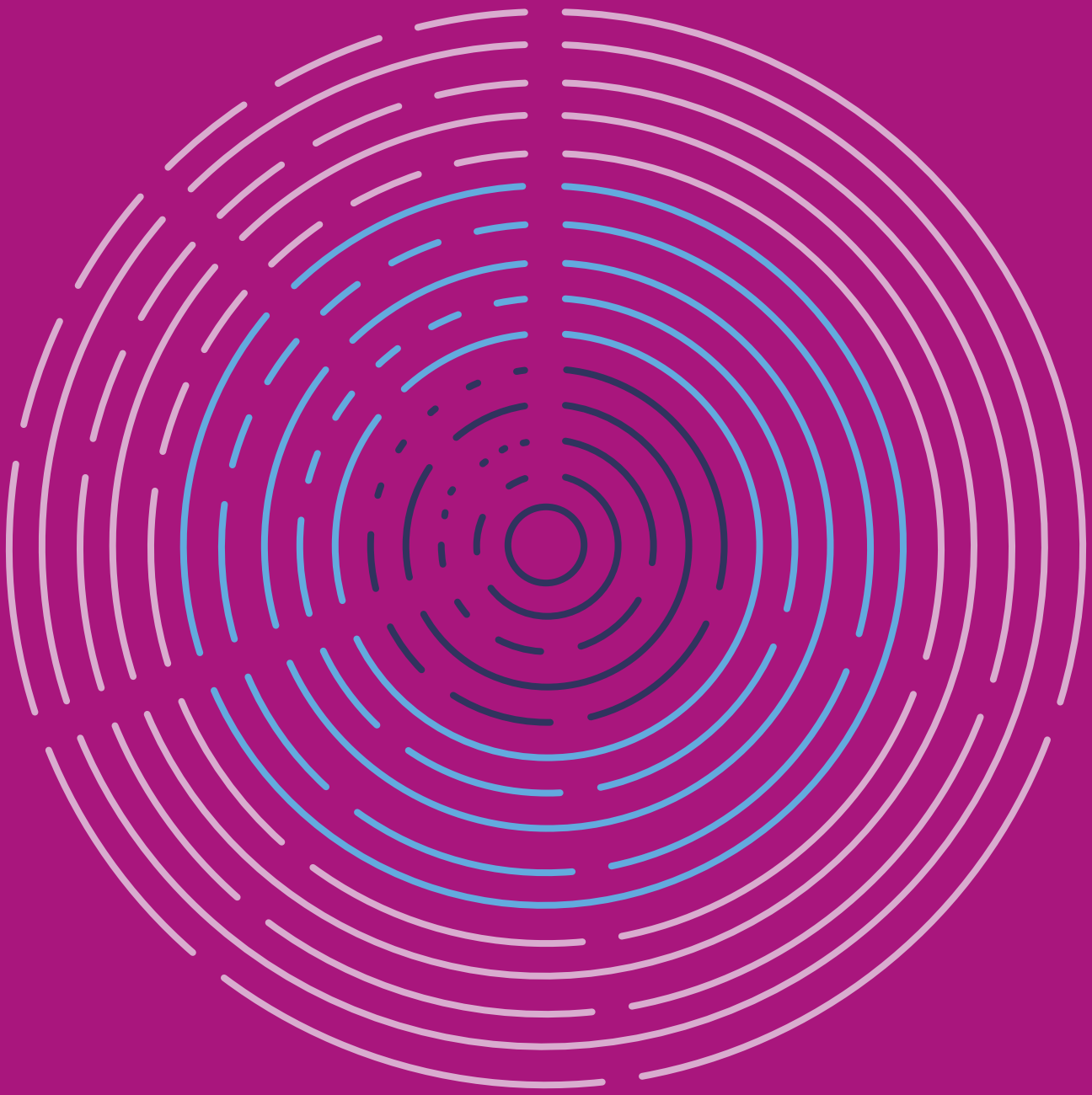

Antifungal agents in clinical and preclinical development

Overview and analysis

World Health Organization

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Antifungal agents in clinical and preclinical development: overview and analysis

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Contents

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Abbreviations

AE	adverse event
AIDS	acquired immune deficiency syndrome
AmB	amphotericin B
AMR	antimicrobial resistance
CNS	central nervous system
CPP	critical priority pathogen
DDI	drug–drug interaction
DNDi	Drugs for Neglected Diseases initiative
DOI	declaration of interest
EMA	European Medicines Agency
FPPL	fungal priority pathogens list
GARDP	Global Antibiotic Research and Development Partnership
HIV	human immunodeficiency virus
IFD	invasive fungal disease
ITT	intended-to-treat
iv	intravenous
MoA	mode of action
NCC	new chemical class
NCE	new chemical entity
NCR	no cross-resistance within and across antimicrobial classes
NT	new target
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetics
po	per os
R&D	research and development
RVVC	recurrent vulvovaginal candidiasis
SAE	serious adverse event
US-FDA	United States Food and Drug Administration
VVC	vulvovaginal candidiasis
WHO	World Health Organization

Executive summary

This report presents the first World Health Organization (WHO) analysis of antifungal agents in preclinical and clinical development. It covers systemic antifungal drugs in development worldwide, including label extension and repurposed products, and critically evaluates how well the current pipeline addresses infections caused by WHO fungal priority pathogens.

The report also assesses whether the agents in development have in vitro and in vivo data showing no known cross-resistance. When no cross-resistance is observed, the candidate drug is considered potentially innovative for the scope of this review. Surrogate criteria for assessing the innovation potential include belonging to a new chemical class, presenting a novel target, and/or having a new mode of action. These criteria are intended to support and/or explain the observed lack of cross-resistance or, in cases where no data on cross-resistance has been generated, predict the potential for a drug to show no cross-resistance.

It is acknowledged that the main innovation criterion is the eventual added clinical benefit shown by an individual agent. However, this can only be evaluated upon the completion of a given drug's clinical development and finally confirmed when real-world data are available. The innovation assessment conducted in this report should be regarded as a predictive tool, used during the early stages of drug development, to estimate the likelihood of an agent becoming an effective treatment against multidrug-resistant fungi.

The scope of the present report is to provide an overview of the current research and development (R&D) landscape and to foster the development of products for the most urgent unmet medical needs. The review also highlights some of the financial and technical limitations associated with current R&D of antifungal drugs, including issues related to access and availability particularly in low-resource settings.

WHO, along with an expert advisory group on the R&D of novel antifungal treatments, conducted a rigorous evaluation of antifungal agents in clinical and preclinical development. The review process with the expert group involved pre-consultation surveys, in-depth discussions during a one-day virtual meeting, and the use of a newly developed assessment matrix. The report was circulated among all members and observers of the expert group for feedback before publication. The full methodology is described.

Key facts about the present antifungal drug arsenal

- Most approved antifungal drugs commercially available pose challenges, including frequent adverse events, significant drug–drug interactions, limited dosage forms, and the need for prolonged treatment courses (often 'in-hospital').
- Within the range of antifungal medications available to adults, there is a lack of antifungals with a child-friendly formulations for paediatric use.

Key facts about newly approved antifungals

- In the past 10 years, only four new antifungal drugs have been approved by the United States Food and Drug Administration, the European Medicines Agency, or by the Chinese National Medical Products Administration.
- All four approved drugs have both in vitro and in vivo data for activity against at least one critical priority pathogen (CPP) according to the WHO Fungal priority pathogens list (FPPL); two candidates have activity against three CPPs, one agent shows activity against two CPPs, and one agent against one CPP.
- Three antifungal drugs have in vitro and in vivo evidence of activity against some of the WHO high- and medium-priority pathogens, also known as other priority pathogens (OPPs).
- Only one of the approved drugs meets any of the criterion agreed by WHO to assess innovation.
- Three out of the four approved drugs have a reduced risk of DDIs.

Key facts about the pipeline of antifungal drugs in clinical development

- Nine agents are currently in clinical development against priority fungal pathogens according to the WHO FPPL; three agents are in phase 3, two in phase 2 and four in phase 1.
- Seven agents out of nine (78%) currently have in vitro and in vivo evidence of activity against at least one CPP according to the WHO FPPL; two candidates have activity against all four CPPs, one candidate (11%) has activity against three CPPs, and one agent shows activity against two CPPs (14%).
- Among the CPPs, *Aspergillus fumigatus* is targeted by the highest number of antifungal candidates, with both in vitro and in vivo data publicly available. It is followed by *Candida albicans* and *Candida auris*, which are targeted by four and three agents respectively.
- Only two agents have in vitro and in vivo evidence of activity against *Cryptococcus neoformans*.
- Three out of nine (33%) candidate antifungal drugs have in vitro and in vivo data against at least one OPP from the WHO FPPL.
- Three antifungal candidates (33%) are in ongoing trials investigating their activity against WHO CPPs. All of them are currently being tested in pulmonary or invasive aspergillosis (IA), while only one (12%) is also undergoing investigation in patients with *C. albicans* or *C. auris* infections. None is under clinical investigation against cryptococcal meningitis.
- Two candidate antifungal drugs out of nine (22%) are currently under clinical investigation against WHO OPPs.
- Among the nine antifungal drugs in clinical development, four (44%) meet at least one innovation criterion. Of these, two (25%) meet all four innovation criteria, while two (22%) meet one innovation criterion.
- Among the nine candidate antifungal drugs, only three (33%) address a new molecular target, one of which is still not clearly identified.
- Overall, there is a lack clinical trials for paediatric indications that explore appropriate dosing (paediatric posology) and/or formulations.

Overall, antifungal agents in the clinical pipeline combined with those approved in the past decade are still insufficient, when considering the key targets and the innovation needed, to address the therapeutically challenging fungal pathogens identified by WHO.

Key facts about the preclinical pipeline of antifungal drugs

The WHO global review of antifungal agents in pre-clinical development captured 22 products targeting the WHO FPPs. The preclinical pipeline remains extremely sparse and insufficient to address the global need to prevent and treat drug-resistant fungal infections. The WHO analysis found that:

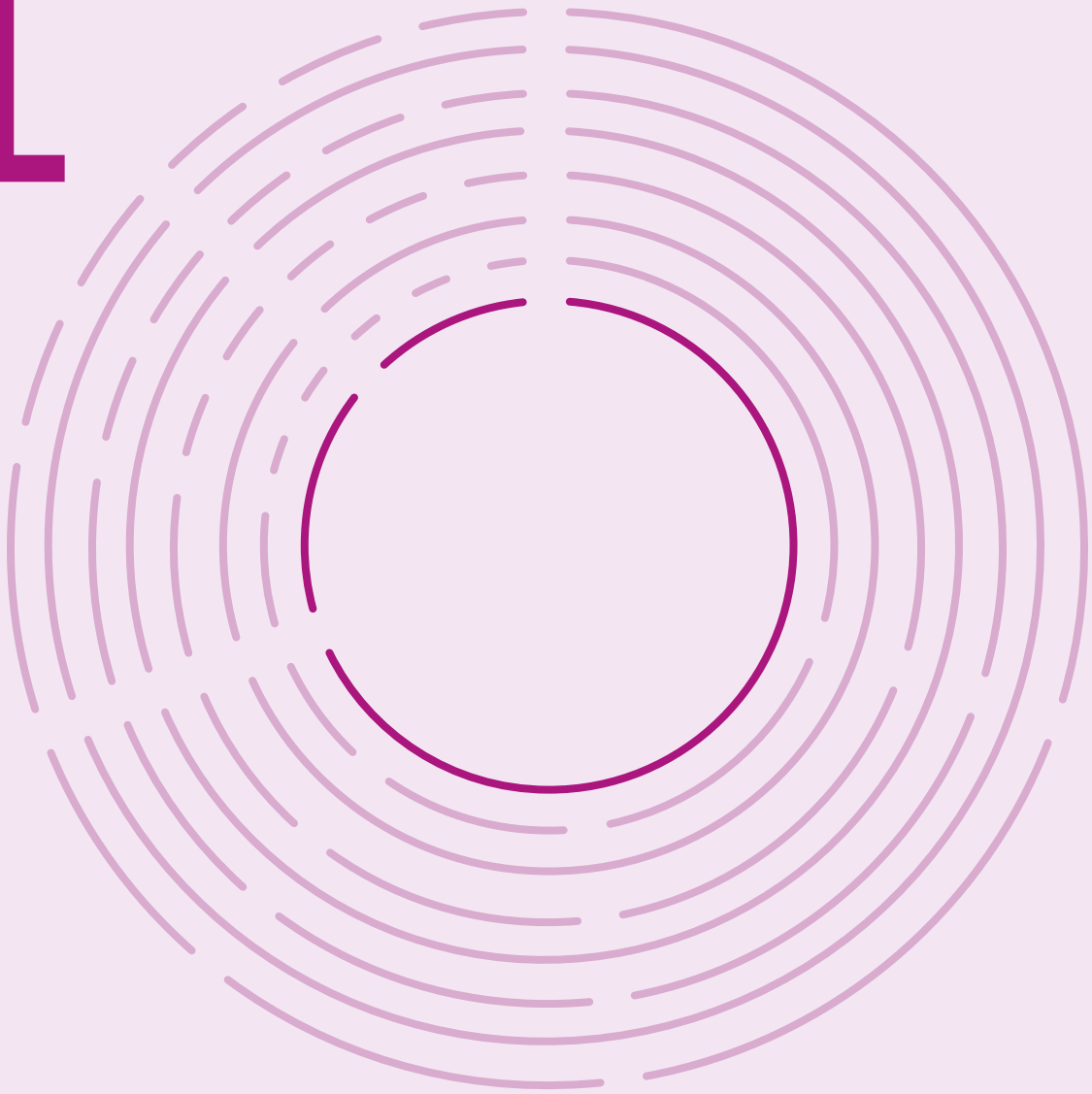
- 18 individual groups are currently progressing 22 programmes that target the WHO FPPs.
- A total of nine drugs (40.9%) demonstrate in vitro activity against all four CPPs.
- Five products (22.7%) are classified as ‘non-traditional’ agents.
- The review captures research projects in all six WHO regions with the majority (54.5%) being developed in the region of the Americas, followed by 27.3% in the European region.

This is the first WHO published overview of the clinical and preclinical antifungal pipeline to date based on publicly available data. The data is available and downloadable on the WHO Global Observatory on Health R&D. WHO will continue to collect and make available this data on a regular basis to promote innovation, collaboration and transparency in the scientifically and economically challenging field of antifungal development, to support development of much needed therapies to treat serious fungal infections.

The clinical and preclinical data contained in this report can be accessed and downloaded from the WHO Global Observatory on Health R&D:

https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antifungal-agents-in-development

1



Introduction

1. Introduction

Recent estimates describe an annual incidence of 6.5 million invasive fungal infections and 3.8 million deaths, of which about 2.5 million (68%; range 35–90%) were directly attributable to those infections *(1)*. This severe and often overlooked burden urgently calls for improved global epidemiological studies that can provide more accurate, high-quality data.

Fungal diseases range from common localized and superficial infections to severe invasive fungal diseases (IFDs) that have a lower overall incidence but are associated with unacceptably high mortality rates, often exceeding 50% even with recommended antifungal therapies *(1–4)*. IFDs are the leading cause of mortality and morbidity in immunocompromised patients *(1)*. The prevalence of IFDs is rising as immunocompromised populations expand globally, and is projected to increase significantly, considering the progress made in other therapeutic areas such as oncology, immunology, solid organ and stem cell transplants, and critical care medicine *(4,5)*. The major at-risk categories for IFDs include patients with haematological malignancies, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), transplant, cancer chemotherapy and patients undergoing intensive care *(4,6)*. Other significant risk factors for IFDs include renal insufficiency, diabetes mellitus, extensive use of antibacterials, haemodialysis, parenteral nutrition, use of corticosteroids and mechanical ventilation, and surgical interventions *(7,8)*. However, the COVID-19 pandemic was associated with a marked increase in reported fungal infections *(9)*, highlighting their potential impact beyond classical high-risk patient groups and emphasizing the need to improve surveillance.

Moreover, at-risk populations are projected to further expand due to conflicts, natural disasters, displacement of people and poverty, which all affect individuals and communities on a growing scale *(10)*. Fungal infections appear to be more common in males from certain racial and ethnic groups, suggesting that social determinants of health and disparities may influence the incidence of these infections *(11–13)*.

Examples of IFDs of serious concern are those caused by the critical priority fungal pathogens identified and described in the World Health Organization (WHO) fungal priority pathogens list (FPPL) *(9)* (Fig. 1). Fungal pathogens identified as critical priority are: *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Candida auris* and *Candida albicans*.

Cryptococcus neoformans may cause systemic infections when fungal spores in the environment are inhaled. Invasive disease develops predominantly in immunocompromised individuals and includes meningoencephalitis and, less frequently, pulmonary cryptococcosis. Cryptococcal meningitis is estimated to affect 194 000 people annually, resulting in 147 000 deaths (75.8% mortality) *(1)*, and is a major health problem in countries with high HIV prevalence and limited health care facilities/access. The clinical management of severe lung infections and cryptococcal meningitis requires a combination of liposomal amphotericin B (L-AmB) and flucytosine followed by fluconazole *(9,14–16)*. Most strains are still sensitive to amphotericin B (AmB), but resistance to fluconazole has emerged, albeit at low rates. However, cryptococcal infections are frequently characterized by relapse and/or refractory illness, as well as high mortality. Indeed, the relationship among fluconazole pre-treatment, in vitro susceptibility data and clinical response is not always straightforward, with inconclusive data obtained from different studies. Current perspectives attribute therapeutic failure to a combination of factors including high fungal burden, insufficient antifungal concentration in brain (or other tissues), slow rates of cerebrospinal fluid sterilization, intracranial hypertension, and altered mental status on admission *(17)*.

Aspergillus fumigatus causes a variety of infectious from allergic diseases to invasive aspergillosis, depending on the host's immune status or pulmonary structure *(5)*. The most recent estimate of annual global incidence of invasive aspergillosis in patients with pulmonary disease, intensive care, lung cancer or haematological malignancy is over 2 million, with a crude annual mortality of roughly 85% *(1)*. *A. fumigatus* infection is treated with triazoles but increasing resistance to triazoles arising from their use both in the clinic and agricultural settings is worrisome *(9,6,18)*. The main mechanism of resistance to triazoles in *A. fumigatus* is the development of mutations in the cyp51A gene, which encodes a 14-α-sterol demethylase participating in ergosterol production *(19)*. Most resistant isolates of *A. fumigatus* show resistance to at least two triazoles and many isolates are pan-azole resistant. Thus, considering that pyrimidines analogues (i.e. flucytosine) are not active against resistant *A. fumigatus* and monotherapy with currently approved echinocandins is not recommended for these infections (and is exclusively intravenous), extremely limited treatment options are available in cases involving resistant strains (i.e.

polyenes and newer azoles). Resistance to *A. fumigatus* has already spread worldwide, although it is largely underestimated due to the lack of routinely performed susceptibility testing and the general poor sensitivity of cultures for filamentous fungi. However, available data show higher resistance rates in Europe followed by United States of America, Asia Pacific and South America *(20)*. In cases of undetected pan-azole-resistant *A. fumigatus*, standard azole therapy proves ineffective, resulting in high failure rates. This presents a significant challenge in low- and middle-income countries where azole therapy is recommended by treatment guidelines, yet antifungal susceptibility testing is not routinely available.

Candida species rank among the most common causes of IFDs. According to recent estimates, more than 1.5 million people contract a *Candida* bloodstream infection or invasive candidiasis (i.e. infections of various organs) each year with 995 000 deaths (66.3% mortality) *(1)*. Among *Candida* species, *C. albicans* is most frequently associated with invasive candidiasis that can manifest as sepsis, with multi-organ dysfunction and septic shock *(21,22)*. Due to its high adaptability, *C. albicans* may develop resistance against all four antifungal classes *(23)* including echinocandins, which are recommended as first-line therapy for IC *(24–26)*. *C. auris* has been isolated from 39 countries and on all continents, it persists in the health care environment and spreads easily among patients in health facilities. Invasive candidiasis outbreaks from *C. auris* can be challenging to control and eradicate *(27)* and can be fatal if not diagnosed and managed promptly. Almost one third of patients with candidaemia due to *C. auris* develop septic shock *(28)*. A surge in *C. auris* bloodstream infections has been observed in the Middle East, South Asia and southern Africa where it has been associated with an epidemiological shift *(29,30)*. *C. auris* is often multidrug resistant. Resistance to at least two classes of antifungal drugs has been observed in more than 40% of clinical isolates, and cases showing resistance to three classes of antifungal drugs (i.e. azoles, echinocandins and polyenes) have been reported in several countries *(31–34)*. Pan-resistant isolates make invasive infections very difficult to treat *(35)*.

The clinical options for treatment of fungal diseases are subject to significant limitations. First, there is a limited number of therapeutic antifungal drug classes available. There are currently only five antifungal classes approved for the treatment of invasive fungal diseases (polyenes, pyrimidines, azoles, echinocandins and triterpenoids), of which only four are used clinically, and most are associated with long treatment courses, off-target toxicities, and drug–drug interactions. Second, the emergence and spread of resistance to most of these classes is a growing concern. Despite intrinsic antimicrobial resistance (AMR) being a natural phenomenon, the rising rates of resistance are being driven, in part, by the long associated treatment regimens and by the widespread use of antifungals – such as those in the class of azoles – both clinically and in agriculture and industry *(36,37)*. Also, the increasing incidence of drug resistance decreases the effectiveness of sequential antifungal combination therapy that is often used against aggressive IFDs. For instance, prior exposure of *Candida* spp. or *A. fumigatus* to azole drugs was shown to increase fungal tolerance to polyenes such as AmB *(38,39)*. All these factors contribute to the selective pressure on fungi and to the spread of pathogenic strains with gene mutations encoding for drug resistance. Third, the development of new antifungals is challenging both scientifically and economically. A major scientific barrier is the identification and inhibition of new selective or unique drug target(s), given that fungi are eukaryotes and share similar molecular targets with human hosts *(40)*.

Although some antifungal drugs are available, clinicians face significant challenges in treating life-threatening invasive fungal infections with a limited range of options. This highlights the urgent need for investment in antifungal research and development (R&D) to provide patients with better therapies and diagnostics. New and safer antifungal agents with improved pharmacological features allowing for predictable dosing strategies – and possibly avoiding the need for therapeutic drug monitoring – are urgently needed to address the concerning rise in drug resistance. Broad-spectrum antifungal agents are also needed to enable prompt empiric treatment, in addition to narrow-spectrum therapies coupled with effective diagnostic tools for detection, identification, susceptibility testing and monitoring of patient recovery.

Scope

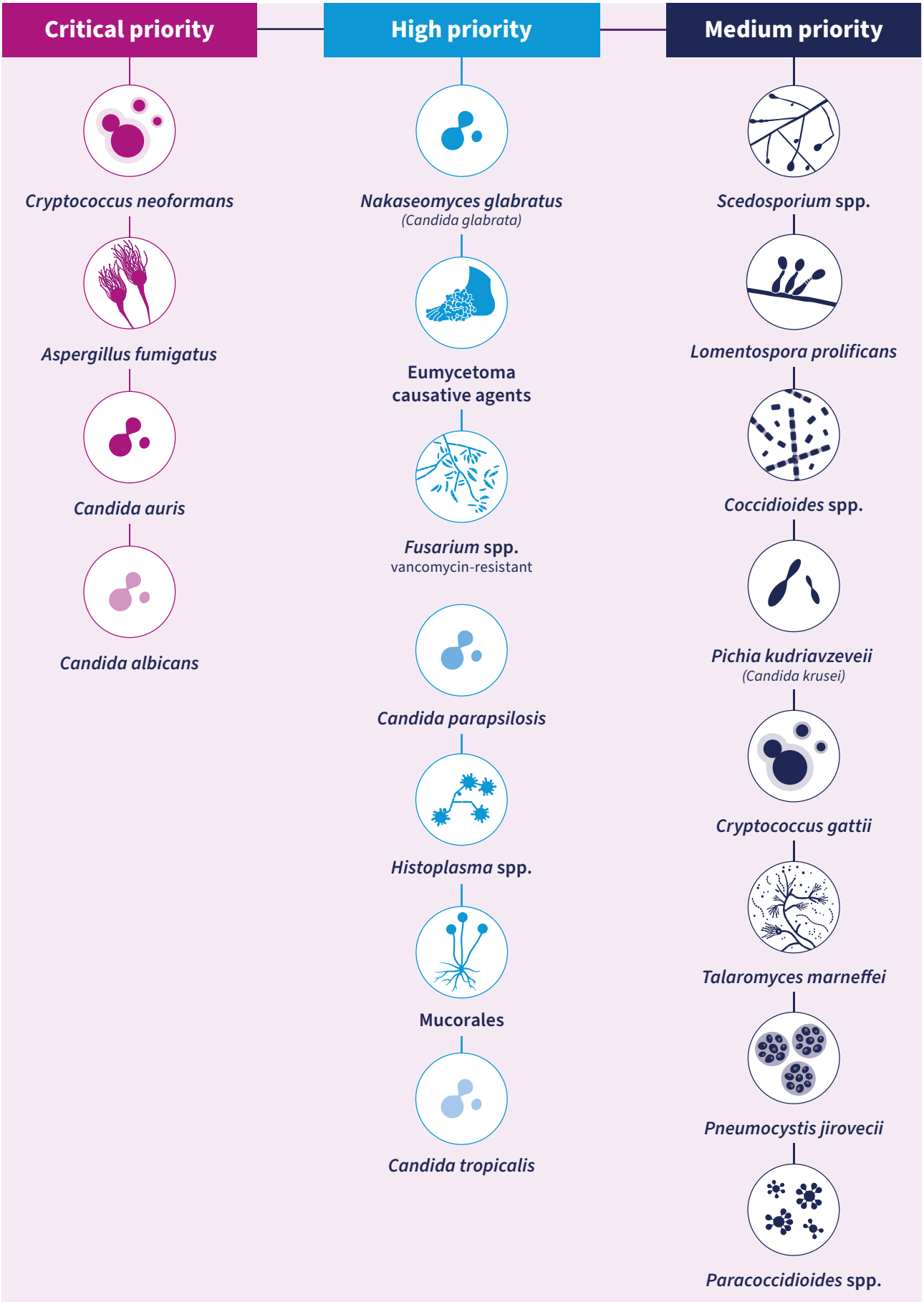
This is the first WHO analysis of the clinical and preclinical pipeline of antifungal medicines. It evaluates how well the global health priorities identified in the WHO FPPL *(9)* are addressed by authorized, novel, repurposed or optimized antifungal agents.

It identifies gaps and opportunities in R&D, aiming to develop effective strategies and complementary or alternative interventions that can guide sufficient investment toward the most urgent public health needs.

Target audiences

The report is intended for drug developers and researchers from large companies, smaller biotech start-ups, academia and product development partnerships (PDPs) to steer R&D, and for public and private research funders to guide their investment decisions. It is also designed to help for policy-makers, regulators, infectious disease researchers and clinicians to assess the current pipeline in preparation for potential new antifungal treatments that may reach clinical use in the coming years. The report also seeks to support health care providers and advocacy groups in their advocacy for appropriate, scalable, affordable and equitable interventions.

Fig. 1. WHO fungal priority pathogens list



2

Antifungal agents that obtained market authorization since 1 January 2014

2. Antifungal agents that obtained market authorization since 1 January 2014

This section provides information on the systemically acting antifungal agents that received marketing authorization in the past 10 years (1 January 2014 to 1 September 2024). During this period only four antifungal agents have been approved either by the United States Food and Drug Administration (US-FDA) or by both the US FDA and the European Medicines Agency (EMA): isavuconazole, ibrexafungerp, oteseconazole and rezafungin. Notably, two of these four agents are currently approved only for treatment of superficial infections (i.e. ibrexafungerp and oteseconazole). One of these agents (ibrexafungerp) represents a novel chemical class of antifungals, although the target exploited is not new.

Agents that received marketing authorization in the past 10 years are presented in Table 1 while a historical overview of antifungal drugs that received marketing authorization is presented in Fig. 2.

Isavuconazole was approved by both the EMA and the US-FDA in 2015 for the treatment of invasive aspergillosis and mucormycosis in adult patients for whom AmB is inappropriate *(41,56–58)*. In December 2023, the US-FDA granted an extension of indication in children from one year old. Isavuconazole is not approved against *Candida* spp. infections as it did not achieve non-inferiority to caspofungin for the treatment of invasive candidiasis *(53)*; although, in vitro and animal data showed activity against many *Candida* spp. *(54)*. Isavuconazole is the active moiety formed after oral (po) or intravenous (iv) administration of the prodrug isavuconazonium sulphate and belongs to the triazole class. Triazoles inhibit cytochrome P-450-dependent enzyme lanosterol 14α-demethylase (ERG11/Cyp51s) and thereby the synthesis of ergosterol, disrupting a key component of the fungal cell membrane. Compared to other triazoles, isavuconazole has not been shown to cause QTc interval prolongation (QT syndrome) and has a more predictable pharmacokinetics (PK) profile so that therapeutic drug monitoring is rarely recommended. It is available for po and iv use, and has a long terminal half-life allowing once daily dosing, and improved tolerability, particularly when compared to voriconazole *(59)*. In addition to the approved indications, isavuconazole has also shown in vitro and in vivo activity against *Cryptococcus* spp., including *C. neoformans* and *C. gattii (42–44)*, and has proved to be efficacious towards the same pathogens in a few patients from two clinical trials or included in a named-patient programme *(60–62)*.

Ibrexafungerp (SCY-078) was approved by the US-FDA in June 2021 for the oral treatment of adult and post-menarcheal paediatric females with vulvovaginal candidiasis (VVC), followed by an extension of indication for the prevention of recurrent VVC (RVVC), in 2022 *(63)*. It is the first member of a novel antifungal class, the triterpenoids *(64,65)*. Ibrexafungerp is orally available and can be administered once daily. It is a CYP3A4 substrate and a reversible inhibitor of CYP2C8 and CYP3A4; however, its potential for drug–drug interactions (DDIs) is lower compared with azoles *(66)*. Ibrexafungerp inhibits glucan synthase, an enzyme involved in the formation of 1,3-β-D-glucan, a critical component of the fungal cell wall *(67)*. It shares the same molecular target with echinocandins, but with a partially different binding site *(68)*. Because both ibrexafungerp and echinocandins target an enzymatic pathway that is not found in human cells, they have a low risk of off-target effects. Similar to echinocandins, ibrexafungerp is highly bound to plasma protein and penetrates the central nervous system (CNS) very poorly; however, it achieves high tissue penetration in the eye, kidney and bladder *(69–70)*. It has shown in vitro activity against several *Candida* spp., including both azole-resistant as well as echinocandin-resistant *C. albicans* and fluconazole-resistant *C. auris* isolates *(71–74)*. The activity of ibrexafungerp against FKS-mutant echinocandin-resistant *Candida* spp. is variable, probably depending on the site/type of mutation; however, overall, the activity was conserved in approximately 75% of tested isolates *(55)*. In vitro and in vivo activity was also demonstrated against *Candida* spp., *Aspergillus* spp. including echinocandin- and azole-resistant strains of *A. fumigatus* *(45,75)*, and Mucorales *(46,47,73)*.

Although at present approved only to treat or prevent VVC, it has the potential for multiple indications in hospitalized patients, including invasive candidiasis, azole-resistant pulmonary aspergillosis and infections from *C. auris*. The drug is also under current investigation as a step-down therapy from iv echinocandins, with the aim to reduce hospital costs and facilitate outpatient treatment (see section 3.2). A further potentially valuable indication could be as combination therapy with other antifungals, although data are currently very limited. Interestingly, in an in vivo animal model of invasive pulmonary aspergillosis, the combination of ibrexafungerp and the triazole isavuconazole resulted in prolonged survival and reduced pulmonary damage compared to monotherapy *(76)*. However, results available online from a phase 2 trial (NCT03672292) evaluating the combination of ibrexafungerp and voriconazole in patients with aspergillosis do not seem to indicate any additional benefit (see section 3.2).

The US-FDA granted qualified infectious disease product (QIDP), fast track review and orphan drug designation to ibrexafungerp in invasive candidiasis (including candidaemia) and invasive aspergillosis (see section 3.2).

