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The other superbugs

Killer viruses and antibiotic-resistant bacteria aren’t the only infectious threats we face – deadly fungi are coming for us too, finds **Nic Fleming**

IN THE month the first lockdown began in England, the number of people seeking emergency hospital treatment fell by around half. It wasn’t that fewer people needed urgent care, but that many feared catching coronavirus, according to doctors. Those concerns are understandable. While control measures have improved since, in May it was estimated that 5 to 20 per cent of people in English hospitals with covid-19 got it while being treated for something else.

The problem of potentially deadly hospital-acquired infections isn’t restricted to the pandemic. Every year, hundreds of millions of people admitted to hospital globally end up with infections that can be more dangerous than their initial condition. The best known causes include methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* (*C. diff*), often called superbugs for their ability to shrug off antibiotic treatments. A growing list of conditions, such as pneumonia, tuberculosis, sepsis and gonorrhoea, are becoming harder to treat because of antibiotic resistance.

As the current pandemic makes painfully clear, bacteria aren’t the only microbes able to adapt at our expense. In the past few years, a new threat has been setting off alarm bells: treatment-resistant fungal infections. There have been outbreaks at hospitals around the world. Worryingly, 90 per cent of infections caused by the main culprit, *Candida auris*, are now resistant to one of our mainstay antifungal drugs.

This resistance is developing at an “unprecedented” pace, according to a recent assessment, which warns that the problem isn’t just spreading in our hospitals, but also in fields, gardens and the very air we breathe. So how big is the problem? And what can be done?
As with bacteria, thousands of different species of fungi live alongside or within us. Most cause no harm or even serve us well, helping us grow crops, brew beer or make the perfect sourdough. But since at least 500 BC, we have known that fungi can also give us dangerous and even deadly infections.

It was only in 1950 that the first effective antifungal treatment was discovered, and the efficacy of early antifungals was hit and miss. Then, in the late 1960s, came a new class of drugs called azoles, which work by disrupting fungal cell membranes. Although marking a huge step forward, these often had harsh side effects. When more targeted versions of these drugs, known as triazoles, were introduced starting in the late 1980s, we finally had powerful, effective antifungal medicines with far fewer side effects. Today, we have three main kinds of medicines that work against fungal infections: triazoles, amphotericin B and echinocandins.

Most people fend off potential fungal infections without treatment. For instance, Aspergillus fumigatus is so abundant in decaying plants and other organic matter that humans inhale hundreds of its spores daily, and they are usually mopped up by immune cells in the lungs. In people with compromised immunity, though, perhaps due to HIV, chronic lung disease, cancer treatment or post-transplant medicines, A. fumigatus can reproduce and get into the bloodstream. Every year, about 250,000 people worldwide get this condition, known as invasive aspergillosis. That is why having effective medicines is so critical. Before triazoles were developed in the 1990s, the death rate for this condition was around 45 per cent. Today it is 30 per cent.

**Hard to kill**

But it is a relative newcomer that is most quickly outpacing our best medicines. A member of the same genus of fungi that causes thrush, C. auris was first identified in a Japanese woman’s ear in 2009. Within a few years, infections by treatment-resistant C. auris were reported in Asia, Africa and the Middle East. Fungi are rarely capable of efficient transmission between people, yet C. auris has spread rapidly in hospitals on six continents. Most strains are resistant to one or two of the three main classes of antifungal drugs. Some are resistant to all three.

The first C. auris outbreak in Europe began in 2015 at the Royal Brompton Hospital in London, where early efforts to kill the fungus and stop it spreading among patients failed. “It’s almost the perfect pathogen,” says Johanna Rhodes, a genomic epidemiologist at Imperial College London, who was called in to help deal with the outbreak. “One of the things that makes Candida auris so scary is the fact it can linger on inanimate surfaces for long periods and withstand whatever you throw at it.” The fungi could remain viable on surfaces for 28 days, despite several rounds of standard hospital disinfectant procedures, Rhodes found. One US hospital had to rip out ceilings and floor tiles to get rid of it.

In all, some 72 patients tested positive for treatment-resistant C. auris during the Royal Brompton outbreak. By February 2019, there had been more than 260 cases in the UK. Since 2009, there have been cases in more than 30 countries, including 1000 in the US, and major outbreaks in Spain, Venezuela, Colombia, India and Pakistan. When C. auris infections get into the bloodstream, they prove fatal within weeks in more than one in three cases, according to the US Centers for Disease Control and Prevention (CDC), although it can be hard to determine whether people die with or because of the infection because it often affects those with other severe health problems.

