 2009 and 2010, as well as retrospective hospital-based investigations in South Africa and Nigeria (23.8%, 73%, and 77%, respectively) [16]; [22]. Results from a prospective case-control study conducted in Cairo, Egypt, show that neutropenia is strongly linked to a diagnosis of candidaemia. Based on blood culture results, 56% and 16% of premature neonates with and without neutropenia, respectively, were diagnosed with candidaemia [23].

Invasive Aspergillosis

A potentially fatal infection that affects people with compromised immune systems is Invasive Aspergillosis (IA) [11]. It is brought on by *Aspergillus species*, which are saprophytic fungi in the ascomycetes class that release easily distributed conidia into the atmosphere [11]. There are around 300 species of Aspergillus, and *A. fumigatus* is responsible for 90% of human infections. Other species that have been implicated include *A. flavus*, *A. terreus*, *A. niger*, and *A. nidulans* [11]. The lungs are frequently infected, and inhaling the conidia causes a wide range of clinical symptoms, including invasive, chronic, and allergic aspergillosis [11].

Every year, IA affects around 300,000 people worldwide, with a death rate ranging from 30 to 80% [24]. The incidence increases as immunosuppression increases because the immune system's phagocytic and neutrophilic functions, which stop conidia germination, are compromised [24]; [11]. IA is therefore frequently observed in patients with persistent granulomatous illness, neutropenia, transplant recipients, and steroid therapy. Individuals with HIV/AIDS, coronavirus disease (COVID-19), influenza virus, diabetes mellitus, chronic obstructive pulmonary disease, and cytomegalovirus, as well as those taking more recent immunosuppressive medications like tumour necrosis factor-alpha inhibitors, may also be impacted [11]. Invasive pulmonary aspergillosis (IPA) is the most prevalent kind. Diagnosis is difficult because IA requires culture of the respiratory specimen, biopsy tissue histology, non-culture-based methods using Aspergillus antigen, computer tomography imaging, magnetic resonance imaging, and molecular techniques using polymerase chain reaction [25].

The estimated prevalence of IA in Africa was between 0.05 and 10.9 per 100,000 people. Nevertheless, the "at-risk population" and the clinical spectrum of invasive aspergillosis are not included in the majority of these estimations. According to [26], the estimations per 100,000 people were 4.8 to 16 in Southern Africa, 0.05 to 10.9 in Northern Africa, and 0.3 to 6.25 in Western Africa, while they ranged from 7.1 to 10.7 in Northern Africa and 3.2 to 6.9 in Central Africa.

Among the rare cases that have been reported in Africa are six case reports, four prospective studies, and one retrospective research. Among the underlying hazards identified in the case reports were HIV, renal transplant patients, antibiotic use, cytomegalovirus, diabetes mellitus, renal failure, and chronic granulomatous disease; however, none were mentioned in the Sudanese cases [11]. According to a case study, Computed Tomography (CT) was used to diagnose an immunocompetent elderly woman from Nigeria. The galactomannan assay in conjunction with CT and/or culture was only carried out in the Tunisian instances listed below. Hodgkin lymphoma, HIV, haematological malignancies like acute myeloid leukaemia (AML), acute lymphoid leukaemia (ALL), and neutropenia, broad-spectrum antibiotics, severe combined immunodeficiency, and bronchiectasis were the underlying risks in the observational studies, where IPA was the only clinical spectrum reported. Following post-mortem examination, the histopathology of the biopsy specimen determined the diagnosis in three of the cases [11].

There is little information on Invasive Aspergillosis in sub-Saharan Africa, which may be due to a lack of medical mycologists and a poor level of clinician awareness of invasive fungal infections (IFI). Significantly, the lack of easily available diagnostic techniques like Aspergillus antigen assays and the high cost of doing CT scans and polymerase chain reaction (PCR) are contributing factors that hinder diagnosis and result in underreporting of cases [11].

Pneumocystis Pneumonia

The fungus *Pneumocystis jirovecii*, which is a member of the phylum Ascomycota, is well-known for infecting immunocompromised people with a deadly pneumonia [8]. Its initial classification as a protozoan was later changed to the kingdom of fungus due to rRNA sequencing [11]. *P. jirovecii* gained prominence during the HIV epidemic as a cause of a severe type of pneumocystis pneumonia (PCP) in individuals with advanced HIV. People living with HIV (PLWH) make up the majority of the epidemiological data that is currently available from Africa, and PCP affects about 15% of newly diagnosed AIDS patients.

Two systematic reviews provided a detailed description of the PCP burden among PLWH in Africa. The overall frequency of PCP was 15.4% in a meta-analysis of hospital-based studies from 18 sub-Saharan African nations, although it was greater in patients

with respiratory symptoms (18.8%), inpatients (22.4%), and inpatients with respiratory symptoms (24%) [27]. According to this meta-analysis, the prevalence of PCP among inpatients decreased over time: it was 28% in the 1990s, 27% between 2000 and 2004, and 9% after 2005 [27]. This pattern was associated with the percentage of individuals starting cotrimoxazole prophylaxis and antiretroviral therapy (ART).

Also, according to [27], the rate of respiratory co-infections (with *P. jirovecii*) was apparently high (29.3%) and included pulmonary tuberculosis (14.8%), bacterial pneumonia (18.7%), pulmonary cytomegalo virus (3.9%), and pulmonary cryptococcosis (1.4%). PCP is treated with high doses of cotrimoxazole without laboratory confirmation in the majority of African nations. Radiology lacks specificity, and for diagnosis, PCR is regarded as the gold standard. However, in Africa, where laboratory confirmation by microscopy and polymerase chain reaction (PCR) on bronchoalveolar lavage is mostly unavailable, the low diagnostic accuracy of clinical and radiological characteristics for PCP prevents an accurate evaluation of the true burden of PCP.

According to a meta-analysis of research from 15 African nations, 19% of adult PLWH with respiratory symptoms had laboratory-confirmed *P. jirovecii* in any respiratory sample [28]. The prevalence ranged from 15% in microscopy-based studies to 22% in PCR-based research. It's interesting to note that the prevalence of laboratory-confirmed *P. jirovecii* was 21% in the pre-ART era (1995–2005) and 18% in the ART era (2006–2020) [28]. According to estimates, 18.8% of PLWH die as a result of PCP [27].

Three small studies from Tanzania, Guinea-Bissau, and Cameroon found that the prevalence of *P. jirovecii* colonization (a positive *P. jirovecii* PCR test in the absence of respiratory symptoms) among PLWH was 0.3%, 3%, and 42.9% (18.9% among HIV-negative individuals), respectively [29]. Although the clinical significance of *P. jirovecii* colonization is unclear, colonization has been linked to exacerbations of chronic obstructive pulmonary disease and may promote *P. jirovecii* transmission and disease progression in at-risk patients [8].

The prevalence of *P. jirovecii* in HIV-negative people in Africa is little documented. PCP can occur in HIV-negative individuals with haematological malignancies, long-term steroid usage, solid cancer patients receiving chemo-radiotherapy, organ transplant recipients, and those with rheumatological disorders [30]. Nevertheless, no research from sub-Saharan Africa is included in systematic reviews on *P. jirovecii* in non-HIV populations [31]; [32]. There are, however, a few child studies; according to one study, 12.8% of HIV-negative children in South Africa who were admitted with hypoxic pneumonia had *P. jirovecii* [11]. Also, according to a different multi-center study, 0.2% of children in the Gambia, 2.4% in Mali, 2.3% in Kenya, 4.1% in Zambia, and 2.1% in South Africa had severe pneumonia brought on by *P. jirovecii* that required hospitalization [33]. Further research is required to describe the illness induced by *P. jirovecii* in people without HIV in sub-Saharan Africa.

Histoplasmosis

In addition to Central, South America, Western Africa, Southern Africa, Eastern Africa, Central Africa, and Southeast Asia, the Ohio and Mississippi river valleys in the United States are home to the dangerous fungus histoplasmosis [34]; [35]; [36]; [37]. *Histoplasma capsulatum* var capsulatum (Hcc) is the culprit of the disease's classical form, whereas *Histoplasma capsulatum* var. duboisii (Hcd) is the cause of the African type [34]; [36].

A frequent way to get a histoplasma infection is inhaling microconidia is. HIV/AIDS, which was designated as an AIDS-defining illness in 1987, is its largest contributing risk factor in the adult population [34]. In retrospect, however, a number of histoplasmosis cases were also documented in Africa before the HIV/AIDS epidemic [34]. Conversely, in children, histoplasmosis is primarily linked to risk factors other than HIV, such as exposure to toxins and the environment, autoimmune disorders, childhood cancers and their treatment, lung conditions, immunosuppressive medications, pancytopenia, T-cell deficiency, and malnutrition [38]; [39].

Clinical characteristics are non-specific and resemble various clinical entities, such as leishmaniasis, cancer, tropical splenomegaly syndrome, and tuberculosis [40]; [36]. While the African-type manifests as extrapulmonary symptoms including bone lesions and ulcers, the classical form typically manifests as a pulmonary disease [34]; [36]. A high index of clinical suspicion is frequently necessary for the diagnosis of histoplasmosis; otherwise, the diagnosis may be delayed or incorrect. Although fungal cultures are the gold standard for diagnosis, most cases are diagnosed by histology since fungal cultures are not regularly available in many African nations. Histoplasma antigen assay, antibody detection, molecular approaches, direct inspection, and peripheral blood smear are other diagnostic modalities [34]; [36].

The actual prevalence of histoplasmosis in sub-Saharan Africa is still unknown despite the apparent rise in reported cases for many reasons: (1) a lack of awareness on the part of clinicians, which led to some cases being diagnosed after death [40]; [36]; (2) a low level of suspicion on the part of clinicians, which caused several cases to be mistakenly diagnosed as other clinical entities [34]; [40]; [36]; (3) insufficient or nonexistent diagnostic capabilities throughout African nations [41]; [42]; (4) information on the disease's incidence, prevalence, morbidity, and mortality in the majority of African nations is inconsistent and possibly unavailable in some of them [34]. Nevertheless, some research has detailed instances in certain African nations as well as throughout the continent.