Oteseconazole was approved by the US-FDA in April 2022 *(77)* but was rejected by EMA in August 2023 due to both quality and efficacy concerns *(78)*. The approved United States indication is RVVC in women who are not of reproductive potential with a history of RVVC *(79)*. The restricted indication is due to the teratogenic risk of the drug *(80)*. There are two recommended dosage regimens: either as monotherapy or in combination with fluconazole. It should be administered orally with food. Recently, in a post-marketing randomized controlled trial oteseconazole has shown superiority versus fluconazole for the treatment of severe VVC *(81)*. Oteseconazole is a novel oral tetrazole antifungal drug acting as a selective inhibitor of lanosterol 14α-demethylase (ERG11/Cyp51s), thereby impairing fungal cell wall synthesis. It has shown in vitro activity against a broad range of *Candida* spp., *C. neoformans*, *C. gattii*, *Coccidioides* spp., and *Rhizopus arrhizus* *(50,52,82,83)*, and in vivo activity in animal models of *C. albicans* infection, Coccidioidomycosis and *Rhizopus arrhizus* infection *(48–50,82,84)*. Oteseconazole has attractive characteristics including a long-half life and scarcity of DDIs; however, the lack of activity against most clinically relevant moulds and its teratogenic risk may limit future extension of indications. The developer's programme for the drug includes cryptococcal meningitis, coccidioidomycosis and invasive candidiasis (IC) (direct company communication). No clinical trial is at present registered for these indications.

Rezafungin (CD101) is an iv-administered echinocandin antifungal drug with a long half-life (80 h), enabling once weekly administration *(85)*. This facilitates treatment in an outpatient setting. It was approved by the US-FDA in March 2023 to treat adult patients with candidaemia and IC who have limited or no alternative therapeutic options *(86)*. A somewhat broader indication of IC in adults was granted by the EMA In January 2024 *(87)*. In the modified intended-to-treat pooled population from the phase 3 trial ReSTORE (NCT02734862) and the phase 2 trial STRIVE (NCT03667690), rezafungin was non-inferior to caspofungin for all-cause mortality, with a potential early treatment benefit *(88)*. A phase 3 clinical trial for the prevention of invasive fungal diseases caused by *Candida* spp., *Aspergillus* spp., and *Pneumocystis* spp. in adults undergoing allogenic blood and marrow transplantation is currently ongoing (NCT04368559; EUCTR2017-004981-85) *(89)*. Rezafungin showed in vitro and in vivo activity against several *Candida* spp. and *A. fumigatus* *(90)*. It does not affect the QTc interval and carries a low risk of DDIs with commonly co-administered drugs *(91)*. Rezafungin was designated as an orphan drug by both the US-FDA (2016) and the EMA (2021).

Table 1. Antifungal agents that gained market authorization between 1 January 2014 and 30 September 2024

Name (trade name)	Marketing authorization holder(s)	Approved by (date)	Antifungal class	Mechanism of action	Route of administration	Approved indication(s)	*Cryptococcus neoformans*	*Candida auris*	*Aspergillus fumigatus*	*Candida albicans*	OPP	No cross-resistance	Differentiating performance characteristics
Isavuconazonium sulfate (Cresemba)	Astellas Pharma Inc.; Basilea Pharmaceutica	Initial FDA Approval (03/2015); EMA Approval (10/2015); paediatric expansion FDA Approved (12/2023)	triazole	fungal ERG11/ Cyp51s inhibitor	iv/po	IA, Mucormycosis	●	? c	●	? c	●	-	Safety: no QTc interval prolongation; more predictable PK: therapeutic drug monitoring rarely recommended; once daily dosing
Ibrexafungerp (Brexafemme)	Scynexis, Inc.; GSK	FDA Approved (VVC 06/2021; RVVC 12/2021)	tritepenoid	glucan synthase inhibitor	po	VVC, RVVC	X	●	●	●	? d	*(-)* e	High tissue penetration in the eye, kidney and bladder; low potential of DDIs
Oteseconazole (VIVJOA)	Mycovia Pharmaceuticals, Inc.; Jiangsu Hengrui Pharmaceuticals Co. Ltd	FDA Approved (04/2022); China Approved (02/2024)	tetrazole	fungal ERG11/ Cyp51s and CYP51B inhibitor	po	RVVC, severe VVC	?	?	X	●	●	-	Long-half life: starting with once daily dosing, once weekly dosing at regimen; low potential for DDIs; teratogenicity
Rezafungin (Rezzayo)	Melinta Therapeutics (US); Cidara Therapeutics; Mundipharma (Ex-US)	FDA Approved (03/ 2023); EMA Approved (12/2023)	echinocandin	glucan synthase inhibitor	iv	IC, candidemia	X	●	●	●	●	-	Safety, low potential for DDIs once weekly administration

Key:

Activity assessment: ● active; ? possibly active; X not active; / not tested or no information available.

NCR: no cross-resistance; ✓ (criterion fulfilled); ? (inconclusive data); - (criterion not fulfilled).

DDI: drug–drug interactions; QTc: based on an electrocardiogram reading; iv: intravenous; po: per oral.

a Indications. IA: invasive aspergillosis; IC: invasive candidiasis; RVVC: recurrent candida vulvovaginosis; VVC: vulvovaginal candidiasis.

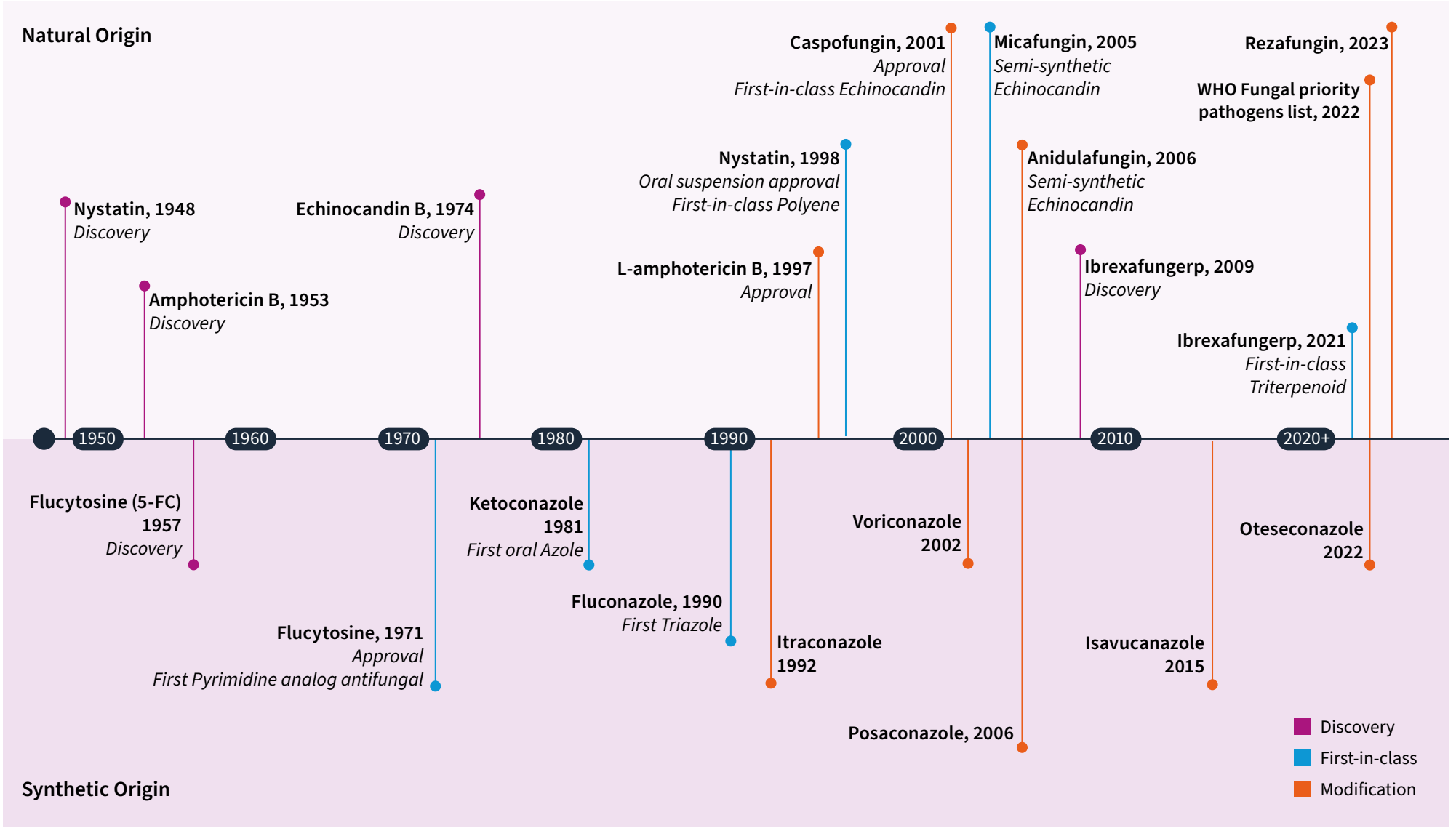
b OPP (other priority pathogens). isavuconazole: Mucorales spp, *C. gattii* (41–44); ibrexafungerp: *Pneumocystis jirovecii* (45), Mucorales (in vivo: (46); in vitro: (47)); oteseconazole: *Coccidioides* **(in vitro and in vivo:(48,49)),** *C. gattii* **(50),** *Rhizopus arrhizus* **(in vitro and in vivo: (51)),** *C.parapsilosis, C. tropicalis* **(52);** rezafungin: *C. tropicalis, C. parapsilosis, P. jirovecii* (in vitro and in vivo: (20)).

c Non-inferiority to caspofungin for the treatment of invasive candidiasis not demonstrated (53), although preclinical data showed activity against many *Candida* spp (54).

d Activity shown in *Pneumocystis jirovecii* mouse models, but inferior to trimethoprim-sulfamethoxazole in outcomes (45).

e Activity against FKS-mutant echinocandin-resistant *Candida* spp. is variable. Overall it was conserved in approximately 75% of tested isolates (55).

Fig. 2. Historical overview of systemic antifungal drugs and their marketing authorization



Note: The above timeline does not include antifungal agents approved for topical use, or any agent found on a discontinued drug product list.

3

Antifungal agents in clinical development against WHO fungal priority pathogens

3. Antifungal agents in clinical development against WHO fungal priority pathogens

There are currently nine antifungal agents in phase 1–3 of clinical development. Three agents are in phase 3, two in phase 2 and four in phase 1. Of these agents, all target at least one of the WHO FPPL critical priority pathogen (CPPs), although for two agents the publicly available evidence is at present limited as only in vitro data are available (see Table 2 where they are assessed as possibly active), and eight of them also target a high- or medium-priority pathogens, although only three have both in vitro and in vivo data available (Table 2). In the present review, the evidence of activity of a candidate antifungal against an individual pathogen is considered sufficient (represented as full dot • in Table 2) if both in vitro and in vivo data supporting activity are publicly available (for the detailed methodology to assess activity, see section 8).

When evaluating the innovation potential of antifungal candidates, four of the nine agents can be considered innovative and all these four address a CPP. Two agents meet all four innovation criteria (i.e. new target (NT), new chemical class (NCC), new mode of action (MoA), no cross-resistance within and across antimicrobial classes (NCR)) with a certain degree of novelty among new chemical entities (NCE) where three new classes of antifungal drugs were identified: orotomides, oxazoles, and siderophores.

Four candidate antifungal drugs (olorofim, opelconazole, fosmanogepix and BAL2062) received orphan designation by either the EMA or the US-FDA, or both.

Table 2. Antifungal agents in clinical development against WHO fungal priority pathogens

								Expected activity against priority pathogens					Innovation				
INN (company code)	Developer	Clinical trial	Phase	Antifungal class	Mechanism of action	Route of administration	Nonclinical data supporting the activity assessment	*Cryptococcus neoformans*	*Candida auris*	*Aspergillus fumigatus*	*Candida albicans*	OPP	NCR	CC	T	MoA	Differentiating performance characteristics
Fosmanogepix (FMGX; formerly APX001, PF-07842805, E1211, APEX)	Amplyx Pharmaceuticals, Pfizer, Basilea Pharmaceutica Ltd.	NCT05421858	3	oxazole (N-phosphono-oxymethylene, prodrug of manogepix)	Inhibition of the fungal enzyme Gwt1	iv/po		?	●	●	●	●	✓	✓	✓	✓	Extended spectrum; low DDIs
Olorofim (F901318)	Shionogi & Co., Ltd. and F2G Ltd	NCT05101187	3	orotomide	Inhibition of DHODH (pyrimidine biosynthesis)	iv/po		X	X	●	X	●	✓b	✓	✓	✓	Safety ?
Opelconazole (PC945)	Pulmocide Ltd.	NCT05238116; NCT05037851	3	triazole	Fungal ERG11/Cyp51s and CYP51B inhibitor	inhalation		?	?	●	● c	?	?	-	-	-	Novel formulation
HRS9432	Fujian Shengdi Pharmaceutical Co., Ltd., Jiangsu Hengrui Pharmaceuticals Co., Ltd.	NCT06194201 d	2	echinocandin	Inhibition of 1,3-beta-glucan synthase	iv	Awaiting further info e	/	/	/	? f	?	/	-	-	-	Low DDIs
BAL2062 (VL-2397, GR-2397, ASP2397) g	Basilea Pharmaceutica Ltd.	NCT03327727, EudraCT 2017-003435-11d	2	siderophore-like agent (cyclic hexapeptide)	Ferrichrome-type siderophore analogue with unidentified intracellular target	iv		?	X	● h	X	?	?	✓	?	?	Safety

Table 2 (continued). Antifungal agents in clinical development against WHO fungal priority pathogens

								Expected activity against priority pathogens					Innovation				
INN (company code)	Developer	Clinical trial	Phase	Antifungal class	Mechanism of action	Route of administration	Nonclinical data supporting the activity assessment	*Cryptococcus neoformans*	*Candida auris*	*Aspergillus fumigatus*	*Candida albicans*	OPP	NCR	CC	T	MoA	Differentiating performance characteristics
VT-1598	Mycovia Pharmaceuticals, National Institute of Allergy and Infectious Diseases (NIAID)	NCT04208321	1	tetrazole	Fungal ERG11/Cyp51s inhibitor	po		●	●	● i	● j	●	- i,j	-	-	-	Low DDIs, safety ?
BSG005	Biosergen AS, Alkem	NCT04921254	1	polyene	Ergosterol-binding, increase of fungal membrane permeability	iv/po	Awaiting further info k	/ l	/ l	/ l	? m	/ k	/	-	-	-	Safety ?
ATI-2307 (T-203)	Appili Therapeutics	NCT02289599 n	1	aromatic diamidine	Inhibition of the respiratory complexes III and IV in yeast mitochondria	po		●	● o	●	● p	?	✓ q	?	? r	? r	Extended spectrum; safety
SF001 (AM2-19)	Elion Therapeutics	not registered s	1	polyene	Ergosterol-binding, increase of fungal membrane permeability	iv (po) t		?	?	●	?	?	? u	-	-	?	Safety ?

Table 2 (continued). Antifungal agents in clinical development against WHO fungal priority pathogens

Key:

Activity assessment: ● active; ? possibly active; X not active; / not tested or no information available.

Innovation assessment: NCR: no cross-resistance; CC: chemical class; T: new target; MOA: new mode of action

✓ criterion fulfilled; ? inconclusive data; - criterion not fulfilled.

DDI: drug-drug interactions; INN: international nonproprietary names; po: per oral; iv: intravenous; OPP: other priority pathogens

a OPP. Fosmanogepix : *Fusarium* spp. (in vitro and in vivo: *(92)*), *C. tropicalis, C. glabrata, C. parapsilosis, Lomentospora prolificans, Scedosporium* spp (in vitro: *(93)*) and *Rhizopus oryzae* (mucorales) (in vitro and vivo data: *(51,94)*.

Olorofim : *Lomentospora prolificans, Scedosporium* spp, and *Coccidioides* spp (in vitro and in vivo), *Fusarium* spp, *Histoplasma* spp, *Talaromyces* spp (in vitro) *(95–97)*.

Opelconazole: *Rhizopus oryzae* (mucorales) (in vitro: *(98)*).

BAL2062: *Fusarium solani*. The MIC90 was 8 µg/ml, while azole antifungal drugs showed no activity against *F. solani* in human serum (in vitro: *(99)*).

VT-1598: *Coccidiodes* (in vitro and in vivo: *(100)*), *C. parapsilosis, Histoplasma* (in vitro: *(101)*).

BSG: No in vitro and in vivo studies retrieved. MIC values for *C.glabrata, C. kruseii* reported *(102)*, *P. jiroveci* and *Mucormicosis* (in vitro: Biosergen interim report for the period January, 2024 – March 31, 2024).

ATI-2307: *C.gattii* (in vitro: *(103)*), *Candida parapsilosis* and *F. solani* (in vitro: *(104)*).

SF001: *C parapilosis, C. glabrata, C. krusei, C.gattii, Coccidioides* spp, *Fusarium* spp, *Histoplasma capsulatum, Talaromyces marneffei* (in vitro: *(105)*), *Mucor circinelloides, Rhizopous arrhizus* (in vitro: *(106)*).

b Exposure of *A. fumigatus* to the agrochemical fungicide, ipfufenoquin, in vitro can select for strains that are resistant to olorofim *(107)*; linked transcriptional networks may cause antagonism of the azoles to olorofim and cross-resistance in A. *fumigatus*, but only at low concentrations of both drugs *(108)*.

c limited data show in vitro activity against some azole-resistant *A. fumigatus* strains *(98)* included in Ref

d A multi-centre, randomized, double-blind, active controlled, parallel groups, phase 2 study to evaluate the efficacy and safety of intravenous HRS9432 in the treatment of subjects with candidaemia and/or invasive candidiasis.

e No in vitro and in vivo studies retrieved. Awaiting further information from the developer.

f Tentative assessment based on the information provided on clinicaltrials.gov

g Basilea Pharmaceutica acquired the compound in October 2023. Start of phase 2 study is planned for Q1 2025.

h Activity against *A. fumigatus* isolates with azole resistance due to alterations in Cyp51s TR/L98H (5 isolates), M220 (9 isolates), G54 (9 isolates), and HapE (1 isolate) *(109)*.

i Not active in vitro against some azole-resistant species. Activity to be determined with susceptibility testing *(101)*.

j While active against the majority of fluconazole-resistant *C. albicans* clinical isolates, few strong resistant isolates were observed in vitro. Activity to be determined with susceptibility testing *(110)*.

k No in vitro or in vivo studies retrieved. MIC values for *C. albicans* reported *(102)*.

l No in vitro and in vivo studies retrieved. The company claim activity in its interim 2024 report: Biosergen interim report for the period January, 2024 – March 31, 2024, Biosergen AB.

m Very limited data in vitro and in vivo activity in a mouse model of invasive *C.albicans* infection *(111)*.

n Phase1 concluded in July 2015, but no results were published. In 2019, ATI-2307 was acquired by Appili Therapeutics and foreseen to be developed in cryptococcal meningitis and refractory and resistant *Candida* infections. No further information available (https://appilitherapeutics.com/2019/11/21/).

o No cross-resistance against fluconazole-resistant *C. auris* (in vitro and in vivo: *(103)*); in a neutropenic murine model of *C.auris:* improvement in survival and reductions in the kidney fungal burden, but no reduction in CFUs within the brain *(112)*.

p No cross-resistance against some echinocandin-resistant as well as fluconazole-resistant and fluconazole-susceptible-dose-dependent *Candida albicans* strains *(104,113)*.

q No cross-resistance both in vitro and in vivo against some azole- and echinocandin-resistant *C. albicans*, and azole-resistant *C. auris* strains *(104,113)*.

r AT-2307 accumulates into fungal cells via a polyamine transporter *(114)* and selectively inhibits yeast mitochondrial respiratory chain complexes III and IV; structuraly-similar pentamidine causes the collapse of the mitochondrial membrane potential within *Saccharomyces cerevisiae*.

s Company announcement of an ongoing, not registered Phase 1 trial.

t Oral formulation in initial development.

u In vitro and in vivo activity against azole-resistant, and echinocandin-resistant *A. fumigatus* isolates *(105)*, but no publicly available data against amphotericin B resistant strains.


In vivo data

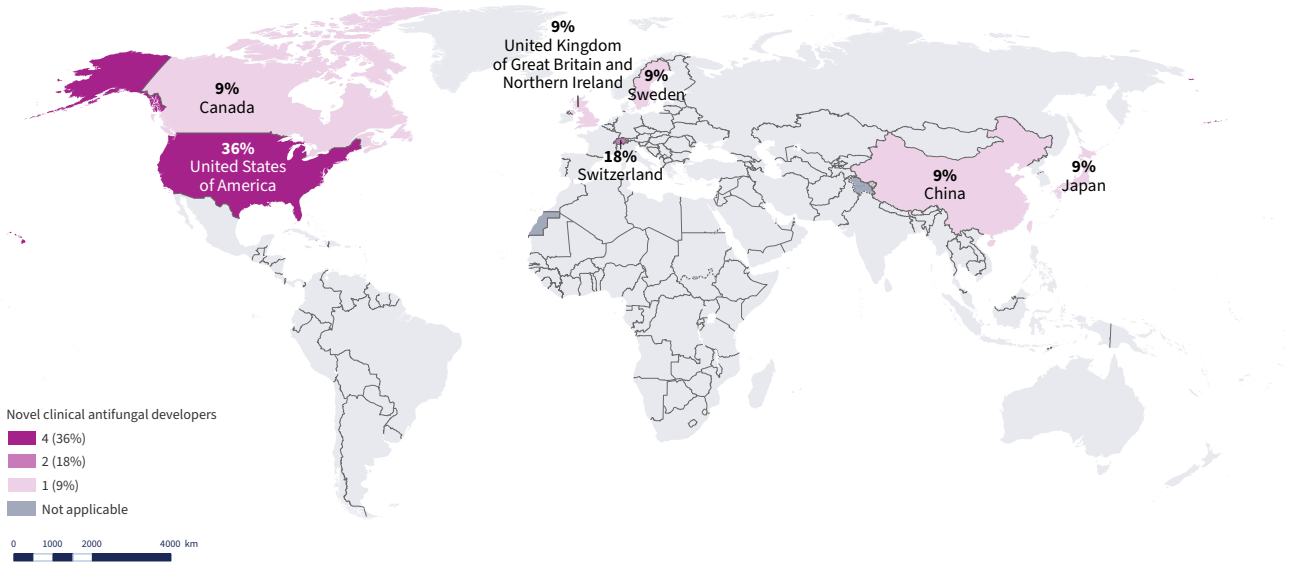

In vitro data

Peer-reviewed data

Not peer-reviewed data

Antifungal drug development is predominantly carried out by companies from high-income and upper-middle-income countries (Fig. 3).

Fig. 3. Geographical distribution of the developers involved in clinical trials for antifungal agents against WHO fungal priority pathogens



3.1 New antifungal agents under development

3.1.1 Orotomides

Orotomides are a new class of α-ketoamide-based molecules that selectively inhibit the enzyme dihydroorotate dehydrogenase catalysing the conversion of dihydroorotate to orotate, which is key in the biosynthesis of pyrimidine. There is no cross-reactivity with the human dihydroorotate dehydrogenase.

Olorofim (F901318) is the first member of this new class of antifungals. The drug is formulated for oral administration and its oral bioavailability ranges between 45–82% in different animal models *(115,116)*. The agent distributes widely into tissues. Olorofim is active against some moulds, including azole-resistant species, both in vitro *(95, 117–119)* as well as in animal models *(96,97,120,121,)*. It is not active against yeasts and the Mucorales *(122)*. Olorofim is metabolized by several cytochrome P450 isoenzymes and is a weak inhibitor of CYP3A4 and CYP2D6 and a weak inducer CYP1A2 and CYP2B6 *(123)*. Human pharmacokinetic data have not been completely published to date; thus, the potential for DDIs remains undisclosed *(122)*.

A new drug application (NDA) was submitted to US-FDA on the basis of the preliminary results of a single-arm, open-label phase 2 study investigating olorofim for the treatment of invasive fungal infections due to *Lomentospora prolificans*, *Scedosporium* spp., *Aspergillus* spp. and other resistant fungi in patients lacking treatment options (NCT03583164; EUDRA2017-001290-17) *(124)*. However, in June 2023 US-FDA requested additional data and analyses that will require further investigations and the submission of an NDA once results are available. In the meantime, the company announced the completion of the enrolment of the phase 2 study. In addition, a phase 3 study for the treatment of invasive aspergillosis (NCT05101187) evaluating olorofim versus treatment with amphotericin B liposome for injection (AmBisome®) followed by standard of care is currently ongoing.

During the development of olorofim, ipflufenoquin, a new fungicide for agriculture use, which works by a similar MoA as olorofim, has been approved by the US Environmental Protection Agency, and by the Australian Pesticides and Veterinary Medicines Authority. Exposure of *A. fumigatus* to ipflufenoquin was shown to favour the rapid evolution of resistance to olorofim, thus potentially weakening the effectiveness of olorofim for treating IFDs *(107)*.

A concerted effort embracing the One Health approach is essential, involving both antifungal drug developers and agricultural fungicide manufacturers. This collaboration is crucial to strike a delicate equilibrium between safeguarding human health, ensuring food security, and protecting the environment.

In addition, an antagonistic action of the triazoles on olorofim that could result in potential cross-resistance was observed in *A. fumigatus*. The negative interaction seems mediated by azole-induced overexpression of the pyrimidine biosynthetic pathway and/or metabolic flux. Reassuringly, the antagonism appeared only at relatively low levels of both drugs *(108)*. No evidence of a negative outcome in patients treated with olorofim in combination therapy with azoles is at present available *(125)*.

Initially developed by F2G Inc., olorofim became the first antifungal agent to receive the breakthrough therapy designation from US-FDA in 2019. It was also granted US-FDA orphan drug designation in 2020 for treatment of coccidioidomycosis, invasive aspergillosis, invasive fusariosis, invasive scopulariopsis /*Microascus* spp., and *Lomentospora* spp. or *Scedosporium* spp. infections. Additionally, olorofim was granted EMA orphan drug designation for the treatment of invasive aspergillosis, scedosporiosis (including lomentosporiosis), and invasive scopulariopsis. In 2022, F2G and Shionogi & Co. Ltd formed a strategic partnership for conducting clinical trials, as well as for the registration and commercialization of olorofim for invasive aspergillosis in Europe and Asia *(126)*.

3.1.2 Triazoles

Triazoles are heterocyclic compounds featuring a five membered ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-membered ring. Triazoles encompass molecules with antimicrobial, anticancer and anticonvulsant activities amongst many others *(127)*. Their MoA as antifungal agents involve the inhibition of the enzyme lanosterol 14α-demethylase (ERG11/Cyp51s) that impairs ergosterol synthesis and therefore compromising the cell membrane integrity. The molecular target (ERG11/Cyp51s) belongs to the cytochrome P450 family, and it is associated with potential side effects.

Opelconazole (PC945) is a triazole antifungal drug to be administered via nebulization. It is the only new agent under development intended to be administered by inhalation. Due to its lipophilic nature, the drug is retained in the lung tissue after inhalation resulting in a high local concentration and high pulmonary activity. The low systemic distribution could potentially result in fewer adverse events (AEs) common to triazoles, including DDIs, that are observed with systemic antifungal therapies *(128,129)*. Opelconazole has shown in vitro and in vivo activity against *A. fumigatus*, including some but not all, azole-resistant strains *(98,130)*, and against *C. albicans* *(131)*, whereas at present only in vitro activity data have been published against *C. neoformans* and *C. auris* *(132)*. Very sparse data of in vitro efficacy are publicly available against the rare mould *Rhizopus arrhizus* *(98)*. Inhaled opelconazole was evaluated in a phase 2 open-label, active-controlled safety trial (NCT05037851) versus standard of care, for the prophylaxis or pre-emptive therapy against pulmonary aspergillosis in lung transplant patients in intensive care. The study was completed in November 2023 and according to topline results *(133)*, among the 65 patients randomized to the study drug after receiving a lung transplant and treated for up to 12 weeks, there was a low incidence of both drug-related AEs as well as treatment-limiting respiratory AEs. Two out of 65 opelconazole patients experienced respiratory AEs leading to treatment discontinuation. There were no dose reductions or discontinuations of opelconazole prophylaxis or immunosuppressant medications due to DDIs. Efficacy was investigated only as an exploratory outcome. The incidence of breakthrough fungal disease in the intended-to-treat (ITT) population was 4% in the opelconazole group and 3% in the standard of care group. Opelconazole eradicated *Aspergillus* colonization in six previously colonized patients and in two additional patients with *Fusarium* spp. and *Penicillium* spp. infections. Standard of care patients who were colonized at study entry also saw eradication.

Opelconazole is also being currently investigated in a phase 3 trial in combination with other antifungal therapy for the treatment of refractory invasive pulmonary aspergillosis (NCT05238116).

As of 2022, the developer (Pulmocide Ltd.) has successfully completed a Series C funding round to advance opelconazole through late-stage development *(134)*. In 2021, opelconazole was granted orphan drug, fast-track, and qualified infectious disease product designation, by the US-FDA for the treatment of invasive aspergillosis *(135)*. It has also been granted orphan drug designation for the treatment of invasive aspergillosis in the European Union by the EMA *(137)*.

3.1.3 Oxazoles

The oxazoles are a new class of antifungal agents inhibiting the fungal enzyme Gwt1 (glycosylphosphatidylinositol (GPI)-anchored wall transfer protein). Inhibition of Gwt1 prevents localization of cell wall mannoproteins, which compromises cell wall integrity, adhesion, pathogenicity, and host immune system evasion *(93)*. They are azoles with an oxygen atom next to the nitrogen that have been derivatized into multiple different analogues *(137)*.

Fosmanogepix (APX001) is the N-phosphonooxymethylene prodrug of manogepix and a first-in-class antifungal agent. Fosmanogepix is rapidly converted in vivo by systemic phosphatases to its active moiety that displays activity against both yeasts, including *Cryptococcus neoformans* (few isolates) and *Candida* spp.

(except *C. krusei*), as well as moulds *(51,94,136–142)*. The molecule has a high oral bioavailability (>90%) enabling switching between iv and po formulations, has limited DDIs, and distributes widely into tissues *(143,144)*. Fosmanogepix has been evaluated in two phase 2 trials with a similar posology: 1000 mg iv twice daily on Day 1, followed by 600 mg iv once daily, and optional switch to 700 mg (NCT03604705) or 800 mg (NCT04148287) orally once daily from Day 4. In the non-comparative phase 2 clinical study for first-line treatment of candidaemia in non-neutropenic adults (NCT03604705; EUDRACT 2017-003571-56-DE), fosmanogepix administration for 14 days resulted in a treatment success rate of 80% (16/20, mITT; end-of-study treatment) with a day 30 survival of 85% (17/20; 3 deaths unrelated to fosmanogepix) *(144)*. In the open-label study NCT04148287, to evaluate fosmanogepix in patients with candidaemia and/or invasive candidiasis caused by *C. auris* (NCT04148287), treatment with fosmanogepix elicited a success rate of 88.9 % (C.I. 95%, 51.8–99.7). There were two deaths and a serious adverse event (SAE) rate of 22.22% (2/9) *(145)*.

An open-label study in patients with invasive mould infections caused by *Aspergillus* spp. or moulds such as *Scedosporium* spp., *Fusarium* spp., and Mucorales (APX001-202; EudraCT 2019-001386-33; NCT04240886) was terminated by the sponsor for strategic reasons. Results posted on the clinicaltrials.gov website showed, in 21 patients enrolled, a global response rate of 40% (C.I. 80%: 24.9–56.7), a mortality rate of 25% and a SAE rate of 62% (13/21 patients).

A phase 3 trial NCT05421858 in candidaemia or invasive candidiasis has been registered but is not yet recruiting.

Fosmanogepix is currently available under expanded access for patients with serious or life-threatening invasive fungal infections with no other treatment options (NCT06433128).

Fosmanogepix was initially licensed by Amplyx Pharmaceuticals in 2015. Amplyx Pharmaceuticals and its investigational assets were later acquired by Pfizer in 2021 *(146)*. In November 2023, Basilea Pharmaceutica Ltd. entered into an asset purchase agreement with Amplyx Pharmaceuticals, Inc., to acquire the rights to fosmanogepix *(147)*. The US-FDA granted fosmanogepix iv and oral formulations fast track, orphan drug and qualified infectious disease product designations for various indications including invasive candidiasis, invasive aspergillosis, coccidioidomycosis, cryptococcosis, and several invasive rare mould infections (including *Scedosporium* spp., *Fusarium* spp., and Mucorales). Additionally, the EMA has designated fosmanogepix as an orphan drug for the treatment of invasive candidiasis and invasive aspergillosis.

