



SCIENCE

Humans are not prepared for a pandemic caused by fungal infections

Changes in the environment and climate, as well as fungicide overuse in agriculture, have driven a rise in fungi capable of infecting people and evading the few drugs designed to fight them.

A colored scanning electron micrograph of fruiting bodies of the fungus *Aspergillus fumigatus*. The round structures (conidia) are covered in tiny spores, about to be released into the air. *A. fumigatus* grows in household dust and decaying vegetable matter. Although har... [Show more](#)

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BY **CONNIE CHANG**


PUBLISHED AUGUST 5, 2022 • 14 MIN READ

When the 48-year-old longtime smoker came to Shmuel Shoham, an infectious diseases expert at Johns Hopkins, she was worried about cancer. The woman, who had received a liver transplant decades before, had been coughing and losing weight for months before seeking treatment. The pulmonologist on call biopsied one of the nodules dotting her lungs fearing a tumor. Instead he found *Aspergillus*, a common fungus—which occurs everywhere from compost piles to carpets to the local flower shop.

“I worry a lot about fungus because of the kind of patients I see,” says Shoham, who treats people with compromised immune systems who are particularly vulnerable to opportunistic microbes like fungi. But lately, fungi have been popping up more often in clinical settings. In India, for example, a perfect storm of respiratory tract injuries, immune suppressing steroid treatments, and uncontrolled diabetes have led to a surge in COVID-19 patients contracting invasive, frequently deadly, black-mold fungal infections. Then there’s *Candida auris*, a virulent, blood-borne fungal infection which emerged out of nowhere to become a major human pathogen—one that’s resistant to multiple antifungals and that can colonize surfaces for months.

“What we worry about all the time in the fungal world, is fungi’s potential to cause human disease,” says Tom Chiller, a medical epidemiologist and chief of the Mycotic Diseases Branch at the Centers for Disease Control and Prevention. “There’s a lot of stuff out there we don’t even understand.”

Only about 120,000 of the five or so million fungal species have been identified—of that number, just several hundred are known to harm humans. At the same time, changes in the environment and climate, as well as fungicide overuse in agriculture, have helped to engineer a fitter microbe—capable of evading the limited arsenal humans possess to fight it.

While drug resistant bacteria like Methicillin-resistant *staphylococcus aureus*, or MRSA, have garnered the most attention, Chiller hopes to shine some of that spotlight on fungi too. “Fungi are here—we’re seeing them develop resistance and people are dying from these resistant infections.” [Some estimates](#) posit a mortality rate from invasive fungal infections of up to 50 percent, which translates, globally, to 1.6 million deaths and \$7.2 billion in medical costs per year, though these figures are likely underestimates given the continuing challenges to accurately diagnose cases.

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But why now, when fungi have long existed on the periphery of medicine? According to Chiller, several factors have pushed fungi to the forefront—among them, the microbes’ ability to evolve quickly, the rise of selective pressures forcing them to adapt, and a growing population of susceptible humans.

The wide world of fungi

The speed at which fungi evolve can be startling. Amelia Barber, a microbiologist at the Hans Knöll Institute in Germany, recalls [the case](#) of a cancer patient, whose skin dwelling fungal *Candida glabrata* infection acquired resistance to echinocandin—one of the three major classes of antifungals available—within days of treatment. “We think this organism was actually part of her microflora, and by giving prophylactic drugs to protect her, it was able to become resistant and propagate.”

When Barber genetically sequenced the patient’s fungal samples, taken 12 days apart, she noticed that the fungus had acquired both mutations previously known to endow echinocandin resistance as well as other new mutations. Barber guesses that these additional tweaks enabled the microbe to live in the bloodstream after it spread from the skin, where it normally resides.

“We hypothesized that the changes helped [the fungus] deal with a new nutrient environment and also stick down because there’s a lot of flow in the blood compared to the skin.” An unfortunate side effect? This also made the pathogen more virulent—better able to adhere to the host’s cells and releasing substances to dodge the body’s immune system.

This virulence is what makes invasive fungal infections so dangerous—as opposed to superficial varieties such as athlete’s foot or thrush. Rampaging fungi excrete toxins that destroy tissue, which they can then feed on—similar to the way they decompose organic matter as part of an ecosystem’s nutrient cycle. Like bacteria, fungi can cause organs to shut down through sepsis, an overreaction of the immune system to microbial attacks. Or they can form fungal balls that push aside organs. Resistance just makes things worse: mortality rates are 25 percent higher when an antifungal-resistant pathogen is involved.

