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The rapid emergence of antifungal resistant human-pathogenic fungi

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Abstract

During recent decades, the emergence of pathogenic fungi has posed an increasing public health threat, particularly given the limited number of antifungal drugs available to treat invasive infections. In this Review, we discuss the global emergence and spread of three antifungal-resistant emerging fungi: *Candida auris*, driven by global healthcare transmission and possibly facilitated by climate change; azole-resistant *Aspergillus fumigatus*, driven by the selection facilitated by azole fungicide use in agricultural and other settings; and *Trichophyton indotineae*, driven by the underregulated use of over-the-counter high potency corticosteroid-containing antifungal creams. The diversity of the fungi themselves and the drivers of their emergence make it clear that we cannot predict what might emerge next. Therefore, vigilance is critical to monitoring for fungal emergence, as well as the rise in overall antifungal resistance.

Graphical Abstract

In this Review, Lockhart, Chowdhary and Gold discuss the global emergence and spread of three antifungal-resistant emerging fungi: *Candida auris*, azole-resistant *Aspergillus fumigatus* and *Trichophyton indotineae*, with the common thread that all three are currently emerging across the globe and have a high rate of acquired resistance.

The authors contributed equally to all aspects of the article.

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Related links:
CDC Infection Prevention and Control for Candida auris: https://www.cdc.gov/fungal/candida-auris/c-auris-infection-control.html

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Introduction

Fungi are among the most abundant and diverse organisms in the world. They are found in and on most humans as a part of the human microbiome and we breathe in hundreds of fungal spores each day (supplementary Box 1). Out of several million species of fungi, only several hundred are known to cause human illness. Most fungal infections are superficial, such as onychomycosis of the nails, dermatophyte infections of the skin such as athlete's foot and mucosal infections (for example, vulvovaginal candidiasis). However, for some people, especially those with frequent healthcare interactions or weakened immune systems, encounters with fungi poses a serious health threat.

The emergence of pathogenic fungi is not a rare event. In recent decades, *Cryphonectria parasitica* nearly destroyed all chestnut trees in the United States and *Fusarium oxysporum* var. *cubense* nearly decimated banana monoculture; *Batrachochytrium dendrobatidis* is destroying amphibian populations, and *Pseudogymnoascus destructans* is killing entire colonies of bats [1–4]. Fungal diseases of plants threaten food security worldwide by causing epiphytotics in staple crops and by contaminating food supplies with toxins. Rice-blast disease, caused by *Magnaporthe oryzae*, destroys 12–30% of annual rice harvests, and a new, virulent strain of *Puccinia graminis* that causes stem rust disease on wheat jeopardizes harvests in Europe, Asia and the Americas[5,6].

Emerging fungi that directly affect human health have been less common. During the early HIV epidemic, *Candida dubliniensis* emerged alongside *Candida albicans* as a cause of azole-resistant mucosal candidiasis, and both *Cryptococcus neoformans* and *Pneumocystis jirovecii* exploited a new population of immunosuppressed hosts to become major causes of death in patients with advanced HIV disease[7–9]. With the HIV epidemic, cancer and immunomodulating medicine, fungal infections in humans have become more common, but until now, the emergence of new human pathogenic fungi has been rare. We are now witnessing both the emergence of new species of fungi, such as *Candida auris* and *Trichophyon indotineae*, as well the emergence and spread of drug-resistant lineages of well-known common fungi such as azole-resistant *Aspergillus fumigatus* [10–12] (Figure 1).

Two important factors are common among *C. auris*, *T. indotineae* and azole-resistant *A. fumigatus*. First, these pathogens are spreading across the globe as essentially clonal lineages, *C. auris* as four clonal clades, *T. indotineae* as a single clonal clade and *A. fumigatus* as a clone (the clonal mutations, $TR_{34,}$ and TR_{46} to be discussed later with recombination. Although this has occurred before with fungi that infect amphibians (*Batrachochytrium dendrobatidis*[3]) and plants *(Puccinia graminis*[6]*)*, this is the first time that human-pathogenic fungi have spread intercontinentally in such a short time frame (a decade for *T. indotineae* and *C. auris*, and several decades for azole-resistant *A. fumigatus*). The mechanisms for this spread may be different among the fungi, but the rapid rate is similar and concerning. What is surprising is that the emergence and spread of these three disparate species has occurred almost simultaneously.

The second commonality among these three fungi is that they share a very high rate of acquired antimicrobial resistance (Box 1). The mechanisms of acquired resistance and

the antifungals to which they are resistant are different for each of the fungi, but it is nonetheless remarkable to have three fungi with high levels of acquired resistance emerge simultaneously, particularly because antifungal resistance in fungi is rare. In the cases of *C. auris* and *T. indotineae*, resistance to more than one class of antifungal can be present, putting these pathogens in the rare category of multidrug-resistant fungi. Although the cause of the sudden emergence and spread of *C. auris*, azole-resistant *A. fumigatus* and *T. indotineae* is unknown, researchers have proposed several potential contributing factors. It has been proposed that climate change may be contributing to the emergence of fungal species, including *C. auris*, but the data confirming this hypothesis for most fungi is lacking[13–16]. As global temperatures rise, selective pressure will favor fungi that survive at increased temperatures such as the temperatures found in the human body. A second proposed factor is the widespread use of antifungal compounds in human and animal medicine, as well for other applications, including for crop agriculture and the preservation of wood products, plastics and paints [17]. In addition to selecting for resistant organisms, this widespread usage of antifungals may also have a secondary harmful role: increasing antimicrobial usage could potentially be changing microbiomes of not only of human hosts but also natural microbiomes [18–20]. Changes to the established microbiome might promote the emergence of never-before-seen colonization or infections by microorganisms not previously detected in microbiomes. These microorganisms might emerge in the setting of the alterations of the natural microbiome that has developed over tens of thousands of years on the surfaces of our mucosa, gastrointestinal tracts and skin. *C. auris* colonization is correlated with changes in the skin microbiome[21,22]. *T. indotineae* infection is associated with the use of combination antifungal, antibiotic and topical steroid products, and research has shown that antibiotics alter the skin microbiome, but a direct correlation *with T. indotineae* infection and changes to the skin microbiome has not yet been shown[23]. Whether the spread of azole-resistant *A. fumigatus* is linked to changes in the environmental microbiome is unclear, but the presence of resistance-causing azoles in soil has been shown to change the soil microbiome[24–27].

In this Review, we discuss *C. auris*, azole-resistant *A. fumigatus* and *T. indotineae*, with the common thread that all three are currently emerging across the globe and have a high rate of acquired resistance, two characteristics that are rare among fungi. Although the precise details of their emergence might remain elusive, we outline and discuss our current understanding of the emergence, epidemiology, evolution, pathogenicity, clinical manifestations, resistance mechanisms and treatment options for these pathogens (Table 1).

Candida auris

Emergence and epidemiology.

The emergence of *C. auris* has been rapid and overwhelming. The first recognized clinical isolate was recovered from the ear of a patient in Japan in 2006 [10] (Table 1). By 2014, *C. auris* had been identified in South Korea, India and South Africa; by 2016, four separate emerging clades had been described on three different continents [28–31](Figure 1a). In just over a decade after its initial discovery, researchers have identified *C. auris* in over 40 countries and on all continents except Antarctica [32] (Figure 1a). A retrospective review of

culture collections across the globe identified some older isolates of *C. auris*, with the oldest isolates now identified from a collection in South Korea from 1996, a collection from Japan in 1997, a collection in France from 2007, and an isolate from Pakistan from 2008 (Refs. [28,31,33–35]). However, these are one-off isolates, which suggests that *C. auris* was extremely rare before the early 2010s, and that the emergence and spread across three continents has been sudden. Molecular clock analysis using whole-genome sequences indicates that the time to the most recent common ancestor of three of the four clades happened as recently as the 1980's, whereas the oldest clade is likely to have only diverged from a common ancestor around 400 years ago [36]. Whole-genome sequencing of isolates from around the world also reveals that the global spread occurred solely through the previously identified four clades and not through emergence of new clades, although a fifth clade has been recently identified exclusively in Iran [36,37].

