Epidemiology and drug resistance among *Candida* pathogens in Africa: *Candida auris* could now be leading the pack

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Globally, 1 565 000 people have invasive candidiasis every year. These individuals are mainly immunocompromised people, including critically ill patients in the intensive care unit, people receiving extended use of broad-spectrum antibiotics, and of late, individuals with complications of post-COVID-19 condition (also known as long COVID). Invasive candidiasis is often misdiagnosed and accounts for 995 000 deaths (63·6% of all cases) annually.[1] As per estimates, Africa has a greater share of the invasive candidiasis burden than the rest of the world. These estimates are rough, and the paucity of accurate epidemiological data due to insufficient fungal diagnostics complicates efforts to accurately contextualise the disease.[2]

The *Candida* genus contains a mix of pathogens showing heterogeneous behaviour and unique pathogenic traits within the human host. For example, *Candida glabrata* commonly infects older individuals (≥65 years), whereas *Candida parapsilosis* is frequently isolated from neonates and infants. *Candida albicans* is the most versatile of all *Candida* pathogens and can cause infection that affects multiple organs, including the lungs and brain. Although these species are not generally transmitted between hosts, a newly emerging species, *Candida auris*, comprising six clades, causes large hospital outbreaks, changing the epidemiological landscape of invasive candidiasis (appendix p 1). For example, in South Africa, *C auris* was a major cause of invasive candidiasis from 2016 to 2017. Although multicentre and national studies are scarce in Africa, available data show that *C auris* accounts for a higher proportion of candidaemia cases than other *Candida* species in Kenya (38% of 201 cases)[3] and among neonates in a cross-sectional study in South Africa (207 of 287 cases);[4] however, *C parapsilosis* is the leading cause of invasive candidiasis in South Africa.[5]

Azole antifungals are used for the prophylaxis and treatment of invasive candidiasis, and these antifungals exert fungistatic activity by blocking the synthesis of ergosterol. However, azoles, especially fluconazole, are increasingly becoming less effective for treating invasive candidiasis due to widespread resistance of *Candida* spp to these antifungals (appendix p 1).[2] Voriconazole and amphotericin B are potent alternatives, but *C auris* remains a major concern due to the emergence of multidrug-resistant strains and even pan-resistant strains. Echinocandins have been adopted by many African countries including South Africa as a first-line treatment for invasive candidiasis. However, *Candida* spp display different intrinsic susceptibility to antifungals, and surveillance in South Africa and other parts of the world has reported an increase in echinocandin-resistant *C auris* and raised concerns about the management of invasive candidiasis due to this fungus.

The mechanisms underlying resistance against antifungals involve the acquisition of point mutations in some hotspot regions of the genomes (for example, in the *ERG* gene for azoles and in the *FKS* gene for echinocandins). However, additional mechanisms for resistance against azoles include gain-of-function mutations in the transcription factors regulating the expression of the efflux pumps, Cdr1[6] and Mdr1.[7] In the case of echinocandins, compensatory upregulation of cell wall chitin is associated with drug tolerance.[8] Other mechanisms of drug resistance in *Candida* spp are yet to be unravelled.

Since its first description in South Africa in 2009, *C auris* has been reported in only a handful of African countries including South Africa, Nigeria, and Kenya.[4,9–13] These reports have shed light on the epidemiology of *C auris* and the role of clade III as a predominant clade.[10,11] Maphanga and colleagues[11] confirmed the presence of clades I and IV in South Africa. Clade I is the most widely distributed in the world and cocirculates with clades III and IV in South Africa; however, the low distribution of clades I and IV in South Africa indicates the importation of these strains.[7]

See Online for appendix

Without confirmation of the evolutionary origin of each clade, isolating a pathogen from a place for the first time might not reflect its origin and could rather be the result of migration and local spread. For instance, in Algeria, Zerrouki and colleagues[12] isolated strains of *C auris* clades I, III, and IV in a hospital outbreak and showed that the strains of clade III were similar to the strains of clade III in South Africa. This similarity in molecular epidemiology suggests possible migration of isolates from distant locales.

Strains of clades I and IV have been isolated in Nigeria. Strains of clade I harboured Erg11:Y132F substitution with 100% mortality.[13] Similarly, in South Africa, isolates of clade

I were more resistant to fluconazole and echinocandin.[10,13] Fluconazole-resistant isolates of clades I, III, and IV harboured a high number of clade-specific substitutions (Erg11:Y132F, VF125AL, and K177A/R/N335S/E343D).[4,10] The Fks1:S639P and D642Y substitutions were predominantly reported in echinocandin-resistant strains of clades I and III.[10,11]

Health-care facilities in South Africa have reported cases of *C auris*, including some large outbreaks.[4] The unavailability of rapid and accurate diagnostics for *C auris* has restricted the understanding of the epidemiology of the fungus, which could be more prevalent than what is reported in Africa. Thus, additional research to improve diagnostics is needed to understand the epidemiology of *C auris*, even as research to unravel the resistance mechanisms of the fungus for improved treatment is underway. In addition, adopting a One Health approach and implementing the Nairobi Declaration will improve the management of invasive candidiasis and patient outcomes in Africa.

We declare no competing interests.

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