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# The Emerging Global Fungal Crisis: Invasive Fungal Diseases, Antifungal Resistance, and One Health Responses

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## ABSTRACT

Invasive fungal diseases are an escalating global health crisis, causing an estimated 6.5 million severe infections and up to 3.8 million deaths each year. Their disability burden likely reaches tens of millions of DALYs, yet remains underestimated because of sparse data and profound diagnostic gaps, especially in low- and middle-income countries. This narrative review synthesizes current evidence on three converging domains: the global burden and ecology of invasive fungal disease, the crisis of antifungal limitation and resistance, and emerging One Health responses. We summarize updated mortality, morbidity, and cost estimates and describe how demographic ageing, expanding immunosuppression, COVID-19, climate change, and agricultural azole fungicide use are enlarging the population at risk and selecting for resistant strains. Four WHO priority pathogen groups—Candida auris, azole-resistant Aspergillus fumigatus, Cryptococcus species, and Mucorales—are used to illustrate patterns of emergence, healthcare transmission, environmental selection, and multidrug resistance, linked to underlying molecular mechanisms such as ERG11 and cyp51A mutations, efflux pump upregulation, FKS-mediated echinocandin resistance, and biofilm-associated tolerance. We review strengths and gaps in diagnostics, including tiered essential diagnostic packages, resistance-aware molecular platforms, and early experience with GLASS Fungi and environmental surveillance. Finally, we discuss the constrained antifungal pipeline, novel agents and vaccines in development, and principles of antifungal stewardship aligned with improved access and agricultural regulation. We conclude with research and policy priorities to operationalize the WHO Fungal Priority Pathogens List and to embed fungal threats within broader antimicrobial resistance strategies, climate adaptation planning, and health system strengthening.

**Keywords:**
*Invasive Fungal Infections;*
*Drug Resistance;*
*One Health;*
*Epidemiological Monitoring;*
*Antifungal Agents;*
*Candida Auris*

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## INTRODUCTION

### *The Rising Threat of Fungal Infections in Global Health*

Fungal diseases have long been overshadowed by bacterial, viral, and parasitic infections in global health discourse. Over the last decade, however, it has become clear that invasive fungal infections (IFIs) are a major and growing cause of morbidity and mortality: recent modelling that incorporates autopsy data and contemporary HIV, cancer, and critical care cohorts estimates 6.5 million severe IFIs and 3.75–3.8 million deaths annually, of which 2.5 million deaths are directly attributable to the fungal infection rather than underlying comorbidities—nearly double earlier estimates [1]. These deaths are concentrated in a relatively small number of syndromes, particularly invasive aspergillosis, invasive candidiasis, chronic pulmonary aspergillosis, cryptococcal meningitis, and Pneumocystis pneumonia [1].

The disability-adjusted life year (DALY) burden of fungal diseases remains poorly quantified but is substantial; recent attempts to synthesise available data suggest that invasive and chronic fungal diseases may account for on the order of 8–49 million DALYs annually, with regional burdens comparable to tuberculosis or malaria in some high-risk populations [1].

The population at risk for invasive mycoses is expanding rapidly. Demographic ageing, increasing prevalence of non-communicable diseases (notably diabetes and chronic lung disease), widespread use of intensive immunosuppressive regimens for malignancy and transplantation, and the scale-up of biologic agents collectively broaden the host pool susceptible to opportunistic fungi [2]. The COVID-19 pandemic further amplified this vulnerability, both by causing virus-associated fungal syndromes such as COVID-associated pulmonary aspergillosis and mucormycosis and by straining already fragile diagnostic and surveillance infrastructures [3, 4].

In parallel, climate change and land-use alterations are reshaping the ecology and geographic range of environmental fungi, eroding long-standing thermal and ecological barriers to human infection [5, 6].

This growing recognition was crystallized in 2022, when the World Health Organization (WHO) released its first Fungal Priority Pathogens List (FPPL), ranking 19 fungal pathogens by public health priority and explicitly framing fungal disease and antifungal resistance as central to the global antimicrobial resistance (AMR) crisis [7]. The FPPL highlights critical pathogens such as Candida auris, Aspergillus fumigatus, and Cryptococcus neoformans because of their high mortality, increasing resistance, and close linkage to healthcare and immunocompromised populations. We return to the policy implications of the FPPL in Section 7.2.

### *The Antifungal Limitation Crisis*

Current antifungal chemotherapy rests on only four major systemic drug classes: polyenes, azoles, echinocandins, and the antimetabolite flucytosine. All four classes target a small set of fungal pathways, many of which are closely homologous to human cellular machinery, reflecting the fundamental challenge that both fungi and humans are eukaryotes [8]. This eukaryotic similarity constrains the therapeutic window and fosters dose-limiting toxicity, particularly for polyenes and flucytosine, while also limiting the spectrum of potential drug targets. No completely new systemic antifungal class has entered routine clinical use since the echinocandins were introduced nearly two decades ago, underscoring stagnation in antifungal innovation [9].

Even within this narrow armamentarium, geographic access is severely unequal; lipid formulations of amphotericin B and flucytosine remain unavailable or unaffordable in many high-burden settings, forcing reliance on suboptimal regimens that are more toxic and less effective [10]. The commercial market for antifungals is relatively small compared with antibacterials and chronic disease therapeutics, and few novel agents have reached late-stage development. Recent reviews identify only a handful of agents from new or re-engineered classes—including ibrexafungerp, fosmanogepix, olorofim, and rezafungin—in phase II–III trials, with many targeting narrow indications [9].

Within this constrained therapeutic space, the rapid emergence and global dissemination of antifungal resistance has created an antifungal limitation crisis. Multiazole-resistant A. fumigatus, multidrug- and pan-resistant C. auris, fluconazole-resistant Cryptococcus in relapse meningitis, and echinocandin-resistant Candida glabrata and C. auris exemplify converging trajectories toward multidrug and sometimes pan-drug resistance in distinct ecological and clinical niches [8, 11]. Resistance commonly arises under therapeutic pressure in individual patients but is increasingly driven by environmental selection, particularly by extensive azole fungicide use in agriculture that cross-selects for resistance to medical triazoles [12]. At the same time, structural market failures—including low expected returns, regulatory hurdles, and competition from cheap generics—continue to disincentivize investment in antifungal research and development [9]. Detailed discussion of the current pipeline and stewardship strategies is provided in Section 8.

This review synthesizes current evidence on the global burden and epidemiology of invasive fungal diseases, the ecological and anthropogenic drivers of their emergence, and the molecular and clinical dimensions of antifungal resistance. We focus on four emblematic WHO-priority pathogen groups—C. auris, azole-resistant A. fumigatus, Cryptococcus spp., and

Mucorales—and integrate these organism-specific narratives with cross-cutting themes in diagnostics, surveillance, therapeutics, and One Health policy. Our aim is to delineate key knowledge gaps and research priorities and to outline a coherent agenda for mitigating the rising threat of fungal infections in a changing world.

## Global Burden and Epidemiological Landscape

### *Quantifying the Mortality and Morbidity Burden*

Recent modelling that incorporates autopsy data and contemporary HIV, cancer, and critical care cohorts estimates that invasive fungal diseases cause 6.5 million episodes of severe infection and 3.75–3.8 million deaths annually, of which 2.5 million deaths are directly attributable to the fungal infection rather than underlying comorbidities—nearly double earlier estimates [1]. The same analysis attributes 1.8 million deaths annually to invasive aspergillosis, 340,000 deaths to chronic pulmonary aspergillosis, 1 million deaths to invasive candidiasis, 147,000 deaths to cryptococcal meningitis, and 214,000 deaths to Pneumocystis pneumonia, underscoring that a small number of syndromes dominate fungal mortality [1].

