Received: 14 February 2021 | Accepted: 22 June 2021

DOI: 10.1111/ppa.13429

Plant Pathology WILEY

REVIEW ARTICLE

Crossover between the control of fungal pathogens in medicine and the wider environment, and the threat of antifungal resistance

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Abstract

Fungal propagules existing in the natural environment can easily be transmitted to the human body, mostly by inhalation of contaminated air or direct contact onto the skin, nails, and mucosa. Fungal infections in humans are, as compared to viral and bacterial infections, rarely serious (life-threatening) unless the immune system is weakened. Because azole fungicides (demethylation inhibitors, DMIs) are among the most important antifungal compounds used broadly in human and animal medicine as well as in agriculture and material protection, fungal propagules may come into contact with azoles almost everywhere, presenting a potential "crossover-use-pattern" and "cross-contamination-risk" for resistant propagules in all areas. A "hot-spot" in terms of the emergence of azole resistance in a fungal species is defined as a habitat in which the species is actively propagating and exposed to a fungicidally effective azole at available concentrations high enough to select for resistant individuals, potentially multiplying and spreading to other habitats. Intrinsic antifungal resistance may exist in less sensitive or insensitive species independent of previous exposure to antifungal compounds, whereas acquired antifungal resistance can evolve if triggered by the exposure of an originally sensitive species (or population) to agricultural or medical antifungal agents, resulting in the selection of resistant individuals. The origin and risks of these developments in medical settings and the wider environment are elucidated for the most relevant life-threatening fungal human pathogens, including several species of *Cryptococcus*, *Candida*, *Pneumocystis*, *Aspergillus*, *Histoplasma*, *Coccidioides*, *Rhizopus*, *Mucor*, *Fusarium*, and *Scedosporium*.

KEYWORDS
antifungal resistance, azole fungicides, fungal human pathogens, fungal plant pathogens, high risk pathogens, resistance hot spot

1 | INTRODUCTION

A primary human pathogen is an agent (fungus, bacterium, virus) causing any kind of disease in humans, either superficially or within the body (invasive, systemic). All fungal propagules (all kind of cells, spores) existing in the natural environment can be transmitted to the human body. Fungal infections usually start in the lung by inhalation of contaminated air, or on the skin, nails, and mucosa (vagina, mouth, sinuses) by direct contact (e.g., through wounds), and rarely also in the gastrointestinal tract by intake of contaminated food or water. Fungal infections in humans are rarely serious (life-threatening) unless the patient's immune system is weakened, for example, by other diseases such as HIV-AIDS, cancer, leukaemia, immunosuppressive drugs (after transplantations), chemotherapy, malnutrition, or aging. Many fungal human pathogens cause disease by taking advantage of an "opportunity not normally available" such as breached protective barriers, altered commensal microbiota, or a weakened immune system (immunocompromised patients) and are then called opportunistic pathogens (c.300 different fungal species). Examples of opportunistic fungal diseases are cryptococcal meningitis, invasive aspergillosis, and oesophageal candidiasis. Besides being airborne (as spores or cells on particles in aerosol originating from plants, animals, soil, compost), the origin of fungal propagules can be foodborne (from fruits, leaves, vegetables), waterborne (in contaminated fresh or drainage water), soilborne (soil particles on food or in air), fomite/equipment-borne (from catheters, lab coats, clothing, shoes, towels, bathroom floor), and vector-borne (diverse animals, e.g., insects as carriers, transmission to humans by contact or wounds). However, within a certain fungal genus, individual species or even ecotypes have evolved often preferring either natural environmental niches or clinical habitats (e.g., within *Candida* and *Fusarium* spp.). Because host and niche specificity can be very high, this review will consider the most relevant fungal human pathogens (Pfaller & Diekema, 2004) down to the species level including 13 yeast species, 6 dimorphic species, and 18 filamentous (mould) species (Table 1).

The term "yeast" describes a typical growth pattern (by budding) of a fungal species rather than the systematic position within the kingdom of fungi. There are yeasts in all classes of fungi, that is, in Zygomycota, Ascomycota, and Basidiomycota (not in Oomycota, which are anyway not part of the fungal kingdom). Dimorphic fungi can grow either as filamentous (mycelial/mould-like) or as yeast-like forms, depending primarily on environmental conditions. They live in mycelial form mostly saprophytically on/in dead organic substrates in the wider environment and on the human body, whereas in yeast form preferentially as human pathogens (or as commensals) on/in the human body.

Globally, about 5 million people suffer from invasive and chronic fungal infections every year, and about 1.6 million patients die (Bongomin et al., 2017). The most prevalent systemic, invasive, life-threatening fungal human infections are caused, in decreasing order of importance, by cryptococcosis (mainly *Cryptococcus*

TABLE 1 Most relevant human pathogenic fungal species considered

Yeasts	Dimorphic fungi	Filamentous fungi (moulds)
Ascomycota	Ascomycota	Ascomycota
Candida albicans	*Histoplasma capsulatum*	*Aspergillus fumigatus*
Candida glabrata	*Blastomyces dermatitidis*	*Aspergillus flavus*
Candida parapsilosis	*Paracoccidioides brasiliensis*	*Aspergillus parasiticus*
Candida tropicalis	*Coccidioides immitis*	*Aspergillus terreus*
Candida krusei	*Sporothrix schenckii*	*Aspergillus niger*
Candida guilliermondii	*Penicillium marneffei*	*Fusarium solani* (FSSC)
Candida auris		*Fusarium oxysporum* (FOSC)
Pneumocystis jirovecii		*Fusarium fujikuroi* (FFSC)
Basidiomycota		*Fusarium verticillioides*
Cryptococcus neoformans		*Scedosporium apiospermum*
Cryptococcus gattii		*Scedosporium boydii*
Trichosporon mucoides		*Scedosporium prolificans* (=*S. inflatum*)
Trichosporon asahii		*Alternaria alternata*
Rhodotorula mucilaginosa		*Paecilomyces lilacinus*
		Zygomycota
		Rhizopus oryzae (=*R. arrhizus*)
		Mucor circinelloides
		Cunninghamella bertholletiae
		Absidia (*Lichtheimia*) *corymbifera*

Note: Many more but clinically less relevant species are mentioned in the text.

TABLE 2 Yearly incidence of systemic life-threatening invasive fungal infections in humans

Fungal disease	Estimated cases per year	Estimated mortality (% of infected)[a]	Geographic origin	Saprophytic habitat[b]
Cryptococcosis (yeast)	>1,000,000	20–70	World	Environment
Candidiasis (yeast)	>400,000	10–75	World	Body
Pneumocystis pneumonia (yeast)	>400,000	20–80	World	Body
Aspergillosis (mould)	>200,000	30–95	World	Environment
Histoplasmosis (dimorph)	c.25,000	28–50	USA/Latin America	Environment
Coccidioidomycosis (dimorph)	c.20,000	1–70	USA	Environment
Mucormycosis (mould)	>11,000	30–90	World	Environment
Penicilliosis (dimorph/mould)	>8,000	2–75	South-East Asia	Environment
Paracoccidioidomycosis (dimorph)	c.4,000	5–27	Latin America	Environment
Blastomycosis (dimorph)	c.3,000	2–68	USA	Environment

Note: Data according to Pianalto and Alspaugh (2016).

[a]Depending on host immune competence and geographic region.

[b]Environment: for example, soil, compost, dust, plants; body: on/in body as inherent part of human microflora; the term "environment" describes the habitat of the (mostly saprotrophic) fungus in natural ecosystems outside hospital settings.

neoformans), candidiasis (several *Candida* spp.), pneumocystis pneumonia and aspergillosis (mainly *Aspergillus fumigatus*) (Table 2) with an estimated total number of 2 million cases per year (Pianalto & Alspaugh, 2016). Much less relevant (mostly below 20,000 cases per year) are histoplasmosis, coccidioidomycosis, mucormycosis, penicilliosis, paracoccidioidomycosis, and blastomycosis (Table 2), with varying numbers of cases depending primarily on geographic regions and climatic conditions. Except for candidiasis and pneumocystis that are caused by inherent members of the human microflora, all other diseases have their origin in fungi from the natural ecosystem (environment). In patients (mainly transplant recipients) suffering from systemic invasive fungal infections (IFI) caused by moulds, the vast majority (over 90%) were affected by aspergillosis (mostly *A. fumigatus*), and only about 10% by other moulds causing mucormycosis (in about 60% of cases, mainly *Rhizopus* and *Mucor* spp.), fusariosis (20% of cases), and scedosporiosis (20%, mainly *Scedosporium apiospermum*) (Park et al., 2011). All of these mostly life-threatening diseases have to be treated with antifungal compounds either prophylactically or during therapy, sometimes over several months.

2 | ANTIFUNGAL COMPOUNDS FOR THE CONTROL OF FUNGAL PATHOGENS IN MEDICINE

Several classes of antifungal compounds (also known as antifungals or fungicides) have been available for many years (as reviewed by Imhof et al., 2005; Pianalto & Alspaugh, 2016; Zhang et al., 2019). The oldest class are the polyenes, having been introduced in 1958 and in a new formulation again in 1995, interacting with ergosterol in the fungal cell membranes. The major compound is amphotericin B (AMB); nystatin and pimaricin are related compounds, all of which have a broad spectrum of antifungal activity and are used exclusively in medicine. In a few cases, resistant isolates have been detected in certain *Candida* and *Aspergillus* spp. carrying mutations in the *erg3* and other genes (Fan et al., 2020; Young et al., 2003). In addition, *A. terreus* seems to be intrinsically insensitive (Blum et al., 2008). In 1960, a single compound, 5-flu[oro]cytosine (5-FC) from the pyrimidine class of antifungals was introduced, inhibiting the thymidylate synthase in DNA and RNA synthesis. Its spectrum of activity is quite narrow, with a strong effect against cryptococcal meningitis and *Candida* septicaemia and endocarditis, mostly in combination with polyenes. There is no use of 5-FC in agriculture. The same is true for the allylamines, available since 1991, with the two compounds, terbinafine and naftifine; they inhibit squalene mono-oxygenase in the sterol biosynthesis of fungal cell membranes (FRAC mode of action group 18, G4; Kuck et al., 2012) and are used mainly against dermatophytes on skin, hair, and nails. Also, the echinocandins, including compounds such as caspofungin (CSP), micafungin, and anidulafungin, are used exclusively in medicine; they were introduced in 2001. The compounds inhibit 1-3-β-D-glucan synthase in cell wall biosynthesis and are especially effective as first-line therapy against candidiasis and aspergillosis. In *Candida glabrata*, resistant isolates were detected carrying several mutations in two hotspot regions of the *FKS1* or *FKS2* genes (Pham et al., 2014).

