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Crop protection practices and risks associated with human fungal infectious diseases: a One Health perspective

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Abstract – We review interactions between crop protection practices (developed to control plant pathogens and invertebrate pests) and human fungal infectious diseases. Unlike viral, bacterial and parasitic infections, fungal infections in humans are usually only superficial in healthy individuals, but can become invasive and pose serious risks to immunosuppressed individuals. Although their global impact is less than that of other infectious diseases, human fungal infections still pose serious public health issues. For instance, the use of synthetic agricultural fungicides, particularly the azole class, under conventional intensive, or efficiency improvement-based crop protection practices, is at risk as far as antimicrobial resistance is concerned, due to cases of cross-resistance to clinical azoles used to treat pulmonary aspergillosis, candidiasis and cryptococcocis. In this respect, the One Health approach, originally designed for other types of human pathogens, looks relevant for human pathogenic fungi. Additionally, some entomopathogenic fungi used as biocontrol products against crop pests in a substitution-based approach, may be potentially pathogenic to humans. Very few examples of redesign-based practices (*i.e.* Agroecological Crop Protection) emerged from our analysis on human fungal diseases. However, discontinuing agricultural azole fungicides (as practiced on organic farms, and which may to some extent be related to the redesign strategy) appears to be the best way to reduce selection pressure and hence the level of azole-resistant human pathogenic fungal strains in the environment.

Keywords: antimicrobial resistance / aspergillosis / azoles / candidiasis / plant protection

Résumé – Protection des cultures et risques associés aux maladies infectieuses humaines d'origine fongique : une perspective « Une seule santé ». Nous effectuons une revue de la littérature sur les interactions entre pratiques de protection des cultures visant à réguler les populations et dégâts d'agents phytopathogènes et de ravageurs invertébrés, et infections humaines d'origine fongique. Contrairement aux infections virales, bactériennes et parasitaires, les infections humaines d'origine fongique restent généralement superficielles chez les individus en bonne santé, mais peuvent revêtir un caractère invasif et poser des risques sérieux aux individus immunodéprimés. Bien que leur impact global soit moindre que celui d'autres maladies infectieuses, elles posent malgré tout de sérieux problèmes de santé publique. Par exemple, l'utilisation de fongicides agricoles de synthèse, particulièrement de la famille des azoles, dans le cadre de pratiques de protection des cultures conventionnelles intensives, ou basées sur l'amélioration de leur efficience, contribue clairement à la résistance aux antimicrobiens, du fait de résistances croisées aux médicaments azolés utilisés dans le traitement d'aspergilloses pulmonaires, de candidoses et de cryptococcoses. À cet égard, l'approche « Une seule santé » (*One Health*), introduite pour d'autres types de pathogènes humains, s'avère particulièrement pertinente pour les champignons pathogènes de l'homme. De façon plus secondaire, certains champignons entomopathogènes utilisés en lutte biologique contre des insectes ravageurs, dans le cadre d'une approche basée sur la substitution aux insecticides de synthèse, peuvent être potentiellement pathogènes pour l'homme. Par ailleurs, très peu d'exemples de pratiques basées sur la reconception de systèmes de culture (c'est-à-dire relevant de la protection agroécologique des

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cultures) sont ressortis de notre analyse concernant les infections humaines d'origine fongique. Cependant, l'arrêt de l'utilisation de fongicides agricoles azolés (tel que mis en œuvre dans les exploitations en agriculture biologique, et qui peut être considéré comme relevant d'une stratégie de reconception), apparaît comme le meilleur moyen de réduire la pression de sélection et ainsi la prévalence dans l'environnement de souches résistantes aux antifongiques azolés de champignons pathogènes pour l'homme.

Mots clés : résistance aux antimicrobiens / aspergillose / azole / candidose / protection des plantes

1 Introduction

In three recent literature reviews (Ratnadass and Deguine, 2021; Ratnadass and Deberdt, 2021; Ratnadass and Martin, 2022), we used the E-S-R framework proposed by Hill and MacRae (1996) to characterize the impacts of crop protection practices on viral zoonoses, human bacterial infectious diseases, and human parasitic diseases. The E-S-R framework, when applied to crop protection, comprises: (i) improvements to the Efficiency (E) of conventional crop protection practices (essentially agrochemical); (ii) Substitution (S) of these practices (mainly with genetic, physical/mechanical or biocontrol methods); and (iii) agroecosystem Redesign (R) to improve resilience to agricultural pests and pathogens (particularly via biological control through habitat conservation and management) (Tab. 1).

