REVIEW

Worldwide emergence of resistance to antifungal drugs challenges human health and food security

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The recent rate of emergence of pathogenic fungi that are resistant to the limited number of commonly used antifungal agents is unprecedented. The azoles, for example, are used not only for human and animal health care and crop protection but also in antifouling coatings and timber preservation. The ubiquity and multiple uses of azoles have hastened the independent evolution of resistance in many environments. One consequence is an increasing risk in human health care from naturally occurring opportunistic fungal pathogens that have acquired resistance to this broad class of chemicals. To avoid a global collapse in our ability to control fungal infections and to avoid critical failures in medicine and food security, we must improve our stewardship of extant chemicals, promote new antifungal discovery, and leverage emerging technologies for alternative solutions.

The rapid emergence of multidrug-resistant pathogenic fungi and the better-publicized threat of antibiotic-resistant bacteria together pose a considerable threat to disease control across diverse anthropogenic systems. These microbes respond adroitly to human-induced natural selection through chemical treatments and nimbly hijack human globalization pathways (*1*), thus disseminating the problems worldwide. Today, crop-destroying fungi account for perennial yield losses of ~20% worldwide, with a further 10% loss postharvest. Fungal effects on human health are currently spiraling, and the global mortality rate for fungal diseases now exceeds that for malaria or breast cancer and is comparable to those for tuberculosis and HIV (*2*). Fungal infections have hitherto been greatly neglected relative to other classes of infectious disease, despite their ubiquity.

The first antifungal chemicals used in human health care, nystatin and the polyenes, were discovered in the 1950s, and copper and sulfur fungicides were first used to control crop disease more than 150 years ago. Today, systemic antifungals and fungicides are used as frontline treatments for fungal diseases in humans and plants. Fungal pathogen control can, however, be ephemeral because of the rapid development of resistance to the chemicals. Fungi have highly plastic genomes and reproduce rapidly. The combination of these properties quickly generates variants selected for resistance. For plant pathogens, the pace of breakdown of antifungal protection is enhanced by monoculture cropping practices, as large swathes of genetically uniform crops provide ideal breeding and feeding grounds for the rapid emergence of fungicide-resistant variants. In humans, long periods of prophylactic treatment in at-risk patients can similarly lead to the emergence of antifungal resistance (*3*). Resistance of clinical pathogens to all licensed systemic antifungals has been documented, although the rate of emergence varies among drug classes (Fig. 1) (*3*). Likewise, despite the wider range of fungicides licensed for use in agriculture, resistance to each main class of fungicides has emerged in some major pathogens (Fig. 1). This threat is exacerbated by the additional threat of withdrawal of some chemical classes because of regulatory changes in jurisdictions such as the European Union (EU).

Antifungals for the treatment of fungal diseases in the clinic and the field

The chemical control of fungal pathogens that cause diseases in animals and crops has progressed from the use of inorganic chemicals to the use of organic surface protectant chemicals and then to the use of systemically acting fungicides. Approximately nine times more antifungal compounds are available to control crop diseases than to treat systemic animal infections. Licensed treatments for humans are limited to four frontline classes of drugs (Fig. 1): The polyenes (such as amphotericin B) disrupt the structure of cell membranes by sequestering the fungal membrane sterol ergosterol. The pyrimidine analog 5-fluorocytosine (5-FC) blocks pyrimidine metabolism and DNA synthesis. The newest class of antifungals, the echinocandins, inhibits (1-3)-β-D-glucan synthase and disrupts cell wall biosynthesis. The fourth and most widely used class of fungicides, the azoles, blocks ergosterol biosynthesis through inhibition of lanosterol 14-α-demethylase. Most fungicides for crop disease target mitochondrial function, the cytoskeleton, or ergosterol biosynthesis (Fig. 1), although some specialized chemicals, such as the azanaphthalenes for powdery mildew control, target other pathways. However, the azoles remain the dominant chemicals in the treatment of fungal infections in crops, humans, and livestock, with five licensed clinical azole antifungals and 31 available for crop protection.