The rapid emergence of *C. auris* is tied to its epidemiology. Three factors differentiate *C. auris* from other species of *Candida*: *C. auris* is primarily associated with the skin rather than the gut or mucosal surfaces; it spreads rapidly in healthcare environments leading to frequent outbreaks; and most isolates have acquired antifungal resistance, with some isolates demonstrating resistance to all three classes of systemic antifungals [38]. Most *Candida* species are considered commensals of mucosal surfaces and the gastrointestinal tract, although some of the same species found on mucosal surfaces can also be found on the skin [39,40]. By contrast, *C. auris* is primarily associated with the skin, although it is occasionally found in the respiratory and gastrointestinal tracts [41]. *C. auris* colonizes the skin of patients in healthcare settings and has been associated with a disruption to the normal skin flora [21,22]. Extensive screening of persons outside of a healthcare setting has not been performed, but two studies that looked for colonization of healthcare workers failed to detect colonization, which implies that an intact skin microbiome may be a barrier to *C. auris* colonization, although it has been shown to be transient on the hands of healthcare workers [41–43]. Because *C. auris* can persist on the skin, it can spread widely in healthcare environments, including both among patients and on environmental surfaces. The degree of skin colonization has been shown to be proportional to the spread within the patient environment [22,44]. Further, skin colonization with *C. auris* is a risk factor for bloodstream infections; approximately 5–10% of patients who are colonized with *C. auris* develop bloodstream infections [45]. Because *C. auris* is a nationally notifiable disease in the United States, the degree of spread has been well documented. Initially, spread was due to importation followed by limited localized transmission. However, most contemporary cases have been acquired through localized transmission, and clinical cases continue to increase [46]. Of great concern, the annual percentage increase in clinical cases of *C. auris* was 44% in 2019 and 95% in 2021 (Ref. [47]).

Evolution.

The sudden, simultaneous emergence of *C. auris* on multiple continents has led to speculation on its origin [13,14,48]. The two clades that have not yet spread outwardly, clade II (East Asian) and clade V (Iran), are primarily associated with the skin of the ear canal, a clue to the possible origin of emergence [33,49]. It is unlikely that both clades independently found their way to this highly specialized niche following emergence, especially because

neither clade seems to be spreading globally; rather, the ear canal may be a natural niche for these clades and could have been the original skin reservoir for all of the *C. auris* clades before emergence[33,35,37]. *C. auris* has been identified in the environment both from coastal wetlands in the Andaman Islands and Colombia, and from apples that had been stored and processed in India [50–52]. What we cannot discern from these environmental sources is whether these are the natural habitat of *C. auris* or a secondary niche following contamination of the environment following colonization of humans. Whether *C. auris* emerged from the environment or from an obscure human commensal niche, selective pressure from antifungal usage, the disruption of microbiomes, and climate change are all possible drivers of the emergence.

Pathogenicity and clinical manifestations.

As a colonizer of the skin, *C. auris* does not cause any symptoms to the colonized patient. This lack of symptoms enables *C. auris* colonization to go undetected and likely plays a substantial role in its ability to spread within healthcare facilities. At this point there is no evidence that *Candida auris* colonizes individuals without healthcare exposures. Outside of its detection in the ear, *C. auris* is not yet found in or on medically naïve persons[41,42]. Because of these factors, infection prevention and control measures [https://www.cdc.gov/fungal/candida-auris/c-auris-infection-control.html] are critical to preventing the spread of *C. auris*

The clinical manifestations seen with *C. auris* are similar to those seen with infections caused by other *Candida* species [53]. Candidemia, urinary tract infections, wound infections, otitis and skin abscesses are the most common infection types, but *C. auris* can also cause disseminated disease [54]. *C. auris* has not been implicated as a frequent pathogen in other more common types of candidiasis (for example, vulvovaginal candidiasis or oral thrush). Risk factors for *C. auris* infection mirror those for infections by other *Candida* species including recent surgery, immunosuppression, neutropenia, extended healthcare exposure and use of antibiotics[55]. One of the primary risk factors for *C. auris* infection is the presence of indwelling medical devices including ventilator tubes, central venous catheters, feeding tubes and urinary catheters, as they provide a mechanism for *C. auris* to disseminate from the skin. The ability of *C. auris* to form biofilms both on these devices as well as robust biofilms on the skin may prolong colonization and increase the risk of a disseminated infection[56–58]. *C. auris* infections made a leap forward during the first few years of the COVID-19 pandemic. Increased medical intervention, limited personal protective equipment due to supply chain issues, and increased corticosteroid use for COVID-19 treatment are likely to have contributed to the increase in cases[59].

In a mouse model of infection *C. auris* is less virulent than *C. albicans* but more virulent than *C. glabrata* and *C. haemulonii*[60]. This decreased overall virulence may be related to the fact that *C. auris* is only able to form rudimentary hyphae, which is notable because hyphae formation is a major virulence factor of other *Candida* species[61]. One of the more intriguing virulence factors of *C. auris* may be its ability to evade phagocytosis by neutrophils[62]. In a zebrafish model of disseminated infection, neutrophils were twice as responsive to *C. albicans* as to *C. auris*[62]. Further work in this area has revealed that mannans in the *C.*

auris cell wall may mask critical components recognized by neutrophils such as β-glucan, and chitin[63]. There is also evidence that *C. auris* can replicate within and escape from macrophages [64]. Under *in vitro* conditions, *C. auris* may be able to kill macrophages as well through the mechanism of rapid replication and glucose depletion[64].

Resistance mechanisms and treatment options.

Aside from intrinsically resistant species, such as *Candida krusei*, fluconazole resistance among *Candida* species is rare. Before the emergence of *C. auris*, the *Candida* species with the highest frequency of acquired resistance was *C. glabrata*, a pathogen whose overall worldwide resistance rate is approximately 10–12% (Ref. [65]). This changed with the emergence of *C. auris*, for which acquired resistance to fluconazole is observed in most clinical isolates [31,66,67]. Resistance seems to be clade-specific, with isolates of clades I and III being almost universally resistant to fluconazole, isolates of clade II being almost universally susceptible to fluconazole, and isolates of clade IV showing variable resistance, depending on the circulating clone[36].

The most common mechanism of azole resistance in *C. auris* is a mutation in the drug target lanosterol 14-a-demethylase (*ERG11*) such as Y132F, K143R and F126L (Figure 2). Increased expression of efflux pumps, including those due to mutations in the gene encoding the transcription factor *TAC1b*, which cause an increase in the expression of the efflux pump Cdr1p, have also been determined to increase resistance[68,69]. Resistance to echinocandins is uncommon. However, resistance can develop during echinocandin therapy and is caused by several different mutations at amino acid S639 (S639Y, S639F or S639P) in hotspot1 of the drug target 1,3-β-D-glucan synthase (*FKS1*)[66,70,71]. A breakpoint for amphotericin B against *C. auris* does not exist, but based on pharmacokinetic–pharmacodynamic values in animal models, a tentative breakpoint of 2 μg/ml was set [72]. Using this value, resistance to amphotericin B has been reported in about 30% of isolates; however, resistance seems to vary based on the clone or the clade being tested [31,32]. Because resistance to amphotericin B is difficult to define, it is unknown whether this represents clinical or *in vitro* resistance. To date, only a single mechanism, a mutation in the *ERG6* gene, has been definitively associated with amphotericin B resistance [73].

Multidrug resistance in most *Candida* species is extremely rare and pan-antifungal resistance has rarely been reported in any *Candida* species[74]. As *C. auris* began to emerge, several pan-antifungal resistant isolates were reported. Fortunately, further spread of these isolates did not occur, and it was speculated that pan-resistance in these organisms was associated with a fitness cost[75]. However, documented transmission of pan-resistant and echinocandin-resistant *C. auris* isolates was later reported from the United States, which suggests that high transmissibility of *C. auris* can lead to spread of drug-resistant clones in healthcare settings despite any actual or perceived fitness cost [70].

Several societies, including the Australasian Society for Infectious Disease and the Federation of Infectious Disease Societies of Southern Africa, have released guidelines that include treatment recommendations for *C. auris*[76–78]. The first option for treating *C. auris* infection in adults and children aged >2 months is an echinocandin, which is in accordance with the Infectious Diseases Society of America guidelines for the treatment of

candidiasis[79]. For a central nervous system infection, for infants aged <2 months or when echinocandins are unavailable, amphotericin B is the recommended treatment. Because antifungal resistance is common, susceptibility testing is recommended for all isolates for which treatment is intended. The use of antifungals in patients who are only colonized is not recommended.