3.1.4 Echinocandins

Echinocandin antifungal drugs decrease the integrity of the cell wall by inhibiting glucan synthase. This target is specific to fungi, limiting adverse reactions in humans which are related to the MoA *(148)*. Echinocandins showed limited potential for cross-resistance with triterpenoids (ibrexafungerp); while they share their MoA, the binding sites do not appear to be identical *(68)*.

HRS9432 is an anidulafungin derivative currently in development for the treatment of candidaemia and invasive candidiasis. Results from a phase 1 study (NCT06194201) were recently published, showing linear pharmacokinetics with a long half-life supporting a weekly dosing frequency *(102)*. Notably, elevated serum alanine transaminases (ALTs) were observed in all dose groups with no apparent dose-dependent relationship. Elevated transaminases are a known safety issue for other echinocandins *(149)* but in the phase 1 study (NCT06194201), no severe adverse hepatic reactions attributed to HRS9432 were reported, likely because HRS9432 is not metabolized by CYP450 enzymes and exhibits minimal inhibition or induction effects on most CYP metabolic enzymes *(102)*.

No published in vitro and in vivo studies are currently available. Results from preclinical investigations are mentioned (with no reference) in the publication of the phase 1 study by Yan et al., 2024 *(102)*. According to the authors, the MIC values of HRS9432 for *Nakaseomyces glabratus* (*Candida glabrata*) CG19, *Candida albicans* CAL6, and *Pichia kudriavzevii* (*Candida* krusei) CK2 were 0.125 µg/mL, 0.06 µg/mL, and 0.25 µg/mL, respectively. Pharmacokinetics/ pharmacodynamics studies conducted in the murine candidaemia model induced by *Nakaseomyces glabratus* CG19 revealed a significant correlation between area under the concentration-time curve (AUC)/minimum inhibitory concentration (MIC) values and in vivo efficacy.

HRS-9432 is being developed by Fujian Shengdi Pharmaceutical Co. Ltd, a subsidiary of Jiangsu Hengrui Pharmaceutical *(150)*.

3.1.5 Siderophores

Siderophores are small iron-chelating compounds that help microorganisms manage iron homeostasis. These antifungals can use siderophore transporters to enter the cell and cause microbe apoptosis by different pathways *(151)*.

BAL2062 (GR-2397, VL-2397, ASP2397) is a novel antifungal drug. It is an aluminium-chelating cyclic hexapeptide siderophore. It acts by being transported into fungal cells through the siderophore iron transporter 1 (Sit1) *(99)*. Sit1 is absent in mammalian cells so BAL2062 specifically acts on fungi and showed an improved safety profile in humans *(152)*. It has a long half-life (71–88h) allowing for once-daily dosing in humans, an apparent low propensity for DDIs with no significant CYP3A4 inhibition *(153)*, and is active against *Aspergillus* spp., including azole-resistant isolates *(99,109,153)*. It was tested in a phase 2 study for treating invasive aspergillosis, but the trial was terminated for business reasons (NCT03327727, EUCTR2017-003435-11).

The product experienced sequential acquisitions and from October 2023 is undergoing a focused preclinical profiling programme for the optimal positioning of the drug *(154)*. Start of a phase 2 study is planned for the first half of 2025 *(154)*. The US-FDA has awarded BAL2062 both qualified infectious disease product and orphan drug designations, in addition to granting it a fast-track review for the treatment of invasive aspergillosis. In September 2024, BARDA announced a partnership with Basilea to support the development of BAL2062 and Fosmanogepix, aligning with its strategic organizational plan. *(155)*.

3.1.6 Tetrazoles

Tetrazoles are a class of twice unsaturated five-membered ring aromatic heterocycles, consisting of one carbon atom and four nitrogen atoms. They exhibit anticancer and antifungal activity through various mechanisms of action *(156)*. They have much lower affinity for human cytochrome P450 isoenzymes, and thus show a lower potential for DDIs compared to triazole *(157)*. They share the same MoA as triazoles, inhibition of fungal lanosterol 14α-demethylase (ERG11/Cyp51s).

VT-1598 is an investigational tetrazole that selectively inhibits fungal CYP51A *(158)*. It showed in vitro activity against various fungi, including *Candida* spp., *Cryptococcus* spp., *Coccidioides* spp, and *Aspergillus* spp. *(101,159)*. It also showed positive results in experimental animal models of invasive fungal infections *(100,160,161)*. Although activity against fluconazole-resistant fungi has generally been observed, few highly azole-resistant *C. albicans* and some *A. fumigatus* strains have been isolated with reduced susceptibility to both triazoles and tetrazoles *(100,110)*. A phase 1 randomized, double-blind, placebo-controlled, single ascending dose study was completed with VT-1598 in healthy individuals (NCT04208321)*(162,163)*. Clinical data showed non-proportional dose-exposure kinetics, a food effect on bioavailability, and a long half-life of 103–126 h. No SAEs or AEs leading to early termination were observed. AEs were predominantly of mild severity and no common azole-characteristic AEs like hepatotoxicity, vision, neurologic or skin and cardiac toxicities were observed in the study.

Mycovia Pharmaceuticals is advancing indication expansion of oteseconazole (VT-1161), while the status of the VT-1598 programme remains uncertain.

3.1.7 Polyene macrolides

Polyenes are a class of antifungals that are poly-unsaturated and contain at least three alternating double and single carbon–carbon bonds *(164)*.

BSG005 is a polyene macrolide with broad antifungal and fungicidal effect claimed to be active against *Candida albicans*, *Cryptococcus* spp., *Aspergillus* spp., and *Fusarium* spp. *(165,166)*. However, only limited data on its activity are available at present including in vitro and in vivo data against *C. albicans (165,167)*. Similar to other members of the polyene group, BSG005 binds to ergosterol and damages fungal cells by increasing the fungal membrane permeability. BSG005 is undergoing a phase 1 safety and tolerability study in male adults (NCT04921254). The trial was estimated to be completed in March 2023, but no further information is available. In September 2023, Biosergen announced the signing of a co-development and licencing agreement with Alkem *(166)*.

SF001 is a next-generation polyene antifungal drug designed to have increased specificity to fungal ergosterol, which is absent in humans, and decreased binding to cholesterol *(167)*. The ergosterol selectivity is believed to be the cause of the significantly less toxic profile that was observed compared to AmB against primary human cells and in mice *(167)*. SF001 demonstrated in vitro and in vivo activity against wild type, azole-resistant, and echinocandin-resistant *A. fumigatus* isolates, and in vitro activity against many fungi, including *Candida* spp, Cryptococcal spp, *Coccidioides* spp. and *Fusarium* spp. *(105,106)*. The compound is currently undergoing evaluation in an unregistered phase 1 trial (direct company communication). An iv dose for weekly administration is currently available, and an oral dose is in its initial development.

SF001 was developed by Elion Therapeutics (previously Sfunga Therapeutics). The drug was granted QIDP and fast track designations from the US-FDA for early antifungal therapy of presumed IFD and treatment of IA. Elion Therapeutics closed its Series B funding round for SF001 in June 2024, led by Deerfield Management and AMR Action Fund *(168)*.

3.1.8 Diamidines

The diamidine class includes compounds that contain two oxidatively coupled amine groups. A few members of this family show broad antifungal activity *(170)*.

ATI-2307 (T-203, E2307) is an aromatic diamidine with broad antifungal activity, including *Candida* spp., *Aspergillus* spp. (at higher MIC values), and *C. neoformans (170)*. Activity was also shown both in vitro and in vivo

against some azole- and echinocandin-resistant *C. albicans*, and azole-resistant *C. auris* strains *(104,113)*. ATI-2307 enters fungal cells via a polyamine transporter *(114)* and selectively inhibits yeast mitochondrial respiratory chain complexes III and IV *(104,112)*. The MoA appears comparable to that of the structurally similar compound pentamidine *(171)*; however, publicly available data do not allow a conclusion on similarity either for the MoA or the molecular target between the two drugs. Contrary to pentamidine, which had restricted indications due to its toxicity *(172)*, ATI-2307 showed an acceptable safety profile both in immunocompetent and neutropenic murine models of IFDs at doses of up to 6 mg/kg/day *(103)*. A phase 1 trial (NCT02289599) was concluded in July 2015, but no results were published.

In 2019, ATI-2307 was acquired from Toyama/Fujifilm by Appili Therapeutics with the aim to evaluate its clinical potential for the treatment of cryptococcal meningitis and refractory and resistant *Candida* spp. infections *(174)*. The drug's future development plans are not detailed in Appili's publicly disclosed long-term pipeline *(174)*.

3.2. Antifungal agents under clinical evaluation for potential label extension

The marketing authorization holder of an authorized medicine could undertake further clinical investigation to broaden the originally approved indication. For example, a drug currently licensed for invasive candidiasis can be studied for infections due to *Aspergillus* spp., or the current target population could be modified (i.e. adding a paediatric population), or new pharmaceutical forms and/or new routes of administration can be introduced and developed. Label extensions are supported by rigorous efficacy and safety trials through regulatory evaluation as the initial registration dossier.

In case an extension of indication is granted, the marketing authorization holder receives additional years of patent protection. This time is variable between the United States (4.5 to 7 years of additional patent protection) and the European Union (EU) (1 year of additional patent protection). If the product is designated as an orphan drug intended for a rare disease affecting under 200 000 patients in the United States or 5 out of 10 000 in the EU, further regulatory incentives apply.

Based on a search of the clinical trial databases, eight drugs were found to be in clinical trials for potential label extension (Table 3).

Table 3. Authorized antifungal agents for which a potential label extension is being investigated

Name	Sponsor	Antifungal class	Route of administration	Phase	Clinical trial number	Trial type	Approved indication/s	Sought indication/s	Status
Ibrexafungerp (SCY078)	Scynexis, Inc., GSK	triterpenoid	po	3	NCT05178862	MC, RCT, DB	Vulvovaginal candidiasis (VVC), recurrent vulvovaginal candidiasis (RVVC)	Invasive candidiasis	Suspended
				3	NCT03363841	MC,OL, SA		Candidiasis caused by *Candida auris*	Completed May 2023
				2	NCT03672292	MC, RCT, DB		Invasive pulmonary aspergillosis	Completed March 2023
				3	NCT03059992	MC,OL, SA		IFDs (several)	Completed August 2023
Fosravuconazole	Drugs for Neglected Diseases	triazole	po	2	NCT03086226	SC, RCT, DB	Onychomycosis	Eumycetoma	Completion date unknown
SUBA-Itraconazole	Mayne Pharma International Pty Ltd, George R Thompson, University of California	triazole	po	2	NCT04809649	RP MC, OL	Onychomycosis, aspergillosis (pulmonary and extrapulmonary), histoplasmosis, blastomycosis	Coccidioidomycosis refractory to fluconazole therapy	Withdrawn
Isavuconazole	Astellas Pharma Inc., Basilea Pharmaceutica	triazole	iv/po	3	NCT00634049	OL, SA, CC	invasive aspergillosis and mucormycosis	Cryptococcosis	Completed May 2016
			iv	3	NCT00412893	RCT, data from subgroup analysis		Cryptococcosis	Completed March 2013
Voriconazole	Hospital of Zhejiang University	triazole	iv	1	NCT04072640	MC, RP	Invasive aspergillosis, candidaemia, fluconazole-resistant serious invasive *Candida* infections, several OPP infections	Cryptococcal meningitis	Unknown
			iv	N/A	NCT03827278	MC, RNC		*Talaromyces*	Unknown

Table 3. (continued) Authorized antifungal agents for which a potential label extension is being investigated

Name	Sponsor	Antifungal class	Route of administration	Phase	Clinical trial number	Trial type	Approved indication/s	Sought indication/s	Status
Caspofungin	Beijing Chao Yang Hospital	echinocandin	iv	N/A	NCT02603575	SC, RP	*Candida* spp., *Aspergillus* spp.	*Pneumocystis jirovecii* (PJP; *Pneumocystis* Pneumonia in non-HIV patients)	Unknown
Rezafungin	Mundipharma Research Ltd.	echinocandin	iv	3	NCT04368559	MC, RCT, DB	Invasive candidiasis and candidaemia	Prevention of IFD in adults undergoing allogeneic BMSCT	Ongoing
				2	NCT05835479	MC, OL, RCT		PJP in HIV patients	Ongoing
				1	NCT05534529	MC, OL, SA		paediatric PK	Suspended
Liposomal Amphotericin B (LAmB)	Federal University of Health Science of Porto Alegre	polyene	iv	2	NCT04059770	MC, RNC, OL	*Aspergillus* spp., *Candida* spp., *Cryptococcus* spp., visceral leishmaniasis, empiric therapy in fungal infections with febrile neutropenia	Histoplasmosis in HIV patients	Completed March 2022

a MC: multicentre; SC: single centre; DB: double-blind; OL: open-label; SA: single-arm; RCT: randomized controlled trial; RNC: randomized non-controlled/randomized non-comparative trial; RP: randomized prospective; CC: case control; BMSCT: bone marrow and stem cell transplantation; N/A: not applicable.

b Suspended due to potential cross-contamination during manufacturing.

c Results posted on clinicaltrials.gov

d Results available from an interim analysis (*103*).

Ibrexafungerp

Ibrexafungerp (SCY-078) was approved by US-FDA for the treatment of VVC and the prophylaxis of RCCV and is currently in late-stage development for multiple indications in hospitalized patients. The completed clinical development included two open-label phase 3 studies and one phase 2 RCT. The open-label studies are in refractive IFIs (NCT03059992; EUCTR2017-000381-29), and in patients with candidiasis caused by *C. auris* (NCT03363841, CTRI/2018/05/013668), respectively. The RCT is in patients with aspergillosis (NCT03672292). Results from an interim analysis of the Fungal diseases that are refractory to or intolerant of standard antifungal treatment (FURI) study (NCT03059992), including 113 enrolled patients with refractive IFIs from 27 centres in the United States, in the United Kingdom of Great Britain and Northern Ireland and in the EU, treated with ibrexafungerp from 2016–2021, showed complete response rates, partial response or clinical improvements of 62.5% (35/56) for invasive candidiasis/candidaemia, 40% (4/10) for invasive aspergillosis, and 53% (17/32) for mucocutaneous (not VVC) candidiasis *(174)*. In the open-label study in patients with candidiasis caused by *C. auris* (CARES) (NCT03363841), results (available on clinicaltrials.gov) showed that oral ibrexafungerp treatment for up to 90 days resulted in a 70% (21/30) global survival rate at end of treatment, with a recurrence rate at 6 weeks follow-up of 4.8% (1/21) and a survival rate at day 42 of 80% (24/30), and at day 84 of 63% (19/30). Ten patients discontinued the treatment because of: seven unrelated deaths, one AE, one physician's decision and one patient's decision. In the phase 2 aspergillosis trial (NCT03672292), results (posted on clinicaltrials.gov) showed that the combination of either iv voriconazole or oral voriconazole with oral ibrexafungerp administered for 6 to 13 weeks compared to monotherapy with voriconazole resulted in four out of 10 vs zero out of 12 patients with treatment emergent AEs, respectively. Two out of 10 discontinuations due to AEs vs four out of 12, and three out of 10 vs one out of 12 deaths (combined primary endpoint), respectively. The percentage of participants with complete or partial response (secondary endpoint) was at end of treatment: 70% (7/10) vs 75% (9/10), at day 42: 40% (4/10) vs 50% (6/12), and at day 86: 40% (4/10) vs 33.3% (4/12).

In September 2023, a review of the drug's manufacturing process revealed a potential cross-contamination risk that prompted the developer to recall the drug from the United States market and place a temporary hold on clinical studies until a mitigation strategy and a re-supply plan were determined *(175)*. Consequently, the ongoing phase 3 trial in patients with invasive candidiasis treated with iv echinocandin followed by either oral ibrexafungerp or oral fluconazole (NCT05178862) is temporarily suspended.

Fosravuconazole

Fosravuconazole is an orally bioavailable triazole and its MoA is inhibition of ERG11/Cyp51s, which hampers the synthesis of ergosterol, essential for fungal cell wall formation. Its PK properties are favourable, it has a low potential for DDIs, and its toxicity is low *(176)*. In Japan, the drug is approved for the treatment of onychomycosis *(177)*. It is a prodrug of ravuconazole that has shown in vitro activity against *Madurella mycetomatis (178)*, one of the causative fungal agents of mycetoma, a progressive chronic granulomatous infection that affects the skin and subcutaneous tissue primarily in tropical and subtropical regions *(179)*. Mycetoma can be caused by fungi (eumycetoma) or bacteria (actinomycetoma). Mycetoma is recognised by WHO as a neglected tropical disease with a significant disease burden, and the fungi responsible for the disease are classified among the WHO high-priority pathogens *(9)*. The therapeutic arsenal for eumycetoma mainly consists of ketoconazole and itraconazole that have suboptimal efficacy, numerous adverse effects, and high costs in endemic countries.

In 2017, Drugs for Neglected Diseases initiative (DNDi), in collaboration with the Mycetoma Research Centre (Sudan) and Eisai, started the first double-blind, phase 2 randomized clinical trial (NCT03086226) for eumycetoma caused by *M. mycetomatis*. The study aimed to assess the superiority of fosravuconazole versus itraconazole, that is the standad of care in endemic areas. Results presented in November 2023, failed to show superiority versus itraconazole, with and efficacy rate of 65% and 85% in the 300 mg arm and the 200 mg fosravuconazole arm, respectively. The itraconazole 400 mg arm showed an efficacy rate of 80% which, according to the investigators, was higher than expected based on historical data *(180)*. While the difference between these efficacy rates was not statistically significant, fosravuconazole may have the advantage compared to the standard of care because of its once weekly versus daily dosing and improved safety profile. Based on these data, fosravuconazole treatment is available in Sudan through compassionate use programmes. Fosravuconazole is also being evaluated for Chagas disease (NCT03378661)*(181)*.

Voriconazole

Voriconazole is a triazole antifungal agent and it can be administered orally or intravenously. Its MoA involves the inhibition of fungal lanosterol 14α-demethylase (ERG11/Cyp51s). It is currently authorized for the treatment of invasive aspergillosis, candidaemia, deep tissue *Candida* infections, oesophageal candidiasis, serious *Scedosporium* apiospermum and *Fusarium* spp. infections. It is also indicated in the prophylaxis of IFIs in at-high-risk patients with haematopoietic allogenic stem cell transplantation.

A phase 1 clinical trial (NCT04072640) exploring the efficacy of voriconazole in combination with flucytosine to treat cryptococcal meningitis in HIV-infected Chinese patients, was scheduled to conclude by December 2022. However, the status of the trial remains unclear.

Also, a case-control study aimed at optimizing the treatment regimen of cryptococcal meningitis during the induction period is registered in China (ChiCTR1900023395). The study compares the efficacy of voriconazole combined with flucytosine versus amphotericin B with flucytosine. However, recent updates on its status are not available. Furthermore, a multicentre, large-sample, non-randomized controlled study (CSHHTVASIT; NCT03827278) is investigating voriconazole versus amphotericin followed by sequential itraconazole therapy in the treatment of *Talaromyces* infections. The completion of this study was anticipated in December 2021, but updated information is not available. Voriconazole is on the WHO Essential Medicines List (EML). In addition, an inhaled powder formulation is under development by TFF Pharmaceuticals.

Itraconazole

Itraconazole is a triazole antifungal drug and, like the other triazole, its MoA involves the inhibition of fungal lanosterol 14α-demethylase (ERG11/Cyp51s). It received its first marketing authorization in 1991 in the EU and in 1992 in the United States. Itraconazole is the first oral agent authorized for aspergillosis in patients with invasive or disseminated disease who have failed or are intolerant to AmB or voriconazole. It is also indicated for blastomycosis, histoplasmosis, candidiasis and cryptococcosis (including cryptococcal meningitis).

Itraconazole has been used in clinic for the treatment of coccidioidomycosis but has not been adequately studied in this indication. A new formulation of itraconazole with improved bioavailability, the SUBA®-itraconazole, was initially approved in Australia in 2013, and some years after in the United States and other countries. The new formulation was granted marketing authorization by the US-FDA *(2018)* for the treatment of blastomycosis, histoplasmosis and aspergillosis in patients intolerant or refractory to AmB therapy. Soon after, a phase 2 clinical trial (NCT04809649) was started to evaluate SUBA®-itraconazole in subjects with proven or probable coccidioidomycosis refractory or intolerant to fluconazole therapy. The study was stopped due to COVID-19-related budget cuts, and no further information is available. Itraconazole is on the WHO Essential Medicines List.

Isavuconazole

Isavuconazole is a triazole, inhibiting fungal lanosterol 14α-demethylase (ERG11/Cyp51s), currently approved for the treatment of invasive aspergillosis and mucormycosis. A subgroup analysis of the phase 3 VITAL trial (NCT00634049) evaluated the efficacy of isavuconazole against *Cryptococcus* spp. (n=9) and dimorphic fungi *(61)*. Additional data of efficacy against these pathogens is derived from very few patients in the phase 3 SECURE trial (NCT00412893) *(60)* and from the use of the drug as part of a named patient programme *(62)*. Albeit limited, these data suggest a potential benefit of isavuconazole in cryptococcosis that could encourage future clinical investigations.

Liposomal amphotericin B

Liposomal AmB (L-AmB) is an intravenous polyene antifungal drug. It binds to ergosterol in fungal cell walls, forming transmembrane channels and altering cellular permeability causing fungal cell death. L-AmB is currently authorized by the US-FDA for the treatment of patients with *Aspergillus* spp., *Candida* spp., *Cryptococcus* spp., for infections refractory to AmB deoxycholate, for the treatment of cryptococcal meningitis in HIV-positive patients, empirical therapy for presumed fungal infection in febrile neutropenic patients, and for the treatment of visceral leishmaniasis. In the EU, L-AmB is approved at the national level with a broader indication in some countries, including for Mucorales infections and independently of the refractory state to AmB deoxycholate.

L-AmB has recently been tested in a phase 2 clinical trial (NCT04059770) to compare the activity and safety of three L-AmB regimens, as induction therapy in disseminated histoplasmosis in HIV-positive patients. L-AmB is the drug of choice for HIV-associated histoplasmosis treatment, but access is restricted in several countries due to the high drug and hospitalization costs of the recommended long treatment regimen.

Results from the phase 2 trial (NCT04059770) demonstrated the safety of one day induction therapy with 10 mg/kg of L-AmB in HIV-related histoplasmosis, and suggest that the clinical response may be non-inferior to standard L-AmB therapy. However, these data would need to be confirmed in a dedicated phase 3 trial *(181)*. Previous evidence of the efficacy of a simplified regimen with a single high dose (10 mg/kg) of L-AmB (combined with flucytosine and fluconazole) instead of a longer treatment with standard dose come from a trial in HIV-associated cryptococcal meningitis performed in Africa *(182)*. The results of this trial showed similar efficacy and lower AEs of the novel protocol and influenced a change in the WHO recommendations on the treatment of the disease *(183)*.

Rezafungin

The long half-life echinocandin, rezafungin, is approved in candidaemia and invasive candidiasis. Two clinical efficacy trials, one phase 2 and one phase 3, are currently ongoing. The phase 3 trial is a randomized controlled trial investigating rezafungin for the prevention of invasive fungal diseases caused by *Candida* spp., *Aspergillus* spp., and *Pneumocystis* spp. in adults undergoing allogenic blood and marrow transplantation (NCT04368559; EUCTR2017-004981-85) *(89)*. It is expected to finish by 2025. The phase 2 study is an open-label, randomized trial evaluating the efficacy and safety of rezafungin in combination with 7 days of co-trimoxazole versus co-trimoxazole monotherapy in HIV-infected adults with *P. jirovecii* pneumonia (PJP) and it is expected (or projected) to finish by the end of 2024 (NCT05835479).

One additional phase 1 trial (NCT06329518) is evaluating the PK and ex-vivo sequestration of rezafungin in critically ill patients receiving extracorporeal membrane oxygenation. In critically ill patients, dosing modifications are often required due to alterations in the PK of antifungals. The study is intended to inform rezafungin dosage in this patient population and is expected to finish by 2024.

To date, there are no completed clinical studies evaluating rezafungin in paediatric subjects. A phase 1 study (NCT05534529) to evaluate the PK and safety of single dose of rezafungin in paediatric patients (from birth to <18 years) receiving systemic antifungals as prophylaxis or treatment for IFIs, was recently suspended waiting for the EMA Paediatric Committee review following a company change in strategy *(184)*.

Caspofungin

Caspofungin is an echinocandin antifungal drug approved by both the US-FDA and the EMA for the treatment of infections caused by *Candida* spp. and *Aspergillus* spp., and for the empirical therapy of presumed fungal infections in febrile, neutropenic patients. It inhibits β-*(1, 3)*-D-glucan synthase and thereby decreases the integrity of the fungal cell wall. Caspofungin is available on the market as solution for injection. In the past, several case-report studies reported the efficacy of caspofungin, mostly in combination with sulfamethoxazole-trimethoprim, in patients with PJP *(185)*. In 2015 the drug was studied in an open label, randomized cross-over study in non-HIV Chinese patients with PJP (NCT02603575). However, the study was projected to end in December 2020, but no information on its status is currently available. Caspofungin is on the WHO Essential Medicines List.

3.3. Drugs under clinical evaluation as repurposed antifungal agents

Compared to the development of new molecules, repurposing a licensed agent that is out of patent and regulatory data protection, for a new indication, is a relatively quick and financially attractive pathway in drug development. The R&D risks are lower as the pharmacological properties of the compound, along with its efficacy and safety profile, are well defined. In general, repurposing requires less time and data to support the new indication.

In addition, repurposing is a way to make medicines easily available to patients, especially those used in clinical practice outside the terms of the marketing authorization (or 'off-label' use). However, there are economic challenges to this approach. As many of these drugs are available as generics, there may be little financial interest from the pharmaceutical industry to invest in clinical trials and file for authorization for use in a new indication for such a product. Consequently, almost all these initiatives are driven by academic or non-profit groups with limited resources, and who may have less direct drug development expertise.

Repurposed drugs for fungal infections are presented in Table 4. These programmes are led entirely by academic groups in hospital settings seeking available, cheaper and less toxic alternatives to treating fungal infections, mainly cryptococcal meningitis. Two of these programmes (tamoxifen and sertraline) failed their efficacy endpoints, one (clindamycin) is completed with published results and one (pioglitazone) is still recruiting.

Table 4. Repurposed antifungal agents intended against WHO fungal priority pathogens

Name	Developer	Clinical trial number	Phase	Drug class	Route of administration	Approved indication	Expected activity against priority pathogens	Status
Clindamycin	Shanghai Zhongshan Hospital and College of medicine, Zhejiang University	NCT04328688	Observational	Lincosamide	po	Antibiotic	*Pneumocystis jirovecii*	Trial completed in 2019. No updates
Sertraline	Pfizer, University of Minnesota (responsible party)	NCT01802385	3	Tetralin (14α-sterol demethylase binder)	po	major depression, obsessive-compulsive disorder, panic disorder, social anxiety	*Coccidioides*, *Cryptococcus* and *Candida auris*	The trial was stopped for futility *(2017)*
Pioglitazone	Conselho Nacional de Desenvolvimiento Cientifico e Tecnológico	RBR-9fv3f4 (Brazil)	1,2	Thiazolidinedione	po	Hypoglycaemic agent	*Cryptococcus*	Currently enrolling; slowed due to COVID-19 limitations
Tamoxifen	Oxford University Clinical Research Unit (OUCRU), Vietnam	NCT03112031	2	Selective estrogen receptor modulator (SERM)	po	Antineoplastic agent	*Cryptococcus*	Lack of syngery; subtherapeutic levels

Clindamycin

Clindamycin is a lincosamide antibiotic approved by the US-FDA and EMA many decades ago for treating a range of bacterial infections. It binds to the 50S ribosomal subunit and inhibits bacterial protein synthesis. It has a short half-life of 2.4 h and is bacteriostatic against Gram-positive aerobes and anaerobes, as well as Gram-negative anaerobes. It has been tested in clinical trials to treat fungal infections. One case-control study tested clindamycin in combination with low dose trimethoprim/sulfamethoxazole on severe *Pneumocystis jirovecii* pneumonia (PJP) after solid organ transplantation (NCT04328688). The study failed to show an increased hospital survival (primary endpoint) in the combination of clindamycin with low trimethoprim/sulfamethoxazole compared to standard dose of trimethoprim/sulfamethoxazole, the current first-line treatment in PJP. However, the combination with clindamycin resulted in an improved oxygenation index (PaO2/FiO2 ratio 1.51 vs. 0.38, P = 0.014) through study completion (average 20 days) and decreased the length of hospital (26.5 vs 39.0 days, P = 0.011) and intensive care stay (12.5 vs. 22.5 days, P = 0.008) *(186)*. Although clindamycin is recommended as a second line treatment in PJP in the guidelines of the American Society of Transplantation *(187)*, these data together combined with a higher risk of Clostridium difficile infection associated with long-term use of clindamycin, make the repurposing of clindamycin in PJP unlikely at this time.

Pioglitazone

Pioglitazone is a thiazolidinedione that increases insulin sensitivity in target tissues, currently used for the treatment of type 2 diabetes mellitus. It is a peroxisome proliferator-activated receptor gamma (PPARɣ) agonist with anti-inflammatory effects and increases host tolerance in malaria by activation of pathways that leads to neuroprotective and neurodegenerative effects. In a murine model, pioglitazone in association with AmB disrupted yeast transmission from the lungs to the brain, contributing to the clearance of yeasts from the central nervous system *(188)*. This proof of concept is currently under validation in a phase 1/2 clinical trial (registered in Brazil: RBR-9fv3f4), for the treatment of cryptococcal meningitis; PIO study *(189)*. Although the study was scheduled to be completed in 2021, recruitment is still ongoing.

Sertraline

Sertraline is a selective serotonin-reuptake inhibitor commonly prescribed for the treatment of depression and anxiety disorders. Sertraline has shown in vitro activity against *Coccidioides* spp., *Cryptococcus* spp. and *Candida auris*. The MoA is through interference with protein synthesis mediated via eukaryotic translational initiation factor 3 (Tif3). Sertraline was investigated in two phase 3 studies. In the first trial (NCT01802385) it was administered in combination with AmB and fluconazole (standard therapy) for the treatment of HIV-associated cryptococcal meningitis. Sertraline did not improve 18-week survival compared to standard therapy. Investigators considered sertraline inactivity to be multifactorial and potentially due to subtherapeutic free drug concentrations. In a second randomized double blind trial sertraline was evaluated in combination with cryptococcal antigen screening (NCT03002012). The study was prematurely stopped because of serious AEs in the intervention arm (acute delirium). More recently, a novel sertraline derivative showed potent in vitro and in vivo activity against *C. neoformans (190)*. However, plans for its clinical development are still not known.

Tamoxifen

Tamoxifen is an oral hormonal antineoplastic agent, competitively binding to oestrogen receptors thereby resulting in a decreased oestrogen receptor signalling-dependent growth in breast tissue. Tamoxifen is currently indicated for the treatment of oestrogen receptor-positive breast cancer, including prophylactic treatment, carcinoma in situ, early stage and metastatic cancer.

The first evidence of tamoxifen employed as an antifungal agent are from 1989 *(191)*, recent evidence *(192)* suggested that it could contribute to the clearance of *Cryptococcus* from the cerebrospinal fluid. In principle it could represent an off-patent, cheap and widely available therapy for cryptococcal meningitis. The phase 2 clinical trial was intended to determine whether tamoxifen could be repurposed in combination with AmB and fluconazole for cryptococcal meningitis (NCT03112031). However, in September 2021 the research group published negative results attributing them to the lack of synergy between tamoxifen and AmB in vivo or to the subtherapeutic concentration of tamoxifen.

3.4. Antifungal agents with improvements in their formulations

The R&D of new formulations for antifungal agents in the past 20 years has significantly impacted treatment outcomes and clinical practice. Most antifungal drugs are characterized by unfavourable physicochemical properties such as poor solubility, low absorption rate and consequently poor bioavailability. In addition, erratic drug plasma concentration–time profiles affect therapeutic outcomes and often requires drug concentration monitoring *(193)*. Hence, efforts have been dedicated to advancing formulation technologies. This has led to the first approval, in 2013 in Australia, of the (SUBA®) itraconazole formulation with enhanced bioavailability that contains a solid dispersion of itraconazole in a pH-dependent polymeric matrix to enhance both dissolution and intestinal absorption *(194)*. In a prospective, randomized, open-label study (NCT03572049) in patients with four different endemic mycoses, SUBA®-itraconazole achieved similar blood levels as conventional itraconazole with a dose approximately one-third lower, less inter-intra-patient variability, and fewer adverse reactions *(195)*.

