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

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Short title: Fungicide resistance threatens health and crops

One sentence summary: Emerging resistance to antifungal drugs and fungicides is compromising our ability to treat fungal diseases in humans and in crops, necessitating new approaches to control endemic and emerging infections.

Abstract

We are witnessing an unprecedented rise in the rate of emergence of pathogenic fungi that are resistant to the limited number of commonly used antifungal agents. For example, the azoles are used for human and animal healthcare, for plant crop protection and in antifouling coatings and timber preservation. The ubiquity and dual-use of azoles has hastened the independent evolution of resistance in many environments. One consequence is an increasing risk emerging from naturally occurring 'opportunistic' and antifungal resistant pathogens, which challenge human healthcare. To avoid a global collapse in our ability to control fungal infections and to avoid critical failures in healthcare and food security, we must improve our stewardship of extant chemicals, promote novel antifungal discovery and leverage emerging technologies for alternative solutions.

Introduction

The rapid emergence of multidrug resistant pathogenic fungi and the better-publicised threat of antibiotic resistant bacteria both 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 globalisation pathways (*1*), so disseminating the problems world-wide. Today, crop-destroying fungi account for perennial yield losses of around 20% worldwide, with a further 10% loss post-harvest. Fungal impacts on human health are currently spiralling and global mortality caused by fungal diseases now exceeds that for malaria, or breast cancer, and is comparable to tuberculosis and HIV (*2*). These infections have, hitherto, been greatly neglected relative to other classes of infectious disease, despite occurring in more than a quarter of the world's population.

The first antifungal chemicals used in human healthcare, Nystatin and the polyenes, were discovered in the 1950s, whilst copper and sulphur fungicides were first used to control crop disease over 150 years ago. Today, systemic fungicides and antifungals are frontline treatments for fungal diseases in both humans and plants. This control can, however, be ephemeral as a result of the rapid development of resistance against the chemicals. Fungi have highly plastic genomes and reproduce rapidly producing large populations. The

combination of these properties quickly generates variants, selected for resistance. In plant pathogens, the pace of breakdown is enhanced by monoculture cropping practices, as large swathes of genetically uniform crops provide ideal feeding and breeding 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 to all licensed systemic antifungals has been documented in clinical pathogens, although the rate of emergence varies between drug classes (Fig. 1) (*3*). Likewise, despite the wider range of fungicides licenced 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 due to regulatory changes in, for example the EU.

figure_1.ai

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 chemistries, through organic surface protectant chemistries, to systemic-acting fungicides. There are approximately nine-fold more antifungal compounds available to control crop diseases than to treat systemic animal infections. Licenced treatments in 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 analogue 5-fluorocytosine (5-FC) blocks pyrimidine metabolism and DNA synthesis. The newest class of antifungals, the echinocandins, inhibit (1-3)-β-D glucan synthase and disrupt cell wall biosynthesis. The fourth and most widely used class of fungicides - the azoles, block ergosterol biosynthesis through inhibition of lanosterol 14-α-demethylase. Most fungicides for crop disease target mitochondrial function, the cytoskeleton, or ergosterol biosynthetic pathways (Fig. 1), although some specialist chemistries, such as the aza-naphthalenes for powdery mildew control, target other pathways.

It is important to highlight that the azoles are the dominant chemistry in the treatment of fungal infections in crops, humans and livestock, with 5 licenced clinical azole antifungals and 31 for crop protection.

Parallel drivers of fungicide resistance in the clinic and the field

Human population growth, urbanisation and economic prosperity have fuelled demands for increasing quantity and variety 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 defences. In parallel, the number of humans at risk from fungal infections is rising rapidly, as susceptible populations increase, either through age, medical interventions or HIV infection. Medical advances leading to greater initial survival of cancer or organ transplants can unfortunately leave patients susceptible to secondary attack from opportunistic fungi, leading to increasing use of antifungal drugs in clinical practice. Consequently, we are now witnessing an unprecedented worldwide increase in antifungal resistance, through both space and time (Fig. 2; Supp Table1).