Treatment options for pan-antifungal resistant isolates of *C. auris* may soon become available. Two new antifungals in development, ibrexafungerp and manogepix, have shown good in-vitro activity against multi-drug resistant isolates of *C. auris*[80,81]. Ibrexafungerp has an FDA-approved indication for the treatment of vulvovaginal candidiasis, but both ibrexafungerp (ClinicalTrials.gov Identifier: NCT03059992) and manogepix (ClinicalTrials.gov Identifier: NCT05421858) are undergoing clinical trials for the treatment of systemic infections, including the treatment of patients with multi-drug resistant *C. auris*.

Azole-resistant *Aspergillus fumigatus*

Emergence and epidemiology.

Aspergillus fumigatus, a globally distributed mold found throughout the environment, is an important opportunistic pathogen in humans. It is the primary cause of invasive aspergillosis, an infection responsible for substantial morbidity (>14,000 annual U.S. hospitalizations) and mortality (>1,200 annual U.S. deaths) [82–84] and requiring treatment with systemic antifungal medications. Globally, there may be as many as 250,000 cases of invasive aspergillosis and 3 million cases of chronic pulmonary aspergillosis each year [85]. In addition to invasive disease, *A. fumigatus* is also responsible for various clinical syndromes, including chronic pulmonary aspergillosis and allergic bronchopulmonary aspergillosis, especially in patients with cystic fibrosis or asthma, that cause considerable morbidity and frequently require treatment with antifungal therapy [86,87].

Isolates of azole-resistant *A. fumigatus* have been recognized almost since the use of azoles for treatment began a few decades ago, but during the last decade or so resistance has noticeably increased [88–90]. Of public health concern, isolates of *A. fumigatus* are increasingly identified that are resistant to some or all azole antifungals [12,91]. Patients acquire azole-resistant *A. fumigatus* infections through two routes: repeated exposure to azoles for the treatment of chronic *Aspergillus* infections or direct inhalation of resistant *A. fumigatus* spores from the environment [92] (Figure 3). Even though active surveillance for drug-resistant molds is absent or minimal in most countries, researchers have identified azole-resistant *A. fumigatus* across the globe [93,94]. As of this report, 20 countries have reported clinical isolates demonstrating azole resistance, and it has been identified in environmental specimens in an even larger number of countries (Figures 1b and 1c). In Dutch studies focused primarily on patients at high risk, >20% of patients with invasive aspergillosis harbored a triazole-resistant strain, with rates varying based on the population studied [95].

Pathogenicity and clinical manifestation.

Aspergillus is a saprophytic fungus whose spores are found throughout the environment. *A. fumigatus* is the most common *Aspergillus* species encountered by humans. Humans inhale *Aspergillus* spores every day, but because the innate immune system can clear these spores, most immunocompetent persons do not develop illness[96]. However, some immunocompetent hosts, especially those with cavitary lesions of the lung, can develop chronic pulmonary aspergillosis, and other immunocompetent hosts can suffer from allergic bronchopulmonary aspergillosis[97,98]. In immunocompromised patients, *Aspergillus* species can colonize the lungs, potentially leading to the development of invasive pulmonary aspergillosis[97–99]. Invasive aspergillosis is the most common infection among patients who received hematopoietic stem cell transplant and the second most common infection among patients who received solid organ transplant [100–102]. *Aspergillus* species colonization and infection are also associated with other chronic conditions such as cystic fibrosis and chronic granulomatous disease[103], and invasive aspergillosis can develop as a secondary complication in patients recovering from tuberculosis, viral influenza and COVID-19 (Refs. [104,105]). In severely immunocompromised patients, mortality from *A. fumigatus* infection can be 40–50% despite the availability of several treatment options[97,98].

Data to understand the clinical significance of azole-resistant *A. fumigatus* infections have generally come from small case series and several larger cohort studies, primarily from Europe [106]. In one cohort study, patients with azole-resistant invasive aspergillosis had a 90-day mortality rate approximately 25% higher than those with azole-susceptible infections [107]. That study also found a higher 42-day mortality among patients with voriconazole-resistant aspergillosis who were started on inappropriate antifungal therapy (for example, voriconazole monotherapy) versus patients receiving appropriate therapy [107]. In another study involving patients with hematologic malignancies, the 6-week mortality was 2.7-times higher among patients with azole resistance-associated mutations in the *Cyp51A* gene [108]. These studies point out that two of the outstanding features of infections due to azole-resistant *A. fumigatus* are resistant infections in azole-naïve patients and treatment failure. Azole-resistant infections not only occur in patients with invasive aspergillosis, they also occur in patients with chronic pulmonary aspergillosis.

Resistance mechanisms.

Recent research has linked the use of azole fungicides, which are chemically similar to azole antifungal compounds used in medicine, to the development of azole-resistant infections in patients [109–111]. Azole fungicides are applied in numerous agricultural and non-agricultural settings around the world. Although *A. fumigatus* is not a plant pathogen, it is found throughout the environment, especially associated with plant debris. The use of azole fungicides, such as tebuconazole, propiconazole, epoxiconazole and difenoconazole, can select for *A. fumigatus* strains that are resistant to antifungal drugs used in clinical medicine to treat aspergillosis [92]. *Aspergillus fumigatus* strains that have developed resistance through exposure to azole fungicides in the environment harbor unique mutations in the target gene *CYP51A*, which encodes lanosterol demethylase, an essential enzyme in the ergosterol pathway (Figure 4). The two most widely dispersed *CYP51A* mutations are TR_{34}/L98H (a 34 base-pair tandem repeat in the promoter sequence and a leucine to histidine

mutation at amino acid 98) and TR_{46}/Y121F/T289A (a 46 base-pair tandem repeat in the promoter sequence and mutations at amino acids 121 and 289) [112,113]. These mutations confer resistance to itraconazole and voriconazole, respectively, but isolates carrying these mutations are often, but not always, pan-azole resistant when tested *in vitro*[113–116]. The tandem repeats in the promoter region cause an upregulation of gene transcription while the amino acid mutations decrease the efficacy of the antifungals by altering the target binding site [117]. The TR_{34} and TR_{46} mutations have been shown to be associated with environmental fungicide exposure, with a recent study confirming that *A. fumigatus* strains that became drug resistant in the environment can cause resistant infections in humans [109]. Although these two mutations are predominant, surveillance of *A. fumigatus* isolates collected during environmental sampling indicates that some of the other *CYP51A* mutations that were long thought to be exclusively associated with long-term azole use in patients, such as mutations at M220 and G54, may also be associated with environmental fungicide exposure [118–120]. In addition, the mutations in the *CYP51A* promoter are evolving both through sexual recombination and random mutation [121,122]. How these newer mutations will affect drug resistance and organism fitness remains to be seen.

Azole resistance acquired during long-term treatment is generally associated with either specific amino-acid substitutions in the *CYP51A* gene or mutations in *HMG1*, a hydroxymethylglutaryl-CoA reductase, which is a rate-limiting enzyme in the ergosterol pathway (Figure 4). Approximately 30% of isolates of *A. fumigatus* that exhibit *in vitro* resistance to azoles have no defined mechanism of resistance. Whether these isolates also exhibit *in vivo* resistance in not known. There are no breakpoints for echinocandins and *A. fumigatus*, but increased minimal effective concentration values are rare[123]. The European Commission on Antimicrobial Susceptibility Testing (EUCAST) has developed breakpoints for *A. fumigatus*, and amphotericin B resistance is rare but not unprecedented[124]. Resistance to multiple classes of medical antifungals in *A. fumigatus* is exceedingly rare, but resistance to multiple classes of fungicides has recently been reported in environmental *A. fumigatus* isolates from the United States [111].

Evolution.

Recent use of whole-genome sequencing that compares TR_{34} isolates collected around the globe to azole susceptible *A. fumigatus* isolates indicates that the TR_{34} isolates are tightly clustered in a single clade [109,111,125]. These data suggest that the TR_{34} and TR_{46} mutations arose only once or, at most, a few times and that the global spread is due to one or a limited number of closely related strains and not the repeated de novo generation of this resistance mechanism [125]. Of concern, in the United States, azole fungicide use has drastically increased in recent years (four-fold increase during 2006–2016), and in Europe, azole fungicide use is also increasing [17,126]. As fields are sprayed year after year, continued selection for azole-resistant strains is a concern. Although not specifically a plant pathogen, the association with agriculture is likely to have a role in the global dispersal of these resistant strains, as TR_{34} *A. fumigatus* has been isolated from flower bulbs and other agricultural products destined for global distribution and are likely to be globally dispersed as aerosols as well [127]. The current distribution of these mutations in the environment is not

known because most countries, including much of the Americas, Africa and Asia, do not have robust surveillance mechanisms in place and have simply not looked for it.

