Comment

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Clouds of dust caused by a fungus engulf a crop field.

Address the growing urgency of fungal disease in crops

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More political and public awareness of the plight of the world's crops when it comes to fungal disease is crucial to stave off a major threat to global food security.

In October 2022, the World Health Organization (WHO) published its first list of fungal pathogens that infect humans, and warned that certain increasingly abundant disease-causing fungal strains have acquired resistance to known antifungals[1]. Even though more than 1.5 million people die each year from fungal diseases, the WHO's list is the first global effort to systematically prioritize surveillance, research and development, and public-health interventions for fungal pathogens.

Yet fungi pose another major threat to human health – one that has received even less attention than infections in people.

Hundreds of fungal diseases affect the 168 crops listed as important in human nutrition by the Food and Agricultural Organization (FAO) of the United Nations. Despite widespread spraying of fungicides and the planting of cultivars bred to be more disease resilient, growers worldwide lose between 10% and 23% of their crops to fungal disease every year, and another 10–20% post-harvest[2]. In fact, the five most important calorie crops – rice, wheat, maize (corn), soya beans and potatoes – can be affected by rice blast fungus, wheat stem rust, corn smut, soybean rust and potato late blight disease (caused by a water mould oomycete), respectively. And losses from these fungi equate to enough food to provide some 600 million to 4,000 million people with 2,000 calories every day for one year[3]. Such losses are likely to increase in a warming world[4,5].

Much more awareness of the plight of the world's crops as a result of fungal disease is needed, as is more government and private-sector investment in crop fungal research.

Adaptive potential unleashed

In a 2019 list of 137 pests and pathogens (ranked according to impact), fungi dominate the first to sixth places for diseases affecting each of the world's 5 most important calorie crops[6]. Wheat, for example, is grown over more land area than any other crop, with production yielding around 18% of all the calories consumed globally each year. Despite mitigation practices, current crop losses worldwide from infections by the Septoria tritici blotch disease-causing fungus *Zymoseptoria tritici*, the main wheat pathogen in temperate areas, range from 5% to 50% (ref. 7). Losses caused by the wheat stem rust fungus *Puccinia graminis*, which frequents more tropical climates, range from 10% to 70% of the harvest[3]. Commodity crops, such as bananas and coffee, which in many countries generate revenue that is used to purchase calorie crops, are also vulnerable to fungal diseases.

Fungi are hugely effective pathogens. They produce massive amounts of spores. The spores of some species can persist in soil and remain viable for up to 40 years. In other species, airborne spores can disperse over distances ranging from a few metres to hundreds or even thousands of kilometres. Wheat stem rust, for example, produces airborne spores that can travel between continents[8], although many other fungi produce prolific numbers of spores more locally, promoting disease spread within and between adjacent fields.

Fungi also exhibit a phenomenal degree of genetic variation and plasticity[9]. Over the past decade or so, genome-wide studies have revealed extensive genetic diversity between and within species of fungi. Although some fungal pathogens undergo frequent sexual recombination, genetic variation can be generated through other processes, too. These include mutational changes conferred by transposable elements (DNA sequences that can change their position in the genome), mitotic (asexual) recombination and the horizontal transfer of genetic material – in some cases, between fungal species, or between fungi and bacteria or plants.

A perfect storm

Current problems have arisen because the adaptability of fungi has met modern agricultural practices.

Most monocultures entail vast areas of genetically uniform crops. (The world's largest monoculture is a field of more than 14,000 hectares of genetically uniform wheat in Canada.) These provide ideal feeding and breeding grounds for such a prolific and fast-evolving group of organisms. Added to this, the increasingly widespread use of antifungal treatments that target a single fungal cellular process (for example, compounds called azoles target an enzyme needed for the formation of fungal cell membranes) has led to the emergence of fungicide resistance.

Together, the azoles, the strobilurins and the succinate dehydrogenase inhibitors (all of which are single-target-site antifungals) comprise more than 77% of the global fungicide market[10]. Moreover, between 2021 and 2028, the market for fungicides is projected to grow by around 4.9% per year – largely thanks to increasing use in low-income countries.