By far the most important class of antifungal compounds are the azoles or DMIs (demethylation inhibitors) affecting lanosterol C14-α-demethylase in ergosterol biosynthesis being catalysed by cytochrome P450 and controlled by the *cyp51/erg11* gene. In the medical sector (human and veterinary), over 30 compounds have been introduced continuously over the last 40 years (e.g., fluconazole [FCZ] in 1981) including more than 20 imidazoles and 10 triazoles, the most recent representatives being also useful for systemic treatments: itraconazole (ITZ), voriconazole (VCZ), posaconazole (PCZ), and isavuconazole (ISA) (Gisi, 2014). Parallel to the use in medicine, even more azoles (mainly

triazoles, FRAC mode of action group 3, G1) have been introduced in the agricultural sector (Kuck et al., 2012), although differences in the chemical structures of the compounds used in the two sectors are quite obvious, except for the common azole moiety being responsible for binding to the target enzyme CYP51. Based on the identical biochemical mode of action—although certain molecules show some variation in binding characteristics—all azoles express general cross-resistance for the majority of isolates within a sensitive fungal species (Gisi, 2014). This behaviour was initially of no concern between medical and agricultural applications, especially because resistance evolution was rather slow in most pathogen species (several years) and different compounds were used against different pathogen species expressing different sensitivity levels.

One exception is quite striking: an identical compound was introduced in the 1980s in both sectors, in agriculture under the name imazalil and in veterinary (and human) medicine as enilconazole (Gisi, 2014). In agriculture, imazalil was registered mainly for postharvest treatments against *Gloeosporium* and *Phomopsis* spp. in fruits and against *Penicillium* spp. in citrus, for seed, flower bulb, and tuber treatments against *Fusarium*, *Phoma*, and *Helminthosporium* spp., and against powdery mildew in vegetables. In veterinary (and human) medicine, enilconazole was recommended for topical treatments against ringworm diseases caused by several dermatophytes such as *Trichophyton*, *Epidermophyton*, and *Microsporum* spp. in horses, dogs, and cats (and humans) and in different application forms (spray, smoke pellets) in chicken hatcheries and poultry farming against *A. fumigatus* and *C. neoformans*. In the natural environment, *A. fumigatus* lives as a saprophytic fungus on/in organic material (e.g., compost, soil), and is not a plant pathogen. However, in medicine, it is an important, life-threatening human pathogen causing invasive aspergillosis in immunocompromised patients; the disease is controlled mostly by systemic azoles. It cannot be excluded that *A. fumigatus* also comes in direct contact with azoles during the control of plant pathogens in certain agronomic situations, either unintentionally as a kind of collateral effect, or via residues in treated plant material, representing a potential crossover for resistance selection and cross-contamination with resistant spores in agriculture and medicine (human and veterinary). In fact, Snelders et al. (2009) and Verweij et al. (2011) claimed this hypothesis mainly because they also discovered azole-resistant *A. fumigatus* isolates in azole-naive patients. Therefore, it is very important to identify the origin and selection mechanisms for azole-resistant isolates in *A. fumigatus* (Gisi, 2014). It is a major goal of this review to evaluate the resistance risk, including all relevant fungal human pathogens (Table 1), in medical and environmental settings.

The most recent class of antifungals for medical use are the orotomides, discovered in 2015 with the experimental compound Olorofim (Van Daele et al., 2019). They inhibit dihydro-orotate dehydrogenase (DHODH) in pyrimidine biosynthesis and are especially active against the most relevant human fungal infections caused by *A. fumigatus* and *A. flavus*, *Scedosporium prolificans*, and several *Fusarium* and *Penicillium* spp. (Lackner et al., 2018; Rivero-Menendez et al., 2019).

3 | RESISTANCE: DEFINITIONS, MECHANISMS, AND EMERGENCE

Antifungal resistance (also known as "fungicide resistance"), as defined in agriculture by FRAC (www.frac.info), refers to "an acquired, heritable reduction in sensitivity of an intrinsically sensitive fungus species to a specific antifungal agent". Resistant isolates within a fungus species generally evolve in natural populations through random mutations prior to the exposure to the specific antifungal agent. The change in sensitivity over time and space is driven by the selection process being applied on populations by the specific antifungal agent (www.frac.info). In medicine, resistance also includes intrinsically resistant (insensitive) fungal species (isolates) (e.g., *Candida krusei* against FCZ) even if related, more active drugs with the same mode of action (e.g., PCZ) may control the same species/isolates. In such a case, resistance cannot be (pre-)selected by prior exposure to another, chemically related compound, for example, in agriculture. Scientifically appropriate alternative terms for intrinsic resistance would be innate immunity, innate resistance (as in molecular plant pathology), or tolerance. For the sake of uniformity, definition of resistance in this review will differentiate as much as possible between the two basic mechanisms: intrinsic antifungal resistance may exist in less sensitive or insensitive species independent of previous exposure to antifungal compounds, whereas acquired antifungal resistance can emerge when an originally sensitive species (population of isolates) is exposed to agricultural or medical antifungal agents, producing a selection of resistant individuals. However, the two types of resistance cannot always be separated entirely from each other.

Because azole fungicides are broadly used in human and animal medicine as well as in agriculture and material protection, fungal propagules can come into contact with azoles almost everywhere. A "hot spot" in terms of the emergence of azole resistance in a fungal species is defined as a habitat in which the species is actively propagating and exposed to a fungicidally effective azole at available concentrations high enough to select for resistant individuals potentially multiplying and spreading to other habitats. Hot spots have to be identified by assessing the resistance risk case by case, that is, for each pathogen species in a defined habitat in a certain geographic area (Gisi, 2020).

Some yeast species are intrinsically resistant to a single drug (e.g., *C. krusei* to FCZ), while others show intrinsic or acquired resistance to several drugs within the same class of antifungals (e.g., azoles, cross-resistance) or within different classes, for example, *Candida auris* with many isolates being simultaneously resistant to azoles, polyenes, and echinocandins (Chowdhary et al., 2018), called multi[drug]-resistance (MDR; Gisi, 2014). Also among filamentous human pathogenic fungi, some species (e.g., *Scedosporium*, *Fusarium*) are multiresistant to azoles, polyenes (AMB), and echinocandins (CSP) (Al-Hatmi et al., 2019). The latter two compounds are used exclusively in medicine and are not available for agricultural uses or material protection. Therefore, if resistance to one of these two compounds is detected in a fungal species, it must originate from medical, not agricultural

treatments. In addition, AMB- and CSP-resistance might serve as a molecular marker for resistance to azoles having evolved in parallel from medical treatments, especially in multidrug-resistant individuals. Vice versa, simultaneous resistance to azole and QoI fungicides (quinone outside respiration inhibitors), for example, in *A. fumigatus* isolates (Fraaije et al., 2020) may indicate that such isolates were exposed at some point to the two classes of antifungals in the environment (agriculture, material protection). It is debatable whether sequential selection is also possible (e.g., first by azoles in hospitals followed by QoIs outside hospitals or entirely in agriculture).

It was suggested that the exposure of fungal cells to sublethal concentrations of azoles in laboratory experiments may result in the evolution of resistant (adapted) individuals. This effect was described for *Candida parapsilosis* and *C. neoformans* exposed to the agricultural fungicide tebuconazole and the medical drug FCZ, respectively (Bastos et al., 2018; Brilhante et al., 2019). The results demonstrate that agricultural and medical azoles have the same biochemical mode of action causing cross-resistance and that it does not matter which azole initially triggered resistance. However, they should not be (mis-)used to predict resistance development in populations under natural conditions, at least not as long as the relevant mutations have not been detected. Artificially adapted or mutated isolates are often less competitive in natural populations.

For azoles, there are four major molecular resistance mechanisms (multiallelic, polygenic): (a) decreased binding of azoles to the target enzyme CYP51 (cytochrome P450-regulated lanosterol C14-α-demethylase) due to amino acid changes as a result of single nucleotide polymorphisms (SNPs) in the *cyp51* (*erg11*) coding sequence (target site mutations). In the plant-pathogenic fungus *Mycosphaerella graminicola*, for example, several SNPs in *cyp51B* are known to code for resistance to agricultural azoles, mainly V136A, Y137F, A379G, I381V, and S524T (Fraaije et al., 2007), whereas in human pathogens, several SNPs/alterations such as TR_{34}/L98H, TR_{46}/Y121F+T289A and M220I/V/K/T in *cyp51A* of *A. fumigatus* (Howard et al., 2009), G129A, Y132H/F, and N136Y in *erg11* of *C. albicans* (Flowers et al., 2015; Morio et al., 2010), and K143R, F145L, S405F, D446E, G448E, F449V, G450E, G464S, R467K, and I471T in other *Candida* spp. (Alvarez-Rueda et al., 2016) are associated with resistance to medical azoles. Using the proposed CYP51B archetype protein from *Zymoseptoria tritici* for amino acid numbering (Mair et al., 2016), Y137F corresponds to Y121F in *A. fumigatus* and to Y132F (ERG11) in *C. albicans* (11 amino acids difference between the latter two). The emergence of new tandem repeats (TR) in the promoter region of *cyp51A* in *A. fumigatus* was also induced by azole exposure (Zhang et al., 2020). (b) Increased expression of *cyp51* (*erg11*) by gene amplification (e.g., duplication and multiple paralogs) as well as alterations in the regulatory region (promoter inserts) resulting in increased production of target enzyme and thus lower activity of azoles. (c) Increased expression of multidrug efflux (transporter) genes (ATP binding cassette, *ABC* genes) including *MDR1*, *CDR1*, and *CDR2* (multidrug and *Candida* drug resistance) genes resulting in an increased activity of specific membrane efflux pumps removing antifungal compounds from fungal cells and thus lower fungicide concentrations at the target site, as reported for many *Candida* spp. (Whaley et al., 2016). (d) Additional resistance mechanisms involving the accumulation of ergosterol precursors (Hagiwara et al., 2018) and reduced intracellular retention of azoles (Wei et al., 2017). All mechanisms may be combined in antifungal resistance within one fungal species.