Parallel drivers of fungicide resistance in the clinic and the field

Human population growth, urbanization, and economic prosperity have fueled demands for increasing quantities and varieties of food. Intensive agriculture has too often responded to this demand with crops bred for maximum productivity under the protection of broad-scale pesticide applications, inadvertently breeding out the plants' own defenses. In parallel, the number of humans at risk from fungal infections is rising rapidly with increases in populations that are particularly susceptible because of age, medical interventions, or HIV infection. Medical advances resulting in greater initial survival rates for patients with cancer or organ transplantation can leave these patients susceptible to secondary attacks from opportunistic fungi, leading to increasing use of antifungal drugs in clinical practice (Fig. 2 and table S1).

The global movement of people and global trade in produce have hastened the free flow of fungal pathogens from country to country, bringing pathogens into contact with naïve hosts (*1*) (Fig. 3). In the clinical setting, new species of multidrug-resistant pathogenic fungi are emerging. *Candida auris,* first described in Japan in 2009 after isolation from a patient's ear, is responsible for rapidly increasing hospital-acquired invasive infections worldwide (*4*). This fungus is now resistant to all clinical antifungals (*5*) and presents a threat to intensive care units because it can survive normal decontamination protocols (*6*). The emergence of resistance in *Candida glabrata* has coincided with this species becoming the predominant bloodstream pathogen recovered from patients, largely because of the increasing prophylactic use of echinocandins and azoles (*7*). There is also a growing threat from filamentous pathogenic fungi that are intrinsically resistant to a broad range of antifungals, such as *Aspergillus terreus* (*8*), *Scedosporium* spp. (*9*), *Fusarium* spp. (*10*), and members of the Mucorales (*11*).

Simultaneously, we are witnessing the continual emergence of new races of plant-infecting fungi able to overcome both host defenses and chemical treatments (*12*), as well as the evolution of these traits in existing major pathogens (*13*, *14*). The first case of resistance against the benzimidazoles (MBCs) was reported in 1969 (*15*), and now MBC resistance is known to occur in more than 90 plant pathogens (*16*). Azole resistance in a plant pathogen was first reported in 1981 (*17*), but azole resistance is generally partial, in contrast to the complete control failures seen for MBCs (*18*). Resistance to strobilurins (QoIs) was reported in field trials even before commercial introduction and in wider field

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populations within 2 years of release (*19*). A new generation of succinate dehydrogenase inhibitors (SDHIs) was introduced in 2007, but by 2017 resistant field isolates were found in 17 pathogen species (*20*). Pathogens with resistance to MBCs, azoles, QoIs, and SDHIs include the major wheat pathogen *Zymoseptoria tritici*, banana black sigatoka pathogen *Mycosphaerella fijiensis*, cereal powdery mildew fungus *Blumeria graminis*, the emerging barley pathogen *Ramularia collo-cygni*, and the apple scab fungus *Venturia inaequalis*. For *Botrytis cinerea* (a generalist pathogen that causes gray mold, particularly on soft fruits), resistance against 15 different classes of systemic and protectant fungicides has been reported (*21*).

Parallel evolution of resistance mechanisms in the clinic and the field

The selective pressure exerted on fungi by single-site–inhibiting fungicides has resulted in similar adaptations arising over time in disparate fungal species. Parallel evolution of resistance extends across clinical and plant-pathogenic fungi, with the same key resistance mechanisms occurring independently in both.

Mutations resulting in conformational changes to the drug target site are the most common form of resistance in pathogenic fungi. Target-site mutations have been reported in candin-resistant clinical pathogens and MBC-, QoI-, and SDHI-resistant plant pathogens, as well as azole-resistant strains in agricultural and clinical settings. A single mutation, Gly^{143}→Ala in cytochrome *b*, has emerged in the field in more than 20 species under selection by QoIs (*14*). Moreover, the Tyr^{137}→Phe substitution in CYP51 (P450 cytochrome) has been found in multiple plant pathogens with partial azole resistance, and Tyr^{132}→Phe also occurs at the equivalent residue in *Candida albicans* (*18*). Promoter changes resulting in up-regulation of the fungicide target are also common across clinical and plant-pathogenic fungi (*22*). In *Aspergillus fumigatus*, tandem repeats in the CYP51A promoter region occur together with downstream single-nucleotide polymorphisms (SNPs) in the coding region, conferring a multi-azole resistance phenotype (*23*).