The *CYP51A* gene, the target of azole resistance, is highly divergent across individual isolates, with many reported amino acid polymorphisms that have not been linked to azole resistance [88,128]. This pleomorphism, in combination with sexual recombination and selective pressure of environmental fungicides may drive the future selection of other resistance mutations [122,129].

Azoles are currently the only class of antifungal used in both human medicine and as agricultural fungicides. However, this may soon be changing with a new class of antifungal, the orotomides, which act by inhibiting the dihydroorotate dehydrogenase (DHODH) enzyme. A new mold-active DHODH inhibitor, olorofim, is active against azole-resistant *Aspergillus* species and is currently in phase 3 clinical trials. Recently, the fungicide ipflufenoquin, also a DHODH inhibitor, has been approved by the U.S. Environmental Protection Agency (EPA) for agricultural use. A recent study shows that resistance mechanisms between the antifungal and the fungicide are similar and therefore may lead to a similar circumstance of environmentally induced resistance to a medically important antifungal[130].

Treatment options.

Azole antifungal drugs (for example, voriconazole, itraconazole, posaconazole and isavuconazole) are the first-line treatment for invasive aspergillosis and the only orally available therapeutic options. The emergence of azole-resistant *A. fumigatus* could limit the clinical use of these life-saving drugs [87,92]. Data to guide the optimal treatment for patients with azole-resistant aspergillosis are limited, and consensus guidelines do not exist [131]. However, expert opinions on the management of patients with azole-resistant infections have been published and emphasize the importance of choosing initial antifungal therapy based on the prevalence of environmental azole resistance. For example, in areas where azole resistance related to environmental mechanisms is more than 10%, clinicians might reconsider voriconazole monotherapy for primary treatment of invasive aspergillosis, pending the availability of susceptibility testing results. For patients with aspergillosis confirmed to be resistant to azoles, therapy could be adjusted to include a drug to which the *A. fumigatus* is susceptible such as amphotericin B [131].

Three new antifungals, ibrexafungerp, fosmanogepix and olorofim, have shown good in vitro activity against azole-resistant isolates[132–134]. Although these new agents are not yet available, clinical trials are underway. Neither trial specifically includes treatment of resistant isolates, but neither excludes them either. The SCYNERGIA trial is a phase 2 randomized double-blind study of ibrexafungerp in combination with voriconazole for the treatment of invasive pulmonary aspergillosis versus voriconazole alone (ClinicalTrials.gov Identifier: NCT03672292). The OASIS study is a phase 3 randomized blinded study to compare treatment of proven invasive aspergillosis with either olorofim or liposomal amphotericin B (ClinicalTrials.gov Identifier: NCT05101187).

Trichophyton indotineae

Emergence and epidemiology.

Dermatophytosis, also known as ringworm or by the syndromic name tinea, is a contagious superficial infection caused by keratinophilic fungi called dermatophytes [135]. The most common causative organisms are *Trichophyton* spp. A substantial public health burden, dermatophytosis affects an estimated 20–25% of the world's population [136]. Patients may acquire dermatophyte infections from fomites or through direct contact with infected persons or animals. Risk factors include living in humid climates and overcrowded conditions, participating in activities involving skin-to-skin contact (for example, certain sports) and having a weakened immune system [137]. Though generally considered a mild, treatable condition, dermatophytosis can cause stigma, debilitating pruritis, immune reactions, and bacterial superinfections, particularly in immunocompromised patients [138].

Historically, clinicians could successfully treat most patients with dermatophytosis using available antifungal drugs, but dermatophyte resistance to conventional antifungal drugs, including terbinafine and itraconazole, is an emerging public health threat [139]. During the past decade, researchers from India have noted an alarming increase in the incidence of difficult-to-treat dermatophytosis cases [140]. These infections can persist for years, spread easily within households, and cause substantial suffering [139]. Researchers identified *Trichophyton interdigitale*/*Trichophyton mentagrophytes* ITS (internal transcribed spacer) Type VIII as the etiologic agent behind the epidemic of antifungal resistant tinea in India. In 2020, researchers determined that these highly terbinafine-resistant *Trichophyton* strains were different enough from the *T. mentagrophytes*/*T. interdigitale* complex to be a new species, *Trichophyton indotineae* [11]. Several lines of evidence support this separation into distinct species. *Trichophyton indotineae* clusters separately from *T. mentagrophytes sensu stricto* and *T. interdigitale* at several unlinked DNA loci[141]. Also, *T. mentagrophytes* is zoophilic and has a sexual cycle, whereas *T. indotineae* has evolved to be a predominantly clonal anthropophilic fungus[141]. And finally, *T. indotineae* is frequently associated with terbinafine resistance, conferred by mutations in the squalene epoxidase gene [142]. A large study of patients from eight geographically dispersed regions in India found that *T. indotineae* was the dominant causative agent for dermatophytosis in all regions studied, representing an epidemiologic shift in the predominant pathogen causing dermatophytosis from *Trichophyton rubrum* [139].

Even though *T. indotineae* as a recognized species is only a few years old, it has already become a major public health concern. Cases of *T. indotineae* infection have been identified in numerous countries outside of India, including Germany, Belgium, Denmark, France, Greece, Italy, Switzerland, Canada, the United States Australia, United Arab Emirates, Oman, Iran, China and Vietnam [143–157] (Figure 1d). The extent of spread is likely to be underestimated because speciation of dermatophytes and antifungal susceptibility testing are not routinely performed in most countries. Most cases of *T. indotineae* in Europe and North America have been linked to international travel, but because the pathogen can be acquired from contact with infected individuals or fomites, there is the potential for domestic spread.

T. indotineae infections have been identified on dogs in India, which suggests the pathogen could start to spread zoonotically as well[158].

The total burden of *T. indotineae* infections is unknown, as identification of dermatophytes to the species level is not routinely performed. Further, identification of *T. indotineae* is challenging because unequivocal identification can only be performed using DNA sequencing [141]. *T. indotineae* has become widespread; therefore, it is important to recognize the risk of local transmission of *T. indotineae* in non-endemic countries that may give rise to a worsening worldwide epidemic scenario of difficult-to-treat infections.

Pathogenicity and clinical manifestations.

As mentioned previously, various underlying conditions (for example, diabetes mellitus, immune-suppressive conditions, Cushing syndrome, atopic dermatitis and systemic corticosteroid therapy) may increase host susceptibility for dermatophytosis[135]. Dermatophytes possess virulence factors that facilitate infection in patients, regardless of host immune status, but immunocompromising conditions may lead to more severe infection. For example, the dermatophytic fungi produce several enzymes, including proteases, lipases, elastases, collagenases, phosphatases and esterases, that have been implicated in host invasion and assimilation of nutrition[159]. The dermatophytic hyphae invades the uppermost, non-living, keratinized layer of the skin, namely the stratum corneum, produce exo-enzyme keratinase, and induce inflammatory reaction at the site of infection. Although studies pertaining to *T. indotineae*-specific immune responses are lacking, the cell-mediated immune response is responsible for the control of dermatophytosis[160].

Typical manifestations of *T. indotineae* include extensive chronic relapsing infection of the body (tinea corporis) and the groin (tinea cruris). Clinical presentation commonly involves multiple lesions in different anatomical locations exhibiting varying degrees of inflammation with peripherally spreading, flat, whitish or brownish pigmentation. One of the hallmarks of infection by *T. indotineae* is the severity of infection compared with those caused by the closely related species *T. mentagrophytes* and *T. interdigitale*. Many infections with *T. indotineae* are highly inflammatory, cover much or all the lower body and groin, and can extend to the extremities and head. Because of the inflammatory nature of the lesions, they are often associated with painful burning and itching and can cause substantial morbidity[161]. It has been speculated that a large proportion of the most severe cases present with steroid-modified dermatophytosis after having used combination creams with steroids[161,162].

