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Review

Revisiting threats associated with neglected and emerging fungal pathogens in sub-Saharan Africa

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Abstract
Despite the increasing morbidity and mortality associated with fungal diseases in low-income and sub-Saharan Africa countries, it is apparent that most of the fungal pathogens involved have been omitted from the dilated list of neglected and emerging tropical diseases (NETDs). Because most of these pathogens are inextricably linked with other underlying diseases such as tuberculosis and AIDS, the main fungal pathogens causing diseases viz. Pneumocystosis and meningitis are categorized as deadly AIDS-associated opportunistic infections, and they most often coexist with tuberculosis. In addition, other infections like candidiasis, keratitis, histoplasmosis, and mycetoma often cause deforming and debilitating illnesses that affect the working class in rural communities, largely due to underlying comorbidities. Inadequate diagnostic tests prevent easy identification of the burden associated with these diseases making treatment very difficult. Likewise, the rise of resistance to most antifungal medications currently accessible in Africa is still extremely concerning, as observed in other locations. To expatiate on the destructive impact of fungal infections on the socioeconomic and health status of sub-Saharan Africa's skint populace and to improve the menace posed by these pathogens, there is a need to stop trivializing and underestimating fungal pathogens of health importance. This viewpoint is intended to revisit threats associated with neglected, emerging, and re-emerging fungal pathogens (NEFPs) in sub-Saharan Africa. As a result, information needed to prioritize strategies for the diagnosis, prevention, and control of neglected fungal pathogens and emerging superbugs will be presented. Revisiting threats and possible diagnoses associated with NEFPs could serve as a better leverage toward curbing the effects of opportunistic pathogens on individuals living with either an underlying health condition or impaired immunological status in sub-Saharan Africa/ low-income countries.

Article Highlights

1. Structural presentation of deforming and debilitating illnesses associated with NEFPs.
2. Reassessment of important therapeutic antibodies against NEFPs.

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3. Improved diagnostic methods for the diagnosis, prevention, and control of neglected fungal pathogens and emerging superbugs.

Keywords Revisiting abandoned fungal pathogens · Resource-limited population · Sub-Saharan Africa · Deforming and debilitating illnesses · *Candida auris*

1 Introduction

The term "neglected tropical diseases" (NTDs) refers to a class of potentially treatable, incapacitating, and disfiguring chronic illnesses caused by microbial and parasite infections that mostly afflict people in rural regions who are living in abject poverty [1]. These diseases have been left off the expanded list of NTDs despite the significant morbidity and mortality associated with them in sub-Saharan Africa. Important fungal diseases such as pneumocystosis and cryptococcosis manifest as relatively common and fatal AIDS-defining opportunistic infections [1–4]. Because few diagnostic tests are available in sub-Saharan Africa, opportunistic infections like these are frequently detected very late or not at all. The neglected, emerging, and re-emerging fungal pathogens (NEFPs) such as Mycetoma and *Candida auris*, which mostly affect rural adults and have a direct impact on the socioeconomic productivity of rural communities, are misdiagnosed due to a lack of resources and clinical awareness. Endemic fungal diseases such as blastomycosis and histoplasmosis are also under-/misdiagnosed [5].

Sub-Saharan Africans account for the largest percentage of all cases of HIV infection and AIDS-related fatalities [6]. Despite significant efforts, only two-third of people harboring the virus in sub-Saharan Africa have started antiretroviral therapy (ART); the remaining patients will need ART in the future. Because of poor access to treatment, limited healthcare infrastructure, and undetected HIV infection, a significant number of HIV-infected people will not receive ART until their immunity is severely impaired and other opportunistic infections emerge. At this point, fungi are frequently sentinel opportunistic infections that increase the mortality rate of infected hosts [6–8].

Few NEFPs individually cause a disease burden that is significant enough to warrant public health attention and monitoring, but studies have shown that the combined disease burden of NEFPs in sub-Saharan Africa is more than twice that of tuberculosis and almost one-half that of malaria. Together with the three deadliest infectious diseases viz. tuberculosis, malaria, and HIV/AIDS, diseases caused by NEFPs have been heaved into the spotlight as important public health diseases. It has been justified for several reasons to tackle the severe disease burden caused by the NEFPs along with the aforementioned diseases. First, the geographic overlap between the disorders associated with the deadliest infections and NEFPs with the highest prevalence. Second, NEFPs may increase vulnerability and aggravate the symptoms of these deadly diseases [9, 10].

We suggest including the following fungal diseases on the list of NETDs: Candidiasis caused by *Candida auris*, Blastomycosis, Sporotrichosis, Histoplasmosis, Mycetoma, *Pneumocystis jirovecii* pneumonia (PCP), and Cryptococcal meningitis. This study will draw attention to the devastating effects of fungal diseases on the socioeconomic and health conditions of the poorest people in sub-Saharan Africa and raise awareness on the efforts to manage these diseases. In this study, we describe the epidemiology, advanced technological methods, and the disease burden of NEFPs in sub-Saharan Africa in order to prioritize measures for their prevention and management.

2 Overview of often neglected and emerging fungal pathogens (NEFPs)

2.1 Mycetoma

The arid African region, a known area with a high prevalence of mycetoma, stretches between the latitudes of 15° S to 30° N and includes nations such as Senegal, Somalia, Sudan, Nigeria, Niger, Cameroon, Chad, Djibouti, Ethiopia, Kenya, and Mauritania. These areas are homes to mycetoma (severely crippling fungal infection) (Fig. 1). There is no question that this fungus has severe socioeconomic repercussions; it typically affects economically active and healthy people, who are believed to get the infection via traumatic implantation with the infection-causing soil-dwelling organisms. It progresses relentlessly with or without surgical and medical intervention. This can potentially lead to additional complications, such as other infections, and ultimately result in paralysis and deformity. Within the 50 s and 60 s, approximately 2500 cases of

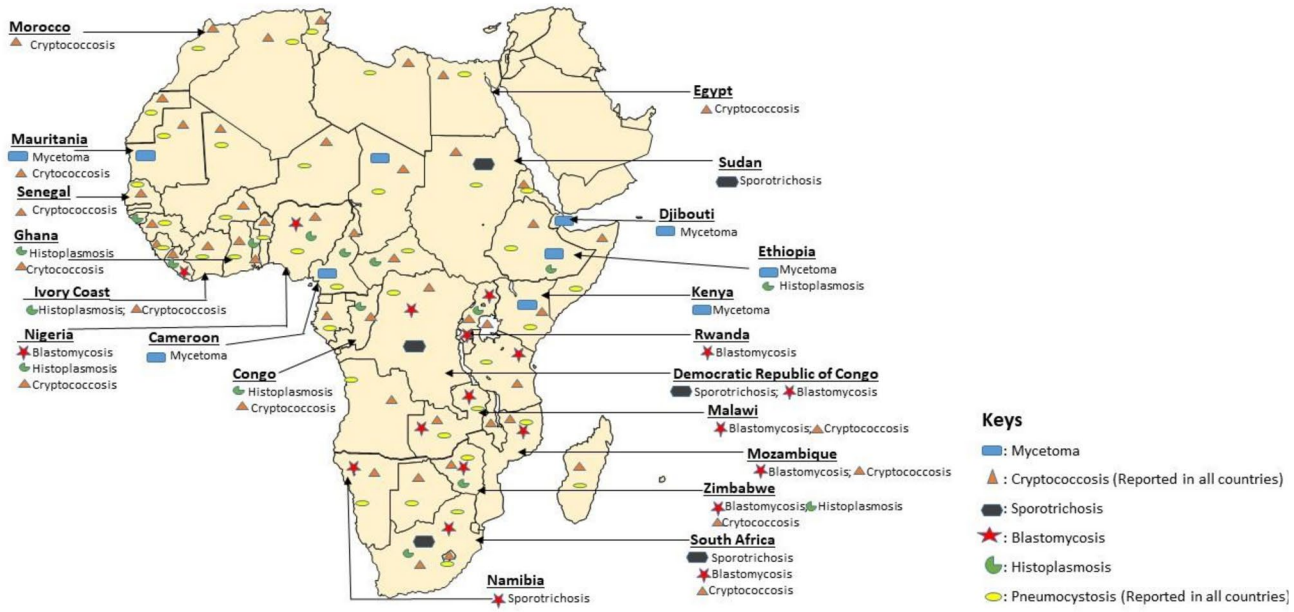

Fig. 1 Countries reporting NEFPs cases in sub-Saharan Africa

mycetoma were diagnosed at various referral hospitals in Sudan [10, 11]. However, no recent update is available on the treatment of most subcutaneous infections. For many reasons, assessing the incidence of mycetoma is challenging. First, although the eumycetoma lesion is characterized by a subcutaneous mass with multiple sinuses draining pus, blood, and black, white, or green fungal grains, other conditions such as foreign body granulomas, soft tissue malignancies, and actinomycetoma may mimic the disease [10].

Second, the diagnosis must be confirmed by a laboratory specialist, which is usually unavailable in endemic regions. Black-grain mycetoma is caused by several different fungi, although *Madurella mycetomatis* has most frequently been linked to this condition. *M. mycetomatis* develops slowly and frequently produces a sterile, melanized mycelium, making it challenging to distinguish phenotypically [12]. Although this fungus may be identified by molecular testing, its use is restricted to environments with limited resources [12, 13]. Radiological, cytological, and histological aspects may also be useful depending on the level of knowledge available. Here is a snippet on the diagnostic growth and biochemical of mycetoma;

2.1.1 Diagnostic growth

Mycetoma typically presents with a triad of painless subcutaneous mass, multiple sinuses, and discharge containing grains.

- *Imaging* Techniques such as ultrasound, MRI, and X-rays help assess the extent of the infection and differentiate mycetoma from other soft tissue infections.
- *Microbiological Culture* Culturing the grains from discharge or tissue biopsies allows for the growth of the causative organism. Fungal cultures are usually grown on Sabouraud dextrose agar, while bacterial cultures require specific media like Lowenstein-Jensen or brain heart infusion agar.
- *Histopathology* Tissue biopsy examination reveals characteristic grains within granulomas, aiding in diagnosis [12].

2.1.2 Biochemicals

- *Enzymatic Activity* Biochemical tests often involve assessing the enzymatic activities of isolates, such as urease production in actinomycetoma [13].

2.1.3 Serological tests

- These detect antibodies against specific mycetoma pathogens, although they are not always reliable due to cross-reactivity.

Third, individuals may be unable to receive medical care or may forgo medical attention completely out of concern for amputation. Simple public health measures like giving away protective clothes and shoes to people who are at high risk might reduce the spread of the infection. Patients with mycetoma may have the best chance of recovery if the disease is detected early and treated appropriately with antifungal medications and surgery. Therefore, it is important to develop quick and accurate diagnostic tools for settings with limited resources as well as quick and efficient treatment regimens. Meanwhile, timely consultation and self-monitoring of injuries related to the infection are also necessary to prevent the entry of opportunistic pathogens.

2.2 Sporotrichosis

Sporothrix schenckii, a saprophytic fungus that thrives on organic material, peat moss, and wood typically causes sporadic lymphocutaneous infection after either contact with an infected animal or traumatic implantation during outdoor activities [1, 14]. Although there is a dearth of ecological information, the fungus is probably indigenous to most tropical and subtropical regions of sub-Saharan Africa [15, 16]. In 1914, South Africa published the first description of the diseases. Inhabitants of Pretoria, South Africa's urban and semi-urban areas, were the victims of 154 cases of lymphocutaneous illness, according to Vismer and Hull [17].

Some South African miners were documented to have been infected in the 1940s by a massive outbreak of sporotrichosis suspected to have been caused by exposure to untreated wood used to support tunnels [18]. In the 1970s, Sudan also had two instances of lymphocutaneous illness documented. During the same period, a case of juvenile sporotrichosis from the Democratic Republic of the Congo was also reported [19, 20]. However, few rare occurrences of disseminated illness have been documented among highly immunosuppressed HIV-infected individuals since the start of the AIDS pandemic in many nations, including Sporotrichosis, which appears to be an opportunistic illness linked with HIV that is infrequently detected (Table 1) [21]. Common diagnostic tests for Sporotrichosis include;

A. *Histopathology* Microscopic examination of stained tissue samples and cells to identify yeast forms of the fungus.
B. *Culture* Growing the fungus from clinical specimens on specialized media. Incubation at 37 °C helps confirm diagnosis by converting mold to yeast phase.
C. *Serological Tests* Detects fungal antigens in body fluids. Identifies antibodies against the fungus, though less commonly used due to cross-reactivity.
D. *Molecular Diagnostics* Amplifies fungal DNA for rapid and accurate identification. Confirms the presence and identity of the fungus.
E. *Direct Microscopy* Rapid preliminary diagnosis by visualizing fungal elements in treated specimens.
F. *Skin Tests* Intradermal injection to detect hypersensitivity, indicating exposure to the fungus (Sporotrichin Test) [18, 21].

Table 1 Reported cases of sporotrichosis infections in sub-Saharan Africa

Country	Causal organism	Number of cases	Clinical presentation	Diagnosis	References
South Africa	*Sporothrix schenckii*	1	Cutaneous, disseminated	Culture, Histopathology, MALDI-TOF	[22]
Madagascar	*Sporothrix schenckii*	63	Cutaneous	Culture, Molecular testing	[16]
Zambia	*Sporothrix schenckii*	1	Cutaneous, Disseminated	Histopathology	[23]
Madagascar	*Sporothrix schenckii*	34	Lymphocutaneous, Cutaneous	PCR, Culture, Microscopy, Histopathology	[16]
Uganda	*Sporothrix schenckii*	1	Lymphocutaneous	Histopathology	[24]
Morocco	*Sporothrix schenckii*	1	Lymphocutaneous	Histopathology	[25]
Tanzania	*Sporothrix schenckii*	1	Lymphocutaneous	Histopathology	[26]
South Africa	*Sporothrix schenckii*	17	Cutaneous	Histopathology, Culture	[27]

2.3 Blastomycosis

In Africa, blastomycosis is rarely identified. Since detection in the 1950s, less than 100 cases have been reported, as documented in the last two decades. South Africa accounted for approximately 25% of the cases [1, 27]. The most obvious differences in the clinical characteristics of blastomycosis in North America and Africa include the involvement of the central nervous system. Moreover, there is a higher prevalence in the bone and distinct morphology of the skin lesions in African patients. The HIV epidemic that has emerged since those earlier case series were published has likely increased the frequency of the disease. This emergence has made blastomycosis more difficult to detect, as it is to some extent an opportunistic infection. A number of interconnected elements complicates the disease associated with blastomycosis. Both radiologically and clinically, blastomycosis commonly mimics pyogranulomatous illnesses and TB [28–30]. Blastomycosis most often affects any part of the bone, complicating spine infection and forming paravertebral abscesses. Pleural involvement may manifest as empyemas, densities, or effusions. It can also present as masses, lobar or segmental consolidation, cavitation, patchy infiltrates, nodules, miliary patterns, or diffuse bronchopneumonia (Table 2). Most times, tuberculosis is frequently the first radiological and clinical diagnosis, which is understandable [31, 32]. Clinicians may thus be reluctant to change or reject this diagnosis. Sometimes, PCP or disseminated histoplasmosis cannot be distinguished from the radiological image. Drug resistance and a lack of laboratory resources for the diagnosis of deep fungal infections and TB-related diseases may reduce the diagnostic options [33].

Studies have revealed at least 12 sub-Saharan African nations and North African nations viz. Morocco, Libya, Algeria, Tunisia, and Egypt have reported cases of blastomycosis [1, 27]. The reports from southern African countries such as Zimbabwe and South Africa predominate; however, this may be due to the availability of diagnostic tools and the location of research rather than the actual prevalence of the disease (Table 2).

2.4 Histoplasmosis

Two *Histoplasma capsulatum* varieties, namely *Histoplasma capsulatum* var. *capsulatum* and var. *duboisii*, causing histoplasmosis are found in sub-Saharan Africa. The most widespread infectious agent in the world, *H. capsulatum* var. *capsulatum*, is linked to severe disseminated illness in people with AIDS and other underlying conditions. Although the sickness induced by the var. *duboisii* strain is not well characterized, it is believed to be virtually exclusively prevalent in Africa and does not have a strong relationship with AIDS [8, 38]. Histoplasmosis cases have been documented in several African nations (Table 3), and the pathogen is believed to be widespread in these countries. Bats and soil disturbance have both been linked to this fungal infection, which are regarded as standard concerns. The spectrum of manifestation ranges from an asymptomatic clinical state to a progressive disseminated form of histoplasmosis (PDH). Because of a strong immunological state and exposure to modest inoculum, immunocompetent individuals often have moderate or asymptomatic, typically pulmonary illness. PDH arising from patients with AIDS or other underlying immunosuppressive diseases may have severe manifestations [4, 39, 40].