4 | ORIGIN AND RELEVANCE OF FUNGAL PATHOGENS

4.1 | Ascomycete yeasts: *Candida*

In nature, yeasts grow saprophytically on many types of surfaces like leaves and fruits (e.g., apple, grape, citrus), grasses, wood, on litter, and in soil. Some yeasts also colonize human and animal outer and inner surfaces either as saprophytes or as pathogens and belong to the intrinsic microflora. There are over 200 *Candida* species existing in nature, but only a few live in humans. Especially frequent in natural environments are the ascomycete yeasts *C. stellata*, which can be used, in addition to the major fermenting yeast *Saccharomyces cerevisiae*, in vinification (Csoma & Sipiczki, 2008), as well as *C. lambica*, *C. albidus*, *C. famata*, and many others. Much less relevant in the natural environment are the potentially human-pathogenic *C. krusei*, *C. tropicalis*, *C. glabrata* (= *Torulopsis glabrata*), and *C. guilliermondii*. A common inhabitant of the phyllosphere and on litter is *Aureobasidium pullulans* ("black yeast"), whereas *Metschnikowia* (= *Candida*) *pulcherrima* and *M. fructicola* are frequent on fruits and often used as biocontrol agents in postharvest disease control. High abundances in nature are also reported for *Kloeckera apiculata* and several *Cyberlindnera* spp. (Deak & Beuchat, 1993; Müller et al., 2007; Uhitil et al., 2009; Vadkertiová et al., 2017). Although clinically relevant *Candida* yeasts can occur in the natural environment, their abundance and competitiveness are far lower there than on human surfaces. Candidiases in humans and animals have been treated with azoles since the early 1980s and resistant isolates have been detected since 1984 in several *Candida* spp. worldwide (Espinel-Ingroff et al., 2014). Therefore, the selection of isolates with intrinsic or acquired azole resistance is primarily a result of medical rather than agricultural applications; few exceptions might exist (e.g., yeasts on azole treated fruits, see below).

Candida albicans, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* are together responsible for up to 90% of all cases of candidiases in humans worldwide, with a rough share of >60%, >20%, <10%, <10% respectively, depending on region and growth conditions. *Candida* spp. do not produce spores nor do they release big quantities of propagules into the air (as do moulds). They are transmitted mostly during people-to-people contacts (e.g., on hands, lab coats) and are an inherent part of the human (and animal) microflora, but they also colonize physical surfaces and medical devices in hospital settings (Anonymous, 2019). *C. albicans* is by far the most relevant

opportunistic yeast worldwide living either on human surfaces (skin, throat, oral and vaginal mucosa) or in the gastrointestinal tract as commensalistic organism of healthy adults. Although *C. albicans* can survive outside the human body, no report has been found describing significant abundance in the natural environment. *C. glabrata* (earlier *Torulopsis glabrata*) is a primarily nonpathogenic yeast growing on human skin and mucosa, but can also be pathogenic in certain gulls (Al-Yasiri et al., 2016) and many other birds, as well as in cows. It especially affects immunocompromised patients, causing infections of the urogenital tract and bloodstream, mainly in western countries; it recently became more important as a human pathogen and is often declared as multidrug-resistant (Chapeland-Leclerc et al., 2010; Cho et al., 2015). It can occasionally be isolated from soil and fruits.

C. parapsilosis is an emerging pathogen causing hospital-acquired *Candida* infections in humans, predominantly in southern Europe, South America, and Asia. It is part of the commensal microflora in humans but also in domestic animals and insects. It is especially frequent on physical surfaces in hospital settings and on medical devices. In the home environment, it can be isolated from kitchen and household surfaces, for example, of dishwashers and refrigerators, rubber seals, and drainage channels. Tap water can act as a vector for dissemination. *C. parapsilosis* can occasionally be isolated from soil. *C. tropicalis* causes serious systemic candidiasis, especially in Asia and in tropical climates. It is a very versatile yeast living on human skin and mucosa, as well as in the gastrointestinal tract of mammals. It can be isolated from soil, animal faeces, water, fish, wild birds, specific food such as fermented cabbage (sauerkraut), molasses, jam, kefir, yoghurt, and some fruits. *C. tropicalis* is considered as an osmotolerant yeast, able to survive high salt and sugar concentrations (Anonymous, 2019). It was also isolated occasionally from the rhizosphere of rice, providing root-promoting activity (Amprayn et al., 2012). In contrast to other opportunistic *Candida* spp., *C. krusei* can be isolated quite frequently from plant material (e.g., grapes; Müller et al., 2007). Because crop plants might have been treated with agricultural azoles (e.g., penconazole, tebuconazole), selection of resistant isolates cannot be excluded in certain agricultural areas. However, most clinical isolates are intrinsically resistant (not sensitive) to FCZ and only moderately sensitive to ITC, VCZ, and PCZ and therefore difficult to control. Intrinsic sensitivity to agricultural azoles is probably rather low. It seems to be accepted by medical experts that azole resistance in *C. krusei* is either intrinsic or acquired through medical treatments.

C. guilliermondii can cause candidiasis, especially onychomycosis on nails and, rarely, invasive infections in humans. It is the sixth important candidiasis in ranking: about 0.5% (USA) to 1% (Europe) to 4% (Latin America) of detected clinical isolates were assigned to *C. guilliermondii* (Anonymous, 2020). About 5%–10% of isolates were reported to be resistant to FCZ and VCZ (Pfaller et al., 2006). Infections are mostly based on poor hygiene and people-to-people transmission. It can also rarely be isolated from nature (e.g., grapes; Uhitil et al., 2009). *C. auris* grows specifically on/in human ear and skin, on physical devices, and hospital equipment. It is hard to control, because many isolates are resistant to several antifungal classes (AMB, azoles, CSP; Chowdhary et al., 2018). The species has been found incidentally as a bloodstream isolate for the first time in 1996 in South Korea (Lee et al., 2011) and was described as a new species in 2009 in Japan (Anonymous, 2018; Satoh et al., 2009;). Reports about an occurrence in the natural environment were not found.

4.2 | Basidiomycete yeasts

There are over 30 *Cryptococcus* species worldwide (basidiomycete teleomorph *Filobasidiella*) of which only four have clinical relevance, mainly *C. neoformans* and *C. gattii*, but also *C. albidus* and *C. laurentii*, causing human and animal cryptococcosis. As for all *Cryptococcus* species, *C. neoformans* and *C. gattii* live in soil, especially when contaminated with droppings of wildlife and domestic birds (e.g., pigeons, chicken), in bird nests, and in decaying wood, trunk hollows, fissures, and bark of several tree species (e.g., *C. gattii* in *Eucalyptus* trees). *C. neoformans* can be found globally, occasionally also on plant material (vegetables, fruits like apples and grapes, fruit juice), whereas *C. gattii* lives mainly in tropical and subtropical regions. In addition to human cryptococcosis, *C. neoformans* can cause disease in many animals including cats, dogs, dolphins, sheep, and several types of birds (e.g., avian cryptococcosis in poultry farming). It is probably disseminated in the environment by birds following their migratory routes. Birds can carry *Cryptococcus* propagules in their body without being diseased. Human infections are probably acquired by inhalation of dust particles contaminated with bird faeces, dehydrated yeast cells, or basidiospores. Most people probably breathe in small amounts of airborne propagules every day without getting diseased. The fungus can survive in the human body for years before disease breaks out. The infection cannot spread from person to person. Cryptococcosis remains the most important life-threatening fungal disease, causing hundreds of thousands of deaths per year globally (Table 1).

Interactions with soil microorganisms (e.g., amoebae, nematodes) and vertebrates probably play a crucial role in *Cryptococcus* to maintain its virulence potential for humans. There are several serotypes within the *C. neoformans/gattii* species complex: *C. neoformans* type A (var. *grubii*) is distributed worldwide (>80% of clinical isolates), with three molecular types (VNI, VNII, VNB); *C. neoformans* type D (var. *neoformans*) is rare, distributed mainly in Europe with one molecular type (VNIV); *C. neoformans* type AD hybrid is also rare, with one molecular type (VNIII); *C. gattii* types B and C are found in tropical and subtropical regions including Australia and South-east Asia. Although the different *Cryptococcus* types may have a preference for certain ecological niches (e.g., type A mainly for pigeon droppings, type B for *Eucalyptus* trees), the genetic flexibility and hybridization potential is high. *C. neoformans* var. *neoformans* was isolated in Mexico from seven out of 74 bird droppings, from 15 out of 169 fruit samples (particularly grapefruits), and 20 out of 468 vegetable samples (López-Martínez & Castañón-Olivares, 1995). It was also isolated from vegetables and fruits in India (in three out of

437 samples; Misra & Randhawa, 2000). It is not clear whether the few reports describing *C. neoformans* on vegetables, fruits, and in fruit juice (Uhitil et al., 2009) reflect occasional contaminations with particles from bird droppings (and soil) containing fungal propagules, rather than true habitats of the fungus on plants.

Additional basidiomycete yeasts have their origins in the natural environment: *Rhodotorula minuta* (= *Cystobasidium minutum*), *R. rubra*, and the occasionally human-pathogenic *R. mucilaginosa*, as well as *Trichosporon* (= *Apiotrichum*, *Cutaneotrichosporon*) *cutaneum* and the potentially human-pathogenic *T. asahii* and *T. mucoides* (Vadkertiová et al., 2017). Many *Trichosporon* spp. colonize human (and animal) skin and hair, but can frequently also be isolated from soil and water. Of the roughly 40 species, eight are known as human pathogens, especially in immunocompromised individuals and cancer patients, with *T. asahii* (formerly *T. beigelii*) and *T. mucoides* accounting for the majority of deep-seated and disseminated trichosporonosis (Anonymous, 2019). *T. asahii* has only low sensitivity to antifungals; many isolates are multidrug-resistant, especially when the fungus originates from biofilms (e.g., on catheters). *Rhodotorula* yeasts are increasingly recognized as human pathogens. *R. mucilaginosa* was the species most frequently recovered (75%), followed by *R. glutinis* (6%). However, their significance in human medicine is low, whereas it is high in the natural environment (Anonymous, 2019). *R. rubra* is a major saprophytic yeast in the phyllosphere and in soil.