Inappropriate use of antifungal drugs, particularly the use of over-the-counter antifungal creams containing high potency steroid clobetasol is likely to have been and is likely to continue to be a driver of dermatophyte resistance and selection in India[162]. These creams are widely available without a prescription in India and are frequently used by patients to self-treat skin conditions[162]. Creams with antifungal medications are available in other countries to treat both dermatophyte infections as well as mucocutaneous candidiasis. These creams do not contain steroids and there is no indication that these creams have led to an increase in antifungal resistant organisms. Although corticosteroids like clobetasol may temporarily relieve symptoms of dermatophytosis, these medications do not treat the

underlying infection and the steroid-associated immunosuppression may ultimately worsen the dermatophytosis[163].

Evolution.

Internal transcribed spacer sequencing, multilocus sequence typing and whole-genome sequencing clearly delineate *T. indotineae* from the *T. mentagrophytes*/*T. interdigitale* complex[11,141,164]. Multilocus sequence data from *T. mentagrophytes* species complex isolates from humans and animals shows that *T. indotineae* has evolved to be distinct from *T. mentagrophytes*, with every genotype unique only to the new species. Although the genomes are clearly different across species, *T. indotineae* is still so young as a clonal species that the overall structural architecture of its genomes is quite similar to the parental species *T. mentagrophytes*. A full analysis of the differences between *T. indotineae* and the *T. mentagrophytes*/*interdigitale* complex has not yet been performed. *Trichophyton indotineae* may still be in the early stages of separation as a species from *T. mentagrophytes*. As it moves across the world reproducing as an anthropophilic rather than a zoonotic fungus, its genome may undergo more changes that cannot be repaired in a predominantly clonal population, and this may further separate it from *T. mentagrophytes*[141]. Although the literature on this new fungus dates from only the past few years, it may have arrived in Europe as early as 2011, and a search of Genbank for sequences corresponding to *T. mentagrophytes* type VIII (the previous designation) indicates it was in Indian, Oman, Iran and Australia by 2013 and possibly as early as 2004 (Refs. [144,145]).

Resistance mechanisms.

Terbinafine is a first-line drug for treatment of dermatophytosis. High terbinafine resistance rates, reaching 80% in at least one study, were one of the first indicators that *T. indotineae* strains from India were different from the usual *T. mentagrophytes/interdigitale* complex [165,166]. More alarming, *T. indotineae* isolates resistant to itraconazole have also been identified, including isolates that are resistant to both itraconazole and terbinafine[167–169].

The mechanisms of resistance to both terbinafine and itraconazole have been determined. Terbinafine-resistant *T. indotineae* isolates exhibit single point mutations in the target gene squalene epoxidase (also known as squalene monooxygenase and designated either as *SQLE* or *ERG1*; which is a key enzyme in the ergosterol biosynthetic pathway), which lead to single amino-acid substitutions, Leu393Phe, Phe397Leu, or Phe415Val[169] (Figure 5). In addition, azole resistance is frequently identified in *T. indotineae*. With the emphasis on terbinafine resistance, few studies have been performed to determine the mechanism of azole resistance[144,167,168]. However, one study identified tandem repeats of the lanosterol demethylase gene *CYP51B*, another study identified specific point mutations associated with resistance, and an early study found a point mutation in SQLE that caused itraconazole resistance while the same isolate was susceptible to terbinafine[144,167,168] Interestingly, neither study identified mutations in the primary lanosterol demethylase *CYP51A*.

Treatment options.

There are no guidelines specifically for the treatment of *Trichophyton* infections, but a frequent and effective choice is terbinafine[170]. However, given the proportion of *T.*

indotineae isolates that are resistant to terbinafine and the general lack of availability of susceptibility testing of dermatophytes, other treatment options require consideration. In one randomized control trial of dermatophyte infection, itraconazole had a higher success rate than terbinafine[171]. There are reports of successful treatment of *T. indotineae* specifically using other topical antifungals such as ciclopirox olamine, bifonazole and miconazole, but these case reports are anecdotal[147]. Topical voriconazole has also been used successfully for treatment of terbinafine-resistant *T. indotineae*, and the newer topical azole antifungal luliconazole exhibits high in vitro activity against *T. indotineae* and could be considered as a treatment option[172,173].

Several public health actions might help prevent further spread of *T. indotineae*. Such actions include increasing laboratory capacity to detect and monitor the spread of resistance, redoubling antifungal stewardship efforts with an emphasis on appropriate diagnostic testing and proper antifungal utilization, and performing further research to quantify the overall burden of disease and identify potential drivers of infection. In addition, guidelines for therapy, partially based on new animal models for infection are warranted.

Summary and outlook

This Review highlights three antifungal-resistant fungi that have recently emerged and are spreading across the globe, posing an ongoing threat to public health. *C. auris* is acquired and spread almost exclusively though the healthcare community. Medical tourism, global migration and the international transfer of patients has promoted the spread of *C. auris* to six continents in a little over a decade. *T. indotineae* is carried on the skin by otherwise healthy individuals and is spread within families and across communities, a situation that is likely to be exacerbated by the overuse and misuse of over-the-counter medications. The spread of azole-resistant *A. fumigatus* is driven by the use of fungicides in agricultural and other settings and is likely facilitated by the international trade in agricultural products[127].

Although each pathogen emerged differently and affects distinct populations, the three fungi share the common thread of antifungal resistance, the potential to become a worsening public health threat, and the likelihood of spreading further through international travel and trade. However, despite the need, fungal disease surveillance is still rare in most countries, and antifungal susceptibility testing is still the exception rather than the norm in most clinical laboratories across the globe, even in resource-rich countries. Because *C. auris* is transferred from person to person within healthcare settings, rigorous infection control practices, screening and surveillance are essential for stopping or slowing the spread. Likewise, robust surveillance for azole-resistant *A. fumigtus* and *T. indotineae* infections is critical to monitor the spread of these pathogens and inform public health actions and policy.

Although this Review focused on three specific examples of fungi that are both spreading globally and carry antifungal resistance, other resistant fungi are quickly becoming a global concern. *C. glabrata* has long had the highest proportion of multidrug-resistant isolates, but fortunately, it does not seem to be spreading and outbreaks of multidrug-resistant isolates have been rare[174]. However, aside from *C. auris*, we may be seeing the emergence of other antifungal resistant *Candida* species. Azole-resistant *C. parapsilosis* has recently caused

outbreaks in several different countries including South Africa, Turkey, Mexico, Brazil and Spain, and we are starting to see a similar emergence of azole-resistant *C. tropicalis* in Asia and South America [175–181]. Similar to what has been seen with *T. indotineae*, reports of terbinafine- and azole-resistant *T. rubrum* have been increasing [143,182,183]. Although species and dissemination may vary, antifungal resistance is a recurring theme. The World Health Organization (WHO) has recently released the WHO fungal priority pathogens list. Two of the fungi in this Review, *C. auris* and *A. fumigatus*, are in the critical group primarily because the WHO recognized that resistance poses such a high public health risk[184]. A cross-sector emphasis on antifungal and fungicide stewardship is urgently needed to protect human health in addition to preventing the emergence of fungicide-resistant plant pathogens[185]. Multiple barriers exist to antifungal stewardship programs. The first is a paucity of effective fungal expertise and fungal diagnostics. Most fungal infections are treated empirically until diagnosis is confirmed, which can take up to a few weeks, if this occurs at all. The second barrier is the lack of availability on a global scale of rapid susceptibility testing. Susceptibility testing can facilitate step-down of therapy to generic or more easily tolerated antifungals. The third barrier is the that only three antifungal classes are currently approved for the treatment of systemic fungal infections. With the availability of three new classes of antifungals in the foreseeable future, the development of antifungal susceptibility testing capacity and effective stewardship programs are of paramount importance. Preventing the emergence of resistant human-pathogenic fungi hinges on the improvement of clinical and environmental fungal surveillance, increasing clinical capacity for fungal speciation and antifungal susceptibility testing, and encouraging policies that improve antifungal stewardship in both the clinical and agricultural realm.

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Box 1

Antifungal resistance.

Two categories of antifungal resistance exist: intrinsic and acquired resistance. Intrinsic resistance means that the wild type of a fungal species naturally exhibits resistance to antifungal compounds. By contrast, acquired resistance means that a fungal species is normally susceptible to antifungal compounds, but certain isolates have acquired mutations or epigenetic changes that confer resistance [186]. In general, when researchers and clinicians discuss antifungal resistance, they are referring to acquired resistance.