[34] found 470 cases of histoplasmosis with HIV-positive patients, accounting for 38% (178) of the cases over a six-decade period (1952–2017). With 179 cases reported, West Africa had the most, with *Histoplasma capsulatum* var. dubuosii (Hcd) accounting for the bulk (n = 162 cases). The bulk (n = 119) of the 150 cases that were reported from the Southern African region were caused by *H. capsulatum* var. capsulatum (Hcc). While Hcd was mostly identified in Madagascar and Central and West Africa, Hcc was discovered to be the most common infectious agent in Africa. Only five countries (Tanzania, Benin, South Africa, Egypt, and Uganda) reported using serology to make a diagnosis; in three of these cases, the samples were processed in Western nations [34]. The majority of reported cases from Africa were diagnosed by culture and histology.

African histoplasmosis in the context of HIV/AIDS was the subject of another review by [43], which found 94 well-documented instances of Hcd infection (1993 to 2019), with 30.1% of the patients being under the age of 18. Fever, lymphadenopathies, and the lack of bone infection were the characteristics that set patients with HIV apart from those without the virus, with an HIV co-infection prevalence of 20.8%. A global assessment (1939–2021) of the African paediatric population identified 65 instances, the majority of which were from Nigeria (n = 13) and the Republic of Congo (n = 26) [38].

In another review (1950–2021) that concentrated on histoplasmosis in the African paediatric population, 44 selected cases from Western Africa (38.6%, n = 17), Eastern Africa (9.1%, n = 4), Southern Africa (9.1%, n = 4), and Central Africa (43.2%, n = 19) were reported. Northern Africa did not have any case reports, and with a mean of 9.2, the age range was 1–17 years. Of the 44 case reports, 8 cases (18.2%, 8/44) were caused by *Histoplasma capsulatum* var. capsulatum, 33 cases (75%, 33/44) were caused by *Histoplasma capsulatum* var. duboisii, and three cases had no species identification. Just one case (2.3%, 1/44) had pulmonary histoplasmosis, while 56.8% (25/44) had disseminated histoplasmosis and just three (6.8%) had HIV [36]. Results from more recent research and other reviews concentrated on certain African nations, but none of the studies provided case fatality rates [38].

Cryptococcosis

The fungal species *Cryptococcus neoformans* and *Cryptococcus gattii* are responsible for the opportunistic fungal infection known as cryptococcosis [44]. It affects one million people each year and is the primary cause of illness and mortality among AIDS patients globally [44]. Over 180,000 HIV-positive patients die each year from the invasive form of the disease [cryptococcal meningitis (CM)], with over 70% of those deaths occurring in low-income nations, especially sub-Saharan African (SSA) nations [45]. In Africa, there are uncommon types of extra-neuromeningococcal cryptococcosis [46], and CM is more common than TB meningitis [47]. Headaches, stiff neck, and altered consciousness are common indications and symptoms of the illness [11]. Other symptoms include low haemoglobin, low body mass index, and low CD4 cell count (less than 100 cells/mm3 in SSA) [48]. According to a 2020 study based on cross-sectional studies, 8.3% (6.1–10.5%) of SSA countries have cryptococcosis [49].

In Eastern and Southern Africa, CrAg positivity and cryptococcal meningitis were estimated to be 75,000 (55,000–95,000) and 63,000 (45,000–80,000) cases respectively, and 22,000 (19,000–26,000) and 19,000 (16,000–22,000) cases, respectively, in Western and Central Africa. According to estimates of the burden of CM throughout time, Algeria has the lowest rate (35 cases annually), and Nigeria has the highest (57,866 cases annually) [50]. These estimates are derived from research conducted in these nations, typically including HIV-positive patients with low CD4 counts [51]; [52]. Studies and information on cryptococcal antigenemia and CM are not always readily available.

Furthermore, according to a multicenter investigation, 2.3% (1.8–3%) of HIV patients with CD4 < 200 cells/mm3 in four locations of Nigeria had cryptococcal antigenemia [53]. However, there are notable regional variations in this prevalence [53], ranging from 1.4% (4/290) to 19.67% (59/300) for cryptococcal antigenemia [54]; [55]; [56] and from 16.8% (31/184) for CM [11]. A prospective study conducted in Uganda between 2009 and 2010 discovered 32 (5.7%) HIV-positive patients who tested positive for cryptococcal antigen (CrAg) [11]. Prevalences of 5.7% and 19% were found in two cross-sectional investigations of HIV-positive patients in Uganda [11].

Also, cryptococcal antigenemia was detected in 5.8% (35,000/600,000) of HIV patients with low CD4 counts in a large screening program conducted in South Africa between 2017 and 2019 [57].

A comparable study conducted in Cameroon revealed a prevalence of 21.7% (5/23) for CM and 23.1% (43/186) for cryptococcal antigenemia [58]. The frequency of cryptococcosis in Ethiopia is little understood. According to [59] and [60], this prevalence varies from 4% to 11.43%, with CD4 < 100 cells/mm3 as a common factor and occasionally co-infection with other diseases. Mali, the Democratic Republic of the Congo (DRC), Togo, Kenya, Ghana, Nigeria, Burkina Faso, Botswana, Senegal, Tanzania, South Africa, Cameroon, and Mozambique have further data on cryptococcosis, sometimes with a high death rate [61]; [62]; [63].

There is little information about cryptococcosis in youngsters and HIV-negative individuals. Research conducted in Nigeria and Mali yielded rates of 18.8% (22/117), 2.5% (1/150), 7% (16/228), and 1.47% (3/204) for CM and cryptococcal antigenemia in HIV-negative patients [11]. According to two investigations conducted in Cameroon, the prevalence of CM and cryptococcal antigenemia in children was 3.6% (12/331) and 6.12% (9/147), respectively [61]; [63]. In certain nations, the only data available are case reports.

Talaromycosis

The fungus *Talaromyces marneffei* (*Penicillium marneffei*) is the cause of talaromycosis, formerly known as penicilliosis. It is a neglected tropical disease that is endemic to East and Southeast Asia [64]. Fever, anaemia, swollen lymph glands, liver, and painless skin lesions on the face and neck are possible symptoms [11]. Immunocompromised patients (such as those with HIV, cancer, organ transplants, long-term steroid use, advanced age, malnourishment, or autoimmune diseases) usually experience it. The genus Talaromyces contains only one thermally dimorphic fungus, *T. marneffei* [11]. It exists as a mould in the environment but develops into tiny, spherical yeast cells in host tissue, just like the majority of dimorphic fungus. There is little information available about its native habitat, but it has been separated from soil [11].

According to evidence, heavy rainfall may create favourable conditions for the fungus's growth and spread [11]. It is believed that inhaling fungal spores from unknown environmental sources causes infection. The fungus can occasionally induce an asymptomatic dormant infection for extended periods of time, and the incubation period can vary [11]. Typically, the diagnosis is made by identifying the fungus from clinical specimens using either culture or microscopy. Histopathology of skin lesions, lymph nodes, and bone marrow biopsies reveals the presence of organisms.

Notably, only two case reports were found [65]. According to these assessments, the two main risk factors are HIV and a history of travel to Asia. The cases range in age from 37 to 83. Multiple umbilicated papules linked to cough, fever, appetite loss, weight loss, urethral discharge, febrile pneumonia, dyspnoea, and "molluscum contagiosum" lesions on the face, arms, neck, and trunk are the most typical clinical presentation. In Africa, culture-based methods are primarily used to diagnose it. Molecular diagnostics are used in several locations; however they are uncommon in Africa. While one patient responded favorably to itraconazole treatment, the other passed away within 12 hours of admission [11].

Mucormycosis

Immunocompromised people are more likely to develop mucormycosis, an opportunistic invasive illness [66]. The consequences is severe and often life threatening [67].

These fungi belong to the order Mucorales, which includes the genera Mucor, Rhizopus, Rhizomucor, Syncephalostrum, and Lichtheimia [67]. They are widely dispersed in the environment as airborne spores that can cause respiratory and skin illnesses in those who are vulnerable [67]. They are frequently found in soil and decomposing vegetation, and they are also known as bread mould and laboratory contaminants [67].

Diabetes mellitus, recipients of solid organ transplants or haematopoietic stem cells, HIV patients, and cancer patients undergoing chemotherapy are immunocompromised conditions that lead to invasive fungal illnesses [66]. Additionally linked are burns, deferoxamine medication, penetrating injuries, steroid use, and consequences from medical operations [66]. The most often documented areas of involvement for mucormycosis infection are rhino-sino-orbital-cerebral, pulmonary, cutaneous, and gastrointestinal [68]; [66]. Since this illness has a high death rate and a reported survival rate of only 3% in the absence of therapy, there is a tremendous need for a high index of suspicion to help with early detection and treatment [11]. Although mortality is still high in the presence of proper medical therapy, prompt treatment initiation is necessary to lower the death rate [11]. First-line antifungal therapy, which includes amphotericin B, isavuconazole, and posaconazole, is combined with surgery to remove all contaminated tissues [69]. Furthermore, to further lower the death rate, a predisposing condition must be identified and treated [11]. All age groups in Africa are infected with mucormycosis. In a case series conducted in Egypt, [70] reported mucormycosis in children between the ages of 1.5 and 12 who were receiving treatment for acute lymphoblastic leukaemia and acute myeloid leukaemia, with a high death rate of 60%. A 10-month-old infant in South Africa also had mucormycosis, which was linked to weakened immunity [11]. Its appearance as documented in case series of rhinocerebral mucormycosis in South Africa, Egypt, and Tunisia [71]; [72]. In South Africa, it was also reported to manifest as gastrointestinal mucormycosis [11]. In Tunisia and Egypt, it manifested as pulmonary mucormycosis [73]; [74]. Additionally, there are case studies in this area [75]; [76].

Murcormycosis is becoming more common in Africa, which is consistent with the rise in diabetes mellitus and immunocompromised people worldwide [68]; [66] as well as the COVID-19 pandemic. [71] and [75] conducted case series from Egypt that demonstrated the bidirectional relationship between COVID-19 and diabetes mellitus with an increased risk of mucormycosis, while COVID-19 patients were found to have both new onset diabetes (NOD) and an exacerbation of pre-existing diabetes mellitus [71]; [75].