Any patient in sub-Saharan Africa who exhibits a fever of unclear etiology, CD4 +T-cell count < 50 cells/L and weight loss should be examined for PDH. The exact burden of the disease is unclear, and due to a dearth of diagnostic tests, it is unquestionably underdiagnosed. Sub-Saharan Africa currently lacks access to diagnostic methods like the urine antigen test, bone marrow biopsy, and culture, which are widely available in developed countries [41, 42]. The diagnostic tests now being created and used in other resource-limited situations must be made available in Sub-Saharan Africa in the near future [51, 52].

2.5 Pneumocystosis (PCP)

The early assumption that PCP, another significant fungal opportunistic illness, is not as common in sub-Saharan Africa as in the advanced world has been negated by recent studies. According to these studies, the prevalence among hospitalized adults and children and HIV-positive individuals is up to 43%, 49%, and 53%, respectively. The false assumption could be a result of factors such as the high prevalence of TB in sub-Saharan Africa, where PCP is frequently misdiagnosed as tuberculosis and the lack of technology and resources for easy diagnosis. Because PCP testing is not frequently performed and empiric treatment is still the norm, there is a likelihood of misdiagnosis [8, 53–57]. In sub-Saharan Africa, studies on the mortality rate of PCP are very low, with reports showing the death rate for PCP ranging from 20 to 27% [58–62]. A low

Table 2 Reported cases of blastomycosis infections in sub-Saharan Africa

Country	Causal organism	Study period	Clinical site	No of cases	Clinical type	Diagnosis	References
Uganda	*B. dermatitidis*	2020	Abdominal wall, Upper limbs, Lower limbs	11	Pulmonary, Cutaneous disease	Histopathology	[24]
Morocco	*B. dermatitidis*	2007	Fore-arm	1	Cutaneous disease	Histopathology	[28]
Nigeria	*B. dermatitidis*	2001	Right Lung	1	Pulmonary	Histopathology	[29]
Tanzania	*B. dermatitidis*	2006	Left upper arm, Left buttock, right forearm, Right hand, Nose, and Lung	1	Pulmonary, Cutaneous disease	Histopathology	[30]
Tunisia	*B. dermatitidis*	2008	Right lung, Right lower limb	1	Pulmonary, Vertebral disease	Radiology, Culture, Histopathology	[31]
Tunisia	*B. dermatitidis*	2006	Right iliac fossa, Left cheek, Right cheek	3	Cutaneous disease	Culture, Histopathology	[32]
Tunisia	*B. dermatitidis*	2017	Right leg	1	Cutaneous disease	Enzyme linked Immunosorbent assay, Histopathology	[33]
Morocco	*B. dermatitidis*	2012	Vertebra and Left lung	1	Pulmonary, Vertebral disease	Histopathology, Radiology	[34]
South Africa	*B. dermatitidis*	2012	Scalp, Face, Neck	1	Cutaneous disease	Culture, Histopathology	[35]
Tunisia	*B. dermatitidis*	2020	Right and left Lungs, Left paravertebral swelling around T10	1	Subcutaneous, Pulmonary disease	Culture, Radiology	[36]
South Africa	*B. persursus, B. emzantsi*	2020	Not specified	20	Cutaneous, Subcutaneous, Pulmonary, Vertebral, Multisystem	PCR, Microscopy, Culture, Histopathology	[37]

Table 3 Reported cases of histoplasmosis infections in sub-Saharan Africa

Country	Number of cases	Clinical sites	Sampled patients	Study population	Diagnosis	References
Uganda	64	Skin	NA	NA	Histopathological analysis	[24]
South Africa	24	Skin	NA	10 females and 14 male	Culture, PCR, and Histopathology	[40]
Democratic Republic of Congo	36	Bones, lymph nodes, Skin	NA	23 females, 13 males	RT-PCR, Im-munohistochemistry, Histopathology	[43]
Togo	17	Ganglion, bones, Skin, mucosa,	NA	6 Females, 11 males,	Microscopy, Culture, Histopathology	[44]
Congo	57	Bones, nodes, lymph, Skin	NA	27 Females, 30 males	Microscopy, Histoplasma antigen assay, Histopathology	[45]
Cameroon	7(13)	Skin, bronchus, Lungs	56	NA	Histopathology	[46]
Cameroon	36(26)	Skin, Lungs	138	101 Females, 37 males	Antigen test using urine sample	[47]
Tanzania	9 (0.9)	NA	970	647 Females, 323 males	Antigen test using urine and serum sample	[48]
Ghana	5 (4.7)	NA	150	109 Females, 41 males	Histopathology and Antigen test using urine	[42]
Nigeria	27 (12.7)	Lungs	213	119 Females, 114 males	PCR and Antigen test using urine	[49]
Nigeria	76 (7.7)	Skin, Lungs	988	611 Females, 377 males	Antigen test using urine	[50]

NA Not Available

prevalence rate < 0.4% was reported in a study conducted in Tanzania, although this result is most likely because of the use of oral-wash specimens, which are subpar for PCP identification (Table 4). Contrary to the results generated during the height of the HIV/AIDS epidemic in Western nations, PCP was the most prevalent opportunistic illness among HIV-infected individuals before ART was widely accessible [63–65]. Given the high prevalence of HIV infection in sub-Saharan Africa, the question arises regarding the true burden of PCP on the continent and what is at stake. The available report provides a rough approximation. For example, a study in Malawi found that less than 12% (75 out of 660) of HIV-infected individuals had PCP [66]. Based on the region's projected HIV prevalence of 22.5 million, it is estimated that approximately 2.5 million adults and children in sub-Saharan Africa have PCP [64]. All HIV-infected individuals who have respiratory symptoms should be suspected of having PCP because it frequently acts as a sentinel opportunistic infection [59]. PCP remains a serious health issue for those who are ignorant of their HIV infection status and have little to no access to care. To replicate the declining status of PCP in developed countries, there is a need to implement an effective public health intervention that would eradicate the sources of PCP infections.

2.6 Cryptococcosis

In several nations in sub-Saharan Africa, *Cryptococcus neoformans* is the most common cause of adult-onset meningitis. In sub-Saharan Africa, cryptococcosis also serves as a sentinel opportunistic infection in people with HIV [3, 73–75]. Although there are variations in the geographic distribution of cases reported in the literature, the inconsistencies are most likely caused by a lack of monitoring resources. Along with a greater prevalence of HIV/AIDS, cryptococcal meningitis is likely to be more common in southern and eastern Africa. With an estimated 750,000 new cases of this AIDS-defining fungal meningitis emerging each year among people with HIV/AIDS, sub-Saharan Africa remains the focal point in the world that is most impacted, as shown in Table 5 [4, 76].

With the aggressive scale-up of ART in southern Africa, cryptococcal meningitis (CM) remains a major infection in AIDs patients. The persistence of CM could be attributed to factors such as late diagnosis of HIV and initiation of ART, immune reconstitution inflammatory syndrome (IRIS), the prevalence of cryptococcal infection, issues with ART adherence and retention, gaps in preventive measures and resource limitations, and the presence of co-infections and comorbidities. Several sources such as ART sites in Malawi and population-based monitoring in South Africa, have reported a similar trend regarding the persistence of CM in AIDS patients. However, the percentage of patients who have not started ART and are experiencing severe immunosuppression remains stable. Patients with no treatment are predisposed to CM [77–80, 82].

In sub-Saharan Africa, it has been estimated that CM causes > 500,000 fatalities per annum compared with > 300,000 deaths from TB. The detection of cryptococcal antigen in blood before the symptoms by adopting a screening method that enables preventive fluconazole therapy and subsequently access to ART offers fresh hope for reducing mortality linked to CM. Meanwhile, asymptomatic treatment becomes more practical with the help of a dipstick test—an affordable, easy lateral flow assay that enhances the detection of cryptococcal antigen [81–85].

2.7 Candidiasis

The first case of *Candida auris* was documented in 2009 after it was isolated from the ear of a patient in Japan. After genomic analysis, the isolate was found to be distinct from the previously identified species but closely related to *C. heveicola, C. ruelliae, C. pseudohaemulonii*, and *C. haemulonii*. Further analysis verifying its ability to assimilate carbon showed an unusual capacity for growth at 42 °C. Subsequently, the author proposed a new species, *C. auris* (Latin name for "ear"), based on these traits [99, 100].

In 2011, *C. auris* was reported in specimens collected from 15 patients in South Korea. As part of a multi-center surveillance investigation of atypical yeasts, ear samples were obtained in 2006 from three hospitals and used to identify the cases. Investigators first classified these isolates as a new species closely related to *C. haemulonii* because the original identification of these isolates occurred before *C. auris* was given a name. After *C. auris* was published from an isolate identified in 2006, the later isolate was identified using an ITS-specific D1/D2 sequencing approach. All studied patients were diagnosed with chronic otitis infection. Based on genomic clustering, researchers proposed that an inter-/intra-hospital transmission of the pathogen had occurred. Afterwards, the first *C. auris* invasive bloodstream infections were reported [101, 102].

A retrospective review of unidentified yeast in South Korea showed that an incidence of *C. auris* reported in 1996 was the oldest occurrence of the pathogen, but the isolate was misdiagnosed and reported as *C. haemulonii*. Two other

Table 4 Pneumocystis pneumonia (PCP) among patients with underlying conditions in sub-Saharan Africa

Country	Years of study	Study population	Diagnosis of PCP	PCP prevalence	Mortality rate	References
Multiple site study including The Gambia, Kenya, Mali, and South Africa	2011–2014	Children with HIV infection from Africa	PCR analyses of bronchial samples	Not indicated	Not indicated	[62]
South Africa	2004–2015	HIV infected patients especially those in ICU	Review of patients records	50%	25.9%	[67]
Mozambique	2006–2007	Children < 5 years with severe pneumonia	PCR analyses of NPA	6.8%	20.8%	[68]
Namibia	2011	≥ 16 with either HIV or TB	PCR and Giemsa analyses of sputum samples	5.3%	Not specified	[69]
Tanzania	2007–2009	Patients negative of AFB	PCR analyses of oral wash	< 0.4%	Not specified	[63]
Ethiopia	2004–2005	AFB negative HIV-infected patients	IFA analyses of BAL and sputum	30%	Not specified	[70]
Malawi	2002–2004	HIV-infected patients	IFA analyses of induced sputum	< 12%	Not specified	[66]
South Africa	2000–2008	HIV-infected patients (post-mortem)	Post-mortem	9%	Not specified	[71]
South Africa	2003	Children in intensive care unit	Review of patients record	< 34%	Not specified	[61]
South Africa	2006–2008	Hospitalized children having hypoxic pneumonia	IFA analyses of BAL and NPA	20%	40%	[72]
South Africa	2000–2001	Hospitalized children with HIV-infection with severe pneumonia	IFA analyses of NPA and IS	< 45%	20%	[58]

PCR polymerase chain reaction, *NPA* nasopharyngeal aspirate, IS induced sputum, *IFA* immunofluorescence assay, *BAL* bronchoalveolar lavage, *AFB* acid-fast bacilli

Table 5 Cryptococcosis among patients with underlying conditions in sub-Saharan Africa

Country	Study population	Period of study	ART status (%)	CD4 counts (Mean/median)	Sample size	Prevalence (%)	References
Cameroon	Hospitalized children with meningitis	2010–2018	NA	29 (10–100)	331	3.60	[86]
Cameroon	HIV infected patients with Signs of meningitis	2009–2011	NA	NA	146	28.08	[87]
Cameroon	HIV infected outpatients	2015–2017	NA	44 (27–75)	187	23.10	[88]
Nigeria	HIV infected patients	2018	NA	NA	290	1.40	[81]
Nigeria	HIV positive patients	2016–2017	81.3	NA	326	11	[83]
Nigeria	HIV infected patients	2014–2017	NA	NA	300	19.67	[89]
Nigeria	HIV infected patients	2016	NA	NA	215	16.70	[90]
Nigeria	HIV-infected Adults	2014–2015	95.3	160 (90–210)	214	8.90	[91]
Nigeria	Hospitalized patients with meningitis	2017–2018	NA	32.5 (8–109)	184	16.80	[92]
Nigeria	HIVpositive/Negative outpatients	2018–2020	NA	NA	342	8.50	[80]
Nigeria	HIV infected patients	2012–2014	NA	74 (6–1264)	432	1.60	[75]
Burkina faso	Patients with meningitis	2002–2010	NA	56 (13–387)	5129	1.80	[93]
Ethiopia	HIV-infected patients	2018–2019	73.5	54 (2–97)	200	4	[94]
Ethiopia	HIV-infected patients	2019	50	NA	140	11.43	[95]
Ethiopia	HIV-infected patients	2017	All patients	434.4	183	7.70	[96]
Ethiopia	HIV-infected patients	2016–2017	52	NA	267	3.40	[97]
South Africa	HIV infected patients	2009–2010	NA	NA	1494	2.10	[98]
DRC	HIV-infected patients	2018	NA	NA	1877	21.80	[85]

NA Not Available

instances in the same country occurred in 2006. Thus, all three patients had hospital-onset infections, and before their initial culture revealed *C. auris*, they had all been in the hospital for at least 12 days. Using ITS-specific genomic sequencing, other isolates misidentified as *Rhodotorula glutinis* and *C. haemulonii* on API 20C and VITEK 2, respectively, were accurately identified as *C. auris*. Two 1-year-olds and a 74-year-old were affected by these instances. Only one child survived the infection. This article was the first to show that *C. auris* could produce serious, sometimes deadly, invasive infections and was not merely limited to the ears as its name may imply [100, 103].

Subsequently, another incidence of *C. auris* bloodstream infections was reported from a university referral hospital in India in 2013. Studies conducted in India revealed four affected institutions: a university hospital, a pediatric center, a hospital critical care unit, and a tertiary care general hospital, all situated in northern and southern India [104–107]. Thereafter, other occurrences were reported in South Africa, Kenya, and Kuwait in 2014 and 2015, respectively. Since the inception of the disease in 2009, *C. auris* has been recorded in at least 50 countries on six continents. *C. auris* is frequently misidentified by commonly used laboratory procedures and clinical laboratories. As such, *C. auris* may exist in other countries but has not yet been found or published. Since the detection of the pathogen in Southern (South Africa) and Eastern (Kenya) parts of Africa in 2014, no progress report has been received on the pathogen making *C. auris* an NEFP (Table 6) [100, 103, 108, 123].

3 Emerging nosocomial fungal infections (ENFI)

Emerging nosocomial fungal infections represent a growing concern in healthcare settings, particularly affecting immunocompromised patients and those undergoing invasive medical procedures. These infections are caused by a variety of fungal pathogens, including *Candida* spp., *Aspergillus* spp., and the more recently recognized multi-drug resistant strains such as *C. auris*. The Centers for Disease Control and Prevention in 2019 released a report on antibiotic resistance threats in the United States, highlighting fungal pathogens as a primary concern [124]. The report identified *Candida auris* as an urgent threat, drug-resistant *Candida* species as a serious threat, and azole-resistant *Aspergillus fumigatus* as a significant threat. The increasing incidence of these infections is attributed to factors such as the widespread use of broad-spectrum antibiotics, immunosuppressive therapies, and the use of indwelling medical devices. Nosocomial fungal infections (NFI) pose significant challenges due to their diagnostic difficulties, resistance to multiple antifungal agents, and high associated morbidity and mortality rates. Effective infection control measures, timely diagnosis, and appropriate antifungal treatment are crucial in managing these infections and preventing their spread within healthcare facilities [125–127].