Intrinsic antifungal resistance is a common phenomenon. For example, Basidiomycetes, Mucormycetes, and *Fusarium* species all exhibit resistance to echinocandins, a class of antifungal drugs that targets one of the proteins responsible for synthesis of β-1,3 glucan in fungal cell walls [187,188]. Because β-1,3 glucan constitutes only a minor component of Basidiomycete, Mucormycete, and *Fusarium* species, these fungi are intrinsically resistant to this drug class. Another example is the intrinsic resistance of *Candida krusei* to fluconazole, an antifungal drug that targets the enzyme lanosterol deacetylase, a protein in the ergosterol synthesis pathway. Fluconazole is ineffective against *C. krusei* because this *Candida* species has an amino acid polymorphism in its lanosterol deacetylase that prevents fluconazole from binding to the protein and inhibiting ergosterol synthesis [189,190].

Acquired resistance is uncommon in fungi. For *Candida* species, among those with established breakpoints, the overall resistance rate to antifungals is 7% (Ref. [191]). Acquired resistance in molds is thought to be even less common, but because antifungal resistance testing of molds is infrequently performed, the true extent of acquired resistance in molds is unknown.

Fungi acquire antifungal resistance through numerous mechanisms. The most common forms of acquired resistance involve mutations to target protein binding-sites, which prevent the antifungal from binding [192]. This mechanism is common among azole-resistant strains of *Candida* species such as *C. albicans*, *C. tropicalis* and *C. parapsilosis*, as well as in azole-resistant *Aspergillus* species [192]. Certain yeast species acquire resistance through mutations in transcription factors that lead to increased expression of the antifungal drug's target, diluting the antifungal's effect. In *C. glabrata*, the most common mechanism of fluconazole resistance involves mutations in transcription factors which lead to increased expression of efflux pumps that remove the antifungal from the cytoplasm before it can bind the target protein [193]. Overexpression of the target protein through polyploidy and chromosomal duplication is another way that fungi overexpress target proteins and dilute the effect of antifungals [194,195]. Although the mechanisms have not been well studied, some fungi may acquire resistance to azoles and amphotericin B by changing the composition of the fungal cell wall or cell membrane, thus compensating for the loss of the product of the target protein [192].

Fungal cells have evolved over hundreds of millions of years to become as efficient as possible. Mutation or overexpression of housekeeping genes can lead to a fitness cost for the cells. With the advent of RNAseq and whole-genome sequencing, data

increasingly suggest that most cells that acquire antifungal resistance undergo multiple other compensatory changes [196]. Some of these changes are epigenetic changes in expression; others are mutations in other proteins. These secondary mutations are generally compensatory, and their role is most likely to alleviate fitness costs that may be associated with the acquired resistance [197–200].

The emergence of antifungal resistance has been a concern for clinicians, as the armamentarium for treating invasive fungal infections is essentially limited to three drug classes: azoles, echinocandins, and polyenes. For invasive mold infections, treatment options are further limited to certain azoles and the polyenes. When a mold becomes azole resistant, the choices remaining are to use combination treatment with an echinocandin or a less effective antifungal like terbinafine, or to use the polyene amphotericin B [131]. Although amphotericin B has excellent efficacy against most fungal infections, it can cause severe side effects.

Figure 1 a.

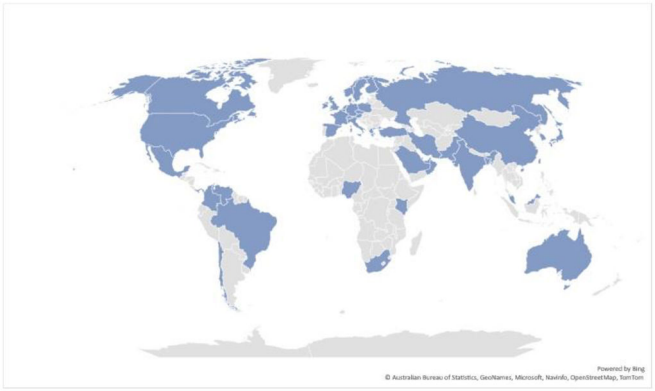

Figure 1b.

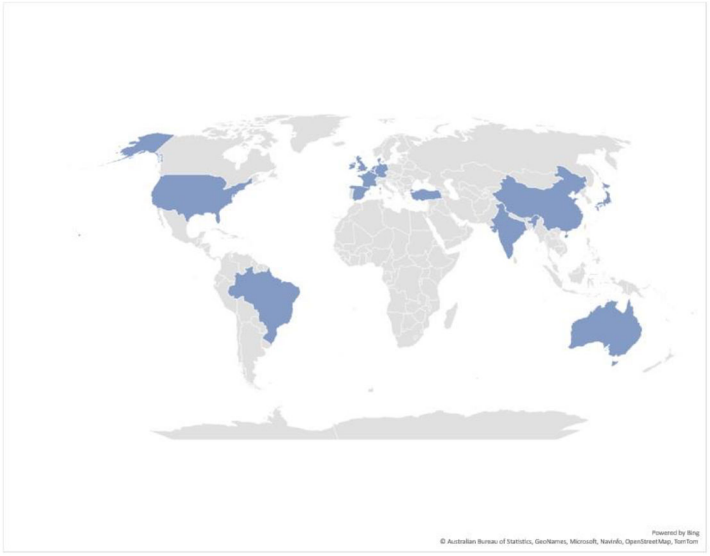

Figure 1c.

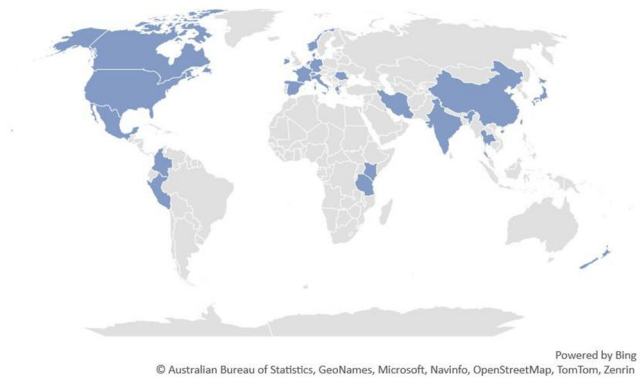

Figure 1d

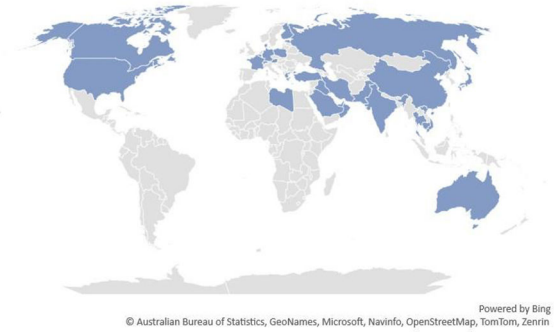

Figure 1. Global disbursement of the three emerging fungi *Candida auris*, azole-resistant *Aspergillus fumigatus* and *Trichophyton indotineae*.

The presence of any of the organisms in a country does not mean they are ubiquitous there, and in some cases may be represented by a single isolate. a). Map of countries that have reported cases of *Candida auris*. b). Map of countries that have reported azole-resistant *Aspergillus fumigatus* containing the TR_{34}/L98H or TR_{46}/Y121F/T289A mutation in patients. c) Map of countries that have reported azole-resistant *A. fumigatus* containing the TR_{34}/L98H or TR_{46}/Y121F/T289A mutation in the environment. D) Map of countries where *Trichophyton indotineae* has been identified from patients or the country where the infection was most likely acquired.