Ongoing developments of innovative formulations are mainly aimed at improving drug delivery to the site of infection in the lungs, decreasing systemic exposure and side-effects. These include: opelconazole for inhalation (see section 3.2, BSG005 Nano and BSG005 Nano Oral formulations (not yet in clinical development but mentioned on the Company's website), and voriconazole inhalation powder. The later takes advantage of the thin film freezing technology allowing the formulation of inhalable therapies *(196,197)*. The concept builds on the experience gained with pulmonary delivery of antimicrobial agents in the treatment of cystic fibrosis. Voriconazole inhalation powder has completed a phase 1 clinical trial (NCT04872231) and is available on an expanded access basis to patients with pulmonary aspergillosis for up to 12 weeks (NCT05897294). In a case report study *(198)* two patients after lung transplantation received voriconazole by inhalation to treat pulmonary fungal infections. Treatment was efficacious and well tolerated with no significant DDIs or AEs, indicating a potential use of this formulation in patients in polytherapy with low therapeutic index, highly metabolized drugs, or as adjunctive therapy in addition to systemic antifungals in case of difficult-to-treat infections.

Another example of innovative formulations is amphotericin B cochleates, a nanoparticle-based formulation that employs a delivery platform enabling targeted oral drug delivery with the aim of decreasing systemic adverse reactions and allowing faster hospital discharge of patients *(199)*. The encochleated AmB (MAT2203, CAmB) formulation has been successfully investigated in the phase 1/2 trial EnACT2 (NCT04031833) that showed MAT2203 efficacy and improved safety profile (less anaemia and hypokalaemia, both associated with mortality) as a step-down therapy following liposomal IV-AmB administration in HIV patients with cryptococcal meningitis *(200)*. A confirmatory phase 3 trial is currently ongoing in the same indication (EnACT3, NCT05541107). Further efficacy and safety data are being collected through the compassionate or expanded use access programmes in individuals suffering from severe IFIs with no other treatment options.

Finally, a consortium of European and African partners, led by DNDi and funded by the European and Developing Countries Clinical Trials Partnership, is developing an extended release flucytosine for cryptococcal infection. The new formulation of flucytosine is intended to be administered twice a day instead of four times a day simplifying inpatient and outpatient treatment *(201)*. A phase 1 trial investigating bioavailability of the candidate drug in healthy volunteers has recently been completed *(202)*.

4

Antifungal drugs that are not under active development or for which there is no recent information

4. Antifungal drugs that are not under active development or for which there is no recent information

There might be various reasons for companies to halt development of a product. The halt sometimes could be only temporary, for instance to wait for a round of investment, or more definitive as in the case of serious AEs, negative results, or commercial considerations. An antifungal agent that has not demonstrated any activity for a period of at least five years was considered to be no longer under active development. There is currently only one agent that falls into this category: isavuconazole for the primary treatment of invasive candidiasis.

Isavuconazole

Isavuconazole is the most recently approved triazole. It was designated as an orphan medicine (i.e. a medicine used in rare diseases) *(53)* for invasive aspergillosis and mucormycosis, and it was authorized by both the EMA and the US-FDA in 2015 for the same indications. Isavuconazole was studied in a phase 3 clinical trial (NCT00413218) for the primary treatment of patients with candidaemia or invasive candidiasis. However, the results did not demonstrate the non-inferiority of isavuconazole to caspofungin for primary treatment of invasive candidiasis *(53)*.

5

Antifungal agents in preclinical development

5. Antifungal agents in preclinical development

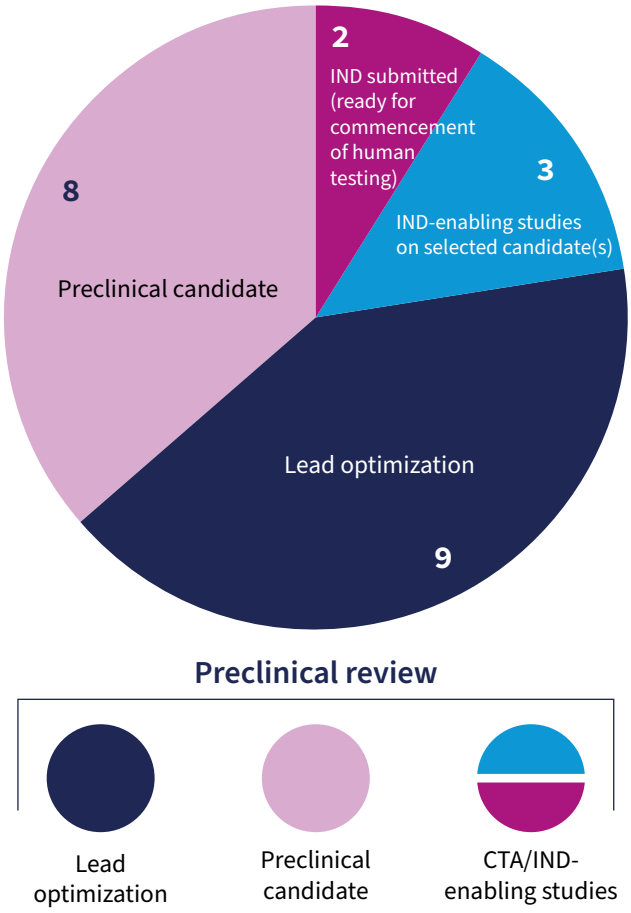
5.1 Categorization of preclinical agents

The review captures 22 preclinical projects grouped according to their self-declared preclinical development stage (Fig. 4). Nine programmes (40.9%) were in lead optimization, eight of which were direct-acting small molecules. Eight programmes (36.4%) where identified as preclinical candidate. Five programmes (22.7%) were listed as in, or having completed, the investigational new drug-enabling phase of preclinical development.

The review also reveals a limited scope of different agents in preclinical development. Most of the programmes were direct-acting small molecules (n=14; 63.6%). There were also direct-acting peptide programmes (n=3; 13.6%). There were five non-traditional biotherapeutic products, representing 22.7% of the preclinical pipeline. This is important considering that there are no non-traditional agents present in clinical development. Developing complementary or synergistic strategies, such as non-traditional agents, could be pivotal to innovation in antifungal therapy.

A total of 20 (90.9%) programmes were being developed as single agents along with two (9.1%) whose development included a combination agent.

Fig. 4. Categorization of preclinical programmes by stage of preclinical development



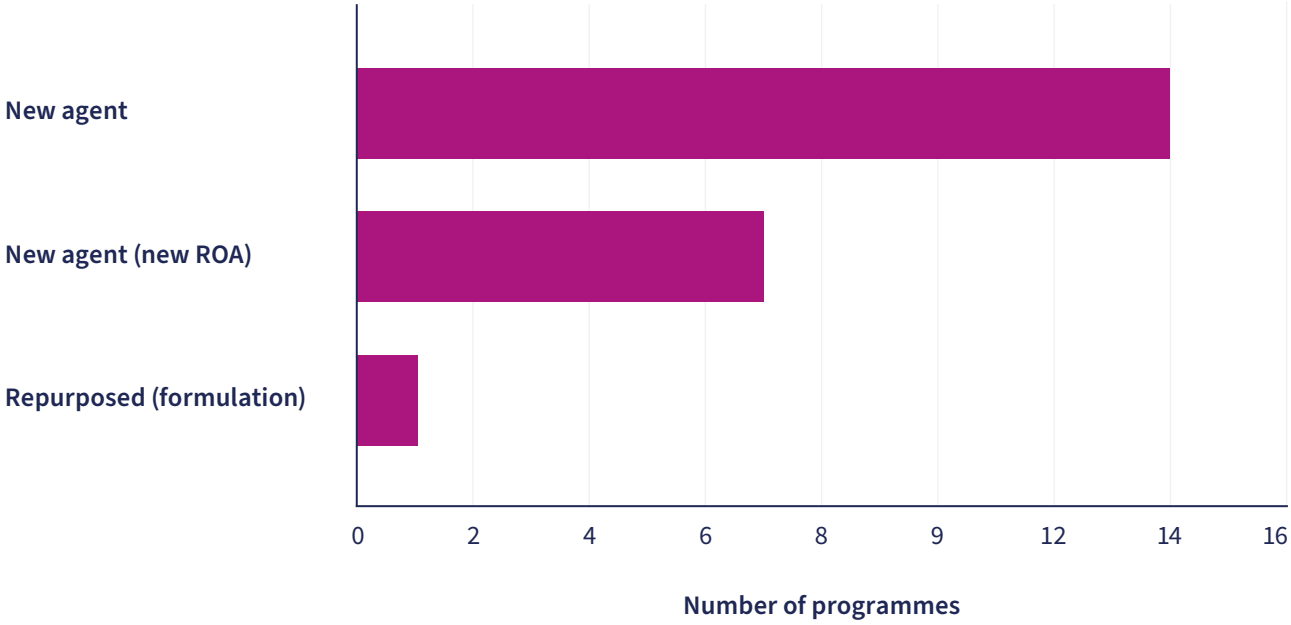
Note: Lead optimization: Iterative in vitro and in vivo screens of lead compounds to generate suitable pharmacological, safety and pharmacokinetic profiles of one or more candidates to progress into preclinical development. Preclinical candidate: A lead compound that passes initial toxicology tests and demonstrates a sufficient safety profile which, when combined with a suitable understanding of pharmacological efficacy, warrants advancement.

CTA: clinical trial application. IND: investigational new drug. CTA/IND studies: Including ADME (absorption, distribution, metabolism and excretion) and GLP (good laboratory practice) toxicology, as well as formulation and manufacturing development necessary to obtain the permission of regulatory authorities to begin human clinical testing.

Source: Adapted from *(203)*.

The antifungal pipeline contains 14 (63.6%) programmes that are classified as being new agents (Fig. 5). The remaining eight programmes are agents where key performance characteristics are being altered to provide clinical differentiation. In seven programmes, this is the investigation of a new route of administration, often of a product that is already undergoing clinical development.

Fig. 5. Categorization of preclinical programmes by type of agent



Note: ROA: route of administration.

5.2 Spectrum of activity of antifungal agents in the preclinical pipeline

The WHO FPPL, published in 2022, prioritized pathogens that cause invasive and resistant infections, highlighting the urgent global need for new antifungal agents. Table 5 shows the number of agents in the preclinical pipeline that have declared activity against each of the fungal priority pathogens.

While all the priority pathogens have products in the preclinical pipeline with evidence of preclinical activity, it is noteworthy that the critical priority pathogens have a significant number of products targeting them. Importantly, there are nine programmes with activity against all four members of the critical pathogen group, seven of which are new agents and two of which are investigating a new route of administration. There was only one programme targeting a single pathogen on the list, an antibody-based programme targeting the Mucorales.

Table 5. Number of preclinical programmes with activity against WHO fungal priority pathogens

WHO fungal priority group	Fungal pathogen	Products
Critical	*Aspergillus fumigatus*	16
	Candida auris	16
	Candida albicans	18
	Cryptococcus neoformans	13
High	*Histoplasma spp.*	5
	Candida parapsilosis	12
	Candida tropicalis	13
	Fusarium spp.	5
	Mucorales	8
	Nakaseomyces glabratus (Candida glabrata)	13
	Eumycetoma causative agents	2
Medium	*Cryptococcus gattii*	7
	Pichia kudriavzeveii (Candida krusei)	11
	Scedosporium spp.	4
	Lomentospora prolificans	2
	Paracoccidioides spp.	2
	Coccidioides spp.	5
	Talaromyces marneffei	2
	Pneumocystis jirovecii	5

5.3 Geographical distribution of preclinical developers

The 22 preclinical projects captured in the analysis are affiliated with 18 institutions distributed across four out of the six WHO regions (Fig. 6). Most of data in the 2024 survey was collected from the Region of Americas (n=12, 54.5%) and the European Region (n=6, 27.3%). A total of 17 institutions were in high-income countries, with a single institution being in India (South-East Asian Region).

Fig. 6. The geographical distribution of the institutions with 22 preclinical pipeline projects in the 2024 analysis

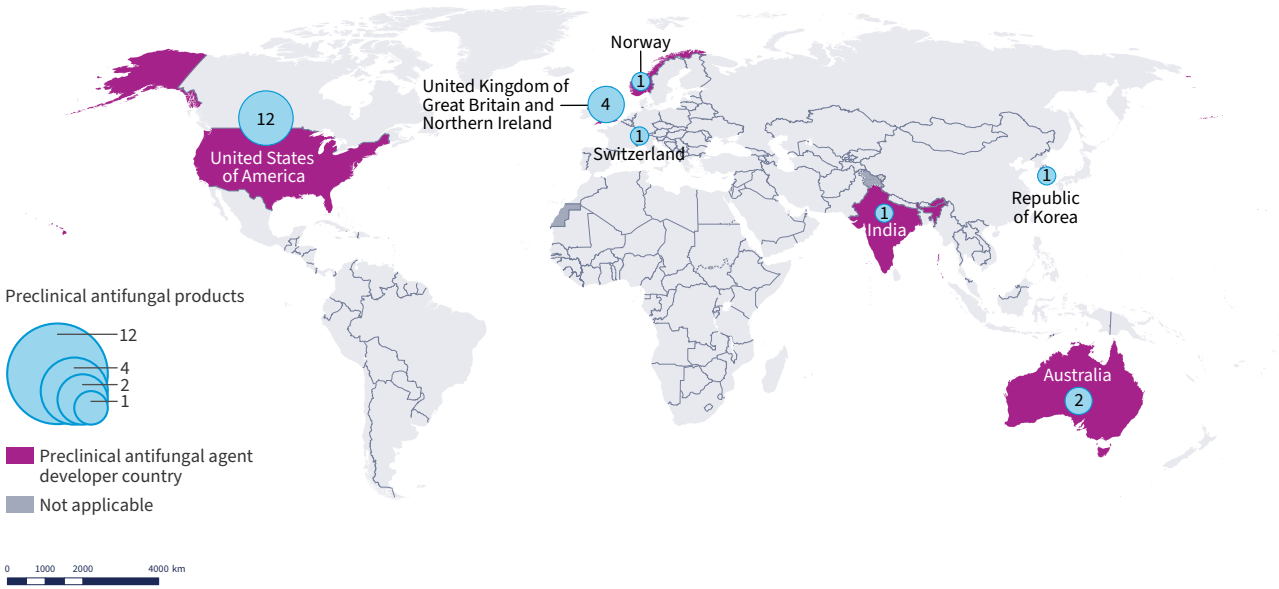
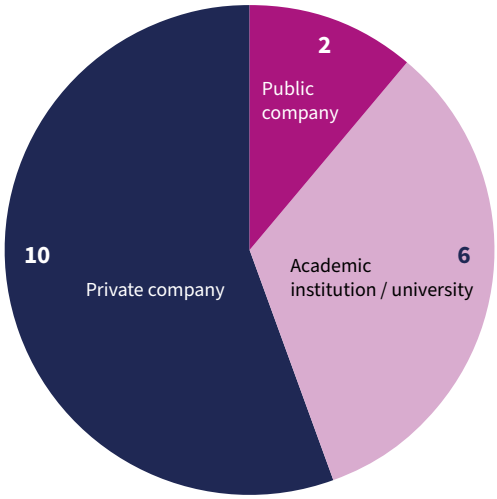


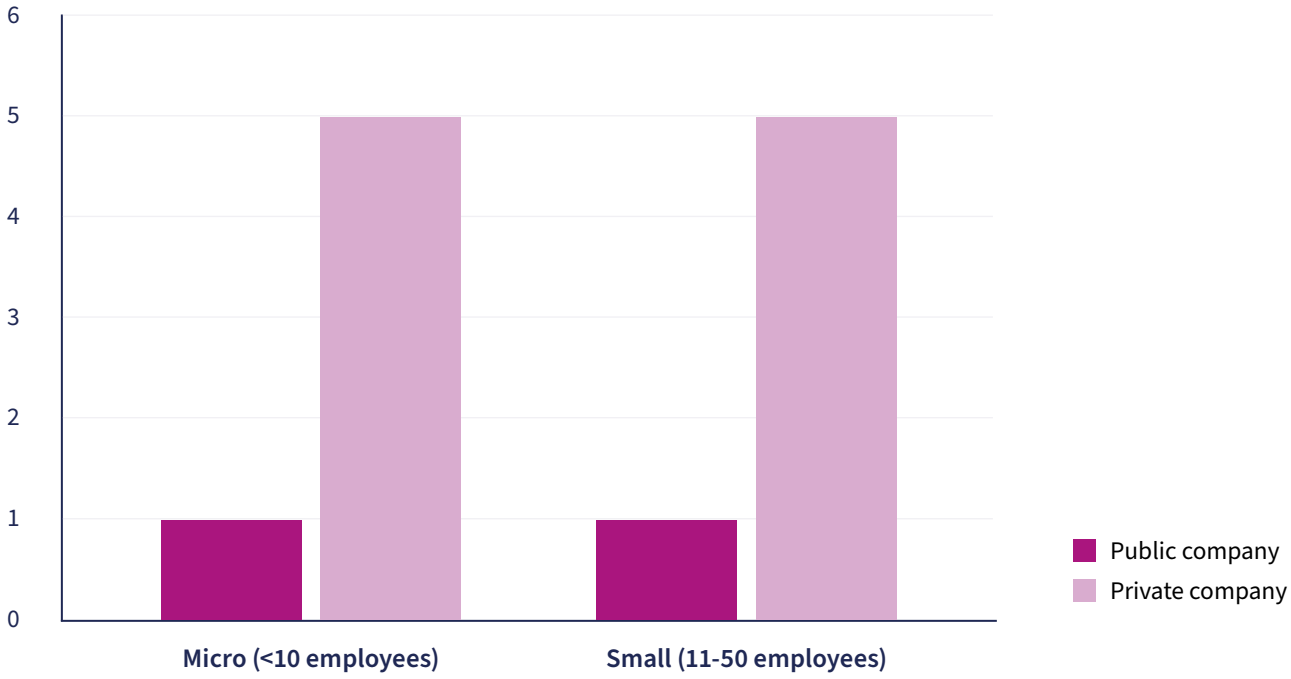
Fig. 7. Categorization of groups with preclinical pipeline projects by type



The 18 institutions were classified as either academic universities or companies (Fig. 7). Most institutions in the 2024 analyses are private commercial companies (n=10, 55.6%), followed by academic Institutions (n=6; 33.3%) and public companies (n=2, 11.1%). The fact that one third of the antifungal programmes are in academic institutions highlights further risk in the preclinical pipeline, as these groups often do not have access to the required experience in the later aspects of drug development and/or resources and may require partnering.

The 12 commercial institutions were also clustered according to the company size, with all companies containing <50 employees and with half having <10 employees (Fig. 8). The confirmation that all the preclinical pipeline developers are small and 'micro' companies is indicative of the number of large companies that have exited the anti-infective discovery area, as the same trend can be observed with preclinical antibacterial programmes.

Fig. 8. Categorization of companies with preclinical pipeline projects by ownership and size



6

Discussion

6. Discussion

6.1 Currently approved antifungal drugs

For currently approved antifungal drugs the clinical arsenal available to mycologists is extremely limited. Only one new class is approved every decade, and paediatric indications and/or optimal paediatric formulations are seldom available.

6.1.1 Assessment of activity

In the past 10 years, only four new antifungal agents have been authorized and added to the limited clinical repertoire, and two of them are at present licensed only to treat superficial infections. In the past 30 years, only three new classes: polyenes (nystatin, 1998), echinocandins (caspofungin, 2001), and triterpenoids (ibrexafungerp, 2021) have been approved, representing an average of one new class approved per decade.

Even though all recently approved agents show some degree of cross-resistance, they possess characteristics that offer enhanced clinical benefits to patients. Most of the older antifungal drugs have some gaps in their spectrum of activity and/or significant toxicity, especially when used in prolonged therapies, or in polytherapy. The activity against *Aspergillus* spp. and Mucorales is of particular interest given that these pathogens cause the two most common invasive mould infections in humans, both being associated with high mortality rates, even when treated appropriately *(204)*. Three out of the four drugs approved in the past ten years have shown some activity against *Aspergillus* spp. and Mucorales spp.; however, indication in invasive aspergillosis and invasive mucormycosis has at present been granted only to isavuconazole, while studies are ongoing for ibrexafungerp and rezafungin in pulmonary aspergillosis, and for ibrexafungerp in invasive mucormycosis (see section 3.2). Of note, in invasive pulmonary aspergillosis, isavuconazole is indicated as an alternative to first-line voriconazole treatment *(205,206)*, while the current international experts' recommendations for the management of mucormycosis still place L-AmB as the initial therapy and restrict isavuconazole use in first-line only in situations of pre-existing renal insufficiency *(207,208)*. The recent assessment of antifungal drug activity against many Mucorales isolates, from the United States, Europe and Asia Pacific, confirmed AmB as the most active agent *(209)*.

A significant limitation among the authorized agents is the paucity of approved paediatric indications. Many antifungals that are authorized for use in adults still do not have authorized indications for paediatric use and often lack optimal formulations for administration to children, infants and neonates. Only one, isavuconazole, among the four antifungal drugs approved in the past 10 years, has a paediatric indication, starting from one year of age, in invasive aspergillosis and invasive mucormycosis. Of note, the indication was granted at the end of 2023, eight years after its first approval in adults. In addition, the terpenoid, ibrexafungerp, was first approved in 2021 in postmenarcheal females. Recently, the PK and safety trial (NCT05534529) of single dose rezafungin in paediatric subjects concomitantly treated with systemic antifungals has been put on hold while the sponsor's new study proposal is under evaluation by the EMA. Among triazoles, only posaconazole has an oral paediatric formulation. Both invasive candidiasis and invasive aspergillosis, two important IFDs in paediatric patients, are currently treated without comparative effectiveness data from paediatric studies, and guidelines recommendation are based largely on results from adult data *(210)*. Only recently the multinational prospective observational Paediatric Antifungal Comparative Effectiveness (PEACE) study *(211)*, sponsored by the Children Oncology Group showed that in children and adolescents with invasive candidiasis, initial directed therapy with an echinocandin was associated with a reduced failure rate at 14 days, compared to triazoles or AmB *(211)*. These data are of interest but need confirmation. While no comparative effectiveness data from studies in immunocompromised children with invasive aspergillosis are at present available, a previous study by the same group evaluated the optimal antifungal prophylaxis in immunocompromised children. The study showed a reduced risk of fungal infection with caspofungin compared to fluconazole in paediatric patients with acute myeloid leukaemia *(212)*.

The extremely limited availability of comparative effectiveness data to inform the selection of the optimal antifungal therapy/prophylaxis in children with IFDs challenges the use of antifungal drugs in children, may result in toxicity or treatment failure and drive antifungal resistance in both children and adults.

Effectiveness studies investigating the optimal therapy of antifungal agents in children with IFDs are needed to inform paediatric therapeutic strategies.

6.2 Antifungal agents in clinical development

The clinical pipeline is currently immature, and inadequate to meet therapeutic needs in the short to medium term.

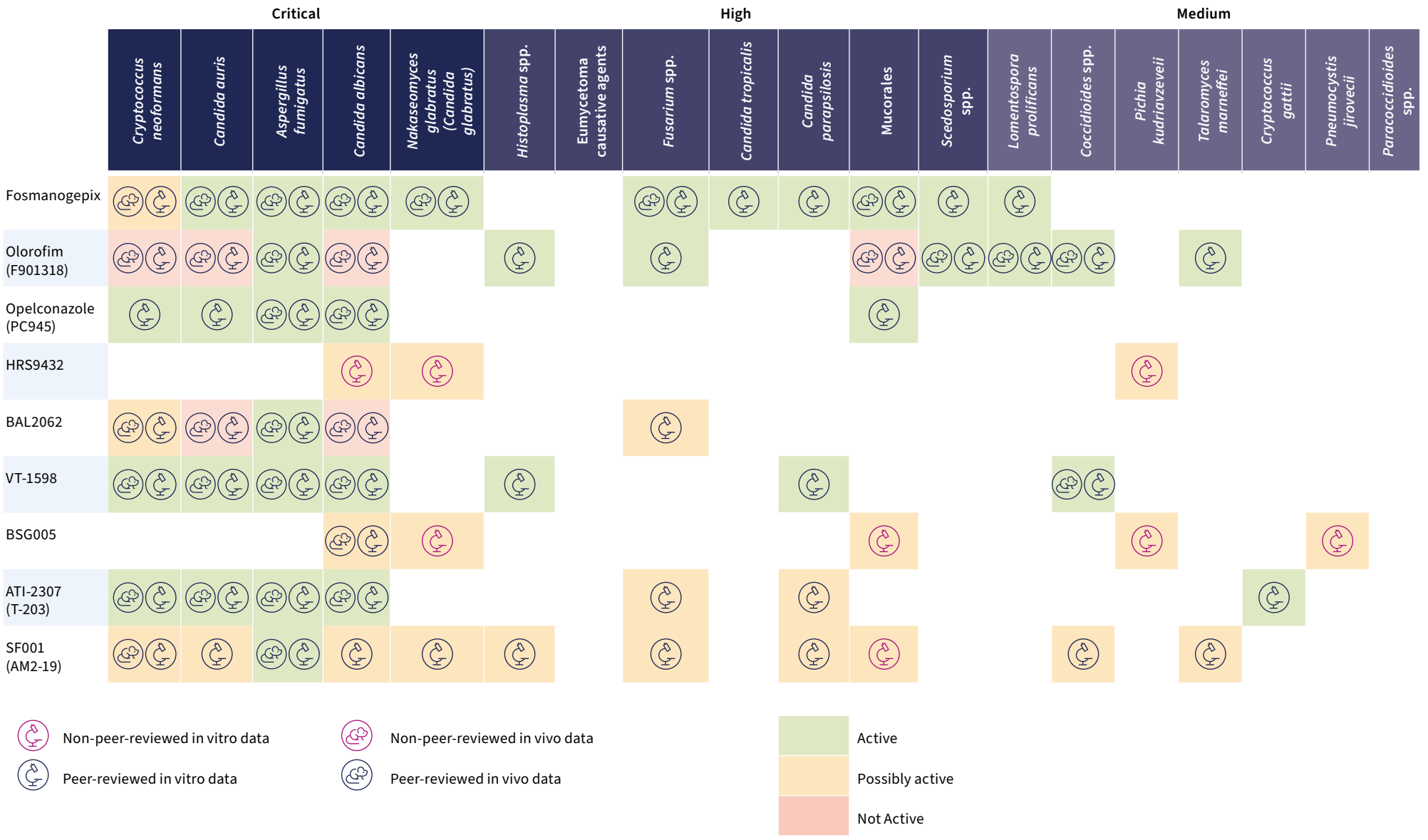
6.2.1 Assessment of potential innovation

Among the nine antifungal drugs in clinical development, four (44%) meet at least one innovation criterion. Two candidates meet only one innovation criterion, while fosmanogepix and olorofim meet all four innovation criteria. However, the potential loss of olorofim activity against fungi exposed to a similar-acting compound marketed as a fungicide, is of concern. The cyclic hexapeptide BAL2062, belonging to a new chemical class and with a still not fully elucidated target and MoA, meets at present only one innovation criterion. The aromatic diamidine, ATI-2307, has shown in vitro and in vivo activity towards azole- and echinocandin-resistant *C. albicans*, as well as azole-resistant *C. auris*, and thus meets the no-cross-resistance criterion. The tetrazole compound, VT-1598, has the same target and MoA as the members of the azole group, and cross-resistance with triazoles has been observed in several *C. albicans* strains, through a still unknown mechanism. While waiting for further confirmation and elucidation of cross-resistance patterns, VT-1598 is at present considered to be non-innovative. The two compounds, HRS9432 and BSG005, have at present incomplete and/or lack of published data; however, they belong to established antifungal classes (i.e. echinocandins and polyenes) and seem to share with compounds of the same class both the MoA and the molecular target. A sound conclusion on their innovation potential will only be possible when data on cross-resistance becomes available. The polyene SF001 demonstrated in vitro and in vivo activity against wild type, azole-resistant, and echinocandin-resistant *A. fumigatus* isolates but has at present no publicly available data against AmB-resistant strains.

6.2.2 Assessment of activity and clinical developmental stage

For the activity assessment, both in vitro and in vivo data were reviewed against fungal priority pathogens according to the methodology detailed in section 8. The assessment of activity, supported by the strength of the available evidence, against both critical and other WHO priority pathogens is visually presented in Table 2 and in Fig. 9 that show if in vitro or in vivo evidence where available to support the assessment. Overall, there are nine products in the clinical pipeline: three agents in phase 3, two in phase 2 and four in phase 1. Of the nine candidates, only seven agents have at present sufficient evidence of activity against at least one critical pathogen according to the WHO FPPL. Of these seven: two candidates have activity against all 4 CPPs and one against three CPPs, one against two CPPs and three against one CPP. In addition, two candidates have activity against three high priority pathogens and one agent shows activity against two priority pathogens. Based on the publicly available in vitro and in vivo data, the critical pathogen targeted by most antifungal candidates (six agents: fosmanogepix, BAL2062, olorofim, VT-1598, ATI-2307, and SF001) is *A. fumigatus*, followed by *C. auris* and *C. albicans* targeted by four and three agents, respectively (fosmanogepix, VT-1598, ATI-2307, and opelconazole). Only two agents, VT-1598 and ATI-2307, have sufficient evidence of activity against *C. neoformans*. Out of the nine products in the pipeline, three (33%) have both in vitro and in vivo activity against OPP.

Fig. 9. Activity of antifungal agents in clinical development as defined by in vitro and in vivo data



6.2.3 Candidate drugs with activity in azole-resistant aspergillosis

Triazoles are the preferred first-line treatment of invasive aspergillosis but increasing incidence of resistance to these drugs is challenging current therapy; moreover, refractory or intolerant patients to first line antifungal treatment necessitating salvage therapy are common *(204)*. L-AmB is at present the main therapeutic option for second-line therapy. Alternatively, but less established, an echinocandin can be used. However, both options require long-term therapy with iv drugs, with potential cumulative side-effects and complicated clinical management. International guidelines recommend a personalized approach, combination therapy and switching drug class, which can be difficult to achieve due to the limited treatment options *(214)*.

Novel antifungal drugs are thus needed to enable a more efficacious, safe and manageable treatment of serious fungal infections. Of the six antifungal candidates targeting *A. fumigatus*, four – fosmanogepix, olorofim, BAL2062 and SF001 – have in vitro and in vivo activity data against azole-resistant strains. The evidence available for fosmanogepix makes this drug a potential candidate for both monotherapy as well as combination therapy with iv L-AmB. In fact, the active moiety of fosmanogepix has shown a synergistic effect with L-AmB in invasive pulmonary aspergillosis, resulting in fungal burden reduction and increased survival rates *(215)*. The potential for drug combination therapy with AmB is further strengthened by the lack of renal toxicity of fosmanogepix in patients with renal insufficiency *(215)*.

The first-in-class compound olorofim selectively targets *A. fumigatus* among WHO critical pathogens, has a convenient safety profile *(124)*, and has been tested in an open label, single arm phase 2b trial (NCT03583164) in a mixed patient population, including 101 patients with *A. fumigatus* infection. Study results showed an adjudicated overall response rate at day 42 of 34.7% (95% C.I. 25.5 to 44.8%), and an acceptable safety profile including mainly gastrointestinal disorders, pyrexia, headache, and alteration of liver function. Confirmation of olorofim efficacy is currently being investigated in a phase 3 trial in comparison to iv AmB, in patients with invasive aspergillosis whose infection is either refractory to or unsuitable for azole therapy (NCT05101187). The current route of administration under investigation for olorofim is oral tablets. Although a phase 1 trial evaluated the PK of both iv and oral olorofim, no further clinical studies are publicly available with the iv formulation and it is not known at present if this formulation will be further pursued. The lack of an iv formulation may limit the use of olorofim as first-line therapy in invasive aspergillosis, possibly predicting its use as an oral step-down treatment following initial iv therapy *(125)*. Like what is observed with azoles, olorofim efficacy could reduce due to the development of resistance in *A. fumigatus* strains exposed to the agrochemical fungicide, ipfufenoquin *(107)*.

