

Yeast-contaminated water as a potential emerging health concern: a review

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Invasive fungal infections pose a serious risk to human health; therefore, it is important to study the dissemination and proliferation of pathogenic fungal species in the environment. This could prove useful in preventing infections in susceptible individuals, such as those who are immune-compromised or suppressed. Pathogenic yeasts belonging to the genera *Candida*, *Cryptococcus* and *Rhodotorula* are commonly found in various water sources that are used for daily activities and are included in the World Health Organization fungal priority pathogens list, further warranting investigation into the possibility that infections may occur through contact with yeast-contaminated water. In addition, the close association between antifungal pollutants and yeast in water may induce acquired antifungal resistance development, further complicating the effective treatment of these infections. Thus, investigating the presence and antifungal susceptibility of yeast found in water and identifying ways to monitor potential fungal pathogens may prove useful in combating invasive fungal infections. This review deals with the occurrence and infection risks posed by pathogenic yeasts in water as well as the possibility of these yeasts acquiring antifungal resistance due to the simultaneous presence of antifungal compounds from medical and agricultural runoff.

INTRODUCTION

Humans can have direct or indirect contact with water-borne fungi that may include pathogenic yeast species. These yeast species pose health risks to individuals who have weakened immune systems (Alcazar-Fuoli and Mellado, 2014; Bongomin et al., 2017; Parslow and Thornton, 2022; Pour et al., 2018), in the form of invasive fungal infections, which according to recent estimates, account for 3.8 million deaths annually (Denning, 2024). Considering the threat that opportunistic pathogenic yeasts pose, it is imperative to investigate how these organisms spread and proliferate in the environment and in what environments they thrive. Potentially pathogenic yeast species have been identified in various water sources, including wastewater, drinking water and seawater (Ayanbimpe et al., 2012; Evans and Seviour, 2012; Pour et al., 2018; Pereira et al., 2009; Yamasato et al., 1974; Yang et al., 2011). Their presence in water may be due to the shedding of these organisms from the human microbiome or from other environmental sources (Adams et al., 2013). Interestingly, potentially pathogenic yeast species belonging to genera such as *Candida*, *Rhodotorula* and *Cryptococcus* seem to be common in all of the above-mentioned water sources as well as in the treated water from wastewater treatment plants (WWTPs) (Kacprzak et al., 2005; Monapathi et al., 2021a; Monapathi et al., 2021b; Pereira et al., 2009; Yamaguchi et al., 2007; Yang et al., 2013). This indicates the lack of effective removal of fungal species by current wastewater treatment methods.

Fungi are also overlooked in the regulation of water quality (Sonigo et al., 2011), further supporting the hypothesis that the vast network of connected water sources contributes to the dissemination of pathogenic yeasts. An additional concern is the development of antifungal resistance due to environmental pollution by antifungals. Antifungals are commonly found in water due to fungicide runoff from the agricultural industry (Dalhoff, 2017), personal care products (e.g., shampoos and topical ointments) being washed down the drain (Liu et al., 2016; Yao et al., 2016) and the excretion of antifungal medication by humans into wastewater systems (Kahle et al., 2008). Previous studies have shown that WWTPs collect antibiotics and antibiotic-resistant bacteria, as well as antimicrobial resistance genes, and that this close association of resistance components may lead to the development of antibiotic-resistant bacteria (Osińska et al., 2020; Turolla et al., 2018). It is theorised that the association between yeast and antifungals in the environment may also lead to an acquired resistance through constant exposure to low levels of antifungals (Fischer et al. 2022). Finding ways to monitor the presence of multidrug-resistant yeast species may help the health sector prepare for and treat fungal infections more effectively and efficiently.

This review aims to highlight the occurrence of potentially pathogenic yeasts in various water sources as well as the risk for the development of antifungal resistance within these habitats. We also advocate for increased surveillance of these emerging pathogens.

FUNGAL INFECTION INCIDENCE AND SEVERITY

Fungal infections, including yeast infections, affect more than a billion people and cause approximately 3.8 million deaths annually (Denning, 2024). The major driver in fungal infection incidence is the increase in cases of cancer, asthma, HIV/AIDS, chronic obstructive pulmonary disease and tuberculosis (Bongomin et al., 2017; Pour et al., 2018). Other causes of invasive fungal infections

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include the use of more aggressive therapeutic approaches (e.g., chemotherapy, immunotherapy, organ transplants) that lead to patients being in a prolonged state of immunosuppression (Alcazar-Fuoli and Mellado, 2014), and other underlying health conditions which increase the probability of opportunistic infection (Parslow and Thornton, 2022).