Figure 2 lin.ai

The main drivers that underpin these changes are explored in Fig. 3. The global movement of people and trade in produce has hastened the free-flow of fungal pathogens from country to country, bringing new pathogens into contact with naïve hosts (*1*). In the clinical setting, new species of multidrug resistant pathogenic fungi are emerging. *Candida auris,* first described in Japan in 2009 following isolation from a patient's ear, is responsible for a rapidly increasing number of hospital-acquired invasive infections around the world (*4*). This fungus is now resistant to all clinical antifungals (*5*) and presents a particular threat to intensive-care units since 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, due largely to the increasing prophylactic use of echinocandins and azoles (*7*). There is also a growing threat from filamentous pathogenic fungi which are intrinsically-resistant to a broad range of antifungals; for example *Aspergillus terreus (8)*, *Scedosporium* spp. (*9*), *Fusarium* spp (*10*) and members of the mucorales (*11*). Simultaneously, we are witnessing the relentless

emergence of new races of plant-infecting fungi able to overcome both host defences 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 MBCs was reported in 1969 (*15*) and now MBC resistance is known in over 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*). QoI resistance was reported in field trials even before commercial introduction, and in wider field populations within two years of release (*19*). A new generation of SDHI fungicides has been introduced from 2007, but by 2017, resistant field isolates had been found in 17 pathogen species (*20*). Pathogens with resistance against MBCs, azole, QoIs and SDHIs include the major wheat pathogen *Zymoseptoria tritici*, banana black sigatoka pathogen *Mycosphaerella fijiensis*, cereal powdery mildews *Blumeria graminis*, the emerging barley pathogen *Ramularia collo-cygni* and the apple scab fungus *Venturia inaequalis*. In *Botrytis cinerea* (a generalist pathogen that causes grey mould, particularly on soft fruits), resistance has been reported against 15 different classes of systemic and protectant fungicides (*21*).

figure3.ai

Parallel evolution of resistance mechanisms in the clinic and the field

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

Mutations resulting in conformation changes to the drug target site constitute the most common resistance mechanism in pathogenic fungi. They have been reported in candin-resistant clinical pathogens; MBC, QoI and SDHI-resistant plant pathogens; and azole-resistant strains in field and clinic. A single mutation, G143A in cytochrome *b*, has emerged in the field in over 20 species under selection by QoIs (*14*). Moreover, the Y137F substitution in CYP51 has been found in multiple plant pathogens with partial azole resistance, and Y132F occurs at the equivalent residue in *C. albicans* (*22*). Promoter changes resulting in upregulation of the fungicide target are also common across clinical and plant pathogenic fungi (*23*). In *A. fumigatus*, tandem repeats in the *CYP51A* promoter region

occur together with downstream SNPs in the coding region, conferring a multi-azole resistance phenotype (*24*).

A third resistance mechanism involves reducing intracellular drug accumulation, through upregulation of efflux pumps. The upregulated efflux pumps may be ABC transporters or major facilitators, and their upregulation may result from promoter insertions or transcription factor gain-of-function mutations (*3, 25*).

Further resistance mechanisms have so far been identified only 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 (*26*). Structural genomic plasticity can result in resistance, with chromosome arm duplications leading to efflux pump and target-site overexpression in *C. albicans* (*25, 27*). Hypermutator strains of *C. glabrata* and *Cryptococcus* were recently reported, with the potential to evolve rapidly in response to host and drug selection (*28, 29*).

Dual-use of azoles in the clinic and the field

The azoles are the most widely-deployed class of fungicides in crop protection, totalling, for example, over 26% of all fungicides across the European Union (*30*). Azoles are also frontline drugs that protect humans and animals against pathogenic fungi. However, dual-use may have promoted azole resistance in an opportunistic pathogen of humans, threatening our ability to use this important class of drugs (*30, 31*). The saprotroph *Aspergillus fumigatus* colonises decaying vegetation in fields, forests and compost heaps and also infects immunocompromised humans. Multi-azole-resistant *A. fumigatus* has been recovered from both environmental and clinical samples across multiple continents. In the Netherlands, over 25% of *Aspergillus* infections carry azole-resistance alleles. Azoles are increasingly failing as frontline therapies, with associated patient mortality approaching 100% (*32*). Population genomic analyses have shown that azole-resistant alleles in *A. fumigatus* are associated with selective sweeps in regions of high azole-usage such as India (*33*). Moreover, recombination also occurs, generating new combinations of azole-resistance alleles (*33*). Investigations are now underway to assess the relative contributions of clinical and environmental selection to azole-resistant *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. Medicine and food security are both vital to human health (*34*), and both fields are in urgent need of a wider range of options to control fungal diseases.