We highlighted that: (i) agroecological crop protection practices (Deguine *et al.*, 2023) generally resulted in a reduction in the risks of viral zoonoses, unlike conventional, agrochemical-based practices which tend to increase risks (Ratnadass and Deguine, 2021); (ii) substitution or biocontrol practices resulted in fewer health risks from infectious bacterial and parasitic diseases (Ratnadass and Deberdt, 2021; Ratnadass and Martin, 2022); (iii) conventional practices or those seeking to increase efficiency generally gave rise to an increased disease risk, whether viral, bacterial or parasitic (Ratnadass and Deguine, 2021; Ratnadass and Deberdt, 2021; Ratnadass and Martin, 2022).

Our analyses therefore showed that despite certain similarities, the conclusions for each group of pathogens in terms of impact of crop protection practices on human and animal health risks could not be extrapolated to other types of pathogens. After studying viral, bacterial and parasitic diseases, it was therefore appropriate to study the last major group of human pathogenic microbial organisms, fungi.

Human-pathogenic fungi and yeasts constitute a very small minority (a few hundred) of the vast number of fungal species in the environment. In contrast to ectothermic animals and plants, mammals are remarkably resistant to invasive fungal diseases (mycoses). Mammalian resistance to invasive fungal diseases is proposed to result from a combination of high basal temperatures, which create a thermal restriction zone, and advanced host defense mechanisms in the form of adaptive and innate immunity (Casadevall *et al.*, 2019). Consequently, fungal infections in humans are usually only superficial, but can become invasive and more serious in immunosuppressed individuals.

Only fungal skin diseases appear specifically in the systematic analysis of the global disease burden study conducted in 2017 by Kyu *et al.* (2018), with an estimated 4,150,000 DALYs (disability-adjusted life-years, which quantifies the harm to human health from specific diseases), compared to 45 million for malaria and 1,430,000 for schistosomiasis. However, according to Banerjee *et al.* (2021), 300,000 cases of invasive aspergillosis and 700,000 cases of invasive candidiasis are reported annually worldwide and when fungal resistance is high, treatment requires a combination of 2 to 3 antifungals.

As regards the integration of plant health into the One Health concept (FAO *et al.*, 2020), and from the perspective of crop protection practices, human mycosis-causing fungi and yeasts are more relevant than other types of human pathogens. This is due to the fact that conventional agricultural fungicides are frequently responsible for antimicrobial resistance, a major One Health issue. The One Health concept stresses that actions and activities in the plant, animal, environment and human health sectors interact and influence the health of the other sectors (Shenge and LeJeune, 2014). Enserink (2009) summarized the controversy over the link between medical azole resistance in *Aspergillus fumigatus* (responsible for pulmonary aspergillosis) and the use of fungicides in agriculture. Although fungicides do not target *A. fumigatus*, which is not a plant pathogen *stricto sensu*, they are suspected to contribute to clinical azole resistance *via* massive use of azole fungicides in European orchards, vineyards and grain fields (Verweij *et al.*, 2009), particularly demethylation inhibitor (DMI) fungicides (Gisi, 2014).

The use of conventional fungicides (including less deleterious synthetic alternatives) pertains to conventional and E-based crop protection strategies (Hill and MacRae, 1996). On the other hand, the impacts of S- or R-based crop protection strategies on human fungal diseases have received less attention. A comprehensive review of the scientific literature was therefore conducted on the impacts of all types of crop protection practices on human fungal or yeast diseases.

2 Review methodology

The data source of this study was Clarivate Analytics' Web of Science Core collection (WoSCC) (Clarivate Analytics, 2021). A systematic review was performed in February 2022. The search equation used was ("fung*" OR "mycos*" OR "mycot*" OR "yeas*") AND ("infect*" OR "diseas*") AND ("human" OR "medic*" OR "public") AND ("health") AND ("crop" OR "crops" OR "plant" OR "plants" OR "vegeta*" OR "agricultur*") AND ("protect*" OR "control" OR "management" OR "practic*" OR "fungicid*"). No restrictions were placed on publication date or language.