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The funaicide connection

Fungal pathogens represent a significant proportion—up to 80 percent—of all diseases affecting plants, destroying [a third of the global crop yield](#) per year. Blue mold, for example, which primarily attacks apples and pears, can propagate quickly through fruit, beginning with soft indentations in the flesh and ending with scattered green-blue spores along the surface. Forests across Europe and North America have been decimated by Dutch elm disease, a fungus spread with the aid of beetles. Overtaking the trees’ vascular system, the infection starves them of water until they wither and die.

But the liberal use of fungicides—the agricultural counterparts to medicinal antifungals for patients—in response to these threats have had unintended consequences.

Application of one common fungicide class, the azoles, for example, quadrupled in the past 10 years, says Marin Brewer, a plant pathologist at the University of Georgia. Analogous to antibiotic use in livestock, fungicide producers promote their product to farmers as a way to bump up crop yields, which leads to their overuse. And because fungicides often employ similar strategies to their pharmaceutical analogs, when fungi become immune to one, they also develop resistance to others.

Although this link had been long suspected, [recently](#) Brewer and her colleague, Michelle Momany, proved it by testing samples of patient-derived *Aspergillus fumigatus*—a fungus that can invade the lungs, forming balls of tangled fungal fibers, and from there, spread to other organs like the brain or kidneys.

Not only were these fungi resistant to azoles, which are used in both hospitals and fields, but also to Quinone outside Inhibitors (QoI), fungicides only used in agriculture. “There is no way that a patient would have a specifically agricultural fungicide-resistant fungal sample, unless that isolate spent time in an agricultural setting,” says Momany, a fungal biologist at the University of Georgia.

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Momany became interested in fungi that were agricultural pests as well as pathogenic to humans while on a research sabbatical in the United Kingdom. There, she learned about the growing concern around azole resistance in *Aspergillus* patients in Europe. When she returned to the U.S., she attended a presentation on the azole-resistant fungal pathogens affecting watermelons given by one of Brewer’s students.

“That’s when we realized we had this intersection of human and plant fungal pathogens and azole resistance,” Momany says.

Similarly, Johanna Rhodes, an infectious disease expert at Imperial College in London, [found](#) that samples of azole-resistant *Aspergillus fumigatus* from the environment were genetically similar to those taken from patients—indicating they came from a common source.

Scientists are still trying to get a handle on the prevalence of such cases. But [one study](#) found that azole-resistant fungal infections in the Netherlands increased from 0 percent in 1997 to 9.5 percent in 2016.

This is a big problem, since developing new antifungal drugs is a lengthy, expensive process, further complicated by the fact that humans and fungi share many genes and biological processes. So, what’s toxic to fungi often impacts us as well, says Momany. Developing drugs that kill fungi while leaving the human body intact—is challenging, and many years elapse between the introduction of new antifungals. Currently, there are only three main classes of antifungals that can be used in patients and several dozen fungicides, says Brewer.

[Common strategies](#)

Seizing on one of the few differences between humans and fungi, fungicides like azoles bind to an enzyme involved in the assembly of ergosterol, a molecule akin to cholesterol in humans and an important component of the fungal cell membrane. Without it, the membrane becomes leaky and disintegrates, killing the microbe.

But resistant fungi outsmart single-target drugs like azoles by evolving a two-fold strategy. First, they change the target enzyme’s shape so that the drug no longer recognizes it. Then, for good measure, they increase production of the enzyme to ensure enough ergosterol gets made and keeps the fungal cells intact.

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A more general tactic that many drug-resistant fungi employ is to manufacture more efflux pumps—transport proteins embedded in the cell membrane—that rid fungal cells of unwanted substances such as heavy metals, pollutants, and other toxic compounds. It’s remarkably effective, says David Fitzpatrick, a fungal researcher at Maynooth University in Ireland, “because the drug goes in and gets pumped back out so quickly that it doesn’t have any time to act on the cell.”

Made for adaptation

Although the mutation rate per generation in fungi is generally lower than those of bacteria or viruses, fungi are master adaptors. And fungi have two key tools: a short life cycle and, in some cases, the ability to reproduce sexually and asexually.

Generations of fungi rise and fall in a matter of hours, so mutations can build up rapidly. But for Brewer, it’s the fungi that can reproduce both sexually and asexually that scare her because they have the highest evolutionary potential. “Maybe resistance to one fungicide develops in one individual and resistance to another fungicide develops in another,” Brewer says. “They can bring those resistances together through sexual reproduction and then it can explode” as their progeny reproduce asexually, spreading spores far and wide.

“And once that mutation is there, the gene that contains it might be duplicated numerous times,” amplifying the fungus’ resistance, says Fitzpatrick. Or a fungus could inherit an entire extra chromosome with multiple mutations that could help it survive in inhospitable environments.