A third resistance mechanism involves reducing intracellular drug accumulation by up-regulation of efflux pumps, such as adenosine triphosphate–binding cassette transporters or major facilitators. Their up-regulation may result from promoter insertions or transcription factor gain-of-function mutations (*3*, *24*).

Further resistance mechanisms have been identified in clinical pathogens. Activation of stress response pathways by Hsp90 can unleash cryptic diversity, potentiating the evolution of resistance to azoles, echinocandins, and polyenes in *Candida* and *Aspergillus* species (*25*). Structural genomic plasticity can result in resistance, with chromosome arm duplications leading to efflux pump and target-site overexpression in *C. albicans* (*24*, *26*). Hypermutator strains of *C. glabrata* and *Cryptococcus neoformans*, with the potential to evolve rapidly in response to host and drug selection, were recently reported (*27*, *28*).

Dual use of azoles in the clinic and the field

The azoles are the most widely deployed class of fungicides in crop protection, totaling in excess of 26% of all fungicides across the EU (*29*). Azoles are also frontline drugs used in humans and animals; however, such multiple use seems to have promoted azole resistance in an opportunistic pathogen of humans (*29*, *30*), the saprotroph *A. fumigatus*. This species colonizes decaying vegetation in fields, forests, and compost heaps but is also capable of invading immunocompromised humans. Multi-azole–resistant *A. fumigatus* has been recovered from environmental and clinical samples globally. In the Netherlands, more than 25% of clinical *Aspergillus* strains carry azole resistance alleles (*31*). Azoles are increasingly failing as frontline therapies, with associated patient mortality approaching 100% (*31*). Population genomic analyses have shown that azole-resistant alleles in *A. fumigatus*