An open question is how the impacts of fungal diseases on crops will be affected by climate change. Although little is known about the response of major plant pathogens to climate change, increasing temperatures in the Northern Hemisphere will drive the evolution of new temperature tolerances in fungal pathogens, and the establishment of pathogens that previously were restricted to more southerly regions[4,5]. In fact, since the 1990s, fungal pathogens have been moving polewards at around 7 km per year[4]. Growers have already reported wheat stem rust infections – which normally occur in the tropics – in Ireland and England.

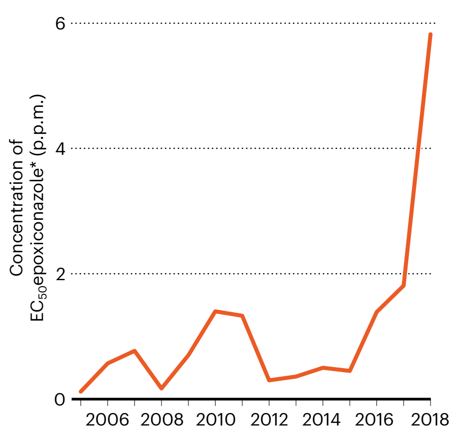
"It is time to move away from reliance on single-target-site fungicides."

Increasing temperatures might also affect interactions between plants and their microbiomes, including endophytic fungi (symbionts that live in plants). Harmless endophytic fungi could become pathogenic as plants change their physiologies in response to environmental stresses[11], which has been demonstrated in studies of the model plant *Arabidopsis thaliana*[12]. Moreover, tolerance to higher temperatures in fungi could increase the likelihood of opportunistic soil-dwelling pathogens hopping hosts, and becoming pathogenic in animals or humans[13].

With the pressures on the food system from a growing human population added to these problems – over the next 30 years, the global population is projected to grow to 9.7 billion – humanity is on track for unprecedented challenges to food production.

EVER HARDER TO CONTROL

The use of antifungals is becoming increasingly widespread in agriculture. This is leading to more fungicide-resistant pathogens.



*Concentration of fungicide needed to inhibit growth of the fungus *Zymoseptoria tritici*, which infects wheat.

SOURCE: T. M. HEICK *ET AL.* IN *APPLIED CROP PROTECTION 2018* CH. 4 (DCA, 2018)

Early promise

Better protecting the world's crops from fungal disease will require a much more unified approach than has been achieved so far – with closer collaboration between farmers, the agricultural industry, plant breeders, plant-disease biologists, governments and policymakers, even philanthropic funders.

It is no longer enough to focus on crop husbandry (such as the clearing or burning of diseased plant tissues), conventional methods of breeding plants for single disease-resistance genes, or the spraying of predominantly single-target-site fungicides. Growers and other stakeholders must exploit various technical innovations to more effectively monitor, manage and mitigate plant disease. Several approaches are already being developed or used to limit disease impacts and protect crop yields; in combination, these approaches could help farmers to sustain their yields in the coming decades.

Discovery and development of antifungals. The development of fungicides has been largely orchestrated in the agrochemical crop-protection industry. It has so far relied on the serendipitous discovery of antifungals following large-scale screening of compounds, such as the by-products of the pharmaceutical industry – and, since the 1980s, on the synthesis of chemical variants of known compounds, such as the strobilurins and the azoles.

However, it is time to move away from reliance on single-target-site fungicides, and to search for compounds that target multiple processes in the pathogen. In 2020, an inter-disciplinary research team at the University of Exeter, UK, revealed an interesting candidate molecule – a lipophilic cation (C_{18}-SMe_2^+) that targets several fungal processes (including the synthesis of the energy-carrying molecule ATP, as well as programmed cell death)[14]. This molecule provides significant crop protection against Septoria tritici blotch in wheat, rice blast in rice[13] and Panama TR4 disease in bananas[15].