4.3 | Filamentous human pathogens

Unlike yeasts, most filamentous fungi produce abundant numbers of spores that are released into the environment. Depending on the area, season, and climate, spore concentrations in the air vary from 10 to over 2,000 cfu/m^3, with typical mean values outdoors of several hundreds (Gabrio, 2010; Schmidt, 2012; Shelton et al., 2002); in hospital air, spore concentrations can be 40–70 cfu/m^3 (Anaissie et al., 2002). Especially frequent in air samples are several species of *Aspergillus* (c.30%), *Penicillium* and *Paecilomyces* (c.15%), and *Cladosporium* (c.15%). *Fusarium*, *Bipolaris*, *Alternaria*, *Epicoccum*, and *Acremonium* spp. (each a few %) and a few yeasts (e.g., *Aureobasidium*, *Rhodotorula* spp.) are also often detected, whereas other relevant fungal human pathogens like Mucorales, *Scedosporium*, *Cryptococcus*, *Histoplasma*, and *Coccidioides* are mostly absent (Anaissie et al., 2002; Shelton et al., 2002). Among *Aspergillus* spp., *A. versicolor* is by far the most abundant species in air samples (up to 50% of species), followed by *A. fumigatus* and *A. niger* (each c.15%), *A. flavus* (c.10%), *A. terreus*, and *A. nidulans* (each a few %) (Gabrio, 2010; Guinea et al., 2006; Shelton et al., 2002). Fungal spores get into the body by accidental inhalation and may cause infections, depending on the host immune system.

A. fumigatus (teleomorph *Neosartorya* sp.) is a global, widespread saprotrophic thermophilic fungus typically found in soil and decaying organic matter, where it plays an essential role in the carbon and nitrogen cycles. It is not a plant pathogen, but an opportunistic pathogen in animal and human tissue causing respiratory allergies and life-threatening invasive aspergillosis, especially in immunocompromised patients (Table 2). The abundance of *A. fumigatus* in commercial growing substrates and composts from European countries was generally rather high (10^3–10^5 cfu/g), whereas in soil from meadows, agricultural land, and forests it was below 10^3 cfu/g (Franceschini et al., 2016; Santoro et al., 2017). Corn plant material conserved anaerobically in silage for 5 months in Italy contained very low *A. fumigatus* concentrations (below 10^2 cfu/g), whereas 1–2 weeks after silo opening, the concentration increased drastically to 10^5–10^8 cfu/g (Spadaro et al., 2019). In the majority of samples collected from corn silage and compost made of oranges, both mating types were present, with mat-2 being more frequent than mat-1 (Pugliese et al., 2018; Spadaro et al., 2019). According to simple sequence repeats (SSR, microsatellite molecular markers) analysis, a high genetic diversity was detected in compost populations (Santoro et al., 2017) suggesting frequent sexual and/or parasexual processes. This was confirmed experimentally in compost by Zhang et al. (2017).

A. flavus (teleomorph *Petromyces flavus*) and *A. parasiticus* (formerly *A. flavus* f. sp. *parasiticus*, teleomorph *Petromyces parasiticus*) are worldwide saprophytes in soil, forage, food, organic debris, and wood (as *A. fumigatus*) but are also potent plant pathogens (different from *A. fumigatus*), mainly on oilseed rape, peanuts, maize and cotton seeds, and tree nuts, causing important pre- and postharvest diseases. In addition, both species can cause invasive aspergillosis (second after *A. fumigatus*, in <15% of cases) in immunocompromised humans and also in animals (e.g., birds) especially in semi-arid and tropical climates in the Middle East, African countries, and India (*A. fumigatus* mostly in temperate climates) (Rudramurthy et al., 2019). Conidia of *A. flavus* can be as frequent in air as *A. fumigatus*, but invasive aspergillosis is mainly caused by *A. fumigatus* (in >80% of cases). Mycelial growth optimum is 36 °C for *A. flavus* and 42 °C for *A. fumigatus*. *A. flavus* produces a range of mycotoxins (aflatoxins) in plants and humans, which are highly carcinogenic. Important plant diseases caused by *A. flavus* are ear, kernel, and storage rot of maize, rice storage rot, peanut kernel and storage rot, and cotton boll rot. Infected maize (corn) cob leftovers after harvest are a source for new infections of maize and cotton the following year. *A. flavus* is frequently found on tree nuts (almonds, pistachios, walnuts) mostly as superficial contaminations, often causing significant aflatoxin residues. Amongst many other pathogens, cotton boll rot caused by *A. flavus* is especially frequent when cotton is attacked by pink bollworm and other insects. In peanuts, *A. flavus* is an important soilborne and postharvest pathogen (Amaike & Keller, 2011) causing seed rot, reducing seed viability and germination (Kumar et al., 2008). Pre- and postharvest aflatoxin contamination in peanuts is a serious threat for food safety and human health.

A. terreus grows as a saprophytic fungus in soil and degrading plant material; it can also grow on food stuff and is not pathogenic to plants. It causes different types of human diseases ranging from allergic bronchopulmonary to invasive aspergillosis (third after *A. fumigatus* and *A. flavus*, <10% of cases); it can also attack skin and nails. Besides excreting harmful secondary metabolites (patulin, citrinin, gliotoxin), it also produces important anticancer polyketides

(lovastatin), organic acids (itaconic acid), and cyclosporines. *A. niger* is a ubiquitous saprophytic fungus primarily living in soil, but also on diverse food stuff, fruits, nuts, and vegetables. It plays an important role in biotechnology for the production of compounds like citric, oxalic, and Koji acids, and pectinase. It is present on human surfaces and can occasionally cause invasive aspergillosis in immunocompromised patients. *A. versicolor* is very frequent in natural environments on different organic substrates; it often releases a high number of spores in air but is clinically not relevant.

Within the genus *Fusarium*, there are many important plant pathogens with broad host specificity and strong saprophytic properties. However, in medicine it is only rarely a serious human and animal pathogen. The genus is systematically very diverse with many species complexes (SC), and it is often not clear how broad/narrow the specificity is for infections in plants, humans, and animals, and if cross-infections are common or rare (Table 3). Human fusariosis (superficial or deep) are caused mainly by the *Fusarium solani* species complex (FSSC, teleomorph *Neocosmospora* spp.) (>60% of cases), the *F. oxysporum* species complex (FOSC, <20% of cases), the *F. dimerum* species complex (FDSC, <10% of cases), and the *F. fujikuroi* species complex (FFSC, <10% of cases, including *F. verticillioides* and *F. proliferatum*) (Al-Hatmi et al., 2016; Al-Maqtoofi & Thornton, 2016; Kischkel et al., 2020; Short et al., 2011). Among the over 40 phylogenetically distinct FSSC (Zhang et al. 2006), there are mainly four clinically important *Neocosmospora* taxa, *N. petroliphila*, *N. keratoplastica*, *N. falciformis*, and *N. metavorans*, causing different forms of superficial infections (e.g., keratitis and eye infections) but occasionally also invasive fusariosis (Table 3) (Sandoval-Denis & Crous, 2018). Major plant pathogens are *N. petroliphila* (FSSC-1, on cucurbits), *N. solani* sensu stricto (FSSC-5, on potato), *N. vasinfecta* (FSSC-8, on cotton), *N. solani* f. sp. *pisi* (FSSC-11, on *Pisum* and *Glycine*), and *N. croci* and *N. macrospora* (on potato and *Citrus sinensis*). Also within FOSC, FFSC, and FDSC, there are important plant pathogens, for example, *F. oxysporum* f. sp. *cubense* causing Fusarium wilt of banana (Panama disease), *F. fujikuroi*, *F. verticillioides*, *F. proliferatum* causing leaf spots on rice (bakanae diseases) and several seedling damping-off diseases. However, these species are not relevant in human medicine.

The genus *Scedosporium* (teleomorph *Pseudallescheria*, syn. *Lomentospora*) comprises several saprophytic spp. that are distributed globally in natural and polluted soils, sewage, manure-enriched environments, and polluted water "especially at sites of high human population density and tourist popularity" (Luplertlop et al., 2019). Several species are also present in hydrocarbon-contaminated soils; being able to degrade aromatic compounds, they have been suggested for use in bioremediation. Their abundance in soil was highest in industrial areas and was quite low in agricultural land (25 cfu/g) (Kaltseis et al., 2009), which is about 100-fold less frequent than *A. fumigatus* at comparable sites (Santoro et al., 2017). There is obviously an ecological species specificity: *S. boydii* is relatively frequent in clinical settings, *S. dehoogii* in the natural environment, whereas *S. apiospermum* was found about equally frequent

TABLE 3 Relevant *Neocosmospora* taxa within the *Fusarium solani* species complex (FSSC) as pathogens in humans, animals, plants, and as saprophytes in the environment

Neocosmospora taxa	FSSC type	In humans	In animals[a]	In plants[a]	In environment
N. petroliphila (= *F. petroliphilum*)	1	Keratitis, nails, skin, nasal mucosa	Fish	Main PP, fruit rot of cucurbits	In plumbing systems in buildings
N. keratoplastica (= *F. keratoplasticum* = *Cephalosporium keratoplasticum* = *Cylindrocarpon vaginae*)	2	Keratitis, corneal infections, nails, skin	Main AP, fish, shrimps, lobster, and others	Occasionally on plants	In hospital water systems and internal pipelines, soil fungus
N. falciformis (= *F. falciforme* = *Cephalosporium falciforme*)	3 + 4	Keratitis	General AP	Pistachio crown rot and stem canker	Soil fungus
N. (= *F.*) *solani* (sensu stricto)	5	Human eye		Main PP on potato	Soil fungus
N. metavorans	6	Main clinical fusariosis, superficial and deep infections		Rarely on plants	
N. gamsii	7	Human eye, bronchia			Humidifier filters
N. vasinfecta	8	Invasive fusariosis		Cotton pathogen	Soil fungus in tropical area
N. tonkinensis	9	Human eye	AP, birds	PP on wild banana[b]	
N. lichenicola (and 9 synonyms)	16	Keratitis, invasive fusariosis		Rare PP on *Camellia*, fruit rot of pomelos	
N. suttoniana	20	Human eye, skin			

Note: Information according to Sandoval-Denis and Crous (2018).

[a]AP: animal pathogen; PP: plant pathogen (most relevant species in bold).

[b]Not to be confused with the much more important soilborne *F. oxysporum* f. sp. *cubense*, causing Panama disease (Fusarium wilt on banana).

in both habitats (Kaltseis et al., 2009). *Scedosporium* spp. can enter the human body either by inhalation of spores or through subcutaneous lesions causing disseminated infections, especially in immunocompromised patients. The most relevant species causing human and animal diseases are *S. apiospermum*, *S. boydii*, and *S. prolificans* (syn. *S. inflatum*); the first two are molecular siblings but morphologically identical (together c.70% of scedosporiosis cases) and clearly differentiated from the third species (c.30% of cases). Very high haplotype diversity was observed among *S. apiospermum* isolates from soil (Luplertlop et al., 2019). It is not known whether the risk for human infections is the same for all types of isolates.