Disability-adjusted life year (DALY) estimates remain highly uncertain due to sparse primary data and limited capture of chronic sequelae, yet available modelling suggests that serious fungal diseases collectively impose on the order of tens of millions of DALYs per year—comparable in some populations to tuberculosis or malaria [5, 6]. Chronic sequelae such as chronic pulmonary aspergillosis after tuberculosis, post-meningitic neurological disability in cryptococcosis, or disfiguring outcomes after mucormycosis contribute substantially to long-term morbidity [1].

Underdiagnosis is pervasive. Routine mycological testing is rarely performed in many high-burden settings, and even in high-income countries, IFIs are often missed or diagnosed late. WHO acknowledges that “the exact global burden of fungal diseases and antifungal resistance is unknown” owing to limited routine testing and weak surveillance, implying that even these elevated mortality estimates likely underestimate the true scale of disease [7].

### *Economic Consequences and Healthcare Costs*

In high-income countries, fungal diseases impose substantial direct healthcare expenditures through prolonged hospitalizations, intensive care, surgery, and expensive antifungal therapy. In the United States, the direct medical costs of serious fungal infections were estimated at approximately 7.5 billion USD in 2017, with broader societal costs including productivity losses approaching 11.5 billion USD; when valued using standard estimates of the statistical value of life, the economic burden attributable to premature mortality alone may exceed 40–48 billion USD annually [2, 13]. Invasive aspergillosis and candidemia are among the costliest conditions on a per-case basis, reflecting both high mortality and prolonged intensive resource utilization [12].

In low- and middle-income countries (LMICs), cost-of-illness data are sparse, but available studies suggest that severe fungal diseases often incur catastrophic out-of-pocket expenditures, particularly where long courses of amphotericin B or prolonged hospitalizations are required and where out-of-pocket payment predominates [10]. The economic burden is amplified when resistant infections necessitate the use of second-line or salvage regimens with higher drug acquisition costs and toxicity monitoring, for example lipid amphotericin B for azole-resistant aspergillosis or pan-resistant C. auris [11]. Lost productivity due to chronic disability, such as vision loss after rhino-orbital mucormycosis or chronic respiratory impairment after CPA, further compounds the economic toll but remains poorly quantified.

### *The Diagnostic Void and Underreporting*

A central driver of uncertainty in burden estimates is the profound diagnostic gap. In many LMIC settings, laboratories lack the capacity to perform fungal culture, histopathology, or antigen and molecular assays, resulting in pervasive underdiagnosis and misclassification of IFIs as bacterial sepsis, smear-negative tuberculosis, or malignancy [7, 14]. Surveys in African and Latin American hospitals show that while basic microscopy is often available, fungal culture, cryptococcal antigen testing, Histoplasma antigen assays, and CT/MRI imaging are frequently absent or unreliable, especially outside tertiary centers [14, 15]. Even in high-income countries, delayed or missed diagnosis of aspergillosis and mucormycosis is common, particularly in non-classical host groups such as ICU patients with COPD or severe viral pneumonia, where clinical suspicion may be low and radiological findings nonspecific [2].

These diagnostic limitations translate directly into surveillance blind spots. Few fungal infections are nationally notifiable, and standardized case definitions and reporting systems are lacking outside of selected high-income settings. The WHO FPPL explicitly identifies strengthening laboratory capacity and surveillance systems as a top priority, emphasizing that without reliable incidence and resistance data, rational allocation of resources and evaluation of interventions are impossible [7]. The under-recognition of IFIs in global health metrics has likely contributed to decades of underinvestment in fungal diagnostics, therapeutics, and vaccines. We return to diagnostic capacity building in Section 6. Table 1 summarizes the approximate annual incidence, crude case fatality, key at-risk populations, and geographic hotspots for the major invasive fungal infections discussed in this review.

## Ecological and Environmental Drivers of Emergence

### *Climate Change and the Erosion of Thermal Barriers*

Mammalian endothermy and homeothermy have historically provided an effective thermal barrier against most environmental fungi, the majority of which cannot thrive at 37 °C [5, 6]. Global warming is narrowing this thermal safety margin by exerting directional selection for thermotolerance in environmental fungal populations. Experimental evolution studies and comparative analyses indicate that environmental isolates of various fungi, including Candida and Cryptococcus relatives, can adapt to higher growth temperatures over relatively short timescales, suggesting that climatic warming can directly shape pathogenic potential [20].

Candida auris has become the paradigmatic example of this "global warming emergence hypothesis": it is phylogenetically related to predominantly environmental, non-pathogenic yeasts, yet can grow efficiently above 40 °C and appeared nearly simultaneously on multiple continents from distinct clades in the late 2000s [20, 21]. Although this remains inferential, the temporal coincidence between rising global temperatures and C. auris emergence, together with its unusual thermotolerance, provides a compelling ecological hypothesis that is explored in more detail in Section 4.1.1.

### *Geographic Range Expansion of Endemic Mycoses*

Changing climatic conditions are reshaping the distributions of endemic dimorphic fungi. Coccidioides spp., agents of Valley fever, were historically confined to arid regions of the southwestern United States and parts of Mexico and Central and South America. Over the last two decades, locally acquired coccidioidomycosis has been documented as far north as Washington State, and ecological niche models incorporating projected temperature and precipitation trends predict substantial northward and eastward expansion of suitable habitat by mid-century [5, 6, 22]. Similar patterns are emerging for Histoplasma capsulatum and Blastomyces dermatitidis, which are increasingly reported outside their traditional river valley and Great Lakes foci in North America, reflecting shifts in temperature, humidity, and land cover that favor their saprobic growth [5, 6].

Cryptococcus gattii, once thought to be limited to tropical and subtropical eucalyptus-associated niches, caused an outbreak on Vancouver Island and in the Pacific Northwest beginning in the early 2000s, affecting immunocompetent hosts and associated with local tree species such as Douglas fir and western red cedar [23]. Multiple hypotheses—including importation via plant material, wind dispersal, and migration of avian hosts—have been proposed, but its establishment in temperate rainforest ecosystems

**Table 1.** Global Burden of Major Invasive Fungal Infections

| Pathogen | Approximate Annual Incidence* | Crude Case Fatality (typical range) | Key At-Risk Populations | Geographic Hotspots |
|---|---|---|---|---|
| **Aspergillus fumigatus (invasive aspergillosis, including CAPA)** | 2.0–2.5 million (1) | 40–90% depending on host and resistance profile (12) | Hematologic malignancy, HSCT and solid organ transplant recipients, COPD, severe influenza or COVID-19 ICU patients | Global, highest burden where cancer and ICU care are expanding |
| **Candida spp. (invasive candidiasis and candidemia)** | 1.5 million (1) | 30–60% (11) | ICU patients, postsurgical, neonates, patients with central lines or broad-spectrum antibiotics | Worldwide; burden recognized in all income settings |
| **Cryptococcus neoformans / gattii (cryptococcal meningitis)** | 190,000 cases in people with HIV (16) | 30–70% at 10 weeks, higher in LMICs (17) | Advanced HIV infection, some solid organ transplant and immunocompetent adults for C. gattii | Sub-Saharan Africa, Asia, Latin America, Pacific Northwest (C. gattii) |
| **Pneumocystis jirovecii (PCP)** | >500,000 (1) | 15–30% with treatment, higher without (18, 19) | Advanced HIV, hematologic malignancy, solid organ transplant, corticosteroid therapy | Global, especially where HIV diagnosis and prophylaxis are delayed |
| **Mucorales (mucormycosis)** | Tens of thousands; highly focal (3, 4) | 40–80% depending on site and speed of diagnosis (3, 4) | Uncontrolled diabetes, ketoacidosis, severe COVID-19 on steroids, hematologic malignancy, trauma and burns | India, Pakistan, Mexico; outbreak-associated clusters after COVID-19 and natural disasters |

*Incidence estimates remain uncertain due to underdiagnosis and incomplete surveillance.

is plausibly facilitated by milder winters and altered precipitation regimes. These examples underscore that climatic trends are not merely abstract drivers but are already altering exposure landscapes and risk profiles in tangible ways.

