Programme

Review Article

Indian J Med Res 153, March 2021, pp 311-319
DOI: 10.4103/ijmr.IJMR_768_21

Quick Response Code:

One Health aspects & priority roadmap for fungal diseases : A mini-review

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Received March 13, 2021

Fungal diseases have not been taken seriously in public health agendas as well as research priorities, despite of globally causing an estimated two million deaths every year, and the emergence of many troublesome fungal pathogens like *Candida auris,* azole resistant *Aspergillus fumigatus*, terbinafine and azole resistant dermatophytes, and zoonotic sporotrichosis in humans. Fungi are also responsible for huge losses of agricultural products and stored crops as well as recent massive and unexpected mortality in animals caused by white-nose syndrome in the bats and *Chytridiomycosis* in amphibians. This review aims to underscore the need for collaborative, multisectoral, and trans-disciplinary approach to include the One Health approach as an essential component of surveillance, prevention, and control of globally emerging fungal diseases. Rigorous evidence based surveillance of the environment as well as strengthening rapid and quality diagnosis of fungal diseases can save millions of lives and reduce significant morbidity.

Key words Fungal diseases - fungus - One Health - zoonotic

Introduction

The past few decades witnessed the emergence of several novel infectious diseases that had their origin primarily in animals and created havoc in the human society. Continued global warming secondary to injudicious human activities like intensification of agriculture, rapid and unplanned urbanization, alteration and destruction of ecosystems, and massive global movement and trade has led to the emergence of a series of novel respiratory viruses like Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and SARS-CoV-2 coronaviruses, human influenza virus from avian and swine sources, and many life-threatening zoonotic viral infections[1]. Public health systems are geared mainly to tackle viral infections especially during the present coronavirus pandemic, forgetting other equally life-threatening bacterial and fungal infections[2]. However, this neglect may have profound long-term impact, which is underestimated.

The term 'One Health' by inclusion of human, animal and plant health together though first coined during the concerted efforts to combat the emergence of SARS coronavirus and H5N1 influenza in 2003-2004[3], the concept gained popularity with the recognition of the evolution of antimicrobial resistance (AMR) in humans, related to the environment, plant and animal health[4].

Along with the emerging viral and multidrug-resistant bacterial pathogens, in the past few decades newly emerging fungal illnesses pertaining to plants and animals, crossing over to humans have obtained great importance[5]. The previously unknown human outbreaks of *Sporothrix brasiliensis* related to close exposure to cats in South America[6], increasing load of fungal keratitis related to agricultural activities without eye protection[7], continued burden of sporotrichosis related to unprotected horticultural activities[8], emergence of histoplasmosis and chromoblastomycosis in newly described geographical areas, the menace of drug-resistant dermatophytosis[9] and aspergillosis[10] to name a few, are the new-age One Health related fungal hazards.

Thriving at 33-37° C is necessary for a fungal species to become a human commensal or pathogen. There are close to 6 million estimated fungal species on earth[11], out of which, nearly 600 fungal species can cause human disease[12]. The number of pathogenic fungal species is growing rapidly due to temperature adaptation. Through advancement of molecular biology and sequencing techniques, it is evidenced that the number of fungal species as a part of the human microbiome – either as a commensal or a pathogen may be grossly underestimated due to the inability to culture many of those, leaving room for new surprises as emerging fungal infections[13]. Other than human, bats and poikilothermic animals like fish and amphibians are prone to serious fungal infections. Recent investigations have suggested high incidence of severe fungal diseases causing extinction of many wild amphibians and bat species[14,15]. It has been proposed that the extinction of the dinosaurs 65 million years ago was driven in part by fungal diseases[16].

Fungi are remarkably resilient and transmissible breaking geographical, environmental and species barriers. Broad groups of fungi were found to survive in areas of high radiation around the Chernobyl nuclear disaster site[17] as well as in the Japanese module of the international space station[18]. The rapid transmission of the newly described drug-resistant invasive fungal species - *Candida auris,* across many critical care units in different continents over the last decade is an example of such a resilient and transmissible human pathogen[19].

Plant pathogenic fungi are responsible for major destruction of staple food crops like wheat, rice and corn, jeopardizing global food security[20,21]. Fungal toxins that contaminate stored food grains can cause acute toxicities or chronic effects like carcinogenesis. These toxins are also lethally deployable as biological weapons against humans and food supplies[22]. Water damaged buildings provide niches for fungal groups, to proliferate with damaging fungal generated volatiles and allergens contributing to ill health.