That is worrying when we are running out of ways to fight back against resistant fungi. “We’re now seeing strains that are resistant to all classes of antifungals,” says Mahmoud Ghannoum, a fungal diseases specialist at Case Western Reserve University in Ohio. “We’ve always had multidrug-resistant bacteria, but we didn’t have the situation with fungus until now.”

Because many healthcare systems don’t have effective monitoring in place, let alone access to the most accurate genetic tests used
to identify resistant strains, figures on the scale and spread of the problem are likely to significantly underestimate the threat. Many cases go undiagnosed or are misdiagnosed as other conditions. What is clear, however, is that the incidence of treatment-resistant infections is on the rise.

Studies in Dutch hospitals have shown that azole resistance in *A. fumigatus* samples taken from patients nearly doubled from 7.6 per cent in 2013 to 14.7 per cent in 2018. In 2019, nearly 7 per cent of *A. fumigatus* strains found in soil samples in southern England tested positive for azole resistance. Resistant strains have also been reported elsewhere in Europe, the Middle East, South-East Asia, the US, Colombia, Australia and Tanzania.

Between 2015 and 2018, resistance in England to three different antifungal drugs rose significantly in samples of *Candida glabrata*, which can cause bloodstream infections. Other *Aspergillus* and *Candida* species also exhibit resistance to antifungals including triazoles, as do other fungal pathogens including *Scedosporium* and *Fusarium* species, both commonly found in soils.

For the most part, all these strains of fungi are resistant to azoles and triazoles. But it isn’t as simple as opting to use the other two main kinds of antifungals instead. In general, amphotericin B and the echinocandins are less effective, have more side effects, can’t be tolerated by some people and often require daily intravenous therapy in hospital. Paul Verweij at Radboud University Medical Center in the Netherlands found that 62 per cent of patients with invasive aspergillosis who were treated with other drugs because they didn’t respond to triazoles died within 90 days, compared with 37 per cent for those without a triazole-resistant infection.

What is driving this shift – and why does it seem to be happening so fast? For some fungi, the first clues may have been apparent nearly 20 years ago. When Verweij and his team were testing patient samples of *A. fumigatus* to establish the optimum doses of triazoles, they noticed something perplexing. It isn’t unusual for fungi to develop resistance to drugs following a period of treatment. “However, we had samples from patients who hadn’t been treated with azoles that were still resistant,” says Verweij. On further investigation, he and his colleagues found that no pre-1999 samples exhibited resistance and of the 32 later samples that did, 30 had the same genetic mutation. “You would expect more genetic diversity if resistance had evolved in patients, suggesting the driver of resistance was in the wider environment,” he says.

More recent work has shown that two genetic mutations are dominant in antifungal-resistant *A. fumigatus* found in the environment, and these account for 80 to 90 per cent of resistant strains of this species collected from patients.

This may be an unfortunate side effect of efforts to adopt a greener agriculture

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“*Candida auris* is scary – it can live on surfaces for long periods and withstand whatever you throw at it”

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*Aspergillus fumigatus* grows in household dust
system and reduce waste. In 2016, the Dutch government adopted a circular economy strategy in which farmers were encouraged to turn green waste such as stalks and dead leaves into compost using long piles called windrows. These contain both huge quantities of *A. fumigatus* spores and residues of azole fungicides used to protect crops. Tulip bulb farms, agricultural green waste and wood chippings provide the ideal conditions for *A. fumigatus* to build up azole resistance. “Thanks to work in the Netherlands, we now know azole resistance is associated with certain intensely farmed environments,” says Matthew Fisher at Imperial College London. Other countries, including China and Iran, have also documented the spread of azole-resistant *A. fumigatus*. Now researchers are trying to work out whether resistance is developing independently in different locations or being carried by spores on the wind.

The cause of rising resistance isn’t quite as clear with *C. auris*. It was initially thought the rapid spread to multiple countries meant it had hitched a lift with travellers. Then, research showed there were four genetically distinct forms, from Japan, India and Pakistan, South Africa and Venezuela. “It’s a real conundrum,” says Fisher. “It implies that *C. auris* was present in these places, without causing disease and at low prevalence, and then something changed in the environment to allow it to take off within a narrow window of time.”

After finding that *C. auris* can grow at higher temperatures than related species, Arturo Casadevall at the Johns Hopkins Bloomberg School of Public Health in Maryland and his colleagues speculated that it has adapted to thrive in warm environments, including the human body, due to climate change.