The cyclic hexapeptide BAL2062 exhibits very encouraging in vitro and in vivo data against *A. fumigatus*, with rapid in vivo fungicidal activity, an improved safety profile and low potential for DDIs *(99)*, but due to several changes by its sponsor, the clinical development has been put on hold temporarily and the drug is expected to re-enter phase 2 development in 2025.

The novel polyene, SF001 is one of the few candidate agents tested in multiple animal models of invasive pulmonary aspergillosis caused by wild type, echinocandin- and azole-resistant *A. fumigatus* species. The compound looks promising in view of its predicted better safety profile, based on in vitro and animal studies, compared to AmB. However, its clinical development is still in phase 1 and no data in humans are currently available.

The triazole opelconazole, formulated for inhalation therapy, has shown in vitro activity against a few azole-resistant isolates *(98)*, but has the same MoA and molecular target as other members of its class and is expected to show some cross-resistance in the clinical setting. On the other hand, its route of administration through inhalation, enabling the achievement of higher drug concentrations in the lung while limiting systemic exposure, results in an attractive safety profile and affords multiple potential uses. These include several prophylaxis settings such as in lung-transplant patients (NCT05238116) or in the intensive care units or in combination therapy with systemic antifungal agents in refractory invasive pulmonary aspergillosis (NCT05037851) *(66)*.

Finally, the aromatic diamidine ATI-2307 has shown in vitro and in vivo activity against *Aspergillus* spp. At present no in vivo data are available against resistant strains, although no cross-resistance with azoles has been observed against *C. albicans* and *C. auris* strains *(104,112)*.

6.2.4 Candidate drugs with activity in drug-resistant *Candida* infections

Four antifungal candidates – fosmanogepix, VT-1598, ATI-2307 and opelconazole – have shown activity against *C. albicans* and/or *C. auris*. However, only the first three compounds have data against drug-resistant *Candida* infections. For both *Candida* species, multidrug-resistant isolates responsible for difficult-to-treat invasive infections have been observed. Although resistance to echinocandins has developed in *Candida* spp., several strains of *C. albicans* and *C. auris* worldwide are still susceptible and echinocandins are used as first-line therapy for azole-sensitive and -resistant *Candida* infections, due to their favourable safety profile and broad antifungal spectrum; however, they are only available iv, and do not achieve sufficient drug levels in potential sites of infection like brain tissue *(216)*.

Fosmanogepix has sufficient evidence of activity against echinocandin-, azole- or AmB -resistant *Candida* mutants. The drug is available as iv and oral formulations, and extensively distributes to most parts of the body, including the brain and eye *(143)*, holding potential for being an efficacious treatment for difficult-to-treat infections caused by both *Candida* spp. (NCT03604705, NCT04148287).

The tetrazole VT-1598 has evidence of activity against the majority of azole-resistant *C. albicans* and *C. auris* strains tested, although no data are currently available in echinocandin-resistant strains. However, its current clinical development seems paused as the developers are focusing their efforts on their parent compound oteseconazole for which indication extension studies are being planned, among others, in invasive *Candida* infections (company communication).

ATI-2307 could be an attractive therapy for echinocandin- as well as azole-resistant *Candida* infections if the promising safety profile seen in animal models is confirmed in clinical studies. In this case, the development of an oral formulation in addition to the parenteral administration used in the phase 1 trial, if possible, would be valuable.

6.2.5 Candidate drugs with activity in *C. neoformans* infections

Presently, there are only two candidate antifungal drugs that have in vitro and in vivo evidence for activity against *C. neoformans*, the aetiological agent of a devastating fungal meningitis, characterized by high morbidity rates, serious side-effects due to the recommended therapy (AmB plus 5-flucytosine followed by fluconazole) and a significant proportion of deaths even with optimal therapy *(161)*. Novel, safer efficacious drugs are thus critically needed.

The tetrazole, VT-1598, is an attractive new agent that has shown both activity as monotherapy in animal models of cryptococcal meningitis as well as potentiality for combination therapy with AmB. While no clinical trial is currently investigating VT-1598 in this indication, the first tetrazole compound ever marketed, Olpeconazole, that shares similar in vitro activity as VT-1598 against *C. neoformans*, is foreseen to be further developed in *Cryptococcus* infections (direct communication from marketing authorization holder).

The broad-spectrum compound ATI-2307 has shown similar antifungal potency in *C. neoformans* clinical isolates with low as well as high fluconazole MIC50 *(170)*. *C. neoformans* isolates with elevated fluconazole MIC values have been documented in several countries throughout the world *(217–219)*, with the potential for therapeutic failure of currently recommended fluconazole dosing in cryptococcal meningitis *(220)*. ATI-2307 could thus be a potential alternative treatment to fluconazole in areas with fluconazole-refractory *C. neoformans*.

Among the other six fungal candidates, fosmanogepix currently has very limited in vitro data and only partially positive in vivo activity data against *C. neoformans (93)*, but the drug has received orphan drug designation from the US-FDA for the treatment of cryptococcus infections, possibly favouring future clinical investigations.

6.2.6 The clinical development of candidate antifungals against WHO critical priority pathogens

Overall, out of the nine antifungal candidates included in the clinical pipeline, only three (43%) (fosmanogepix, opeconazole and olorofim) are in ongoing trials investigating their activity versus WHO CPPs. All of them are currently being tested in pulmonary or invasive aspergillosis, while only one, fosmanogepix, is also undergoing investigation in patients with *C. albicans* or *C. auris* infections. None of these agents are under clinical investigation for cryptococcal meningitis. The clinical developmental stage of the antifungal pipeline is largely insufficient to effectively address – in the short and medium term – the critical clinical priorities identified by WHO.

6.2.7 Candidate drugs with activity towards infections caused by OPPs

Only three (fosmanogepix, olorofim and VT-1596) out of the nine (33%) candidate antifungal drugs have publicly available in vitro and in vivo data against some of the WHO OPPs, namely *Lomentospora prolificans*, *Scedosporium* spp., *Coccidioides* spp., *Fusarium* spp., and the mucormycosis causal agent *Rhizopus oryzae*.

> Testing against the WHO fungal priority pathogens list (FPPL) is recommended and should be routinely performed to maximize the assets available in the pipeline.

WHO high-priority fungi *Lomentospora* spp. and *Scedosporium* spp. generally have low susceptibility to currently available systemic antifungal agents *(221)* and cause diseases with high mortality rates *(222)*. First-line treatment in susceptible species typically relies on voriconazole. Combination treatments have also been tested but with variable outcomes or very limited evidence in humans *(223)*. Among the more recently approved agents, the triazole isavuconazole and the triterpenoid ibrexafungerp demonstrated good in vitro activity against *Scedosporium* spp. complex and *L. prolificans*, but at present there are no clinical trials registered to evaluate this activity in patients *(224,225)*.

Olorofim showed activity against *Lomentospora* spp. and *Scedosporium* spp. *(96)* and has received US-FDA breakthrough therapy designation for the treatment of these invasive mould infections. However, the new drug application presented by Olorofim to US-FDA for the treatment of resistant fungi, including *Lomentospora* prolificans, *Scedosporium* spp. and *Aspergillus* spp. was recently rejected, with further studies being required (see section 3.1). Results of the phase 2 trial included in the registration dossier showed that in the 26 patients infected with *Lomentospora* and in the 22 infected with *Scedosporium* the rate of adjudicated overall responses at day 42 were 42.3% (95% C.I. 23.4–63.1%) and 36.4% (95% C.I. 17.2–59.3%), respectively.

Fosmanogepix was proven active against *Scedosporium* species *(92,226)* and has been granted orphan drug status for several invasive rare mould infections including *Scedosporium* spp. A phase 2 study (NCT04240886) of fosmanogepix for the treatment of invasive fungal infections due to these pathogens was prematurely terminated in May 2022 for strategic reasons, with the claim by the sponsor that a phase 3 study in the same indication will soon be started (see the sponsor statement posted on clinicaltrials.gov website for study NCT04240886). At present, fosmanogepix is available under expanded access for patients with serious or life-threatening invasive fungal infections with no other treatment options (NCT06433128).

The WHO medium-priority fungi, *Coccidioides* spp. are responsible for endemic mycosis, with CNS infections or disseminated/progressive disease, requiring long-term antifungal therapy, and often leading to high overall morbidity and mortality rates. Olorofim has received US-FDA breakthrough therapy designation for the treatment of CNS coccidioidomycosis that are refractory or that cannot be treated with standard-of-care therapy. In a murine model of CNS coccidioidomycosis, olorofim treatment resulted in an early improved survival at 30 days compared to controls, and caused eradication of the organism in some mice, suggesting its potential as a safer and more efficacious treatment in the human disease *(97)*. Preliminary data from 41 patients with extrapulmonary coccidioidomycosis, enrolled in a phase 2 trial (NCT03583164) for refractory, resistant endemic mycoses, appear to support the benefits of olorofim. As reported in a published abstract, olorofim treatment induced complete or partial clinical response in 76% of cases at days 30 and 42, and in 73% of cases at day 84 *(124, 227)*.

VT-1598 and fosmanogepix also target *Coccidioides* spp. VT-1598 induced the suppression of fungal burden within the brain tissue 48 hours post treatment, including undetectable fungal growth in some mice infected with *C. posadasii*, and caused significant improvements in survival in both *C. posadasii* and *C. immitis* infected animals *(100)*. Comprehensive in vitro and in vivo activity data are not publicly available for fosmanogepix. However, the US-FDA breakthrough designation for fosmanogepix suggests promising potential for its future clinical development in this indication.

Fusariosis can cause serious disseminated infections in severely immunocompromized patients, which are often associated with poor outcomes *(228)*. International guidelines recommend voriconazole and/or lipid-based AmB formulations as first-line therapy for patients with severe *Fusarium* infections, with posaconazole as salvage therapy *(229)*. However, mortality rates are high (80–100%), especially in those patients with prolonged immunosuppression *(230)*. Alternative treatment options are urgently needed. Based on the evidence from animal models of disseminated fusariosis *(92)*, and the few patients recruited in the terminated phase 2 open-label, multicentre study on rare moulds, (NCT04240886), fosmanogepix has been successfully utilized for treating cases of *Fusarium* meningitis outbreaks that occurred as part of the 2023 outbreaks in Mexico *(231,232)*.

Fosmanogepix presents evidence of activity against *Rhizopus arrhizus*, one of the agents of mucormycosis. Mucormycosis are difficult to treat with mortality rates between 40–80%, despite advances in treatment. High mortality rates, up to 80% in CNS-disseminated disease *(207)*, have been observed. Treatment challenges are amplified by difficulties in differential diagnosis with aspergillosis, as both infections have similar risk factors and clinical features *(233)*. Co-infections or consecutive infections of mucormycosis and aspergillosis were also observed *(234)*. The activity of fosmanogepix observed against both pathogens favours its potential future clinical use for both infections and it is anticipated to have an impact on the clinical practice, easing the therapeutic decision-making process in co-infected patients.

Except for olorofim and fosmanogepix that are currently under investigation in clinical trials for some rare moulds, no other candidate antifungal drugs are currently being tested in the clinic against WHO OPPs. Thus, it seems unlikely that the clinical need for new safe and efficacious antifungal drugs, conferring protection against most of the therapeutically challenging fungal infections identified by WHO, will be satisfied soon.

6.3 Additional strategies for pipeline improvement: extension of indications and drug repurposing

6.3.1 Extension of indication

Alongside the development of novel antifungal drugs, additional strategies to optimize the therapeutic arsenal against fungal pathogens include extension of indications of approved drugs and repurposing of marketed medicines as antifungal agents. Eight antifungal drugs have started clinical evaluation for potential label extension, across a total of 15 clinical trials. Three clinical trials (involving three agents) are being conducted in refractory invasive fungal diseases. Additionally, five studies test sequential or combination

therapy in invasive candidiasis (two agents), cryptococcal meningitis (two agents), and *Talaromyces* infection (one agent). Furthermore, two studies investigate combination therapy in PJP, while four studies investigate antifungal drug monotherapy in mycetoma, *Coccidioides* infections, Histoplasmosis, and in *C. auris* infections. Lastly, one study investigates prophylaxis in patients undergoing allogenic blood and marrow stem cell transplantation. Results are available for seven out of the 15 trials (47%): two trials are ongoing, two are suspended, one is stopped, three trials were intended to be completed several years ago, but no information is currently available on their status. Indeed, the overall landscape does not appear very promising. A total of five studies out of 15 (33%) will likely not produce meaningful information; two studies are being conducted in a mixed population including only a very limited number of patients in the studied indication (isavuconazole in *Cryptococcus* infection). Moreover, one study (NCT03672292) shows no apparent additional benefit from the combination of ibrexafungerp with voriconazole compared to voriconazole monotherapy in invasive aspergillosis, despite evidence of ibrexafungerp monotherapy efficacy from the interim results of the FURI trial (see section 3.2). Notably, terpenoids and azoles have different MoA and affecting the cell membranes and the ergosterol synthesis simultaneously should produce a synergistic effect. While in vitro and in vivo data consistently support the potential use of rezafungin in the treatment of aspergillosis (as discussed in section 3.2), an extension of indications for rezafungin as salvage therapy in invasive aspergillosis is not foreseen in the near future. Currently, rezafungin is only under clinical evaluation for prevention in adults undergoing allogenic blood and marrow cells transplantation (NCT04368559; EUCTR2017-004981-85) *(89)*, with completion expected by December 2025. A more promising outlook emerges from the positive results of the orally available, first-in-class compound ibrexafungerp in refractive invasive fungal infections and in candidiasis caused by *C. auris*. Although only topline data are at present available from both studies, they are clinically relevant (see section 3.2), especially considering the challenges associated with treating these frequently drug-resistant infections. In addition, although failing to show superiority of fosravuconazole versus itraconazole in mycetoma, data from study NCT03086226 are clinically interesting; fosravuconazole offers an attractive weekly posology and seems to be more tolerable and less prone to DDIs compared to the classical therapy with ketoconazole and itraconazole (see section 3.2).

6.3.2 Drug repurposing

Of potential interest for the low cost and time-sparing attributes, repurposing of marketed drugs as antifungal agents has unfortunately proven unfruitful. Very few medicinal products have undergone clinical evaluation as potential antifungal drugs and results have not been promising. Out of four trials investigating the potential of clindamycin, pioglitazone, sertraline and tamoxifen as antifungal drugs, two failed (clindamycin and tamoxifen), one was terminated for excessive toxicity (sertraline), and the fourth, evaluating the efficacy of pioglitazone in cryptococcal meningitis, was delayed due to the COVID-19 pandemic and is still ongoing. Recently, a novel derivative of sertraline, which may have fewer side-effects, is undergoing pre-clinical studies and is expected to be studied in the clinical setting. Of note, all repurposed drug programmes identified in this review are led by academic groups, which may experience difficulties in gathering or generating sufficient efficacy evidence, even when working with established medicines. To address this issue, in 2021 the EMA launched a pilot project to support not-for-profit organizations and academia in repurposing generic medicines in new indications. This pilot may also cover the label extensions of generic products *(235)*.

6.4 Challenges in the research and development of novel antifungals

As this WHO review of the clinical and preclinical pipeline of antifungal drugs against FPPs reveals, the identification and development of efficacious, safe, and tolerable agents for difficult-to-treat IFDs is a slow and complicated process. Among several challenges, one is represented by the scientific barrier in identifying appropriate new targets as many essential biochemical and cell biological processes are conserved between fungal pathogens and the human host. Among the nine candidate antifungal drugs, only three address a new target, including BAL2062, the target of which has still not been fully elucidated. Hopefully, progress in the basic scientific research focusing on the structure and biology of fungal cells will lead to the identification of new drug targets, some of which are already being explored in the literature, including interference with fungal resistance mechanisms (e.g. efflux pumps and heat shock protein 90) *(236)*. In addition, the pursuit of complementary or synergistic strategies, often employed in the R&D of new antibacterial agents through non-traditional methods, could similarly be beneficial in the creation of innovative antifungal therapies. Novel non-traditional antifungal agents targeting anti-virulence factors able to inhibit fungal virulence mechanisms like filamentation and biofilm formation could be explored *(237–239)*, as well as immunotherapy with monoclonal antibodies. In addition, cellular immunotherapies aiming to foster antifungal immunity are starting to be tested. Among others, fungal-specific T-cells treatment in haematopoietic stem cell transplant patients is in clinical development. These include *Aspergillus* Th1 cells to treat such patients with confirmed invasive aspergillosis *(240,241)*.

R&D in the antifungal field could also leverage targeted drug delivery technologies. These approaches facilitate the effective accumulation of antifungal drugs at the infection site, enhancing efficacy while minimizing toxicity *(242,243)*. Notably, this is currently being explored for opelconazole for inhalation, BSG005 Nano and BSG005 Nano oral formulations, thin film freezing voriconazole inhalation powder, and AmB cochleate.

Finally, preventive strategies including vaccines could also have a role in treating IFDs.

6.5 Challenges in the design and conduct of clinical trials with antifungals

Clinical trials for antifungal drugs face several constraints. A difficult-to-solve problem concerns the slow recruitment process, which affects several clinical trials involving antifungal drugs. The enrolment issue is due to multiple factors, including the rarity of the diseases, the lack of uniform diseases definitions, the challenges in the definition of inclusion criteria due to the heterogeity of patients with fungal disease (including patients with serious underlying conditions), the appropriate use of diagnostic tools including imaging, the lack of surrogate markers of infections, as well as the lack of a broad surveillance networks that could facilitate the localization of endemic regions to establish clinical study centres *(244)*. Clinical trial networks should be promoted whenever possible to help speed up enrolment. Consequences of the recruitment issue beyond the lengthy development and the longer time for new antifungal drugs to be introduced to the market, include the suboptimal data package supporting the indication of several antifungals and the scarcity of comparative effectiveness trials that hamper the optimization of therapeutic strategies especially in the paediatric patient population.

6.6 Antifungal agents in preclinical development

The WHO global analysis of the publicly available preclinical antifungal pipeline projects bears a resemblance to the programmes in clinical development.

Overall, there is a lack of preclinical projects in the antifungal space relative to the scale of global mortality from fungal infections, and a significant number of those programmes are being carried out in academic institutions where they are less likely to progress. Further, a significant proportion of the programmes are investigating new administration routes for existing compounds (either approved or in clinical development), and while these products may make a difference in clinical management of patients, it does also reduce the level of novel molecules being developed.

However, while still inadequate to address the large number of deaths attributed to fungal infections *(1)*, between 2022 and 2024 there was a marked increase in the number of products in the preclinical pipeline targeting these key pathogenic species that increased from eight agents in preclinical stages affiliated with seven developers in 2022 to 22 projects being pursued by 18 groups in 2024.

With respect to the institutions, the preclinical antifungal pipeline solely relies on micro (<10 employees) and small (<50 employees) entities and academic institutions to progress science and development of innovative treatment products for fungal infections. This also contributes to the overall fragility of the pipeline. However, of the preclinical programmes that were available for analysis, it is reassuring that many are active against the four critical priority pathogens identified by WHO, including nine programmes (40.9%) that demonstrate activity against all of the critical pathogens.

Although this analysis did exclude antifungal vaccine programmes, it should be noted that there are several active programmes, both univalent and multivalent, looking to progress fungal vaccines toward clinical development and registration. This strategy provides a useful addition to the prospect of prevention of fungal infections, which would be very valuable in susceptible and high-risk populations.

Ultimately greater transparency in the preclinical pipeline, coupled with the clinical pipeline, can lead to stronger collaboration around potentially innovative but challenging projects, support a community of scientists and drug developers, and generate more interest and funding into drug development for novel antifungal agents.

WHO will continue to monitor the preclinical pipeline on a regular basis and make this data available on the WHO R&D Health Observatory.

6.7 Limitations

The analysis and assessment of the preclinical pipeline relies largely on data submitted by the respective developers through the open WHO data call. A thorough data cleaning was undertaken and where available other sources were used for additional information, or the developer was contacted to clarify or fill gaps in the submission. In the absence of clinical data as well as detailed data on the different molecules in development, no independent assessment was undertaken with respect to the fungal targets or innovativeness of the individual projects. This review should be considered a snapshot and not a complete analysis. WHO would welcome any additional information and/or feedback on the data presented in this document, which should be sent to antifungalpipeline@who.int. WHO encourages wide participation in any future clinical and preclinical data calls.

7

Conclusion

7. Conclusion

7.1. Gaps and constraints in the present antifungal arsenal and in the current clinical research and development landscape

Marketed antifungal drugs

- Most approved antifungal drugs on the market presents a complex PK and safety profile, with high–medium potential for DDIs, lack of oral formulations and require long-lasting therapies especially in case of invasive disease. This translates to lengthy and poorly tolerated therapies leading to poor compliance and, in some cases, poor therapeutic outcomes.
- Since fungi are very diverse organisms ranging from yeast to filamentous fungi, true broad-spectrum antifungals are not available and possibly not pursuable. Consequently, in many cases, antifungal therapy requires precise diagnostic activity, which is not always possible or available worldwide. This hampers a timely start of empiric treatment, impacting therapeutic outcomes.
- Clinical trials to inform the paediatric posology and/or suitable paediatric formulations are seldom conducted with authorized antifungal agents.
- The availability of comparative effectiveness data necessary for the selection of the optimal antifungal therapy/prophylaxis in children with IFDs is extremely limited. This challenges the use of antifungal drugs in children, may result in toxicity or treatment failure and drive antifungal resistance in both children and adults.

Clinical research and development

- With only two candidate drugs in phase 3 of development, few marketing authorizations are expected in the next 10 years within the current R&D framework.
- Currently there are no clinical trials to investigate new treatments for *C. neoformans* meningitis.
- The innovation potential of the candidate antifungal drugs is limited. Among the nine antifungal drugs in clinical development, only two (22%) meet all four innovation criteria, while two (22%) meet one innovation criterion. The other five candidates are considered not innovative at present.

7.2 Policy implications to address gaps in the antifungal pipeline

1. To mobilize political will and resources towards R&D for new therapies, investments should be focused to strengthen global surveillance systems on IFDs burden with quality data on the burden due to emerging fungal pathogens such as filamentous fungi, antifungal resistance patterns, and treatment outcomes. Coordination efforts for sharing epidemiological data between countries and international organizations are also crucial.
2. Allocate resources and funding to basic research on fungal biology, genetics and drug targets to better elucidate the mechanisms of fungal resistance and virulence. This is crucial for the identification of novel drug targets, and the development of effective antifungal drugs with a longer lifespan.
3. Develop target product profiles for antifungal drugs with novel mechanisms, favourable PK profiles, including high oral bioavailability and tissue penetration, and fungicidal activity.
4. Expand financial incentives for antifungal drug discovery and development, including grants for academic research groups and institutions, start-ups, biotech and/or pharmaceutical companies. Public–private partnerships/product development partnerships and R&D accelerators should focus their efforts on accelerating their research and clinical trials for novel antifungal agents.
5. Broaden the scope of national services providing preclinical studies to support development of antifungal drugs. Clinical trials networks and platforms should be expanded, leveraging existing examples and/or establishing international research consortia dedicated to antifungal agents in endemic areas. Such cross-country collaborations can accelerate R&D by sharing knowledge, resources and data.

6. Raise awareness of the existing regulatory mechanism and flexibilities that support R&D of novel antifungal agents.[a]
7. Investigate the potential clinical utility of non-traditional approaches, such as immunomodulatory strategies.
8. Explore the clinical benefit of currently available therapies; study the potential clinical benefit of their combination, keep exploring the potential for repurposing existing drugs and improve their delivery system (e.g., new formulations, route of administration).
9. The availability and affordability of efficacious antifungal drugs is not always known in regions with the highest burden of IFDs, including cryptococcosis, such as countries from sub-Saharan Africa, Latin America, and Southeast Asia. Stewardship should be implemented in clinical practice as well as promoting equitable and global access to novel and existing antifungals. Local research and innovation combined with technology transfer and local production should be considered as possible mechanisms to improve access in countries bearing the highest burden of disease.
10. Novel targets and mechanisms of action need to be identified to balance the acceleration seen in the emergence and spread of drug resistance. Investigation could include interference with fungal resistance mechanism and/or virulence factors, biofilm formation or implementation of immunotherapy.
11. A multipronged approach, including uniform disease definitions, appropriate use of diagnostic imaging, available, affordable and accessible diagnostics with high sensitivity, specificity and reasonable turnaround time, surrogate markers of infections, as well as broad surveillance networks and implementation of clinical trial networks, needs to be undertaken to address the challenges in recruitment that affect several clinical studies with antifungal drugs.
12. 80% of all plant diseases are caused by fungi and the efficacy of novel antifungal drugs in clinical development can be jeopardized by widespread use of agriculture fungicides with shared targets or similar MoAs. A recent example is offered by an approved fungicidal azole, ipflufenoquin, and a candidate drug, olorofilm, highlighting the need for a collaborative One Health approach to preserve both human health and food security.

Similar to antibacterials, the antifungal pipeline is in a profound crisis. Globally coordinated collaboration, innovation and sustained investment are essential to address the pipeline crisis effectively.

[a] This includes the US-FDA Tropical Disease Priority Voucher programme, for which agents intended against cryptococcus disease would qualify. Further extension of market exclusivity may be granted in the United States to foster the development of antibacterial and antifungal drug products to treat serious or life-threatening infections. This policy has been implemented by the United States Government within the Generating Antibiotic Incentives Now (GAIN) Act. In force of the GAIN act, the US-FDA designates antibacterial or antifungal agents against resistant pathogens, including novel or emerging infectious pathogens, as a qualified infectious disease product (QIDP). A product that qualifies as QIDP receives additional years of market exclusivity. The QIDP designation is applicable to new drugs, authorized drugs with a new use (extension of indication), or drugs for a rare disease (orphan drug). The EMA has also developed a pilot programme to support R&D by academia and non-profit organizations.

8

Methods

8. Methods

The evaluation of antifungal agents in clinical and preclinical development was conducted through a rigorous process led by the WHO secretariat pipeline team, in collaboration with the WHO expert group on the R&D of antifungal treatments. This expert group consists of highly qualified clinicians, mycologists, chemists, researchers, regulators and experts well-versed in antibiotic R&D, PK/PD and antimicrobial resistance. To ensure a comprehensive and insightful evaluation, the experts were presented with pre-reading material meticulously prepared by the WHO secretariat, and soon after engaged in a pre-consultation survey encompassing both methodological and product-specific aspects. The formal consultation, held over a 1-day virtual expert group meeting on 8 July 2024, provided a platform for in-depth discussions. Notably, during the consultation the expert group reviewed and endorsed the newly developed assessment matrix, which served as a robust framework to methodically evaluate the potential activity of each agent (see section 8.1.4.1.) and the newly introduced innovation criteria for antifungal agents.

To maintain the integrity of the process, members of the expert group with potential conflicts of interest pertaining to specific companies or agents (see Annex 1) were excluded from relevant discussions to ensure impartiality and transparency. Prior to publication, the report was circulated among all members of the expert group to solicit feedback, enabling refinement and improvement.

8.1. Clinical pipeline analysis

8.1.1 Scope and inclusion/exclusion criteria

Inclusion

This review covers new chemical entities in clinical (Phase 1, 2, 3 and new drug /marketing authorization applications) and preclinical development worldwide that do not have marketing authorization for human use by a stringent regulatory authority or a WHO listed authority. It also includes antifungal agents that were approved between 1 January 2014 and 1 September 2024. The review was restricted to antifungal agents for systemic treatment, including formulations for inhalation, of serious acute and sub-acute fungal diseases caused by WHO fungal priority pathogens.

Repurposed antibacterial agents are also included in this review regardless of the primary indication (i.e. drugs from any therapeutic area including infectious disease), including reporting failed attempts as lessons learned.

This report also presents potential label extensions (i.e. medicines that already received marketing authorization and that are now under evaluation in a different indication). In addition, new formulations of known molecules are also discussed.

Candidate drugs for which information is not known or which are not under active development are presented in section 7. Development programmes are considered inactive if no change in the clinical development were presented over the past five years.

Exclusion

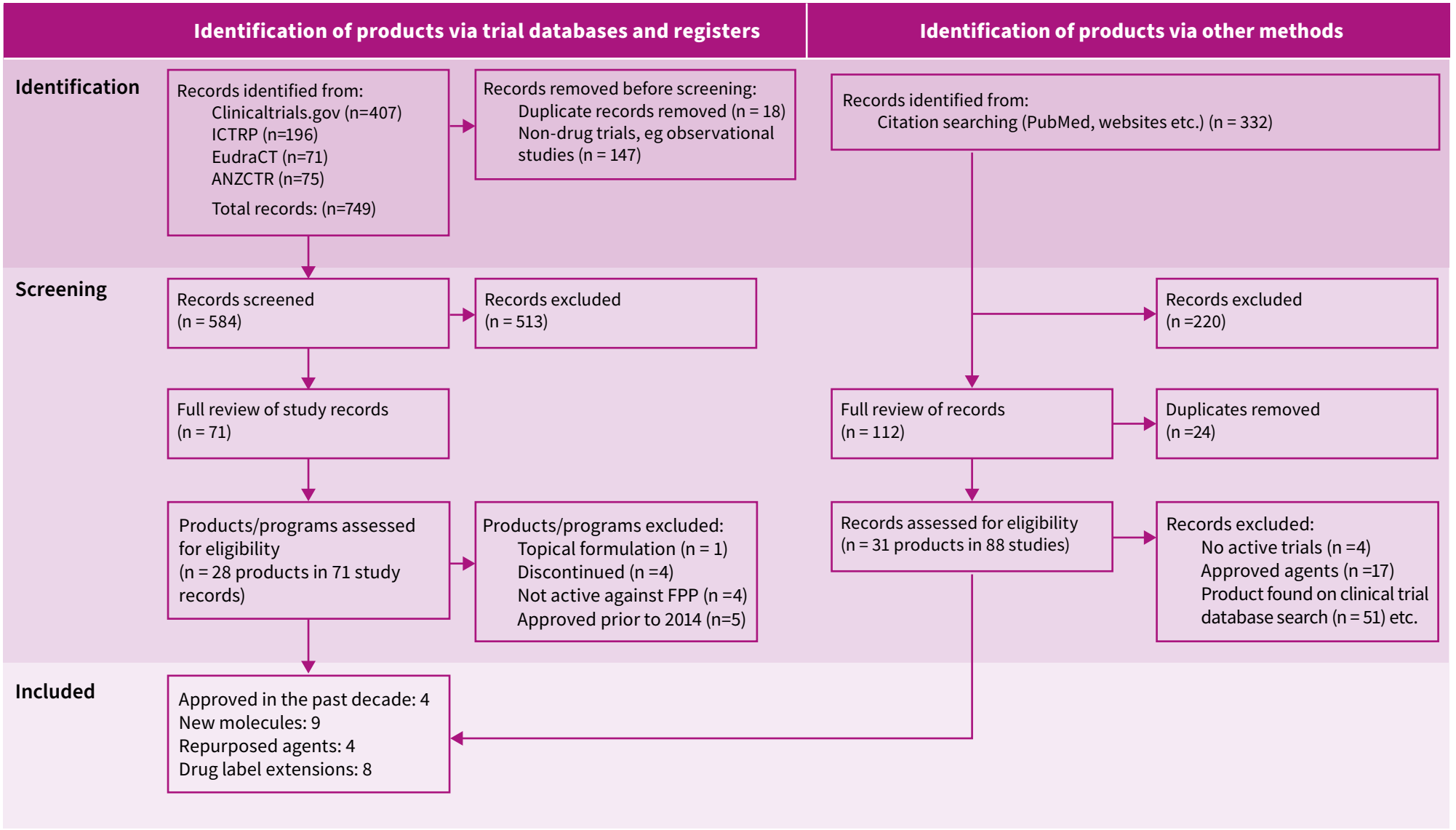
Treatment for dermatophytes (i.e. fungi that infect keratinized tissues such as skin or nails) are not included in the scope of the present report but might be considered in future iterations due to the burden of dermatophytes in population living in poverty and with underlying health issues, as well in light of the increasing reported resistance rates. Inhaled antifungal agents in development for the treatment of allergic aspergillosis and fungal asthma are also not included.

Herbal medicines/extracts were excluded unless the relevant molecule was specified and quantified for the intended treatment.