Significant advancements in understanding fungal pathogenesis have greatly enhanced our knowledge of ENFIs. Key developments include:

Table 6 Reported cases of candidemia infections in sub-Saharan Africa

Country	Causal organism	Number of cases	Diagnosis	References
Tunisia	*C. tropicalis, C. krusei, C. parapsilosis, C. albicans*	4	PCR, Blood culture	[109]
South Africa	*C. krusei C. glabarata, C. auris, C. parapsilosis, C. albicans*	618	Blood culture	[110]
Tunisia	*C. parapsilosis, C. glabrata, C. albicans, C. tropicalis*	130	Blood culture	[111]
Egypt	*C. glabarata,, C. tropicalis, C. parapsilosis, C. albicans*	88	Blood culture	[112]
South Africa	*C. auris*	45	Blood culture	[113]
Nigeria	*C. krusei, C. albicans*, Others	27	Blood culture	[114]
South Africa	Multiple cases (*C. auris* and a non-auris species), *C. krusei, C. tropicalis, C. glabarata, C. auris, C. albicans, C. parapsilosis*	6669	Blood culture	[115]
Kenya	*C. albicans, C. auris,* Other	224	Blood culture	[116]
Algeria	*C. dubliniensis, C. glabarata, C. albicans, C. parapsilosis, C. tropicalis*	66	Blood culture	[117]
South Africa	*C. albicans, C. parapsilosis*	2996	Blood culture	[118]
South Africa	*C. krusei, C. tropicalis, C. albicans, C. glabrata*, and *C. parapsilopsis*	2172	Blood culture	[119]
South Africa	*C. krusei*	48	Blood culture	[120]
South Africa	*C. tropicalis, C. parapsilosis, C. glabrata, C. albicans,* Others	108	Blood culture	[121]
South Africa	*C. auris*	1	Blood culture	[122]

3.1 Molecular mechanisms of pathogenicity

Recent research has provided a deeper understanding of the molecular mechanisms underlying fungal pathogenicity. Key discoveries include the identification of virulence factors such as adhesins, proteases, and toxins that enable fungi to adhere to host tissues, invade tissues, and evade immune responses. For example, the role of the *C. albicans* adhesin Als3 in adherence and invasion has been well-characterized, highlighting its importance in pathogenicity [125].

3.2 Biofilm formation

Advancements in our understanding of fungal biofilm formation have been pivotal in explaining how fungi persist in the host and on medical devices. Biofilms, composed of fungal cells embedded in a protective matrix, contribute to persistent infections and resistance to both immune responses and antifungal treatments. Research has elucidated the genetic and environmental factors that influence biofilm formation, providing targets for novel therapeutic strategies [127].

3.3 Host–pathogen interactions

Recent studies have enhanced our understanding of the interactions between fungal pathogens and the host's immune system. These interactions include how fungi sense and adapt to host environments, such as changes in temperature and pH, and how they evade immune detection. For example, the ability of *C. neoformans* to produce a protective capsule that shields it from immune cells has been a key focus of research [127].

3.4 Genetic and epigenetic regulation

Advances in genomics and epigenomics have revealed how genetic and epigenetic factors regulate fungal virulence. Studies have identified specific genes and regulatory networks involved in fungal pathogenicity, including those related to stress response, metabolism, and cell wall biosynthesis. For instance, the discovery of the role of histone modifications in regulating *C. albicans* virulence has provided new insights into fungal pathogenesis [128].

3.5 Antifungal resistance mechanisms

Understanding the mechanisms of antifungal resistance has been a major area of research. Advances have identified various resistance mechanisms, such as mutations in drug targets, increased efflux of antifungal agents, and biofilm-associated resistance. Research on *C. auris*, for example, has highlighted its resistance to multiple antifungal classes and the need for novel therapeutic approaches [126].

3.6 Environmental and epidemiological factors

Research has also explored how environmental factors and epidemiological trends influence fungal pathogenesis. Studies have examined how changes in hospital practices, such as increased use of broad-spectrum antibiotics and the introduction of new medical devices, contribute to the emergence and spread of ENFIs. Understanding these factors has been crucial for developing effective infection control measures [125].

3.7 Fungal adaptation and evolution

Advances in evolutionary biology have provided insights into how fungi adapt to changing environments and selective pressures, such as antifungal treatments and host immune responses. This includes the study of genomic evolution in response to environmental stresses and the emergence of new pathogenic strains. For example, research on the evolutionary pathways of *Aspergillus fumigatus* has shed light on its adaptation mechanisms and resistance profiles [126].

Patients at risk for emerging nosocomial fungal infections (ENFIs) include those who are immunosuppressed (due to therapies like corticosteroids or conditions such as HIV/AIDS), have severe underlying conditions (like malnutrition

or chronic diseases), use invasive medical devices (such as catheters), or are in intensive care units (ICUs). Additional risk factors include environmental exposures within hospital settings, particularly during construction, and certain demographic factors, such as age and genetic predispositions. Identifying these high-risk patients is crucial for implementing preventive measures and ensuring timely treatment [125, 128].

In the past decade, key advances have been made in understanding the role of the mycobiota—fungal communities within the human body—in emerging nosocomial fungal infections (ENFIs). Research has improved our knowledge of fungal diversity, pathogenesis, and interactions with the host's immune system. Disruptions in the mycobiota due to antimicrobial treatments and the formation of biofilms have been linked to ENFIs. Genomic studies and insights into environmental factors have further clarified how fungal species become pathogenic. Additionally, interactions between the mycobiota and bacterial microbiota have shown how these relationships can impact infection risk. These advances are crucial for developing effective diagnostics, prevention strategies, and treatments for ENFIs [126, 127].

Overtime, fungal diagnostic methods have witnessed a significant improvement, identify druggable targets, and bring new antifungal agents into clinical use. In the past decade, substantial progress has been made in understanding the pathogenesis of fungal infections, the cellular and molecular mechanisms of antifungal immunity, genetic and pharmacologic susceptibility, and the role of endogenous fungal communities (mycobiota) in nosocomial fungal infections. These advances are crucial for guiding research priorities to address the growing threat of nosocomial fungal infections [125, 126, 128].

4 Underestimated problems associated with NEFPs

NEFPs are either neglected, emerging, or re-emerging fungal pathogens of medical importance. Because the pathogens are mainly associated with the impairment of host immunity, they tend to be ignored because of their association with the underlying conditions of their host. For emerging and re-emerging fungal pathogens, most of the infections are misdiagnosed using commonly used laboratory procedures. Likewise, at the time of the inception of NEFP, few antifungal medications were authorized for use in humans at this time [129]. According to Rodrigues et al. [130], the last antifungal agent approved for human consumption was approved in 2002. This situation may be related to an imbalance in the financing and death rates for fungal illnesses. Meanwhile, according to a report by the World Health Organization, cryptococcal meningitis causes < 190 000 fatalities worldwide each year, as opposed to 1.6 million deaths from TB and 429 000 deaths from malaria [131]. However, tuberculosis and malaria are better funded with about 35.5% of the entire expenditure in research and development for infectious illnesses, while cryptococcosis had < 0.5% [132]. Current treatments for fungal illnesses are still ineffective; thus, major funding for focused research is needed to create new therapeutic options [133]. Researchers have developed various antifungal agents that are still under clinical trial. Some of the new substances include; AR-12, BHBM, CD101, E1210/11, F901318, and Ilicicolin H [134–138]. For instance, VT-119 and Nikkomycin Z are some of the new classes of medications, working on various molecular targets and different mechanisms that are quite different from the old medications with approval. These drugs may offer a much-needed supplement to the accessible drugs. Programs that explicitly support mycological research are required to further the development efficient antifungal treatments and, ultimately, lower the death rate from fungal illnesses [131].

5 Revisiting therapeutic antibodies against NEFPs

Invasive fungal infections (IFIs) are difficult to treat and remain a global threat to individuals with underlying diseases. There are few or no effective broad-spectrum antifungal medications, and even well-tolerated medications used as preventatives usually cause resistance. The risk of death from an IFI, especially in immunocompromised patients can be more than 40%, even with the best available therapy. This statistic is far worse for low-income nations because many invasive infections are always lethal without treatment. Meanwhile, the estimates of fungal infection-related mortality worldwide are as high as 1.5 million per year [139–141]. Considerably, comorbidity and mortality in HIV patients are caused by fungal infections. According to modeling studies, proper treatment might, over the course of five years, save the lives of 1.6 million HIV patients [142].

These important fungal pathogens will be the subject of this discussion: Candidiasis, Pneumocystis, Paracoccidioides, and Cryptococcosis. Monoclonal antibodies (mAbs) can be used as checkpoints to regulate the host immune response in addition to antibodies that directly target and inhibit the fungus. This strategy may be very helpful when

dealing with fungal diseases with prolonged infection characterized by a change from the protective response of Th1 or Th17 cells to a non-inflammatory Th2 response. Although it is evident that the therapeutic usage of anti-IL-17 in rheumatoid arthritis worsens fungal infection, it is unknown if activating this pathway in the other direction has any clinically helpful effects [143, 144].

The most prevalent fungal pathogen worldwide, *Candida albicans*, is linked to severe morbidity and death, particularly in people with tuberculosis or HIV infection. A recent study revealed that B cell cultures made from *C. albicans*-infected individuals allowed for the cloning of antibody genes. These antibodies provide defense in a mouse model of disseminated candidiasis by promoting the activities of macrophages [145, 146].

Although less common globally than Pneumocystis or *Cryptococcus*, *Paracoccidioides brasiliensis* is the main contributor to IFIs in Latin America. Glycoprotein 43 (gp70) and gp43 which are the main *P. brasiliensis* antigens have been targeted by monoclonal antibodies (mAbs). In the study using a mouse model of infection, anti-gp43 activity mediated by mAb E3-enhanced phagocytosis of *P. brasiliensis* cells, increased the production of interferon-γ and decreased the burden of fungal infection. In contrast, the fungal colony-forming units were significantly decreased by anti-gp70 mAbs and nearly eliminated granuloma formation in the lungs [147, 148]. Antibodies produced against these cells diminished CD25 + cells, causing less severe tissue inflammation and decreased mortality in susceptible mice. This indicates the capability of mAbs to control fungus infection, either through modification of host responses or incapacitating the fungus cells [147].

Pneumocystis has an estimated incidence of up to 500,000 cases annually. Similar to *Cryptococcus*, *Pneumocystis* is a significant opportunistic infection in patients with impaired immunity [139]. However, *Pneumocystis* spp. are commensals, with several species inhabiting the lungs of numerous animals, in contrast to *Cryptococcus*, which is acquired from the environment. *Pneumocystis* is a desirable target for immune-prophylaxis because of its ability for endogenous infection and acquisition from asymptomatic carriers. To this effect, a number of initiatives are being undertaken to create a *Pneumocystis* vaccine, and passive immunization experiments using mAbs produced to *Pneumocystis* epitopes [149, 150, 151]. The viability of this strategy was demonstrated by the ability to inhibit the spread of *Pneumocystis* pneumonia from infected to susceptible cohoused mice, a mAb that binds the *Pneumocystis* kexin-like protein KEX1. Recent studies in this field are greatly encouraged by emerging evidence of the significance of B cell-mediated immunity against *Pneumocystis* infection [147, 148].

Cryptococcus neoformans primarily causes opportunistic infections in individuals with HIV/AIDS, resulting in a substantial burden of AIDS-related illnesses and fatalities, particularly in sub-Saharan Africa [153]. Despite a recent reduction in infection rates, which are most often attributed to significantly enhanced access to antiretroviral therapy (ART), mortality among those infected has not seen a corresponding decrease. This highlights the inadequacy of antifungal development to keep pace with advancements in antiviral treatment. Initially presenting as a pulmonary disease, *cryptococcosis* subsequently disseminates through the bloodstream to the cerebrospinal fluid and brain, causing meningitis and meningoencephalitis. The added challenge of traversing the blood–brain barrier contributes to the complexity of drug development in addressing this condition [144, 153].

Several mAbs that target the polysaccharide capsule, an important virulence factor and the main host–pathogen interface of *Cryptococcus* infection, have been shown to be effective in combating lethal cryptococcal infections in mice. One of them, mAb 18B7, was examined in a Phase I clinical study and was discovered to result in a moderate decrease in circulating cryptococcal antigen [154, 155]. However, financing challenges for a condition with minimal financial returns have made further research difficult—a dilemma that plagues neglected infectious illnesses in general. Other studies on monoclonal antibodies (mAbs) that target different features of *Cryptococcus*. These include glucosylceramide, melanin, and -glucan. Another target to improve the immune response has been the host CD40 [156–162]. These findings not only highlight the therapeutic potential of mAbs but also demonstrate the broad spectrum of inhibitory effects that mAbs may have on *Cryptococcus* cells. Inhibiting fungal growth, encouraging the release of capsular polysaccharides, preventing the formation of biofilms, increasing opsonization and phagocytosis, and boosting the host's immunological response are only a few of these activities [163–166].

In conclusion, monoclonal antibodies (mAbs) have considerable promise for improving antifungal therapies. They provide several possible targets, have shown promise in animal models, and can suppress fungal pathogens and strengthen the host's immune response. To further combat different fungal diseases, combining mAbs or focusing on panfungal antigens may be useful. A possible strategy is to combine mAbs with already available antifungal medications. It is crucial to recognize that not all mAbs are inhibitory; some may worsen infections. Specificity to certain species and strains may be difficult, and various mAbs may have quite diverse inhibitory mechanisms [144, 152].

6 Fun(gi) omics: a diverse and advanced technological process to unveil NEFPs and the defined mechanisms of antifungal resistance

NEFP have recently risen to prominence as infamous pathogens that may be destructive to humans and animals. The study of fungi's function as potential pathogens remains the focus of most researchers. Given the prevalence of systemic and superficial fungal infections, which cut across the soft tissues and other systems, affect more than 1 billion people worldwide [167, 168]. In fact, NEFPs remain under-recognized. Because of unacceptably high mortality rates, which are most frequently documented in people with immunodeficiency predispositions and are predicted to cause more than 1.6 million fatalities yearly [140], NEFPs that can cause systemic illness in humans are in the limelight. This situation is worsened by the unavailability of vaccines, restricted repertoire of antifungal medicines, coupled with other issues such as the lack of appropriate documentation of the diseases and deficits in developmental and research funding [131, 169–171].

The growing numbers of infectious fungal agents include various disease-causing species, many of which have biological advantages over their hosts. The development of adaptability is hastened by factors including robust dispersion cycles, rapid sexual maturation, and genomic plasticity with horizontal gene transfer, hybridization, and recombination [172]. Additionally, the unnatural dissemination of fungi is caused by the introduction of NEFPs, which is frequently hastened by the effects of human activities, including rising global temperatures and globalized transport. These occurrences have helped expose previously undiscovered or uncommon fungal species and aided in the colonization of previously uninhabited and unsuitable locations [173]. For instance, the colonization of NEFPs associated with infections such as pneumocystosis, cryptococcosis, Candidiasis, mycetoma, histoplasmosis, and blastomycosis, occurring either as an opportunistic or comorbid pathogen in patients with underlying conditions, has created a mysterious and highly sensitive medical mayhem in need of immediate intervention.

In-depth investigations are required to unravel the molecular processes of host vulnerability and fungal pathogenesis to combat the fungal threat to global health and food security, as well as to lessen the future burden on health care systems. Advanced molecular methods have ushered in the "omics" era, giving researchers access to cutting-edge tools for metabolomics, proteomics, transcriptomics, and genome analysis (Fig. 2). A modern viewpoint on comprehending the intricacies of fungal illness, including the mechanisms of virulence, host adaptability, and potential therapeutic targets, is captured by the invention of omics technology when paired with high computing capacity, bioinformatics, and systems biology [174]. Each level of the omics platform offers unique insights into the pathogen under study; for instance, improvements in next-generation sequencing (NGS) reliably detect often misdiagnosed fungal pathogens, such as *Candida haemulonii* and *C. auris* [175]. Meanwhile, a deeper understanding of the interaction between the molecular levels controlling such pathogenesis is also made possible by using multi-omics approaches (i.e. the integration of multiple omics) to study NEFPs. This can quickly reveal the systems-scale architecture of fungal pathogenesis.

The section below narrates the advanced molecular techniques used for diagnosing NEFP infections and identifying associated resistomes. These techniques include first, second, and third-generation analyses, as well as combinations of one or more of these methods, as illustrated in Fig. 2.