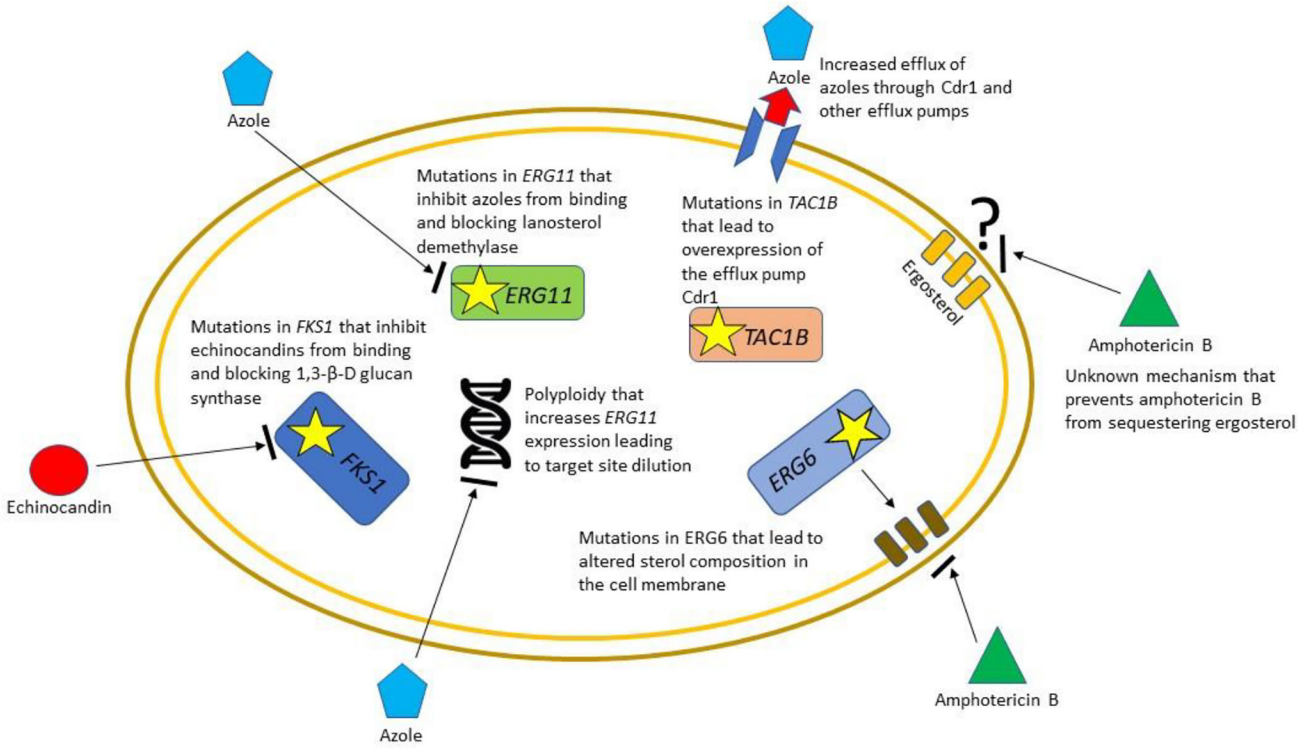

Figure 2.

The more common mechanisms of acquired antifungal resistance of *Candida auris*. One of the most remarkable aspects of *C. auris* is the number of different mechanisms of acquired antifungal resistance that have been identified. For the azoles, especially fluconazole, these include mutations in the target enzyme lanosterol demethylase (*ERG11*), mutations in transcription factors such as *TAC1B* that lead to the over-expression of efflux pumps, and changes in ploidy that lead to overexpression of *ERG11* and target site dilution. For the echinocandins, the predominant mechanism of resistance is a change in the amino acid sequence at the target site hotspot in Fks1p the mechanism that is conserved across *Candida* species. For amphotericin B, a specific amino acid change in Ergp6 that alters membrane sterol composition has been identified, but other, as yet unidentified, mechanism that prevent ergosterol sequestration have been identified phenotypically but not molecularly.

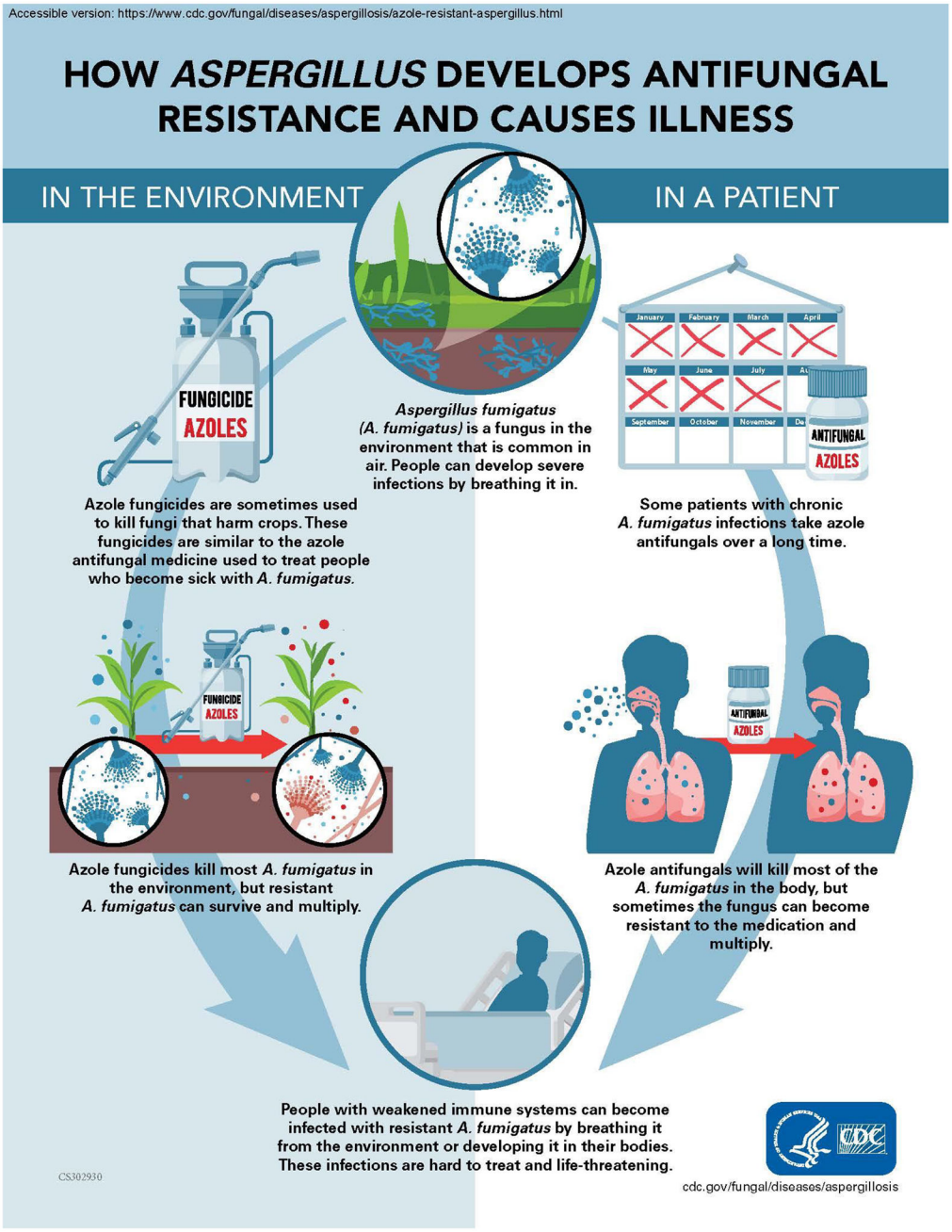

Figure 3.

Diagram of possible routes of acquisition of antifungal resistant *Aspergillus fumigatus*.