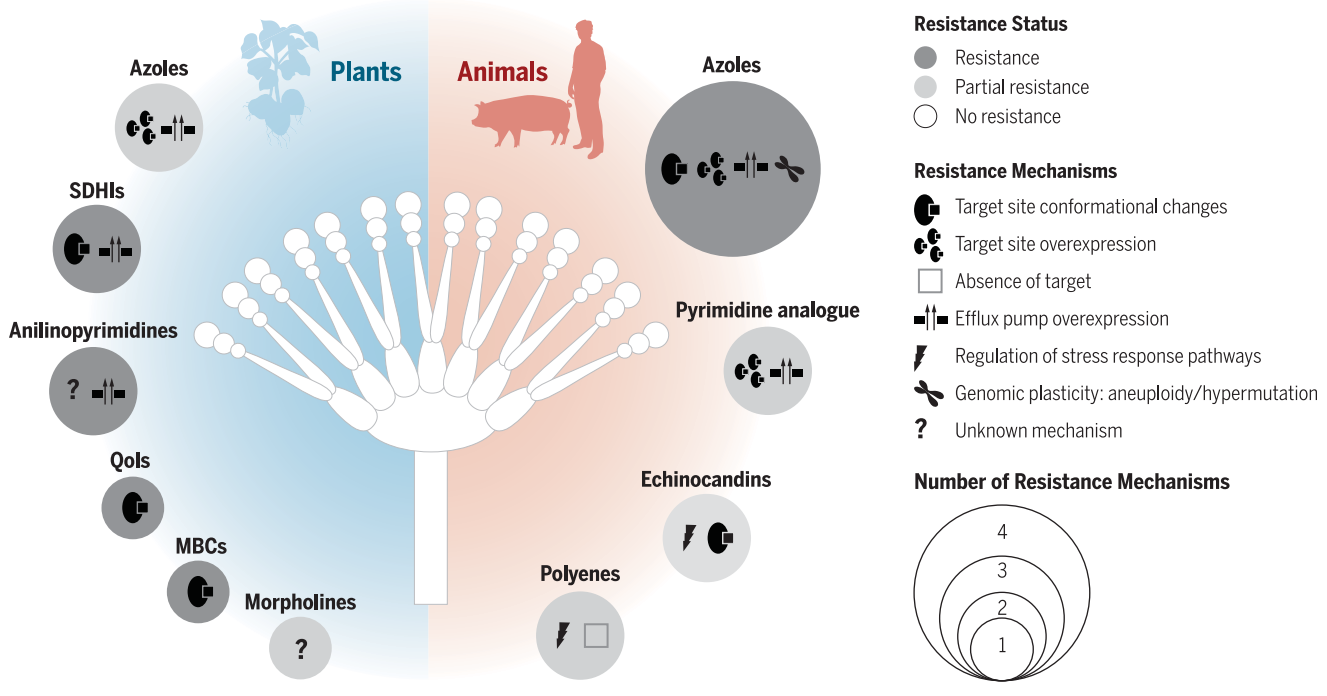

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Fig. 1. Current classes of drugs used against plant and animal fungal infections and known mechanisms of resistance to them. The six main classes of fungicides are the morpholines, which inhibit two target sites within the ergosterol biosynthetic pathway, Δ14-reductase and Δ8-Δ7-isomerase (this reduces the risk of target-site resistance, but their intrinsic antifungal activity spectrum is narrower than those of other antifungals); the azoles (used also in animal infections), which target the ergosterol biosynthetic pathway; the benzimidazoles (MBCs), which interfere with the cytoskeleton by binding to β-tubulin, thus preventing the assembly of microtubules; the strobilurins (QoIs) and succinate dehydrogenase inhibitors (SDHIs), which both inhibit the electron transfer chain of mitochondrial respiration, with the SDHIs inhibiting complex II (succinate dehydrogenase) and the QoIs inhibiting complex III (the quinone outside binding pocket of cytochrome *b*); and the anilinopyrimidines, which may target mitochondrial signaling pathways. Three other antifungal classes are used for animal fungal infections: the echinocandins, which inhibit cell wall biosynthesis; the pyrimidine analogs, which interfere with nucleic acid biosynthesis; and the polyenes, which bind ergosterol.

are associated with selective sweeps when azole use is high, as in India (*32*). Moreover, recombination in *A. fumigatus* generates new combinations of azole resistance alleles (*32*). Investigations are now under way to assess the relative contributions of clinical and environmental selection to azole resistance in *A. fumigatus* and to identify the most problematic environmental applications of azoles. The potential conflict between the level of agricultural use and the durability of clinical effectiveness of azoles highlights how limited the antifungal toolbox is, where neither "side" can afford to lose a mode of action (*33*).

Most cases of fungicide and antifungal resistance across field and clinic settings appear to have arisen by the repeated independent evolution of resistance to successive fungicides within numerous fungal species. This is where evolution of antifungal resistance differs fundamentally from that of antibacterial resistance, which is frequently transferred between pathogens of animals and humans via the "mobilome" of plasmids and phage (*34*). Some evidence indicates horizontal gene transfer among fungi (*35*), but this fungal gene transfer occurs over longer time scales than gene transfer among bacteria and the dynamics of resistance arising by this route is thus far negligible.