8.1.2 Search and selection strategy

A systematic search was performed by WHO in the following clinical trial databases: International Clinical Trials Registry Platform (ICTRP), Clinicaltrials.gov, European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) and the Australian New Zealand Clinical Trials Registry (ANZCTR), using the “name of the pathogen” or the “name of the disease” to find clinical trials evaluating drugs for fungal infections. The search was restricted to studies registered after 1 January 2014. In addition, a search was performed on PubMed using the key words “antifungal” AND the “name of the pathogen” OR the “name of the disease” to find relevant review articles. The literature review was performed with the data cut-off of 1 September 2024. Additionally, a search was conducted on specific company pipeline websites, guided by the results from clinical trials and PubMed. Data obtained directly from developers or the WHO expert group were appraised by the WHO pipeline team to determine if they met the predefined inclusion and exclusion criteria. Other sources consulted for drug candidates in clinical development were the AMR Industry Alliance, the AMR Action Fund, the Biotech companies from Europe innovating in Anti-Microbial resistance research (BEAM Alliance), the Biotechnology Innovation Organization (BIO), and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). The search was complemented by experts' review. A flow diagram showing the search and selection strategy is provided in Fig. 10.

Fig. 10. Flow diagram showing the systematic search and selection strategy



Source: Adapted from *(245)*.

8.1.3 Data extraction

The following data were extracted: antifungal name, antifungal class, route of administration, activity (i.e. for which fungi is the agent under investigation), innovation criteria (no cross-resistance within and across antimicrobial classes, new chemical class, new target, new mode of action), name, geographical location, country income-level (n.b. for this analysis, economies are divided into four income groups (i.e. low, lower-middle, upper-middle and high) according to the World Bank 2023 classification *(246)*, and size of developer (i.e. small, medium, large), and type of sponsor (i.e. academic, commercial, foundation). Data extraction from clinical trials was limited to the most advanced development stage (e.g. if a phase 3 study was available no data extraction was performed for a phase 2 in the same indication). Data extraction from a clinical trial included: product name, clinical trial number, sponsor, phase, status (e.g. recruiting, completed etc.), study design, sample size, indication, patient population, inclusion/exclusion criteria, drug dose, treatment duration, primary outcome, primary efficacy endpoint, primary efficacy evaluation and adverse effects.

8.1.4 Evidence supporting the activity and innovation assessment

Evidence for activity against WHO fungal priority pathogens and innovation was retrieved from peer-reviewed publications. For agents in the early stages of development, information from presentations and posters at scientific conferences and information published by the developers was also used. Information was considered valid only if it was publicly available and scientifically sound, as reviewed by WHO and by the expert group. Information from developing companies about drugs being evaluated in unregistered phase 1 clinical trials was referenced when available.

8.1.4.1 Assessment of the expected activity against priority pathogens

The evidence supporting the expected activity increases with the development stage. The first level of evidence is usually gained by in vitro experiments. Subsequently, preclinical results are produced using animal disease models in the sought indication or in a broader one. Moving to the clinical phases, safety and tolerability data in healthy volunteers are usually generated followed by dose–response and efficacy data. The WHO evaluation of antifungal activity against priority pathogens is thus an evolving assessment that incorporates new pieces of information as they are made available during drug development.

The strength of evidence supporting the activity assessment is presented in Table 2 and Fig. 9 that show if in vitro or in vivo evidence where available to support the assessment, highlighting if they are derived from peer-reviewed or non-peer-reviewed publications, and if they are based on in vivo or in vitro data.

To standardize and define the expected product activity against priority fungi, a matrix for the assessment of activity was proposed by the WHO secretariat, then discussed and endorsed by the expert group (Fig. 11).

Fig. 11. Matrix for the activity assessment of novel antifungal agents in clinical development

Symbol	Definition/Evidence required
•	**Active** Peer-reviewed in vitro and in vivo data or at least peer-reviewed in vitro data and not peer-reviewed in vivo data or vice versa, if the mechanism of action, and/or the number of isolates tested support activity
?	**Possibly active** Non-peer-reviewed in vitro and in vivo data or company's website information; or only in vitro data without in vivo data
X	**Not active**
/	**Activity not tested/No information available**

- **For a new antifungal belonging to an already established antifungal class:** Activity against the WHO FPPL was assessed by comparing the new antifungal minimum inhibitory concentration (MIC) or minimum effective concentration (MEC) data with clinical breakpoints or epidemiological cut-off values for antifungal drugs of the same class and taking into account: PK/PD data in animals, clinical exposure levels and dose-limiting adverse effects, when available.
- **For first-in-class antifungals:** Activity was assessed by comparing the new antifungal MIC or MEC data and in vitro susceptibility rates with those of antifungal drugs with activity against the same pathogen and taking into account PK/PD data in animals, clinical exposure levels and dose-limiting adverse effects, when available.
- **For fungal pathogens with no established interpretive criteria** (i.e. either a breakpoint or an epidemiological cut-off value), MIC/MEC values may have no clear clinical interpretation. In this case, in vitro activity was defined as the ability to inhibit growth or kill the pathogen, taking into account PK/PD data in animals, clinical exposure levels and dose-limiting adverse effects, when available.

8.1.4.2 Assessment of the potential innovation of antifungal agents authorized and in clinical development

It is acknowledged that the key criterion for innovation is the demonstration of additional clinically significant benefit exerted by an individual agent. This can only be assessed when the clinical developmental programme is completed, and in some cases re-evaluated when real world data are available. For the scope of this review, an agent was considered potentially innovative if it had no (known) cross-resistance to existing antifungals.

In this context, cross-resistance is defined as within as well as across classes that can be measured by systematic susceptibility testing in vitro of a diverse panel of genetically defined pathogens, combined with genetic characterization of mutants and molecular structural analysis. Surrogate predictors for the absence of cross-resistance that were also assessed include the following:

- new class (new scaffold);
- new target (new molecular binding site); and
- new MoA.

Surrogate criteria for lack of cross-resistance, in our analysis, are used as predictors of possible 'no cross-resistance' when in vitro data on cross-resistance are still incomplete, not publicly available or the in case of first-in-class agents. When data on cross-resistance are available, surrogate criteria are interpreted as supporting elements that reinforce/contribute to explain the observed in vitro lack of cross-resistance. Agents that do not show absence of cross-resistance may still be endowed with added clinical benefit for individual patients, including, but not limited to, increased activity against priority pathogens, a better safety profile compared to existing therapies or a less invasive route of administration (e.g. oral versus iv).

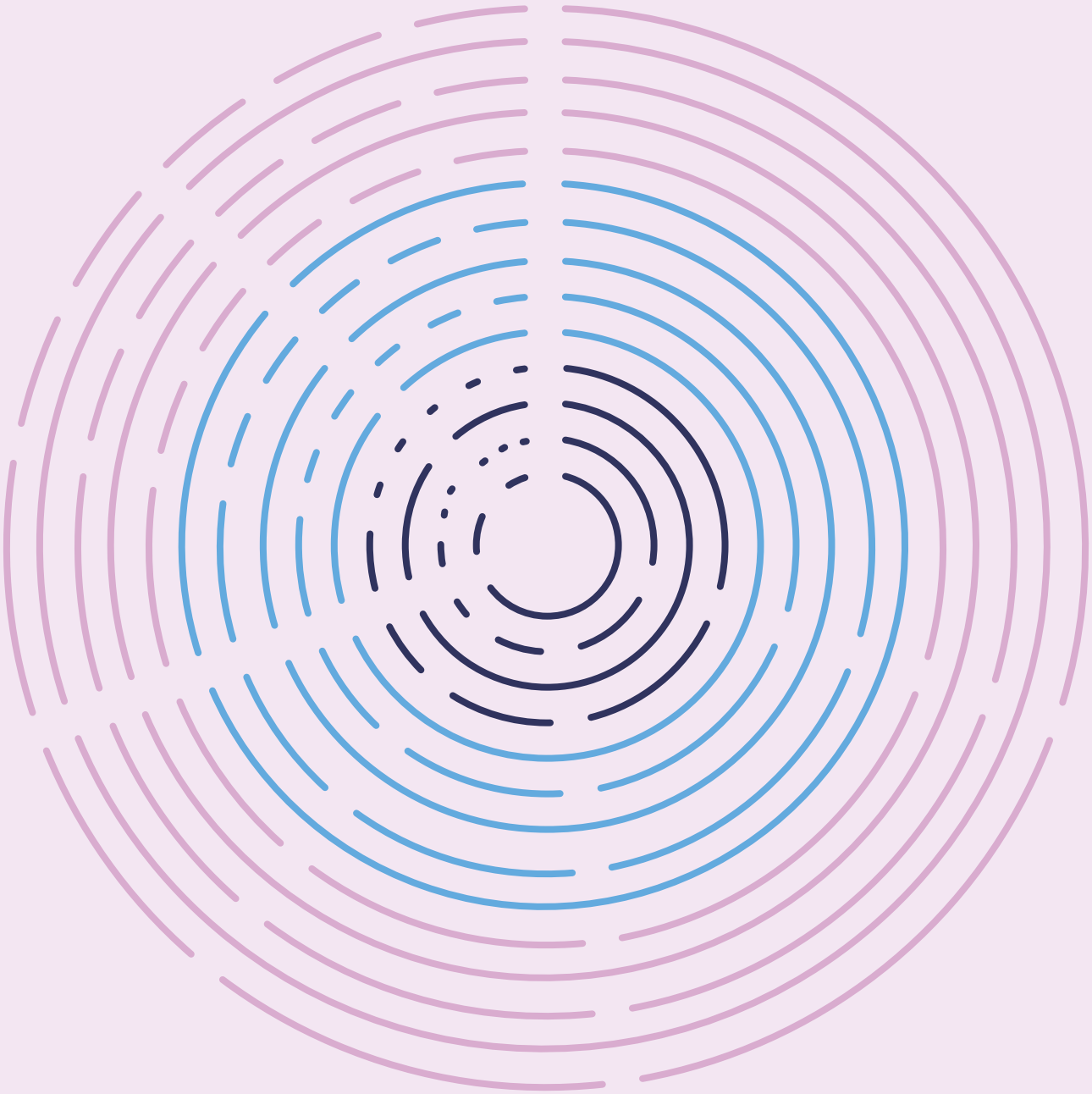
8.2. Preclinical pipeline analysis

8.2.1 Scope and inclusion criteria

The review focuses on antifungal agents that target the WHO priority pathogens that are in lead-optimization (post hit expansion), preclinical candidate, to formal investigational new drug application also termed clinical trial application (or for regulatory authorities that do not use these terms this is indicative of the commencement of human testing). The review includes both traditional and non-traditional approaches including direct and indirect acting antifungals, small and large molecules, antivirulence agents and biofilm disruptors, potentiators, microbiome modifying agents, immunomodulators, re-purposed agents including those with a new proposed route of administration. The review did not include vaccines, diagnostics, antibacterials, antivirals and antiparasitics. Wound care agents, unspecific supportive treatments, medical devices, industrial or animal use agents were also not included.

8.2.2 Data collection

A WHO online call was opened in April 2024 and generated the primary data. A targeted search of products in preclinical development was undertaken and the data was supplemented with information from the Beam Alliance and national funding agencies, among others. Where required, updates were solicited by email. Data presented is self-declared from the institutions and where possible, WHO confirmed the data through publications, conference abstracts or posters, institutional websites and other information in the public domain.



References

9. References

1. Denning DW. Global incidence and mortality of severe fungal disease. Lancet Infect Dis. 2024;24(7):e428–38 (https://doi.org/10.1016/S1473-3099(23)00692-8, accessed 15 October 2024).
2. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71(6):1367–76 (https://doi.org/10.1093/cid/ciz1008, accessed 15 October 2024).
3. Bassetti M, Azoulay E, Kullberg BJ, Ruhnke M, Shoham S, Vazquez J et al. EORTC/MSGERC definitions of invasive fungal diseases: summary of activities of the Intensive Care Unit working group. Clin Infect Dis. 2021;72;Suppl 2:S121–7 (https://doi.org/10.1093/cid/ciaa1751, accessed 15 October 2024).
4. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med. 2012;4(165):165rv13 (https://doi.org/10.1126/scitranslmed.3004404, accessed 15 October 2024).
5. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. J Fungi (Basel). 2017;3(4):57 (https://doi.org/10.3390/jof3040057, accessed 15 October 2024).
6. Rüping MJ, Vehreschild JJ, Cornely OA. Patients at high risk of invasive fungal infections: when and how to treat. Drugs. 2008;68(14):1941–62 (https://doi.org/10.2165/00003495-200868140-00002, accessed 15 October 2024).
7. Hoenigl M, Seidel D, Sprute R, Cunha C, Oliverio M, Goldman GH, et al. COVID-19-associated fungal infections. Nat Microbiol. 2022;7(8):1127–40 (https://doi.org/10.1038/s41564-022-01172-2, accessed 15 October 2024).
8. Shah K, Deshpande M, Shah P. Healthcare-associated fungal infections and emerging pathogens during the COVID-19 pandemic. Front Fungal Biol. 2024;5:1339911 (https://doi.org/10.3389/ffunb.2024.1339911, accessed 15 October 2024).
9. WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/363682, accessed 15 October 2024).
10. El Eid R, Chowdhary A, El Zakhem A, Kanj SS. Invasive fungal infections in wars, following explosives and natural disasters: A narrative review. Mycoses. 2024;67(7):e13762 (https://doi.org/10.1111/myc.13762, accessed 15 October 2024).
11. Egger M, Hoenigl M, Thompson GR 3rd, Carvalho A, Jenks JD. Let's talk about sex characteristics-As a risk factor for invasive fungal diseases. Mycoses. 2022;65(6):599–612 (https://doi.org/10.1111/myc.13449, accessed 15 October 2024).
12. Jenks JD, Aneke CI, Al-Obaidi MM, Egger M, Garcia L, Gaines T et al. Race and ethnicity: risk factors for fungal infections? PLOS Pathog. 2023;19(1):e1011025 (https://doi.org/10.1371/journal.ppat.1011025, accessed 15 October 2024).
13. Jenks JD, Prattes J, Wurster S, Sprute R, Seidel D, Oliverio M et al. Social determinants of health as drivers of fungal disease. EClinicalmedicine. 2023;66:102325 (https://doi.org/10.1016/j.eclinm.2023.102325, accessed 15 October 2024).
14. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. N Engl J Med. 2018;378(11):1004– 17 (https://doi.org/10.1056/NEJMoa1710922, accessed 15 October 2024).
15. Cryptococcosis. In. CDC/Fungal Diseases [website]. Atlanta: U.S. Centres for Disease Control and Prevention; 2024 (https://www.cdc.gov/cryptococcosis/treatment/index.html, accessed 27 November 2024).
16. Chang CC, Harrison TS, Bicanic TA, Chayakulkeeree M, Sorrell TC, Warris A, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM. Lancet Infect Dis. 2024; S1473–3099(23)00731–4 (https://doi.org/10.1016/S1473-3099(23)00731-4. Erratum in: Lancet Infect Dis. 2024; S1473;3099(24):00426–2 (https://doi.org/10.1016/S1473-3099(24)00426-2, accessed 27 November 2024).

17. Melhem MS, Leite Júnior DP, Takahashi JP, Macioni MB, Oliveira L, de Araújo LS, et al. Antifungal resistance in cryptococcal infections. Pathogens. 2024;13(2):128 (https://doi.org/10.3390/pathogens13020128, accessed 27 November 2024).

18. Rhodes J, Abdolrasouli A, Dunne K, Sewell TR, Zhang Y, Ballard E, et al. Population genomics confirms acquisition of drug-resistant Aspergillus fumigatus infection by humans from the environment. Nat Microbiol. 2022;7(5):663–74 (https://doi.org/10.1038/s41564-022- 01091-2. Erratum in: Nat Microbiol. 2022;7(11):1944 (https://doi.org/10.1038/s41564-022-01160-6, accessed 27 November 2024).

19. Meis JF, Chowdhary A, Rhodes JL, Fisher MC, Verweij PE. Clinical implications of globally emerging azole resistance in Aspergillus fumigatus. Philos Trans R Soc Lond B Biol Sci. 2016;371(1709):20150460 (https://doi.org/10.1098/rstb.2015.0460, accessed 27 November 2024).

20. Wiederhold NP. Epidemiology and prevalence of azole-resistant Aspergillus fumigatus: what is our understanding of the situation? Curr Fungal Infect Rep. 2023;17(3):177–87 (https://doi.org/10.1007/s12281-023-00469-x, accessed 27 November 2024).

21. Richardson JP. Candida albicans: A major fungal pathogen of humans. Pathogens. 2022;11(4):459 (https://doi.org/10.3390/pathogens11040459, accessed 27 November 2024).

22. Logan C, Martin-Loeches I, Bicanic T. Invasive candidiasis in critical care: challenges and future directions. Intensive Care Med. 2020;46(11):2001–14 (https://doi.org/10.1007/s00134-020-06240-x, accessed 27 November 2024).

23. Costa-de-Oliveira S, Rodrigues AG. Candida albicans antifungal resistance and tolerance in bloodstream infections: the triad yeast-host-antifungal. Microorganisms. 2020;8(2):154 (https://doi.org/10.3390/microorganisms8020154, accessed 27 November 2024).

24. Clinical practice guideline for the management of candidiasis: 2016 Update by IDSA. In: IDSA/guidelines [website]. Arlington: Infectious Diseases Society of America; 2016 (https://www.idsociety.org/practice-guideline/candidiasis/#FullRecommendations, accessed 27 November 2024).

25. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1–50 (https://doi.org/10.1093/cid/civ933, accessed 27 November 2024).

26. Chatelon J, Cortegiani A, Hammad E, Cassir N, Leone M. Choosing the right antifungal agent in ICU patients. Adv Ther. 2019;36(12):3308–20 (https://doi.org/10.1007/s12325-019-01115-0, accessed 27 November 2024).

27. Kohlenberg A, Struelens MJ, Monnet DL, Plachouras D, Candida auris survey collaborative group. Candida auris: epidemiological situation, laboratory capacity and preparedness in European Union and European Economic Area countries, 2013 to 2017. Euro Surveill. 2018;23(13):18–00136 (https://doi.org/10.2807/1560-7917.ES.2018.23.13.18-00136, accessed 27 November 2024).

28. Cristina ML, Spagnolo AM, Sartini M, Carbone A, Oliva M, Schinca E et al. An overview on Candida auris in healthcare settings. J Fungi (Basel). 2023;9(9):913 (https://doi.org/10.3390/jof9090913, accessed 27 November 2024).

29. Rudramurthy SM, Chakrabarti A, Paul RA, Sood P, Kaur H, Capoor MR, et al. Candida auris candidaemia in Indian ICUs: analysis of risk factors. J Antimicrob Chemother. 2017;72(6):1794–801.(https://doi.org/10.1093/jac/dkx034, accessed 27 November 2024).

30. van Schalkwyk E, Mpembe RS, Thomas J, Shuping L, Ismail H, Lowman W, et al. Epidemiologic shift in candidemia driven by Candida auris, South Africa, 2016–2017. Emerg Infect Dis. 2019;25(9):1698–707 (https://doi.org/10.3201/eid2509.190040, accessed 27 November 2024).

31. Lockhart SR. Candida auris and multidrug resistance: defining the new normal. Fungal Genet Biol. 2019;131:103243 (https://doi.org/10.1016/j.fgb.2019.103243, accessed 27 November 2024).

32. Ostrowsky B, Greenko J, Adams E, Quinn M, O'Brien B, Chaturvedi V, et al. Candida auris isolates resistant to three classes of antifungal medications - New York, 2019. MMWR Morb Mortal Wkly Rep. 2020;69(1):6–9 (https://doi.org/10.15585/mmwr.mm6901a2, accessed 27 November 2024).

33. Lyman M, Forsberg K, Reuben J, Dang T, Free R, Seagle EE, et al. Notes from the field: transmission of pan-resistant and echinocandin-resistant Candida auris in health care facilities - Texas and the District of Columbia, January–April 2021. MMWR Morb Mortal Wkly Rep. 2021;70(29):1022–3 (https://doi.org/10.15585/mmwr.mm7029a2, accessed 27 November 2024).

34. Gonzales P, Ostrosky-Zeichner L. Guide to Infection Control in the healthcare setting. Candida auris. In ISID/publications [website]. Boston: International Society for Infectious Diseases; 2023 (https://isid.org/guide/pathogens/candida-auris/, accessed 27 November 2024).

35. Surveillance for Candida auris. In CDC/Public Health/Surveillance [website]. Atlanta: Centers for Disease Control and prevention; 2024 (https://www.cdc.gov/candida-auris/tracking-c-auris/index.html, accessed 27 November 2024).

36. Report on activities for 2020. In GAFFI/news [website] Geneva: Global Action Fund for Fungal Infections (GAFFI); 2021 (https://gaffidocuments.s3.eu-west-2.amazonaws.com/GAFFI+Annual+report+2020+final+2.pdf, accessed 27 November 2024).

37. Rodrigues ML, Nosanchuk JD. Fungal diseases as neglected pathogens: A wake-up call to public health officials. PLOS Negl Trop Dis. 2020;14(2):e0007964 (https://doi.org/10.1371/journal.pntd.0007964, accessed 27 November 2024).

38. Rajendran R, Mowat E, Jones B, Williams C, Ramage G. Prior in vitro exposure to voriconazole confers resistance to amphotericin B in Aspergillus fumigatus biofilms. Int J Antimicrob Agents. 2015; 46(3):342–5 (https://doi.org/10.1016/j.ijantimicag.2015.03.006, accessed 27 November 2024).

39. Vazquez JA, Arganoza MT, Boikov D, Yoon S, Sobel JD, Akins RA. Stable phenotypic resistance of Candida species to amphotericin B conferred by preexposure to subinhibitory levels of azoles. J Clin Microbiol. 1998; 36(9):2690–5 (https://doi.org/10.1128/JCM.36.9.2690-2695.1998, accessed 27 November 2024).

40. Vallabhaneni S, Mody RK, Walker T, Chiller T. The global burden of fungal diseases. Infect Dis Clin North Am. 2016;30(1):1–11 (https://doi.org/10.1016/j.idc.2015.10.004, accessed 27 November 2024).

41. Seyedmousavi S, Verweij PE, Mouton JW. Isavuconazole, a broad-spectrum triazole for the treatment of systemic fungal diseases. Expert Rev Anti-Infect Ther. 2015;13(1):9–27 (https://doi.org/10.1586/1478721 0.2015.990382, accessed 27 November 2024).

42. Thompson GR 3rd, Wiederhold NP, Fothergill AW, Vallor AC, Wickes BL, Patterson TF. Antifungal susceptibilities among different serotypes of Cryptococcus gattii and Cryptococcus neoformans. Antimicrob Agents Chemother. 2009;53(1):309–11 (https://doi.org/10.1128/AAC.01216-08, accessed 27 November 2024).

43. Espinel-Ingroff A, Chowdhary A, Gonzalez GM, Guinea J, Hagen F, Meis JF, et al. Multicenter study of isavuconazole MIC distributions and epidemiological cutoff values for the Cryptococcus neoformans-Cryptococcus gattii species complex using the CLSI M27-A3 broth microdilution method. Antimicrob Agents Chemother. 2015;59(1):666–8 (https://doi.org/10.1128/AAC.04055-14, accessed 27 November 2024).

44. Wiederhold NP, Kovanda L, Najvar LK, Bocanegra R, Olivo M, Kirkpatrick WR et al. Isavuconazole is effective for the treatment of experimental cryptococcal meningitis. Antimicrob Agents Chemother. 2016;60(9):5600–3 (https://doi.org/10.1128/AAC.00229-16, 27 November 2024).

45. El Ayoubi LW, Allaw F, Moussa E, Kanj SS. Ibrexafungerp: A narrative overview. Curr Res Microb Sci. 2024;6:100245 (https://doi.org/10.1016/j.crmicr.2024.100245, accessed 27 November 2024).

46. Gebremariam T, Alkhazraji S, Gu Y, Najvar LK, Borroto-Esoda K, Patterson TF, et al. Ibrexafungerp is efficacious in a neutropenic murine model of pulmonary mucormycosis as monotherapy and combined with liposomal amphotericin B. Antimicrob Agents Chemother. 2024;68(5):e0154523 (https://doi.org/10.1128/aac.01545-23, accessed 27 November 2024).

47. Ghannoum M, McCormick T, Long L, Gowen R. Evaluation of the effect of Ibrexafungerp alone and in combination with amphotericin B or posaconazole against Mucor strains using time-kill kinetics and scanning electron microscopy. Presented at European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen, Denmark; 15–18 April 2023; Poster P2020 (https://www.scynexis.com/wp-content/uploads/2023/04/ECCMID-Rhizopus-SCY-2023-POSTER_P2020-Final.pdf, accessed 27 November 2024).

48. Shubitz LF, Trinh HT, Galgiani JN, Lewis ML, Fothergill AW, Wiederhold NP, et al. Evaluation of VT-1161 for treatment of coccidioidomycosis in murine infection models. Antimicrob Agents Chemother. 2015;59(12):7249-54 (https://doi.org/10.1128/AAC.00593-15, accessed 27 November 2024).

49. Shubitz LF, Roy ME, Trinh HT, Hoekstra WJ, Schotzinger RJ, Garvey EP. Efficacy of the investigational antifungal VT-1161 in treating naturally occurring coccidioidomycosis in dogs. Antimicrob Agents Chemother. 2017;61(5):e00111–17 (https://doi.org/10.1128/AAC.00111-17, accessed 27 November 2024).

50. Lockhart SR, Fothergill AW, Iqbal N, Bolden CB, Grossman NT, Garvey EP, et al. The investigational fungal Cyp51 inhibitor VT-1129 demonstrates potent in vitro activity against Cryptococcus neoformans and Cryptococcus gattii. Antimicrob Agents Chemother. 2016;60(4):2528–31 (https://doi.org/10.1128/AAC.02770-15, accessed 27 November 2024).

51. Gebremariam T, Alkhazraji S, Alqarihi A, Wiederhold NP, Shaw KJ, Patterson TF, et al. Fosmanogepix (APX001) is effective in the treatment of pulmonary murine mucormycosis due to Rhizopus arrhizus. Antimicrob Agents Chemother. 2020;64(6):e00178–20 (https://doi.org/10.1128/AAC.00178-20, accessed 27 November 2024).

52. Sobel JD, Nyirjesy P. Oteseconazole: an advance in treatment of recurrent vulvovaginal candidiasis. Future Microbiol. 2021;16:1453–61 (https://doi.org/10.2217/fmb-2021-0173, accessed 27 November 2024).

53. Kullberg BJ, Viscoli C, Pappas PG, Vazquez J, Ostrosky-Zeichner L, Rotstein C, et al. Isavuconazole versus caspofungin in the treatment of candidemia and other invasive candida infections: the ACTIVE trial. Clin Infect Dis. 2019;68(12):1981–9 (https://doi.org/10.1093/cid/ciy827, accessed 27 November 2024).

54. Thompson GR 3rd, Wiederhold NP. Isavuconazole: a comprehensive review of spectrum of activity of a new triazole. Mycopathologia. 2010;170(5):291–313 (https://doi.org/10.1007/s11046-010-9324-3, accessed 27 November 2024).

55. Pfaller MA, Messer SA, Rhomberg PR, Borroto-Esoda K, Castanheira M. Differential activity of the oral glucan synthase inhibitor SCY-078 against wild-type and echinocandin-resistant strains of Candida species. Antimicrob Agents Chemother. 2017;61(8):e00161–17 (https://doi.org/10.1128/AAC.00161-17, accessed 27 November 2024).

56. Assessment report: Cresemba. In EMA/documents [website] Amsterdam: European Medicines Agency; 2015 (https://www.ema.europa.eu/en/documents/ assessment-report/cresemba-epar-public-assessment-report_en.pdf, accessed 27 November 2024).

57. Highlights of prescribing information: Cresemba. In: FDA/labels [website]. Silver Spring: Maryland, United States Food and Drug Administration (US FDA); 2015 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207500s008,207501s007lbl.pdf, accessed 27 November 2024).

58. Lamoth F, Kontoyiannis DP. Therapeutic challenges of non-aspergillus invasive mold infections in immunosuppressed patients. Antimicrob Agents Chemother. 2019;63(11):e01244–19 (https://doi.org/10.1128/AAC.01244-19, accessed 27 November 2024).

59. Lewis JS 2nd, Wiederhold NP, Hakki M, Thompson GR 3rd. New perspectives on antimicrobial agents: isavuconazole. Antimicrob Agents Chemother. 2022;66(9):e0017722 (https://doi.org/10.1128/aac.00177-22, accessed 27 November 2024).

60. Schwartz S, Cornely OA, Hamed K, Marty FM, Maertens J, Rahav G et al. Isavuconazole for the treatment of patients with invasive fungal diseases involving the central nervous system. Med Mycol. 2020;58(4):417–24 (https://doi.org/10.1093/mmy/myz103, accessed 27 November 2024).

61. Thompson GR 3rd, Rendon A, Ribeiro Dos Santos R, Queiroz-Telles F, Ostrosky-Zeichner L, Azie N et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. Clin Infect Dis. 2016;63(3):356–62 (https://doi.org/10.1093/cid/ciw305, accessed 27 November 2024).

62. O'Kelly B, Mohamed A, Bergin C, Lyons F, Rogers TR, O'Connell B et al. Successful treatment of cryptococcal meningitis and Cryptococcoma with isavuconazole in a patient living with HIV. J Fungi (Basel). 2021;202:7(6):425 (https://doi.org/10.3390/jof7060425, accessed 27 November 2024).

63. Highlights of prescribing information: Brexafemme (ibrexafungerp). In FDA/labels [website]. Silver Spring: Maryland, United States Food and Drug Administration (US FDA); 2021 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214900s000lbl.pdf, accessed 27 November 2024).

64. Hector RF, Bierer DE. New β-glucan inhibitors as antifungal drugs. Expert Opin Ther Pat. 2011;21(10):1597–610 (https://doi.org/10.1517/13543776.2011.603899, accessed 27 November 2024).

65. Larkin EL, Long L, Isham N, Borroto-Esoda K, Barat S, Angulo D et al. A novel 1,3-Beta-d-Glucan inhibitor, ibrexafungerp (formerly SCY-078), shows potent activity in the lower pH environment of vulvovaginitis. Antimicrob Agents Chemother. 2019;63(5):e02611–18 (https://doi.org/10.1128/AAC.02611-18, accessed 27 November 2024).

66. Hoenigl M, Sprute R, Egger M, Arastehfar A, Cornely OA, Krause R et al. The antifungal pipeline: fosmanogepix, ibrexafungerp, olorofim, Opelconazole, and rezafungin. Drugs. 2021;81(15):1703–29 (https://doi.org/10.1007/s40265-021-01611-0, accessed 27 November 2024).

67. Wring SA, Randolph R, Park S, Abruzzo G, Chen Q, Flattery A et al. Preclinical pharmacokinetics and pharmacodynamic target of SCY-078, a first-in-class orally active antifungal glucan synthesis inhibitor, in murine models of disseminated candidiasis. Antimicrob Agents Chemother. 2017;61(4):e02068–16 (https://doi.org/10.1128/AAC.02068-16, accessed 27 November 2024).

68. Jiménez-Ortigosa C, Perez WB, Angulo D, Borroto-Esoda K, Perlin DS. De novo Acquisition of Resistance to SCY-078 in Candida glabrata Involves FKS Mutations That both Overlap and Are Distinct from Those Conferring echinocandin Resistance. Antimicrob Agents Chemother. 2017;61(9):e00833–17 (https://doi.org/10.1128/AAC.00833-17, accessed 27 November 2024).

69. Angulo DA, Alexander B, Rautemaa-Richardson R, Alastruey-Izquierdo A, Hoenigl M, Ibrahim AS et al. Ibrexafungerp, a novel triterpenoid antifungal in development for the treatment of mold infections. J Fungi (Basel). 2022;8(11):1121 (https://doi.org/10.3390/jof8111121, accessed 27 November 2024).

70. Siebert RS, Juneja D, Nguyen MH, Vasquez J, Azie NE, Angulo DA. Outcomes of Oral Ibrexafungerp in subjects with urinary tract infections from two phase 3 open-label studies: difficult-to-treat invasive fungal infections (FURI) and infections with Candida auris (CARES). Presented at ECCMID. Copenhagen, Denmark; 15–18 April 2023; Poster MEM0404 (https://www.scynexis.com/wp-content/uploads/2023/04/ECCMID-2023-UTI-Poster-Landscape-Final.pdf, accessed 27 November 2024).