The American Academy of Microbiology Colloquium on One Health aspects of fungal diseases strongly support development of new approaches to protect frogs, salamanders, bats, and other animals from pathogenic fungi[12] and develop new methods of preventing fungal infections in crop plants by reducing azole dependence in the face of rising azole resistance among *Aspergillus* species[23] by promoting the use of gene silencing methods and genetically modified crop production[12].

Fungal diseases are silent killers - out of public health priority

Fungi are silent killers, causing the death of over two million people every year[24] - this makes fungal diseases one of the top global causes of death ahead of tuberculosis and malaria, yet concealed by only listing the primarily underlying diseases (*i.e*. leukaemia or COPD). With the advancement of cancer chemotherapy, solid organ and stem cell transplants, increased survival of acute respiratory distress syndrome and other critically ill patients in the intensive care, and the extensive use of indwelling medical devices, the gross number and proportion of patients susceptible to serious invasive systemic fungal illnesses have increased significantly in the past few decades[25]. Worldwide annual occurrence of over 300,000 cases of invasive aspergillosis and 700,000 invasive candidiasis cases are reported[26], vulnerable people are disproportionately affected and those afflicted with long term fungal disease and its sequelae live in misery due to morbidity, the inability to work and stigma. Global estimates of fungal illnesses[24,26] suggest a global annual occurrence of more than three million cases of chronic pulmonary

aspergillosis, and 10 million cases of fungal asthma, a large part of which is undiagnosed in resource limited settings[27]. Despite of advancement of HIV treatment, there are global reports of more than 200,000 cases of cryptococcal meningitis, and 500,000 cases of *Pneumocystis jirovecii* pneumonia, which are otherwise largely preventable and treatable[28]. It is estimated that nearly a million eyes lose vision due to fungal keratitis, mostly related to agricultural activities, out of which, a significant proportion is from the developing world and the global south[24,26,29]. Fungi causing skin and subcutaneous diseases, endemic fungal infections, fungal rhinosinusitis and fungal keratitis mostly affect people without any pre-existing conditions, living and working closely in certain environmental niches. Fungal asthma, caused by airborne fungi such as *Aspergillus* spp., exacerbates asthma in millions of adults and children. Limited diagnosis and poor measurement of disease morbidity means that the true scale of the problem is only partially known[28].

Most important fungal pathogens affect humans from the environment, underscoring the need for coordinated One Health monitoring and vigilance

Most of the invasive and endemic fungal human pathogens are transmissible from the environment rather than from fellow human beings. Among all the environmentally transmitted fungal pathogens, *Aspergillus* spp., the fungi causing mucormycosis, *Cryptococcus* spp., *Histoplasma* spp., *Sporothrix* spp., and agents causing mycetoma, deserve special mention in the Indian context due to the sheer volume of patients affected by them in the subcontinent.

Aspergillosis: *Aspergillus* spp. is a pathogen which cause the broadest array of illnesses in human beings- ranging from superficial infection (otomycosis, onychomycosis and keratitis), chronic pulmonary aspergillosis (CPA), allergic bronchopulmonary aspergillosis (ABPA), saprophytic pulmonary or sinusoidal aspergillomas, a rapidly evolving invasive form – which is almost always fatal unless diagnosed and treated promptly[30]. In the last decade, the issue of azole resistance has become a significant menace in the treatment for all the forms of aspergillosis. It is postulated that in cases of CPA and ABPA, the azole-resistance may develop during antifungal treatment, but, in case of acute invasive aspergillosis (IA), it is always primarily a resistant strain acquired from the environment[10]. IA has also become increasingly recognised in patients without neutropenia, and is more common in patients hospitalized with COPD[31], lung cancer[32] and occasionally other solid tumours, corticosteroid therapy, liver failure, transplant recipients, notably allogeneic stem cell and lung, but also renal and heart recipients, complicating severe influenza (19%)[33] and severe COVID-19[34,35].

The environmental route of resistance occurs as a result of exposure to azole fungicides or sterol 14α-demethylation inhibitor (DMI) fungicides in the environment. The development of azole resistance is mostly a bystander effect on *Aspergillus fumigatus,* as the agricultural targets for DMI fungicides are usually other fungi[36]. In areas where the azole resistance rates in *Aspergillus* exceeds 10%, current guidelines recommend voriconazole or isavuconazole in combination with an echinocandin or liposomal amphotericin B instead of azole monotherapy alone[30]. Hence the knowledge of the antifungal resistance status of the surrounding environmental *Aspergillus* spp. can be vital to the survival of IA patients.