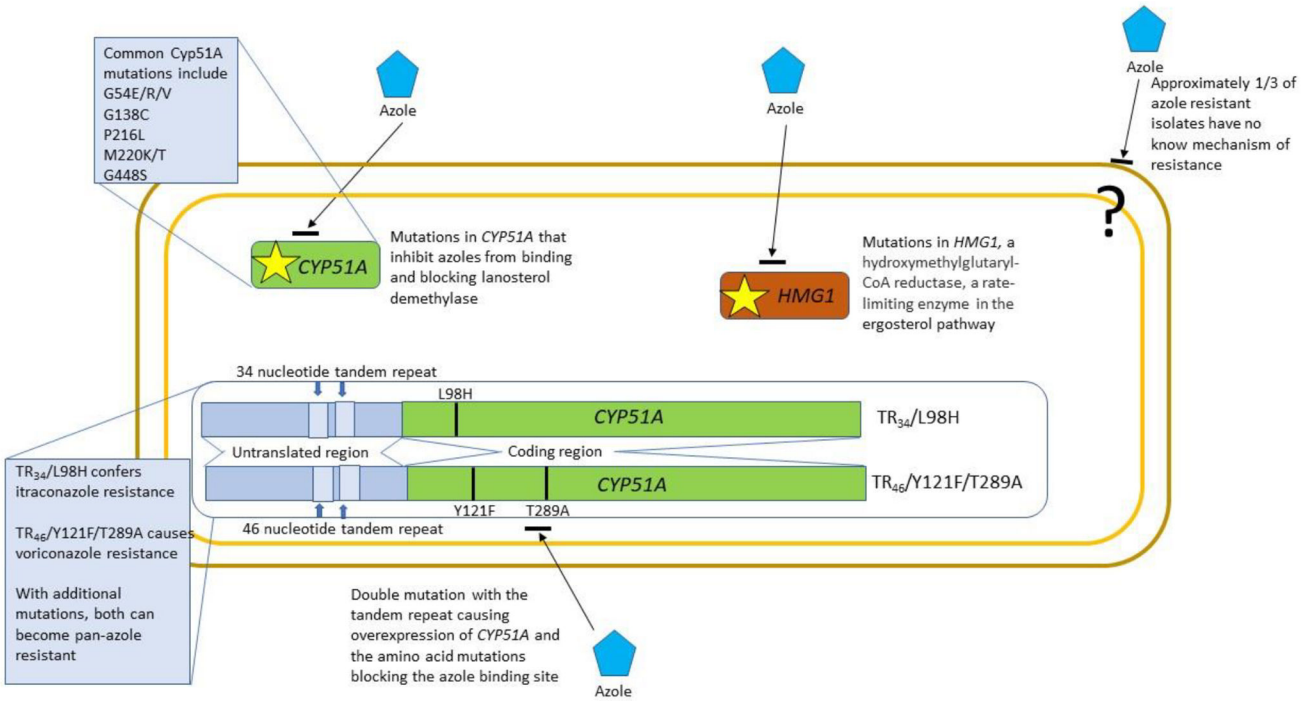

Figure 4.

Mechanisms of acquired resistance of azole-resistant *Aspergillus fumigatus*. Azole resistance in *A. fumigatus* appeared almost as soon as azoles became available. Approximately 30% of isolates have no identified mechanism of resistance, but the other 70% have changes either in the azole target enzyme lanosterol demethylase (*CYP51A*), or in *HMG1*, the gene encoding hydroxymethylglutaryl-CoA reductase, a rate-limiting enzyme in the ergosterol pathway. Some target site mutations, such as those at amino acids G54, G138, P216, M220 and G448, are associated predominantly with acquired resistance following long-term azole treatment. There is a unique set of targets, TR_{34}/L98H (TR_{34}) and TR_{46}/Y121F/T289A (TR_{46}) that are specifically associated with environmental acquisition of resistance due to exposure to agricultural fungicides. These mutations consist of both a duplication in the 5' untranslated region that causes increased transcription and a single or double amino acid change in the target binding site. The TR_{34} mutation leads to pan-azole resistance while the TR_{46} mutation is specific for voriconazole resistance.

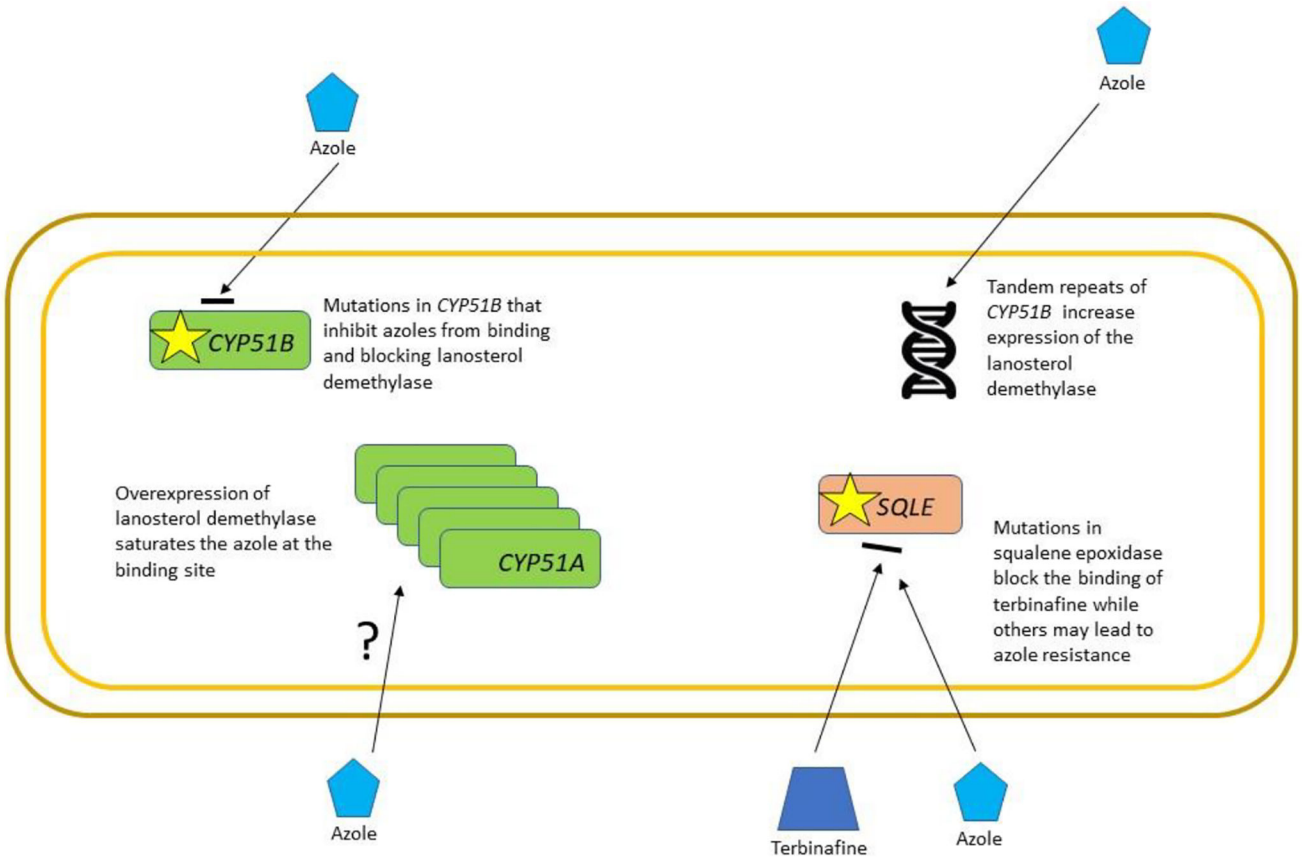

Figure 5.

Mechanisms of acquired resistance of *Trichophyton indotineae*. *T. indotineae* is a newly emerging species so our current knowledge of the mechanisms of resistance is limited. Resistance to terbinafine is caused by specific mutations in the target enzyme, squalene epoxidase, which may also lead to azole resistance as it is a component of the ergosterol pathway. Azole resistance has been linked to changes in the target enzyme lanosterol demethylase (*CYP51B*) either through amino acid mutation, changes in ploidy, or mutations in transcription factors that result in overexpression.

Table 1

Features of *Candida auris*, azole-resistant *Aspergillus fumigatus* and *Trichophyton indotineae*.

Feature	***Candida auris***	**Azole-resistant *Aspergillus fumigatus***	***Trichophyton indotineae***
Antifungal resistance	Nearly all isolates are fluconazole resistant; amphotericin B, echinocandin and flucytosine resistance has been recorded	TR_{34} – itraconazole; TR_{46} – voriconazole; through additional mechanisms, some isolates may become pan-azole resistant	Frequently resistant to terbinafine, sometimes resistant to azole antifungals (for example, itraconazole)
Country or region where first cases have been identified	East Asia, Indian subcontinent, South Africa and Venezuela	Europe	Southern and Southeast Asia
Current treatment options	For azole- and amphotericin B resistant isolates the treatment of choice is an echinocandin; for pan-resistant isolates there are ongoing clinical trials for new the antifungals ibrexafungerp and fosmanogepix	Amphotericin B; there are ongoing clinical trials for the new antifungals ibrexafungerp and olorofim	Terbinafine remains a treatment option, but for resistant isolates itraconazole or other triazoles are an option
Current distribution	Worldwide distribution, predominantly from the clades that originate from the Indian subcontinent, South Africa and Venezuela	Predominant in Europe but has been identified in Africa, North America, South America, Asia and Australia	Predominantly in India; cases have been reported throughout Asia, Europe, Africa, and North America; cases in Europe have generally been associated with travel or migration
Clinical presentation	Can be present as both a skin or urinary tract commensal with no symptoms or a pathogen in the bloodstream with typical symptoms of candidemia	Typical presentation for aspergillosis but may be refractory to initial therapy	Inflammatory dermatophyte infection, most commonly affecting the face and body, occasionally affecting nails