71. Pfaller MA, Messer SA, Motyl MR, Jones RN, Castanheira M. Activity of MK-3118, a new oral glucan synthase inhibitor, tested against Candida spp. by two international methods (CLSI and EUCAST). J Antimicrob Chemother. 2013;68(4):858–63 (https://doi.org/10.1093/jac/dks466, accessed 27 November 2024).

72. Jiménez-Ortigosa C, Paderu P, Motyl MR, Perlin DS. Enfumafungin derivative MK-3118 shows increased in vitro potency against clinical echinocandin-resistant Candida species and Aspergillus species isolates. Antimicrob Agents Chemother. 2014;58(2):1248–51 (https://doi.org/10.1128/AAC.02145-13, accessed 27 November 2024).

73. Berkow EL, Angulo D, Lockhart SR. In vitro activity of a novel glucan synthase inhibitor, SCY-078, against clinical isolates of Candida auris. Antimicrob Agents Chemother. 2017;61(7):e00435–17 (https://doi.org/10.1128/AAC.00435-17, accessed 27 November 2024).

74. Quindós G, Miranda-Cadena K, San-Millán R, Borroto-Esoda K, Cantón E, Linares-Sicilia MJ, et al. In vitro antifungal activity of ibrexafungerp (SCY-078) against contemporary blood isolates from medically relevant species of Candida: A European study. Front Cell Infect Microbiol. 2022;12:906563 (https://doi.org/10.3389/fcimb.2022.906563, accessed 27 November 2024).

75. Rivero-Menendez O, Soto-Debran JC, Cuenca-Estrella M, Alastruey-Izquierdo A. In vitro activity of ibrexafungerp against a collection of clinical isolates of Aspergillus, including cryptic species and Cyp51A mutants, using EUCAST and CLSI methodologies. J Fungi (Basel). 2021;7(3):232 (https://doi.org/10.3390/jof7030232, accessed 27 November 2024).

76. Petraitis V, Petraitiene R, Katragkou A, Maung BB, Naing E, Kavaliauskas P, et al. Combination therapy with ibrexafungerp (formerly SCY-078), a first-in-class triterpenoid inhibitor of (1→3)-β-d-glucan synthesis, and isavuconazole for treatment of experimental invasive pulmonary aspergillosis. Antimicrob Agents Chemother. 2020;64(6):e02429–19 (https://doi.org/10.1128/AAC.02429-19, accessed 27 November 2024).

77. Highlights of prescribing information: Vivjoa (Oteseconazole). In FDA/labels [website]. Silver Spring: United States Food and Drug Administration (US FDA); 2022 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215888s000lbl.pdf, accessed 27 November 2024).

78. Vivjoa (Oteseconazole). In EMA/EPAR [website]. Amsterdam: European Medicines Agency; 2023 (https://www.ema.europa.eu/en/medicines/human/EPAR/vivjoa, accessed 27 November 2024).

79. De SK. Oteseconazole: first approved orally bioavailable and selective CYP51 inhibitor for the treatment of patients with recurrent vulvovaginal candidiasis. Curr Med Chem. 2023;30(37):4170–5 (https://doi.org/10.2174/0929867330666230220130024, accessed 27 November 2024).

80. Oteseconazole. Am J Health Syst Pharm;79(23):2083-5 (https://doi.org/10.1093/ajhp/zxac247, accessed 27 November 2024).

81. Wang X, Chen L, Ruan H, Xiong Z, Wang W, Qiu J, et al. Oteseconazole versus fluconazole for the treatment of severe vulvovaginal candidiasis: a multicenter, randomized, double-blinded, phase 3 trial. Antimicrob Agents Chemother. 2024;68(1):e0077823 (https://doi.org/10.1128/aac.00778-23 accessed 27 November 2024).

82. Gebremariam T, Alkhazraji S, Lin L, Wiederhold NP, Garvey EP, Hoekstra WJ et al. Prophylactic treatment with VT-1161 protects immunosuppressed mice from Rhizopus arrhizus var. arrhizus infection. Antimicrob Agents Chemother. 2017;61(9):e00390–17 (https://doi.org/10.1128/AAC.00390-17 accessed 27 November 2024).

83. Vanreppelen G, Nysten J, Baldewijns S, Sillen M, Donders G, Van Dijck P. Oteseconazole (VIVOJA) for prevention of recurrent vulvovaginal candidiasis. Trends Pharmacol Sci. 2023;44(1):64–5 (https://doi.org/10.1016/j. tips.2022.10.004 accessed 27 November 2024).

84. Garvey EP, Hoekstra WJ, Schotzinger RJ, Sobel JD, Lilly EA, Fidel PL Jr. Efficacy of the clinical agent VT-1161 against fluconazole-sensitive and -resistant Candida albicans in a murine model of vaginal candidiasis. Antimicrob Agents Chemother. 2015;59(9):5567–73 (https://doi.org/10.1128/AAC.00185-15 accessed 27 November 2024).

85. Garcia-Effron G. Rezafungin-mechanisms of action, susceptibility and resistance: similarities and differences with the other echinocandins. J Fungi (Basel). 2020;6(4):262 (https://doi.org/10.3390/jof6040262 accessed 27 November 2024).

86. Highlights of prescribing information: Rezzayo, FDA prescribing information. In FDA/labels [website]. Silver Spring: United States Food and Drug Administration (US FDA); 2023 (https://www.accessdata.fda.gov/drugsatfda_docs/ label/2023/217417s000lbl.pdf, accessed 27 November 2024).

87. Rezzayo. In EMA/EPAR [website]. Amsterdam: European Medicines Agency; 2023 (https://www.ema.europa.eu/en/documents/product-information/rezzayo-epar-product-information_en.pdf, accessed 27 November 2024).

88. Thompson GR 3rd, Soriano A, Honore PM, Bassetti M, Cornely OA, Kollef M, et al. Efficacy and safety of rezafungin and caspofungin in candidaemia and invasive candidiasis: pooled data from two prospective randomised controlled trials. Lancet Infect Dis. 2024;24(3):319–28 (https://doi.org/10.1016/S1473-3099(23)00551-0 accessed 27 November 2024).

89. Ham YY, Lewis JS 2nd, Thompson GR 3rd. Rezafungin: a novel antifungal for the treatment of invasive candidiasis. Future Microbiol. 2021;16(1):27–36 (https://doi.org/10.2217/fmb-2020-0217 accessed 27 November 2024).

90. Wiederhold NP. Pharmacodynamics, mechanisms of action and resistance, and spectrum of activity of new antifungal agents. J Fungi (Basel). 2022;8(8):857 (https://doi.org/10.3390/jof8080857 accessed 27 November 2024).

91. Ong V, Wills S, Watson D, Sandison T, Flanagan S. Metabolism, excretion, and mass balance of [14C]-rezafungin in animals and humans. Antimicrob Agents Chemother. 2022;66(1):e0139021 (https://doi.org/10.1128/AAC.01390-21 accessed 27 November 2024).

92. Alkhazraji S, Gebremariam T, Alqarihi A, Gu Y, Mamouei Z, Singh S et al. Fosmanogepix (APX001) is effective in the treatment of immunocompromised mice infected with invasive pulmonary scedosporiosis or disseminated Fusariosis. Antimicrob Agents Chemother. 2020;64(3):e01735–19 (https://doi.org/10.1128/AAC.01735-19, accessed 27 November 2024).

93. Shaw KJ, Ibrahim AS. Fosmanogepix: A review of the first-in-class broad spectrum agent for the treatment of invasive fungal infections. J Fungi (Basel). 2020;6(4):239 (https://doi.org/10.3390/jof6040239 accessed 27 November 2024).

94. Gebremariam T, Alkhazraji S, Gu Y, Alqarihi A, Mamouei Z, Shaw KJ, et al. 726. APX001 (fosmanogepix) is effective in an immunosuppressed mouse model of Rhizopus oryzae infection. Open Forum Infect Dis. 2019;6;Suppl 2:S325–6 (https://doi.org/10.1093/ofid/ofz360.794 accessed 27 November 2024).

95. Oliver JD, Sibley GE, Beckmann N, Dobb KS, Slater MJ, McEntee L et al. F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase. Proc Natl Acad Sci U S A. 2016;113(45):12809–14 (https://doi.org/10.1073/pnas.1608304113 accessed 27 November 2024).

96. Seyedmousavi S, Chang YC, Youn JH, Law D, Birch M, Rex JH et al. In vivo efficacy of olorofim against systemic scedosporiosis and Lomentosporiosis. Antimicrob Agents Chemother. 2021;65(10):e0043421 (https://doi.org/10.1128/AAC.00434-21 accessed 27 November 2024).

97. Wiederhold NP, Najvar LK, Jaramillo R, Olivo M, Birch M, Law D et al. The Orotomide olorofim is efficacious in an experimental model of central nervous system coccidioidomycosis. Antimicrob Agents Chemother. 2018;62(9):e00999–18 (https://doi.org/10.1128/AAC.00999-18 accessed 27 November 2024).

98. Colley T, Alanio A, Kelly SL, Sehra G, Kizawa Y, Warrilow AG, et al. In vitro and in vivo antifungal profile of a novel and long-acting inhaled azole, PC945, on Aspergillus fumigatus infection. Antimicrob Agents Chemother. 2017;61(5):e02280–16 (https://doi.org/10.1128/AAC.02280-16 accessed 27 November 2024).

99. Shaw KJ. GR-2397: review of the novel siderophore-like antifungal agent for the treatment of invasive aspergillosis. J Fungi (Basel). 2022;8(9):909 (https://doi.org/10.3390/jof8090909 accessed 27 November 2024).

100. Wiederhold NP, Shubitz LF, Najvar LK, Jaramillo R, Olivo M, Catano G, et al. The novel fungal Cyp51 inhibitor VT-1598 is efficacious in experimental models of central nervous system coccidioidomycosis caused by Coccidioides posadasii and Coccidioides immitis. Antimicrob Agents Chemother. 2018;62(4):e02258–17 (https://doi.org/10.1128/AAC.02258-17 accessed 27 November 2024).

101. Wiederhold NP, Patterson HP, Tran BH, Yates CM, Schotzinger RJ, Garvey EP. Fungal-specific Cyp51 inhibitor VT-1598 demonstrates in vitro activity against Candida and Cryptococcus species, endemic fungi, including Coccidioides species, Aspergillus species and Rhizopus arrhizus. J Antimicrob Chemother. 2018;73(2):404–8 (https://doi.org/10.1093/jac/dkx410 accessed 27 November 2024).

102. Yan X, Huang Y, Xie J, Wu Q, Yang S, Yang X et al. Safety, tolerability, and pharmacokinetics of HRS9432(A) injection in healthy Chinese subjects: a phase-I randomized, double-blind, dose escalation, placebo-controlled study. Antimicrob Agents Chemother. 2024;68(7):e0052424 (https://doi.org/10.1128/aac.00524-24 accessed 27 November 2024).

103. Wiederhold NP. Review of T-2307, an investigational agent that causes collapse of fungal mitochondrial membrane potential. J Fungi (Basel). 2021;7(2):130 (https://doi.org/10.3390/jof7020130 accessed 27 November 2024).

104. Mitsuyama J, Nomura N, Hashimoto K, Yamada E, Nishikawa H, Kaeriyama M, et al. In vitro and in vivo antifungal activities of T-2307, A novel arylamidine. Antimicrob Agents Chemother. 2008;52(4):1318–24 (https://doi.org/10.1128/AAC.01159-07 accessed 27 November 2024).

105. Lepak AJ, VanScoy B, Rubino C, Ambrose PG, Andes DR. In vivo pharmacodynamic characterization of a next-generation polyene, SF001, in the invasive pulmonary aspergillosis mouse model. Antimicrob Agents Chemother. 2024;68(3):e0163123 (https://doi.org/10.1128/aac.01631-23 accessed 27 November 2024).

106. Wiederhold NP, Patterson H, Garcia V. The next generation polyene SF001 demonstrates broad-spectrum antifungal activity against yeasts, moulds, and endemic fungi. Presented at Clinical Mycology Today, the biennial meeting of the Mycoses Study Group Education and Research Consortium (MSGERC). Albuquerque, NM; 7–9 September 2022.

107. van Rhijn N, Storer IS, Birch M, Oliver JD, Bottery MJ, Bromley MJ. Aspergillus fumigatus strains that evolve resistance to the agrochemical fungicide ipflufenoquin in vitro are also resistant to olorofim. Nat Microbiol. 2024;9(1):29–34 (https://doi.org/10.1038/s41564-023-01542-4 accessed 27 November 2024).

108. van Rhijn N, Hemmings S, Storer IS, Valero C, Bin Shuraym H, Goldman GH et al. Antagonism of the azoles to olorofim and cross-resistance are governed by linked transcriptional networks in Aspergillus fumigatus. mBio. 2022;13(6):e0221522 (https://doi.org/10.1128/mbio.02215-22 accessed 27 November 2024).

109. Arendrup MC, Jensen RH, Cuenca-Estrella M. In vitro activity of ASP2397 against aspergillus isolates with or without acquired azole resistance mechanisms. Antimicrob Agents Chemother. 2016;60(1):532–6 (https://doi.org/10.1128/AAC.02336-15 accessed 27 November 2024).

110. Nishimoto AT, Wiederhold NP, Flowers SA, Zhang Q, Kelly SL, Morschhäuser J et al. In vitro activities of the novel investigational tetrazoles VT-1161 and VT-1598 compared to the triazole antifungals against azole-resistant strains and clinical isolates of Candida albicans. Antimicrob Agents Chemother. 2019;63(6):e00341–19 (https://doi.org/10.1128/AAC.00341-19 accessed 27 November 2024).

111. Brautaset T, Sletta H, Nedal A, Borgos SE, Degnes KF, Bakke I et al. Improved antifungal polyene macrolides via engineering of the nystatin biosynthetic genes in Streptomyces noursei. Chem Biol. 2008;15(11):1198–206 (https://doi.org/10.1016/j.chembiol.2008.08.009 accessed 27 November 2024).

112. Wiederhold NP, Najvar LK, Jaramillo R, Olivo M, Patterson H, Connell A et al. The novel arylamidine T-2307 demonstrates in vitro and in vivo activity against Candida auris. Antimicrob Agents Chemother. 2020;64(3) (https://doi.org/10.1128/AAC.02198-19 accessed 27 November 2024).

113. Wiederhold NP, Najvar LK, Fothergill AW, Bocanegra R, Olivo M, McCarthy DI et al. The novel arylamidine T-2307 maintains il vitro and in vivo activity against echinocandin-resistant Candida albicans. Antimicrob Agents Chemother. 2015;59(2):1341–3 (https://doi.org/10.1128/AAC.04228-14 accessed 27 November 2024).

114. Nishikawa H, Sakagami T, Yamada E, Fukuda Y, Hayakawa H, Nomura N et al. T-2307, a novel arylamidine, is transported into Candida albicans by a high-affinity spermine and spermidine carrier regulated by Agp2. J Antimicrob Chemother. 2016;71(7):1845–55 (https://doi.org/10.1093/jac/dkw095 accessed 27 November 2024).

115. Wiederhold NP. Review of the novel investigational antifungal olorofim. J Fungi (Basel). 2020 Jul 30;6(3):122 (https://doi.org/10.3390/jof6030122 accessed 27 November 2024).

116. Law, D.; Birch, M.; Oliver, J.; Sibley, G.; Goodwin, J.; Livermore, J.; Whalley, S.; Hope, W. Pharmacokinetics of the novel antifungal agents F901318 in mice, rats, and cynomolgus monkeys (abstr. F-757). In Proceedings of the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, USA, 17–22 September 2015.

117. Wiederhold NP. Review of the novel investigational antifungal olorofim. J Fungi (Basel). 2020;6(3):122 (https://doi.org/10.3390/jof6030122, accessed 27 November 2024).

118. Jørgensen KM, Astvad KM, Hare RK, Arendrup MC. EUCAST determination of olorofim (F901318) susceptibility of mold species, method validation, and MICs. Antimicrob Agents Chemother. 2018;62(8):e00487–18 (https://doi.org/10.1128/AAC.00487-18 accessed 27 November 2024).

119. Georgacopoulos O, Nunnally NS, Ransom EM, Law D, Birch M, Lockhart SR et al. In vitro activity of novel antifungal olorofim against filamentous fungi and comparison to eight other antifungal agents. J Fungi (Basel). 2021;7(5):378 (https://doi.org/10.3390/jof7050378 accessed 27 November 2024).

120. Hope WW, McEntee L, Livermore J, Whalley S, Johnson A, Farrington N, et al. Pharmacodynamics of the Orotomides against Aspergillus fumigatus: new opportunities for treatment of multidrug-resistant fungal disease. mBio. 2017;8(4):e01157–17 (https://doi.org/10.1128/mBio.01157-17 accessed 27 November 2024).

121. Seyedmousavi S, Chang YC, Law D, Birch M, Rex JH, Kwon-Chung KJ. Efficacy of olorofim (F901318) against Aspergillus fumigatus, A. nidulans, and A. tanneri in murine models of profound neutropenia and chronic granulomatous disease. Antimicrob Agents Chemother. 2019;63(6):e00129–19 (https://doi.org/10.1128/AAC.00129-19 accessed 27 November 2024).

122. Feuss A, Bougnoux ME, Dannaoui E. The role of olorofim in the treatment of filamentous fungal infections: a review of in vitro and in vivo studies. J Fungi (Basel). 2024;10(5):345 (https://doi.org/10.3390/jof10050345 accessed 27 November 2024).

123. Rauseo AM, Coler-Reilly A, Larson L, Spec A. Hope on the horizon: novel fungal treatments in development. Open Forum Infect Dis. 2020;7(2):ofaa016 (https://doi.org/10.1093/ofid/ofaa016 accessed 27 November 2024).

124. Maertens JA, Thompson GR, Spec A, Hammond SP, Rijnders B, Lewis White PL, et al. 754. Olorofim for treatment of invasive fungal infections (IFI) due to moulds in patients with limited or no treatment options: interim results from a Phase 2b open-label study (NCT03583164, Study 32). Open Forum Infect Dis. 2022;9;Suppl 2 (https://doi.org/10.1093/ofid/ofac492.039 accessed 27 November 2024).

125. Hoenigl M, Arastehfar A, Arendrup MC, Brüggemann R, Carvalho A, Chiller T et al. Novel antifungals and treatment approaches to tackle resistance and improve outcomes of invasive fungal disease. Clin Microbiol Rev. 2024;37(2):e0007423 (https://doi.org/10.1128/cmr.00074-23 accessed 27 November 2024).

126. Shionogi Co., Ltd. and F2G Enter Strategic Collaboration to Develop and Commercialize the New Antifungal Agent Olorofim in Europe and Asia. (https://f2g.com/press-release/shionogi-co-ltd-and-f2g-enter-strategic-collaboration-to-develop-and-commercialize-the-new-antifungal-agent-olorofim-in-europe-and-asia/, accessed 27 November 2024).

127. Sahu JK, Ganguly S, Kaushik A. Triazoles: a valuable insight into recent developments and biological activities. Chin J Nat Med. 2013;11(5):456–65 (https://doi.org/10.1016/S1875-5364(13)60084-9 accessed 27 November 2024).

128. Cass L, Murray A, Davis A, Woodward K, Albayaty M, Ito K et al. Safety and nonclinical and clinical pharmacokinetics of PC945, a novel inhaled triazole antifungal agent. Pharmacol Res Perspect. 2021;9(1):e00690 (https://doi.org/10.1002/prp2.690 accessed 27 November 2024).

129. Murray A, Cass L, Ito K, Pagani N, Armstrong-James D, Dalal P, et al. PC945, a Novel Inhaled Antifungal Agent, for the Treatment of Respiratory Fungal Infections. J Fungi (Basel). 2020;6(4):373 (https://doi.org/10.3390/jof6040373 accessed 27 November 2024).

130. Colley T, Strong P, Rapeport G. Ito K. Proceedings of the 8th advances against aspergillosis conference; Lisbon, Portugal. February 1–3 2018; PC945 shows a higher barrier than itraconazole to induction of Aspergillus fumigatus resistant mutants.

131. Nishimoto Y, Ito K, Kimura G, Lucas KA, Daly L, Strong P, et al. Antifungal effects of PC945, a novel inhaled triazole, on Candida albicans pulmonary infection in immunocompromised mice. J Exp Pathol. 2021;2(1):1-15 (https://doi.org/10.33696/pathology.2.011 accessed 27 November 2024).

132. Rudramurthy SM, Colley T, Abdolrasouli A, Ashman J, Dhaliwal M, Kaur H, et al. In vitro antifungal activity of a novel topical triazole PC945 against emerging yeast Candida auris. J Antimicrob Chemother. 2019;74(10):2943–9 (https://doi.org/10.1093/jac/dkz280, accessed 27 November 2024).

133. Pulmocide: topline results of NCT05037851. In. Pulmocide/Press release [website]. London: Pulmocide; 2024 (https://pulmocide.com/press-release/pulmocide-announces-successful-results-from-the-opera-s-study-a-phase-2-safety-study-with-inhaled-opelconazole/, accessed 27 November 2024).

134. Pulmocide Raises $52 Million to Fund Additional Late-Stage Development of Opelconazole (https://uk.finance.yahoo.com/news/pulmocide-raises-52-million-fund-120000735.html, accessed 27 November 2024).

135. Orphan Drug Designations and Approvals (opelconazole) (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=824121, accessed 27 November 2024).

136. EU/3/22/2745 - orphan designation for treatment of invasive aspergillosis (https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-22-2745, accessed 27 November 2024).

137. Das S, Chanda K. An overview of metal-free synthetic routes to isoxazoles: the privileged scaffold. RSC Adv. 2021;11(52):32680–705 (https://doi.org/10.1039/d1ra04624a, accessed 27 November 2024).

138. Hager CL, Larkin EL, Long L, Zohra Abidi F, Shaw KJ, Ghannoum MA. In vitro and in vivo vvaluation of the antifungal activity of APX001A/APX001 against Candida auris. Antimicrob Agents Chemother. 2018;62(3):e02319–17 (https://doi.org/10.1128/AAC.02319-17, accessed 27 November 2024).

139. Shaw KJ, Schell WA, Covel J, Duboc G, Giamberardino C, Kapoor M, et al. In vitro and in vivo evaluation of APX001A/APX001 and other Gwt1 inhibitors against Cryptococcus. Antimicrob Agents Chemother. 2018;62(8):e00523–18 (https://doi.org/10.1128/AAC.00523-18, accessed 27 November 2024).

140. Zhao M, Lepak AJ, VanScoy B, Bader JC, Marchillo K, Vanhecker J et al. In vivo pharmacokinetics and pharmacodynamics of APX001 against Candida spp. in a neutropenic disseminated candidiasis mouse model. Antimicrob Agents Chemother. 2018;62(4):e02542–17 (https://doi.org/10.1128/AAC.02542-17, accessed 27 November 2024).

141. Rivero-Menendez O, Cuenca-Estrella M, Alastruey-Izquierdo A. In vitro activity of APX001A against rare moulds using EUCAST and CLSI methodologies. J Antimicrob Chemother. 2019;74(5):1295–9 (https://doi.org/10.1093/jac/dkz022, accessed 27 November 2024).

142. Almajid A, Bazroon A, Al-Awami HM, Albarbari H, Alqahtani I, Almutairi R, et al. Fosmanogepix: the novel anti-fungal Agent's comprehensive review of in vitro, in vivo, and current insights from advancing clinical trials. Cureus. 2024;16(4):e59210 (https://doi.org/10.7759/cureus.59210, accessed 27 November 2024).

143. Mansbach R, Shaw KJ, Hodges MR, Coleman S, Fitzsimmons ME. Absorption, distribution, and excretion of 14C-APX001 after single-dose administration to rats and monkeys. Open Forum Infect Dis. 2017;4;Suppl 1:S472 (https://doi.org/10.1093/ofid/ofx163.1209, accessed 27 November 2024).

144. Pappas PG, Vazquez JA, Oren I, Rahav G, Aoun M, Bulpa P et al. Clinical safety and efficacy of novel antifungal, fosmanogepix, for the treatment of candidaemia: results from a Phase 2 trial. J Antimicrob Chemother. 2023;78(10):2471–80 (https://doi.org/10.1093/jac/dkad256, accessed 27 November 2024).

145. An open-label study of APX001 for treatment of patients with candidemia/ invasive candidiasis caused by Candida auris (APEX). In Clinicaltrials.gov/study results [website]. Bethesda: US National Library of Medicine; 2024 (https://clinicaltrials.gov/study/T04148287?term=NCT04148287&rank=1&tab=results, accessed 27 November 2024).

146. Pfizer Acquires Amplyx Pharmaceuticals. In Pfizer/Press_releases [website]; 2021 (https://www.pfizer.com/news/press-release/press-release-detail/pfizer-acquires-amplyx-pharmaceuticals, accessed 27 November 2024).

147. Basilea initiates clinical phase 3 study with antifungal fosmanogepix in candidemia and invasive candidiasis. In Basilea/news [website]. Switzerland: Basilea Pharmaceutica International Ltd; 2023 (https://www.basilea.com/news/#news_1516, accessed 27 November 2024).

148. Sucher AJ, Chahine EB, Balcer HE. Echinocandins: the newest class of antifungals. Ann Pharmacother. 2009;43(10):1647–57 (https://doi.org/10.1345/aph.1M237, accessed 27 November 2024).

149. Zhou ZX, Yin XD, Zhang Y, Shao QH, Mao XY, Hu WJ, et al. Antifungal drugs and drug-induced liver injury: A real-world study leveraging the FDA Adverse Event Reporting System database. Front Pharmacol. 2022;13:891336 (https://doi.org/10.3389/fphar.2022.891336, accessed 27 November 2024).

150. Hengrui medicine: hrs9432 for injection of long-acting antifungal drugs has been approved for clinical use (https://equalocean.com/briefing/20210812230068708, accessed 27 November 2024).

151. Kramer J, Özkaya Ö, Kümmerli R. Bacterial siderophores in community and host interactions. Nat Rev Microbiol. 2020;18(3):152–63 (https://doi.org/10.1038/s41579-019-0284-4, accessed 27 November 2024).

152. Mammen MP, Armas D, Hughes FH, Hopkins AM, Fisher CL, Resch PA, et al. First-in-human phase 1 study to assess safety, tolerability, and pharmacokinetics of a novel antifungal drug, VL-2397, in healthy adults. Antimicrob Agents Chemother. 2019;63(11):e00969–19 (https://doi.org/10.1128/AAC.00969-19, accessed 27 November 2024).

153. Nakamura I, Ohsumi K, Takeda S, Katsumata K, Matsumoto S, Akamatsu S, et al. ASP2397 Is a novel natural compound that exhibits rapid and potent fungicidal activity against Aspergillus species through a specific transporter. Antimicrob Agents Chemother. 2019;63(10):e02689–18 (https://doi.org/10.1128/AAC.02689-18, accessed 27 November 2024).

154. Basilea announces acquisition of novel clinical-stage antifungal for treatment of Aspergillus mold infections. In Basilea/news [website]. Switzerland: Basilea Pharmaceutica International Ltd; 2023 (https://www.basilea.com/news/news?tx_news_pi1%5Baction%5D=detail&tx_news_pi1%5Bcontroller%5D=News&tx_news_pi1%5Bnews%5D=1454&type=1546938654&cHash=e659eeed08bf55efa82f84ea140b5705, accessed 27 November 2024).

155. BARDA awards $29 million to Basilea Pharmaceutica for first-in-class anti-fungal treatments (https://medicalcountermeasures.gov/newsroom/2024/basilea/, accessed 27 November 2024).

156. Neochoritis CG, Zhao T, Dömling A. Tetrazoles via multicomponent reactions. Chem Rev. 2019;119(3):1970–2042 (https://doi.org/10.1021/acs.chemrev.8b00564, accessed 27 November 2024).

157. Warrilow AG, Parker JE, Price CL, Nes WD, Garvey EP, Hoekstra WJ, et al. The investigational drug VT-1129 Is a highly potent inhibitor of Cryptococcus species CYP51 but only weakly inhibits the human enzyme. Antimicrob Agents Chemother. 2016;60(8):4530–8 (https://doi.org/10.1128/AAC.00349-16, accessed 27 November 2024).

158. Yates CM, Garvey EP, Shaver SR, Schotzinger RJ, Hoekstra WJ. Design and optimization of highly-selective, broad spectrum fungal CYP51 inhibitors. Bioorg Med Chem Lett. 2017;27(15):3243–8 (https://doi.org/10.1016/j.bmcl.2017.06.037, accessed 27 November 2024).

159. Wiederhold NP, Lockhart SR, Najvar LK, Berkow EL, Jaramillo R, Olivo M, et al. The fungal Cyp51-specific inhibitor VT-1598 demonstrates in vitro and in vivo activity against Candida auris. Antimicrob Agents Chemother. 2019;63(3):e02233–18 (https://doi.org/10.1128/AAC.02233-18, accessed 27 November 2024).

160. Break TJ, Desai JV, Healey KR, Natarajan M, Ferre EM, Henderson C, et al. VT-1598 inhibits the in vitro growth of mucosal Candida strains and protects against fluconazole-susceptible and -resistant oral candidiasis in IL-17 signalling-deficient mice. J Antimicrob Chemother. 2018;73(8):2089–94 (https://doi.org/10.1093/jac/dky170, accessed 27 November 2024).

161. Garvey EP, Sharp AD, Warn PA, Yates CM, Schotzinger RJ. The novel fungal CYP51 inhibitor VT-1598 is efficacious alone and in combination with liposomal amphotericin B in a murine model of cryptococcal meningitis. J Antimicrob Chemother. 2018;73(10):2815–2822 (https://doi.org/10.1093/jac/dky242, accessed 27 November 2024).

162. Mycovia pipeline presentation to FDA. In FDA/media [website]. Maryland: United States Food and Drug Administration; 2020 (https://www.fda.gov/media/141112/download, accessed 27 November 2024).

163. Gu K, Spitz R, Hammett E, Jaunarajs A, Ghazaryan V, Garvey EP et al. Safety and pharmacokinetics of antifungal agent VT-1598 and its primary metabolite, VT-11134, in healthy adult subjects: phase 1, first-in-human, randomized, double-blind, placebo-controlled study of single-ascending oral doses of VT-1598. Med Mycol. 2024;62(4):myae032 (https://doi.org/10.1093/mmy/myae032, accessed 27 November 2024).

164. Caffrey P, Aparicio JF, Malpartida F, Zotchev SB. Biosynthetic engineering of polyene macrolides towards generation of improved antifungal and antiparasitic agents. Curr Top Med Chem. 2008;8(8):639–53 (https://doi.org/10.2174/156802608784221479, accessed 27 November 2024).

165. Tevyashova AN, Olsufyeva EN, Solovieva SE, Printsevskaya SS, Reznikova MI, Trenin AS et al. Structure-antifungal activity relationships of polyene antibiotics of the amphotericin B group. Antimicrob Agents Chemother. 2013;57(8):3815–22 (https://doi.org/10.1128/AAC.00270-13, accessed 27 November 2024).

166. Biosergen receives the final permission required to test lead candidate BSG005 in patients with invasive fungal infection. In New Cision/Biosergen AB [website]. United Kingdom: News Cision; 2024 (https://news.cision.com/biosergen-ab/r/biosergen-receives-the-final-permission-required-to-test-lead-candidate-bsg005-in-patients-with-inva,c3998952, accessed 27 November 2024).

167. Maji A, Soutar CP, Zhang J, Lewandowska A, Uno BE, Yan S et al. Tuning sterol extraction kinetics yields a renal-sparing polyene antifungal. Nature. 2023;623(7989):1079–85 (https://doi.org/10.1038/s41586-023-06710-4, accessed 27 November 2024).

168. Elion Therapeutics Closes $81 Million Series B Funding Round Led by Deerfield Management and AMR Action Fund (https://www.prnewswire.com/news-releases/elion-therapeutics-closes-81- million-series-b-funding-round-led-by-deerfield-management-and-amr-action-fund-302174159.html, accessed 27 November 2024).

169. Monte ZS, Silva AM, Lima GM, Silva TG, Marques KM, Rodrigues MD et al. Synthesis and evaluation of arylamidine derivatives for new antimicrobial and cytotoxic activities. An Acad Bras Cienc. 2017;89(2):1051–9 (https://doi.org/10.1590/0001-3765201720160801, accessed 27 November 2024).