However, most cases of fungicide and antifungal resistance across field and clinic 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 antibacterial resistance, which is frequently transferred between animals and humans via the ‘mobilome’ of plasmids and phage (*35*). There is some evidence of horizontal gene transfer among fungi, (*36*) but this occurs on longer timescales than gene transfer among bacteria and the dynamics of resistance arising by this route is thus far negligible.

Prospects for diversifying the toolbox for fungal control

To counter the escalating risks of fungal disease we need to discover antifungal chemistries with novel modes of action, hinder the emergence of resistance in extant chemistries by better stewardship, and develop novel disease control strategies to avoid over-reliance on fungicides:

Development of novel 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 parallels the situation for antibiotics. There is thus a need for increased research activity to develop new antifungal drugs (*37*). Recently, there has been significant progress in this field, with at least 11 antifungals in Phase I-II clinical trials and at least 2 in the AgChem pipeline. Several of these are derivatives of commonly used antifungal chemicals, such as ergosterol biosynthesis and cell wall biosynthesis inhibitors, engineered for higher efficacy, whilst others have new modes of action. Further, combining molecular modelling, combinatorial chemistry and high-throughput screening has the potential to develop chemistries with reduced resistance risk due to the complexity of the molecular changes required (*38*).

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 as alternating treatments, may slow the emergence of resistance. A clinical trial has shown that combinations of fluconazole, flucytosine and amphotericin-B can effectively treat HIV-associated cryptococcal meningitis (*39*). In agriculture, mixtures of fungicides with different modes of action are already widely recommended (*40*), with some formulations only available as mixed products. Where target-site mutations confer high levels of resistance lower doses of antifungals should be favoured (*41*, *42*). However, this results in a trade-off between immediate effectiveness of treatment and slowing the selection of resistance. There is also a need to improve molecular diagnostics, both for the identification of fungal pathogens so antifungals can be used appropriately, and for the detection of specific resistance-alleles as the monitoring of resistance is a vital part of stewardship (*43*).

Integrated disease management: To reduce our reliance on chemical control alone we must develop more non-chemical control measures, to use where effective fungicides are no longer available, or to use in combination with fungicides to reduce the selective pressure on each component. In crops, the development of innate disease resistance through the selection of major pathogen-resistant (R) 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 still takes around a decade (*44*). Transgene cloning or gene editing is faster still (*circa* 2 years), but no crops with transgenic antifungal disease resistance have yet been released commercially. The high degree of specificity between host and pathogen in major R genes (*45*) means pathogens can also rapidly evolve to overcome this control measure. 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 (r), such as the antifungal chitinases and glucanases, carry the advantage of broad spectrum activity (*46*), but suffer the possible disadvantage of yield penalties as well as incomplete protection. Further sources of genetic disease resistance can be found in the gene pools of crop wild relatives, which may be introduced to modern crop varieties through introgression or transgenesis (*44*).

In humans, advances in combination anti-retroviral therapy to halt HIV-AIDS progression, gene therapies under development for cystic fibrosis, or tissue engineering for rejection-free transplants, can reduce vulnerability to fungal infections in such patient cohorts. Also, the first antifungal vaccine, against *C. albicans*, is undergoing clinical trials (*47*) and the use of bioengineered T cells to augment host immunity is being explored (*48*). Finally, the identification of human genetic biomarkers associated with susceptibility to fungal diseases, for example *PTX3* SNPs and *A. fumigatus* (*49*), 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 converging on antifungal treatments using RNA interference (RNAi). Bidirectional cross-kingdom microRNA (miRNA) trafficking between plants and fungi is being developed as a novel strategy to tackle pathogens (*50*), such as *Botrytis cinerea* which uses miRNA virulence effectors to silence host plant immune genes (*51, 52*). 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 (*51-53*). Whilst such approaches have not yet been utilised to treat fungal infections in the clinic, the discovery and use of RNAi as a clinical antifungal approach represents a potentially transformational approach to tackling human fungal infections.

Conclusion

In both fungi and bacteria, the emergence of resistance has outpaced the supply of new antimicrobial compounds. There is an urgent need to increase the pipeline of new active compounds, to improve anti-resistance stewardship of existing products, and to diversify our control toolbox with the development of novel non-chemical control methods.