#### *One Health Interfaces: Agricultural Fungicide Use*

A particularly well-characterized ecological driver of antifungal resistance is the extensive use of demethylation inhibitor (DMI) azole fungicides in agriculture. These compounds, structurally similar to medical triazoles, are applied to crops and ornamentals to prevent plant fungal diseases and have become ubiquitous in many high-intensity agricultural regions [24] D. Aspergillus fumigatus, a saprobe that thrives in decaying organic matter and compost heaps, is repeatedly exposed to residual DMI azoles in soil and plant waste. Under these conditions, resistant mutants arise and are selectively amplified, giving rise to populations that are cross-resistant to multiple medical triazoles and can infect humans who have never received antifungal therapy [24] D.

The One Health implications are direct: resistant A. fumigatus spores generated in agricultural hotspots—particularly compost heaps, flower bulb waste piles, and greenhouses—become airborne and can be inhaled by humans, leading to azole-resistant invasive aspergillosis with high treatment failure rates [24, 25]. Agricultural and environmental surveillance in Europe, Asia, and Africa consistently demonstrates strong correlations between intensity of DMI fungicide use, environmental prevalence of resistant A. fumigatus, and clinical resistance rates in nearby hospitals [25]. We return to the regulatory implications of agricultural fungicide use in Section 7.2.2.

## Key Emerging Pathogens

### *Candida auris: The Paradigm of Multidrug-Resistant Emergence*

#### *Origins, Environmental Reservoirs, and Emergence Drivers*

Candida auris was first described in 2009 from the external ear canal of a patient in Japan. Retrospective and contemporaneous surveillance subsequently revealed that genetically distinct clades had emerged almost simultaneously in South Asia, South America, and South Africa, with an additional East Asian clade and later a potential Iranian clade, indicating polyphyletic emergence rather than single-source dissemination [26]. Whole-genome sequencing shows deep divergence among these clades, supporting the notion that C. auris evolution toward human pathogenicity occurred independently in geographically separated environmental reservoirs that experienced similar selective pressures [26].

The first isolation of C. auris from natural environments in the Andaman Islands provided crucial insight into its ecology. Investigators cultured C. auris from a remote salt marsh and a more anthropized sandy beach; the marsh isolate was antifungal-susceptible and grew poorly at 37 °C, whereas beach isolates were multidrug-resistant, more thermotolerant, and genomically close to clinical South Asian clade strains [21]. These findings support a model in which C. auris is native to saline wetland ecosystems, where climate-driven thermal adaptation and anthropogenic contamination with antifungal agents, disinfectants, and other pollutants in human-impacted coastal sites selected for thermotolerant, drug-resistant lineages that subsequently entered healthcare settings [20, 21].

#### *Colonization Dynamics and Healthcare Transmission*

Clinically, C. auris is notable for its robust and persistent colonization of human skin and mucosa, particularly in the axillary and inguinal regions. Longitudinal cohort studies from the United States indicate that colonization can persist for months to years, and that approximately 7 percent of colonized patients eventually develop invasive infection, typically bloodstream infection, with a median time from first colonization detection to candidemia of around three months, though ranging from days to more than a year [27]. Risk factors for progression include high comorbidity burden, presence of multiple invasive devices, prolonged ICU or long-term acute care hospitalization, and severe functional debility, all of which reflect both increased exposure to contaminated environments and impaired host defense [28].

C. auris is adapted to the built healthcare environment. It forms resilient biofilms on plastics and fabrics, withstands desiccation, and contaminates a wide range of surfaces and shared medical equipment in affected units [29-31]. Routine disinfectants based on quaternary ammonium compounds are often ineffective, necessitating the use of chlorine-releasing agents or hydrogen peroxide products for environmental decontamination [18, 19]. Outbreak investigations repeatedly implicate lapses in environmental cleaning and disinfection of multiuse devices such as temperature probes and blood pressure cuffs in propagating transmission. The movement of colonized patients between long-term care facilities and acute care hospitals creates regional transmission networks that can rapidly seed new institutions in the absence of active screening and isolation protocols [27].

#### *Resistance Profile and Therapeutic Challenges*

C. auris exhibits an alarming propensity for multidrug resistance. Globally, more than 90 percent of isolates are resistant to fluconazole, approximately 30 percent to amphotericin B, and 2–10 percent to echinocandins, with 30–40 percent resistant to two classes and a growing number of pan-resistant strains [26, 32]. Resistance mechanisms include hotspot

mutations in ERG11 (for example Y132F, K143R) and upregulation of ABC transporters such as CDR1 for azoles, and FKS1 hotspot mutations (such as S639F) for echinocandins [8, 33]. Interpretation of MICs is complicated by the lack of species-specific, fully validated CLSI or EUCAST breakpoints; current breakpoints are tentative and based on limited clinical-outcome correlations [34].

Current guidelines recommend echinocandins as first-line therapy for invasive C. auris, with rapid switch to liposomal amphotericin B or combination regimens if resistance or clinical failure is documented [34]. Optimal therapeutic strategies for pan-resistant infections remain uncertain and increasingly depend on access to investigational agents such as ibrexafungerp and fosmanogepix via compassionate use, which have shown encouraging activity in vitro and in early salvage case reports [8, 34].

## *Aspergillus fumigatus: The Agricultural–Clinical Resistance Nexus*

### *Environmental Selection of Azole Resistance*

Aspergillus fumigatus is a ubiquitous saprophytic mold and the principal cause of invasive aspergillosis in immunocompromised hosts. While azole resistance can arise in vivo during prolonged triazole therapy, a large and increasing fraction of resistant infections occur in azole-naïve patients and are caused by strains harboring environmentally selected cyp51A mutations [24]D. The archetypal environmental resistance mechanism, TR34/L98H, consists of a 34-bp tandem repeat in the promoter region that increases cyp51A expression and a leucine-to-histidine substitution at codon 98 that reduces azole binding, conferring high-level resistance to itraconazole and reduced susceptibility to voriconazole and posaconazole [12]. TR46/Y121F/T289A, involving a 46-bp promoter repeat and two amino acid substitutions, particularly compromises voriconazole activity [12].

These resistance genotypes have been recovered at high frequency from soils, compost, bulb waste, and greenhouse environments in intensive agricultural settings where DMI fungicides are widely used, and molecular epidemiology has demonstrated close genetic relatedness between environmental and clinical TR34/TR46 isolates within the same geographic region, strongly linking agricultural fungicide selection to human disease [24, 25]. The environmental route of resistance acquisition has profound implications: it means that even prudent medical azole stewardship cannot fully prevent resistant disease if environmental selection pressure remains unchecked.