Invasive candidiasis (including candidemia) is a common fungal infection caused by yeast species from the *Candida* genus, with an estimated occurrence of 1 500 000 cases per year (Fig. 1). Five *Candida* species, namely, *Candida albicans*, *Candida glabrata*, *Pichia kudriavzevii* (anamorph = *Candida krusei*), *Candida tropicalis* and *Candida parapsilosis*, cause more than 90% of these cases (Parslow and Thornton, 2022), with *C. albicans* being the predominant causative agent (Pfaller et al., 2007). Another *Candida* species which is also considered to be an emerging nosocomial pathogen with global occurrence is *Candida auris* (Al-Rashdi et al., 2021; Du et al., 2020). Reports indicate that *C. auris* is associated with high mortality rates (30–60%), especially in immunocompromised individuals (CDC, 2019).

Even though literature frequently highlights the severity of candidiasis, these infections are still neglected by public health authorities (Parslow and Thornton, 2022). This has prompted the World Health Organisation (WHO) to publish the first Fungal Priority Pathogens list, which includes *Candida* spp. among the critical and high priority groups (WHO, 2022).

Other yeast genera containing species capable of causing invasive fungal infections include *Cryptococcus* and *Rhodotorula*, which are frequently isolated from the aquatic environment. According to the National Institute of Communicable Diseases in South Africa (NICD, 2022), *Cryptococcus* is the leading cause of meningitis as well as the second leading cause of death among adults living with HIV in low- and middle-income countries (Rajasingham et al., 2022). It is estimated that there are 194 000 annual cases of cryptococcal meningitis that result in 118 000 directly attributable cryptococcal-related deaths globally (Denning, 2024). *Cryptococcus neoformans* was also recently included in the critical priority group of the Fungal Priority Pathogens group by the WHO (WHO, 2022). *Rhodotorula* spp. are currently considered emerging pathogens, mainly infecting immune-compromised individuals (Gomez-Lopez et al., 2005; Jarros et al., 2020). Members of this genus show resistance against azoles and echinocandins, limiting available treatment options, and in China this yeast is the main non-*Candida* causative agent for invasive fungal infections (Chen et al., 2021; Xiao et al., 2018). Infections by *Rhodotorula* can

cause systemic, central nervous system, ocular and intraabdominal infections, with *Rhodotorula mucilaginosa* being the most common causative agent (Ferreira et al., 2022).

RISK OF YEAST EXPOSURE THROUGH WATER

Approximately 25% of people worldwide lack access to basic drinking water management services (UN Water, 2021). The countries with the lowest access are those in sub-Saharan Africa and Oceania. Furthermore, 35% of the 2 billion people without access to basic sanitation live in sub-Saharan Africa (WHO and UNICEF, 2019), with 37% of households in South Africa still without access to water-borne sewage systems (StatsSA, 2017). These households still make use of non-sewered sanitation systems like pit, bucket and chemical toilets. Pit latrines are typically not isolated from the surrounding soil; thus water from these latrines can seep into groundwater. Heavy rainfall can also cause pit latrines to overflow, placing surrounding residents in danger of exposure to possible pathogens (Graham and Polizzotto 2013; Sengupta et al., 2018). This makes it important to assess the risk of contracting invasive fungal infections from water polluted by opportunistic or pathogenic yeasts.

Steffen and colleagues (2023) aimed to shed light on the risk of contracting invasive yeast infections by developing a Quantitative Microbial Risk Assessment framework to determine the potential risk of yeast infection from consuming water from high- and low-pollution water samples from river water in Stellenbosch, South Africa. This framework considered variables such as the pathogenic potential of the species, based on clinical data considering the fraction of symptomatic infections, the infecting inoculum and the fraction of deaths from infection, as well as the estimated dose that will be received during both accidental and intentional ingestion of the water. Several assumptions were made during the establishment of the framework, including that people ingest yeast-containing water every day; that all strains of a species react similarly when ingested; that 37°C mimics the stress a yeast will be exposed to in a host; that translocation from the intestines to the bloodstream happens post-ingestion and that the murine model mimics human hosts. This framework was applied to six clinically relevant yeast species (*C. albicans*, *C. tropicalis*, *C. glabrata*, *Candida lusitanae*, *Meyerozyma guilliermondii* (anamorph = *Candida guilliermondii*) and *P. kudriavzevii*). In highly polluted water, *C. albicans* and *C. tropicalis* had the highest annual probability of causing infection via ingestion. *C. glabrata* had the highest risk assessment of strains detected in both