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Figure Legends

Figure 1. Current antifungal drug classes used against plant and animal fungal infections, and their known resistance mechanisms. There are six main classes of fungicides. These 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); the azoles used also in animal infections), which target the ergosterol biosynthetic pathway; the MBCs (benzimidazoles), which interfere with the cytoskeleton by binding to β-tubulin, so preventing the assembly of microtubules; the QoIs (strobilurins), and SDHIs (succinate dehydrogenase inhibitors), which both inhibit the electron transfer chain of mitochondrial respiration, with the SDHIs inhibiting complex II (succinate dehydrogenase) and the QoIs inhibiting complex III (cytochrome b, Quinone outside binding pocket) and the anilinopyrimidines which may target mitochondrial signalling pathways.

Figure 2. Fungal species with reported antifungal resistance, by country. Increasing colour intensity (red scale) reflects growing number of reports. Plant map reports spatio-temporal records of resistance of crop pathogens to azoles. Human map reports spatio-temporal records of resistance of the pathogens *Aspergillus fumigatus*; *Candida albicans*, *C. auris* and *C. glabrata*; and *Cryptococcus gattii* and *C. neoformans* to azoles. Database derived from peer-reviewed publications as of March 2018, reporting cases of resistance occurring up to 2017 available in Supplementary Information 1.

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

Supplementary content

Supplementary Table 1. Published reports of azole fungicide resistance in plant and clinical pathogens, as illustrated in Figure 2. Plant records comprise spatio-temporal reports (country and year) of resistance to azoles in any plant pathogen species. Human records comprise spatio-temporal reports (country and year) of azole resistance in the pathogens *Candida albicans, C. glabrata, C. auris*, *Cryptococcus* spp., and *Aspergillus fumigatus*. Database derived from peer-reviewed publications as of March 2018, reporting cases of resistance occurring up to 2017.

Supplementary content

Supplementary Table 1. Published reports of azole fungicide resistance in plant and clinical pathogens, as illustrated in Figure 2. Plant records comprise spatio-temporal reports (country and year) of resistance to azoles in any plant pathogen species. Human records comprise spatio-temporal reports (country and year) of azole resistance in the pathogens *Aspergillus fumigatus*; *Candida albicans*, *C. auris* and *C. glabrata*; and *Cryptococcus gattii* and *C. neoformans*. Database derived from peer-reviewed publications as of March 2018, reporting cases of resistance occurring up to 2017.

Pathogen	Country	Year [1]	Reference
Clinical pathogens			
Aspergillus fumigatus	United States	1989	(54)
	Sweden	1995	(55)
	Netherlands	1998	(56)
	Italy	1998	(57)
	Japan	1998	(58)
	United Kingdom	1999	(59)
	France	1999	(60)
	Turkey	2000	(61)
	Norway	2001	(62)

	Spain	2003	(63)
	Iran	2003	(64)
	Australia	2004	(65)
	India	2005	(66)
	Belgium	2006	(67)
	Poland	2006	(68)
	Denmark	2007	(69)
	China	2008	(70)
	Morocco	2010	(71)
	Germany	2011	(72)
	Taiwan	2011	(73)
	Kuwait	2013	(74)
	Tanzania	2013	(75)
	Colombia	2015	(76)
	Romania	2015	(77)
	Pakistan	2016	(78)
	Switzerland	2016	(79)
	Argentina	2017	(80)
Candida albicans	United Kingdom	1984	(81)
	USA	1984	(82)
	Germany	1985	(83)
	Switzerland	1990	(84)
	Poland	1990	(85)
	France	1991	(86)
	Italy	1992	(87)
	Spain	1992	(88)
	Scandinavia	1992	(89)
	South Africa	1992	(90)
	Austria	1992	(91)
	Ireland	1992	(92)
	China	1994	(93)
	Sweden	1995	(94)
	Finland	1995	(95)
	Greece	1996	(96)
	Lebanon	1996	(97)
	Japan	1996	(98)
	Argentina	1997	(99)
	Netherlands	1997	(99)
	Australia	1997	(99)
	Portugal	1997	(99)
	Thailand	1997	(99)
	Venezuela	1997	(99)
	Turkey	1997	(99)
	Czech Republic	1997	(100)
	Singapore	1997	(100)