### *Global Epidemiology and Resistance Hotspots*

The prevalence of azole-resistant A. fumigatus shows marked geographical heterogeneity. Multicenter European surveys have reported resistance in 3–5 percent of clinical isolates on average, but with hospital-level prevalences exceeding 15–20 percent in parts of the Netherlands, the United Kingdom, and Germany [35, 36]. In India and parts of China and Iran, studies have documented resistance rates of 10–15 percent or higher among clinical isolates, with accompanying high environmental prevalence of TR34/TR46 in agricultural soils [12]. Environmental surveys in Vietnam have reported azole-resistant A. fumigatus in up to 80% of sampled agricultural sites in some regions, illustrating the intensity of selection in certain fungicide-intensive systems [37]. Conversely, in the United States and many Latin American countries, resistance has historically been uncommon (<2% in most series) but is rising and often under-recognized due to limited routine susceptibility testing [37].

Fitness studies indicate that dominant environmental resistance genotypes such as TR34/L98H generally do not incur substantial fitness penalties in vitro or in mammalian infection models, and some may even exhibit modest fitness advantages over wild-type strains in certain conditions [38]. This fitness neutrality facilitates their environmental persistence and spread even in the absence of continued fungicide pressure, suggesting that once established, resistant A. fumigatus lineages are unlikely to disappear rapidly even with improved agricultural stewardship.

### *Clinical Implications and Treatment Thresholds*

Clinically, azole-resistant invasive aspergillosis is associated with significantly higher mortality, frequently approaching 80–90 percent when infections are treated with azole monotherapy to which the infecting strain is resistant [39]. Recognizing this, expert guidelines now recommend that in regions where local azole resistance prevalence in A. fumigatus exceeds 10 percent, first-line empiric therapy for invasive aspergillosis should be modified away from voriconazole monotherapy to either liposomal amphotericin B or combination therapy with voriconazole plus an echinocandin, pending susceptibility data [40]. Implementation of such strategies requires timely access to phenotypic susceptibility testing or molecular assays capable of detecting cyp51A resistance mutations directly from respiratory specimens—such as the AsperGenius® platform—underscoring diagnostics as a limiting step in resistance-aware clinical decision-making [41].

## *Cryptococcus Species: Resistance, Access, and Prevention*

### *Fluconazole Resistance and Heteroresistance Mechanisms*

In cryptococcal meningitis, primary fluconazole resistance at baseline remains relatively uncommon in many settings; however, prolonged fluconazole exposure during suboptimal induction or maintenance regimens can select for resistant and heteroresistant

subpopulations that compromise long-term outcomes [42]. Heteroresistance, characterized by transient subpopulations capable of growth at high fluconazole concentrations due to chromosome 1 disomy and consequent increased dosage of ERG11 and efflux pump genes, can emerge rapidly under drug pressure and may not be fully captured by standard MIC testing [43]. Relapse isolates from patients treated with fluconazole monotherapy frequently show elevated MICs, and rising trends in reduced susceptibility have been documented over time in high-burden African cohorts, particularly in the context of repeated or prolonged azole exposure [44].

### *The Flucytosine and Amphotericin B Access Crisis*

Despite compelling evidence from the AMBITION-cm and other trials that short-course regimens combining amphotericin B and flucytosine dramatically reduce mortality and toxicity compared with historical regimens, access to both liposomal amphotericin B and flucytosine remains severely constrained in most high-burden countries [17, 45]. Regulatory, pricing, and supply chain barriers have resulted in a situation where flucytosine is unregistered or unavailable in many African and Asian markets, and liposomal amphotericin B, although offered at preferential prices through global agreements, remains inconsistently procured and distributed [10, 45].

Both drugs are included on the WHO Essential Medicines List and are central to WHO-recommended CM regimens, yet national formularies and procurement systems often lag behind global guidance [10, 17]. Recent Unitaid- and donor-supported initiatives have begun to improve access by securing reduced pricing, prequalification of generics, and pooled procurement mechanisms, but coverage remains patchy [45]. This access failure forces clinicians to rely on fluconazole monotherapy or prolonged amphotericin B deoxycholate courses, regimens associated with higher mortality and greater risk of resistance selection.

### *Vaccine Development and Environmental Considerations*

Vaccine development for cryptococcosis is advancing but remains preclinical. Several strategies, including conjugate vaccines targeting capsular glucuronoxylomannan, live-attenuated or killed whole-cell vaccines, and mRNA-based platforms encoding cryptococcal antigens, have demonstrated protection in murine models, including partial protection in CD4-deficient hosts, suggesting feasibility for immunocompromised target populations [46, 47]. Concurrently, the environmental emergence of C. gattii in temperate ecosystems, together with evidence of extensive environmental reservoirs of C. neoformans in pigeon guano and decaying wood, highlights the need for improved environmental surveillance and exposure mitigation strategies, particularly for heavily immunosuppressed individuals [23].

## *Mucorales and COVID-Associated Mucormycosis*

### *The Syndemic of Diabetes, Steroids, and Viral Illness*

Mucormycosis, formerly a rare opportunistic infection, surged dramatically during the second wave of COVID-19 in India and neighboring countries, where tens of thousands of cases of rhino-orbital-cerebral disease were reported in a matter of months [48]. Case series and analytic studies consistently attribute this epidemic to the intersection of poorly controlled diabetes mellitus, widespread and sometimes indiscriminate use of systemic corticosteroids for COVID-19, and the systemic inflammatory and endothelial effects of SARS-CoV-2 itself [3, 4]. Diabetic ketoacidosis increases available free iron and impairs neutrophil function, while corticosteroids suppress cellular immunity and exacerbate hyperglycemia, collectively creating a highly permissive milieu for angioinvasive Mucorales [49].

### *Diagnostic Imperatives and Early Detection*

Timely diagnosis of mucormycosis remains extremely challenging. Clinical signs such as unilateral facial pain, black eschar on nasal turbinates or palate, cranial nerve palsies, and rapidly progressive pulmonary infiltrates are highly suggestive but often appear late [3, 4]. Histopathology demonstrating broad, ribbon-like, pauciseptate hyphae with angioinvasion remains the gold standard, but obtaining deep tissue biopsies may be logistically or clinically difficult in unstable patients. Molecular diagnostics, particularly pan-Mucorales PCR assays on serum or BAL, have shown promise in detecting circulating fungal DNA days before conventional diagnosis—median detection times 5–10 days earlier in some series—and may significantly improve outcomes if incorporated into risk-stratified screening algorithms for high-risk patients such as those with diabetic ketoacidosis and severe COVID-19 [50, 51]. Metagenomic sequencing can also identify Mucorales directly from clinical specimens in culture-negative cases but is currently restricted to specialized centers [51]. In recognition of the scale of the COVID-associated epidemic, India made mucormycosis a notifiable disease in 2021, illustrating how surveillance policy can be rapidly adapted to emerging fungal threats.

### *Multimodal Therapeutic Approaches*

Successful management of mucormycosis demands rapid initiation of high-dose liposomal amphotericin B, aggressive surgical debridement of all necrotic tissue where anatomically feasible, and correction of underlying predisposing factors, including meticulous glycemic control and tapering or discontinuation of corticosteroids whenever possible [3, 4]. Posaconazole and isavuconazole are

important second-line or step-down agents, with oral formulations facilitating prolonged outpatient therapy. The evidence base for adjunctive modalities such as hyperbaric oxygen therapy and iron chelation remains limited and conflicting, and these should be considered only on a case-by-case basis [49]. Outcomes remain poor in disseminated disease despite optimal therapy, underscoring the primacy of early recognition and intervention. The resistance profiles, ecological drivers, treatment implications, and major diagnostic or access gaps of these WHO-priority fungal pathogens are summarized in Table 2.

## Molecular Mechanisms of Antifungal Resistance

Antifungal resistance arises through a limited set of recurrent mechanisms—target alterations, efflux pump upregulation, biofilm-mediated tolerance, and stress-response-driven adaptations—but the specific genetic and phenotypic routes vary by drug class and pathogen [8]. In this section, we first consider azole resistance (Section 5.1), then echinocandin resistance (Section 5.2), biofilm-mediated resistance and persistence (Section 5.3), and finally the fitness and evolutionary dynamics that shape the spread of resistance (Section 5.4).