Within the Mucorales, the most relevant species as an opportunistic human pathogen is *Rhizopus oryzae* (syn. *R. arrhizus*) occasionally causing cutaneous and deep mucormycosis. It grows as a saprophytic filamentous fungus in dung, rotting vegetation, and soil across the entire world. The soil habitats are quite diverse, ranging from grassland and cultivated soils under crops like lupin, maize, wheat, peanuts, sugar cane, rice, and citrus plantations to salt-marshes, farm manure, and sewage-containing soils. *R. oryzae* is used commercially in the food and pharmaceutical industries for the production of enzymes such as glucoamylases and lipases, organic acids, ethanol, and fermented food stuff. It is a frequent contaminant of kernels (peanuts, beans, cowpeas, pecans, hazelnuts, pistachios, wheat, barley, sorghum, maize), potato tubers, and various tropical fruits. *Mucor circinelloides* is a saprophytic soil and dung-inhabiting fungus found across the entire world. It can spoil various food like cheese, jam, meat, hazelnuts, walnuts, maize, beans, and soybeans. It occasionally causes human infections and quite frequently affects animals such as cattle, pigs, and fowls. *Cunninghamella bertholletiae* is found primarily in soil, fruits, vegetables, nuts, and waste in Mediterranean and subtropical climates. Although infections are rare, *C. bertholletiae* is an emerging opportunistic human pathogen. It is often highly invasive and more difficult to control with antifungals than other species of the Mucorales. Additional members of the Mucorales are less relevant as pathogens in medicine.

4.4 | Dimorphic human pathogens

In the ascomycete family Ajellomycetaceae, there are three closely related, clinically important genera that live as saprophytic filamentous fungi in soil and as human-pathogenic yeasts primarily in the lungs of patients: *Histoplasma*, *Blastomyces*, and *Paracoccidioides*. The dimorphic fungus *Histoplasma capsulatum* (teleomorph *Ajellomyces capsulatus*) causes histoplasmosis especially in South, Central, and North America, Indonesia, and some African countries, whereas it is rare in Western Europe. The fungus is strongly associated with droppings of certain birds and bats, for example, around chicken houses, in bat caves, attics, and hollow trees, and easily proliferates in soil contaminated with bird faeces. Histoplasmosis outbreaks are typically associated with the inhalation of wind-blown spores and contaminated dust during clearance of guano accumulations and guano-covered vegetation and constructions. The fungus can stay in latent yeast form in the epithelial lung tissue for a long time, causing disease only when the patient's immune system becomes weakened. *Blastomyces dermatitidis* (teleomorph *Ajellomyces dermatitidis*) is a dimorphic fungus living in soil and wet, decaying wood and leaves, often close to rivers. It is one of the most ecologically mysterious fungi, with very poor understanding of where and how it grows in nature; it has been isolated from the environment only rarely (Anonymous, 2019). The fungus is endemic to parts of eastern North America, and it also occurs in some African countries, the Arabian Peninsula, and in India. Fungal spores can reach the human body by inhalation; in the lung the fungus then grows as yeast causing blastomycosis (in humans and animals) with symptoms similar to influenza, and also penetrates other parts of the body.

Although the habitat of *Paracoccidioides brasiliensis* remains unclear, it is often isolated from soils of coffee plantations. However, it has rarely been encountered outside the human host. Paracoccidioidomycosis is geographically restricted to Latin America, mainly Brazil, Colombia, and Venezuela. It invades the nose and sinuses, progressing then to the lung, lymphoid tissue, gastrointestinal tract, bones, and prostate. *Coccidioides immitis* (within Onygenaceae, neighbour family of Ajellomycetaceae) is a saprophytic dimorphic fungus in dry, alkaline, sandy soils in desert regions of south-western United States, Central and South America. *C. immitis* (and less frequently *C. posadasii*) causes pulmonary coccidioidomycosis in the lung, commonly called valley fever. After inhalation of airborne spores, the infection spreads from the lung to other parts of the body through transport of yeast cells in the bloodstream. It can affect many organs, particularly the liver, brain, bones, meninges, and heart.

Two other dimorphic human pathogens can create serious problems in certain regions. *Penicillium* (teleomorph *Talaromyces*) *marneffei* is the only human-pathogenic species within the genus causing life-threatening systemic infections (talaromycosis) with similar symptoms as cryptococcosis in people with a weakened immune system (especially in HIV patients). The disease is endemic to Southeast Asia and the fourth most common disease there (after tuberculosis, cryptococcosis, and aspergillosis). The fungus has been found in bamboo rats (and their burrows), suggesting that these animals serve as a reservoir for the fungus (Anonymous, 2019). The transfer of the fungus from rats or soil to humans is still unclear. *Sporothrix schenckii* is present worldwide (mainly in subtropical regions, rarely in Europe) in soil and decomposing material such as peat, but also on living plants (e.g., roses). It infects both humans and animals (cats, dogs, horses, cattle, monkeys, rats) causing sporotrichosis, and can switch from animals to humans and vice versa; however, it is rarely life-threatening. The most common route of infection is the introduction of spores through a cut or puncture wound in the skin (e.g., through rose thorns, cat bites, or scratches).

5 | COMBINED RELEVANCE OF YEASTS, FILAMENTOUS, AND DIMORPHIC FUNGI IN MEDICINE AND THE WIDER ENVIRONMENT

The relevance of the mentioned yeasts, filamentous fungi, and dimorphic fungi in medicine was validated against their relevance in the natural environment using a scale from 1 (very low) to 5 (very high) in a combined matrix (Figure 1). Relevance in this context describes the occurrence and severity of pathogens causing

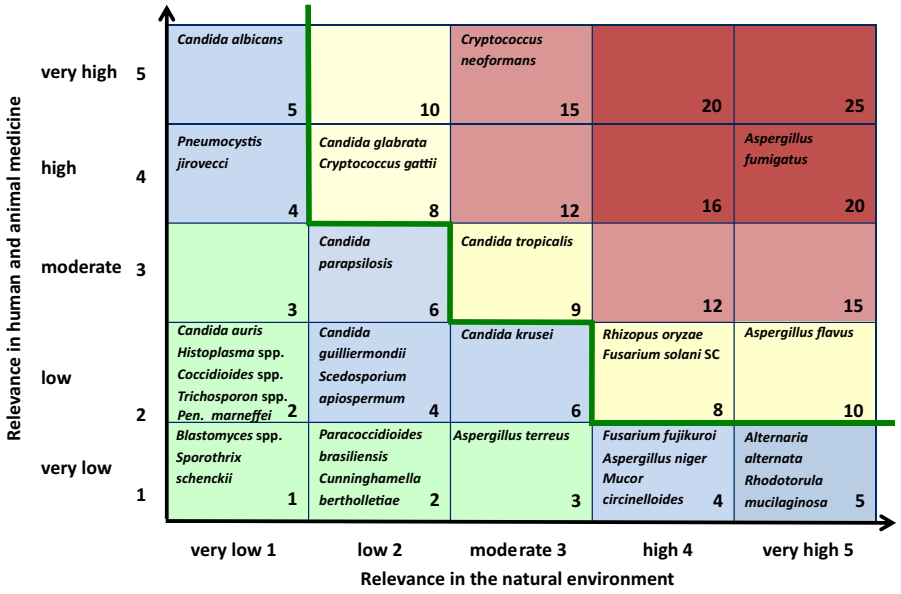

FIGURE 1 Combined relevance of important yeasts, filamentous fungi, and dimorphic fungi in medicine (as human and animal pathogens) and in the natural environment (as saprophytes)

life-threatening diseases in humans and animals and the abundance and growth of the same species as saprophytes in the environment producing propagules (e.g., spores, infested particles, or droplets in air or in any other form) potentially reaching the human body. Typical plant pathogens (e.g., powdery and downy mildews, rusts, leaf spots) are not relevant in this context because they do not cause disease in humans despite the fact that they produce abundant amounts of airborne spores. The position of an organism in the combined relevance matrix (Figure 1) depends on many factors such as local growth conditions (climate, composition of substrate, host immune system), genomic plasticity of the fungus and—last but not least—the reviewer's judgement. It is the relative rather than the absolute position in the matrix that differentiates species from one another. By far the most relevant crossover fungus is *A. fumigatus* (20 relevance points), followed by *C. neoformans* (15), *Aspergillus flavus* (10), *Candida tropicalis* (9) as well as *C. glabrata*, *Cryptococcus gattii*, *R. oryzae*, and *F. solani* (species complex), each with eight relevance points. All other fungi are considered to be less relevant in the combined assessment, although certain fungi are especially relevant in either one area or the other, for example, *C. albicans* and *Pneumocystis jirovecci* as pathogens in medicine and *Alternaria alternata* and *Rhodotorula mucilaginosa* as saprophytes in the environment (Figure 1).

6 | IN VITRO SENSITIVITY AND RESISTANCE TO MEDICAL ANTIFUNGALS

6.1 | Clinically relevant yeast species

The standard procedure for measuring the sensitivity of human fungal pathogens is growth inhibition of isolates by a series of inhibitor concentrations yielding, for example, the MIC_{90} level, according to the EUCAST microdilution method (or comparable approaches) (Arendrup et al., 2012; Mortensen et al., 2010). In such tests, *C. albicans* seems to be generally the most sensitive yeast species for the majority of isolates, with MIC_{90} values for seven important antifungals of 0.12–1.00, 0.50, 0.25–2.00, 0.03–0.25, 0.02–0.06, 0.02–0.06, and 0.25 mg/L, for AMB, 5-FC, FCZ, ITZ, VCZ, PCZ, and CSP, respectively (Figure 2; Cuenca-Estrella et al., 2006; Lockhart et al., 2017; Sabatelli et al., 2006). In general, the intrinsic activity of medical antifungals against the tested *Candida* spp. is PCZ ~VCZ > ITZ > AMB ~CSP > 5-FC ≫ FCZ. The intrinsic species sensitivity within *Candida* is: *albicans* ~ *parapsilosis* ~ *tropicalis* ~ *kefyr* ~ *lusitaniae* > *guilliermondii* > *krusei* > *glabrata* >*auris* > *famata*, *rugosa*, *dubliniensis*, with the latter six species being less sensitive or intrinsically resistant to azoles for the majority of isolates (Figure 2). A species can be considered as less sensitive to a specific compound when the mean MIC value of isolates is c.20–100 times higher than that of the reference species (*C. albicans*) and intrinsically resistant when MIC is more than 100-fold higher (Figure 2). However, it is not always clear whether resistance (to azoles) of a species is acquired or intrinsic. Generally, an isolate is considered as resistant to a specific compound if the MIC is more than 10 times higher than the mean MIC of the sensitive population. Accordingly, in all *Candida* spp. acquired resistance has been described after clinical use of antifungals for some isolates by many authors for many years (Chapeland-Leclerc et al., 2010; Cho et al., 2015; Espinel-Ingroff et al., 2014; Yoo et al., 2009).