The second step was to review the relevance of all references based on their title and abstract, then on the full text. Finally, all the WoSCC-indexed references cited in the selected literature reviews were also reviewed and those relevant to the topic selected (Fig. 1).

Table 1. Processes and examples of agricultural crop protection practices sorted by E-S-R framework category.
Tableau 1. *Processus et exemples de pratiques de protection des cultures classés selon les catégories du cadre conceptuel E-S-R.*

E-S-R positioning	Process*	Examples
Conventional/efficiency (E)	Intensive use of synthetic inputs (particularly pesticides) and move towards a more rational use of the same to improve efficiency	Application of fungicide to crop fields/orchards Fungicide resistance management Bioremediation to limit accumulation of azole fungicides in soil
Substitution (S)	Substitution of synthetic pesticides with non-synthetic pesticides, or substitution of other levers (*e.g.* mechanical) for the same purpose	Entomopathogenic fungi for biological pest control Bat guano for phytopathogenic nematode control
Redesign (R)	Redesign of the entire system as an agro-ecosystem based on ecological processes rather than external inputs	On farm-produced manure and plant waste compost for phytopathogenic nematode control

* After Hill and MacRae (1996) and Dupré *et al.* (2017).

The query resulted in a total of 947 references. Of these, only 31 (21 literature reviews and 10 original research articles) were selected as relevant, after reading the title, abstract and full text. For example, as our review focuses on infectious human diseases, literature on diseases linked to mycotoxins was not selected. Similarly, many references pertained to plant fungal pathogens, the effect of pesticides (including fungicides) on human health or the fungicidal effect of plant extracts on either plant or human pathogens, without reference to human infectious diseases or crop protection practices; these references were therefore discarded. The reverse search carried out on the 21 literature reviews yielded an additional 37 original research articles, making a total of 47 references (Fig. 1).

Only 3 original research articles were published before 2010. A majority (27, or 57%) dealt with aspergillosis, followed by candidiasis (9, or 19%) and cryptococcosis (4, or 9%). The geographical scope was quite broad, with France, Brazil and the Netherlands emerging as leading countries (Fig. 2).

3 Review outcomes

3.1 Aspergillosis

A total of 38 references dealt with agricultural azole fungicides, and 3 with non-azole fungicides. Specifically regarding aspergillosis, agricultural azole fungicides have been demonstrated in the lab to induce cross resistance to medical triazoles since 2012 (Allizond *et al.*, 2021; Garcia-Rubio *et al.*, 2021; Snelders *et al.*, 2012; Zhang *et al.*, 2017; Meireles *et al.*, 2019). Resistance in *A. fumigatus* is frequently caused by alterations in the *cyp51A* gene encoding for lanosterol 14-α demethylase, a key enzyme in the biosynthesis of ergosterol, an essential component of fungal cell membranes (Barber *et al.*, 2020; Cao *et al.*, 2021). It may also be due to overexpression of efflux pumps resulting in a decrease in intracellular drug accumulation (Cao *et al.*, 2021).

The presence of resistant isolates in patients with no previous exposition to triazole is considered to be evidence of the environmental origin of these resistant strains (Beer *et al.*, 2018). The high incidence of azole resistance in agricultural environments has been demonstrated in the UK (Bromley *et al.*, 2014),