### *Azole Resistance Mechanisms*

#### *Target Site Alterations and Gene Overexpression*

Triazole antifungals inhibit lanosterol 14α-demethylase, a cytochrome P450 enzyme encoded by ERG11 in yeasts and cyp51A (or paralogs) in molds. Inhibiting this enzyme disrupts ergosterol biosynthesis and compromises membrane integrity. Point mutations in these genes that diminish azole binding, such as ERG11 Y132F and K143R in Candida spp. and numerous cyp51A substitutions in A. fumigatus, represent a principal resistance pathway [8]. Promoter alterations, including tandem repeats such as TR34 and TR46 in A. fumigatus, drive overexpression of the target enzyme, effectively titrating out the drug [12]. These changes often confer cross-resistance within the azole class, although MIC shifts can vary by compound due to structural differences.

#### *Efflux Pump Upregulation*

Overexpression of drug efflux pumps is a second major azole resistance mechanism. In Candida albicans, gain-of-function mutations in transcriptional regulators such as TAC1 and MRR1 upregulate ABC transporters CDR1/CDR2 and MFS transporter MDR1, respectively,

**Table 2.** WHO Fungal Priority Pathogens – Resistance Profiles and Clinical Challenges

| Pathogen (WHO priority tier) | Primary Resistance Concern | Key Resistance Mechanisms | Ecological / Environmental Driver | First-Line Treatment in Invasive Disease | Major Access / Diagnostic Gaps |
|---|---|---|---|---|---|
| **Candida auris (critical)** | Multidrug resistance, emerging pan-resistance | ERG11 mutations; ABC transporter overexpression; FKS1 mutations | Climate-driven emergence in coastal wetlands; persistence on healthcare surfaces | Echinocandin (if susceptible); liposomal amphotericin B if failure or resistance (34) | Misidentification without MALDI-TOF or molecular ID; limited susceptibility testing in many regions |
| **Aspergillus fumigatus (critical)** | Triazole resistance (itraconazole, voriconazole, posaconazole) | cyp51A TR34/L98H, TR46/Y121F/T289A; HMG1 and hapE mutations | Widespread DMI azole fungicide use in agriculture; compost and greenhouse hotspots | Voriconazole or isavuconazole in low-resistance regions; liposomal amphotericin B or azole–echinocandin combination where resistance >10 percent (40) | Lack of routine azole susceptibility testing; limited availability of resistance PCR assays |
| **Cryptococcus neoformans / gattii (critical)** | Fluconazole resistance and heteroresistance in relapse disease | ERG11 mutations; aneuploidy (Chr1 disomy); efflux pump upregulation | Soil and avian guano reservoirs; tree-associated niches for C. gattii; climate-mediated range expansion | Amphotericin B plus flucytosine induction, followed by high-dose fluconazole (17) | Inadequate access to flucytosine and liposomal amphotericin B; incomplete coverage of CrAg LFA in HIV programs |
| **Mucorales (including Rhizopus spp.) (high)** | Intrinsic resistance to most azoles and echinocandins | Low β-glucan content; distinct sterol pathways | Ubiquitous environmental molds; outbreaks linked to hospital construction and contaminated linens; excess diabetes and steroid use | High-dose liposomal amphotericin B plus aggressive surgical debridement (3, 4) | Absence of rapid specific diagnostics; limited amphotericin B access in many LMICs |
| **Candida glabrata and other Candida spp. (high)** | Azole and echinocandin resistance; emerging pan-resistance | PDR1 GOF mutations and efflux; FKS1/FKS2 hotspot mutations | Gastrointestinal microbiota under antibiotic and antifungal pressure | Echinocandin for candidemia; amphotericin B or novel agents for multi-class resistance (11) | Routine AFST not consistently performed on bloodstream isolates in many hospitals |

markedly reducing intracellular azole concentrations [8, 52]. Similar PDR1 gain-of-function mutations in C. glabrata increase expression of multiple efflux pumps and confer broad triazole resistance, sometimes accompanied by enhanced virulence [53]. In C. auris, efflux-mediated azole resistance is common and often coexists with ERG11 mutations [8].

#### *Non-Canonical Resistance Pathways*

Beyond classical target and efflux mechanisms, fungi exploit non-canonical pathways including stress response networks and genomic plasticity. The Hsp90–calcineurin axis in Candida spp. and Aspergillus spp. supports tolerance to azoles by stabilizing key stress response effectors; inhibition of Hsp90 or calcineurin can resensitize otherwise resistant isolates in vitro [54]. Aneuploidy and segmental chromosomal duplications, exemplified by chromosome 1 disomy in fluconazole-heteroresistant C. neoformans, transiently increase copy number of ERG11 and efflux genes and generate reversible high-level tolerance [43]. In A. fumigatus, mutations in hmg1 and hapE have been implicated in azole resistance in cyp51A wild-type isolates, indicating that alternative components of the sterol pathway and transcriptional networks can modulate susceptibility [55].

### *Echinocandin Resistance*

#### *FKS Gene Mutations and Clinical Emergence*

Echinocandins inhibit β-1,3-D-glucan synthase, a key enzyme in fungal cell wall biosynthesis. Resistance results primarily from missense mutations in conserved hotspot regions of FKS genes encoding the catalytic subunits. In Candida glabrata, FKS2 mutations such as S663P and F659del confer dramatic MIC elevations and are associated with breakthrough candidemia during therapy; echinocandin resistance in C. glabrata has risen to 3–10% of bloodstream isolates in some surveillance series [8, 32]. In C. auris, FKS1 mutations at S639 and adjacent residues similarly confer echinocandin resistance, and clusters of such resistant isolates have been reported in the context of prior echinocandin exposure [32, 33]. Although overall echinocandin resistance remains relatively uncommon at a global level, rising rates in C. glabrata and C. auris are alarming because these species often already exhibit azole resistance.

#### *Multi-Class Resistance and Therapeutic Implications*

The co-occurrence of azole and echinocandin resistance in Candida glabrata and C. auris creates pan-resistant phenotypes for which amphotericin B is often the only remaining licensed option, despite its toxicity and limited efficacy in some deep-seated infections [11]. Novel glucan synthase inhibitors such as ibrexafungerp retain activity against some FKS-mutant isolates but can display cross-resistance for high-level mutants, and their clinical role in invasive disease is still being defined [8]. These developments underscore the need for susceptibility-guided therapy, for diversification of the antifungal pipeline beyond existing targets, and for robust stewardship to limit unnecessary echinocandin exposure. Table 3 summarizes the principal molecular mechanisms of antifungal resistance by drug class, including key target genes, representative pathogens, and common clinical detection methods.

### *Biofilm-Mediated Resistance and Persistence*

#### *Biofilm Architecture and Drug Exclusion*

Biofilms represent structured microbial communities embedded in an extracellular matrix that fundamentally alter antifungal susceptibility. Candida biofilms on catheters or prosthetic devices exhibit up to 1000-fold increases in azole and polyene tolerance relative to planktonic cells, attributable to restricted drug penetration, matrix-mediated sequestration, altered metabolism, and distinct transcriptional programs [56]. Matrix β-1,3-glucans can bind azoles, reducing free-drug availability at target cells, and biofilm-associated cells upregulate efflux pumps and stress response genes that further diminish drug efficacy [57]. Device-associated candidemia and endocarditis therefore often cannot be cured without removal of the infected foreign body.