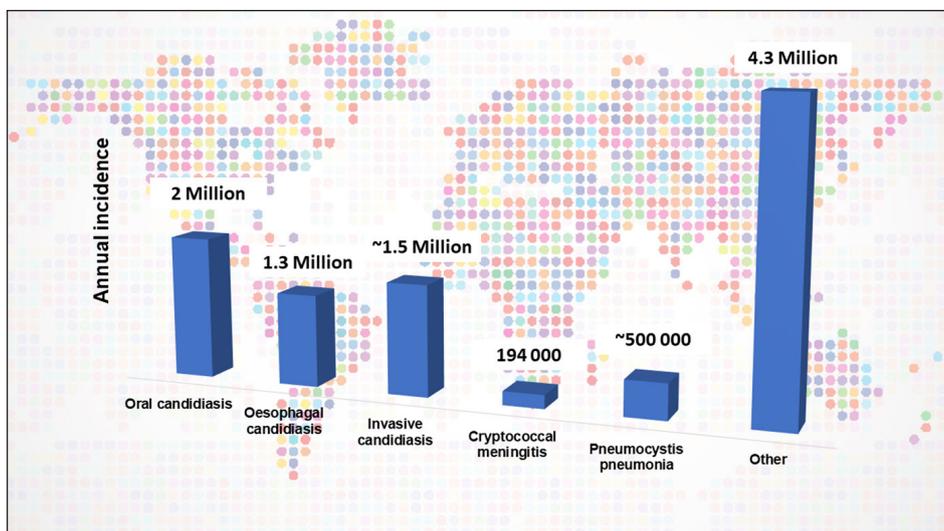


Figure 1. Annual incidence of fungal infections (based on data from Denning, 2024)

highly polluted and less polluted samples. Although the risk of *C. neoformans* infection from water was not assessed and may indeed be low due to infection being primarily via inhalation, it is known that direct inoculation into tissues is possible (Christianson et al., 2003). In addition, *C. neoformans* can occasionally cause gastrointestinal infection (Maziarz and Perfect, 2026; Naranjo-Saltos et al., 2020). Thus, water contaminated with pathogenic yeast may pose a health risk to communities that come into contact with them, although for *C. neoformans* more research into the possible risk is needed.

HOW COMMON ARE PATHOGENIC YEASTS IN WATER?

Fungi have been identified in various water sources, including the marine environment, freshwater sources, hospital water and WWTPs (Arvanitidou et al., 1999; Medeiros et al., 2012; Yamasato et al., 1974; Yang et al., 2011). Although yeasts are generally present in low numbers in water, they can reach significant densities. Hagler and Ahearn (1987) reported average counts of up to 50 colony forming units (CFUs)/L in seawater, 100 CFUs/L in lakes and 500 CFU/L in rivers, while urban estuaries have been reported to contain 2 800 CFUs/L. It is also known that yeasts can survive for prolonged periods of time in water (Starmer and Lachance, 2011). For example, *R. mucilaginosa* has a mean survival of over 600 days in river water (Peter and Peter, 1988).

Recent studies have expanded our knowledge regarding the occurrence of pathogenic yeasts in various water sources. Fourteen rivers and four lakes from the Doce River basin in Brazil were studied (Medeiros et al., 2012), and *Candida* spp., including the opportunistic pathogens *M. guilliermondii*, *C. parapsilosis* and *P. kudriavzevii*, were found. Similar results were also found in surface water from the North West Province, South Africa (Monapathi et al., 2021a). Here *Candida* was also the dominant genus, with *C. tropicalis* the most abundant species in all the sampling sites in this study.

Pereira and co-workers (2009) investigated the presence of yeasts in three different drinking water sources (surface, spring and groundwater) in Portugal. Various *Candida* spp. were also identified in bottled mineral water dispensers and municipally supplied tap water in Brazil, with *C. parapsilosis* most frequently isolated, followed by *C. glabrata* and *C. albicans* (Yamaguchi et al., 2007).