6.1 Genomic diagnosis of NEFPs, infections, and associated resistomes

In line with the genome sequencing revolution, new fungal infections have emerged, enabling opportunities to further our understanding of how these diseases have evolved in terms of geographic spread, virulence, and host range. De novo assembly of a genome for a novel species and resequencing using a single reference genome are two current methods for genomic study [176, 177]. Assembling and resequencing can be performed using different techniques, such as Illumina sequencing (viz. short-read sequence technology) and long-read technology, which is advantageous for repetitive genomes (such as Oxford Nanopore and Pacific Biosciences) [178–183]. This development could easily unveil essential knowledge about the genome makeup of rapidly evolving fungus species and identify gene family expansions and gene loss events that define their functional potential for virulence and host infection (Fig. 2). Even in advanced studies, researchers assess community structure, genetic variations, and functional annotation of a specific fungal pathogen, and the other features highlighted above using meta-omics processes, as presented in Fig. 3 [184].

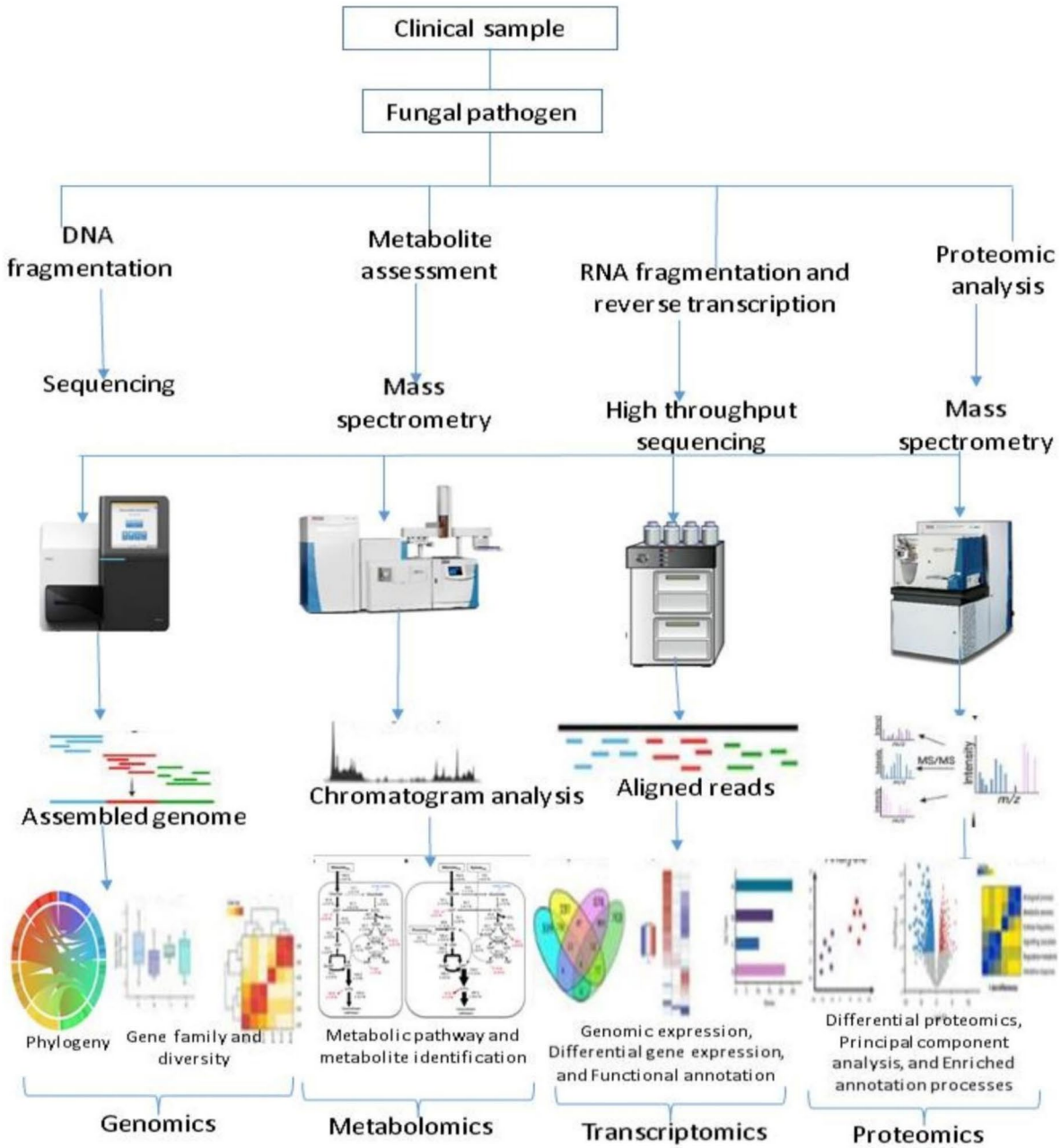

Fig. 2 Outline of the in-depth omics analysis presented in the review. Each process involves the application of advanced genomics, metabolomics, transcriptomics, and proteomics platforms. These molecular methods are presented with important components, possible outcomes, and interpretation

6.1.1 De novo *sequencing for genome assembly*

The accessibility of low-cost, high-throughput whole-genome sequencing for de novo sequencing allows assemblies for a larger range of fungal diseases, including recently developed and seldom reported species [185, 186]. With a high incidence of hospital acquisition, *Candida* spp., for instance, are a common source of fungal infections in patients with impaired immunity [187]. *C. albicans* has traditionally been the most frequent cause of candidemia; nevertheless, a rising number of emerging and neglected species, such as *C. auris*, *Candida glabrata*, and *Candida inconspicua*, are now included in the clinical epidemiology [100, 188]. A comparative genomic analysis was conducted with the adoption of complete-genome assemblies from isolates within each of the four clades as well as closely related species within the *C. haemulonii* clade to fill information gaps about the unusual evolution of *C. auris* [189]. When compared with closely

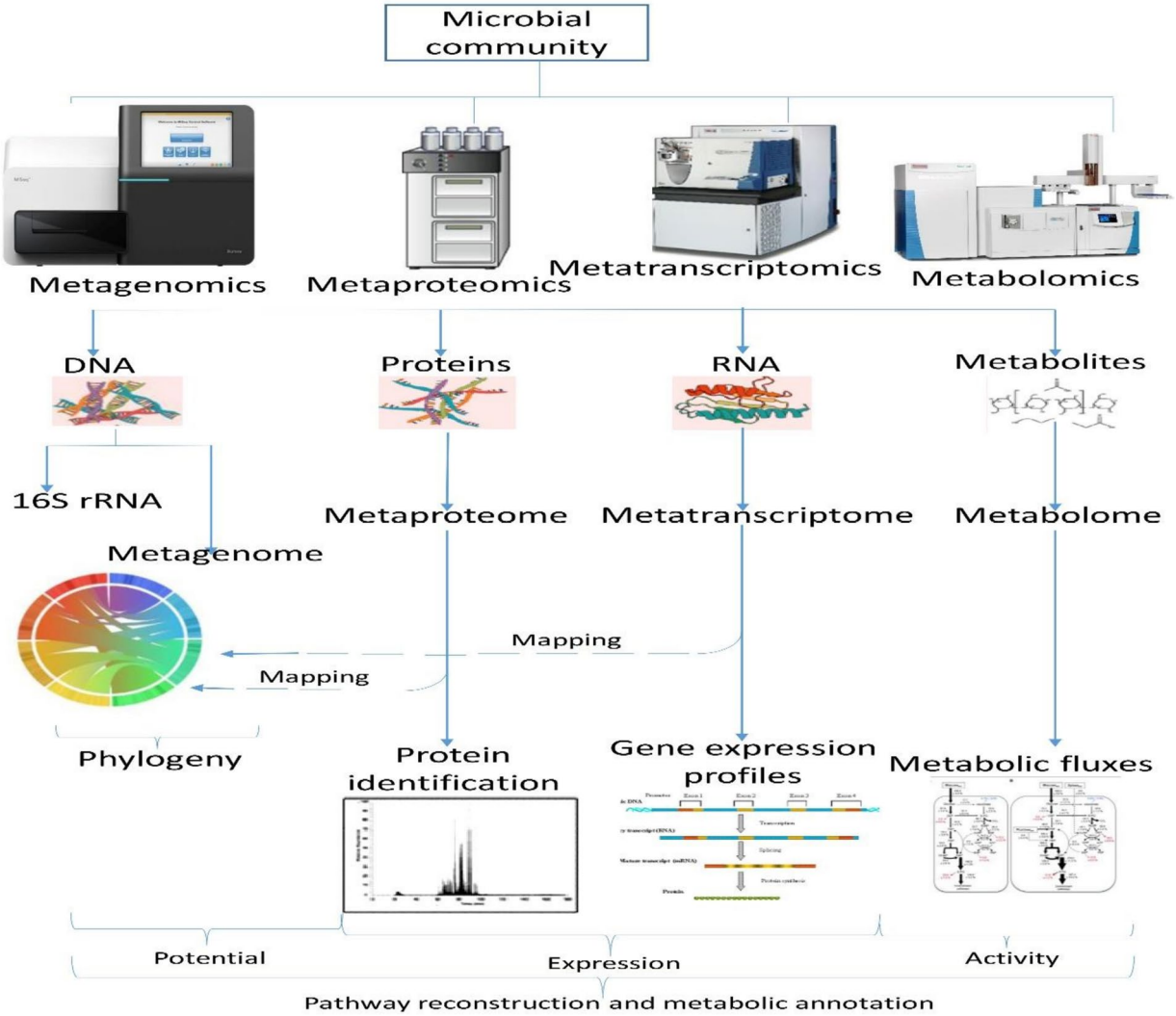

Fig. 3 A Flowchart representing meta-omics approaches

related species, gene family changes and phylogeny in *C. auris* showed gene expansions that contributed to antifungal resistance and virulence exhibited by all *C. auris* clades. These expansions included species-specific increases in secreted lipases, siderophore iron transporters, and oligopeptide transporters. In addition, amplification and alterations of the *ERG11* gene were associated with azole resistance in MDR *C. auris* isolates [190]. A recent study detected several *Erg11* amino acid alterations in clinical isolates from two different *C. auris* clades, which confirmed the hypothesis that *ERG11* point mutations are associated with azole resistance. This assertion offers value as a potential resistant molecular marker for isolates belonging to a particular clade [191].

6.1.2 Identifying gene markers

The comparison of isolate sequences representing populations or clinical outbreaks is encouraged by the use of publicly accessible genome sequences and enhanced reference assemblies to identify conserved gene markers. In medicine, a strong pipeline to develop sequencing methodologies of fungal community members of the lower respiratory tract during infection, based on an NGS-based amplicon of internal transcribe spacer 1 (ITS1), was adopted by McTaggart et al. [192]. The myco-biome of bronchoalveolar lavage (BAL) specimens taken from the lower respiratory tracts with known *Blastomyces* culture status was examined using this barcoding methodology. *Blastomyces* was identified with 91.4% accuracy, and other current fungal taxa were profiled objectively to propose novel gene markers [192]. These findings conveyed the essence of a reliable gene marker technologies that provide a different chance for the accurate,

culture-independent identification of new fungal species that are difficult to identify. In the case of meta-omics for disease diagnosis, a shotgun metagenomics technology enables unbiased sequencing of polymicrobial communities that were sequenced directly from clinical samples, as well as powerful antimicrobial resistance prediction capabilities, virulent gene identification, and high resolution when performing molecular typing [193].

6.1.3 Duplication and expansion of genes

In a way to differentiate protein family expansions and duplications for niche adaptation, a comparative whole-genome study of clinical isolate variance and nonpathogenic isolate variation (environmental) was conducted. For instance, *Fusarium oxysporum* has several species, i.e., variants that include both clinical and soil-borne pathogens [194]. A distantly related pathogenic species causing fusariosis in tomato was tested against two *F. oxysporum* human isolates with no clinical symptoms. A complete-genome shotgun technique was used to sequence an invasive fusariosis strain that can result in opportunistic invasive infections. RNA-Seq was used to confirm the genomic expression and supplement annotation, and the results showed > 99% alignment of transcripts [195]. Four distinct chromosomal lineages specific to an isolate linked to the Fusarium keratitis epidemic in 2005–2006 were detected [196]. These identified chromosomal lineages possess virulence-related genes needed to overcome nutritional immunity, such as cation transporters and metal ions. Likewise, both strains have an alkaline pH-responsive transcription factor (PacC/Rim1p) for virulence, as well as homologs of ceruloplasmin—a substantial copper-carrying protein in the blood. Inference from this study identified two human pathogenic fungal genomes' transposon-rich lineage-specific chromosomes as a focal point for host adaptability and pathogenicity for infecting humans.

6.1.4 Bioinformatics pipeline and databases

Different databases are available for confirming pathogens at the species level, functional annotation, and genomic attributes of isolated microorganisms. Invariably, these databases provide a different method for mapping the genetic diversity of antifungal-resistant and virulent isolates. In order to describe emerging strains within the azole-resistant *Aspergillus fumigatus* meta-population, a public bioinformatics pipeline was recently created [197]. *A. fumigatus* is a widely distributed opportunistic disease with death rates of 40% to 90% in immunocompromised patients. The severity of an infection is caused by the development of drug resistance to azoles because of the widespread use of both azoles for crop protection [198–200].

6.2 Metabolomic diagnosis of NEFPs, infections and associated resistomes

Metabolomics analysis networks of tiny, low-molecular-weight metabolites. Chromatography-based MS is used to culminate all biological processes and represents the whole physiology of genomics, proteomics, and transcriptomics inside an organism or cell. Chromatography-based MS is a crucial analytical technique for creating thorough metabolic profiles, chemical signaling, and underlying regulatory processes, as well as for contrasting the features of metabolic profiles across various species [201–203]. For instance, to assess the multifaceted abilities of secondary metabolites and biosynthetic gene clusters (BGCs) produced by filamentous fungi, especially thermophiles associated with hot springs, are of high interest in pharmaceutical and agricultural research as well as in fungal pathogenesis, including host colonization and interactions with other microbes [204]. Some of the important features involved in genomic analysis of secondary metabolites include (i) assessing the features of effector molecules, (ii) checking antifungal resistance, (iii) regulation of distinct growth stages of microorganisms, and (iv) biomarker discovery.

6.2.1 Assessing the features of effector molecules

An alternative viewpoint to the upstream annotation from the genome, transcriptome, and proteome is offered by analyzing metabolites, or effector chemicals from complex biological systems. An example can be seen in *Candida* spp., particularly *C. albicans*, which uses morphological adaptation via the generation of phenotype-switching metabolites to form genuine hyphae (during the process of dimorphism) as one of their primary virulence strategies. The new superbug *C. auris* can only produce pseudohyphae rather than real hyphae [205, 206]. The activation of hypha-inhibiting metabolites and biofilm-forming compounds like tyrosol was the most notable difference between *C. auris*' metabolic profile and *C. albicans*' under hypha-forming circumstances, as detected using GC–MS analyses [203]. The secretion (metabolites)

produced by *C. auris* represents a profile capable of infecting the host, including secreted fatty acids to hinder the body's normal ability to fight off microbes, a pyrazine derivative implicated in host-microbe colonization, and propanoic acid to inhibit the immune system. In summary, data derived from chromatography-based MS encourage the creation of a tool that can accurately identify changes within complicated cascades involved in both fungal infection and host defense systems for disease diagnosis and the development of antifungal drugs [203].

6.2.2 Antifungal drugs

Using GC–MS and LC–MS (hydrophilic interaction) for comparative metabolomic study of drug-sensitive and -resistant strains of fungi and phospholipid-specific metabolism, respectively, ensures easy assessment of the metabolites involved in resistance to antifungal treatment [207]. Numerous biomarkers for drug stress and resistance were discovered using MS-based techniques, with a tendency toward implications for phospholipid metabolism, sphingolipid, and amino acid. This metabolomic study considerably improved our understanding of the evolution of drug resistance in fungal species and provides a complementary method to other genomics techniques for detecting resistance.

6.2.3 Regulation of distinct growth stages of microorganisms

The distinct pathogenic feature of *Colletotrichum sublineola* (i.e. temporal metabolome variations) were revealed by an alternate method of untargeted LC–MS [202]. As harmful phytopathogen features such as the biotrophic host penetration and necrotrophic nutrient acquisition of *Colletotrichum* spp. pose a severe danger to the security of the world's crops [208]. These features were assessed using principal component analysis (PCA) models and chemometrical characterization of the time-related groups of endo- and exo-metabolite space, which showed dynamic changes in *C. sublineola* metabolism throughout growth. Early adaption during the stationary stage, transition, and biotrophic necrotrophic phases were identified as the important stages of development. *C. sublineolum* showed an upregulation of phytotoxin secretion, irrespective of the carbon source during the necrotrophic and biotrophic stages.