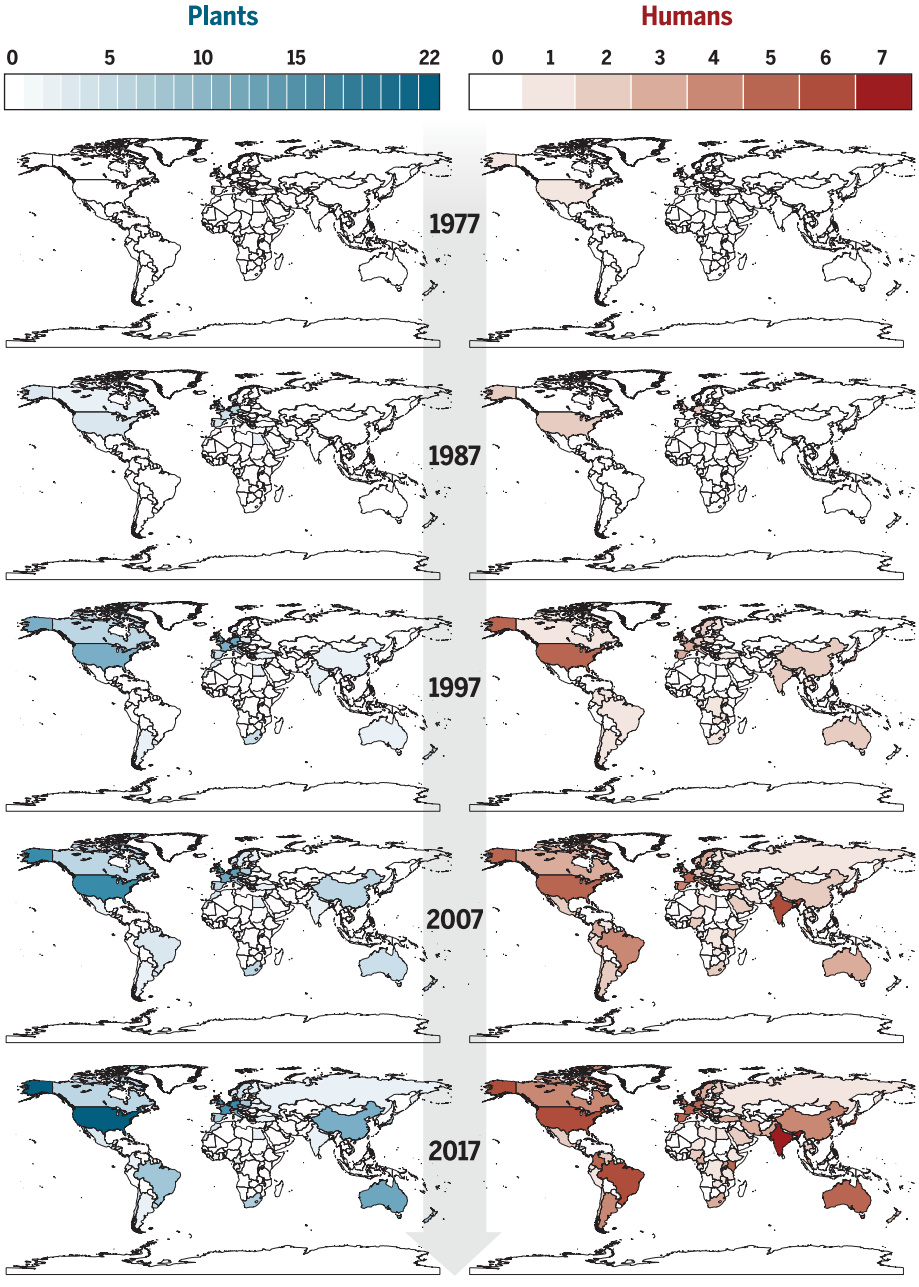

Fig. 2. Fungal species with reported antifungal resistance, by country. Increasing color intensity reflects a growing number of reports. The plant maps depict spatiotemporal records of resistance of crop pathogens to azoles (blue scale). The human maps depict spatiotemporal records of resistance of the pathogens *A. fumigatus*, *C. albicans*, *C. auris*, *C. glabrata*, *Cryptococcus gattii*, and *Cryptococcus neoformans* to azoles (red scale). The data are derived from peer-reviewed publications as of March 2018, reporting the occurrence of cases of resistance up to 2017 (the list of publications is available in table S1).

Prospects for diversifying the toolbox for fungal control

To counter the escalating risks of fungal disease, we need to discover antifungal chemicals with new modes of action, hinder the emergence of resistance in extant chemicals by better stewardship, and develop new disease control strategies to avoid overreliance on fungicides.