Increasing diversity in agricultural fields. Planting seed mixtures that combine several crop cultivars carrying different resistance genes could provide an important way to slow

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Corn smut, a disease caused by the fungus *Ustilago maydis*, affects maize (corn) crops.

down pathogen evolution.

In 2022, around 25% of the total wheat production in Denmark used mixed cultivars, selected because they grow at a similar pace and carry complementary disease-resistance genes. This collaborative venture (involving breeders, farmers, environmentalists and scientists) provided promising results in terms of reducing the severity of both Septoria tritici blotch and yellow and brown rust in mixed cultivars without incurring yield loss (L. Nistrup Jørgensen, pers. comm.).

Indeed, these cultivars could reduce the spread of disease and the erosion of crop-resistance genes[16].

Early disease detection and surveillance. Artificial intelligence (AI), satellites, remote-sensing tools (such as drones), incentives to persuade farmers to report disease and community-science projects that engage the public in the reporting of plant diseases (both in crops and in wild species) are beginning to engender more effective surveillance of fungal disease.

A collaborative scientist initiative called OpenWheatBlast aims to collect research outputs and data on the emerging wheat blast disease. The fast and easy data sharing allows discoveries to be made, resulting in faster disease control (see go.nature.com/42s25a3). Meanwhile, for the Cape Citizen Science project, an initiative funded by Stellenbosch University in South Africa, researchers are asking people who are interested in science to hunt for the oomycete *Phytophthora* spp. in South African vegetation (https://citsci.co.za/disease/) — to create records of the presence and spread of this pathogen.

Data collected through AI, community-science projects and so on could be integrated with disease records and collated into, for example, the PlantwisePlus programme (see go.nature.com/3mlgxnn) led by the Centre for Agricultural and Bioscience International, a non-profit intergovernmental organization. The results could also be integrated with climate data obtained from meteorological offices (for example, see go.nature.com/3ukk5hu) and so inform the building of models that predict when and where plant fungal diseases will occur[5]. More accurate disease predictions could, in turn, trigger early interventions to offset the loss of crops.

Disease resistance and plant immunity. Conventional plant-breeding practices have involved introducing into a given cultivar one or two genes that confer resistance to a particular disease, known as R genes. But although pathogens can overcome this R-gene-mediated resistance in a few years, it can take 10–20 years to go from researchers unmasking an R gene to an agriculture company selling the new cultivar. Incorporating two or more R genes (known as R-gene pyramiding or stacking) can broaden resistance to a diversity of pathogens. Yet field studies have documented how resistance achieved through this means can be short-lived[17].

Most R genes encode proteins with a nucleotide-binding site and a leucine-rich repeat region, which act as receptors in the plant cell. These receptors recognize particular pathogen-produced molecules. However, plants possess an earlier detection system for pathogens, involving extracellular receptor proteins that recognize pathogen elicitor molecules, such as chitin and glucan. (Chitin and glucan are present in the fungal cell wall.) These receptors are known as pattern-recognition receptors (PRRs). This type of 'immune boosting' could be combined with new R-gene-edited cultivars or through R-gene pyramiding using conventional breeding to provide more durable and broader resistance to major pathogens.

A significant barrier to exploiting this approach in a way that is fast and efficient — particularly in Europe — is public and political resistance to the use of transgenic plants. In March, however, the UK Genetic Technology (Precision Breeding) Act was passed into law; this will enable the development and marketing of gene-edited crops in the United Kingdom. In principle, practices such as 'immune boosting', combined with the incorporation of two or more R genes into crops, could endow more durable and broader disease resistance.

Exploiting biologics and crop biotics. Biologics are a broad category of products derived from living organisms. Just as interest in probiotics in medicine has grown over the past decade, so too has interest in the use of biologics in crop protection. This is evidenced by the projected rise in investment by governments and stakeholders.

