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LETTER TO THE EDITOR

Dear medical mycologists, it is time to look outside the box

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One sentence summary: Recent studies demonstrated that our environment can represent an alternative niche for several opportunistic fungal pathogens that can be a concern for human health.

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ABSTRACT

Opulente *et al.* (Opulente DA, Langdon QK, Buh KV *et al.* Pathogenic budding yeasts isolated outside of clinical settings. *FEMS Yeast Res* 2019;19:foz032) published early this year a study aiming to investigate the diversity of wild yeast species, by collecting 1000 environmental samples coming from different substrates across the United States of America. The main finding of this work is the recovery of 54 strains of budding yeasts of which several are having a pathogenic potential in the clinical setting, such as *Candida albicans*, *C. parapsilosis*, *C. tropicalis*, *Nakaseomyces glabrata* and *Pichia kudriavzevii*. These findings, discussed here in light of other recent studies highlighting the role of fungicides in the rise of antifungal resistance in the clinical setting or the emergence of *Candida auris*, demonstrate that our environment can represent an alternative niche for several opportunistic fungal pathogens that can be a concern for human health.

Keywords: yeast; antifungal resistance; environment; pesticides; opportunistic fungi; one health

I read with interest the manuscript of Opulente *et al.* (2019) published early this year. To gain further insights into the diversity of wild yeast species, the authors collected 1000 environmental samples (different substrates) across the United States of America. The main finding of this work is the recovery of 54 strains of budding yeasts of which several are having a pathogenic potential in the clinical setting, such as *Candida albicans*, *C. parapsilosis*, *C. tropicalis*, *Nakaseomyces glabrata* and *Pichia kudriavzevii* (the two latter known as *Candida glabrata* and *Candida krusei*, respectively in the clinical setting). The authors also highlighted that *P. kudriavzevii* is significantly associated with plants and *C. tropicalis* with soil.

Despite a relatively modest number of isolates of opportunistic yeasts (54 out of the 5000 isolates), these observations confirm earlier studies reporting human pathogenic yeasts

outside the clinical setting (Van Uden, De Faia and Assis-Lopes 1956; Yang *et al.* 2012; Wójcik, Kurnatowski and Błaszowska 2013; Wojcik *et al.* 2016; Bensasson *et al.* 2019). For example, *C. albicans*, a major human pathogen and also a commensal of the human gut, has been recently reported in oaks in the United Kingdom (Bensasson *et al.* 2019). We also observed similar findings during a pilot study in western France, including 40 soil samples. Despite a different protocol and incubation at 30°C to expect a possible enrichment in medically relevant species, we identified, along with various basidio- and ascomycete yeasts, several opportunistic pathogens including *C. tropicalis* ($n = 2$), *Pichia guilliermondii* ($n = 2$), *Pichia norvegensis* ($n = 1$), *Clavispora lusitaniae* ($n = 1$), *Candida pelliculosa* ($n = 1$), *Cyberlindnera fabianii* ($n = 1$) and *Candida sake* ($n = 4$) (unpublished data). Altogether this provides further evidence on the role of the environment as

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a source of clinically relevant fungal pathogens. This is of major interest as, despite small variation between countries, *Candida* species rank in the top three or four pathogens responsible for health-care-associated bloodstream infections and are associated with a 10 to 20% attributable mortality (Pappas et al. 2018).

Despite the huge diversity of fungi evolving in our environment, their impact on human fungal diseases has been mainly highlighted for molds. One example is *Aspergillus fumigatus*, occurring in the environment as a saprophyte but which can cause a wide range of clinical manifestations, ranging from asthma to life-threatening infections, in susceptible hosts (van de Veerdonk et al. 2017). Since 10 years, physicians and researchers dealing with aspergillosis are facing antifungal resistance (Denning and Perlin 2011). Actually, environmental sampling has unveiled an unexpected environmental route of azole resistance that is turning into a public health issue (Verweij et al. 2009; Le Pape et al. 2016; Lavergne et al. 2017). Basically, when exposed to azole fungicides in the environment (fungicides are widely used for cereal or flower crop protection), *A. fumigatus* can develop acquired resistance mechanisms that also confer cross resistance to medical azoles. This is the scenario explaining the worrisome increase of azole resistance in *A. fumigatus* in the clinical setting. Actually, there are several other examples of environmental filamentous fungi impacting human health, such as dermatophytes, *Alternaria* spp., *Fusarium* spp. and Mucorales (Bongomin et al. 2017).