A changing climate

Fungi may be evolving in response to a warming planet, posits Arturo Casadevall, a microbiologist and immunologist at Johns Hopkins.

Most of us don’t realize that our body temperature is a component of our microbial defense system. “But the fact that we’re very hot relative to the environment means that many organisms simply cannot grow at human body temperature,” Casadevall says. He estimates that over 90 percent of fungal species can’t survive temperatures close to 37 degrees Celsius, or 98.6 degrees Fahrenheit, preferring instead a range from 25 to 30 degrees Celsius.

With warmer temperatures becoming more frequent, however, Casadevall fears the balance is shifting. “I worry about the organisms out there, loaded with virulence factors, that can grow at 34, 35 degrees.” Now think of the really hot days that have become more common, Casadevall says. “Think of places like Texas, where temperatures can reach triple digits—those are your selection events,” or situations that drive the proliferation of some traits over others.

He contends that *Candida auris* is the first example of a previously unknown fungal pathogen to emerge as a direct result of climate change. Beginning in 2012, *Candida auris* materialized almost simultaneously on three continents—ready to resist antifungal attacks and invade its victims. “This organism was sitting out there, already drug resistant, when it acquired the capacity to survive at higher temperatures,” Casadevall says.

The mechanism of this heat adaptation is unknown at the moment and is the subject of ongoing studies. But Rhodes thinks it won’t hinge on a single or even a handful of mutations. “It’s going to involve more massive changes,” she says, ranging from edits to genes to adjustments in protein levels to shifts in metabolic strategies.

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For now, fungal pathogens remain opportunistic ones—their danger largely confined to vulnerable populations, including the immunocompromised and the elderly.

“But fungi are constantly evolving to exploit new niches,” says Rhodes, and their path can be difficult to predict. “A pathogen might come along and say, ‘You know what, I’m just going to rip through this population of seemingly healthy people.’”

The threat from fungal pathogens has been historically underappreciated. But Chiller relishes the challenge of grappling with a heretofore low-profile menace. Between college and medical school, he worked for two years at a hospital in Paraguay—helping to diagnose patients with parasitic diseases and malaria, and delivering vaccines to villages by horseback. “I like being the underdog and trying to do things that are challenging because, ultimately, we’re saving lives and helping people.”

So, in the face of uncertainty, what should our next steps be?

Better surveillance, which would help with transmission control, should top the list, says Rhodes. Doctors should be able to easily contribute to and access information to make quicker diagnoses and devise targeted treatment plans.

Chiller agrees, adding that the field also needs additional funding and better laboratory capacity to isolate and test fungal pathogens. In 2018, as a first step, the U.S. Centers for Disease Control and Prevention established the antimicrobial resistance laboratory network, aiming to connect local and national health resources to identify and contain multi-drug-resistant outbreaks—whether they are bacterial, viral, or fungal. “They’re beginning to test for resistant *Candida auris* and *Aspergillus*; and as those numbers come in, it’ll give us a better idea about [disease] burden,” Chiller says.

In the meantime, research into alternatives and adjuncts to antifungals are keeping apace. For example, [several fungal vaccines](#) are currently in clinical trials. And Fitzpatrick and colleagues recently developed [a diagnostic test](#) using a monoclonal antibody that, like the now familiar COVID-19 tests, recognizes a protein on *Aspergillus* and spits out a rapid result.

Fungi are all around us, and play a vital role in our planet’s ecosystem—so coexistence, rather than eradication, is the goal. We should approach fungicide use more thoughtfully, says Brewer. “Only use them when you need them and use them effectively,” rather than spraying them indiscriminately. Here, the rapid acquisition of azole-resistance in *Aspergillus* in the Netherlands serves as a cautionary tale. “*Aspergillus* is not even a plant pathogen—it’s just ubiquitous in the soil,” says Momany.

But because it happened to be in the environment when crops and flowers were sprayed with azole, the pathogen quickly developed resistance to it.

Unfortunately, history seems poised to repeat itself. Researchers cheered when Olorofim, part of a promising new class of antifungals that’s been in development for the past 15 years, finally became available to patients. So many were dismayed to discover that a fungicide with a similar mechanism of action has just been approved by the EPA for agricultural use in almonds and other plants. Clearly, opening lines of dialogue between the different communities, all with their own concerns, is crucial.

“At the CDC, we’re working on having those conversations and thinking through the risks to human health,” while taking into account the importance of fungicides to our global food supply, says Chiller. Brewer is similarly disturbed by the news: “It’s concerning to a lot of people right now that, after this whole issue with the azole drugs, this might happen again.”

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