6.2.4 Biomarker discovery

Recently, the properties of the metabolic profiles of several fungus species were compared using GC–MS to uncover biomarkers [209]. The metabolic profile of *C. neoformans*-infected lung epithelial cells under precise GC–MS conditions showed possible disease progression indicators at the early colonization and infection phases [210]. Pantothenic acid—a novel prospective biomarker with the ability to differentiate *C. neoformans* infection, and metabolite features that change across co-incubation durations were found by this temporal study. Pantothenic acid (a well-known quorum sensing chemical in *C. neoformans*) has been linked to the virulence of melanization and titan cell production [211, 212].

6.3 Proteomic diagnosis of NEFPs, infections, and associated resistomes

The outstanding technical upgrade of mass spectrometry (MS)-based proteomics has allowed for a significant breakthrough in fungal-related studies during the past 20 years [213]. A wide picture of gene expression patterns is profiled by proteomics, which includes interaction networks, alternative protein isoforms, post-translational modifications, and the measurement of protein synthesis [214]. High-resolution MS may be used to generate two different proteomic applications: targeted proteomics, which quantifies specific proteins of interest, and top-down proteomics, which introduces fully intact proteins to be quantified and is particularly sensitive to proteoform differentiation. For studies on NEFPs, the unbiased, highly sensitive platform of bottom-up proteomics is used. This method submits the proteins to enzymatic digestion prior to MS analysis [215–218]. To ensure functional and genomic annotation profiling of fungal pathogenesis, involving biomarker development, virulence traits, and host-fungal interactions, these unique MS-based applications are capable of profiling from supernatants to the genomic level.

6.3.1 Immunomodulation

Fungal secreted proteins have recently attracted attention because of their importance in host-fungal interactions and potential vaccine candidates, biomarkers, and therapeutic targets [166]. A bottom-up proteomics and cell surface "trypsin shaving" on *Candida tropicalis*, *C. parapsilosis*, and *C. glabrata* was used [219]. All *Candida* spp. experience protein

moonlighting to mimic an infection. Atypical cell walls proteins such as glyceraldehyde-3-phosphate dehydrogenase, enolase, and pyruvate decarboxylase were found in all isolates. The transfer of cytoplasmic proteins predominantly involved in internal metabolic activities to the extracellular environment for engagement in unrelated, frequently virulence-associated tasks is known as moonlighting. These proteins are a recently found virulence factor for fungal infections. Karkowska-Kuleta et al. [220] conducted a downstream analysis to characterize the extracellular vesicular proteome of non-albicans *Candida* spp. a significant proportion of identified proteins were classified similarly as moonlighting proteins and naturally featured a large overlap with proteins identified on the cell surface. Some moonlighting proteins discovered here play functions in adhesion to human extracellular matrix proteins, including laminin, vitronectin, and fibronectin. In addition, patients with invasive candidiasis have shown a significant abundance of the enolase *Eno1* orthologue as an immune-dominant antigen belonging to *C. albicans* [221, 222]. These immunogenic proteins secreted on the fungal cell wall or in vesicles could be used as possible diagnostics and vaccines for treating candidiasis.

6.3.2 Identifying biomarkers

Intracellular pathogens of alveolar macrophages and *Paracoccidioides* spp. are most often associated with the newly discovered systemic granulomatous illness paracoccidioidomycosis (PCM). In a study by Moreira et al. [223], immune-proteomics was used to explore potential biomarkers that help improve the ability of laboratory species-specific diagnosis. Here, BALB/c mice were immunized with extracellular extracts from different species of the *Paracoccidioides* complex. Immunoprecipitation from this infection was used to identify reactive fungal extracellular antigens. The complex contained 79 exo-antigens, of which two were unique to *Paracoccidioides lutzii*. In addition, 44 epitomes belonging to the *Paracoccidioides* complex and 12 distinctly specific antigenic sequences with potential application in diagnostic and epidemiological surveillance were detected [223].

6.3.3 Defining virulence

The integration of two proteomic platforms for evaluating fungus response to signaling pathway regulation offers a cutting-edge technology for use with novel fungal infections to gain knowledge about potential new therapeutic approaches and the identification of biomarkers. For instance, the infection process of *Cryptococcus gattii* is comparable to that of other *Cryptococcus* spp., but it progresses more aggressively because of its strong proliferative potential, making it difficult to control [224]. Recently, bottom-up proteomics was used to map the survey of protein alterations seen in rat lungs infected with a virulent or avirulent strain of *C. gattii* [225]. In this study, more than 2,000 host proteins were found, of which 77 had differential synthesis. This included upregulation of key glucose transporters and glycolytic enzymes, along with decreased production of proteins involved in the tricarboxylic acid (TCA) cycle. By creating new supply channels for nutrients and metabolites, the host cells' metabolism shifts away from oxidative phosphorylation and toward glycolytic processes of ATP production that help the pathogen replicate energetically. By measuring the levels of lactate and lactate dehydrogenase in *C. gattii*-infected lungs and lung fibroblast cells, it was determined that the glycolytic pathway had been activated and the TCA cycle had been downregulated. The Warburg effect, which causes cancer cells to proliferate, is reflected in the metabolic state of activated glycolysis and lactate build-up [226].

6.4 Transcriptomic diagnosis of NEFPs, infections, and associated resistomes

The first effort to identify the signature of various gene expressions in a cell at a certain time came from transcriptome analysis. Incorporating genomic-scale techniques, such as serial analysis of gene expression (SAGE) and DNA microarrays that assess the abundance of specified transcript pools, has advanced transcript profiling beyond reverse transcriptase quantitative PCR (RT-qPCR) [227–229]. RNA-Seq, a cutting-edge approach that combines high-throughput sequencing and computational bioinformatics to precisely determine relative gene expression levels, is now the method of choice for transcriptome analysis [230]. Understanding the complex regulatory networks involved in infection governed by nutrition availability, environmental factors, and developmental stages is made possible by deep sampling of the transcriptome.

6.4.1 Survival and stress responses

Biological responses to stress frequently control the survival conditions of pathogenic fungi and their receptivity to antimicrobial drugs. Recent research has revealed many molecular mechanisms through which fluconazole resistance

varies in response to acidic niches in *C. glabrata* biofilms. There is a high risk of death in immunocompromised persons exposed to *C. glabrata*, which causes candidemia, a nosocomial blood-stream infection, compared with other non-albicans spp. [231]. Additionally, the capacity of the pathogen to build biofilms because they adhere to host tissues and medical equipment increases its resistance to antifungal agents. More than 4000 upregulated genes were discovered using Illumina sequencing for whole-transcriptomics of *C. glabrata* biofilms treated with acetate and fluconazole [232]. An enrichment analysis showed enhanced gene expression in the processes of DNA replication, ubiquinone production, and ergosterol synthesis. Meanwhile, it was observed that the degree to which fluconazole activates genes associated with ergosterol depends on the carbon supply. An 11.5-Mb transcriptome with more than 5000 genes was built from sequencing sample data in different research using *C. auris* biofilm cells produced throughout a range of time intervals [233]. Many genes encoding efflux pumps and key facilitators (i.e. the superfamily transporters) were found during the mature phases of biofilm production. These temporal studies using transcriptomics offer important new insights into the mechanisms of antifungal resistance, especially studies on Candida biofilms that have demonstrated resistance to the three types of antifungals.

6.4.2 Diverse host–pathogen interface interactions

Comprehending the diverse interactions at the host–pathogen interface is critical to discover new targeted treatment approaches. Assessing expression levels throughout the colonization and spread of an invasive fungus and the host's defensive reaction allows for a better understanding of this method. Host cell induction of molecular feedback during infection provides crucial insights into the virulence, invasion, and pathogenesis of the pathogenic fungi. An example is the use of Illumina RNA-Seq to examine the response of alveolar epithelial cells to *S. aurantiacum* infection. This study revealed more than 3,000 differentially expressed genes [177, 234]. Elevated genes with tendencies toward cell repair, wound healing, inflammation, and cell death were implicated in the infected host alveolar cells. Conspicuously, the mucin-producing gene MUC5 showed greater expression levels during infection, showing a positive reaction of the alveolar epithelial cells toward clearing the infection. The inflammatory NF-$_k$B pathway and the pro-inflammatory cytokines, i.e. interleukin IL-11 and IL-8 were upregulated, as predicted by the gene network analysis. When other filamentous lung pathogens like *A. fumigatus* infect human respiratory epithelial cells, the NF-$_k$B inflammatory pathway promotes the generation of IL-8 [235, 236]. Host profile transcriptomics revealed that lung epithelial cells have the capacity to build physical barriers for defense against inhaled fungal diseases, identify nascent conidia, and initiate a predetermined defensive response.

6.4.3 Determination of the virulence factor

To identify virulence factors in NEFPs, a genome-wide study combined with targeted transcriptomics remains a powerful tool. The respiratory tract is frequently colonized by *Scedosporium* spp., which are common environmental fungi previously ignored in infections in people with cystic fibrosis (CF) [237, 238]. A recent bioinformatics tool explored the use of *A. fumigatus* iron-related protein to uncover orthologues of *S. apiospermum* genes putatively involved in iron metabolism, which was made possible by the sequenced genome of *S. apiospermum* [239]. The assessment of several iron-regulating genes, viz. a vacuolar iron importer gene, reductive iron assimilation (including ferric reductase, multicopper ferroxidase, and iron permease), ferrisiderophore transport, and intra- and extra-cellular siderophore biosynthesis, was validated by targeted transcriptomics using RT-qPCR of conidia growth under iron excess or deprivation conditions [239]. *S. apiospermum* uptake of iron was confirmed using transcriptomics, and this discovery identified a crucial virulence component for infection establishment in the particular iron-rich environment of a CF lung.

6.5 Multi-omic diagnosis of NEFPs, infections, and associated resistomes

The emergence of omics technologies for scientific findings has provided a unique understanding of the structure and organization of biological interactions inside an organism. However, the growing trends of readily accessible and reasonably priced high-throughput technologies bestow the additive power of multilayer data analyses and encourage the integration of several omics platforms to gain a more unified holistic perspective (Fig. 3) [240]. To link the phenotype and genotype, this integrated systems-level method combines single omics data. Advanced bioinformatics methodologies are also needed to fully integrate the biological system in order to evaluate the overwhelming flood of information [241,

242]. Fungal studies are revolutionized by this substantial advancement, which enables unbiased exploration of minor to large biological interactions with predicted accuracy.

Recent omics-based research has provided a clear understanding of the particular biological system under study. In the case of *Rhizopus* and *Mucor* strains, the combination of comparative genomic and RNA-seq dual-organism transcriptomic studies inside human airway epithelial cells showed fungal and host molecular pathways leading to disease [243]. The fungus Mucorales can sometimes infect healthy people, leading to outbreaks of cutaneous necrotizing soft tissue mucormycosis [244, 245]. Mucormycosis is a severe opportunistic invasive human illness. The study of 41 annotated genomes revealed a distinct concentration of CotH-invasins in Mucorales fungus; the presence and gene copy number of CotH is related to species-specific pathogenicity. In RNA-sequencing of *Rhizopus delemar* and *Rhizopus oryzae* interactions with host cells, CotH also showed increased expression. In addition, receptor B signaling associated with platelet growth factor was present in the host transcriptional response to Mucorales, supporting an angio-invasive cause of mucormycosis. Another comprehensive omics research identified a special mannan on the surface of MDR *C. auris* that could strongly associate with human blood mannan-binding lectin proteins and IgG through the cell wall proteome and glycome [246]. Recent studies on the host immunological response to *C. auris* revealed that opsonization via human serum was necessary to trigger the release of cytokines in human mononuclear cells [247]. Mannans were also identified as essential elements for eliciting a larger cytokine response than that produced by *C. albicans* in structural and functional analyses. These results are important because *C. auris* colonization of human skin is extremely challenging to eliminate because it binds firmly and displaces the normal skin microbiota [248].

An in-depth comparison of two clinical *C. auris* isolates with a reference *C. albicans* strain emphasized the originality of combining the metabolome, proteome, and lipidome. Compared to *C. auris* using proteomic profiling with enrichment in the lipid metabolism and proteins in the TCA cycle, quantitative profiling revealed a substantial difference between proteins with greater abundance in the gluconeogenesis and glycolysis pathways in *C. albicans*. The combination of proteomics data and metabolite analysis supported this difference in central carbon metabolism. The route of ergosterol biosynthesis was also cogently delineated by this integration, showing that one of the *C. auris* isolates had larger concentrations of ergosterol itself as well as ergosterol production enzymes [249]. Likewise, the lipid profile revealed that *C. auris* had larger levels of glycerophospholipids and lysophospholipids than *C. albicans*, which was supported by proteome profiling. This method addressed a variety of issues related to NEFPs and related infections, antifungal resistance, and adaptability of this alarming developing pathogen, pointing to the potential for the creation of alternative therapies. Understanding NEFPs through the application of integrated omics technology offers vital system-level data ensuing disease phenotype, relating the virulence-determining factors, and the ability for emergence and endemism [177].

7 Conclusions and future prospects

The study of neglected, emerging, and re-emerging fungal pathogens remains an important area of research and public health concern. These pathogens are frequently overshadowed by other well-known diseases that pose a growing threat to global health. For instance, the emergence of superbugs, such as *Candida auris*, has revealed the potential for widespread outbreaks and high mortality rates. Future possibilities in this field are both difficult and promising.

Meanwhile, the dogma of molecular biology, which outlines the transfer of genetic information from DNA to RNA to protein for creating functional products, simplifies what is actually a complex and interconnected process within biological systems. Omics technology reflects a more dynamic understanding of biological processes and presents a modern approach to mycology research for the management of fungal pathogens. This approach involves tracing the evolution of emerging species, including lineage-specific chromosomes, identifying potential biomarkers, and describing finely-tuned interactions within infection settings. This wealth of information has predictive value for anticipating the emergence of fungal pathogens and also holds promise for precision medicine. These concepts provide an opportunity to mitigate the future consequences of infectious diseases. This perspective promotes swift and accurate diagnosis, followed by efficient targeting and elimination of mycoses without causing harm to the host.

There is a need for increased awareness, surveillance, and research funding to better understand the biology and epidemiology of these fungal pathogens. For early detection and intervention, better diagnostics and monitoring techniques are crucial. Additionally, there is hope for reducing the effects of these pathogens through the development of effective antifungal medications and treatments, including the possible application of monoclonal antibodies. Collaboration among academics, healthcare providers, public health organizations and Government agencies is essential to address the challenging healthcare constraint posed by neglected, emerging, and re-emerging fungal infections. Moving forward,

it is crucial to continue to be cautious, flexible, and aggressive in dealing with these fungal pathogens because they can pose large obstacles in the dynamic world of infectious diseases.