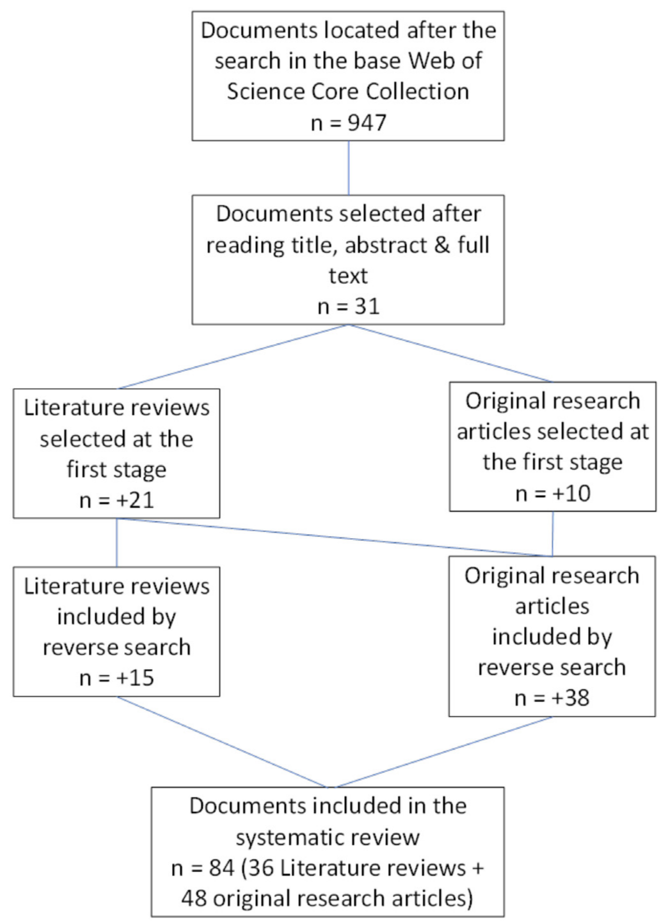

Fig. 1. General outline of the literature search.
Fig. 1. *Schéma général de la recherche bibliographique.*

India (Chowdhary *et al.*, 2012), Denmark (Mortensen *et al.*, 2010), the Netherlands (Schoustra *et al.*, 2019) and Germany (Barber *et al.*, 2020) and is attributed to different crops (summary in Tab. 2).