By comparison, this field of research has been less investigated and is almost neglected when dealing with yeast infections. In the clinical setting, as some *Candida* species belong to the natural flora (such as the gut for *C. albicans* and *C. glabrata*, and the skin for *C. parapsilosis*), the infective strain is usually considered to originate from the patient's endogenous flora (Neville et al. 2015). Hence, the occurrence of alternate environmental niches for these yeasts challenges this dogma. Be that as it may, a literature review of the last years provides additional arguments. One example is *C. tropicalis*, ranking first in patients with haematological malignancies with invasive candidiasis and being the second or third etiological agent of candidemia in Asia and Latin America (Horn et al. 2009; Nucci et al. 2013; Tan et al. 2016; Pappas et al. 2018). Since 2009, China is witnessing an increased prevalence of fluconazole-resistant *C. tropicalis* isolates in hospital wards (Fan et al. 2017). In a recent study, fluconazole non-susceptibility in clinical isolates of *C. tropicalis* reached 33% in Taiwan (Hii et al. 2019). Notably, molecular typing revealed the circulation of genetically related *C. tropicalis*-resistant clones across different hospitals and in soil samples (Yang et al. 2012; Chen et al. 2019). This explains why antifungal-naïve patients can develop invasive infections caused by *de novo* resistant isolates (Chen et al. 2019). This situation strongly reminds the *Aspergillus fumigatus* scenario described above. Therefore, in addition to act as niche for pathogenic yeasts, our environment is also a possible reservoir of *de novo* antifungal-resistant isolates resulting from cross-resistance with pesticides (Brilhante et al. 2019). An additional example is the elegant demonstration using population genetic analysis that *P. kudriavzevii* clinical isolates are not genetically distinct from environmental isolates suggesting that susceptible hosts can acquire *P. kudriavzevii* infections from the environment (Douglass et al. 2018). Last but not the least, *Candida haemulonii*, a multidrug-resistant species formerly described from fish guts and later isolated in cassava roots, has been responsible for invasive infections in the clinical setting (Van Uden and Kolipinsky 1962; Khan et al. 2007; Ferreira et al. 2010). Yet there are countless other examples, like

Diutina catenulata (known in the clinical setting as *Candida catenulata*), another pathogenic yeast whose draft genome has been recently published from an environmental isolate from Ireland (O'Brien et al. 2018). Susceptible hosts can also be occasionally infected by species associated with specific reservoirs or environments, such as the black yeast *Exophiala xenobiotica*, inhabiting environments rich in monoaromatic hydrocarbons and alkanes (Morio et al. 2012) or the neurotropic basidiomycetes *Cryptococcus gattii*, which causes ~225 000 new cases globally every year, and is associated with soil, pigeon droppings and tree hollows (Herkert et al. 2017). Finally, *Candida auris*, an emerging species in the clinical setting, has also been proposed to come from our environment, subjected to climate change and to spread worldwide with birds, as illustrated with *C. glabrata* (Al-Yasiri et al. 2016; Casadevall, Kontoyiannis and Robert 2019).

Besides the clinical interest, environmental sampling also has the potential to improve our knowledge about yeast biodiversity. For example, by bringing together public citizens and mycologists, the Citizen Science initiative conducted by the Westerdijk Fungal Biodiversity Institute and the Utrecht University Museum led to the discovery of at least six new ascomycetes yeast species in Dutch garden soil (Groenewald et al. 2018).

These findings also raise some questions: Do these observations only demonstrate that some spots are highly trafficked by humans or that the environment can serve as an alternate natural habitat for these yeasts? How environmental pressures exerted by climate change and fungicides could fade the boundaries between our environment and human health? Applying the 'One Health' concept, time has come to encourage any initiative aiming to extend our view about the role of the environment and its impact on human health. Such projects would require collaborative efforts at a global scale and the involvement of various specialists, including clinicians, medical mycologists, environmental specialists and veterinarians, along with support from governmental institutions. It is time to go ahead and look outside the box!

Conflicts of interest. None declared.

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