Development of new antifungals

The rate of emergence of fungicide resistance (Fig. 2) is greater than the pace of fungicide discovery, and the long registration process for new compounds adds further delays. This situation parallels the situation for antibiotics. Increased research activity is thus needed to develop new antifungal drugs (*36*). Recently, substantial progress has occurred in this field, with at least 11 antifungals in phase 1 and 2 clinical trials and at least two in the agricultural chemicals pipeline. Several of these are derivatives of commonly used antifungal chemicals, such as ergosterol biosynthesis and cell wall biosynthesis inhibitors, engineered for higher efficacy, and others have new modes of action. Combining molecular modeling, combinatorial chemistry, and high-throughput screening has the potential to develop chemicals with reduced resistance risk (*37*).

Stewardship of existing compounds

Robust global strategies are needed to slow the development of antifungal resistance. Combining different modes of action, either in mixtures or in alternating treatments, may slow the emergence of resistance. For example, combinations of fluconazole, flucytosine, and amphotericin B can effectively treat HIV-associated cryptococcal meningitis (*38*). In agriculture, mixtures of fungicides with different modes of action are already widely recommended (*39*), with some formulations available only as mixed products. Where target-site mutations confer high levels of resistance, lower doses of antifungals should be favored (*40*, *41*). However, this results in a trade-off between the immediate gain of treatment effectiveness and the longer benefit from slowing the selection of resistance. Improvements in molecular diagnostics are also needed, both for the identification of fungal pathogens so that antifungals can be used appropriately and for the detection of specific resistance alleles, as the monitoring of resistance is a vital part of stewardship (*42*).

Integrated disease management

To reduce our reliance on chemical control alone, we must develop more nonchemical control measures to use where effective fungicides are no longer available or to use in combination with fungicides to reduce the selective pressure

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Fig. 3. Evolutionary drivers of antifungal resistance: heritable variation, high reproductive output, and differential survival.

on each component. In crops, the development of innate disease resistance through the selection of major pathogen-resistance alleles is widely used to breed disease-resistant cultivars. However, this approach is slow, with a 20-year lag from finding a suitable disease-resistance gene to releasing it in commercial lines. Marker-assisted breeding can speed up the recombination of multiple disease-resistance alleles, but it still takes approximately a decade (*43*). Transgene cloning, or gene editing, is faster still (requiring ~2 years), but no crops with transgenic antifungal disease resistance have yet been released commercially. The high degree of specificity between host and pathogen for major resistance genes (*44*) means that pathogens can also rapidly evolve to overcome this strategy. However, "evolution-smart" disease-resistant crops with pyramided pathogen-resistance genes or mosaic deployment of resistant varieties may provide greater durability of disease control. Minor resistance genes, such as those for the antifungal chitinases and glucanases, carry the advantage of broad-spectrum activity (*45*) but introduce the possible disadvantage of yield penalties, as well as providing incomplete protection. Further sources of genetic disease resistance can be found in the gene pools of crops' wild relatives, which may be introduced into modern crop varieties through introgression or transgenesis (*43*).

In humans, advances in combination antiretroviral therapy to halt HIV-AIDS progression, gene therapies under development for cystic fibrosis, and tissue engineering for rejection-free transplantation can reduce vulnerability to fungal infections in the corresponding patient cohorts. Also, the first antifungal vaccine against *C. albicans* is undergoing clinical trials (*46*), and the use of bioengineered T cells to augment host immunity is being explored (*47*). Lastly, the identification of human genetic biomarkers associated with susceptibility to fungal diseases, such as SNPs in the immune mediator *PTX3* (*48*), provides a new path to identify patient groups in which antifungal treatments could be reduced.

The rapidly growing fields of synthetic biology and epigenomics are now converging to develop antifungal treatments on the basis of RNA interference (RNAi). Bidirectional cross-kingdom microRNA (miRNA) trafficking between plants and fungi is being developed to fight pathogens (*49*) such as *B. cinerea*, which uses miRNA virulence effectors to silence host plant immune genes (*50*, *51*). Current research avenues include identifying new targets for RNAi and, crucially, developing systems for the stable and targeted delivery of RNA silencing through genetic engineering of the host plant or exogenous application of synthetic RNA (*50*–*52*). Although such approaches have not yet been used to treat fungal infections in the clinic, the discovery of RNAi as a promising clinical antifungal strategy is potentially transformational.

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Table S1
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