Similarly, a study done on 150 water samples, from Jos, Nigeria, identified *C. tropicalis* as the most prominent species in the water samples (Ayanbimpe et al., 2012). Investigation of potable water from hospitals and community taps in Thessaloniki, Greece (Arvanitidou et al., 1999), as well as biofilms in water distribution systems in Springfield, Missouri (Doggett 2000), identified species of *Candida* and *Rhodotorula*. In addition, Novak Babić and co-workers (2016) found that ground and tap water contain various opportunistic yeasts, including *R. mucilaginosa*, *C. parapsilosis*, and *M. guilliermondii*.

Numerous studies point to sewage acting as an ideal medium to support the growth of various filamentous fungi as well as yeast (Cooke 1970; Cooke and Pipes 1969; Fakhru'l-Razi and Molla 2007; Kacprzak et al., 2005), where these may play a role in degradation of polysaccharides and production of secondary metabolites, which may influence the surrounding bacterial community. Importantly, some of the yeasts in activated sludge are known pathogens, including *C. albicans* and *P. kudriavzevii* (Cooke 1970; Cooke and Pipes 1969; Kacprzak et al., 2005).

From all these studies it can be concluded that water frequently contains pathogenic yeast species, yet the inclusion of fungal regulation in water quality assessments is still sparse. For instance, the South African Water Quality Guidelines (DWAF, 1996) do not regulate the fungal load in treated water. Given that there is a risk of infection due to ingestion of water containing some of these yeasts, further research is needed regarding the need for regulation.

ANTIFUNGALS PRESENT IN WATER AND ASSOCIATED RESISTANCE

Antifungals are frequently found in the environment due to use in pharmaceutical, veterinary and agricultural industries. Azoles are the most commonly used antifungals in the treatment of superficial and invasive mycoses (Vanreppelen et al., 2023), and they are used in agricultural fungicides (Hof 2001; Li et al., 2019; Toda et al., 2019). Antifungals are also used as food preservatives (Dalhoff, 2017) and in personal care products (Liu et al., 2016; Yao et al., 2016). Thus, it is not surprising that they are pollutants in water sources such as freshwater, groundwater and WWTPs (Fig. 2) (Assres et al., 2020; Chen et al., 2014; Huang et al., 2010; Huang et al., 2013; Lindberg et al., 2010; Liu et al., 2016; Monapathi et al., 2017; Monapathi et al., 2021b; Yao et al., 2016).

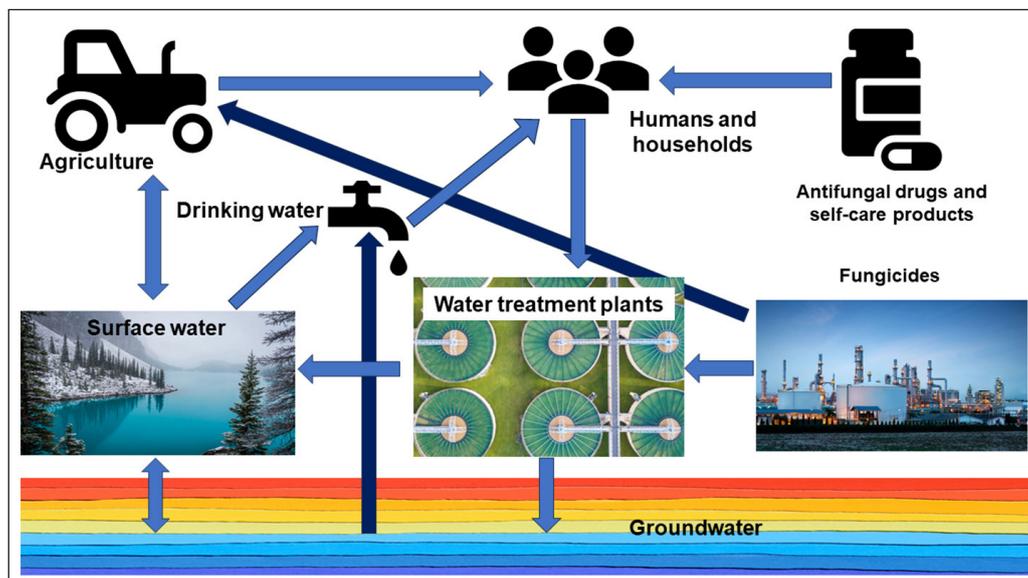


Figure 2. Route of transmission of antifungals from various sources to water. Antifungals enter water through waste discharge from industrial, hospital and domestic sources as well as from agricultural runoff. Humans have frequent contact with various of these antifungal polluted water sources through daily activities.