	India	1997	(101)
	Canada	1997	(102)
	Brazil	1998	(103)
	Israel	1998	(104)
	Philippines	1998	(105)
	Colombia	1999	(100)
	Ecuador	1999	(100)
	Hungary	1999	(100)
	Peru	1999	(100)
	Iceland	1999	(106)
	Malaysia	2001	(100)
	Russia	2001	(100)
	Slovakia	2001	(100)
	Libya	2001	(107)
	Saudi Arabia	2001	(107)
	Denmark	2003	(108)
	Chile	2003	(109)
	Nigeria	2004	(110)
	Korea	2004	(111)
	Mexico	2005	(112)
	Kuwait	2005	(113)
	Niger	2005	(110)
	Tunisia	2006	(114)
	Lithuania	2006	(115)
	Cuba	2007	(116)
	Ethiopia	2008	(117)
	Romania	2008	(118)
	Lebanon	2008	(119)
	Iran	2008	(120)
	Pakistan	2009	(121)
	Kenya	2010	(122)
	Cameroon	2012	(123)
	Egypt	2013	(124)
	Uganda	2013	(125)
	Serbia	2015	(126)
	New Zealand	2015	(127)
Candida auris	Japan	2008	(128)
	Pakistan	2008	(128)
	Korea	2009	(129)
	South Africa	2012	(128)
	India	2012	(128)
	Venezuela	2012	(128)
	USA	2013	(130)
	Colombia	2013	(131)
	Kuwait	2014	(132)

	UK	2015	(133)
	Panama	2016	(134)
	Norway	2016	(129)
	Kenya	2016	(129)
	Spain	2017	(129)
	Germany	2017	(129)
Candida glabrata	Germany	1985	(83)
	UK	1988	(135)
	Switzerland	1990	(84)
	Ireland	1991	(136)
	USA	1993	(137)
	France	1993	(138)
	Italy	1994	(139)
	Spain	1994	(140)
	China	1996	(93)
	Japan	1996	(98)
	Chile	1996	(141)
	Greece	1996	(96)
	Lebanon	1996	(97)
	India	1997	(101)
	Netherlands	1997	(99)
	Australia	1997	(99)
	Portugal	1997	(99)
	Philippines	1998	(105)
	Israel	1998	(104)
	Iceland	1999	(106)
	Malaysia	1999	(142)
	Brazil	1999	(143)
	Taiwan	1999	(144)
	Turkey	1999	(145)
	Saudi Arabia	2001	(107)
	Argentina	2001	(146)
	Singapore	2002	(147)
	Belgium	2002	(148)
	Sweden	2003	(149)
	Denmark	2003	(108)
	Slovakia	2004	(150)
	Korea	2004	(111)
	Mexico	2005	(112)
	Kuwait	2005	(113)
	Nigeria	2005	(110)
	Canada	2005	(151)
	Lithuania	2006	(115)
	Iran	2008	(120)
	Tunisia	2009	(114)

	Kenya	2010	(122)
	Finland	2011	(152)
	Uganda	2013	(125)
	New Zealand	2015	(127)
Cryptococcus gattii	USA	1965	(153)
	Colombia	1989	(153)
	France	1993	(154)
	Zambia	1993	(155)
	Taiwan	1997	(156)
	Canada	1999	(153)
	India	2006	(157)
	Malaysia	2006	(158)
	Brazil	2009	(159)
	Australia	2010	(153)
	Denmark	2016	(160)
	Cameroon	2016	(161)
Cryptococcus neoformans	UK	1986	(162)
	USA	1992	(163)
	Spain	1994	(164)
	Rwanda	1994	(165)
	Congo	1994	(165)
	Gabon	1994	(165)
	Japan	1996	(166)
	Uganda	1996	(162)
	Brazil	1997	(167)
	Cambodia	1998	(165)
	Israel	1998	(168)
	Italy	1999	(168)
	Korea	2001	(169)
	Taiwan	2002	(170)
	Serbia	2002	(171)
	Kenya	2003	(172)
	Romania	2003	(173)
	Kenya	2003	(172)
	France	2003	(174)
	South Africa	2005	(175)
	Brazil	2006	(176)
	India	2006	(157)
	India	2006	(177)
	Malaysia	2006	(158)
	Colombia	2006	(178)
	China	2009	(179)
	Germany	2009	(180)