Out of 321 recipients of kidney transplants in Tunisia, 11 cases (3.4%) had a high death rate of 72% [11]. Given that there are now 46 kidney transplant recipients in Africa, this emphasises the need for increased suspicion of this fungal disease entity in these patients [77]. Four cases of mucormycosis caused by unknown fungi that affected several body parts and were detected by PAS stain and microscopy were also found in a 70-year retrospective research carried out in Uganda [78]. Histopathology is the primary method of diagnosis; other methods include microscopy [71]; [72], culture, and PCR [74]; [71]. Mucormycosis infections are difficult to diagnose and treat in sub-Saharan Africa due to a number of issues, including late patient presentation, the illness's apparent rarity, which delays diagnosis, and limited access to antifungal drugs for patient care [79].

To prevent and lower morbidity and mortality in affected persons, a more extensive surveillance protocol must be established in African countries due to the widespread involvement of invasive mucormycosis and the related higher mortality [11].

Blastomycosis

Inhaling spores of soil-dwelling Blastomyces species can result in blastomycosis, a fungal infection [80]. *Blastomyces percursus* is a prevalent cause of blastomycosis in sub-Saharan Africa. The disease primarily affects the lungs and skin, but it can also affect other organs like the brain [81]; [82]; [80]. Nonetheless, blastomycosis most frequently manifests as extra-pulmonary illness [83]. Alveolar infiltrates, consolidation, and cavitation are radiological signs of pulmonary illness that can be noticed on a simple chest radiograph [81]. In their article, [81] demonstrated that *B. dermatitidis* is the cause of blastomycosis in middle and east Africa, which is the second most endemic region. The disease is diagnosed by direct microscopy using potassium hydroxide (KOH), culture, histology, antibody test, and PCR identification using specimens such as wound secretion, sputum, or bronchial lavage [11]. Antifungal medications, such as amphotericin B is used for at least 12 months for mild to moderate disease [84]; [80].

A study conducted in South Africa on 20 instances of blastomycosis found that *B. percursus* was responsible for 12 of the cases, while *B. emzantsi* was responsible for just 8 [84]. According to [85], the patients with *B. percursus* had extra-pulmonary disease (n = 7), pulmonary disease (n = 3), cutaneous disease (n = 4), spinal disease (n = 1), and multisystem disease (n = 4). In contrast, those with *B. emzantsi* experienced both lung and vertebral illness (n = 2) as well as a subcutaneous abscess (n = 1) [85]. Voriconazole, posaconazole, itraconazole, amphotericin B, and micafungin were the antifungals with the highest in vitro potency for the isolates from all 20 cases [85].

There have been multiple reports of cutaneous blastomycosis without pulmonary involvement in South Africa, Tunisia, and Morocco [86]. In Tunisia, Morocco, and Tanzania, *B. dermatitidis* has been linked to multiple cases of pulmonary, subcutaneous, vertebral, and paravertebral blastomycosis [82]. A 37-year-old Nigerian patient with pulmonary blastomycosis and a right-sided pleural effusion was treated with ketoconazole and saline pleural lavage, and the patient's condition eventually improved, according to a previously published case [11]. Similarly, blastomycosis accounted for 1.6% of the deep mycoses detected by histology in a 70-year retrospective research carried out in Uganda [78].

Emergomycosis

Emergomyces (formerly known as Emmonsia) is the fungus that causes emergomycosis which is a systemic fungal illness. There are five species of the dimorphic fungus Emergomyces that have been identified worldwide [87]. These species are *Es. Canadensis*, *Es. Africanus*, and *Es. Pasteurianus*. South Africa has the most cases of Orientalis, *Es. Europaeus*, *Es. pasteurianus*, and *Es. africanus*, which are frequently isolated from Africa [87]. Within this group, *Es. africanus* is a recently identified fungus that has only been detected in southern Africa thus far.

Additionally, Emergomyces is a thermally dimorphic fungus that is known to cause illness worldwide, primarily in individuals with severe HIV sickness [88]. It is present in soil, and humans contract it by breathing in fungus spores.

Asia, Europe, Africa, and North America are the four continents where emergomycosis has been documented thus far. However, given the rising global HIV burden, it is assumed that the illness must be widespread and that many instances go undiagnosed [89].

Histology and/or culture are used to confirm the difficult diagnosis. Given the significant clinical and histological similarities between the two conditions, it should be taken into account while making the differential diagnosis of histoplasmosis. As of right now, there are no accepted recommendations for treating emergomycosis. Oral itraconazole must be taken for a minimum of 12 months after using antifungal medications, such as amphotericin B, for one to two weeks [11]. The majority of the information regarding emergomycosis in Africa is found in case reports and series. Some of the documented cases of Emergomycosis from Africa were compiled by [11]. The majority of the cases were from South Africa. However, given the prevalence of HIV in Africa, more cases (including those in sub-Saharan Africa) go undiagnosed because of a low index of clinical suspicion and a lack of diagnostic tools. The median age of the patients in these documented cases is roughly 34. The majority of cases have an undetectable viral load and a CD4 count of less than 200 cells/mm3, making HIV the primary risk factor [11]. Skin lesions are the main symptom in the majority of patients. Anaemia, pneumonia, gastroenteritis, herpes gingivostomatitis, and weight loss are other manifestations. A mix of histology, culture, and molecular assays (mostly sequencing) was used to make the difficult diagnosis. The majority of these patients were treated with itraconazole and amphotericin B. Fluconazole was used to treat a few of the instances that were found. Itraconazole, voriconazole, or posaconazole should be used after amphotericin B, according to South African in vitro susceptibility data. According to [90], fluconazole was comparatively less effective.

Additionally, [90] compiled the clinical features, geographic distribution, and treatment of 54 instances of disseminated emmonsiosis that were reported throughout South Africa between January 2008 and February 2015. In South Africa, two further occurrences were reported, one involving an immunocompetent patient and the other involving a patient undergoing immunosuppressive treatment after having a kidney transplant. The authors state that this one instance of disseminated emmonsiosis in an apparently immunocompetent individual prompted concerns about whether the patient had an undiscovered immunological disease, was exposed to a significant volume of inoculum, or was infected with a more virulent strain or distinct species. Also, *Es. africanus* was isolated from 34 days' worth of air samples taken over 11 weeks in Cape Town, South Africa [91], and 30% of soil samples from a variety of South African ecosystems had it extracted by PCR [92].

Chromoblastomycosis

The World Health Organization listed chromoblastomycosis, a subcutaneous mycosis caused by various dematiaceous fungi, as a neglected tropical illness along with mycetoma. It is more common in tropical and subtropical regions and is frequently linked to poverty. *Fonsecaea species*, *Cladophialophora species*, and *Phialophora species* are the primary causative agents [11]. Another implantation mycosis that is spread via transcutaneous inoculation of fungal spores is chromoblastomycosis. The soil and vegetation are frequently contaminated by the causative microorganisms.

The danger of infection is increased by activities like farming and gardening that interfere with the fungi's ecological niche. The majority of chromoblastomycosis patients live in rural areas. The emergence of cutaneous or subcutaneous lesions on the face, neck, and limbs is the clinical symptom [11].

All continents have recorded cases of chromoblastomycosis, but South and Central America, Asia, and Africa account for the bulk of cases. Case reports and series make up the majority of the current epidemiological data in Africa. Madagascar is the hotspot on the African continent, where numerous case studies, prospective studies, and surveillance studies—including recent ones—have been conducted [93]. Africa had the second-highest number of recorded cases, after South America, with 1875 instances from 22 countries, according to a survey assessing the global burden of chromoblastomycosis from 1947 to 2018 [94]. More than 80 other instances have since been reported in Ethiopia, Uganda, and Madagascar [93]; [95].

Chromoblastomycosis was most prevalent in Madagascar and South Africa. The West African sub-region had the fewest instances, and the disease was found to be uncommon in desert regions. Geographical location affected the causing pathogen, however *F. pedrosoi* is the most common, followed by *Cladophialophora spp*. and *Phialophora spp*. [11]. But according to recent research conducted in Madagascar, *F. nubica* is the most common cause of chromoblastomycosis. Males were more afflicted than females, similar to other implantation mycoses.

Traditional direct microscopy, histology, and/or culture are the main methods used in laboratory diagnostics. Molecular and MALDI-TOF techniques were used in a recent surveillance research in Madagascar to confirm diagnosis in suspected cases [96]. Chromoblastomycosis treatment was mostly nonexistent and not fully documented. Nonetheless, it was noted that treatment consisted of a mix of manual techniques, surgical excision, and antifungal treatments. The common antifungal utilized was itraconazole and rarely fluconazole, ketoconazole, and potassium iodide. There was rarely any follow-up data provided. Patients were treated for 4–26 months, depending on the severity of the disease, in a recent study with comprehensive therapy and follow-up data in Madagascar. Despite the lack of a full cure or healing, there was either a significant or minor clinical improvement [11].

Coccidioidomycosis

The soil-dwelling spores of the fungus Coccidioides are the cause of coccidioidomycosis, also known as valley fever. Valley fever is caused by two distinct pathogenic organisms, *Coccidioides immitis* and *Coccidioides posadasii*. Despite having the same morphology, the two species differ in terms of genetics and epidemiology [11]. While *Coccidioides immitis* is unique to the San Joaquin Valley of California, *Coccidioides posadasii* is a soil fungus that is native to some arid to semi-arid regions of the southwestern United States, northern sections of Mexico, and South America. The two species overlap geographically in Southern California [11].

Inhaling the airborne spores of the dimorphic fungus is how coccidioidomycosis is spread. Coccidioides from the soil (*C. immitis* and *C. posadasii*). The most common times to contract the fungus are during the summer or late fall. Wind and storms disrupt the soil during these dry months. Rarely, exposure to contaminated cotton balls or other fomites might cause illness outside of the endemic area [11]. Outside of America, its frequency is incredibly rare.

The few cases from Asia and Europe that have been documented have been in visitors to these endemic regions, and when they return home, the sickness may become clinically significant or be spread through contaminated objects [97]. Additionally, it is hypothesized that coccidioidomycosis instances exist in Africa but have not yet been documented due to misdiagnosis and diagnostic failure due to the disease's resemblance to other lung diseases [97]. There have been no reports of lung infections spreading from person to person.