Strategies currently being explored include the exploitation of living antagonists of plant pathogens, such as the fungus *Trichoderma* spp., and spraying crops with natural antimicrobial compounds, such as polyoxins, which inhibit the synthesis of chitin (for example, polyoxin D zinc salt)[18]. *Trichoderma* strains can impede fungal phytopathogens either indirectly, for example by competing for nutrients and space, or directly, by parasitizing fungi. And in the past decade, researchers have identified other fungal and bacterial endophytes that can help to suppress disease.

Plants do not grow alone — they associate with diverse microbial communities, which can play a part in plant development, stress tolerance and disease resistance. Over the past decade, new methods for profiling microbes have revealed the existence of beneficial microbial networks. The discovery that some microbial species always co-occur, whereas others never do, is essential knowledge in the design of consortia of microbes that can be applied to soil to promote plant growth and enhance disease protection. Indeed, the challenges ahead will include translating these discoveries from laboratory settings to fields of crops, and ensuring that synthetic, beneficial microbial communities persist once they are introduced, and do not adversely affect the native microbiota, or become pathogenic themselves[18].

RNA trafficking between plants and fungi. In 2013, a research team showed that small RNAs (sRNAs) from the grey mould fungus *Botrytis cinerea* can silence plant host genes involved in immunity[19]. Some of the researchers then showed that double stranded RNAs (dsRNAs) and sRNAs from the fungus could protect vegetables and fruit against grey mould disease for up to ten days[20]. However, RNAs (usually encapsulated in tiny vesicles) are not only transferred from the fungus to the host – plant hosts also dispatch vesicles to suppress fungal virulence genes.

A growing number of researchers and newly founded technology companies are now looking to harness these naturally occurring RNA interference (RNAi) based trafficking systems to better protect crops against fungal disease. Currently, investigators are exploring two possible ways of using RNAs. One of these, called host-induced gene silencing or HIGS, relies on the genetic modification of crops. But this approach is lengthy, costly and can't be implemented in the many countries where genetically modified plants remain banned. Therefore the main focus is now on spray-induced gene silencing or SIGS, in which sRNAs or dsRNAs are directly applied to plants, as a new, environmentally friendly and non-genetically modified crop-protection strategy[21].

Several studies have documented the efficacy of RNAi in providing resistance to common fungal pathogens[22]. However, research is still needed to understand how these external RNAs are taken up and transported between the plant and fungal cells. Moreover, although progress is being made in the application of RNAs to crops, questions remain about the stability of the molecules.

A global body for plant health

Between January 2020 and January 2023, the UK Research and Innovation (UKRI) council allocated around US$686 million to COVID-19 research, and almost 225,000 papers on COVID-19 were published globally. (We conducted a search on the Scopus and Web of Science databases, using 'COVID' and 'SARS-CoV-2' as keywords.) During the same period, the UKRI spent around $30 million on fungal crop research and, globally, around 4,000 papers on crops and fungal disease were published. (Scopus and Web of Science key words were 'crops' and 'fungal disease'.) Given that food security engenders health and well-being, agriculture and farmers are arguably just as crucial to human health as medicine and health-care providers.

> **"Agriculture and farmers are arguably just as crucial to human health as medicine and health-care providers."**

Addressing the threat to human health posed by fungal crop diseases will require greater engagement with the problem, and more investment in research from governments, philanthropic organizations and private companies.

The International Plant Protection Convention (IPPC) is a body supported by the FAO that aims to protect the world's plant resources from pathogens. It is much less well known than other bodies that deal with threats to human well-being, such as the WHO. The 180 member states that are signatories of the IPPC treaty must work together to change that.

Because viruses and bacteria dominate as agents of human disease, these microbes have received much more attention than have fungi. Yet in crops, fungi are by far the most important agents of disease. The WHO's list of fungal pathogens that infect humans is a step towards bringing more attention to this extraordinary but understudied group of microbes. But addressing the greatest threats to food security – and so to human health – must include tending to the devastating impacts fungi are having, and will keep having, on the world's food supply.

A quarantined banana farm near Cairns in Queensland, Australia.

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