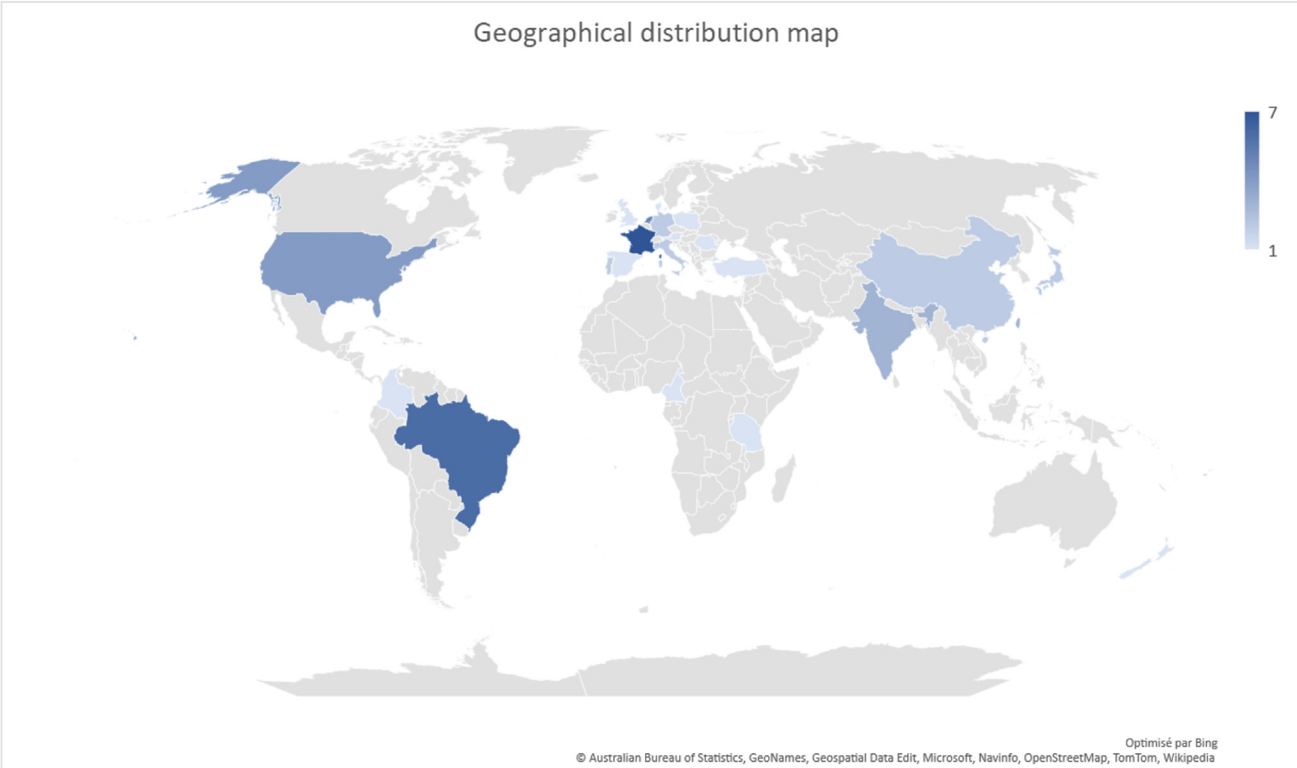

Fig. 2. Geographical distribution of research articles identified for the review, with number of relevant articles shown on the right-hand side bar.
Fig. 2. *Distribution géographique des articles de recherche identifiés pour la revue bibliographique ; le nombre d'articles pertinents est indiqué dans la barre de droite.*

Some studies, however, found a low number of azole resistant isolates in cereal crops treated by fungicides (Fraaije *et al.*, 2020; Toyotome *et al.*, 2016) making the implication of ornamental crops more likely (Godeau *et al.*, 2021; Hagiwara, 2020; Rocchi *et al.*, 2021). Similarly, Barber *et al.* (2020) concluded that given the overall low azole resistance in agricultural isolates, azole use on crops did not significantly contribute to resistance in *A. fumigatus*. Kano *et al.* (2015) also concluded that spraying crops with agricultural tetraconazole did not induce resistance to medical itraconazole in *A. fumigatus*.

On another note, Hagiwara (2020) found that fungicide treatment of tulip bulbs with benomyl or prochloraz effectively reduced the rate of contamination by azole-resistant *A. fumigatus*. Lastly, Léchenault-Bergerot *et al.* (2019) and Godeau *et al.* (2021) described how the use of hemp-based materials could limit the accumulation of fungicides (*e.g.* difenoconazole) in soils, which should limit the development of resistance.

3.2 Candidiasis and cryptococcosis

The antimicrobial resistance phenomenon was also reported with other pathogenic fungi and other type of fungicides, due to the similarity of the molecules used in agriculture and in medical treatments which induce the same resistance mechanisms. For instance, the increased expression of transmembrane transporters of the ATP-binding cassette family (ABC) is described as the main mechanism for azole resistance in *Candida* spp. (Rocha *et al.*, 2016). The major mechanism of resistance to azole drugs demonstrated for *Cryptococcus* spp. is the overexpression of efflux pump genes (Bastos *et al.*, 2018).

Cross resistance reported in pathogenic yeasts *Candida* spp. (Brilhante *et al.*, 2019; Chen *et al.*, 2019; Faria-Ramos *et al.*, 2014; Lo *et al.*, 2017; Müller *et al.*, 2007; Potocki *et al.*, 2020; Rocha *et al.*, 2016; Yang *et al.*, 2012) and *Cryptococcus* spp. (Bastos *et al.*, 2018, 2019: Carneiro *et al.*, 2020; Dongmo *et al.*, 2016) were ascribed to fungicide treatments on various crops (summary in Tab. 3). Some insecticides were reported as producing azole resistance in pathogenic *Candida* spp. (Potocki *et al.*, 2020).

3.3 Other pathogenic fungi or yeasts

Some pathogens (*e.g.*, *Fusarium* spp.) have not been found to have this resistance to azole drugs (Homa *et al.*, 2018). Similarly, Serfling *et al.* (2007) found no evidence for a direct relationship between resistance in *Colletotrichum graminicola* to agricultural azoles and the development of resistance to medical anti-fungal agents. Conversely, comparisons have been made between organic and non-organic agriculture, which confirmed the growth of resistant strains of pathogenic fungi (responsible mainly for mycotoxicosis or allergies, and also opportunistic fungal infections), in environments where fungicides are used repeatedly (Barber *et al.*, 2020; Rocchi *et al.*, 2021; Schoustra *et al.*, 2019; Zukiewicz-Sobczak *et al.*, 2012).