#### *5Persister Cells and Phenotypic Tolerance*

Within biofilms, a subpopulation of persister cells enters a dormant, non-dividing state that is tolerant to otherwise lethal concentrations of fungicidal agents such as amphotericin B. These cells rely on stress-induced metabolic reprogramming and upregulation of protective pathways, survive antifungal exposure, and can reseed the biofilm once drug pressure subsides, resulting in clinical relapse despite adequate therapy [58]. Conventional susceptibility tests, which measure net growth inhibition in planktonic populations, do not detect persister-mediated tolerance, complicating interpretation of in vitro results in chronic biofilm-associated infections.

#### *Strategies for Biofilm Eradication*

Strategies to overcome biofilm-mediated resistance emphasize aggressive source control and adjunctive anti-biofilm interventions. Removal or replacement of colonized intravascular catheters, prosthetic valves, and urinary catheters is strongly associated with improved outcomes in candidemia and endocarditis and is enshrined in treatment guidelines [56]. Antifungal lock therapy using high-concentration echinocandin or amphotericin B instilled into catheter lumens may help in selected situations where device removal is not feasible, although evidence remains limited. Experimental approaches targeting the matrix, such as co-administration of β-1,3-glucanases or other matrix-degrading enzymes, and novel small molecules like

turbinmicin that disrupt vesicular trafficking required for biofilm maturation, show promise in preclinical models and may complement systemic therapy in the future [59].

### *Fitness Costs and Evolutionary Dynamics*

#### *Fitness-Neutral Resistance and Persistence*

The evolutionary trajectory of resistance is shaped by its fitness cost. Mutations that preserve or enhance baseline fitness are more likely to persist and disseminate than those that impose metabolic burdens. Many clinically important resistance determinants appear to be fitness-neutral or minimally costly in relevant environments. For example, TR34/L98H A. fumigatus isolates exhibit growth and virulence comparable to wild type in animal models, which helps explain their widespread environmental success [38]. Similarly, PDR1 gain-of-function mutations in C. glabrata often do not significantly impair growth and can even enhance survival in the host [53]. Compensatory evolution can further ameliorate initial costs, stabilizing resistance in fungal populations even if selective drug pressure fluctuates.

#### *Virulence Enhancement in Resistant Strains*

In some instances, resistance mechanisms are directly linked to increased virulence. C. glabrata PDR1 mutations that upregulate efflux pumps have been associated with greater adherence, immune evasion, and higher fungal burdens in murine models, suggesting that acquisition of azole resistance can simultaneously enhance pathogenic fitness in vivo [53, 60]. If such dual-benefit mutations disseminate, they may contribute disproportionately to disease burden and complicate efforts to reverse resistance by stewardship alone. Understanding the interplay between resistance and virulence is therefore critical to anticipating the long-term epidemiological impact of specific resistance genotypes.

## Diagnostic Challenges and Innovations

### *The Current Diagnostic Landscape*

#### *Infrastructure Gaps and Regional Disparities*

Diagnostic capacity for fungal diseases is unevenly distributed both between and within countries. Many hospitals in LMICs lack on-site mycology laboratories capable of performing fungal culture, histopathology with fungal stains, or antigen and molecular assays; even where microscopy is available, its application to diagnose fungal disease is inconsistent [14]. In such settings, invasive fungal infections are rarely confirmed and are frequently misdiagnosed as bacterial sepsis, tuberculosis, or malignancy, leading to inappropriate treatment and high mortality [7]. In high-income settings, sophisticated diagnostics such as MALDI-TOF and galactomannan assays are increasingly available but are not universally implemented, and misidentification of emerging species like C. auris by biochemical identification systems remains a problem

**Table 3.** Mechanisms of Antifungal Resistance by Drug Class

| Drug Class | Primary Molecular Target | Principal Resistance Mechanisms | Key Genes Involved | Example Pathogens | Common Clinical Detection Methods |
|---|---|---|---|---|---|
| **Azoles** | Lanosterol 14α-demethylase (Erg11/Cyp51) | Target-site mutations; promoter repeats and overexpression; efflux upregulation; aneuploidy; Hsp90–calcineurin–mediated tolerance | ERG11, cyp51A/B/C; TAC1, MRR1, PDR1; HMG1, hapE; HSP90, calcineurin subunits | Candida albicans, C. auris, A. fumigatus, Cryptococcus neoformans | Broth microdilution or commercial MIC panels; ERG11 and cyp51A PCR/sequencing; MALDI-TOF plus WGS in reference centers |
| **Echinocandins** | β-1,3-D-glucan synthase (Fks complex) | Hotspot mutations in catalytic subunit genes; altered cell wall stress responses and tolerance | FKS1, FKS2, FKS3 | Candida glabrata, C. auris, C. parapsilosis | MIC testing by CLSI or EUCAST methods; targeted FKS hotspot sequencing |
| **Polyenes** | Ergosterol in fungal cell membrane | Altered sterol composition via mutations in ergosterol biosynthesis; oxidative stress response | ERG2, ERG3, ERG5, ERG6; oxidative stress regulators | Candida lusitaniae, rare Cryptococcus isolates | Phenotypic MICs; sterol profiling in research settings |
| **Flucytosine** | Thymidylate synthase and RNA/DNA synthesis (after intracellular conversion) | Loss-of-function mutations in cytosine permease and deaminase; pyrimidine salvage pathway alterations | FCY1, FCY2, FUR1 | Cryptococcus neoformans, Candida spp. | MIC testing; sequencing of FCY and FUR1 in refractory cases |
| **Novel agents (e.g., ibrexafungerp, fosmanogepix, olorofim)** | Various (β-1,3-glucan synthase, Gwt1, dihydroorotate dehydrogenase) | Target-site mutations; potentially shared mechanisms with related classes | FKS1, GWT1, DHODH and others | Candida spp., Aspergillus spp., rare molds | Under evaluation in clinical trials; WGS in resistance investigations |

in laboratories without updated databases or access to molecular methods [26]. Diagnostic delay is strongly associated with mortality in invasive aspergillosis, candidemia, and mucormycosis, emphasizing the clinical impact of these gaps [2].

#### *Essential Diagnostic Packages by Healthcare Level*

To rationalize investments, several groups have proposed tiered "essential diagnostic packages" aligned with healthcare level. At primary care and HIV clinics, point-of-care cryptococcal antigen lateral flow assays and Histoplasma antigen tests are critical for early detection of life-threatening opportunistic infections and have been added to the WHO Essential Diagnostics List [61]. At district and secondary hospitals, capacity for fungal culture, microscopy, and histopathology, together with serum galactomannan and β-D-glucan where feasible, provides a minimum platform for diagnosing most invasive mycoses. Tertiary and reference laboratories should add MALDI-TOF mass spectrometry, species-level identification of yeasts and molds, antifungal susceptibility testing, and molecular assays for pathogens and resistance markers, as well as therapeutic drug monitoring for triazoles [62]. Strengthening referral networks to allow specimens to be sent to reference labs for specialized testing is essential to ensure equitable diagnostic access across health systems.

### *Advances in Rapid and Molecular Diagnostics*

#### *Multiplex PCR and Resistance-Aware Platforms*

Syndromic multiplex PCR panels for blood cultures and cerebrospinal fluid—such as the BioFire FilmArray Blood Culture Identification (BCID) and Meningitis/Encephalitis (ME) panels—can identify common Candida species and Cryptococcus within hours of specimen positivity, substantially shortening time to targeted therapy compared with conventional culture-based workflows [63]. More sophisticated assays, such as the AsperGenius platform, integrate pathogen detection with simultaneous interrogation of cyp51A mutations associated with azole resistance in A. fumigatus directly from bronchoalveolar lavage specimens, enabling early "resistance-aware" treatment decisions for suspected invasive aspergillosis [41]. Wider deployment of such resistance-informed diagnostics could help operationalize guideline recommendations that hinge on local resistance prevalence and individual-level susceptibility.