In healthy individuals, coccidioidomycosis typically has no symptoms, and about 60–65% of patients experience this. The lungs are the site of the main infection. The illness may manifest as widespread, chronic, or acute. The symptoms of acute pulmonary coccidioidomycosis, such as fever, sore throat, cough tiredness, etc., are typically minimal or nonexistent. In immunocompetent people, it self-limits after an incubation period of seven to twenty-one days [11].

Lung abscess, empyema, bronchopleural fistula, or scarring (fibrosis) are possible manifestations of chronic pulmonary coccidioidomycosis, which might appear 20 years or longer after the initial infection. Although extrapulmonary disseminated infections are common in people with weakened immune systems, they also arise via hematogenous dissemination, immunosuppressive diseases, such as cancer, diabetes, or HIV infection [11]. It could appear weeks, months, or even years after the initial infection. Although it can affect any organ in the body, it tends to spread to the skin, soft tissues, joints, and central nervous system. A contaminated puncture may result in cutaneous coccidioidomycosis [97].

A thorough history and physical examination are necessary for the diagnosis of coccidioidomycosis. Imaging tests are then performed, and a chest X-ray reveals primary pulmonary illness, including pleural effusions, hilar adenopathy, and varied nonspecific infiltrates. Cavities and nodules are examples of findings that show the development of pulmonary coccidioidomycosis into the complicated or residual stage. Coccidioidomycosis must be confirmed by isolating the fungus in culture, identifying it through histology, or using serologic testing [98]. Demonstration of endospores or endosporulating spherules is necessary for pathological diagnosis.

Coccidioidomycosis patients typically have no symptoms and merely need supportive care. Patients with symptoms are managed based on their clinical syndrome [98]. Azoles or amphotericin B deoxycholate are typically the cornerstones of antifungal therapy. Azoles like ketoconazole, fluconazole, and itraconazole are used to treat mild cases of coccidioidomycosis, but amphotericin B is used to treat severe cases. Therapy takes a long time; for some individuals, it may take months or even years [98].

In Africa, histology revealed just four cases of coccidioidomycosis. Unidentified Coccidioides species were the cause of all four instances. According to [78], none of the cases had an accurate clinical diagnosis. According to [97], a 23-year-old HIV-positive male from Uganda had a 10-month history of hemoptysis and respiratory difficulties, as well as a 6-month history of localized swellings on his extremities, accompanied by drenching sweats and weight loss. He stated that he had never left Uganda. A bronchoscopic examination revealed that the right major bronchus was blocked by two masses. Results from a bronchoscopic biopsy were consistent with coccidioidomycosis. After receiving antifungal therapy, the patient recovered and was released [97].

Sporotrichosis

The thermal dimorphic fungi of the genus Sporothrix are the cause of sporotrichosis, a subacute to chronic infection. In tropical and subtropical regions, it is more prevalent. Known as implantation mycosis, it is typically spread via traumatic implantation that makes it easier for spores to enter a host. According to [99], the clinical presentation can be generally categorised into cutaneous, mucosal, systemic, and immunoreactive types. The most prevalent symptoms, which were seen in disseminated cases, are cutaneous/subcutaneous and lymph node lesions. Although sporotrichosis is rarely fatal, it can cause serious morbidity and a lower quality of life. The fungus primarily inhabits soil and decomposing vegetation in its biological habitat. Activities including farming, gardening, raising animals, and mining are typically where infections start [11]. Zoonotic transmission occurs frequently.

Recently, sporotrichosis was added to the list of deep mycoses that are considered neglected tropical diseases. Different continents or geographical areas have varied sporotrichosis ecology and epidemiology. Except for a few nations like Madagascar and South Africa, the epidemiology of sporotrichosis in Africa has not been thoroughly investigated [100]. Over 3,300 undocumented instances are thought to exist in South Africa, and they have been linked to outbreaks among mine workers in the 20th century [11]. There have been occasional case reports or series in other African nations. Many cases, according to experts, are misdiagnosed, and many more are either unreported or undocumented. The impact of climate change on the dynamics of deep fungal infections, including sporotrichosis, is currently a growing concern [101].

In Africa, Madagascar and South Africa were the two countries where sporotrichosis was most common. Although it affects people of various ages, young adults were the ones who reported it the most. Males were the most impacted, most likely as a result of environmental and occupational exposure dangers that are mostly linked to men. Nodular, usually ulcerating lymphocutaneous lesions, primarily affecting the limbs and faces, were the most prevalent presentation noted. Muscle, osteoarticular, and visceral lesions are among the other atypical signs that do happen [100]. Seldom are systemic cases documented. Although few incidences of sporotrichosis in immunocompromised patients (such as one in an HIV patient) were documented in South Africa, the disease typically affected immunocompetent persons [102].

In general, culture and/or histology were used to make the diagnosis; on rare occasions, a clinical specimen was directly examined. *Sporothrix schenckii*, which is now known as *S. schenckii sensu stricto* together with other closely related varieties, was the most often isolated fungus. MALDI-TOF was used to validate culture reports in the most recent South African case report [102]. Before the 20th century, potassium iodide was a common therapy option. Itraconazole has been the most commonly used medication for treatment in the last few decades, but terbinafine or fluconazole are sometimes used when the latter is unavailable. Most outcomes are not lethal.

Paracoccidioidomycosis

Thermally dimorphic fungi can cause paracoccidioidomycosis, a systemic mycosis: Paracoccidioides lutz and Paracoccidioides brasiliensisii. The majority of Latin American countries (Brazil, Argentina, Colombia, and Venezuela) and portions of Central America have subtropical humid regions where it can be found [103].

The main source of infection is the lungs, when conidia and mycelial pieces are inhaled. Although the infection is typically asymptomatic, there are two types of paracoccidioidomycosis: the chronic form, also called adult paracoccidioidomycosis, and the acute/subacute form, also called juvenile paracoccydioidomycosis [11]. Both sexes are equally affected by the acute or subacute clinical manifestations, which account for 10% of clinical cases and are common in infants and adolescents (less than 16 years old). Lymphadenopathy, hepatosplenomegaly, fever, weight loss, malaise, and many skin lesions are typical clinical characteristics, and respiratory symptoms and mucous membranes are uncommon [11].

The chronic form is more common in adults (older than 16 years), with a male to female ratio of 20:1. This difference may be due to oestrogens' inhibition of mycelial-to-yeast conversion. Other symptoms include mucous membrane involvement, oral lesions, cutaneous lesions, and cervical lymphadenopathy. Risk factors for paracoccidiodomycosis include agricultural work, malnutrition, smoking, and alcoholism [11].

Microscopy is used to diagnose paracoccidioidomycosis. Diagnostic characteristics include rounded, thick-walled yeast cells (usually 15–30 μm in diameter, sometimes up to 60 μm) with several buds (ship wheel, pilot wheel, or Mickey Mouse ear-like cells). Non-invasive tests, like serological testing, are used to diagnose the majority of patients in endemic areas. The most popular reference assay is the immunodiffusion assay (IMMY, Norman, OK, USA). This assay has a high sensitivity (about 80%) and specificity (>95%) and is reasonably priced [103].

Itraconazole has been used extensively for patients with trimethoprim (sulfamethoxazole), which has demonstrated that co-trimoxazole or maintenance treatment with an azole derivative is necessary [11]. For patients with mild-to-moderate forms of paracoccidioidomycosis, itraconazole (200 mg daily for 9–12 months) is the preferred treatment; co-trimoxazole (for 18–24 months) is the primary therapeutic substitute for itraconazole. For severe instances or immunocompromised patients, amphotericin B induction therapy is limited to two to four weeks. 200–400 mg of itraconazole should be administered after amphotericin B induction therapy. In order to reduce fibrotic sequelae, surgical therapy involves relieving granuloma-induced spinal cord compression [11].

Notably, a 35-year-old Hausa woman from the Kano area had infiltrated, greatly enlarged, unevenly eroded lips with regional adenopathy; no visceral affection was discovered; Paracoccidioides brasiliensis was cultured; sections taken from the lip and a cervical lymph node also showed characteristic spherule budding cells; the patient responded to long-acting sulphormethoxine (Fanasil) [11].

Antifungal: Availability and Resistance in Sub-Saharan Africa

There are few therapeutic alternatives available for treating fungal infections and illnesses [104]. The tight evolutionary link between fungus and humans has contributed to the delayed pace of antifungal discovery by restricting the number of fungal-specific targets that can be used for medication development [105]. In fact, there are only three main kinds of antifungal medications used in clinical settings to treat invasive fungal illnesses (Figure 1).

The earliest antifungal medications used in medicine to treat systemic fungal infections are polyenes, such as amphotericin B. Similar to a "sterol sponge," these amphipathic polymers extract ergosterol from lipid bilayers to provide fungicidal action [105].

Although polyenes show broad-spectrum bioactivity against mould and yeast species, their substantial host toxicity precludes its therapeutic application [105]. But in environments with limited resources, amphotericin B is still the preferred treatment, especially for *C. neoformans* infections. In particular, the first-line treatment for HIV-positive individuals with cryptococcal meningitis is a combination regimen of amphotericin B and the antimetabolite pyrimidine analogue flucytosine [106].

For many years, the azoles (a class of five-membered heterocyclic compounds) have been used extensively in clinical settings to treat systemic fungal infections [105]. Azoles target the fungal cell membrane similarly to polyenes, however they are fungistatic against Candida and function by blocking the cytochrome P450 lanosterol 14-α-demethylase (Erg11) [105]. As a result, ergosterol production is blocked, and Δ-5,6-desaturase (Erg3) produces a hazardous sterol that accumulates [105]. Azoles are well tolerated, but because they also inhibit mammalian cytochrome P4505, a major disadvantage is that they may interfere with the metabolism of other medications [105].

Lastly, echinocandins, such as caspofungin, are cyclic hexapeptides with lipid side chains that inhibit (1,3)-β-D-glucan synthase to target the fungal cell wall [105]. Echinocandins are ineffective against Candida neoformans, despite having fungicidal and fungistatic effects against Aspergillus and Candida, respectively [105].