IA primarily occurs through environmental spore contamination of hospitals and intensive care units. It has been shown that construction works in and around hospital premises accounts for about half (49%) of the causes of nosocomial aspergillosis outbreaks[37]. The authorities of the hospitals serving the high-risk groups for IA must conduct active surveillance for airborne fungal spores and the wards for such patients should be equipped with appropriate ventilation systems[38,39].

Several environmental studies on azole-resistant *Aspergillus* show that resistance was acquired during stockpiling of inappropriately processed plant waste material, producing potential hot spots for the evolution and selection of azole resistant *Aspergillus*[40]. The environmental route of resistance selection is thus a One Health challenge that must involve cross-cutting discussions and actions among different stakeholders, for example, clinicians, mycologists, agricultural researchers, pesticide and fungicide industrial houses, farmers and horticulturists, legislators and policy makers, regulatory and municipal bodies[10].

Mucormycosis: Fungi causing mucormycosis are ubiquitous and can be found in decaying organic matter and in the soil. Depending upon the clinical syndromes various modes of transmission have been described. Inhalation of the spores from environmental sources is considered as the most common mode of transmission[41]. Percutaneous implantation of spores during trauma,

burns and illicit injections are other important modes of transmission. Gastrointestinal mucormycosis is transmitted by ingestion of the spores contaminating various foods and beverages. Renal mucormycosis, which is rarely described outside of India, is likely to be caused by the inhalation of spores which disseminate hematogenously to the kidneys or through invasive procedures of the urinary tract[41,42]. In a recent multi-centre study of mucormycosis from India 56.8 per cent of the total 303 patients with mucormycosis had underlying diabetes mellitus and 31 per cent had diabetic ketoacidosis. In patients with rhino-orbito-cerebral mucormycosis 65.7 per cent had underlying diabetes mellitus[43]. Other common risk factors include glucocorticoid use, haematological malignancies, haematopoetic stem cell transplantation, solid organ transplantation, iron overload conditions, treatment with desferrioxamine and AIDS[41]. Post-pulmonary tuberculosis has been recently recognized as a risk factor for pulmonary mucormycosis[43]. Probably the burden of mucormycosis is grossly under reported, because cultures are so often negative and only recently has the first PCR assay been commercialised. Incidence and prevalence of this disease is difficult to estimate because of various factors including lack of awareness of the disease even among trained physicians and lack of standardized diagnostic strategies. Lack of proper denominators to express the disease burden is another important obstacle[44]. A computational model based on Indian literature using Monte Carlo algorithms estimated an overall mucormycosis prevalence of 0.14 cases per 1000 population in India, coming to a total burden of 187,460 patients[45,46]. The overall mortality in mucormycosis when well treated ranges from 30 to 46.7 per cent[43,47,48]. Based on the aforementioned computational model[45,46], considering an attributable death rate of 38 per cent per year, mucormycosis kills over 105,000 people in the WHO South East Asian Region (SEAR) per year.

Cryptococcus: Cryptococcus is an important fungus causing meningitis and sometimes pulmonary and disseminated diseases with substantial mortality. It predominantly affects patients with late stage HIV infection and other immunocompromised conditions and sometimes can even involve immunocompetent persons[49]. *C. neoformans* var *grubii* and var *neoformans* have been found in soil samples from around the world in areas frequented by birds, especially pigeons and chickens[50]. This fungus has also been isolated from roosting sites of pigeons and in association with rotting vegetation[51]. Most of the case reports and studies from the WHO SEAR suggest that the diagnosis is made in the local and community hospitals only on direct microscopy, and not the more sensitive antigen test. Early asymptomatic cryptococcal antigenaemia precedes meningitis by a mean of three weeks, (~40% of cases) and is therefore missed and initiation of treatment is delayed[52].

Despite the cryptococcal antigen detection test having a sensitivity and specificity more than 99 per cent[53], the test is not available in majority of the laboratories of the SEAR[54]. This test should be made routinely available for HIV patients with low CD4 counts or in the presence of other AIDS defining symptoms, as well as solid organ and stem cell transplant recipients. New patients with HIV infection admitted to hospital or symptomatic should be screened routinely for Cryptococcal antigen.