170. Gerlach ES, Altamirano S, Yoder JM, Luggya TS, Akampurira A, Meya DB et al. ATI-2307 exhibits equivalent antifungal activity in Cryptococcus neoformans clinical isolates with high and low fluconazole IC50. Front Cell Infect Microbiol. 2021;11:695240 (https://doi.org/10.3389/fcimb.2021.695240, accessed 27 November 2024).

171. Shibata T, Takahashi T, Yamada E, Kimura A, Nishikawa H, Hayakawa H et al. T-2307 causes collapse of mitochondrial membrane potential in yeast. Antimicrob Agents Chemother. 2012;56(11):5892–7 (https://doi.org/10.1128/AAC.05954-11, accessed 27 November 2024).

172. Hafiz S, Kyriakopoulos C. Pentamidine. In StatPearls [internet] Treasure Island: StatPearls Publishing; 2024 (https://www.ncbi.nlm.nih.gov/books/NBK557586/, accessed 27 November 2024).

173. Appili Therapeutics diversified pipeline driving near- and long-term value. In Appili Therpeutics/pipeline [website]. Halifax: Appili Therapeutics; 2024 (https://appilitherapeutics.com/pipeline, accessed 27 November 2024).

174. Thompson GR, King T, Azie N, Angulo DA, Prattes J. 871. Oral ibrexafungerp outcomes by fungal disease in patients from an interim analysis of a Phase 3 open-label study (FURI). Open Forum Infect Dis. 2022;9;Suppl 2, Issue Supplement_2, December 2022:ofac492.064 (https://doi.org/10.1093/ofid/ofac492.064, accessed 27 November 2024).

175. U S Securities and Exchange Commission Form 8k SCYNEXIS Inc. In Scynexis Inc/filings [website]. New Jersey: Scynexis Inc; 2023 (https://ir.scynexis.com/sec-filings/all-sec-filings/content/0000950170-23-049544/0000950170-23-049544.pdf, accessed 27 November 2024).

176. Ishii Y, Ito Y, Matsuki S, Sanpei K, Ogawa O, Takeda K et al. Clinical drug-drug interaction potential of BFE1224, prodrug of antifungal ravuconazole, using two types of cocktails in healthy subjects. Clin Transl Sci. 2018;11(5):477–86 (https://doi.org/10.1111/cts.12557, accessed 27 November 2024).

177. Watanabe S, Tsubouchi I, Okubo A. Efficacy and safety of fosravuconazole L-lysine ethanolate, a novel oral triazole antifungal agent, for the treatment of onychomycosis: A multicenter, double-blind, randomized phase III study. J Dermatol. 2018;45(10):1151–9 (https://doi.org/10.1111/1346-8138.14607, accessed 27 November 2024).

178. Ahmed SA, Kloezen W, Duncanson F, Zijlstra EE, de Hoog GS, Fahal AH et al. Madurella mycetomatis is highly susceptible to ravuconazole. PLOS Negl Trop Dis. 2014;8(6):e2942 (https://doi.org/10.1371/journal.pntd.0002942, accessed 27 November 2024).

179. Yadlapati S, Sathe NC, Chaudhari SP. Eumycetoma. In StatPearls [internet] Treasure Island: StatPearls Publishing; 2024.

180. Mycetoma Fosravuconazole. In DNDi/research and development portfolio [website]. Geneva: Drugs for Neglected Diseases initiative (DNDi); 2024 (https://dndi.org/research-development/portfolio/fosravuconazole/, accessed 27 November 2024).

181. Pasqualotto AC, Lana DD, Godoy CS, Leitão TD, Bay MB, Damasceno LS et al. Single high dose of liposomal amphotericin B in human immunodeficiency virus/AIDS-related disseminated histoplasmosis: A randomized trial. Clin Infect Dis. 2023;77(8):1126–32 (https://doi.org/10.1093/cid/ciad313, accessed 27 November 2024).

182. Jarvis JN, Lawrence DS, Meya DB, Kagimu E, Kasibante J, Mpoza E et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. N Engl J Med. 2022;386(12):1109–20 (https://doi.org/10.1056/NEJMoa2111904, accessed 27 November 2024).

183. Guidelines for diagnosing, preventing and managing cryptococcal disease among adults, adolescents and children living with HIV. In WHO/Publications [website]. Geneva: World Health Organization (WHO); 2022 (https://iris.who.int/handle/10665/360423, accessed 27 November 2024).

184. Paediatric investigation plans. In EMA/Paediatric medicines/research and development [website]. Amsterdam: European Medicines Agency (EMA); 2024 (https://www.ema.europa.eu/en/human-regulatory-overview/research-development/paediatric-medicines-research-development/paediatric-investigation-plans, accessed 27 November 2024).

185. Nevez G, Le Gal S. Caspofungin and pneumocystis pneumonia: it is time to go ahead. Antimicrob Agents Chemother. 2019;63(10):e01296–19 (https://doi.org/10.1128/AAC.01296-19, accessed 27 November 2024).

186. Gu ZY, Liu WJ, Huang DL, Liu YJ, He HY, Yang C et al. Preliminary study on the combination effect of clindamycin and low dose trimethoprim-sulfamethoxazole on severe pneumocystis pneumonia after renal transplantation. Front Med (Lausanne). 2022;9:827850 (https://doi.org/10.3389/fmed.2022.827850, accessed 27 November 2024).

187. Fishman JA, Gans H, AST Infectious Diseases Community of Practice. Pneumocystis jiroveci in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9):e13587 (https://doi.org/10.1111/ctr.13587, accessed 27 November 2024).

188. ibeiro NQ, Santos AP, Emídio EC, Costa MC, Freitas GJ, Carmo PH et al. Pioglitazone as an adjuvant of amphotericin B for the treatment of cryptococcosis. Int J Antimicrob Agents. 2019;54(3):301–8 (https://doi.org/10.1016/j.ijantimicag.2019.06.020, accessed 27 November 2024).

189. Gouveia-Eufrasio L, Ribeiro NQ, Santos JR, da Costa MC, Emídio EC, de Freitas GJ et al. Randomized, phase 1/2, double-blind pioglitazone repositioning trial combined with antifungals for the treatment of cryptococcal meningitis - PIO study. Contemp Clin Trials Commun. 2021;22:100745 (https://doi.org/10.1016/j.conctc.2021.100745, accessed 27 November 2024).

190. Li W, Yun Z, Ji C, Tu J, Yang W, Li J et al. Discovery of novel sertraline derivatives as potent anti-cryptococcus agents. J Med Chem. 2022;65(9):6541–54 (https://doi.org/10.1021/acs.jmedchem.1c01845, accessed 27 November 2024).

191. Wiseman H, Cannon M, Arnstein HR. Observation and significance of growth inhibition of Saccharomyces cerevisiae (A224A) by the anti-oestrogen drug tamoxifen. Biochem Soc Trans. 1989;17(6):1038–9 (https://doi.org/10.1042/bst0171038, accessed 27 November 2024).

192. Butts A, Martin JA, DiDone L, Bradley EK, Mutz M, Krysan DJ. Structure–activity relationships for the antifungal activity of selective estrogen receptor antagonists related to tamoxifen. PLOS ONE.2015;10(5):e0125927 (https://doi.org/10.1371/journal.pone.0125927, accessed 27 November 2024).

193. Gómez-López A. Antifungal therapeutic drug monitoring: focus on drugs without a clear recommendation. Clin Microbiol Infect. 2020;26(11):1481–7 (https://doi.org/10.1016/j.cmi.2020.05.037, accessed 27 November 2024).

194. Abuhelwa AY, Foster DJ, Mudge S, Hayes D, Upton RN. Population pharmacokinetic modeling of itraconazole and hydroxyitraconazole for oral SUBA-itraconazole and Sporanox apsule formulations in healthy subjects in fed and fasted states. Antimicrob Agents Chemother. 2015;59(9):5681–96 (https://doi.org/10.1128/AAC.00973-15, accessed 27 November 2024).

195. Spec A, Thompson GR, Miceli MH, Hayes J, Proia L, McKinsey D, et al. MSG-15: Super-Bioavailability Itraconazole Versus Conventional Itraconazole in the Treatment of Endemic Mycoses-A Multicenter, Open-Label, Randomized Comparative Trial. Open Forum Infect Dis. 2024;11(3):ofae010 (https://doi.org/10.1093/ofid/ofae010, accessed 27 November 2024).

196. Pardeshi SR, Kole EB, Kapare HS, Chandankar SM, Shinde PJ, Boisa GS et al. Progress on thin film freezing technology for dry powder inhalation formulations. Pharmaceutics. 2022;14(12):2632 (https://doi.org/10.3390/pharmaceutics14122632, accessed 27 November 2024).

197. Brunet K, Martellosio JP, Tewes F, Marchand S, Rammaert B. Inhaled antifungal agents for treatment and prophylaxis of bronchopulmonary invasive mold infections. Pharmaceutics. 2022;14(3):641 (https://doi.org/10.3390/pharmaceutics14030641, accessed 27 November 2024).

198. Gardiner BJ, Ivulich SP, Snell GI. Voriconazole inhalation powder: A novel therapeutic alternative for invasive pulmonary fungal infections. Transpl Infect Dis. 2024;26(3):e14264 (https://doi.org/10.1111/tid.14264, accessed 27 November 2024).

199. Segarra I, Movshin DA, Zarif L. Pharmacokinetics and tissue distribution after intravenous administration of a single dose of amphotericin B cochleates, A new lipid-based delivery system. J Pharm Sci. 2002;91(8):1827–37 (https://doi.org/10.1002/jps.10173, accessed 27 November 2024).

200. Boulware DR, Atukunda M, Kagimu E, Musubire AK, Akampurira A, Tugume L et al. Oral lipid nanocrystal amphotericin B for cryptococcal meningitis: A randomized clinical trial. Clin Infect Dis. 2023;77(12):1659–67 (https://doi.org/10.1093/cid/ciad440, accessed 27 November 2024).

201. Makoni M. Improving cryptococcal meningitis treatment in Africa. Lancet Microbe. 2022;3(6):e406 (https://doi.org/10.1016/S2666-5247(22)00129-X. Erratum in: Lancet Microbe. 2022;3(8):e563 (https://doi.org/10.1016/S2666-5247(22)00159-8, accessed 27 November 2024).

202. Goyal V, Krantz E, Simon F, Neven A, Eriksson J, Saayman A et al. Bioavailability of three novel oral, sustained-release pellets, relative to an immediate-release tablet containing 500 mg flucytosine: A randomized, open-label, crossover study in healthy volunteers. Clin Transl Sci. 2024;17(3):e13756 (https://doi.org/10.1111/cts.13756, accessed 27 November 2024).

203. 2021 antibacterial agents in clinical and preclinical development: an overview and analysis Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/376944, accessed 27 November 2024).).

204. Egger M, Bellmann R, Krause R, Boyer J, Jakšić D, Hoenigl M. Salvage treatment for invasive aspergillosis and mucormycosis: challenges, recommendations and future considerations. Infect Drug Resist. 2023;16:2167–78 (https://doi.org/10.2147/IDR.S372546, accessed 27 November 2024).

205. Diagnosis and management of Aspergillosis. Arlington: Infectious Diseases Society of America; 2022 (www.guidelinecentral.com/guideline/21923/, accessed 27 November 2024).

206. Tissot F. ECIL-6 guidelines for the treatment of invasive candidiasis, Aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017;102:433 (https://doi.org/10.3324/haematol.2016.152900, accessed 27 November 2024).

207. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SC, Dannaoui E, Hochhegger B et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19(12):e405–21 (https://doi.org/10.1016/S1473-3099(19)30312-3, accessed 27 November 2024).

208. Muthu V, Agarwal R, Patel A, Kathirvel S, Abraham OC, Aggarwal AN et al. Definition, diagnosis, and management of COVID-19-associated pulmonary mucormycosis: Delphi consensus statement from the Fungal Infection Study Forum and Academy of Pulmonary Sciences, India. Lancet Infect Dis. 2022;22(9):e240–53 (https://doi.org/10.1016/S1473- 3099(22)00124-4. Erratum in: Lancet Infect Dis. 2022;22(6):e159 (https://doi.org/10.1016/S1473-3099(22)00268-7, accessed 27 November 2024).

209. Carvalhaes CG, Rhomberg PR, Huband MD, Pfaller MA, Castanheira M. Antifungal activity of isavuconazole and comparator agents against contemporaneous Mucorales isolates from USA, Europe, and Asia-Pacific. J Fungi (Basel). 2023;9(2):241 (https://doi.org/10.3390/jof9020241, accessed 27 November 2024).

210. Yeoh DK, Blyth CC, McMullan BJ. Echinocandins in pediatric invasive candidiasis and the challenges of antifungal use in children. J Pediatr Infect Dis Soc. 2021;10(7):755–6 (https://doi.org/10.1093/jpids/piab039, accessed 27 November 2024).

211. Fisher BT, Zaoutis TE, Xiao R, Wattier RL, Castagnola E, Pana ZD et al. Comparative effectiveness of echinocandins vs triazoles or amphotericin B formulations as initial directed therapy for invasive candidiasis in children and adolescents. J Pediatr Infect Dis Soc. 2021:piab024 (https://doi.org/10.1093/jpids/piab024, accessed 27 November 2024).

212. Fisher BT, Zaoutis T, Dvorak CC, Nieder M, Zerr D, Wingard JR, et al. Effect of caspofungin vs fluconazole prophylaxis on invasive fungal disease among children and young adults with acute myeloid leukemia: a randomized clinical trial. JAMA. 2019;322(17):1673–81 (https://doi.org/10.1001/jama.2019.15702, accessed 27 November 2024).

213. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24;Suppl 1:e1–e38 (https://doi.org/10.1016/j.cmi.2018.01.002, accessed 27 November 2024).

214. Gebremariam T, Gu Y, Alkhazraji S, Youssef E, Shaw KJ, Ibrahim AS. The combination treatment of fosmanogepix and liposomal amphotericin B is superior to monotherapy in treating experimental invasive mold infections. Antimicrob Agents Chemother. 2022;66(7):e0038022 (https://doi.org/10.1128/aac.00380-22, accessed 27 November 2024).

215. Pappas P, Kullberg BJ, Vazquez JA, Oren I, Rahav G, Aoun M et al. 147. Clinical safety and efficacy of novel antifungal, fosmanogepix, in the treatment of candidemia: results from a Phase 2 proof of concept trial. Open Forum Infect Dis. 2020;7;Suppl 1:S203–4 (https://doi.org/10.1093/ofid/ofaa439.457, accessed 27 November 2024).

216. Liu Y, Mittal R, Solis NV, Prasadarao NV, Filler SG. Mechanisms of Candida albicans trafficking to the brain. PLOS Pathog. 2011;7(10):e1002305 (https://doi.org/10.1371/journal.ppat.1002305, accessed 27 November 2024).

217. Chen YC, Chang TY, Liu JW, Chen FJ, Chien CC, Lee CH, et al. Increasing trend of fluconazole-non-susceptible Cryptococcus neoformans in patients with invasive cryptococcosis: A 12-year longitudinal study. BMC Infect Dis. 2015;15:277 (https://doi.org/10.1186/s12879-015-1023-8, accessed 27 November 2024).

218. Smith KD, Achan B, Hullsiek KH, McDonald TR, Okagaki LH, Alhadab AA, et al. Increased antifungal drug resistance in clinical isolates of Cryptococcus neoformans in Uganda. Antimicrob Agents Chemother. 2015;59(12):7197–204 (https://doi.org/10.1128/AAC.01299-15, accessed 27 November 2024).

219. Naicker SD, Mpembe RS, Maphanga TG, Zulu TG, Desanto D, Wadula J et al. Decreasing fluconazole susceptibility of clinical South African Cryptococcus neoformans isolates over a decade. PLOS Negl Trop Dis. 2020;14(3):e0008137 (https://doi.org/10.1371/journal.pntd.0008137, accessed 27 November 2024).

220. Chesdachai S, Rajasingham R, Nicol MR, Meya DB, Bongomin F, Abassi M, et al. Minimum inhibitory concentration distribution of fluconazole against Cryptococcus species and the fluconazole exposure prediction model. Open Forum Infect Dis. 2019;6(10):ofz369 (https://doi.org/10.1093/ofid/ofz369, accessed 27 November 2024).

221. Lackner M, de Hoog GS, Verweij PE, Najafzadeh MJ, Curfs-Breuker I, Klaassen CH et al. Species-specific antifungal susceptibility patterns of Scedosporium and Pseudallescheria species. Antimicrob Agents Chemother. 2012;56(5):2635–42 (https://doi.org/10.1128/AAC.05910-11, accessed 27 November 2024).

222. McCarthy MW, Katragkou A, Iosifidis E, Roilides E, Walsh TJ. Recent advances in the treatment of scedosporiosis and Fusariosis. J Fungi (Basel). 2018;4(2):73 (https://doi.org/10.3390/jof4020073, accessed 27 November 2024).

223. Jabr R, Hammoud K. Scedosporium apiospermum fungemia successfully treated with voriconazole and terbinafine. IDCases. 2020;22:e00928 (https://doi.org/10.1016/j.idcr.2020.e00928, accessed 27 November 2024).

224. Lamoth F, Alexander BD. Antifungal activities of SCY-078 (MK-3118) and standard antifungal agents against clinical non-Aspergillus mold isolates. Antimicrob Agents Chemother. 2015;59(7):4308–11 (https://doi.org/10.1128/AAC.00234-15, accessed 27 November 2024).

225. McCarthy MW, Moriyama B, Petraitiene R, Walsh TJ, Petraitis V. Clinical pharmacokinetics and pharmacodynamics of isavuconazole. Clin Pharmacokinet. 2018b;57(12):1483–91 (https://doi.org/10.1007/s40262-018-0673-2, accessed 27 November 2024).

226. Pfaller MA, Huband MD, Flamm RK, Bien PA, Castanheira M. In vitro activity of APX001A (manogepix) and comparator agents against 1,706 fungal isolates collected during an international surveillance program in 2017. Antimicrob Agents Chemother. 2019;63(8):e00840–19 (https://doi.org/10.1128/AAC.00840-19, accessed 27 November 2024).

227. Maertens JA, Verweij PE, Lanuza EF, Harvey EL, Dane A, Zinzi D et al. 870 Olorofim for the treatment of invasive mould infections in patients with limited or no treatment options: comparison of interim results from a phase 2B open-label study with outcomes in historical control populations (NCT03583164, FORMULA-OLS, Study 32). Open Forum Infect Dis. 2022;9(2):ofac492.063 (https://doi.org/10.1093/ofid/ofac492.063, accessed 27 November 2024).

228. Bhatt VR, Viola GM, Ferrajoli A. Invasive fungal infections in acute leukemia. Ther Adv Hematol. 2011;2(4):231–47 (https://doi.org/10.1177/2040620711410098, accessed 27 November 2024).

229. Tortorano AM, Richardson M, Roilides E, van Diepeningen A, Caira M, Munoz P et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: fusarium spp., Scedosporium spp. and others. Clin Microbiol Infect. 2014;20;Suppl 3:27–46 (https://doi.org/10.1111/1469-0691.12465, accessed 27 November 2024).

230. Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. Clin Microbiol Rev. 2007;20(4):695–704 (https://doi.org/10.1128/CMR.00014-07, accessed 27 November 2024).

231. Fungal Meningitis Outbreak Associated with Procedures Performed under Epidural Anesthesia in Matamoros, Mexico. In CDC/emergency preparedness and response[website]. Atlanta: Centers for Disease Control and Prevention. Division of Healthcare Quality Promotion (DHQP); 2023 (https://emergency.cdc.gov/han/2023/han00491.asp, accessed 27 November 2024).

232. Smith DJ, Gold JA, Chiller T, Bustamante ND, Marinissen MJ, Rodriquez GG et al. Update on Outbreak of Fungal Meningitis Among US Residents Who Received Epidural Anesthesia at Two Clinics in Matamoros, Mexico. Clin Infect Dis. 2024;78(6):1554–8 (https://doi.org/10.1093/cid/ciad570, accessed 27 November 2024).

233. Mahadevaiah AH, Rajagopalan N, Patil M, Shivaprasad C. Coinfection of pulmonary mucormycosis and aspergillosis presenting as bilateral vocal cord palsy. BMJ Case Rep. 2013;2013:bcr2013009615 (https://doi.org/10.1136/bcr-2013-009615, accessed 27 November 2024).

234. European Medicines Agency (EMA) launches pilot project on drug repurposing. In EJP Rare Diseases/EMA [website]. France; The European Joint Programme on Rare Diseases; 2022 (https://www.ejprarediseases.org/european-medicines-agency-ema-launches-pilot-project-on-drug-repurposing/, accessed 27 November 2024).

235. Repurposing of authorised medicines: pilot to support not-for-profit organisations and academia (https://www.ema.europa.eu/en/news/repurposing-authorised-medicines-pilot-support-not-profit-organisations-and-academia, accessed 27 November 2024).

236. Ivanov M, Ćirić A, Stojković D. Emerging antifungal targets and strategies. Int J Mol Sci. 2022;23(5):2756 (https://doi.org/10.3390/ijms23052756, accessed 27 November 2024).

237. Holmes AR, Cardno TS, Strouse JJ, Ivnitski-Steele I, Keniya MV, Lackovic K et al. Targeting efflux pumps to overcome antifungal drug resistance. Future Med Chem. 2016;8(12):1485–501 (https://doi.org/10.4155/fmc-2016-0050, accessed 27 November 2024).

238. de Aguiar FL, Santos NC, de Paula Cavalcante CS, Andreu D, Baptista GR, Gonçalves S. Antibiofilm activity on Candida albicans and mechanism of action on biomembrane models of the antimicrobial peptide Ctn [15–34]. Int J Mol Sci. 2020;21(21):8339 (https://doi.org/10.3390/ijms21218339, accessed 27 November 2024).

239. Roscetto E, Contursi P, Vollaro A, Fusco S, Notomista E, Catania MR. Antifungal and anti-biofilm activity of the first cryptic antimicrobial peptide from an archaeal protein against Candida spp. clinical isolates. Sci Rep. 2018;8(1):17570 (https://doi.org/10.1038/s41598-018-35530-0, accessed 27 November 2024).

240. Tischer-Zimmermann S, Salzer E, Bitencourt T, Frank N, Hoffmann-Freimüller C, Stemberger J et al. Rapid and sustained T cell-based immunotherapy against invasive fungal disease via a combined two step procedure. Front Immunol. 2023;14:988947 (https://doi.org/10.3389/fimmu.2023.988947, accessed 27 November 2024).

241. Gottlieb DJ, Clancy LE, Withers B, McGuire HM, Luciani F, Singh M et al. Prophylactic antigen-specific T-cells targeting seven viral and fungal pathogens after allogeneic haemopoietic stem cell transplant. Clin Transl Immunology. 2021;10(3):e1249 (https://doi.org/10.1002/cti2.1249, accessed 27 November 2024).

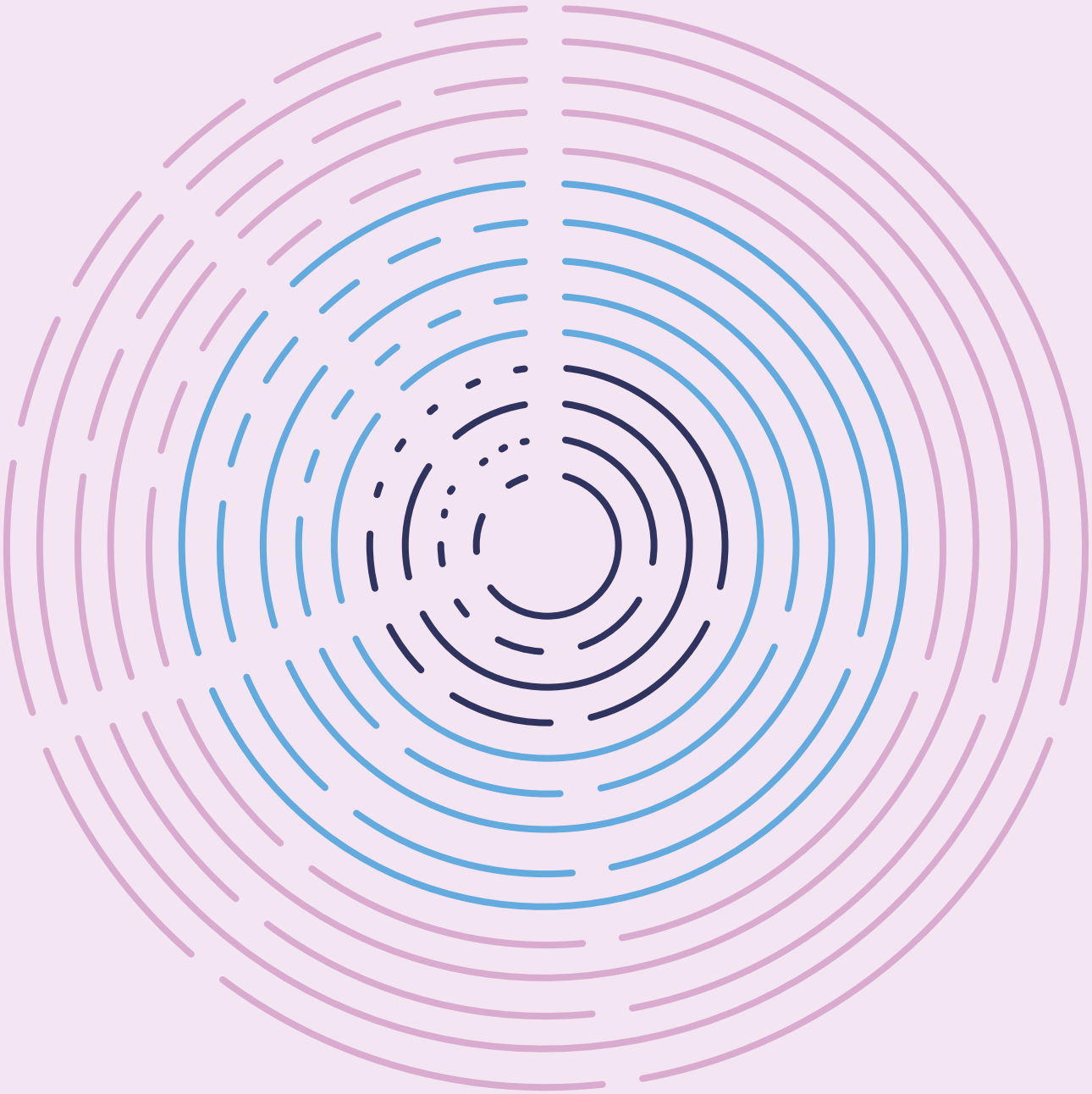
242. Manzari MT, Shamay Y, Kiguchi H, Rosen N, Scaltriti M, Heller DA. Targeted drug delivery strategies for precision medicines. Nat Rev Mater. 2021;6(4):351–70 (https://doi.org/10.1038/s41578-020-00269-6, accessed 27 November 2024).

243. Wu S, Song R, Liu T, Li C. Antifungal therapy: novel drug delivery strategies driven by new targets. Adv Drug Deliv Rev. 2023;199:114967 (https://doi.org/10.1016/j. addr.2023.114967, accessed 27 November 2024).

244. Rex JH, Walsh TJ, Nettleman M, Anaissie EJ, Bennett JE, Bow EJ, et al. Need for alternative trial designs and evaluation strategies for therapeutic studies of invasive mycoses. Clin Infect Dis. 2001;33(1):95–106 (https://doi.org/10.1086/320876, accessed 27 November 2024).

245. Page MJ, Mckenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PROSMA statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71 (https://doi.org/10.1136/bmj.n71, accessed 27 November 2024).

246. World Bank country and lending groups. In: World Bank/Data [website]. Washington (DC): World Bank; 2024 (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups, accessed 27 November 2024).



Annex

Annex. Declaration of interests of expert group members

Management of conflicts of interest was a priority throughout the analysis and decision-making for the antifungal clinical and preclinical pipeline. The declarations of interest (DOIs) were collected and thoroughly reviewed by the WHO AMR Division following WHO standard operating procedures in coordination with the WHO Ethics unit.

Prior to the expert group meeting, all experts submitted written disclosures of competing interests that had arisen during a period of four years preceding the WHO advisory work and that were relevant for consideration before their confirmation as participants in the meeting, including employment by a commercial entity, consultancy, board or advisory board membership, lecture fees, expert witness income, industry-sponsored grants (including contracted research, patents received or pending, royalties, stock ownership or options), other personal financial interests, as well as whether the institution or employer had a financial relationship with a commercial entity that had an interest in antifungal products evaluated by the expert group.

Experts were also asked to disclose academic or scientific activities that included leadership of research or grant applications, in either primary clinical studies or reviews, directly bearing on a decision about an antifungal product. In addition, at the start of the meeting, all members were asked to provide updates about their declaration if any new conflicts had arisen in the meantime.

The experts who declared no potential conflicts of interest were: Jan-Willem Alffenaar, Prabhavathi Fernandes, Nelesh Govender, Souha S Kanj, Mical Paul and Norio Ohmagari. These experts were allowed full participation in the meeting.

The following experts disclosed minor conflicts and were also granted full participation: David Boulware, Arnaldo Lopes Colombo, Leah Cowen, Lloyd Czaplewski, Roman Kozlov:

- David Boulware disclosed that he provided consultancies to Elion therapeutic without receiving any income. He also declared having received research support from Matinas Biopharma and Gilead in the past, and currently by Elion therapeutics which supports meningitis research activities.
- Arnaldo Lopes Colombo disclosed that he provided consultancies to Mundipharma and had been awarded financial support in the previous four years for research by Knight, and for an education programme by United Medical and Sandoz. Speaking honoraria were also received from Gilead, and United Medical.
- Leah Cowen disclosed that she had been awarded financial support in the previous four years for research by 5Metis, Oerth Bio, Whitehead Institute, Bright Angel Therapeutics and Kapoose Creek. She also declared Stocks, bonds, stock options, other securities (e.g. short sales) and patents, trademarks, or copyrights (including pending applications).
- Lloyd Czaplewski disclosed that he provided consultancies and had been awarded financial support in the previous four years from Clarametyx, Novo Repair Impact Fund, Novo Holdings, Chemical Biology Ventures Ltd and Curza.
- Roman Kozlov disclosed that his research unit had been awarded financial support in the previous four years from Merck Sharp and Dohme, Pfizer and Astellas Pharma.

The experts who disclosed potentially significant conflicts of interest were: Justin Beardsley, Methee Chayakulkeeree, Thuy Lee, Christine Mandengue, Marisa Miceli, Olga Morrissey, Rita Oladele, Alessandro Pasqualotto, María Isabel Ruiz Camps, and Peter Williamson:

- Justin Beardsley disclosed that he received research support from Pfizer to develop educational materials on fungal diagnostics in Viet Nam and non-monetary support by Gilead.
- Methee Chayakulkeeree disclosed that his university received research support from Cidara and F2G. He also declared having received non-monetary support from F2G Ltd..
- Christine Mandengue disclosed that she received research support from the Fungal Infection Trust (United Kingdom). She also declared having received non-monetary support for travel by The Pan African Mycology Working Group (PAMWG).
- Thuy Lee disclosed that her University, Duke University School of Medicine, received research support form Gilead Sciences for an investigator-initiated research grant.
- Marisa Miceli disclosed that she provided consultancies to Scynexis. She also declared having received research support from Scynexis, F2G Ltd., Pulmocide, AN2, as principal investigator in clinical trials for which no financial remuneration was received.
- Orla Morrissey disclosed that her Clinical Research Unit received research support from F2G Ltd., and Pulmocide to conduct sponsored trials.
- Rita Oladele disclosed that she provided consultancies as member of the Pfizer Virtual Advisory Board Council. She also declared having received non-monetary support from Pfizer (honorarium and travel costs), and from Pfizer-IMMY diagnostic symposium TIMM.
- Alessandro Pasqualotto disclosed that he received research support from Gilead Science, speaker honoraria from Pfizer, Knight Therapeutic, Sandoz, Teva, Multipharma, Gilead, Immy and MSD in the past five years. He also declared having consulted for WHO in the region of Americas (PAHO).
- María Isabel Ruiz Camps disclosed that she provided consultancies to Gilead and Pfizer. She also received non-monetary support from Gilead and Pfizer.
- Peter Williamson disclosed that the United States National Institutes of Health for which he works received research support from Matinas Biopharma for preclinical studies.

Following assessment of their DOIs, these experts were excluded from discussions involving products from commercial entities or other organizations listed above.

All reported interests were disclosed to the meeting participants by the technical unit in a plenary presentation: the interests are also disclosed in this report and in relevant publications.

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