Additionally, voriconazole, the first-line medication for invasive aspergillosis, has been demonstrated to improve leukaemia and transplant patients' chances of survival [104]. Invasive cryptococcosis is best treated with amphotericin B and 5-flucytosine combination therapy, whereas invasive candidosis is best treated with echinocandins, which are also effective against multidrug-resistant Candida auris and fluconazole-resistant Candida albicans [104].

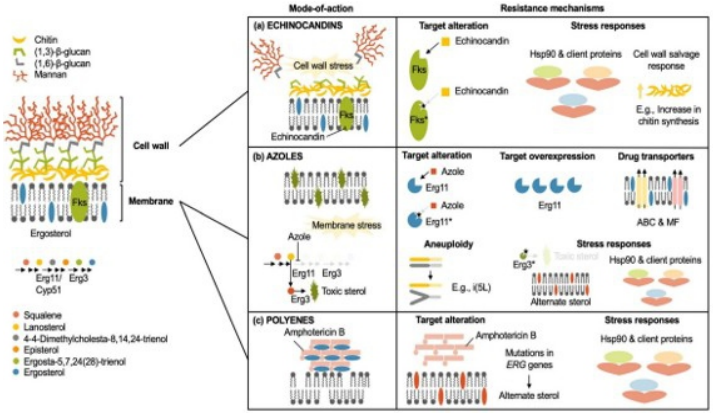

Figure 1: Antifungal Mode-of-action and Mechanisms of Resistance
***Source:** [105]*

a By inhibiting (1,3)-β-D-glucan synthase, the echinocandins cause severe cell wall stress and compromise the integrity of the cell wall. Mutations in the drug target gene FKS1 in Aspergillus, Candida, and Cryptococcus are the main cause of echinocandin resistance. Both FKS1 and its paralogue FKS2 are mutated in C. glabrata. The molecular chaperone Hsp90, several Hsp90 client proteins, and genes that control cell wall salvage signals (such as compensatory increase of chitin production) are cellular components that facilitate responses to echinocandin-induced stress.

b By inhibiting lanosterol 14-α-demethylase (Erg11), which prevents ergosterol biosynthesis and causes an accumulation of a toxic sterol intermediate (14-α-methyl-3,6-diol) generated by Erg3, the azoles act on the fungal cell membrane. Target overexpression or mutations in the medication target (ERG11) can result in azole resistance. By preventing the buildup of poisonous sterols, loss-of-function mutations in ERG3 can also provide azole resistance; this process depends on Hsp90 and its client proteins. Efflux, which involves the overexpression of ABC and MF transporters, is another important factor influencing azole resistance. The dosage of the azole target Erg11 and efflux pumps can be increased by aneuploidies, such as a duplication of the left arm of chromosome 5 (referred to as isochromosome (i5(L)). c As a sterol "sponge," the polyene medication amphotericin B creates extramembranous aggregates that draw ergosterol out of fungal cell membranes. Although resistance is still very uncommon, it can be acquired via mutations in the genes involved in ergosterol production, which lead to the buildup of alternative sterols and the depletion of ergosterol. Amphotericin B resistance is based on Hsp90-dependent stress responses, similar to resistance to other antifungals.

Except for fluconazole, which is quite expensive, these medications are hardly accessible in sub-Saharan Africa [107]. In Africa, liposomal amphotericin B is only accessible in Benin, Ethiopia, Zambia, and South Africa, but 5-flucytosine is only accessible in Ghana and Tanzania [104]. The lack of essential medications like 5-flucytosine in sub-Saharan Africa has led clinicians to turn to less effective combinations like fluconazole and amphotericin B for the treatment of cryptococcal meningitis, which improves patient survival by 30% as opposed to 60% with 5-flucytosine and amphotericin B [108]. Only minimal progress has been made despite the availability of these medications in affluent nations; invasive aspergillosis and invasive candidosis still have mortality rates of up to 50% and >50%, respectively [104]. Drug resistance and drug bioavailability problems may be the cause of these unsatisfactory treatment results [104].

The rise of drug-resistant isolates in the clinic is a concerning danger to our limited repertoire of antifungal medications [105]. Drug target modification or overexpression, increased efflux pump activity, or activation of cellular stress response pathways are all common mechanisms of resistance (Figure 1). The increasing prevalence of naturally drug-resistant fungi, such as the newly emerging non-albicans Candida species Candida auris and Candida glabrata, exacerbates this public health hazard [109].

In the case of Cryptococcus and the echinocandins, resistance to antifungal agents can be acquired when the bacteria have single nucleotide polymorphisms (SNPs) in genes encoding protein targets (Fks1, Fks2 for echinocandins, or Cyp51A for azoles), which change the antifungal agents' site of action and reduce or eliminate their effectiveness. In Africa, azole-resistant *Aspergillus species* are becoming a bigger issue [110]. Echinocandin resistance has been documented more recently [18], and azole (fluconazole, voriconazole)-resistant *Candida species* are also prevalent [111]. Echinocandin and azole resistance: Amphotericin B, which is frequently nephrotoxic and has limited bioavailability, is vulnerable to Candida glabrata, making it challenging to treat some infections. A clinical red flag is that while amphotericin B and posaconazole are effective against zygomycetes, no currently approved medication is effective against *Scedosporium species* [104].

Sub-therapeutic dose and the emergence of treatment resistance have been connected to drug abuse and a lack of standardization in generic antifungal drug formulations (Otu et al., 2021b). Purchasing over-the-counter medications without a prescription is widespread in several African nations. Additionally, cross resistance to antifungal medication analogues is being caused by the extensive use of antifungal pesticides in agriculture, which share chemical structures with some antifungal drugs [110]. These negative effects can be avoided by using these pesticides sparingly or by employing different tactics like chemosensitization.

CONCLUSION

The epidemiology of IFDs in sub-Saharan Africa was discussed in this review, with a focus on the well-documented IFDs. The most prevalent IFD in the area, cryptococcosis is a major cause of HIV-related mortality, particularly in high-burden sub-Saharan Africa. Invasive aspergillosis is becoming more frequently documented, although it is still largely misdiagnosed. It is primarily associated with pulmonary tuberculosis and has a similar tendency to affect HIV-positive individuals. In a similar vein, reports of histoplasmosis, which was formerly thought to be non-endemic in sub-Saharan Africa, are growing, especially among PLWH. The burden of PCP has considerably decreased due to increased antiretroviral medication uptake among HIV-positive individuals in the region and worldwide. There have also been reports of other uncommon IFDs, including mucormycosis, talaromycosis, emergomycosis, blastomycosis, and coccidiomycosis. The emergence of resistance to the majority of antifungal medications available in sub-Saharan Africa is noteworthy. The fact that IFDs are far more prevalent than anticipated and significantly increase mortality and morbidity in sub-Saharan Africa was further confirmed by this review. Also, while cryptococcal meningitis, a major cause of death for HIV/AIDS patients in the region, has received significant funding, other invasive fungal infections including invasive aspergillosis and histoplasmosis continue to receive little attention. Clinical research, diagnosis, and treatment of these fungal infections, which significantly increase morbidity and death, require a large expenditure. Important areas of research include diagnostics and therapies, adapted to the low- and middle-income nature of most sub-Saharan African countries.

REFERENCES

1. White, S.K., Schmidt, R.L. and Walker, B.S. (2020). (1→3)-β-D-glucan testing for the detection of invasive fungal infections in immunocompromised or critically ill people. *Cochrane Database Syst. Rev*., 7(7): CD009833.
2. Hall, R.A. and Noverr, M.C. (2017). Fungal interactions with the human host: exploring the spectrum of symbiosis. *Curr. Opin. Microbiol*., 40: 58–64.
3. Boakye-Yiadom, E., Odoom, A., Osman, A., Ntim, O.OK, Kotey, F.C.N., Ocansey, B.K. and Donkor, E.S. (2024). Fungal Infections, Treatment and Antifungal Resistance: The Sub-Saharan African Context. *Ther. Adv. Infect. Dis*., 11, pp. 1–25 DOI: 10.1177/20499361241297525
4. Fisher, M.C., Gurr, S.J., Cuomo, C.A., Blehert, D.S., Jin, H. and Stukenbrock, E.H. (2020). Threats posed by the fungal kingdom to humans, wildlife, and agriculture. *mBio*., 11(3):e00449-20.
5. Rodrigues, M.L. and Nosanchuk, J.D. (2020). Fungal diseases as neglected pathogens: a wake-up call to public health officials. *PLoS Negl. Trop. Dis*., 14(2):e0007964.