Against FCZ, the mean percentage of resistant isolates (among thousands of tested isolates globally) was up to 5% in *C. albicans*, *C. tropicalis*, and *C. parapsilosis*, up to 8% in *C. glabrata*, and up to 97% in *C. krusei* (Espinel-Ingroff et al., 2014). FCZ-resistant isolates may be controlled in many cases by more active azoles (e.g., PCZ; Choi et al., 2016). In *C. tropicalis*, up to 80% of isolates recovered from a specific soil in Taiwan were resistant to FCZ (Yang et al., 2012).

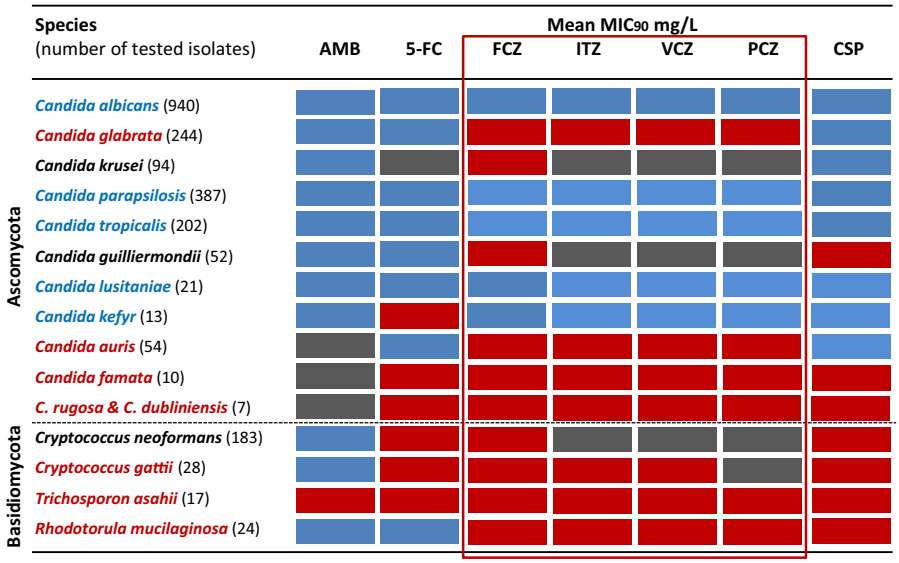

FIGURE 2 In vitro sensitivity of clinically relevant ascomycete and basidiomycete yeast species to medical antifungals. AMB, Amphotericin B; 5-FC, 5-Flucytosine; FCZ, Fluconazole; ITZ, Itraconazole; VCZ, Voriconazole; PCZ, Posaconazole; CSP, Caspofungin. Sensitive spp. in blue; less sensitive spp. in grey; intrinsically resistant (not sensitive) spp. in red. Definition of sensitivity within antifungal inhibitors: less sensitive spp.: c.10- to 100-fold higher MIC value than reference sp.; resistant: >100-fold higher MIC value than reference species. Reference species is *Candida albicans* (most sensitive species). Collected data from Cuenca-Estrella et al. (2006), Sabatelli et al. (2006), and Lockhart et al. (2017) (for *C. auris*)

Unfortunately, it was not elucidated whether FCZ-resistant isolates originated from medical or environmental treatments and whether and in which direction cross-contamination occurred. Yeast cells do not normally escape from soil environments to infect humans (as do mould spores) unless infested soil particles are inhaled or ingested. However, it is not clear if such air- or foodborne particles may cause candidiasis. More likely is a transmission from treated above-ground plant parts (leaves, fruits) or from the human body (any type of excrements) to the environment. VCZ and the two agricultural azoles, tebuconazole and penconazole, were much less effective against FCZ-resistant isolates (Yang et al., 2012), supporting cross-resistance among azoles.

In *C. glabrata* and *C. auris*, a certain proportion of tested isolates expressed acquired resistance to all main antifungal classes after clinical use in some regions (Chapeland-Leclerc et al., 2010; Cho et al., 2015; Chowdhary et al., 2018). In India, about 95%, 50%, 10%, and 10% of *C. auris* isolates collected between 2009 and 2017 were resistant to FCZ, VCZ, PCZ, and ISA, respectively, whereas 4%, 8%, and 2% were resistant against all azoles, AMB, and CSP, respectively, and only about 0.2% were simultaneously resistant against the three main antifungal classes (Chowdhary et al., 2018). Therefore, acquired resistance in *C. auris* can emerge quite rapidly through medical treatments, but so far only for a limited number of isolates.

Basidiomycete yeasts are generally much less, or not at all, sensitive to azoles as well as to 5-FC and CSP, with *C. gattii* and *Trichosporon asahii* being least sensitive or intrinsically resistant; only AMB shows reasonable activity against *C. neoformans*, *C. gattii*, and *R. mucilaginosa* (Figure 2). *C. neoformans* is moderately sensitive to ITZ, VCZ, and PCZ, but about 10- to 20-fold less sensitive than *C. albicans*, and is entirely resistant to FCZ. Environmental *Cryptococcus* spp. such as *C. albidus*, *C. laurentii*, *C. terrestris*, and *C. flavescens* are about as sensitive to ITZ and VCZ as *C. neoformans*, but much less sensitive to the agricultural azoles difenoconazole and epoxiconazole, and even to cyproconazole (Drummond et al., 2007; Takahashi et al., 2020), a fungicide known to be especially effective against basidiomycete plant pathogens. Therefore, agricultural azoles are considered as being too weak for *Cryptococcus* control and resistance selection under agricultural conditions, also because applied field rates and potential residue concentrations in soil are way too low for selecting resistance (Gisi, 2014). In fact, Takahashi et al. (2020) stated that "up to now, no data exist on resistance to triazoles among *Cryptococcus* environmental isolates from cultivated agricultural areas under fungicide pressure". Most isolates of *T. asahii* are up to 100-fold less sensitive than those of *C. albicans* and are considered as intrinsically resistant to all medical antifungals (Figure 2). Newer results from several countries including Turkey and India confirm multidrug-resistance to AMB, 5-FC, CSP, and FCZ; however, some control was observed for VCZ (de Almeida & Hennequin, 2016; Dabas et al., 2017; Hazirolan et al., 2013).

6.2 | Clinically relevant filamentous and dimorphic fungal species

Most *Aspergillus* species are sensitive to AMB and azoles (Figure 3) with mean MIC_{90} values of 0.5–2.0 mg/L for AMB, ITZ, and VCZ, and 0.25–1.0 mg/L for PCZ (Cuenca-Estrella et al., 2006; Sabatelli et al., 2006). *A. fumigatus* and *A. flavus* are about equally sensitive, whereas *A. niger* is slightly less sensitive (up to 10-fold), especially to ITZ. *A. terreus* is

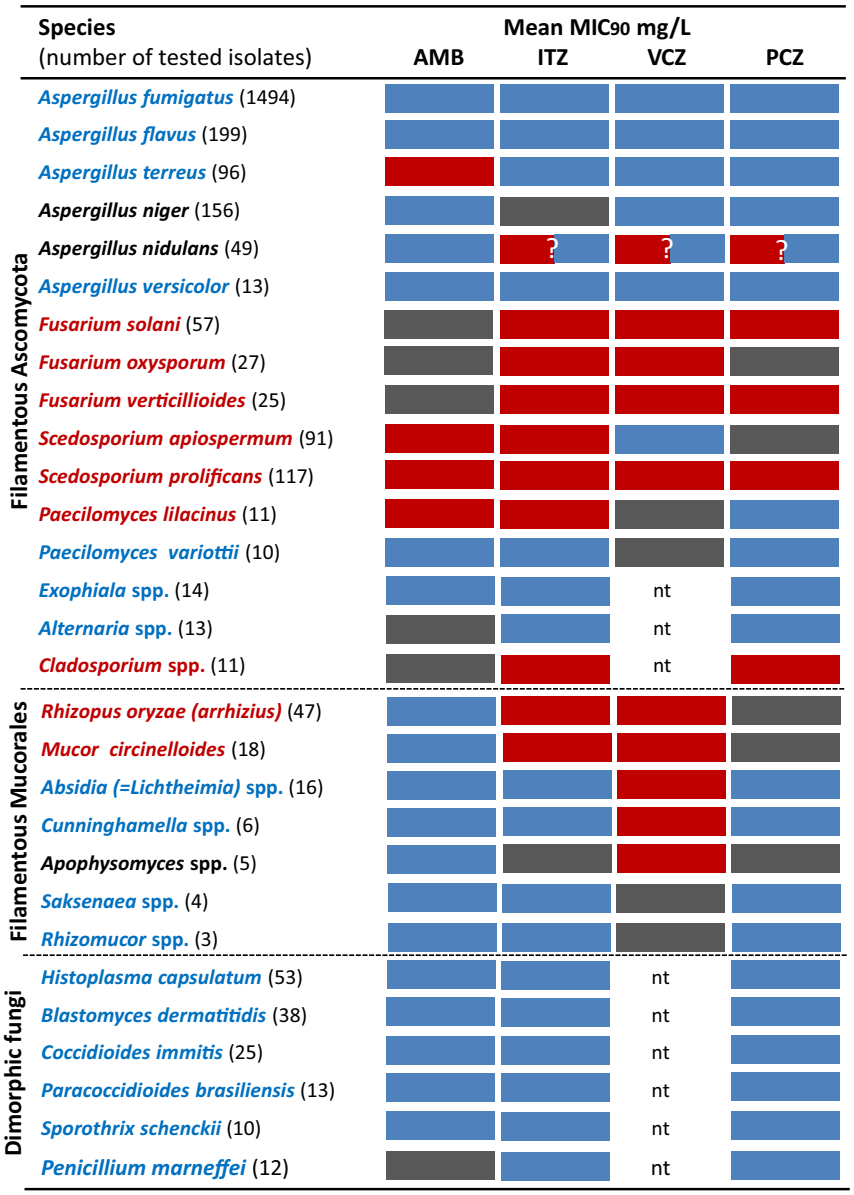

FIGURE 3 In vitro sensitivity of clinically relevant filamentous and dimorphic fungal species to medical antifungals. AMB, Amphotericin B; ITZ, Itraconazole; VCZ, Voriconazole; PCZ, Posaconazole. Sensitive spp. in blue; less sensitive spp. in grey; intrinsically resistant (not sensitive) spp. in red. Definition of sensitivity within antifungal inhibitors: less sensitive spp.: c.10- to 100-fold higher MIC value than reference species; resistant: >100-fold higher MIC value than reference species. Reference species is *Aspergillus fumigatus*. nt: not tested. ?: inconsistent results. Collected data from Cuenca-Estrella et al. (2006), Sabatelli et al. (2006), Zeng et al. (2004), and Lackner et al. (2012) (for *S. apiospermum*)