Others point to the wide use of azole-based fungicides, which make up around a quarter of those used in agriculture in the European Union, for example. Recent work suggests that different *C. auris* strains share a natural resistance to azole-based compounds, meaning this adaptation probably isn’t recent. It is more likely that this natural defence allowed *C. auris* to move into niches vacated by more susceptible fungal rivals, says Tom Chiller at the US Centers for Disease Control.

Most in the field are convinced that *C. auris* emerged because humans suppressed other fungal pathogens, but many researchers believe this has largely taken place in hospitals through the widespread use of triazoles. “The most compelling hypothesis is that overuse of azoles in the clinic has created an open ecological niche for *C. auris* and led to a restructuring of the fungal populations that parasite humans,” says Fisher.

There are now several large-scale efforts to better understand the causes of antifungal resistance and how to combat it. In March, UK research charity the Wellcome Trust awarded £2.2 million to a group including Fisher and Verweij to sequence samples from thousands of patients infected with *A. fumigatus*. Another group in the Netherlands is seeking to better understand how large-scale composting drives resistance, and to find solutions. “Keeping green waste out of the rain might make it too dry for

“It is harder to make new antifungals than antibiotics because we are more closely related to fungi”

Use of antifungals in agriculture may be driving resistance
Aspergillus to grow,” says Verweij.

For some, the answer is to place greater restrictions on fungicides. “We need to selectively withdraw some azole-based fungicides from use on non-essential crops like the flower and bulb industry, and perhaps things like strawberries,” says David Denning, who researches fungal diseases at the University of Manchester, UK.

Against the resistance

As well as cutting back on the use of fungicides, everyone New Scientist spoke to for this piece agreed that we also need new antifungal drugs. These are harder to develop than antibiotics, in part because we are more closely related to fungi than bacteria. That means substances that kill fungi are more likely to be toxic to us. Clinical trials of potential antifungals can be especially difficult to run because those most vulnerable to fungal infections are often in more fragile health, and the relative lack of attention to fungal pathogens in general has translated into a lack of funding of work on new treatments.

Two drugs, ibrexafungerp and rezafungin, are being tested in trials of large numbers of people, while others are less far along. One of these, olorofim, is part of a new class of drugs that work by blocking production of pyrimidine, a key precursor of DNA. There are others at earlier stages of development, but it could be five years before new drugs are available for patients. When they are, many warn that we should learn from our mistake of using antifungals in agriculture. “When the new antifungal drugs come out, they should be used exclusively for the treatment of human disease, not as fungicides,” says Verweij.

There is another possible technique that could help us halt the rise in resistance: preventing fungal pathogens from disabling our immune defences. During gene expression, information stored as DNA is copied to produce messenger RNA, which is then copied to make proteins. In recent years, researchers have revealed how pathogens use so-called RNA interference to interrupt this process.

Hailing Jin at the University of California, Riverside, has shown how Botrytis cinerea, a fungus that rots many food crops, can transfer small RNA molecules to its hosts to attack their defence mechanisms. She was able to genetically engineer tomato plants that are less susceptible to infection because they produce RNA molecules that undermine these assaults. She also found that fungal pathogens can take up short bits of RNA from the environment. “You could topically apply RNA molecules to the surface of plants so they can get into the cells of a fungus trying to infect them and silence their virulence or growth-related genes,” says Jin. Others are investigating whether azole-resistant A. fumigatus could be targeted in the same way.

It might seem like a strange time to highlight the risks of infectious disease agents other than the new coronavirus. Yet doctors report that people with covid-19 can be more vulnerable to dangerous fungal infections. A small study in India found that 2.5 per cent of people in intensive care for covid-19 developed treatment-resistant Candida bloodstream infections, and that C. auris was to blame for the majority.

Researchers have also identified dozens of cases of covid-19-associated pulmonary aspergillosis (CAPA), in Europe, Asia and South America. In some locations, as many as one in three people in intensive care with covid-19 also had CAPA. The combination of covid-19 and multi-triazole-resistant A. fumigatus has been found to be particularly deadly.

While the broader health burdens and death tolls of drug-resistant fungal pathogens aren’t making headlines, they are certainly large and growing. A critical lesson of the current pandemic is that we must boost our spending on infectious disease preparedness. “Covid-19 teaches us how a pandemic can emerge unexpectedly to have far-reaching impacts on our health, economy and social structure,” says Ghannoum. “We need to invest more in research and development, and prepare our defences – against all types of infectious pathogens.”

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