#### *Metagenomic Next-Generation Sequencing*

Unbiased metagenomic next-generation sequencing (mNGS) of blood, CSF, or tissue is emerging as a powerful adjunct in diagnostically challenging cases where conventional tests are negative or infeasible. mNGS can detect DNA or RNA from a broad spectrum of fungal pathogens, including rare and unexpected agents, and can, in principle, capture resistance-associated mutations if coverage is sufficient [63, 64]. Case series in immunocompromised patients with undiagnosed pneumonia or CNS disease have demonstrated that mNGS can identify pathogens such as Coccidioides, Talaromyces, or Mucorales when culture and histopathology were non-contributory, directly affecting management. High cost, specialized bioinformatic requirements, and challenges in discriminating true infection from environmental or commensal DNA currently limit routine use; at present, mNGS is best reserved for high-risk, culture-negative, or otherwise unexplained infections in tertiary centers. Rapid improvements in sequencing technology and analysis workflows are likely to expand clinical application in the coming decade.

### *Surveillance Diagnostics and Resistance Monitoring*

#### *Clinical Surveillance Integration*

Effective surveillance for fungal disease and antifungal resistance depends on integrating diagnostic data into structured reporting systems. The WHO GLASS-Fungi pilot demonstrated the feasibility of collecting standardized data on candidemia species distribution and fluconazole susceptibility from sentinel hospitals across multiple countries, but also highlighted deficits in routine antifungal susceptibility testing and data management in many participating sites [65]. Candidemia is a tractable surveillance target because of its relative frequency and the feasibility of blood culture diagnostics; systematic reporting of species and susceptibility profiles can track the emergence of C. auris, shifts toward intrinsically less susceptible species like C. glabrata and C. parapsilosis, and the spread of azole and echinocandin resistance [65].

#### *Environmental and Wastewater Surveillance*

Environmental surveillance for azole-resistant A. fumigatus through systematic sampling of compost, agricultural soils, and ambient air, coupled with susceptibility testing and genotyping, provides critical information on resistance hotspots and can inform regulatory action on fungicide use [25]. Wastewater-based epidemiology, successfully used for SARS-CoV-2, is being explored for fungal pathogens such as C. auris; detection of C. auris DNA in sewage can indicate community or institutional circulation even before clinical cases are recognized [66]. Integrating such environmental and wastewater data with clinical surveillance in a One Health framework can provide an early warning system for emerging threats.

## Surveillance, One Health, and Policy Frameworks

### *Building Sustainable Surveillance Systems*

#### *Clinical Surveillance Infrastructure*

Establishing sustainable fungal surveillance requires investment in both laboratory and

information systems. Sentinel hospital networks with trained staff capable of species-level identification and antifungal susceptibility testing, supported by reference laboratories that can perform molecular typing and whole-genome sequencing, form the backbone of such systems [65]. Mandatory or strongly encouraged reporting of selected high-priority entities such as C. auris, cryptococcal meningitis, and serious mold infections enables timely outbreak detection and resource mobilization. Integration of fungal AMR surveillance into existing national AMR action plans and IT platforms, rather than constructing stand-alone systems, offers efficiency and promotes recognition of fungal resistance as part of the broader AMR agenda [7].

#### *Environmental and Agricultural Surveillance*

Parallel surveillance structures in environmental and agricultural sectors are necessary to capture One Health dimensions of antifungal resistance. Routine monitoring of agricultural azole use volumes by crop and geography, coupled with periodic sampling of high-risk environments such as flower bulb farms, greenhouses, and composting facilities for A. fumigatus resistance, can identify drivers and hotspots of environmental selection [24, 25]. Data-sharing mechanisms between agricultural regulatory agencies, environmental health authorities, and public health institutions are essential to link changes in fungicide policy with trends in clinical resistance and to coordinate such as restricting the most problematic DMI fungicides. Table 4 outlines a One Health surveillance framework linking human health, environmental, and agricultural indicators with surveillance methods, data-integration points, and responsible sectors.

### *Policy Responses and International Coordination*

#### *The WHO Fungal Priority Pathogens List as Policy Driver*

The WHO FPPL provides a strategic framework to prioritize investment, research, and capacity-building for fungal diseases, analogous to bacterial priority pathogen lists that have guided antibiotic R&D and stewardship initiatives [67]. By classifying pathogens into critical, high, and medium priority tiers based on burden, resistance, transmissibility, and availability of countermeasures, the FPPL signals to national governments and donors where efforts are most urgently needed. Countries are encouraged to incorporate fungal threats into their national action plans on AMR, to define surveillance and diagnostic targets, and to allocate specific resources for laboratory strengthening, drug procurement, and infection prevention and control for FPPL organisms. The FPPL also serves as an advocacy tool to elevate fungal diseases on the global health agenda and to justify inclusion of antifungal R&D in international funding mechanisms.

#### *Regulatory Considerations for Agricultural Fungicides*

Regulatory interventions on agricultural fungicide use are central to addressing environmental selection of resistance, particularly in A. fumigatus. Options include restricting or phasing out specific DMI compounds with greatest structural similarity to medical azoles, promoting integrated pest management and non-azole fungicide classes, and implementing stewardship programs akin to antibiotic stewardship in human medicine [9]. International coordination is needed to avoid regulatory arbitrage in global fungicide markets and to account for cross-border spread of resistant spores through trade and atmospheric transport. Collaborative assessments by WHO, the Food and Agriculture Organization, and the World Organization for Animal Health can help harmonize policies and quantify co-benefits in plant and human health.

#### *Predictive Modeling and Preparedness*

Predictive modeling tools that integrate climate projections, land use, fungicide application patterns, pathogen genomics, and clinical surveillance data can identify future hotspots of fungal emergence and resistance. Machine learning approaches applied to genomic and phenotypic data already achieve high accuracy in predicting resistance in bacteria and are beginning to be applied to fungal pathogens such as Candida and Aspergillus [68]. Geospatial niche models for Coccidioides and A. fumigatus under various climate scenarios can guide preparedness efforts, including pre-positioning of diagnostics and training clinicians in newly at-risk regions [22, 69]. Incorporating such predictive analytics into national and global early warning systems would allow a shift from reactive to anticipatory responses to fungal threats.

## Therapeutic Landscape And Future Directions

### *Optimizing Treatment of Resistant Infections*

#### *Current Treatment Strategies for Multidrug-Resistant Pathogens*

Treating infections caused by multidrug-resistant fungal pathogens frequently requires individualized, aggressive regimens that deviate from standard guidelines. For C. auris, echinocandins remain first-line but must be rapidly switched to liposomal amphotericin B, with or without flucytosine or a second azole, in the setting of documented echinocandin resistance or clinical failure [34]. Management of azole-resistant aspergillosis typically involves liposomal amphotericin B monotherapy or, in some centers, combination therapy with a triazole and an echinocandin, particularly in hosts with profound immunosuppression [40]. For echinocandin- and azole-resistant C. glabrata, amphotericin B-based

regimens, sometimes combined with flucytosine, represent a last-line option [11]. Therapeutic drug monitoring for triazoles is crucial in these scenarios to ensure adequate exposure relative to elevated MICs and to minimize toxicity.

