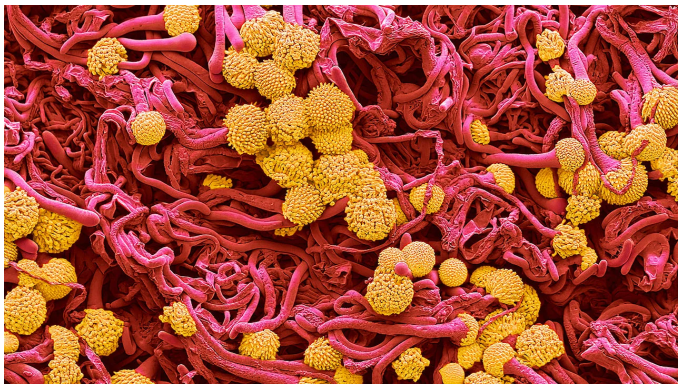
Science & technology | Breaking the mould

# Lethal fungi are becoming drug-resistant—and spreading

New antifungals offer a glimmer of hope



**Spores for thought** PHOTOGRAPH: STEVE GSCHMEISSNER/SCIENCE PHOTO

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FOR MANY people, the looming threat of antimicrobial resistance has become synonymous with bacteria that can withstand antibiotics. That conflation makes sense. Bacterial infections kill almost 8m people a year, and most are associated with resistant bacteria. But in recent years another kind of microbe has displayed worrying levels of resistance: fungi.

Dangerous fungal infections are rising across the world, especially among the growing number of people with weak immune systems. These infections—systemic, lethal infestations of the body's deep tissues and organs—have little in common with the inconveniences of everyday fungal pathogens such as athlete's foot and ringworm. They are now responsible for an estimated 7m life-threatening infections and more than 2.5m deaths a year. Like their bacterial counterparts, fungi are evolving resistance to the drugs that are meant to fight them. The good news is that more powerful classes of medicines are finally starting to emerge.



Although there are more than a dozen different types of antibiotics, there are currently only three main classes of antifungals: polyenes, azoles and echinocandins. Each attacks a different part of a fungus's cell membrane or cell wall, protective structures that surround the fungal cell and without which it cannot survive. The last of these classes, the echinocandins, were introduced in the early 2000s and since then no new classes have

been approved. Part of the reason is that fungi are much more closely related to animals than bacteria are: anything that kills a fungus may well kill the cells it has infected.

This limited arsenal is shrinking. Just like bacteria, fungi can evolve to withstand drugs through genetic mutations. Azoles, for example, work by targeting an enzyme involved in building and maintaining the fungal cell membrane. Should a genetic mutation cause the enzyme to change, though, the azoles will be ineffective. Scientists believe such mutations arise when fungi are exposed to agricultural fungicides. Though these specifically target fungi that infect plants, they may inadvertently come into contact with human-infecting species in compost heaps or in soil. If a fungicide works by a similar mechanism to an antifungal medicine—say, by targeting the same enzyme—human-infecting fungi can develop resistance to the antifungal even though they have only ever been exposed to the fungicide.

All that has made finding new classes of drugs a priority. Unfortunately pharmaceutical companies rarely see new antifungals as worth the investment. Not only will these drugs become ineffective in turn should resistance ever arise, but people take them only for short periods. That makes them less appealing than drugs taken continuously, such as statins.



Despite these hurdles, wholly new classes of antifungals are finally on the cusp of reaching the

clinic. There is ibrexafungerp, developed by Scynexis and commercialised by GSK, and fosmanogepix, made by Amplyx Pharmaceuticals (which has since been bought by Pfizer). Each has a novel technique for attacking the cell wall, and is in trials against severe and resistant infections. Initial data from small phase-two trials suggest both are effective in around 80% of patients. Another promising candidate is olorofim, developed by F2G, a company based in the British city of Manchester. Instead of affecting the cell wall, olorofim interferes with a fungus's ability to make DNA. In a recent phase-two trial against invasive moulds, it showed a 29% success rate in patients whose infections could not be treated by other drugs.

There may also be more mileage in existing classes of antifungals. On March 19th a group of Chinese scientists reported in *Nature* that they had found a new polyene compound that targets a different part of the fungal cell membrane than older polyenes. In laboratory experiments, it was effective against multi-drug resistant fungi and less toxic than another potent polyene. Though it is still too soon to say how much impact these drugs will have, their arrival is a positive step.

Should the new drugs pass muster, maintaining their lethality will be crucial. But the chance to do so may be slipping away. Regulators in America, Canada, Japan and South Korea have already approved a fungicide called ipflufenoquin that works like olorofim. This has scientists worried; a study published in 2023 showed that strains of one fungus that evolved resistance to ipflufenoquin also showed resistance to olorofim in the lab. The new fungicide aminopyrifen, which targets the same enzyme as fosmanogepix, also contributes to fears that the new drugs may not be effective for long. "It's a giant issue," says Leah Cowen, a fungal geneticist at the University of Toronto.

Regulators and policymakers are starting to take notice. America's Environmental Protection Agency decided in October to make sure it is aware of resistance risks when approving new fungicides. Agencies in the European Union investigated the

use of azole antifungals and fungicides for the first time in January, and likewise recommended that approval of new fungicides should bear antifungal resistance in mind. But exactly what decisions such awareness will prompt remains unclear. Fungicides also do life-saving work: fungal infections are the leading cause of crop failures, destroying up to 40% of the world's annual harvest, the equivalent of food for 4bn people. Regulators consequently cannot just ask farmers to stop using fungicides or refuse to approve new ones. "There is this really difficult balance between the need for food security and the need for protection of our [antifungals]," says Michael Bromley, a microbiologist from the University of Manchester.

The world needs more ways to kill fungi. Innovation might come from faster and cheaper genome sequencing, which allows scientists to search microbial genomes for genes that produce new antifungal compounds as well as find targets that exist in fungi but not in humans. Another potential avenue is to exploit the mycoviruses that infect fungi in nature. Just as viruses that infect bacteria can be used as natural antibiotics, some scientists think that mycoviruses could yield new antifungal therapies. They will need to come up with something, or the rot really will set in. ■



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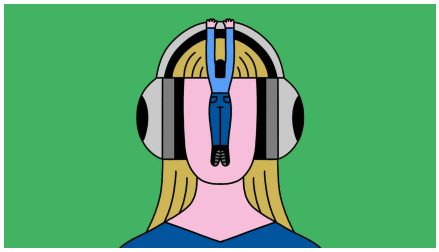

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