Histoplasma: *Histoplasma capsulatum* is a dimorphic fungus, which can thrive at both temperate as well as tropical countries, and is found in various parts of the world, including all countries of the SEAR[55,56]. But the best environmental conditions for its growth are mean temperature of 22 to 29°C, an annual precipitation of 35 to 50 inches, and a relative humidity of 67 to 87 per cent[57]. It has been found to be present within 20 cm of the surface of acidic soil, high in nitrogen content. There is a strong environmental association with decaying bird and bat guano in cool, moist soil away from the sunlight[58,59]. Various activities that lead to disruption of soil surface, like excavation, spelunking (cave exploration), construction, bird handling and recreational activities, that can lead to the release of its infectious conidia, which are subsequently inhaled, causes the pulmonary or disseminated multisystem disease, known as the Darling's disease[60,59]. In a recent review, the most commonly associated environmental and wilderness-related risk factors for histoplasmosis were found to be bird and bat watching, cave and cave entrance exploration, and bamboo removal and burning. Whereas occupational risk factors for histoplasmosis were found to be road construction, roofing, bridge and water tower work, demolition, and masonry[61].

Among a case series reporting 31 cases from a single centre in New Delhi, India, 17 patients had a history of occupational exposure to agriculture and 10 had significant occupational or domestic exposure to birds. These two exposures combined together comprised of 87 per cent of the cases[58]. Among a total

of 213 cases reviewed from the Indian subcontinent, 56 per cent of affected people were found to be apparently immunocompetent and 31 per cent were immunocompromised. A significant number of patients (55%) of disseminated histoplasmosis from India are reported to have adrenal gland involvement[58,62]. A peculiarity of the disseminated histoplasmosis is its strong gender predisposition towards male gender; the male : female ratio is reported to be as high as 6:1 from India[58] as well as worldwide[63]. Chronic pulmonary histoplasmosis is barely known in India, probably because a lack of *Histoplasma* antibody diagnosis[56].

A programme for establishing the rates of histoplasmin skin sensitivity in India should be undertaken to understand the exposure rate of the population wherever cases have been documented and prioritise local diagnostic testing, especially in the north of the country. This diagnostic intervention can also be guided by One Health monitoring of the environment and ecological niches of the natural *Histoplasma* habitat. *Histoplasma* antigen testing should be implemented in hyperendemic localities of histoplasmin sensitivity, particularly for advanced HIV cases. In fact at least one to two laboratories per region of India should have the facility of *Histoplasma* antigen and antibody tests on a referral basis.

Mycetoma and Sporotrichosis – occupation associated subcutaneous mycoses

Mycetoma is a chronic, progressive destructive infection of the distal limbs involving all tissues. It is recognized as a neglected tropical disease (NTD) by the WHO[64], but it is not a notifiable disease except in Sudan. Numerous different organisms may be implicated, and the appropriate treatment depends on the causative organism. Mycetoma is an implantation disease. Any age can be affected. Minor breaks in the skin from thorns or handling infected materials result in a slowly progressive local lesion. The foot is the most common site of infection. From the skin and subcutaneous tissue, the disease typically invades bone and produces hypertrophic, gross lesions. The agents of eumycetoma are almost always resistant to amphotericin B and flucytosine. Some respond to voriconazole or itraconazole, but most are intrinsically resistant to all antifungals, especially *Madurella* spp. Eumycetoma patients usually respond poorly to medical therapy. Improvement is slow and hard to evaluate, even after months of therapy. Many patients eventually fail to complete education or lose their jobs and become a burden on families and the community[65].

Sporotrichosis can present with cutaneous, lymphocutaneous and systemic manifestations. Severity depends on infecting species and the host immune status. Majority of the cases of sporotrichosis occur when the fungal spores are introduced through a cut or puncture in the skin while gardening or handling vegetation or organic matter. Historically environmental transmission from vegetations was the most common source, but recently zoonotic infections have emerged with *Sporothrix brasiliensis* in South America via the bite, scratch, and contact with the exudate of an infected cat[6]. In India, however, the sapronotic transmission seems to be the major route of transmission, which can be well prevented by wearing gloves and wearing boots while gardening to prevent puncture wounds[66].