6. Global Action Fund for Fungal Infections [GAFFI] (2020). Priority fungal infections, global. action fund fungal infection. Geneva, Switzerland: Global Action Fund for Fungal Infections.
7. Bongomin, F. and Adetona, F.S. (2021). Epidemiology of fungal diseases in Africa: A review of diagnostic drivers. *Curr. Med. Mycol*., 7(1): 63-70. DOI: 10.18502/cmm.7.1.6246
8. Bongomin, F., Kibone, W., Okot, J., Nsenga, L., Olum, R. and Baluku, J.B. (2022b). Fungal diseases in Africa: Epidemiologic, diagnostic and therapeutic advances. *Ther. Adv. Infect. Dis*., 9, 20499361221081440.
9. Firacative, C. (2020). Invasive fungal disease in humans: Are we aware of the real impact? *Mem. Inst. Oswaldo Cruz*, 115, e200430.
10. Kamwiziku, G.K., Makangara, J.C.C., Orefuwa, E. and Denning, D.W. (2021). Serious fungal diseases in Democratic Republic of Congo—Incidence and prevalence estimates. *Mycoses*, 64, 1159–1169.
11. Bongomin, F., Ekeng, B.E., Kibone, W., Nsenga, L., Olum, R., Itam-Eyo, A., Kuate, M.P.N., Pebolo, F.P., Davies, A.A. and Manga, M. (2022a). Invasive Fungal Diseases in Africa: A Critical Literature Review. *J. Fungi*, 8, 1236. https://doi.org/10.3390/jof8121236
12. Dangarembizi, R., Wasserman, S. and Hoving, J.C. (2023). Emerging and re-emerging fungal threats in Africa. *Parasite Immunol*., 45: e12953.
13. Hussain, M., Whitelaw, A. and Parker, A. (2022). A five-year retrospective descriptive study on the clinical characteristics and outcomes of candidaemia at a tertiary hospital in South Africa. *IJID Reg*., 3, 79–83.
14. Lockhart, S.R., Etienne, K.A., Vallabhaneni, S., Farooqi, J., Chowdhary, A., Govender, N.P., Colombo, A.L., Calvo, B., Cuomo, C.A. and Desjardins, C.A. (2017). Simultaneous Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by WholeGenome Sequencing and Epidemiological Analyses. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.*, 64, 134–140.
15. Rhodes, J. and Fisher, M.C. (2019). Global epidemiology of emerging *Candida auris*. *Curr. Opin. Microbiol*., 52, 84–89.
16. Naicker, S.D., Govender, N., Patel, J., Zietsman, I.L., Wadula, J., Coovadia, Y., Kularatne, R., Seetharam, S., Govender, N.P. and TRAC-SA Group. (2016). Comparison of species-level identification and antifungal susceptibility results from diagnostic and reference laboratories for bloodstream Candida surveillance isolates, South Africa, 2009–2010. *Med. Mycol*., 54, 816–824.
17. Parak, A., Stacey, S.L. and Chibabhai, V. (2022). Clinical and laboratory features of patients with *Candida auris* cultures, compared to other Candida, at a South African Hospital. *J. Infect. Dev. Ctries*., 16, 213–221.
18. Adam, R.D., Revathi, G., Okinda, N., Fontaine, M., Shah, J., Kagotho, E., Castanheira, M., Pfaller, M. and Maina, D. (2019). Analysis of *Candida auris* fungemia at a single facility in Kenya. *Int. J. Infect. Dis*., 85: 182–7.
19. Chibabhai, V. (2022). Incidence of candidemia and prevalence of azole-resistant candidemia at a tertiary South African hospital—A retrospective laboratory analysis 2016–2020. *South Afr. J. Infect. Dis*., 37, 326.
20. Shuping, L., Mpembe, R., Mhlanga, M., Naicker, S.D., Maphanga, T.G., Tsotetsi, E., Wadula, J., Velaphi, S., Nakwa, F. and Chibabhai, V. (2021). Epidemiology of Culture-confirmed Candidemia Among Hospitalized Children in South Africa, 2012–2017. *Pediatr. Infect. Dis. J.*, 40, 730–737.
21. Megri, Y., Arastehfar, A., Boekhout, T., Daneshnia, F., Hörtnagl, C., Sartori, B., Hafez, A., Pan, W., Lass-Flörl, C. and Hamrioui, B. (2020). *Candida tropicalis* is the most prevalent yeast species causing candidemia in Algeria: The urgent need for antifungal stewardship and infection control measures. *Antimicrob. Resist. Infect. Control*, 9, 50.
22. Ezenwa, B.N., Oladele, R.O., Akintan, P.E., Fajolu, I.B., Oshun, P.O., Oduyebo, O.O. and Ezeaka, V.C. (2017). Invasive candidiasis in a neonatal intensive care unit in Lagos, Nigeria. *Niger Postgrad. Med. J.*, 24, 150–154.
23. Ramy, N., Hashim, M., Abou Hussein, H., Sawires, H., Gaafar, M. and El Maghraby, A. (2018). Role of Early Onset Neutropenia in Development of Candidemia in Premature Infants. *J. Trop. Pediatr*., 64, 51–59.
24. Bongomin, F., Gago, S., Oladele, R. and Denning, D. (2017). Global and Multi-National Prevalence of Fungal Diseases—Estimate Precision. *J. Fungi*, 3, 57.
25. Ullmann, A.J., Aguado, J.M., Arikan-Akdagli, S., Denning, D.W., Groll, A.H., Lagrou, K., Lass-Flörl, C., Lewis, R.E., Munoz, P. and Verweij, P.E. (2018). Diagnosis and management of Aspergillus diseases: Executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis*., 24 (Suppl. S1), e1–e38.
26. Yerbanga, I.W., Diallo, S.N., Rouamba, T., Denis, O., Rodriguez-Villalobos, H., Montesinos, I. and Bamba, S. (2022). A systematic review of epidemiology, risk factors, diagnosis, antifungal resistance, and management of invasive aspergillosis in Africa. *J. Med. Mycol*., 33, 101328
27. Wasserman, S., Engel, M.E., Griesel, R. and Mendelson, M. (2016). Burden of pneumocystis pneumonia in HIV-infected adults in sub-Saharan Africa: A systematic review and meta-analysis. *BMC Infect. Dis*., 16, 482.
28. Wills, N.K., Lawrence, D.S., Botsile, E., Tenforde, M.W. and Jarvis, J.N. (2021). The prevalence of laboratory-confirmed Pneumocystis jirovecii in HIV-infected adults in Africa: A systematic review and meta-analysis. *Med. Mycol*., 59, 802–812
29. Hviid, C.J., Lund, M., Sørensen, A., Eriksen, S.E., Jespersen, B., Dam, M.Y., Dahlerup, J.F., Benfield, T., Jespersen, S. and Østergaard, L. (2017). Detection of Pneumocystis jirovecii in oral wash from immunosuppressed patients as a diagnostic tool. *PLoS ONE*, 12, e0174012.
30. White, P.L., Price, J.S. and Backx, M. (2019). Pneumocystis jirovecii pneumonia: Epidemiology, clinical manifestation and diagnosis. *Curr. Fungal Infect. Rep*., 13, 260–273.
31. Cillóniz, C., Dominedò, C., Álvarez-Martínez, M.J., Moreno, A., García, F., Torres, A. and Miro, J.M. (2019). Pneumocystis pneumonia in the twenty-first century: HIV-infected versus HIV-uninfected patients. *Expert Rev. Anti-Infect. Ther*., 17, 787–801.
32. Ding, L., Huang, H., Wang, H. and He, H. (2020). Adjunctive corticosteroids may be associated with better outcome for non-HIV Pneumocystis pneumonia with respiratory failure: A systemic review and meta-analysis of observational studies. *Ann. Intensive Care*, 10, 1–15.
33. O'Brien, K.L., Baggett, H.C., Brooks, W.A., Feikin, D.R., Hammitt, L.L., Higdon, M.M., Howie, S.R., Knoll, M.D., Kotloff, K.L. and Levine, O.S. (2019). Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: The PERCH multi-country case-control study. *Lancet*, 394, 757–779.
34. Oladele, R.O., Ayanlowo, O.O., Richardson, M.D. and Denning, D.W. (2018). Histoplasmosis in Africa: An emerging or a neglected disease? *PLoS Negl. Trop. Dis*., 12, e0006046.
35. Kuate, M.P.N., Nyasa, R., Mandengue, C., Tendongfor, N., Bongomin, F. and Denning, D.W. (2021). Screening for acute disseminated histoplasmosis in HIV disease using urinary antigen detection enzyme immunoassay: A pilot study in Cameroon. *J. Microbiol. Methods*, 185, 106226.
36. Ekeng, B.E., Oladele, R.O., Emanghe, U.E., Ochang, E.A. and Mirabeau, T.Y. (2022). Prevalence of Histoplasmosis and Molecular Characterization of Histoplasma species in Patients with Presumptive Pulmonary Tuberculosis in Calabar, Nigeria. *Open Forum Infect. Dis*., 9, ofac368.