Table 2. Main references demonstrating impacts of the use of agricultural azole fungicides in specific crops on the emergence of clinical azole-resistant strains of *Aspergillus fumigatus*.
Tableau 2. *Principales références démontrant les impacts de l'utilisation de fongicides agricoles azolés sur des cultures spécifiques, sur l'émergence de souches d'*Aspergillus fumigatus *résistantes aux antifongiques cliniques azolés.*

References	Countries	Crops	Agricultural azoles*	Clinical azoles**	Percent of resistance
Alvarez-Moreno *et al.* (2019)	Colombia	Carrots, potatoes, maize, strawberries, pea	ns	Itraconazole, voriconazole	25% of soil samples had resistant strains
Barber *et al.* (2020)	Germany	Wheat, barley	Difenoconazole, tebuconazole	Itraconazole, voriconazole, posaconazole	1–3% of agricultural isolates
Bromley *et al.* (2014)	UK	Wheat, barley, oilseed rape	Prothioconazole, tebuconazole, cyproconazole, epoxiconazole	Itraconazole, voriconazole, posaconazole	1.7% of rural isolates
Cao *et al.* (2021)	China	Rice	Tebuconazole, difenoconazole, posaconazole, propiconazole, hexaconazole, prochloraz	ns	2.4–20.0% of soil samples
Godeau *et al.* (2020)	France	Tulip	ns	Itraconazole, voriconazole	71% of soil samples around a clinical area
Kano *et al.* (2015)	Japan	Vegetables	Tetraconazole	Itraconazole	0%
Prigitano *et al.* (2014)	Italy	Apple, cucurbit	ns	Itraconazole, voriconazole, posaconazole	21% of environmental soil samples
Ren *et al.* (2017)	China	Vegetables, fruits	Epoxiconazole, tebuconazole, propiconazole, hexaconazole, metconazole	Itraconazole, voriconazole	5.8% of soil samples from greenhouses
Rocchi *et al.* (2014)	France	Wheat, barley	Epoxiconazole, tebuconazole, propiconazole	Itraconazole, voriconazole	0.7% of agricultural soil isolates
Rocchi *et al.* (2018)	France	Vegetables	Difenoconazole	Itraconazole, voriconazole	10% of market garden soil samples
Schoustra *et al.* (2019)	The Netherlands	Wheat, maize, fruits, flowers	Azaconazole, bromuconazole, cyproconazole, difenoconazole, epoxiconazole, flusilazole, flutriafole, metconazole, penconazole, propiconazole, prothioconazole, tebuconazole, thiabendazole, cyazofamid, fenamidone, iprodione, triazoxide, imazalil, prochloraz	Itraconazole	na
Sharma *et al.* (2015)	India, Romania, Tanzania	Sunflower, flowers	Bromuconazole, cyproconazole, difenoconazole, epoxiconazole, penconazole, tebuconazole, triadimefon	Itraconazole, voriconazole, posaconazole, isavuconazole	25% of soil and woody debris samples

ns: not specified; na: not applicable.
* Molecules applied to crops in the environment.
** Molecules in clinical use for which isolates found in the environment have been tested for sensitivity.

Table 3. Main references demonstrating impacts of the use of agricultural pesticides on the emergence of clinical azole-resistant strains of *Candida* and *Cryptococcus* yeasts.
Tableau 3. *Principales références démontrant les impacts de l'utilisation de pesticides agricoles sur l'émergence de souches de levures* Candida *et* Cryptococcus *résistantes aux antifongiques cliniques azolés.*

Reference	Countries	Yeasts	Agricultural pesticides*	Clinical azoles**
Brilhante *et al.* (2019)	Brazil	*Candida parapsilosis* complex	Tebuconazole, tetraconazole	Fluconazole, itraconazole, voriconazole
Chen *et al.* (2019)	Taiwan	*Candida tropicalis*	ns	Fluconazole
Faria-Ramos *et al.* (2014)	Portugal	*Candida glabrata*	Prochloraz	Fluconazole, posaconazole
Lo *et al.* (2017)	Taiwan	*C. tropicalis*	Triadimenol	Fluconazole
Müller *et al.* (2007)	Germany	*Candida albicans*	Fluquinconazole, penconazole, tebuconazole, triadimenol	Ketoconazole, itraconazole, fluconazole, voriconazole
Potocki *et al.* (2020)	Poland	*C. albicans*, *Candida pulcherrima*, *C. glabrata*, *C. tropicalis*	Epoxiconazole, acetamiprid, thiacloprid	ns
Rocha *et al.* (2016)	Brazil	*C. parapsilosis*	Tetraconazole	Fluconazole
Yang *et al.* (2012)	Taiwan	*C. tropicalis*	ns	Fluconazole
Bastos *et al.* (2018)	Brazil	*Cryptococcus gattii*, *Cryptococcus neoformans*	Tebuconazole	Fluconazole, itraconazole, ravuconazole
Bastos *et al.* (2019)	Brazil	*C. gattii*	Pyraclostrobin	Fluconazole, itraconazole, ravuconazole
Carneiro *et al.* (2020)	Brazil	*C. gattii*	Benomyl	Fluconazole

ns: not specified.
*Molecules applied to crops in the environment.
**Molecules in clinical use for which isolates found in the environment have been tested for sensitivity.