apparently intrinsically resistant to AMB; in addition, up to 5% of tested isolates expressed acquired resistance to azoles (Lass-Flörl, 2018). The sensitivity results for *A. nidulans* were inconsistent with intrinsically sensitive and/or resistant isolates, depending on the author (Figure 3). Isolates with acquired resistance to azoles have been described in *A. fumigatus* since the early 1990s (Denning et al., 1997). Since then, many authors have reported acquired resistance in clinical and environmental isolates from different regions worldwide (Howard et al., 2009; Resendiz-Sharpe et al., 2018; Sabino et al., 2016). Recent resistance frequencies in clinical isolates are around 2% in the UK (Abdolrasouli et al., 2018), 6% in Denmark (Jensen et al., 2016), and 15% in the Netherlands (Buil et al., 2019). Depending on regions, the local resistance frequencies vary between 0% and 26%; about 6% among a total of 2,026 isolates collected from 13 countries in four continents were resistant (Ashu et al., 2017). Against *A. flavus*, exclusive chemical control in agriculture is not appropriate due to its sporadic appearance. However, fungicides are used quite intensively in peanuts to control other diseases such as early and late leaf spot, peanut rust, and soilborne diseases like white mould, root rot, and Sclerotinia blight. Alongside other chemicals, azoles are used in peanuts (e.g., in the USA) up to six times per season, potentially selecting for resistance in *A. flavus* and thus presenting a possible crossover between agricultural and medical azole uses.

Due to the complexity of systematic grouping within *Fusarium*, the species sensitivity to antifungals is also quite inscrutable. AMB shows reasonable activity against most *Fusarium* spp., whereas CSP and 5FC are inactive. Also FCZ and ITZ are not effective (intrinsic resistance), whereas VCZ and PCZ show limited activity against FSSC (including *F. petroliphilum*, *F. lichenicola*, *F. keratoplasticum*, *F. falciforme*, *F. solani* sensu stricto) and some activity against FFSC (including *F. fujikuroi*, *F. proliferatum*, *F. oxysporum*, *F. verticillioides*) (Figure 3; Alastruey-Izquierdo et al., 2008; Al-Hatmi et al., 2016; Herkert et al., 2019; O'Donnell et al., 2008). Also, the agricultural azoles tebuconazole, difenoconazole, and propiconazole are not effective against clinical isolates of FSSC (Herkert et al., 2019). Thus, for unknown reasons, nearly all *Fusarium* spp. (and species complexes) are intrinsically multidrug-resistant (except to AMB). As a consequence, evolution of acquired resistance in *Fusarium* spp. to both medical and agricultural azoles may not happen. Clinical and environmental isolates collected before 1970 and after 1990 did not reveal statistically significant differences in mean MIC values (Al-Hatmi et al., 2019). Whether this general insensitivity (resistance) is based on the presence of three CYP51 paralogues, CYP51-A, -B, -C, in *Fusarium* spp. remains hypothetical. Interestingly, two new medical (topical) azoles, luliconazole and lanoconazole, are very effective against environmental and clinical isolates of FSSC, FOSC, and FFSC (in vitro about 100 times more active than VRZ; Abastabar et al,I., 2018). Thus, the genus *Fusarium* per se may not be intrinsically resistant to all azoles as claimed by Al-Hatmi et al. (2019) and might theoretically develop acquired resistance to the two recent medical azoles after prolonged exposure.

Against *Scedosporium apiospermum*, only VCZ provides reasonable control, whereas PZC and CSP are only moderately active, and ITZ, ISA, and AMB are inactive (Figure 3; Lackner et al., 2012). No difference in sensitivity was found between *S. apiospermum*, *S. boydii*, *S. ellipsoideum*, *S. dehoogii*, *S. aurantiacum* and between clinical and environmental isolates (Lackner et al., 2012). Against *S. prolificans*, all tested antifungals are inactive (Figure 3); thus, the species can be considered as intrinsically multidrug-resistant. *Paecilomyces variottii*, *Exophiala* spp., and *Alternaria* spp. are generally quite sensitive to AMB and azoles, whereas against *P. lilacinus* only PCZ, and against *Cladosporium* spp. only AMB showed some antifungal activity (Figure 3).

All tested spp. of the Mucorales are sensitive to AMB, whereas against azoles there are significant differences (Figure 3) based on chemical structures of the inhibitors and their binding characteristics to the CYP51 protein. *R. oryzae* (= *R. arrhizus*) is up to 40-fold less sensitive to PCZ and ISA than *A. fumigatus* and is claimed to be intrinsically resistant to FCZ and VCZ (Macedo et al., 2018). Also *R. microsporus*, *M. circinelloides*, *Absidia* (=*Lichtheimia*) *corymbifera*, *C. bertholletiae*, and *Rhizomucor pusillus* are intrinsically resistant to the latter two azoles (Alastruey-Izquierdo et al., 2009; Gomez-Lopez et al., 2001; Vitale et al., 2012). At position 129 of the CYP51A protein of all Mucorales (corresponding to 140 in *C. albicans*), there is phenylalanine (F129) instead of tyrosine (Y129), as in ascomycetes and basidiomycetes. This molecular configuration obviously hinders binding of short-tailed azole compounds (with short side chain, as FCZ and VCZ) to the target site, whereas long-tailed azoles (PCZ, ISA) are quite effective (Caramalho et al., 2017). However, ITZ, a long-tailed azole, is not really effective against *Rhizopus* and *Mucor* spp. (Figure 3). Therefore, there must be additional structural properties affecting antifungal activity of azoles against Mucorales. All agricultural azoles (DMIs) are short-tailed compounds and have only limited or no activity against Mucorales.

All six investigated dimorphic fungal species are quite sensitive to ITV and PCZ (Figure 3) and VCZ, whereas FCZ is much less effective (Wheat et al., 2006). One year after daily treatment with FCZ (800 mg/patient), sensitivity of *H. capsulatum* isolates in 13 of 17 patients decreased (comparing pre- and posttreatment), and the mutation Y136F (Y132F in resistant *C. albicans*) was detected in less-sensitive isolates (Wheat et al., 2006). Therefore, azole therapy over extended periods may select for resistant isolates in *H. capsulatum*. The dimorphic fungus *C. immitis* is about as sensitive to azoles as *A. fumigatus*. Intrinsic azole activity is VCZ ~PCZ > ITZ (= AMB) >> FCZ (Thompson et al., 2017). Acquired resistance to azoles was reported in clinical isolates (Kriesel et al., 2008), but the amount of isolates with decreased sensitivity is still very low (Eltayeb et al., 2019; Thompson et al., 2017). However, based on the long exposure time (months to years) of *C. immitis* to azoles during human therapy, the evolution of acquired resistance in medicine is likely to occur. Resistance selection in the natural environment is rather unlikely though, because the fungus lives primarily in locations where agricultural azoles are not applied (dry desert soil).

7 | ESSENCE OF ANALYSIS: RESISTANCE RISK ASSESSMENT FOR AZOLES IN FUNGAL HUMAN PATHOGENS AND IDENTIFICATION OF HOT SPOTS

Although *C. neoformans* can be isolated quite frequently from specific environmental sites (e.g., bird droppings, soil, decaying wood), the exposure to azoles is believed to be low. In addition, agricultural azoles are not very effective against *C. neoformans*, and most medical azoles have only moderate intrinsic activity, especially against *C. gattii*. If azole resistance in *Cryptococcus* spp. would appear, it is probably a medically generated problem (therapy over months), although some medical experts also claim environmental selection as a possible origin of resistance (Bastos et al., 2018). However, special attention should be given to poultry farming: if azoles were used to suppress *C. neoformans* and/or *A. fumigatus*, resistance selection is likely to occur (Figure 4).

As stated above, *Candida* yeasts are inherent inhabitants of the human body. Potential transmission of *Candida* yeasts from the environment to the human body is far from obvious. Therefore, cross-contamination with azole-resistant *Candida* isolates from outside medicine (e.g., from agricultural fields, treated material) to patients is probably rather low. Most human and environmental *Candida* species have their typical habitats, are niche-separated, and may not