37. Oladele, R.O., Osaigbovo, I.I., Akanmu, A.S., Adekanmbi, O.A., Ekeng, B.E., Mohammed, Y., Alex-Wele, M.A., Okolo, M.O., Ayanbeku, S.T. and Unigwe, U.S. (2022). Ascertaining the current prevalence of Histoplasmosis in Nigeria's Advanced HIV disease population. *EID*., 28, 2261–2269.
38. Ekeng, B.E., Edem, K., Amamilo, I., Panos, Z., Denning, D. and Oladele, R.O. (2021). Histoplasmosis in Children; HIV/AIDS Not a Major Driver. *J. Fungi*, 7, 530.
39. MacInnes, R. and Warris, A. (2021). Paediatric Histoplasmosis 2000–2019: A Review of 83 Cases. *J. Fungi*, 7, 448.
40. Mandengue, C.E., Ekeng, B.E. and Oladele, R.O. (2021). Disseminated histoplasmosis; a threat in advanced HIV disease population in sub-Saharan Africa. *J. Adv. Med. Med. Res*., 33, 115–144.
41. Osaigbovo, I.I., Oladele, R.O., Orefuwa, E., Akanbi, O.A. and Ihekweazu, C. (2021). Laboratory Diagnostic Capacity for Fungal Infections in Nigerian Tertiary Hospitals: A Gap Analysis Survey. *West Afr. J. Med*., 38, 1065–1071.
42. Driemeyer, C., Falci, D.R., Oladele, R.O., Bongomin, F., Ocansey, B.K., Govender, N.P., Hoenigl, M., Gangneux, J.P., Lass-Flörl, C. and Cornely, O.A. (2022). The current state of clinical mycology in Africa: A European Confederation of Medical Mycology and International Society for Human and Animal Mycology survey. *Lancet Microbe*., 3, e464–e470.
43. Develoux, M., Amona, F.M. and Hennequin, C. (2021). Histoplasmosis Caused by *Histoplasma capsulatum* var. duboisii: A Comprehensive Review of Cases From 1993 to 2019. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.*, 73, e543–e549.
44. Okolo, M.O., Onyedibe, K.I., Dabe, F., Obishakin, E.F., Envuladu, E.A. and Egah, D.Z. (2021). Cryptococcal Meningitis amomg HIV-Infected and HIV-Uninfected Patients in Jos, North Central Nigeria. *J. Biomed. Res. Clin. Pract*., 4, 1–7.
45. Ocansey, B.K., Otoo, B., Asamoah, I., Ganu, V., Berko, K.P., Oladele, O., Amankwa, E.A., Opoku-Asare, B., Agyei, M. and George, L. (2022). Cryptococcal and Histoplasma Antigen Screening Among People with Human Immunodeficiency Virus in Ghana and Comparative Analysis of OIDx Histoplasma Lateral Flow Assay and IMMY Histoplasma Enzyme Immunoassay. *Open Forum Infect. Dis*., 9, ofac277.
46. Lakoh, S., Rickman, H., Sesay, M., Kenneh, S., Burke, R., Baldeh, M., Jiba, D.F., Tejan, Y.S., Boyle, S. and Koroma, C. (2020). Prevalence and mortality of cryptococcal disease in adults with advanced HIV in an urban tertiary hospital in Sierra Leone: A prospective study. *BMC Infect. Dis*., 20, 141.
47. Oladele, R.O., Akanmu, A.S., Nwosu, A.O., Ogunsola, F.T., Richardson, M.D. and Denning, D.W. (2016). Cryptococcal Antigenemia in Nigerian Patients with Advanced Human Immunodeficiency Virus: Influence of Antiretroviral Therapy Adherence. *Open Forum Infect. Dis.,* 3, ofw055.
48. Rajasingham, R., Smith, R.M., Park, B.J., Jarvis, J.N., Govender, N.P., Chiller, T.M., Denning, D.W., Loyse, A. and Boulware, D.R. (2017). Global burden of disease of HIV-associated cryptococcal meningitis: An updated analysis. *Lancet Infect. Dis*., 17, 873–881.
49. Alemayehu, T., Ayalew, S., Buzayehu, T. and Daka, D. (2020). Magnitude of Cryptococcosis among HIV patients in sub-Saharan Africa countries: A systematic review and meta-analysis. *Afr. Health Sci*., 20, 114–121.
50. Rajasingham, R., Govender, N.P., Jordan, A., Loyse, A., Shroufi, A., Denning, D.W., Meya, D.B., Chiller, T.M. and Boulware, D.R. (2022). The global burden of HIV-associated cryptococcal infection in adults in 2020: A modelling analysis. *Lancet Infect. Dis*., in press.
51. Pfavayi, L.T., Denning, D.W., Baker, S., Sibanda, E.N. and Mutapi, F. (2021). Determining the burden of fungal infections in Zimbabwe. *Sci. Rep*., 11, 13240.
52. Lmimouni, B.E., Hennequin, C., Penney, R.O.S. and Denning, D.W. (2022). Estimated Incidence and Prevalence of Serious Fungal Infections in Morocco. *J. Fungi*, 8, 414.
53. Ezeanolue, E.E., Nwizu, C., Greene, G.S., Amusu, O., Chukwuka, C., Ndembi, N., Smith, R.M., Chiller, T., Pharr, J. and Kozel, T.R. (2016). Geographical Variation in Prevalence of Cryptococcal Antigenemia among HIV-infected Treatment-Naïve Patients in Nigeria: A multicenter cross-sectional study. *J. Acquir. Immune Defic. Syndr*., 73, 117.
54. Chukwuanukwu, R.C., Uchenna, N., Mbagwu, S.I., Chukwuanukwu, T.O. and Charles, O. (2020). Cryptococcus neoformans seropositivity and some haematological parameters in HIV seropositive subjects. *J. Infect. Public Health*, 13, 1042–1046.
55. Ezenabike, C., Ashaka, O.S., Omoare, A.A., Fadeyi, A., Salami, A.K. and Agbede, O.O. (2020). Cryptococcal antigen among HIV1-infected individuals in north-central Nigeria. *Curr. Med. Mycol*., 6, 43–48.
56. Odegbemi, O., Dada-Adegbola, H., Adeoye, I. and Fayemiwo, S.A. (2020). Epidemiology of Cryptococcal antigenemia among HIV infected patients in South-western Nigeria. *Int. J. Infect. Dis*., 101, 387.
57. Greene, G., Desanto, D., Matlapeng, P. and Govender, N. (2019). Cryptococcal Antigen Screening Surveillance Report, South Africa, February 2017–July 2019; NICD Public Health Surveillance Bulletin: Johannesburg, South Africa.
58. Temfack, E., Kouanfack, C., Mossiang, L., Loyse, A., Fonkoua, M.C., Molloy, S., Koulla-Shiro, S., Delaporte, E., Dromer, F. and Harrison, T. (2018). Cryptococcal antigen screening in asymptomatic HIV-infected antiretroviral naive patients in Cameroon and evaluation of the new semi-quantitative Biosynex CryptoPS test. *Front. Microbiol*., 9, 409.
59. Negash, M., Wondmagegn, T. and Tajebe, F. (2020). Opportunistic Cryptococcal Antigenemia in the HAART Era at HIV Epidemic Settings of Northwest Ethiopia. *Can. J. Infect. Dis. Med. Microbiol*., 2020, 5017120.
60. Jemal, M., Deress, T., Belachew, T. and Adem, Y. (2021). Prevalence of Cryptococcal Antigenemia and Associated Factors among HIV/AIDS Patients at Felege-Hiwot Referral Hospital, Bahir Dar, Northwest Ethiopia. Int. J. Microbiol. 2021, 2021, 8839238.
61. Nguefack, S., Taguebue, J., Wandji, Y., Kago, D., Bate, B., Chelo, D. and Ndombo, P.O.K. (2020). Neuromeningeal Cryptococcosis in children: Clinical and prognostic aspects in a Pediatric hospital in Yaoundé-Cameroon. *Pediatr. Oncall J*., 17, 77–81.
62. Ngoy, D.K., Kange, D.M., Kakwaba, S.K., Mutombo, C.T., Takulilwe, A.K., Nsambi, V.M., Ilunga, W.K.J.-M., Ilunga, Y.I., Masangu, M.S. and Mbuyu, G.K.K.H. (2021). Mortalité liée à la Cryptococcose chez les Personnes Vivant avec l 'infection à VIH/SIDA à Lubumbashi. *Rev. L'infirmier Congo*., 5, 56–62.
63. Kalla, G.C.M., Mboumnyemb, J.F., Assob, J.C.N., Mandeng, M.N.E., Noubi, N.K., Assoumou, M.C.O., Mbopi-Keou, F.-X. and Monebenimp, F. (2021). Cryptococcal antigen carriage among HIV infected children aged 6 months to 15 years at Laquintinie Hospital in Douala. *PLoS ONE*, 16, e0253781.s
64. Narayanasamy, S., Dat, V.Q., Thanh, N.T., Ly, V.T., Chan, J.F.-W., Yuen, K.-Y., Ning, C., Liang, H., Li, L. and Chowdhary, A. (2021). A global call for talaromycosis to be recognised as a neglected tropical disease. *Lancet Glob. Health*, 9, e1618–e1622
65. Guiguemde, K.T., Sawadogo, P.M., Zida, A., Cisse, M., Sangare, I. and Bamba, S. (2019). First case report of Talaromyces marneffei infection in HIV-infected patient in the city of Ouagadougou (Burkina Faso). *Med. Mycol. Case Rep*., 26, 10–12.
66. Stemler, J., Hamed, K., Salmanton-García, J., Rezaei-Matehkolaei, A., Gräfe, S.K., Sal, E., Zarrouk, M., Seidel, D., Khedr, R.A. and Ben-Ami, R. (2020). Mucormycosis in the Middle East and North Africa: Analysis of the FungiScope(®) registry and cases from the literature. *Mycoses*, 63, 1060–1068.