Some fungi used as entomopathogens in biological pest control (*e.g. Beauveria bassiana* and *Metarhizium anisopliae*) are reported to potentially cause disease in humans (Dorin *et al.*, 2015; Gürcan *et al.*, 2006; Kisla *et al.*, 2000; Tucker *et al.*, 2004). Finally, one article referred to the possible issues arising from guano manipulation (excreta of pigeons or bats, used for phytopathogenic nematode control purposes, or as organic fertilizer) which may carry pathogenic fungi (Dongmo *et al.*, 2016).

4 Discussion

4.1 Relevance of the review methodology followed

The high exclusion rate (96.7%) of articles obtained in the literature search using the proposed search equation could indicate that the selection criteria were not sufficiently well defined at the outset. However, it also ensures that no relevant references were missed. On the other hand, although this review did not use the terms of the E-S-R conceptual framework (Hill and MacRae, 1996) in its search equation, it showed that the conceptual framework used in above-mentioned earlier literature reviews could be used to characterize the impact of crop protection practices on the risk of fungal diseases in humans, a notion supported by several literature references.

4.2 Conventional and efficiency-based practices

As *A. fumigatus*, *Candida* spp. and *Cryptococcus* spp. are not agricultural pathogens of significant importance, they are not targets of fungicidal field applications. However, agricultural azole fungicides are suspected to increase the risk of fungal diseases in humans *via* the selection of human pathogenic strains of *e.g. A. fumigatus*, *Candida* spp. and *Cryptococcus* spp. with cross-resistance to medical azoles (Jørgensen and Heick, 2021). The massive use of fungicides in agriculture has been demonstrated to increase the risk of pathogen resistance to antifungal medical treatments (*e.g.* Brilhante *et al.*, 2019 for *C. parapsilosis*), a major health concern (Sewell *et al.*, 2019).

The mutations leading to the resistance of *A. fumigatus* to azole fungicides are well-known (reviewed in Berger *et al.*, 2017). The presence of resistant isolates in patients who have not been previously exposed to azole drugs (azole naïve patients) and the type of mutations (TR/L98H, which consist of a substitution at codon 98 of *cyp51A* and a 34-bp tandem repeat in the gene-promoter region: Verweij *et al.*, 2009) emphasized that the sources of these isolates were more likely environmental rather than due to selection within the patient (Buil *et al.*, 2019; Chowdhary *et al.*, 2013).

The recent review by Burks *et al.* (2021) supported the idea that azole-resistant *A. fumigatus* might spread via contaminated plant material and dispersal.

One option to limit this risk, within the E-based strategy, is the recourse to synthetic fungicides other than azoles. However, some non-azole fungicides, and even some insecticides, were found to contribute to increased cross-resistance. Corkley *et al.* (2022) reviewed fungicide (including DMI azole) resistance management options (central to the E-based strategy), and stressed that even when fungicides individually select for mutations with partial or negative cross-resistance, their combined use may instead select for generalized resistance mechanisms.

The use of azole fungicides is important in crop protection, and limiting the use of these molecules on crops to prevent antimicrobial resistance affecting their clinical use could result in a reduction in yield which may threaten global food supply. Using bioremediation to limit the accumulation of azole fungicides in soils and the development of antimicrobial resistance is another E-based strategy (Léchenault-Bergerot *et al.*, 2019; Godeau *et al.*, 2021). Conversely, Yu *et al.* (2022) found that biogas residues, substitutes for chemical fertilizers, affected the dissipation of the fungicide difenoconazole in rice fields by lengthening its half-life.

4.3 Substitution-based practices

The deployment of crop varieties resistant to specific pathogens may be part of an "S" approach. This strategy aims to delay the development of AMR to agricultural triazoles and associated medical antifungal cross-resistance, if it is concomitant with the discontinuation of agricultural fungicides.