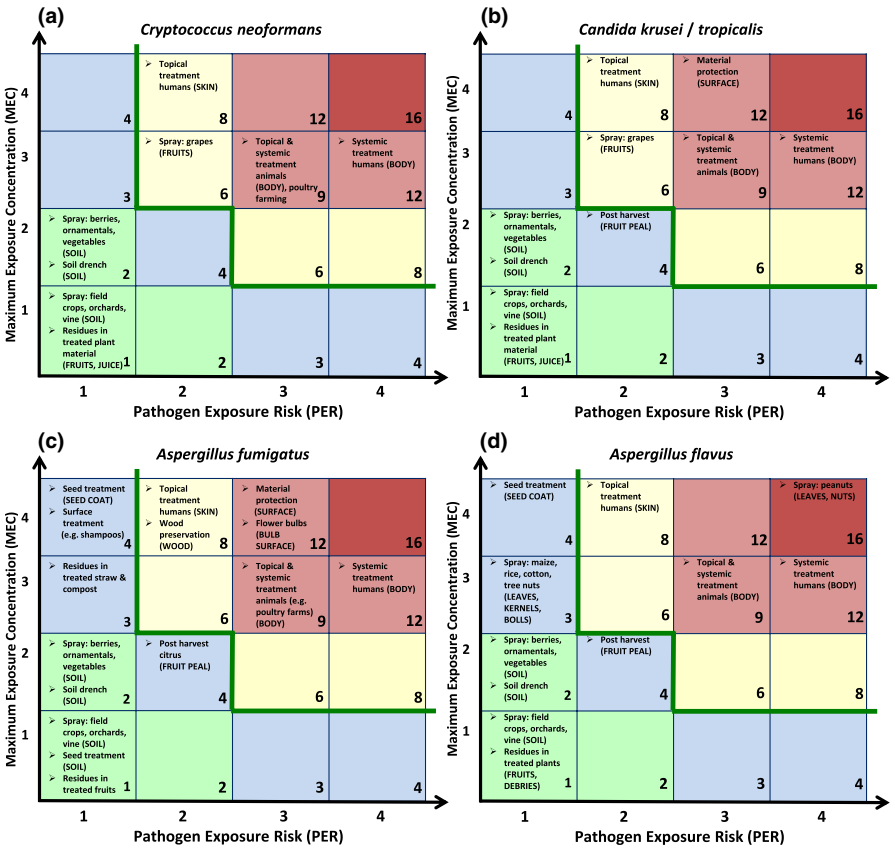

FIGURE 4 Exposure of *Cryptococcus neoformans* (a), *Candida krusei*/*Candida tropicalis* (b), *Aspergillus fumigatus* (c), and *Aspergillus flavus* (d) to azoles: matrix for assumed selection risk (ASR = MEC × PER) and "hot spots" for azole resistance. ASR scale: 1–2 very low; 3–4 low; 6–8 medium; 9–12 high; 16 very high. *A. fumigatus* matrix according to Gisi (2014, 2020)

cause crossover resistance problems. Therefore, azole resistance in *Candida* probably evolved during long-standing medical treatments. Furthermore, resistance in human-pathogenic *Candida* spp. is also known to AMB and CSP, antifungals that have been used for a long time exclusively in medicine. Multidrug resistance has evolved after medical treatments in several spp. (e.g., *C. auris*). However, two species, *C. tropicalis* and *C. krusei*, can be found quite frequently in natural ecosystems where they might come in contact with agricultural azoles. A potential critical spot for resistance selection may be fruits (e.g., grapes) (Figure 4).

After *Cryptococcus* and *Candida* spp., *P. jirovecci* is the third important human pathogen worldwide (Table 2). It grows as an obligate parasite (pathogen) in the human body, causing life-threatening pneumonia. In rats, *P. carinii* causes similar symptoms. In *Pneumocystis* cell membranes, the functional sterol is cholesterol (as in humans and animals) instead of ergosterol (as in fungi). Because azoles inhibit ergosterol biosynthesis, they are inactive against *Pneumocystis* (intrinsic resistance, innate immunity) and consequently cannot select (acquired) resistance. Trimethoprim-sulfamethoxazole (TMP-SMX) provides reasonable control of *Pneumocystis* pneumonia (and the parasitic protozoan disease toxoplasmosis).

All *Aspergillus* spp. are intrinsically resistant (insensitive) to FCZ, whereas newer clinical azoles are generally very effective against wildtype isolates. However, *A. lentulus* is claimed to be intrinsically resistant to all azoles. In *A. flavus* and *A. terreus*, clinical isolates with acquired resistance have been reported harbouring specific mutations in *cyp51C* (a second copy of *cyp51A*; Hawkins et al., 2014) often combined with overexpression of the target gene and efflux pumps (Rudramurthy et al., 2019). Because *A. flavus*—besides being a frequent saprophyte in soil and on foodstuffs—is also an important plant pathogen on crops like peanuts, maize, cotton, and rice, it may be exposed—unintentionally or directly—to agricultural azoles (Mateo et al., 2017). However, no resistant isolates have been detected in the agricultural environment so far. Sexual reproduction has been reported to occur quite frequently in laboratory experiments (Rudramurthy et al., 2019), but it is not known whether this also happens under field conditions. A comparative study on sexual reproduction and genomic plasticity may provide hints as to whether the azole resistance risk may be lower in *A. flavus* than in other *Aspergillus* spp. (Rudramurthy et al., 2019). A potential hot spot for azole resistance selection in *A. flavus* may be peanuts (e.g., in the USA; Figure 4). *A. terreus* and *A. niger*—although occasionally causing invasive aspergillosis—are typical saprophytes in the soil environment probably not being exposed to agricultural azoles; the risk of resistance selection is estimated to be low (Figure 4).

In contrast, the risk of azole resistance selection in *A. fumigatus* is estimated to be high both in medicine and in certain areas of the natural environment (Gisi, 2014, 2020): Flower bulbs (e.g., tulips, daffodils) are treated with azoles at rather high concentrations (300–3,000 mg/L on/in bulb surface; Gisi, 2014) to protect them against rotting, and also foliar application rates are rather high, resulting in significant residues in composted bulb leftovers. Therefore, *A. fumigatus* may be exposed to relevant azole concentrations in this specific habitat. In fact, resistant isolates

were detected in Dutch stockpiled plant waste heaps preceding composting (Schoustra et al., 2019), but not in commercial composts from other European sites (Santoro et al., 2017). In France, resistant isolates were detected at low frequencies (<3%) in timber wood having been processed by tank dipping in azoles at 1,000 mg/L (Jeanvoine et al., 2017). In other habitats (e.g., agricultural soils), *A. fumigatus* is less frequent and competitive with low reproduction rates (Santoro et al., 2017), and azole residue concentrations are rather low (Gisi, 2014). Resistant isolates were only very rarely detected in agricultural soils (Barber et al., 2020; Fraaije et al., 2020). Migration and transmission of *A. fumigatus* (spores, contaminated material) is often quite high, allowing easy distribution of propagules (including resistant spores) from hot spots to new habitats (e.g., on flower bulbs from the Netherlands to Ireland [Dunne et al., 2017], and to Japan [Hagiwara, 2020]). Also, various birds can serve as important carriers, distributing *A. fumigatus* globally, because they pick up infested material and excrete spores with their droppings (Martins Melo et al., 2020). In addition, they often suffer from aspergillosis and distribute the pathogen either by their moving around or dying in nature or in captivity, where they may have been treated with azoles (Martins Melo et al., 2020). Recently, dissemination of airborne spores from patient to patient and from patient to environment through coughs and sputum has been postulated as an additional way of spreading *A. fumigatus* (Engel et al., 2019; Lemaire et al., 2018).

In order to identify hot spots for the selection of resistance and assessment of the assumed selection risk (ASR), the two most important elements have to be considered: (a) the maximum exposure concentration (MEC) of the antifungal compound a pathogen may come into contact with during application (calculated based on the recommended use rates), and (b) the pathogen exposure risk (PER) describing the likelihood of the pathogen to be present and actively propagating in the treated substrate (Gisi, 2014). In all types of risk assessments, risk elements are multiplied to estimate the overall risk. Assigning risk factors, for example, 1–4 (from low to high) to each element, the overall assumed selection risk, ASR = MEC × PER, results in a range of values from 1 to 16, with 16 representing the highest selection risk and probability for a hot spot. On the basis of these considerations, the ASR matrices for different azole application types against four important fungal human pathogens, *C. neoformans*, *C. krusei*/*C. tropicalis*, *A. fumigatus*, and *A. flavus* were constructed (Figure 4). For all four pathogens, extended azole use in medicine (human and animal) is considered as causing a rather high probability of selecting for (acquired) resistance (risk factor 12). Outside the medical area, potential hot spots for azole resistance selection in *A. fumigatus* are flower bulb production (factor 12, as predicted already by Gisi [2014] and confirmed by Verweij et al. [2020]), material protection (factor 12), and poultry farming (factor 9), in addition to peanut growing for *A. flavus* (factor 16) (Figure 4). Semi-hot spots may be defined as situations in which the ASR indicates intermediate values (risk factors 6–8) and in which a small change of either MEC or PER may already result in either a hot spot or a "cold spot" (risk factor <5; Figure 4). As a consequence, semi-hot spots may be found for topical skin treatments in human medicine (for all four pathogens), spray treatments of grapes for *C. neoformans* and *C. krusei*/*tropicalis*, and wood preservation for *A. fumigatus*. All other application types can be considered as cold spots, for example, spray applications in field crops (Figure 4). The four selection risk matrices can be considered as typical candidates for crossover of azole resistance between medical and environmental (agricultural) applications. The resistance risk matrices for medical applications are almost trivial for all those fungal human pathogens that are not relevant in the natural environment (data not shown) such as *C. albicans*, *C. auris*, *T. asahii*, *H. capsulatum*, *B. dermatitidis*, and *C. immitis*.

8 | CONCLUSIONS

Compared to antimicrobial/antibacterial resistance (AMR/ABR), antifungal resistance (AFR) may be of lower practical importance, mainly because life-threatening diseases caused by fungal pathogens are much less frequent compared to those caused by bacteria. In addition to several hard-to-control *Candida* spp., the number one problematic fungal human pathogen is *A. fumigatus*, particularly as resistance to azoles as first-line treatments is becoming more and more of a serious problem in human medicine. Resistant isolates have increased in frequency after prolonged use both in medical and agricultural/environmental settings. In addition, *A. fumigatus* can easily be disseminated globally as spores or infested particles and droplets via air, infested plant material (e.g., flower bulbs, compost) by global commerce, and vectors like animals (e.g., birds). Therefore, a one-health approach is essential, taking all stakeholders on board, including experts dealing with human and animal health, plant pathology and environmental sciences, farmers' associations, agrochemical and pharmaceutical companies, compost manufactures, and registration specialists in governmental organizations (Martins-Melo et al., 2020; Verweij et al., 2020). All crossover approaches should have the common goal to limit the spread of fungal pathogens of humans and antifungal resistance in all areas. Hot, semi-hot, and cold spots for resistance selection have to be identified case by case by assessing the risk separately for every application type in different local habitats and conditions. Special attention should be given to fungal pathogens relevant to human and animal medicine as well as in agriculture and material protection.

ACKNOWLEDGEMENTS

This review was in part supported by a grant from Crop Life International, Brussels. Helpful discussions with Dietrich Hermann, Helge Sierotzki, Klaus Stenzel, Andreas Goertz, Martin Semar, Kevin Doughty, Bart Fraaije, and Paul Verweij contributed to streamline the complex project, and they are greatly acknowledged.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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How to cite this article: Gisi U. Crossover between the control of fungal pathogens in medicine and the wider environment, and the threat of antifungal resistance. *Plant Pathol*. 2022;71:131–149. https://doi.org/10.1111/ppa.13429