Antifungals/fungicides identified in freshwater include fluconazole, econazole, miconazole, climbazole, flucytosine, ketoconazole, propiconazole, tebuconazole and carbendazim (Chen et al., 2014; Huang et al., 2013; Monapathi et al., 2021a; Monapathi et al., 2021b). Monapathi et al. (2021a) found a positive correlation between fluconazole concentration and the presence of *C. tropicalis*. To further support the idea of antifungal resistance originating in aquatic environments, Monapathi and co-workers (2017) tested antifungal resistance of pathogenic yeasts isolated in 2013 and 2014 from the same freshwater sources in the North West Province of South Africa and found all the isolates to be resistant to miconazole and flucytosine. In addition, 88.5% of isolates were resistant to fluconazole and econazole, 62.8% were resistant to miconazole, and 64.1% were resistant to ketoconazole.

Similar to fresh water, antifungals including clotrimazole, econazole, fluconazole, itraconazole, ketoconazole, posaconazole and miconazole are repeatedly found in WWTPs (Assress et al., 2019; Assress et al., 2020; Huang et al., 2012; Kahle et al., 2008; Peng et al., 2012), with fluconazole being the most abundant azole in wastewater influent and effluent (Assress et al., 2019; Assress et al., 2020). WWTPs can function as important hubs that aid in the dissemination of bacterial resistance genes into environmental waters. This is frequently seen in the identification of antibiotic-resistant bacteria in treated and untreated wastewater as well as surrounding waters (Alexander et al., 2020; Kotlarska et al., 2015; Osińska et al., 2020). Many studies have concluded that WWTPs have become a collection area for antibiotics, antibiotic-resistant bacteria as well as resistance genes, and that treatment plants contribute to the development of antimicrobial resistance in bacteria (Birošová et al., 2014; Naquin et al., 2015; Osińska et al., 2020; Turolla et al., 2018;). However, few reports are available on how the presence of antifungals in WWTPs can contribute to the development of antifungal resistance, although the occurrence of both fungi and antifungal drugs may result in conditions which are favourable for development of acquired resistance in fungi (Fischer et al. 2022). Using the risk quotient method, Assress et al. (2020) determined that the risk for selection of resistance to the azoles by fungi was moderate to high for fluconazole and itraconazole in the studied South African WWTPs.

WASTEWATER SURVEILLANCE AND ITS APPLICATION

Wastewater surveillance, or wastewater-based epidemiology (WBE), is the monitoring of wastewater for agents of interest, such as viruses, that could indicate a possible disease outbreak and overall health of a community. It is well documented that monitoring wastewater can help to determine the potential disease burden of a community (Brumfield et al., 2022; McCall et al., 2020), since pathogens are frequently shed by humans during active infection (Feachem et al., 1983; Sinclair et al., 2008). In addition, WBE can also point to possible future outbreaks, aiding healthcare professionals to prepare accordingly (McCall et al., 2020). Clinical data on disease incidence only cover a select proportion of the population who are admitted to or voluntarily go to the hospital, while WBE assesses the complete community of an area, including individuals who prefer home care or who cannot afford to go to hospitals. Thus, it is more accurate and less biased as an indicator on the overall health of a community. Figure 3 depicts the basic workflow of wastewater surveillance.

Previously wastewater surveillance has been used to monitor poliomyelitis outbreaks in Charlestown, North Carolina (Paul et al., 1939), and in recent times this method has been used to detect vaccine-derived poliovirus in the sewage of north and east London as well as detection of wild poliovirus type 1 in Israel, before the virus caused any cases of paralysis (Anis et al., 2013; Wise 2022). Another recent application of WBE is in the monitoring of SARS-CoV-2 viral loads to predict Covid-19 outbreaks in specified areas (Brumfield et al., 2022; Hart and Halden 2020; Peccia et al., 2020; Wu et al., 2021). WBE has also detected various bacteria, including human pathogens, and detection of coliforms present in WWTPs are essential for the evaluation of the efficacy of wastewater treatment procedures.

Although WBE seems to be ideal for use as an early warning system and to provide reliable and rapid information regarding the health of a community, there are limitations to this method. These include cost and logistics, complexity of the wastewater matrix (including the presence of PCR inhibitors) (Walden et al., 2017) and dilution and stability of biomarkers (Mao et al., 2020).