67. Pan, J., Tsui, C., Li, M., Xiao, K., de Hoog, G.S., Verweij, P.E., Cao, Y., Lu, H. and Jiang, Y. (2020). First Case of Rhinocerebral Mucormycosis Caused by *Lichtheimia ornata*, with a Review of Lichtheimia Infections. *Mycopathologia*, 185, 555–567.
68. Prakash, H. and Chakrabarti, A. (2019). Global Epidemiology of Mucormycosis. *J. Fungi* 2, 5, 26.
69. Riley, T.T., Muzny, C.A., Swiatlo, E. and Legendre, D.P. (2016). Breaking the Mold: A Review of Mucormycosis and Current Pharmacological Treatment Options. *Ann. Pharmacother*., 50, 747–757.
70. El-Mahallawy, H.A., Khedr, R., Taha, H., Shalaby, L. and Mostafa, A. (2016). Investigation and Management of a Rhizomucor Outbreak in a Pediatric Cancer Hospital in Egypt. *Pediatr. Blood Cancer*, 63, 171–173.
71. Alfishawy, M., Elbendary, A., Younes, A., Negm, A., Hassan, W.S., Osman, S.H., Nassar, M. and Elanany, M.G. (2021). Diabetes mellitus and Coronavirus Disease (Covid-19) Associated Mucormycosis (CAM): A wake-up call from Egypt. *Diabetes Metab. Syndr*., 15, 102195.
72. Alloush, T.K., Mansour, O., Alloush, A.T., Roushdy, T., Hamid, E., El-Shamy, M. and Shokri, H.M. (2022). Rhino-orbito-cerebral mucormycosis during the COVID-19 third wave in 2021: An Egyptian preliminary report from a single tertiary hospital. Neurol. *Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol*., 43, 799–809.
73. Madney, Y., Khedr, R., Al-Mahellawy, H., Adel, N., Taha, H., Zaki, I., Youssef, A., Taha, G., Hassanain, O. and Hafez, H. (2017). "Mucormycosis" the Emerging Global Threat; Overview and Treatment Outcome Among Pediatric Cancer Patients in Egypt. *Blood*, 130, 4830
74. Feki, W., Sellami, S., Charfi, S., Ketata, W. and Msaad, S. (2018). Successful Medical Treatment of Pulmonary Mucormycosis in Diabetic Patients. *J. Pulm. Respir. Med*., 8, 2.
75. El-Hameed, A., Ayman, R., Abdelsalam, N.M., Saleh, A.M.A., Awad, A.M.M. and ElShabrawy, A.M. (2022). COVID-19 associated mucormycosis and diabetes mellitus: An exploratory study. *Microbes Infect. Dis*., 3, 270–278.
76. Shabana, R.R., Eldesouky, M.A. and Elbedewy, H.A. (2022). Exenterate or Not: A Simple Proposed Management Algorithm for Mucormycosis During the Era of COVID-19 in a Tertiary Eye Care Center in Egypt. *Clin. Ophthalmol*., 16, 1933–1940.
77. Ulasi, I., Ijoma, C., Ifebunandu, N., Arodiwe, E., Ijoma, U., Okoye, J., Onu, U., Okwuonu, C., Alhassan, S. and Onodugo, O. (2020). Organ Donation and Transplantation in Sub-Saharan Africa: Opportunities and Challenges. In Organ Donation and Transplantation; Mihaylov, V., Ed.; IntechOpen: Rijeka, Croatia.
78. Kwizera, R., Bongomin, F. and Lukande, R. (2020). Deep fungal infections diagnosed by histology in Uganda: A 70-year retrospective study. *Med. Mycol*., 58, 1044–1052.
79. Khaba, M.C., Nevondo, L.M., Moroatshehla, S.M. and Makhado, N.A. (2021). Disseminated mucormycosis presenting as a renal mass in an human immunodeficiency virus-infected patient: A case report. *S. Afr. J. Infect. Dis*., 36, 202.
80. Schwartz, I.S. and Kauffman, C.A. (2020). Blastomycosis. Semin. *Respir. Crit. Care Med*., 41, 31–41.
81. Salzer, H.J., Burchard, G., Cornely, O.A., Lange, C., Rolling, T., Schmiedel, S., Libman, M., Capone, D., Le, T. and Dalcolmo, M.P. (2018). Diagnosis and Management of Systemic Endemic Mycoses Causing Pulmonary Disease. *Respiration*, 96, 283–301.
82. Abdallah, F.C.B., Bachouch, I., Belloumi, N., Kacem, M., Mlika, M., El Mezni, F. and Fenniche, S. (2020). Pulmonary blastomycosis. *Pan Afr. Med. J*., 36, 220.
83. Bongomin, F. and Fayemiwo, S.A. (2021). Epidemiology of fungal diseases in Africa: A review of diagnostic drivers. *Curr. Med. Mycol*., 7, 63–70
84. Schwartz, I.S., Kenyon, C. and Thompson, G.R. (2016). 3rd. Endemic Mycoses: What's New About Old Diseases? *Curr. Clin. Microbiol. Rep*., 3, 71–80.
85. Maphanga, T.G., Birkhead, M., Muñoz, J.F., Allam, M., Zulu, T.G., Cuomo, C.A., Schwartz, I.S., Ismail, A., Naicker, S.D. and Mpembe, R.S. (2020). Human Blastomycosis in South Africa Caused by *Blastomyces percursus* and *Blastomyces emzantsi* sp. nov., 1967 to 2014. *J. Clin. Microbiol.*, 58, e01661-19.
86. Salem, M.B., Hamouda, M., Mohamed, M., Aloui, S., Letaief, A., Moussa, A., Skhiri, H., Zakahama, A. and Dhia, N.B. (2017). Blastomyces dermatitidis in a Renal Transplant Recipient: A Case Report. *Transpl. Proc*., 49, 1583–1586.
87. Schwartz, I.S., Govender, N.P., Sigler, L., Jiang, Y., Maphanga, T.G., Toplis, B., Botha, A., Dukik, K., Hoving, J.C. and Muñoz, J.F. (2019). Emergomyces: The global rise of new dimorphic fungal pathogens. *PLoS Pathog*., 15, e1007977.
88. Reddy, D.L., Nel, J. and Govender, N.P. (2022). Emergomycosis. *J. Med. Mycol*., 33, 101313.
89. Samaddar, A. and Sharma, A. (2021). Emergomycosis, an emerging systemic mycosis in immunocompromised patients: *Current trends and future prospects. Front. Med*., 8, 670731.
90. Maphanga, T.G., Britz, E., Zulu, T.G., Mpembe, R.S., Naicker, S.D., Schwartz, I.S. and Govender, N.P. (2017). In vitro antifungal susceptibility of yeast and mold phases of isolates of dimorphic fungal pathogen Emergomyces africanus (formerly Emmonsia sp.) from HIV-infected South African patients. J. Clin. Microbiol. 2017, 55, 1812–1820.
91. Schwartz, I.S., McLoud, J.D., Berman, D., Botha, A., Lerm, B., Colebunders, R., Levetin, E. amd Kenyon, C. (2018a). Molecular detection of airborne *Emergomyces africanus,* a thermally dimorphic fungal pathogen, in Cape Town, South Africa. *PLoS Negl. Trop. Dis*., 12, e0006174.
92. Schwartz, I.S., Lerm, B., Hoving, J.C., Kenyon, C., Horsnell, W.G., Basson, W.J., Otieno-Odhiambo, P., Govender, N.P., Colebunders, R. and Botha, A. (2018b). *Emergomyces africanus* in Soil, South Africa. *Emerg. Infect. Dis*., 24, 377–380.
93. Rasamoelina, T., Raharolahy, O., Rakotozandrindrainy, N., Ranaivo, I., Andrianarison, M., Rakotonirina, B., Maubon, D., Rakotomalala, F., Andrianarivelo, M.R. and Andriantsimahavandy, A. (2017). Chromoblastomycosis and sporotrichosis, two endemic but neglected fungal infections in Madagascar. *J. Mycol. Med*., 27, 312–324.
94. Santos, D.W.C.L., Azevedo, C.D.M.P.E.S.D., Vicente, V.A., Queiroz-Telles, F., Rodrigues, A.M., de Hoog, G.S., Denning, D.W. and Colombo, A.L. (2021). The global burden of chromoblastomycosis. *PLOS Negl. Trop. Dis*., 15, e0009611.
95. Abate, D.A., Ayele, M.H. and Mohammed, A.B. (2021). Subcutaneous mycoses in Ethiopia: A retrospective study in a single dermatology center. *Trans. R. Soc. Trop. Med. Hyg*., 115, 1468–1470.
96. Rasamoelina, T., Maubon, D., Andrianarison, M., Ranaivo, I., Sendrasoa, F., Rakotozandrindrainy, N., Rakotomalala, F.A., Bailly, S,; Rakotonirina, B. and Andriantsimahavandy, A. (2020). Endemic Chromoblastomycosis Caused Predominantly by Fonsecaea nubica, Madagascar(1). *Emerg. Infect. Dis*., 26, 1201–1211.
97. Yoo, S.D., Lusiba, J.K., Lukande, R. and Shin, K. (2020). Disseminated Coccidioidomycosis in *Africa. Eur. J. Case Rep. Intern. Med*., 7, 1659.
98. Van Dyke, M.C.C., Thompson, G.R., Galgiani, J.N. and Barker, B.M. (2019). The Rise of Coccidioides: Forces Against the Dust Devil Unleashed. *Front. Immunol*., 10, 2188.
99. Orofino-Costa, R., de Macedo, P.M., Rodrigues, A.M. and Bernardes-Engemann, A.R. (2017). Sporotrichosis: An update on epidemiology, etiopathogenesis, laboratory and clinical therapeutics. *Bras Dermatol*., 92, 606–620.
100. Rasamoelina, T., Maubon, D., Raharolahy, O., Razanakoto, H., Rakotozandrindrainy, N., Rakotomalala, F.A., Bailly, S., Sendrasoa, F., Ranaivo, I. and Andrianarison, M. (2019). Sporotrichosis in the Highlands of Madagascar, 2013-20171. *Emerg. Infect. Dis*., 25, 1893–1902.

101. Gadre, A., Enbiale, W., Andersen, L.K. and Coates, S.J. (2022). The effects of climate change on fungal diseases with cutaneous manifestations: A report from the International Society of Dermatology Climate Change Committee. *J. Clim. Change Health*, 6, 100156.
102. Tshisevhe, V., Skosana, L., Motse, K., Maphosa, T. and Mitton, B. (2021). Disseminated sporotrichosis in a person with human immunodeficiency virus disease. *Access Microbiol*., 3, 000262.
103. Wagner, G., Moertl, D., Eckhardt, A., Sagel, U., Wrba, F., Dam, K. and Willinger, B. (2016). Chronic Paracoccidioidomycosis with adrenal involvement mimicking tuberculosis—A case report from Austria. *Med. Mycol. Case Rep*., 14, 12–16.
104. Ibe, C. and Otu, A.A. (2022). Recent advances and challenges in the early diagnosis and management of invasive fungal infections in Africa. *FEMS Yeast Research*, 22, 1–7 DOI: 10.1093/femsyr/foac048
105. Lee, Y., Robbins, N. and Cowen, L.E. (2023). Molecular mechanisms governing antifungal drug resistance. *npj Antimicrobials & Resistance*, 1:5, https://doi.org/10.1038/s44259-023-00007-2
106. Iyer, K. R., Revie, N. M., Fu, C., Robbins, N. and Cowen, L.E. (2021). Treatment strategies for cryptococcal infection: challenges, advances and future outlook. *Nat. Rev. Microbiol*., 19, 454–466.
107. Kneale, M., Bartholomew, J.S. and Davies, E. (2016). Global access to antifungal therapy and its variable cost. *J. Antimicrob. Chemother*., 71:3599– 606
108. Molloy, S.F., Kanyama, C. and Heyderman, R.S. (2018). Antifungal combinations for treatment of *Cryptococcal meningitis* in Africa. *N. Engl. J. Med*., 378:1004–17.
109. Pfaller, M. A., Diekema, D. J., Turnidge, J. D., Castanheira, M. and Jones, R. N. (2019). Twenty years of the SENTRY antifungal surveillance program: results for Candida species from 1997–2016. *Open. Forum. Infect. Dis*., 6, S79–S94 (2019).
110. Otu, A., Osaigbovo, I. and Orefuwa, E. (2021a). Collaborative one health approaches can mitigate increasing azole-resistant Aspergillus fumigatus in Africa. *Lancet Microbe*., 2:e490–1
111. Govender, N.P., Patel, J. and Magobo, R.E. (2016). Emergence of azole-resistant *Candida parapsilosis* causing bloodstream infection: results from laboratory-based sentinel surveillance in South Africa. *J. Antimicrob. Chemother*., 71:1994–2004.
112. Otu, A., Osifo-Dawodu, E. and Atuhebwe, P. (2021b). Beyond vaccine hesitancy: time for Africa to expand vaccine manufacturing capacity amidst growing COVID-19 vaccine nationalism. *Lancet Microbe*., 2:e347–8.