	Cameroon	2009	(181)
	Australia	2010	(182)
	Canada	2010	(182)
	Thailand	2011	(183)
	Argentina	2015	(184)
	Denmark	2016	(160)
Plant pathogens			
Blumeriella jaapii	1995	USA	(185)
Botryosphaeria dothidea	2000	USA	(186)
Botryosphaeria theobromae	2007	Brazil	(187)
Botrytis cinerea	1990	Israel	(188)
	1992	Germany	(189)
	1997	France	(190)
	2006	China	(191)
Calonectria pauciramosa	2009	Italy	(192)
Calonectria polizzi	2009	Italy	(192)
Cercospora beticola	1995	Greece	(193)
	2002	USA	(194)
	2007	Serbia	(195)
	2012	Germany	(196)
	2012	France	(196)
	2013	Italy	(196)
	2013	Switzerland	(196)
Cladosporium caryigenum	2003	USA	(197)
Colletotrichum gloeosporioides	1988	Costa Rica	(198)
	2001	Taiwan	(199)
	2003	Mexico	(200)
	2013	China	(201)

Colletotrichum nymphaeae	2016	USA	(202)
Colletotrichum truncatum	2013	China	(203)
	2016	USA	(202)
Erysiphe graminis f. sp. hordeii	1980	UK	(204)
	1990	Italy	(205)
	1990	Spain	(205)
	1990	Austria	(205)
	1990	Germany	(205)
	1990	Poland	(205)
	1990	Switzerland	(205)
	1990	France	(205)
	1990	Czech Republic/Slovakia	(205)
	1990	Denmark	(205)
	1991	Canada	(206)
	2014	Australia	(207)
Erysiphe graminis f. sp. tritici	1981	Germany	(208)
	1982	Netherlands	(209)
	1991	France	(210)
	1993	Czech Republic	(211)
	1993	Austria	(211)
	1993	Hungary	(211)
	1993	Slovakia	(211)
	1994	China	(212)
	1997	UK	(213)
	2009	Australia	(214)
	2013	USA	(215)
	2016	Belgium	(214)
	2016	Poland	(214)
Exserohilum turcicim	2009	USA	(216)
Fusarium asiaticum	2007	China	(217)

Fusarium graminearum	2008	China	(217)
	2008	Germany	(218)
	2010	Brazil	(219)
	2011	Italy	(218)
	2011	USA	(220)
	2014	Hungary	(221)
Fusarium moniliforme	2013	China	(222)
Geotrichum candidum	2007	USA	(223)
Golovinomyces cichoracearum	2002	Czech Republic	(224)
Leptosphaeria maculans	2013	Australia	(225)
Magnaporthe grisea	2017	China	(226)
Monilinia fructicola	1992	New Zealand	(227)
	1995	USA	(228)
	2008	Brazil	(229)
	2010	Spain	(230)
Mycosphaerella fijiensis	1994	Costa Rica	(231)
	2000	Cuba	(232)
	2008	Colombia	(233)
	2009	Honduras	(234)
	2009	Guatemala	(234)
	2010	Ecuador	(235)
	2010	Mexico	(236)
	2011	Dominican Republic	(237)
	2012	Philippines	(234)
	2014	Belize	(234)
	2014	Panama	(234)
	2016	Cameroon	(238)
	2016	Ivory Coast	(238)
Mycosphaerella musicola	2014	Australia	(234)

Mycovellosiella nattrassii	1998	Japan	(239)
Penicillium digitatum	1986	USA	(240)
	1989	Argentina	(241)
	1989	Cyprus	(241)
	1989	Greece	(241)
	1989	Israel	(241)
	1989	Italy	(241)
	1989	Morocco	(241)
	1989	Spain	(241)
	1989	Uruguay	(241)
	1990	Japan	(242)
	2011	South Africa	(243)
	2011	Chile	(243)
	2011	Australia	(243)
	2013	China	(244)
Parastagonospora nodorum	1994	Switzerland	(245)
	2001	China	(245)
	2005	Denmark	(245)
	2005	Sweden	(245)
			(53)
Penicillium italicum	1983	Egypt	(246)
	1989	Morocco	(241)
	1989	Turkey	(241)
	1989	Uruguay	(241)
	1994	USA	(247)
Phakopsora pachyrhizi	2009	Brazil	(248)
Podosphaera aphanis	2006	France	(249)
Pseudocercosporella herpotrichoides var. herpotrichoides	1985	France	(250)
	1986	Germany	(251)
	1986	UK	(251)