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Author contributions SAA, ROA, and MIB conceived of the study. SAA, EE, AMA and RAAA designed the study. SAA, RAAA, MOB, and SO were involved in the data acquisition and analysis. SAA, IAA, IES, and TTA drafted the manuscript. SAA, RAAA, ROA, and IAA critically reviewed the manuscript. All authors participated in the interpretation and discussion of the results and provided comments. All the authors approved the final version of the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

1. Govender NP, Chiller TM, Poonsamy B, Frean JA. Neglected fungal diseases in sub-Saharan Africa: a call to action. Curr Fungal Infect Rep. 2011;5:224–32.
2. W.H.O. World Health Organization. Neglected Tropical Diseases. http://www.who.int/neglected_diseases/diseases/en/. Accessed Sep 2023.
3. Jarvis JN, Wainwright H, Harrison TS, Rebe K, Meintjes G. Pulmonary cryptococcosis misdiagnosed as smear-negative pulmonary tuberculosis with fatal consequences. Int J Infect Dis. 2010;14:e310–2.
4. Bongomin F, Ekeng BE, Kibone W, et al. Invasive fungal diseases in Africa: a critical literature review. J Fungi. 2022;8(12):1236.
5. Kamwiziku GK, Makangara JCC, Orefuwa E, Denning DW. Serious fungal diseases in Democratic Republic of Congo-Incidence and prevalence estimates. Mycoses. 2021;64(10):1159–69.
6. UNAIDS. Report on the Global AIDS Epidemic. 2008. http://www.unaids.org/en/dataanalysis/epidemiology/. Accessed Sep 2023.
7. UNAIDS. AIDS at 30: Nations at the crossroads. http://www.unaids.org/unaids_resources/aidsat30/aids-at-30.pdf. Accessed Sep 2023.
8. Bongomin F, Kibone W, Okot J, et al. Fungal diseases in Africa: Epidemiologic, diagnostic and therapeutic advances. In: Therapeutic Advances in Infectious Disease. London: SAGE Publications Sage UK; 2022.
9. Chekiri-Talbi M, Denning D. Burden of fungal infections in Algeria. Eur J Clin Microbiol Infect Dis. 2017;36:999–1004.
10. Odukoya O, Ekeng BE, Oladele RO. Fatal disseminated histoplasmosis in a Nigerian woman: a case report. Microb Infectious Dis. 2023;4(1):205–8.
11. Fahal A. Hygiene. Mycetoma: a thorn in the flesh. Trans Royal Soc Trop Med Hyg. 2004;98(1):3–11.
12. Fahal AH. Mycetoma. In: Current progress in medical mycology. Cham: Springer International Publishing; 2017. p. 355–80.
13. Hao X, Cognetti M, Burch-Smith R, Mejia EOS, Mirkin G. Mycetoma: development of diagnosis and treatment. J Fungi. 2022;8(7):743.
14. Orofino-Costa R, Macedo PMd, Rodrigues AM, Bernardes-Engemann AR. Sporotrichosis: an update on epidemiology, etiopathogenesis, laboratory and clinical therapeutics. Anais Bras de Dermatol. 2017;92:606–20.
15. Chakrabarti A, Bonifaz A, Gutierrez-Galhardo MC, Mochizuki T, Li S. Global epidemiology of sporotrichosis. Sabouraudia. 2014;53(1):3–14.
16. Rasamoelina T, Maubon D, Raharolahy O, et al. Sporotrichosis in the Highlands of Madagascar, 2013–2017. Emerg Infect Dis. 2019;25(10):1893.
17. Vismer H, Hull P. Prevalence, epidemiology and geographical distribution of *Sporothrix schenckii* infections in Gauteng South Africa. Mycopathologia. 1997;137:137–43.
18. Quintal D. Sporotrichosis infection on mines of the Witwatersrand. J Cutan Med Surg. 2000;4(1):51–4.
19. Gumaa S. Sporotrichosis in Sudan. Trans Royal Soc Trop Med Hyg. 1978;72(6):637–40.
20. Callens SF, Kitetele F, Lukun P, et al. Pulmonary *Sporothrix schenckii* infection in a HIV positive child. J Trop Pediatr. 2005;52(2):144–6.
21. Gadre A, Enbiale W, Andersen LK, Coates SJ. 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. 2022;6:100156.
22. Tshisevhe V, Skosana L, Motse K, Maphosa T, Mitton B. Disseminated sporotrichosis in a person with human immunodeficiency virus disease. Access Microbiol. 2021;3(9):000262.

23. Patel A, Mudenda V, Lakhi S, Ngalamika O. A 27-year-old severely immunosuppressed female with misleading clinical features of disseminated cutaneous sporotrichosis. Case Rep Dermatol Med. 2016;2016:9403690.
24. Kwizera R, Bongomin F, Lukande R. Deep fungal infections diagnosed by histology in Uganda: a 70-year retrospective study. Med Mycol. 2020;58(8):1044–52.
25. Benchekroun L, Kabbaj L, El Kadi MA, et al. Sporotrichose à *Sporothrix schenckii:* À propos d'une observation. J Mycol Méd. 2008;18(1):43–5.
26. Pönnighaus J, Grosser S, Baum H-P, Mischke D, Kowalzick L. Sporotrichosis as the cause of a leg ulcer. Hautarzt. 2003;54:64–6.
27. Govender NP, Maphanga TG, Zulu TG, et al. An outbreak of lymphocutaneous sporotrichosis among mine-workers in South Africa. PLoS Negl Trop Dis. 2015;9(9): e0004096.
28. Harket A, Oukabli M, Al Bouzidi A, et al. Cutaneous blastomycosis revealing intravascular B-cell lymphoma: a case in Morocco. Méd Trop: Revue du Corps de Santé Colon. 2007;67(3):278–80.
29. Ibrahim T, Edinol S. Pleural effusion from blastomycetes in an adult Nigerian: a case report. Niger Postgrad Med J. 2001;8(3):148–9.
30. Alvarez G, Burns B, Desjardins M, et al. Blastomycosis in a young African man presenting with a pleural effusion. Can Respir J. 2006;13:441–4.
31. Cheikh Rouhou S, Racil H, Ismail O, et al. Pulmonary blastomycosis: a case from Africa. Sci World J. 2008;8:1098–103.
32. Ferchichi L, Mekni A, Bellil K, et al. Three cases of cutaneous blastomycosis. Med Mal Infect. 2006;36(5):285–7.
33. Salem MB, Hamouda M, Mohamed M, et al. Blastomyces dermatitidis in a renal transplant recipient: a case report. Transpl Proc. 2017;49:1583–6.
34. Rais H, Jghaimi F, Baalal H, et al. Blastomycosis in Morocco: imported mycosis. Rev Pneumol Clin. 2011;68(1):45–9.
35. Motswaledi HM, Monyemangene FM, Maloba BR, Nemutavhanani DL. Blastomycosis: a case report and review of the literature. Int J Dermatol. 2012;51(9):1090–3.
36. Abdallah FCB, Bachouch I, Belloumi N, et al. Pulmonary blastomycosis. Pan Afr Med J. 2020;36:220–220.
37. Maphanga TG, Birkhead M, Muñoz JF, et al. Human blastomycosis in South Africa caused by Blastomyces percursus and Blastomyces emzantsi sp. nov., 1967 to 2014. J Clin Microbiol. 2020. https://doi.org/10.1128/jcm.01661-19.
38. Loulergue P, Bastides F, Baudouin V, et al. Literature review and case histories of Histoplasma capsulatum var. duboisii infections in HIV-infected patients. Emerg Infect Dis. 2007;13(11):1647.
39. Antinori S, Magni C, Nebuloni M, et al. Histoplasmosis among human immunodeficiency virus-infected people in Europe: report of 4 cases and review of the literature. Medicine. 2006;85(1):22–36.
40. Khathali LC, Nhlonzi GB, Mwazha A. Histoplasma capsulatum var. duboisii: a KwaZulu-Natal, South Africa public sector perspective. J Cutan Pathol. 2022;49(2):139–46.
41. Inojosa W, Rossi MC, Laurino L, et al. Progressive disseminated histoplasmosis among human immunodeficiency virus-infected patients from West-Africa: report of four imported cases in Italy. Infez Med. 2011;19(1):49–55.
42. Ocansey BK, Otoo B, Asamoah I, et al. 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 infectious diseases. Oxford: Oxford University Press; 2022.
43. Pakasa N, Biber A, Nsiangana S, et al. African histoplasmosis in HIV-negative patients, Kimpese, Democratic Republic of the Congo. Emerg Infect Dis. 2018;24(11):2068.
44. Darré T, Saka B, Mouhari-Touré A, et al. Histoplasmosis by Histoplasma capsulatum var. duboisii observed at the laboratory of pathological anatomy of Lomé in Togo. J Pathogens. 2017;2017:1.
45. Amona FM, Denning DW, Moukassa D, Develoux M, Hennequin C. Histoplasmosis in the Republic of Congo dominated by African histoplasmosis, Histoplasma capsulatum var duboisii. PLoS Negl Trop Dis. 2021;15(5): e0009318.
46. Mandengue CE, Ngandjio A, Atangana PJ. Histoplasmosis in HIV-infected persons, Yaoundé, Cameroon. Emerg Infect Dis. 2015;21(11):2094.
47. Kuate MPN, Nyasa R, Mandengue C, et al. Screening for acute disseminated histoplasmosis in HIV disease using urinary antigen detection enzyme immunoassay: a pilot study in Cameroon. J Microbiol Methods. 2021;185:106226.
48. Lofgren SM, Kirsch EJ, Maro VP, et al. Histoplasmosis among hospitalized febrile patients in northern Tanzania. Trans Royal Soc Trop Med Hyg. 2012;106(8):504–7.
49. Ekeng BE, Oladele RO, Emanghe UE, Ochang EA, Mirabeau TY. Prevalence of histoplasmosis and molecular characterization of histoplasma species in patients with presumptive pulmonary tuberculosis in Calabar, Nigeria. Open forum infectious diseases. Oxford: Oxford University Press; 2022. p. ofac368.
50. Oladele RO, Osaigbovo II, Akanmu AS, et al. Prevalence of histoplasmosis among persons with advanced HIV disease, Nigeria. Emerg Infect Dis. 2022;28(11):2261.
51. Oladele RO, Ayanlowo OO, Richardson MD, Denning DW. Histoplasmosis in Africa: an emerging or a neglected disease? PLoS Negl Trop Dis. 2018;12(1): e0006046.
52. Scheel CM, Samayoa B, Herrera A, et al. Development and evaluation of an enzyme-linked immunosorbent assay to detect *Histoplasma capsulatum* antigenuria in immunocompromised patients. Clin Vaccine Immunol. 2009;16(6):852–8.
53. Mahomed A, Murray J, Klempman S, et al. Pneumocystis carinii pneumonia in HIV infected patients from South Africa. East Afr Med J. 1999;76(2):80–4.
54. Morris A, Lundgren JD, Masur H, et al. Current epidemiology of Pneumocystis pneumonia. Emerg Infect Dis. 2004;10(10):1713.
55. Helweg-Larsen J. S-adenosylmethionine in plasma to test for Pneumocystis carinii pneumonia. Lancet. 2003;361(9365):1237.
56. Aderaye G, Woldeamanuel Y, Asrat D, et al. Evaluation of Toluidine Blue O staining for the diagnosis of *Pneumocystis jiroveci i*n expectorated sputum sample and bronchoalveolar lavage from HIV-infected patients in a tertiary care referral center in Ethiopia. Infect Drug Res. 2008;36:237–43.
57. Huang L, Crothers K. HIV-associated opportunistic pneumonias. Respirology. 2009;14(4):474–85.
58. Madhi SA, Cutland C, Ismail K, et al. Ineffectiveness of trimethoprim-sulfamethoxazole prophylaxis and the importance of bacterial and viral coinfections in African children with *Pneumocystis carinii* pneumonia. Clin Infect Dis. 2002;35(9):1120–6.
59. Zar HJ, Dechaboon A, Hanslo D, et al. Pneumocystis carinii pneumonia in South African children infected with human immunodeficiency virus. Pediatr Infect Dis J. 2000;19(7):603–7.

60. Chakaya J, Bii C, Amukoye E, et al. Pneumocystis carinii pneumonia in HIV/AIDS patients at an urban district hospital in Kenya. East Afr Med J. 2003;80(1):30–5.
61. Morrow BM, Hsaio N-Y, Zampoli M, Whitelaw A, Zar HJ. Pneumocystis pneumonia in South African children with and without human immunodeficiency virus infection in the era of highly active antiretroviral therapy. Pediatr Infect Dis J. 2010;29(6):535–9.
62. O'Brien KL, Baggett HC, Brooks WA, et al. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet. 2019;394(10200):757–79.
63. Jensen L, Jensen AV, Praygod G, et al. Infrequent detection of *Pneumocystis jirovecii* by PCR in oral wash specimens from TB patients with or without HIV and healthy contacts in Tanzania. BMC Infect Dis. 2010;10(1):1–7.
64. Hull MW, Phillips P, Montaner JS. Changing global epidemiology of pulmonary manifestations of HIV/AIDS. Chest. 2008;134(6):1287–98.
65. Kelley CF, Checkley W, Mannino DM, et al. Trends in hospitalizations for AIDS-associated *Pneumocystis jirovecii* pneumonia in the United States (1986 to 2005). Chest. 2009;136(1):190–7.
66. Van Oosterhout JJ, Laufer MK, Perez MA, et al. Pneumocystis pneumonia in HIV-positive adults, Malawi. Emerg Infect Dis. 2007;13(2):325.
67. Chiliza N, Du Toit M, Wasserman S. Outcomes of HIV-associated pneumocystis pneumonia at a South African referral hospital. PLoS ONE. 2018;13(8): e0201733.
68. Lanaspa M, O'Callaghan-Gordo C, Machevo S, et al. High prevalence of Pneumocystis jirovecii pneumonia among Mozambican children< 5 years of age admitted to hospital with clinical severe pneumonia. Clin Microbiol Infect. 2015;21(11):1018.
69. Nowaseb V, Gaeb E, Fraczek MG, Richardson MD, Denning DW. Frequency of *Pneumocystis jirovecii* in sputum from HIV and TB patients in Namibia. J Infect Dev Countries. 2014;8(03):349–57.
70. Aderaye G, Bruchfeld J, Aseffa G, et al. *Pneumocystis jiroveci* pneumonia and other pulmonary infections in TB smear-negative HIV-positive patients with atypical chest X-ray in Ethiopia. Scand J Infect Dis. 2007;39(11–12):1045–53.
71. Garcia-Jardon M, Bhat VG, Blanco-Blanco E, Stepian A. Postmortem findings in HIV/AIDS patients in a tertiary care hospital in rural South Africa. Trop Doct. 2010;40(2):81–4.
72. Rabie H, de Boer A, van den Bos S, et al. Children with human immunodeficiency virus infection admitted to a paediatric intensive care unit in South Africa. J Trop Pediatr. 2007;53(4):270–3.
73. Hakim JG, Gangaidzo IT, Heyderman RS, et al. Impact of HIV infection on meningitis in Harare, Zimbabwe: a prospective study of 406 predominantly adult patients. AIDS. 2000;14(10):1401–7.
74. Bogaerts J, Rouvroy D, Taelman H, et al. AIDS-associated cryptococcal meningitis in Rwanda (1983–1992): epidemiologic and diagnostic features. J Infect. 1999;39(1):32–7.
75. Balogun TM, Okokon M, Dasola F, et al. Cryptococcal antigenaemia among treatment-naïve Adult HIV-infected Nigerian patients. World J AIDS. 2016;6(01):1–7.
76. Park BJ, Wannemuehler KA, Marston BJ, et al. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS. 2009;23(4):525–30.
77. Makombe SD, Nkhata A, Schouten EJ, Kamoto K, Harries AD. Burden of cryptococcal meningitis in Malawi. Trop Doct. 2009;39(1):32–4.
78. N.I.C.D. National Institute for Communicable Diseases, a division of the National Health Laboratory Service. GERMS-SA Annual Report, 2010. http://www.nicd.ac.za. Accessed Sep 2023.
79. Jarvis JN, Boulle A, Loyse A, et al. High ongoing burden of cryptococcal disease in Africa despite antiretroviral roll out. AIDS. 2009;23(9):1182.
80. Odegbemi O, Dada-Adegbola H, Adeoye I, Fayemiwo SA. Epidemiology of Cryptococcal antigenemia among HIV infected patients in South-western Nigeria. Int J Infect Dis. 2020;101:387.
81. Chukwuanukwu RC, Uchenna N, Mbagwu SI, Chukwuanukwu TO, Charles O. *Cryptococcus neoformans* seropositivity and some haematological parameters in HIV seropositive subjects. J Infect Pub Health. 2020;13(7):1042–6.
82. Jarvis JN, Lawn SD, Wood R, Harrison TS. Cryptococcal antigen screening for patients initiating antiretroviral therapy: time for action. Clin Infect Dis. 2010;51(12):1463–5.
83. Mohammed Y, Olayinka AT, Giwa FJ, Abubakar AA. Prevalence and factors associated with cryptococcosis among human immunodeficiency virus-infected patients of a tertiary hospital in Northwestern Nigeria. Ann Trop Pathol. 2019;10(1):52.
84. Jarvis JN, Percival A, Bauman S, et al. Evaluation of a novel point-of-care cryptococcal antigen test on serum, plasma, and urine from patients with HIV-associated Cryptococcal meningitis. Clin Infect Dis. 2011;53(10):1019–23.
85. Ngoy DK, Kange DM, Kakwaba SK, et al. Mortalité liée à la Cryptococcose chez les personnes Vivant avec l'infection à VIH/SIDA à Lubumbashi. Rev L'infirmier Congo. 2021;5:56–62.
86. Nguefack S, Taguebue J, Wandji Y, et al. Neuromeningeal Cryptococcosis in children: clinical and prognostic aspects in a pediatric hospital in Yaoundé-Cameroon. Pediatr Oncall J. 2020;17(3):77–81.
87. Ngouana TK, Dongtsa J, Kouanfack C, et al. Cryptoccocal meningitis in Yaoundé (Cameroon) HIV infected patients: diagnosis, frequency and *Cryptococcus neoformans* isolates susceptibility study to fluconazole. J Mycol Med. 2015;25(1):11–6.
88. Temfack E, Kouanfack C, Mossiang L, et al. Cryptococcal antigen screening in asymptomatic HIV-infected antiretroviral naïve patients in Cameroon and evaluation of the new semi-quantitative Biosynex CryptoPS test. Front Microbiol. 2018;9:409.
89. Ezenabike C, Ashaka OS, Omoare AA, et al. Cryptococcal antigen among HIV1-infected individuals in north-central Nigeria. Curr Med Mycol. 2020;6(2):43.
90. Goni B, Kida I, Saidu I, et al. *Cryptococcal neorformans* antigenemia among HIV-Infected Patients in North Eastern Nigeria. Transm Dis Immun. 2017;1(1):1–8.
91. Oladele RO, Akanmu AS, Nwosu AO, et al. Cryptococcal antigenemia in Nigerian patients with advanced human immunodeficiency virus: influence of antiretroviral therapy adherence. Open forum infectious diseases. Oxford: Oxford University Press; 2016. p. ofw055.
92. Okolo M, Onyedibe K, Dabe F, et al. Cryptococcal Meningitis amomg HIV-Infected and HIV-Uninfected Patients in Jos, North Central Nigeria. J BioMed Res Clin Pract. 2021;4(2):1–7.
93. Bamba S, Zida A, Sangaré I, et al. Burden of severe fungal infections in Burkina Faso. J Fungi. 2018;4(1):35.
94. Negash M, Wondmagegn T, Tajebe F. Opportunistic cryptococcal antigenemia in the HAART era at HIV epidemic settings of northwest Ethiopia. Can J Infect Dis Med Microbiol. 2020;2020:5017120.