As part of the "S" strategy, non-synthetic alternatives to azole (DMI) fungicides for agricultural fungal pathogen control include mineral fungicides, notably mixtures (*e.g.*, sulfur for powdery mildew) or mycopesticides (*e.g.*, *Lecanicillium*). On the other hand, replacing synthetic insecticides with entomopathogenic fungi is a very promising agroecological crop protection strategy. In some cases, these entomopathogenic fungi were reported to have negative impacts on human health. This is notably the case for the hyphomycetes *Metarhizium* spp. (Nourrisson *et al.*, 2017) and the entomophthorale *Conidiobolus coronatus* (Chappity and Hallur, 2021; Vilela and Mendoza, 2018). Such cases remain rare and usually only affect vulnerable, *e.g.* immunosuppressed individuals.

Bat guano can be used as fertilizer and for its antimicrobial and anti-nematode effect (Keleher, 1996; Zuhair *et al.*, 2022). Handling bat guano risks exposing users to pathogenic fungi *e.g.*, *Cryptococcus* spp. (Dongmo *et al.*, 2016). The risk to health is even higher from inhalation of fungal spores from *Histoplasma capsulatum*, causing life-threatening histoplasmosis in humans (Jayasvati and Jayasvati, 2018). However, the risk may be reduced with adequate composting (Gómez Londoño *et al.*, 2019).

4.4 Redesign-based practices

Organic agriculture is often presented as an example of redesign, especially when done at the farm scale and relying on "alternative on-farm inputs" as proposed by Dupré *et al.* (2017) in their framework adapted from Hill and MacRae (1996). At the farm level, fertility management, pest and disease management and crop-livestock integration must be reconsidered. The use of azole fungicides is not permitted on organic farms and this is the best way to decrease selection pressure and therefore the degree of resistant strains in the environment (Rocchi *et al.*, 2021).

The use of often complex organic fertilizer not only improves soil fertility and plant growth, but may also regulate pathogens and pests. Farm-produced animal manure may be used on cultivated crops, in part due to its capacity to reduce plant parasitic nematode populations (Amulu and Adekunle, 2015; Renčo and Kováčik, 2012), although the effect is less pronounced than with plant compost. However, plant waste, compost and woody debris are effective culture media for human pathogenic fungi and should be used with care (*e.g.* Avery *et al.*, 2012). Spore-forming organisms are more resistant to the composting process than most bacteria, viruses and parasitic organisms.

5 Conclusion

The main objective of crop protection practices is to improve the health of cultivated plants by reducing damage caused by crop pests and pathogens. However, crop protection practices may affect the health of humans, domestic animals and the environment in diverse ways. Specifically, they may affect (positively or negatively) the risk of infectious diseases in humans, as is the case for viral zoonoses (Ratnadass and Deguine, 2021), bacterial infections (Ratnadass and Deberdt, 2021) and parasitic diseases (Ratnadass and Martin, 2022). This review ends our series of literature reviews on the impact of crop protection practices on human infectious diseases. It confirms that in terms of the impact of crop protection practices on human diseases, despite certain similarities, the lessons learnt for one type of human pathogen cannot necessarily be extrapolated to others.

This analysis highlighted the importance of buildup of clinical azole resistance in human populations suffering from pulmonary aspergillosis or candidiasis (and to a lesser extent cryptococcosis) following exposure to agricultural fungicides, particularly triazoles. Antimicrobial resistance is a major public health concern which is particularly relevant to One Health and this trend is associated more with the use of agricultural fungicides than with agricultural antibiotics.

Furthermore, "E"-based strategies were found to be as irrelevant for fungal diseases as for parasitic diseases. "S"-based strategies yielded mixed results, a positive effect when they resulted in a reduction of azole fungicides, but a negative effect when they aggravated disease risks. However, compared with other types of infectious diseases, virtually no examples of "R"-based (or agroecological crop protection) practices *per se* emerged from our analysis on fungal diseases. Nevertheless, discontinuing the use of azole fungicides (as on organic farms, where practices are close to "R"-based or agroecological crop protection, relying on on-farm inputs) appears to be the best way to decrease selection pressure and hence the level of azole-resistant strains in the environment.

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