	1992	South Africa	(252)
	2000	New Zealand	(253)
	2015	Czech Republic	(254)
Pseudocercosporella herpotrichoides var. acuformis	1984	Germany	(251)
	1986	UK	(251)
	1986	France	(251)
Puccinia horiana	1992	Netherlands	(210)
	1997	Germany	(255)
	1999	UK	(256)
Puccinia striiformis	1997	UK	(257)
Puccinia triticina	1997	France	(258)
	1997	Germany	(258)
	1997	UK	(258)
	2007	Brazil	(259)
Pyrenopeziza brassicae	2003	UK	(260)
	1984	New Zealand	(261)
Pyrenophora teres	1986	UK	(262)
	1991	USA	(263)
	1991	Germany	(263)
	1992	Canada	(264)
	1996	South Africa	(265)
	2007	Poland	(266)
	2013	Australia	(267)
	2017	France	(196)
Pyrenophora tritici-repentis	1990	Germany	(268)
Ramularia collo-cygni	2015	Germany	(207)
	2016	Denmark	(214)
	2016	Sweden	(214)
	2017	Ireland	(196)
	2017	Belgium	(196)
	2017	France	(196)

	2017	Austria	(196)
	2017	UK	(196)
Rhizoctonia solani	2011	USA	(269)
	2013	India	(270)
Rhynchosporium commune	1985	UK	(271)
	1988	New Zealand	(261)
	1995	South Africa	(272)
	1999	Switzerland	(273)
	2005	Spain	(273)
	2008	France	(271)
Sclerotinia homoeocarpa	1992	USA	(274)
	1994	Canada	(275)
	2001	Italy	(276)
Septoria pyricola	2006	Greece	(277)
Sphaerotheca clandestina	2005	USA	(278)
Sphaerotheca fuligenea	1981	Netherlands	(279)
	1982	Greece	(280)
	1982	Israel	(280)
	1982	Jordan	(280)
	1982	Spain	(280)
	1982	Syria	(280)
	1983	Norway	(279)
	1983	UK	(279)
	1986	USA	(281)
	1989	Japan	(282)
	1993	Australia	(283)
	2001	Czech Republic	(224)
	2008	South Korea	(284)
Sphaerotheca mors-uvae	1988	Poland	(285)
Sphaerotheca pannosa	1999	Israel	(286)
Stagonosporopsis	2013	USA	(287)

caricae			
	2016	Brazil	(287)
Uncinula necator	1988	Portugal	(288)
	1989	France	(288)
	1989	USA	(289)
	1990	Italy	(288)
	1996	Switzerland	(290)
	1996	Israel	(290)
	1996	India	(290)
	1996	Austria	(291)
	1998	South Africa	(292)
	1998	Australia	(293)
	2008	Chile	(294)
Venturia inaequalis	1984	Canada	(295)
	1985	Germany	(296)
	1985	France	(297)
	1986	Italy	(298)
	1988	USA	(299)
	1990	New Zealand	(300)
	2000	Czech Republic	(301)
	2001	Poland	(302)
	2002	Australia	(303)
	2007	UK	(304)
	2008	Chile	(305)
	2009	Serbia	(306)
	2010	Uruguay	(307)
	2016	Japan	(214)
Venturia nashicola	1995	Japan	(308)
Zymoseptoria tritici	1991	UK	(309)
	1992	Denmark	(310)
	1993	France	(311)
	1996	Germany	(311)
	1999	Switzerland	(312)
	2003	Ireland	(313)
	2007	Belarus	(314)
	2007	Belgium	(314)
	2007	Finland	(314)
	2007	Latvia	(314)
	2007	Norway	(314)
	2007	Poland	(314)
	2007	Sweden	(314)
	2008	Tunisia	(315)

	2009	Russia	(316)
	2009	Czech Republic	(316)
	2009	Austria	(317)
	2009	Lithuania	(318)
	2012	Ukraine	(319)
	2012	USA	(320)
	2012	Australia	(321)
	2013	New Zealand	(322)
	2014	Netherlands	(214)
	2014	Luxembourg	(214)
	2014	Estonia	(323)
	2015	Hungary	(324)

[1] Year of collection of earliest resistant isolate where given (latest year in range where only multi-year pooled data are reported); otherwise, year of publication.