Collaborative One Health approaches can mitigate increasing azole-resistant *Aspergillus fumigatus* in Africa

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Aspergillus fumigatus is a species of fungus that is commonly found in the environment, household dust, soil, and decaying plant matter. The fungus produces spores which are inhaled by humans daily, although the host defence mechanisms of most people limit inflammatory responses and promote fungal clearance. Inhalation of the spores of *A fumigatus* triggers a wide spectrum of diseases in immunocompromised individuals, depending on the patient group affected and the pathways of pathogenesis. Forms of aspergillosis that are becoming a major public health issue include invasive aspergillosis, allergic bronchopulmonary aspergillosis, and chronic pulmonary aspergillosis.

Estimates suggest that approximately 2·2 million people suffer from invasive aspergillosis annually worldwide,[1] and it mostly occurs in immunocompromised individuals with chronic obstructive pulmonary disease, tuberculosis, or leukaemia, and more recently, as a complication of COVID-19. Left untreated, invasive aspergillosis is fatal.

Triazole antifungals are used for the prophylaxis and treatment of invasive fungal infections, acting by inhibiting the ergosterol biosynthesis pathway and disrupting the fungal cell membrane. Surveillance studies from various geographical locations have reported an increase in triazole-resistant *A fumigatus* (TRAF), raising concerns about the management of diseases caused by the fungus.[2]

The underlying resistance mechanism commonly involves point mutations in the *cyp51A* gene, with occasional non-*cyp51* mutations. TRAF precludes the use of oral antifungals for treating aspergillosis, leaving only intravenous options, such as amphotericin B and echinocandins, which are not available in many African countries. The growing reports of TRAF have been linked to the use of fungicides in agriculture, with the development of cross-resistance to medical triazoles.

There have been several reports of TRAF from the eastern and western African subregions following the first report from Tanzania in 2014 (appendix).[3-10] In Tanzania and Kenya, TRAF was identified in both environmental and clinical samples, with isolation rates ranging from 14% to 27%.[3-7] In one study, all five clinical isolates of *A fumigatus* were triazole resistant, giving a prevalence of 100%,[4] with the TR34/L98H mutation being the predominant resistance phenotype in soils in Tanzania and Kenya. The TR46/Y121F/T289A mutation has also been detected in Tanzania, with all six clinical isolates seen so far—predominantly in cases of otitis media—bearing the TR34/L98H mutation (appendix).

Chowdhary and colleagues[3] found a genetic relatedness of Tanzanian TR46/Y121F/T289A strains to Dutch isolates, and the TR34/L98H isolates were identical to the Indian TR34/L98H genotype.[3,7] These similarities in molecular epidemiology suggest possible migration of isolates harbouring resistance traits from distant locales. In Kenya, although the prevalence of TRAF was higher in fungicide-experienced soil, TRAF was also present in fungicide-naive soil samples.[5] This finding implies that TRAF might spread locally from areas of fungicide use to places where fungicides have not been used.

More recently, TRAF has been isolated from environmental samples in Burkina Faso and Nigeria.[9,10] Unlike in east Africa, TRAF isolation rates have been low, ranging from 2·0% to 2·2%, and tandem repeat mutations have not been identified. The *cyp51A* gene mutations detected in TRAF from Burkina Faso and Nigeria were F46Y/M172V/E427K and M172V respectively (appendix).[9,10]

Despite the absence of surveillance data on TRAF from other African countries, there is a possibility that TRAF is more widespread, given the extensive use of azole fungicides for agricultural purposes in the continent.[9] The inherent ability of *A fumigatus* to sporulate and survive in almost any environment facilitates its dispersal across long distances, with potential for transmission across national boundaries.

Given the interconnectedness of humans, plants, and animals in shared environments, tackling the problem of TRAF in Africa will require innovative, collaborative, multisectoral, and transdisciplinary One Health approaches. Greater collaboration between the agricultural and health sectors within Africa is urgently required. One Health policy adoptions and greater funding by African governments will catalyse

See Online for appendix

coordinated data sharing, interdisciplinary surveillance, and laboratory collaboration on TRAF. Existing public–private partnerships such as the Africa One Health University Network could be leveraged to promote resource sharing and economies of scale.

Community engagement and advocacy are crucial to promote the adoption of safer and sustainable agricultural practices. Alternative strategies to community practices such as the use of azole fungicides should be promoted, along with a more judicious use of triazoles in clinical settings. Chemosensitisation, which involves the use of natural compounds that interact synergistically with antifungals thereby lowering effective dosages and negative effects, holds great promise in this regard. Coordinated capacity-building and research are crucial for identifying and responding to clinical and environmental TRAF in Africa. Urgent action is required to address TRAF and its attendant challenges in Africa, and adopting One Health approaches might be the turning point.

We declare no competing interests.

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