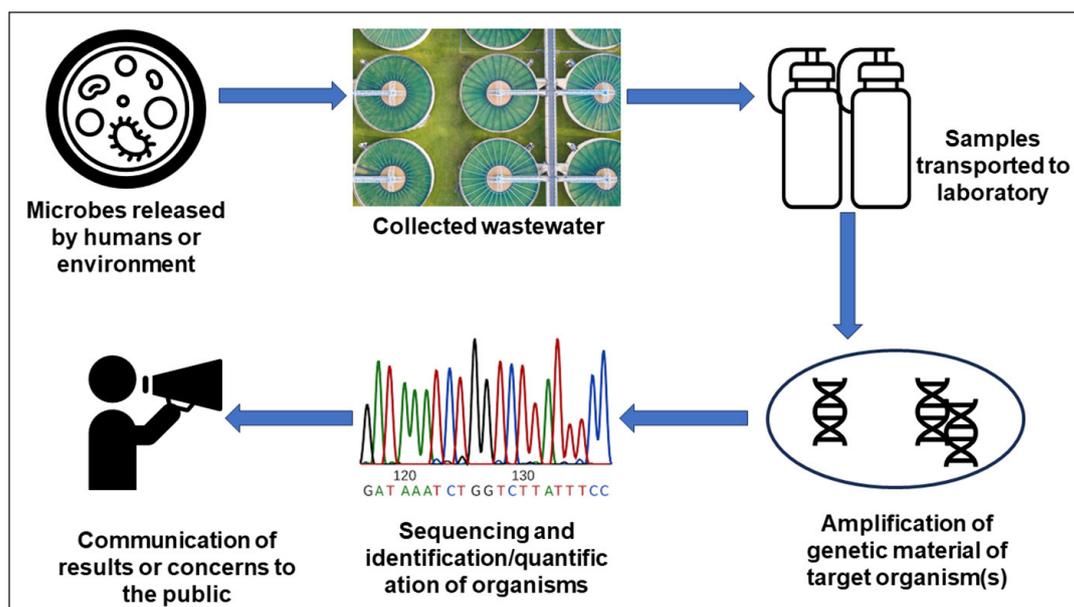


Figure 3. Basic workflow of wastewater surveillance. Wastewater is transported to a central location for treatment, samples are collected at these locations or any other sewage access point according to a method the researchers deem most fit. Collection is followed by processing and the extraction of genetic material, either RNA or DNA, from the samples in a laboratory. After extraction, biomarkers in genetic material are amplified and identified using reverse transcription–polymerase chain reaction and next-generation genomic sequencing to identify pathogens or other target microorganisms. Data obtained are then communicated to the public.

Applying this system for the identification of pathogenic yeast may also present unique challenges. One of these challenges is that fungal species can only be identified if the genome database used contains the specific sequence (Ryberg and Nilsson 2018). Since fungal genome databases still have limited reference sequences, this can lead to the false identification of a yeast. Despite these challenges, recent attempts at targeted WBE for the important emerging pathogen, *C. auris*, have shown promise (Babler et al., 2023; Barber et al., 2023; Rossi et al., 2023; Zulli et al., 2024), laying the foundation for future application of this system for other pathogenic yeasts.

CONCLUSIONS

Pathogenic yeasts are commonly found in various water sources with which humans and animals are in frequent contact. Considering that yeasts are cultured from the effluent of WWTPs, the lack of regulations regarding the presence of fungi in treated wastewater and the insufficiency of wastewater treatment processes is evident. In addition, the presence of pathogenic yeast strains in drinking water might pose a risk of infection as shown for *C. albicans* and *C. kudriavzevii*. These yeasts may be disseminated via water transport systems, thus allowing them to reach a larger proportion of the population with both healthy and susceptible individuals.

The presence of yeast in water, along with the pollution of water sources with antifungals originating from the pharmaceutical and cosmetic industries and agricultural runoff, are cause for concern due to the possibility of antifungal resistance development. Taking this into consideration, monitoring possible multidrug-resistant yeast in the environment can prove useful in preparing the healthcare sector for the potential occurrence of fungal infections with otherwise unexpected antifungal resistance profiles.

Wastewater surveillance has proven useful in the past in the monitoring of polio outbreaks, as well as in the detection of possible Covid-19 hotspots, so if this tool could be applied to the monitoring of pathogenic yeast, it could be valuable. Further investigation is needed to assess its efficiency and accuracy.

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AUTHOR CONTRIBUTIONS

TB wrote the original draft of the manuscript; JA, OS and JM provided supervision and edited the manuscript; CHP initiated and supervised the study, drew the figures and edited the final version of the manuscript.

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