95. Jemal M, Deress T, Belachew T, Adem Y. 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.
96. Geda N, Beyene T, Dabsu R, Mengist HM. Prevalence of Cryptococcal antigenemia and associated factors among HIV/AIDS patients on second-line antiretroviral therapy at two hospitals in Western Oromia, Ethiopia. PLoS ONE. 2019;14(12): e0225691.
97. Hailu K, Niguse S, Hagos K, Abdulkader M. Cryptococcal antigenemia and associated risk factors among ART-naïve and ART-experienced HIV-infected peoples at selected health institutions of Mekelle, Northern Ethiopia. Microbiologyopen. 2019;8(6): e00746.
98. Govender N, Roy M, Mendes J, et al. Evaluation of screening and treatment of cryptococcal antigenaemia among HIV-infected persons in Soweto South Africa. HIV Med. 2015;16(8):468–76.
99. Satoh K, Makimura K, Hasumi Y, et al. *Candida auris* sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital. Microbiol Immunol. 2009;53(1):41–4.
100. Forsberg K, Woodworth K, Walters M, et al. *Candida auris*: The recent emergence of a multidrug-resistant fungal pathogen. Med Mycol. 2019;57(1):1–12.
101. Oh BJ, Shin JH, Kim M-N, et al. Biofilm formation and genotyping of *Candida haemulonii*, *Candida pseudohaemulonii*, and a proposed new species (*Candida auris*) isolates from Korea. Med Mycol. 2011;49(1):98–102.
102. Schelenz S, Hagen F, Rhodes JL, et al. First hospital outbreak of the globally emerging *Candida auris* in a European hospital. Antimicrob Res Infect Control. 2016;5(1):1–7.
103. Lee WG, Shin JH, Uh Y, et al. First three reported cases of nosocomial fungemia caused by *Candida auris*. J Clin Microbiol. 2011;49(9):3139–42.
104. Xess I, et al. Epidemiology of candidemia in a tertiary care centre of north India: 5-year study. Infect Immun. 2007;35:256–9.
105. Chowdhary AC, et al. New clonal strain of *Candida auris,* Delhi India. Emerg Infect Dis. 2013;19:1670–3.
106. Chowdhary A, et al. Multidrug-resistant endemic clonal strain of *Candida auris* in India. Eur J Clin Microbiol Infect Dis. 2014;33:919–26.
107. Sarma S, et al. Candidemia caused by amphotericin B and fluconazole resistant *Candida auris*. Ind J Med Microbiol. 2013;31(1):90.
108. Calvo B, Melo AS, Perozo-Mena A, et al. First report of *Candida auris* in America: clinical and microbiological aspects of 18 episodes of candidemia. J Infect. 2016;73(4):369–74.
109. Saghrouni F, Nouri S, Gheith S, Fathallah A, Sboui H. Double fungemia. Report of four Tunisian cases. J Mycol Med. 2012;22(2):192–6.
110. Chibabhai V. 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. 2022;37(1):326.
111. Sellami A, Sellami H, Néji S, et al. Antifungal susceptibility of bloodstream Candida isolates in Sfax hospital: Tunisia. Mycopathologia. 2011;171:417–22.
112. Hegazi M, Abdelkader A, Zaki M, El-Deek B. Characteristics and risk factors of candidemia in pediatric intensive care unit of a tertiary care children's hospital in Egypt. J Infect Dev Countries. 2014;8(05):624–34.
113. Parak A, Stacey SL, Chibabhai V. Clinical and laboratory features of patients with *Candida auris* cultures, compared to other Candida, at a South African Hospital. J Infect Dev Countries. 2022;16(01):213–21.
114. Ezenwa BN, Oladele RO, Akintan PE, et al. Invasive candidiasis in a neonatal intensive care unit in Lagos Nigeria. Niger Postgrad Med J. 2017;24(3):150–4.
115. Van Schalkwyk E, Iyaloo S, Naicker SD, et al. Large outbreaks of fungal and bacterial bloodstream infections in a neonatal unit, South Africa, 2012–2016. Emerg Infect Dis. 2018;24(7):1204.
116. Adam RD, Revathi G, Okinda N, et al. Analysis of *Candida auris* fungemia at a single facility in Kenya. Int J Infect Dis. 2019;85:182–7.
117. Megri Y, Arastehfar A, Boekhout T, et al. Candida tropicalis is the most prevalent yeast species causing candidemia in Algeria: the urgent need for antifungal stewardship and infection control measures. Antimicrob Res Infect Control. 2020;9:1–10.
118. Shuping L, Mpembe R, Mhlanga M, et al. Epidemiology of culture-confirmed candidemia among hospitalized children in South Africa, 2012–2017. Pediatr Infect Dis J. 2021;40(8):730–7.
119. Naicker SD, Govender N, Patel J, et al. Comparison of species-level identification and antifungal susceptibility results from diagnostic and reference laboratories for bloodstream Candida surveillance isolates, South Africa, 2009–2010. Sabouraudia. 2016;54(8):816–24.
120. Van Schalkwyk E, Mpembe RS, Thomas J, et al. Epidemiologic shift in candidemia driven by *Candida auris,* South Africa, 2016–2017. Emerg Infect Dis. 2019;25(9):1698.
121. Hussain M, Whitelaw A, Parker A. A five-year retrospective descriptive study on the clinical characteristics and outcomes of candidaemia at a tertiary hospital in South Africa. IJID Regions. 2022;3:79–83.
122. Lockhart SR, Etienne KA, Vallabhaneni S, et al. Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis. 2017;64(2):134–40.
123. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Focus on: Candida auris. Toronto, ON: King's Printer for Ontario. 2023. https://www.publichealthontario.ca/
124. Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States. Atlanta: CDC; 2019.
125. Lionakis MS, Hohl TM. Call to action: how to tackle emerging nosocomial fungal infections. Cell Host Microbe. 2020;27(6):859–62.
126. William A, et al. Prevalence of Candidemia with susceptibility pattern in a tertiary care hospital in North India. Evid Based Med Healthc. 2021;8(16):1041–6.
127. Yue H, et al. Filamentation in Candida auris, an emerging fungal pathogen of humans: passage through the mammalian body induces a heritable phenotypic switch. Emerg Microbes Infect. 2018;7(1):1–13.
128. Lionakis MS, Levitz SM. Host control of fungal infections: lessons from basic studies and human cohorts. Annu Rev Immunol. 2018;36(1):157–91.
129. Pianalto KM, Alspaugh JA. New horizons in antifungal therapy. J Fungi. 2016;2(4):26.
130. Rodrigues ML. Funding and innovation in diseases of neglected populations: the paradox of cryptococcal meningitis. PLoS Negl Trop Dis. 2016;10(3): e0004429.
131. Almeida F, Rodrigues ML, Coelho C. The still underestimated problem of fungal diseases worldwide. Front Microbiol. 2019;10:214.
132. Moran M, Chapman N, Abela-Oversteegen L, et al. Neglected disease research and development: the Ebola effect. Sydney: Policy Cures; 2015.

133. Coelho C, Casadevall A. Cryptococcal therapies and drug targets: the old, the new and the promising. Cell Microbiol. 2016;18(6):792–9.
134. Mor V, Rella A, Farnoud AM, et al. Identification of a new class of antifungals targeting the synthesis of fungal sphingolipids. MBio. 2015. https://doi.org/10.1128/mbio.00647-15.
135. Zhao Y, Perez WB, Jiménez-Ortigosa C, et al. CD101: a novel long-acting echinocandin. Cell Microbiol. 2016;18(9):1308–16.
136. Pfaller MA, Duncanson F, Messer SA, et al. In vitro activity of a novel broad-spectrum antifungal, E1210, tested against *Aspergillus* spp. determined by CLSI and EUCAST broth microdilution methods. Antimicrob Agents Chemother. 2011;55(11):5155–8.
137. Wiederhold NP, Law D, Birch M. Dihydroorotate dehydrogenase inhibitor F901318 has potent in vitro activity against *Scedosporium* species and *Lomentospora prolificans*. J Antimicrob Chemother. 2017;72(7):1977–80.
138. Singh SB, Liu W, Li X, et al. Antifungal spectrum, in vivo efficacy, and structure–activity relationship of ilicicolin H. ACS Med Chem Lett. 2012;3(10):814–7.
139. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases—estimate precision. J Fungi. 2017;3(4):57.
140. Brown GD, Denning DW, Gow NA, et al. Hidden killers: human fungal infections. Sci Transl Med. 2012;4(165):16513–16513.
141. Armstrong-James D, Meintjes G, Brown GD. A neglected epidemic: fungal infections in HIV/AIDS. Trends Microbiol. 2014;22(3):120–7.
142. Denning DW. Minimizing fungal disease deaths will allow the UNAIDS target of reducing annual AIDS deaths below 500 000 by 2020 to be realized. Philos Trans Royal Soc B: Biol Sci. 2016;371(1709):20150468.
143. Saunte D, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. Br J Dermatol. 2017;177(1):47–62.
144. Hooft van Huijsduijnen R, Kojima S, Carter D, et al. Reassessing therapeutic antibodies for neglected and tropical diseases. PLOS Negl Trop Dis. 2020;14(1): e0007860.
145. Kim J, Sudbery P. *Candida albicans*, a major human fungal pathogen. J Microbiol. 2011;49:171–7.
146. Rudkin FM, Raziunaite I, Workman H, et al. Single human B cell-derived monoclonal anti-Candida antibodies enhance phagocytosis and protect against disseminated candidiasis. Nat Commun. 2018;9(1):5288.
147. Buissa-Filho R, Puccia R, Marques A, et al. The monoclonal antibody against the major diagnostic antigen of *Paracoccidioides brasiliensis* mediates immune protection in infected BALB/c mice challenged intratracheally with the fungus. Infect Immun. 2008;76(7):3321–8.
148. de Mattos GD, De Almeida SR, Mariano M, Lopes JD. Characterization of gp70 and anti-gp70 monoclonal antibodies in *Paracoccidioides brasiliensis* pathogenesis. Infect Immun. 2003;71(11):6534–42.
149. Tesini BL, Wright TW, Malone JE, et al. Immunization with Pneumocystis cross-reactive antigen 1 (Pca1) protects mice against Pneumocystis pneumonia and generates antibody to *Pneumocystis jirovecii*. Infect Immun. 2017. https://doi.org/10.1128/iai.00850-16.
150. Kling HM, Norris KA. Vaccine-induced immunogenicity and protection against Pneumocystis pneumonia in a nonhuman primate model of HIV and Pneumocystis coinfection. J Infect Dis. 2016;213(10):1586–95.
151. Gigliotti F, Haidaris CG, Wright TW, Harmsen AG. Passive intranasal monoclonal antibody prophylaxis against murine Pneumocystis carinii pneumonia. Infect Immun. 2002;70(3):1069–74.
152. Kolls JK. An emerging role of B cell immunity in susceptibility to pneumocystis pneumonia. Am J Respir Cell Mol Biol Am Thorac Soc. 2017;56:279–80.
153. Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17(8):873–81.
154. Dromer F, Charreire J, Contrepois A, Carbon C, Yeni P. Protection of mice against experimental cryptococcosis by anti-*Cryptococcus neoformans* monoclonal antibody. Infect Immun. 1987;55(3):749–52.
155. Larsen RA, Pappas PG, Perfect J, et al. Phase I evaluation of the safety and pharmacokinetics of murine-derived anticryptococcal antibody 18B7 in subjects with treated cryptococcal meningitis. Antimicrobial Agents Chemother. 2005;49(3):952–8.
156. Rosas ANL, Nosanchuk JD, Casadevall A. Passive immunization with melanin-binding monoclonal antibodies prolongs survival of mice with lethal *Cryptococcus neoformans* infection. Infect Immun. 2001;69(5):3410–2.
157. Torosantucci A, Chiani P, Bromuro C, et al. Protection by anti-β-glucan antibodies is associated with restricted β-1, 3 glucan binding specificity and inhibition of fungal growth and adherence. PLoS ONE. 2009;4(4): e5392.
158. Rodrigues ML, Shi L, Barreto-Bergter E, et al. Monoclonal antibody to fungal glucosylceramide protects mice against lethal *Cryptococcus neoformans* infection. Clin Vaccine Immunol. 2007;14(10):1372–6.
159. Rodrigues ML, Travassos LR, Miranda KR, et al. Human antibodies against a purified glucosylceramide from *Cryptococcus neoformans* inhibit cell budding and fungal growth. Infect Immun. 2000;68(12):7049–60.
160. Nimrichter L, Rodrigues ML. Fungal glucosylceramides: from structural components to biologically active targets of new antimicrobials. Front Microbiol. 2011;2:212.
161. Antachopoulos C, Walsh T. Immunotherapy of Cryptococcus infections. Clin Microbiol Infect. 2012;18(2):126–33.
162. Zhou Q, Gault RA, Kozel TR, Murphy WJ. Immunomodulation with CD40 stimulation and interleukin-2 protects mice from disseminated cryptococcosis. Infect Immun. 2006;74(4):2161–8.
163. Bowen A, Wear MP, Cordero RJ, Oscarson S, Casadevall A. A monoclonal antibody to *Cryptococcus neoformans* glucuronoxylomannan manifests hydrolytic activity for both peptides and polysaccharides. J Biol Chem. 2017;292(2):417–34.
164. Martinez LR, Moussai D, Casadevall A. Antibody to *Cryptococcus neoformans* glucuronoxylomannan inhibits the release of capsular antigen. Infect Immun. 2004;72(6):3674–9.
165. Casadevall A, Pirofski LA. Immunoglobulins in defense, pathogenesis, and therapy of fungal diseases. Cell Host Microbe. 2012;11(5):447–56.
166. Di Mambro T, Guerriero I, Aurisicchio L, Magnani M, Marra E. The yin and yang of current antifungal therapeutic strategies: how can we harness our natural defenses? Front Pharmacol. 2019;10:80.
167. Köhler JR, Casadevall A, Perfect J. The spectrum of fungi that infects humans. Cold Spring Harbor Perspect Med. 2015;5(1):a019273.
168. Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. Mycoses. 2008;51:2–15.
169. Datta K, Hamad M. Immunotherapy of fungal infections. Immunol Invest. 2015;44(8):738–76.
170. Bermas A, Geddes-McAlister J. Combatting the evolution of antifungal resistance in *Cryptococcus neoformans*. Mol Microbiol. 2020;114(5):721–34.