#### *Novel Antifungal Agents in Development*

Several novel antifungals with new mechanisms of action are in late-stage development and hold promise for treating resistant infections. Ibrexafungerp, a triterpenoid glucan synthase inhibitor distinct from echinocandins, has oral bioavailability and activity against many azole- and echinocandin-resistant Candida isolates, including some C. auris strains, and is being evaluated for invasive candidiasis [8]. Fosmanogepix, a first-in-class inhibitor of the Gwt1 enzyme required for glycosylphosphatidylinositol anchor biosynthesis, exhibits broad-spectrum activity against Candida (including C. auris), Aspergillus, and other molds and is in phase 2–3 trials [9]. Olorofim, targeting dihydroorotate dehydrogenase in pyrimidine biosynthesis, is active against Aspergillus (including azole-resistant strains) and some rare molds and is being studied for refractory invasive mold disease [9]. Ensuring that these agents are evaluated in populations with resistant infections and that regulatory pathways facilitate timely global access will be crucial to realizing their potential.

### *Antifungal Stewardship Programs*

#### *Principles and Implementation*

Antifungal stewardship (AFS) seeks to optimize antifungal use in order to improve outcomes and limit resistance. Core elements include promoting early and appropriate therapy for proven or strongly suspected IFIs, while avoiding unnecessary empirical or prophylactic use in low-risk settings, and facilitating de-escalation or discontinuation based on diagnostic results [70]. Diagnostic stewardship is integral, emphasizing timely procurement of blood cultures, imaging, and fungal biomarkers, as well as the appropriate use of advanced diagnostics such as galactomannan and PCR panels to refine pre-test probabilities before initiating prolonged antifungal courses. Pharmacist- and infection specialist–led AFS programs have demonstrated reductions in antifungal consumption, drug expenditures, and inappropriate prescribing in both high- and middle-income settings [71].

#### *Balancing Access and Stewardship*

In many LMICs, the primary antifungal challenge is underuse rather than overuse, driven by lack of diagnostic capacity, limited drug availability, and financial barriers. Stewardship in these contexts must therefore be carefully calibrated to avoid inadvertently restricting access. Rather than focusing on constraining use, AFS programs should prioritize ensuring that high-risk patients, such as those with advanced HIV or hematologic malignancy, receive timely, guideline-concordant antifungal therapy and that essential drugs like amphotericin B and flucytosine are consistently stocked [45]. Global policy must explicitly recognize that antifungal stewardship and improved access are complementary, not competing, goals: “access + stewardship” should be seen as a single integrated agenda in which expanded availability of high-quality drugs and diagnostics is paired with systems to ensure their rational, equity-focused use.

### *Research Priorities and Policy Incentives*

#### *Addressing Market Failures in Antifungal R&D*

Antifungal drug development faces classic market failures: small and heterogeneous patient populations, complex and risky clinical trials, and limited commercial returns compared to chronic disease therapeutics. To overcome these barriers, a mix of push and pull incentives is required, including public and philanthropic grants for early-stage discovery, tax credits, market entry rewards, transferable

**Table 4.** One Health Surveillance Framework for Fungal Diseases

| Domain | Key Indicators | Methodology | Data Integration Points | Responsible Sectors |
|---|---|---|---|---|
| **Human health** | Incidence of candidemia by species and resistance; rates of azole-resistant aspergillosis; cryptococcal meningitis incidence and outcomes | Sentinel hospital reporting; GLASS-Fungi; case-based notifications; laboratory-based surveillance | National AMR databases; WHO GLASS; linkage with HIV and cancer registries | Ministries of Health; national reference laboratories; hospitals |
| **Environment** | Prevalence of azole-resistant A. fumigatus in soil, compost, and air; presence of C. auris or Cryptococcus in natural and built environments | Systematic environmental sampling; culture on azole-containing media; molecular typing; wastewater surveillance | Shared One Health dashboards linking environmental and clinical data | Environmental protection agencies; public health institutes |
| **Agriculture** | Volume and type of agricultural azole fungicide use; resistance in plant-pathogenic fungi; on-farm A. fumigatus resistance rates | Pesticide sales and use reporting; plant pathology lab surveillance; farm-level environmental sampling | Joint databases across agriculture and health; risk mapping for hotspot identification | Ministries of Agriculture; pesticide regulatory authorities; extension services |

priority review vouchers, and subscription-type reimbursement models that delink revenue from sales volume [72]. Public–private partnerships akin to CARB-X for antibacterial agents should explicitly include fungal pathogens prioritized in the FPPL, and regulatory agencies should harmonize and streamline approval pathways for antifungals, particularly for indications involving resistant organisms where randomized trials may be logistically difficult.

### *Vaccine Development and Immunotherapy*

Vaccines and immunotherapies targeting major fungal pathogens represent a critical but underdeveloped frontier. Candidate vaccines for Candida, Aspergillus, and Cryptococcus are at various preclinical and early clinical stages, employing strategies such as recombinant proteins, conjugates, and mRNA platforms, and aim either to prevent infection in high-risk populations or to reduce relapse and chronic colonization[46, 47]. Immunomodulatory approaches, including adjunctive interferon-gamma or granulocyte-macrophage colony-stimulating factor in refractory mold infections, and monoclonal antibodies directed at fungal antigens, are also under investigation. Prioritizing these interventions in global research agendas and ensuring that target product profiles reflect the constraints and needs of high-burden settings will be essential to achieving preventive impact.

## Conclusion

The emerging fungal crisis is characterized by the convergence of multiple reinforcing drivers: a rapidly expanding population of immunocompromised and critically ill patients; accelerating climate change and land-use alterations that erode thermal and ecological barriers and expand the range of environmental fungi; agricultural and environmental practices, particularly DMI fungicide use, that select for clinically relevant resistance; and a constrained antifungal armamentarium confronted by rising multidrug resistance. These dynamics are compounded by profound diagnostic and surveillance gaps, especially in LMICs, which obscure the true magnitude of the problem and delay lifesaving therapy. Pathogens such as C. auris, azole-resistant A. fumigatus, Cryptococcus spp., and Mucorales exemplify different but interconnected facets of this challenge, from healthcare-associated transmission and pan-resistance to access failures and climate-driven emergence.

Addressing this threat requires coordinated action along several axes. First, strengthening diagnostic and surveillance infrastructure, guided by tiered essential diagnostic packages and integrated One Health surveillance frameworks, is indispensable for accurate burden estimation, timely outbreak detection, and resistance monitoring. Second, cross-sectoral One Health interventions, including fungicide stewardship in agriculture and environmental monitoring, must complement clinical antifungal stewardship to curb the environmental generation and spread of resistance. Third, equitable access to essential antifungals and diagnostics must be ensured, particularly for high-burden conditions like cryptococcal meningitis and mucormycosis, through regulatory reforms, pooled procurement, and dedicated financing mechanisms. Finally, sustained investment in antifungal R&D, including drugs, vaccines, and diagnostics, supported by innovative economic incentives and global partnerships, is needed to expand the therapeutic and preventive toolbox.

If current trajectories of climate change, agricultural fungicide use, and healthcare expansion continue without substantial investment in fungal diagnostics, therapeutics, and surveillance, invasive fungal infections and antifungal resistance are likely to increase in incidence, geographic scope, and complexity, eroding gains in cancer care, transplantation, intensive care, and HIV management. Conversely, a coordinated global response that integrates fungal threats into AMR strategies, climate adaptation planning, and health system strengthening offers an opportunity to shift from reactive crisis management to proactive prevention and control. The WHO FPPL has created a policy window for elevating fungal diseases on the global health agenda; the challenge now is to translate this recognition into concrete, sustained action that can avert a future in which common medical interventions are once again constrained by untreatable fungal infections.

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