171. Horianopoulos LC, Gluck-Thaler E, Benoit Gelber I, et al. The Canadian fungal research network: current challenges and future opportunities. Can J Microbiol. 2021;67(1):13–22.
172. Richards TA, Soanes DM, Jones MD, et al. Horizontal gene transfer facilitated the evolution of plant parasitic mechanisms in the oomycetes. Proc Natl Acad Sci. 2011;108(37):15258–63.
173. Bebber DP, Ramotowski MA, Gurr SJ. Crop pests and pathogens move polewards in a warming world. Nat Clim Chang. 2013;3(11):985–8.
174. Sun YV, Hu Y-J. Integrative analysis of multi-omics data for discovery and functional studies of complex human diseases. Adv Genet. 2016;93:147–90.
175. Kathuria S, Singh PK, Sharma C, et al. Multidrug-resistant *Candida auris* misidentified as *Candida haemulonii*: characterization by matrix-assisted laser desorption ionization–time of flight mass spectrometry and DNA sequencing and its antifungal susceptibility profile variability by Vitek 2, CLSI broth microdilution, and Etest method. J Clin Microbiol. 2015;53(6):1823–30.
176. Sohn JI, Nam JW. The present and future of de novo whole-genome assembly. Brief Bioinform. 2018;19(1):23–40.
177. Ball B, Langille M, Geddes-McAlister J. Fun (gi) omics: Advanced and diverse technologies to explore emerging fungal pathogens and define mechanisms of antifungal resistance. MBio. 2020;11(5):e01020-e1120.
178. Akinola SA, Ayangbenro AS, Babalola OO. The diverse functional genes of maize rhizosphere microbiota assessed using shotgun metagenomics. J Sci Food Agric. 2020. https://doi.org/10.1002/jsfa.10948.
179. Akinola SA, Ayangbenro AS, Babalola OO. The immense functional attributes of maize rhizosphere microbiome: a shotgun sequencing approach. Agriculture. 2021;11(2):118.
180. Akinola SA, Ayangbenro AS, Babalola OO. The diverse functional genes of maize rhizosphere microbiota assessed using shotgun metagenomics. J Sci Food Agric. 2021;101(8):3193–201.
181. Akinola SA, Ayangbenro AS, Babalola OO. Metagenomic insight into the community structure of maize-rhizosphere bacteria as predicted by different environmental factors and their functioning within plant proximity. Microorganisms. 2021;9(7):1419.
182. Akinola SA, Babalola OO. The importance of adverse soil microbiomes in the light of omics: implications for food safety. Plant, Soil Environ. 2020;66(9):421–30.
183. Akinola SA, Babalola OO. The fungal and archaeal community within plant rhizosphere: a review on their contribution to crop safety. J Plant Nutr. 2021;44(4):600–18.
184. Babalola OO, Akinola SA, Ayangbenro AS. Shotgun metagenomic survey of maize soil rhizobiome. Microbiol Resour Announc. 2020;9(39):e00860-e920.
185. Grigoriev IV, Cullen D, Goodwin SB, et al. Fueling the future with fungal genomics. Mycology. 2011;2(3):192–209.
186. Spatafora J. 1000 fungal genomes to be sequenced. IMA Fungus. 2011;2(2):41–5.
187. Geddes-McAlister J, Shapiro RS. New pathogens, new tricks: emerging, drug-resistant fungal pathogens and future prospects for antifungal therapeutics. Ann N Y Acad Sci. 2019;1435(1):57–78.
188. Pfaller M, Diekema D, Gibbs D, et al. Global antifungal surveillance group results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of Candida species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. J Clin Microbiol. 2010;48:1366–77.
189. Muñoz JF, Gade L, Chow NA, et al. Genomic insights into multidrug-resistance, mating and virulence in *Candida auris* and related emerging species. Nat Commun. 2018;9(1):5346.
190. Marichal P, Gorrens J, Bellens D, Moereels H, Janssen P. Mutation in cytochrome P-450-dependent 14α-demethylase results in decreased affinity for azole antifungals. Biochem Soc Trans. 1990;18(1):56–9.
191. Healey KR, Kordalewska M, Jiménez Ortigosa C, et al. Limited ERG11 mutations identified in isolates of *Candida auris* directly contribute to reduced azole susceptibility. Antimicrob Agents Chemother. 2018. https://doi.org/10.1128/aac.01427-18.
192. McTaggart LR, Copeland JK, Surendra A, et al. Mycobiome sequencing and analysis applied to fungal community profiling of the lower respiratory tract during fungal pathogenesis. Front Microbiol. 2019;10:512.
193. Couto N, Schuele L, Raangs EC, et al. Critical steps in clinical shotgun metagenomics for the concomitant detection and typing of microbial pathogens. Sci Rep. 2018;8(1):13767.
194. O'Donnell K, Sarver BA, Brandt M, et al. Phylogenetic diversity and microsphere array-based genotyping of human pathogenic Fusaria, including isolates from the multistate contact lens-associated US keratitis outbreaks of 2005 and 2006. J Clin Microbiol. 2007;45(7):2235–48.
195. Zhang Y, Yang H, Turra D, et al. The genome of opportunistic fungal pathogen *Fusarium oxysporum* carries a unique set of lineage-specific chromosomes. Commun Biol. 2020;3(1):50.
196. Khor W-B, Aung T, Saw S-M, et al. An outbreak of *Fusarium keratitis* associated with contact lens wear in Singapore. JAMA. 2006;295(24):2867–73.
197. Sewell TR, Zhu J, Rhodes J, et al. Nonrandom distribution of azole resistance across the global population of *Aspergillus fumigatus*. MBio. 2019. https://doi.org/10.1128/mbio.00392-19.
198. Chowdhary A, Kathuria S, Xu J, Meis JF. Emergence of azole-resistant *Aspergillus fumigatus* strains due to agricultural azole use creates an increasing threat to human health. PLoS Pathog. 2013;9(10): e1003633.
199. Snelders E, Camps SM, Karawajczyk A, et al. Triazole fungicides can induce cross-resistance to medical triazoles in *Aspergillus fumigatus*. PLoS ONE. 2012;7(3): e31801.
200. Edel-Hermann V, Lecomte C. Current status of *Fusarium oxysporum* formae speciales and races. Phytopathology. 2019;109(4):512–30.
201. Riekeberg E, Powers R. New frontiers in metabolomics: from measurement to insight. FResearch. 2017;6:1148.
202. Tugizimana F, Djami-Tchatchou AT, Fahrmann JF, et al. Time-resolved decoding of metabolic signatures of in vitro growth of the hemibiotrophic pathogen *Colletotrichum sublineolum*. Sci Rep. 2019;9(1):3290.
203. Semreen MH, Soliman SS, Saeed BQ, et al. Metabolic profiling of *Candida auris*, a newly-emerging multi-drug resistant *Candida* species, by GC-MS. Molecules. 2019;24(3):399.
204. Keller NP. Fungal secondary metabolism: regulation, function and drug discovery. Nat Rev Microbiol. 2019;17(3):167–80.
205. Wang X, Bing J, Zheng Q, et al. The first isolate of *Candida auris* in China: clinical and biological aspects. Emerg Microbes Infect. 2018;7(1):1–9.

206. Bravo Ruiz G, Ross ZK, Gow NA, Lorenz A. Pseudohyphal growth of the emerging pathogen *Candida auris* is triggered by genotoxic stress through the S phase checkpoint. Msphere. 2020. https://doi.org/10.1128/msphere.00151-20.
207. Li L, Liao Z, Yang Y, et al. Metabolomic profiling for the identification of potential biomarkers involved in a laboratory azole resistance in *Candida albicans*. PLoS ONE. 2018;13(2): e0192328.
208. Cannon P, Damm U, Johnston P, Weir B. Colletotrichum: current status and future directions. Stud Mycol. 2012;73(1):181–213.
209. Fernández-García M, Rojo D, Rey-Stolle F, García A, Barbas C. Metabolomic-based methods in diagnosis and monitoring infection progression. In: Metabolic Interaction in Infection. Cham: Springer International Publishing; 2018. p. 283–315.
210. Liew KL, Jee JM, Yap I, Yong PVC. In vitro analysis of metabolites secreted during infection of lung epithelial cells by *Cryptococcus neoformans*. PLoS ONE. 2016;11(4): e0153356.
211. Hommel B, Mukaremera L, Cordero RJ, et al. Titan cells formation in *Cryptococcus neoformans* is finely tuned by environmental conditions and modulated by positive and negative genetic regulators. PLoS Pathog. 2018;14(5): e1006982.
212. Albuquerque P, Nicola AM, Nieves E, et al. Quorum sensing-mediated, cell density-dependent regulation of growth and virulence in *Cryptococcus neoformans*. MBio. 2014. https://doi.org/10.1128/mbio.00986-13.
213. Ball B, Bermas A, Carruthers-Lay D, Geddes-McAlister J. Mass spectrometry-based proteomics of fungal pathogenesis, host–fungal interactions, and antifungal development. J Fungi. 2019;5(2):52.
214. Cox J, Mann M. Is proteomics the new genomics? Cell host microbe. 2007;130(3):395–8.
215. Aebersold R, Mann M. Mass-spectrometric exploration of proteome structure and function. Nature. 2016;537(7620):347–55.
216. Mann M, Kulak NA, Nagaraj N, Cox J. The coming age of complete, accurate, and ubiquitous proteomes. Mol Cell. 2013;49(4):583–90.
217. Toby TK, Fornelli L, Kelleher NL. Progress in top-down proteomics and the analysis of proteoforms. Annu Rev Anal Chem. 2016;9:499–519.
218. Aebersold R, Bensimon A, Collins BC, Ludwig C, Sabido E. Applications and developments in targeted proteomics: from SRM to DIA/SWATH. Proteomics. Hoboken: Wiley Online Library; 2016. p. 2065–7.
219. Karkowska-Kuleta J, Satala D, Bochenska O, Rapala-Kozik M, Kozik A. Moonlighting proteins are variably exposed at the cell surfaces of *Candida glabrata*, *Candida parapsilosis* and *Candida tropicalis* under certain growth conditions. BMC Microbiol. 2019;19:1–13.
220. Karkowska-Kuleta J, Kulig K, Karnas E, et al. Characteristics of extracellular vesicles released by the pathogenic yeast-like fungi *Candida glabrata*, *Candida parapsilosis* and *Candida tropicalis*. Cells. 2020;9(7):1722.
221. Pitarch A, Nombela C, Gil C. Serum antibody signature directed against *Candida albicans* Hsp90 and enolase detects invasive candidiasis in non-neutropenic patients. J Proteome Res. 2014;13(11):5165–84.
222. Marin E, Parra-Giraldo CM, Hernandez-Haro C, et al. *Candida albicans* shaving to profile human serum proteins on hyphal surface. Front Microbiol. 2015;6:1343.
223. Moreira ALE, Oliveira MAP, Silva LOHS, et al. Immunoproteomic approach of extracellular antigens from *Paracoccidioides* species reveals exclusive B-cell epitopes. Front Microbiol. 2020;10:2968.
224. Byrnes EJ III, Li W, Lewit Y, et al. Emergence and pathogenicity of highly virulent *Cryptococcus gattii* genotypes in the northwest United States. PLoS Pathog. 2010;6(4): e1000850.
225. Rosa RL, Berger M, Santi L, et al. Proteomics of rat lungs infected by *Cryptococcus gattii* reveals a potential Warburg-like effect. J Proteome Res. 2019;18(11):3885–95.
226. Weerasinghe H, Traven A. Immunometabolism in fungal infections: the need to eat to compete. Curr Opin Microbiol. 2020;58:32–40.
227. Becker-Andre M, Hahlbrock K. Absolute mRNA quantification using the polymerase chain reaction (PCR). A novel approach by a P CR aided t ranscipt t itration assay (PATTY). Nucl Acids Res. 1989;17(22):9437–46.
228. Velculescu VE, Zhang L, Vogelstein B, Kinzler KW. Serial analysis of gene expression. Science. 1995;270(5235):484–7.
229. Lockhart DJ, Dong H, Byrne MC, et al. Expression monitoring by hybridization to high-density oligonucleotide arrays. Nat Biotechnol Nat Biotechnol. 1996;14:1675–80.
230. Wang Z, Gerstein M, Snyder M. RNA-Seq: a revolutionary tool for transcriptomics. Nat Rev Genet. 2009;10(1):57–63.
231. Gupta A, Gupta A, Varma A. *Candida glabrata* candidemia: an emerging threat in critically ill patients. Ind J Crit Care Med Peer-Rev, Off Publ Ind Soc Crit Care Med. 2015;19(3):151.
232. Alves R, Kastora SL, Gomes-Gonçalves A, et al. Transcriptional responses of *Candida glabrata* biofilm cells to fluconazole are modulated by the carbon source. Npj Biofilms Microbiomes. 2020;6(1):4.
233. Kean R, Delaney C, Sherry L, et al. Transcriptome assembly and profiling of *Candida auris* reveals novel insights into biofilm-mediated resistance. Msphere. 2018. https://doi.org/10.1128/msphere.00334-18.
234. Kaur J, Kautto L, Penesyan A, et al. Interactions of an emerging fungal pathogen *Scedosporium aurantiacum* with human lung epithelial cells. Sci Rep. 2019;9(1):5035.
235. Chen F, Zhang C, Jia X, et al. Transcriptome profiles of human lung epithelial cells A549 interacting with *Aspergillus fumigatus* by RNA-Seq. PLoS ONE. 2015;10(8): e0135720.
236. Bellanger A-P, Millon L, Khoufache K, et al. *Aspergillus fumigatus* germ tube growth and not conidia ingestion induces expression of inflammatory mediator genes in the human lung epithelial cell line A549. J Med Microbiol. 2009;58(2):174–9.
237. Chen M, Kondori N, Deng S, et al. Direct detection of *Exophiala* and *Scedosporium* species in sputa of patients with cystic fibrosis. Med Mycol. 2018;56(6):695–702.
238. Guarro J, Kantarcioglu AS, Horré R, et al. *Scedosporium apiospermum*: changing clinical spectrum of a therapy-refractory opportunist. Sabouraudia. 2006;44(4):295–327.
239. Le Govic Y, Papon N, Le Gal S, et al. Genomic organization and expression of iron metabolism genes in the emerging pathogenic mold *Scedosporium apiospermum*. Front Microbiol. 2018;9:827.
240. Yan J, Risacher SL, Shen L, Saykin AJ. Network approaches to systems biology analysis of complex disease: integrative methods for multi-omics data. Brief Bioinform. 2018;19(6):1370–81.
241. Bersanelli M, Mosca E, Remondini D, et al. Methods for the integration of multi-omics data: mathematical aspects. BMC Bioinform. 2016;17:167–77.
242. Subramanian I, Verma S, Kumar S, Jere A, Anamika K. Multi-omics data integration, interpretation, and its application. Bioinform Biol Insights. 2020;14:1177932219899051.

243. Chibucos MC, Soliman S, Gebremariam T, et al. An integrated genomic and transcriptomic survey of mucormycosis-causing fungi. Nat Commun. 2016;7(1):12218.
244. Andresen D, Donaldson A, Choo L, et al. Multifocal cutaneous mucormycosis complicating polymicrobial wound infections in a tsunami survivor from Sri Lanka. Lancet. 2005;365(9462):876–8.
245. Etienne KA, Gillece J, Hilsabeck R, et al. Whole genome sequence typing to investigate the Apophysomyces outbreak following a tornado in Joplin, Missouri, 2011. PLoS ONE. 2012;7(11): e49989.
246. Yan L, Xia K, Yu Y, et al. Unique cell surface mannan of yeast pathogen *Candida auris* with selective binding to IgG. ACS Infect Dis. 2020;6(5):1018–31.
247. Bruno M, Kersten S, Bain JM, et al. Transcriptional and functional insights into the host immune response against the emerging fungal pathogen *Candida auris*. Nat Microbiol. 2020;5(12):1516–31.
248. de Jong AW, Hagen F. Attack, defend and persist: how the fungal pathogen *Candida auris* was able to emerge globally in healthcare environments. Mycopathologia. 2019;184(3):353–65.
249. Zamith-Miranda D, Heyman HM, Cleare LG, et al. Multi-omics signature of *Candida auris*, an emerging and multidrug-resistant pathogen. MSystems. 2019. https://doi.org/10.1128/msystems.00257-19.