Emergence of human-to-human transmissible fungal pathogens and concerning antifungal resistance

Invasive candidiasis: Multiple studies have shown the annual incidence of bloodstream infections with *Candida* spp. to be 1.2–26 cases/100,000 population, across the world. Only seven per cent are community-acquired, the remainder are hospital-acquired[24]. A 2015 prospective study from 27 ICUs in India showed a mean incidence of 6.51 cases of ICU-acquired candidemia per 1,000 ICU admissions and a death rate of 35 –75 per cent[67]. An estimated 14.3 million patients are admitted to ICUs in India each year. Blood culture is only ≈40 per cent sensitive for invasive candidiasis (and lower for intra-abdominal candidiasis). Further, the antifungal agents including, fluconazole and echinocandins substantially reduces the yield from blood culture. Therefore, it is probable that the actual number of cases of invasive and intra-abdominal candidiasis in ICUs in India exceeds 200,000, resulting in ≈100,000 deaths. Bloodstream infection caused by *Candida* spp. outside ICUs is twice as common as in ICUs, and so in India >600,000 persons each year are estimated to have invasive candidiasis.

Inappropriate use of antimicrobials as well as several disruptive practices in farming, pisciculture, deforestation and natural habitat destruction is said to have contributed to the emergence of *C. auris*. Almost all outbreak investigations carried on nosocomial outbreaks of *C. auris* have concluded that the organism was acquired from extraneous sources rather than from

the patients' endogenous flora. This finding suggests that despite no environmental reservoir reported till date, it is possible that *C. auris* might have its own environmental niche[19,68]. *Candida* species are not exclusive human pathogens or commensals and have been found in insects and different plants like mangrove forests, rubber and cassava plantations[68]. Adequate One Health monitoring of environmental niches are required to track the emergence of similar pathogens.

Dermatophytes: In India, the most common species causing skin and nail infections is the dermatophyte *Trichophyton rubrum* - an exclusively human pathogen, followed by *Trichophyton mentagrophytes* - erstwhile considered a zoonotic pathogen usually transmitted from companion domestic animals and *Microsporum gypseum* - a soil associated pathogen. *T. mentagrophytes* is recently found to be on the rise in India[69]. Terbinafine and azole resistant, stubborn and recalcitrant dermatophyte infection is nowadays considered as one of the most difficult to treat conditions in dermatology clinical practice. Cases are complicated with the widespread use of topical corticosteroids in combination with antifungal agents. Potent molecules like clobetasol propionate are available over the counter and are grossly abused which include buying over the counter with or without the prescription of general practitioners and local application for weeks to years[70]. The steroid combinations cost much lesser than pure potent antifungal creams, which make these popular. These are used often only for symptom control without any instructions or supervision and patients often stop using them when the itching and redness are mitigated and reapply when the symptoms reappear[70,71].

Combating antifungal resistance and investing in diagnosis of fungal illnesses: The Indian government's effort to ban colistin in animal usage by creating a strong legislation is a laudable one considering the increasing menace of transmissible plasmid mediated colistin resistance gene *mcr-1*[72]. Similar concerted effort with agricultural universities, farmer's unions, pesticide manufacturers and API manufacturers are needed to reduce usage of traditional azoles in farming as well as newer congeners of recently developed antifungals.

Promotion of composting under controlled aerobic conditions where aeration can be done through natural convection or forced aeration under ambient tropical summer and monsoon temperature which can actively reduce the levels of azole-resistant *Aspergillus*. Large scale facilities for composting household biowaste, market and food storage facility waste and industrial organic wastes, rather than unprocessed dumping and landfilling have been shown to significantly reduce the burden of pathogenic fungi as well as its associated drug resistance[10]. These should be actively encouraged as best practice and advocated to policy makers and legislators.

Hospitals catering to the needs of immunocompromised patients as well as critically ill patients, should be positively incentivized for regularly running environmental monitoring protocols for the hospital air surveillance of fungal spores and reporting of resistances once detected. Similar environmental monitoring should be made compulsory, whenever such a healthcare facility has an ongoing demolition or construction programme.

Rapid, non-culture based testing is now important to diagnose life-threatening fungal infections, as recognised by the WHO in listing several diagnostics as essential. Cryptococcal antigen testing and histoplasma antigen testing should be made routinely available at all the referral antiretroviral therapy centres and hospitals seeing new HIV patients. *Aspergillus* antigen, *Pneumocystis* PCR and B-D-glucan should be available as rapid tests for cancer treatment and transplant centres. *Aspergillus* antibody testing should be routinely available for all respiratory services, especially those managing TB. Precise diagnosis will contribute to reducing premature deaths, low morbidity, lower wasted healthcare expenditure and AMR control are reducing incorrect empirical antibiotic usage (Table).

Conclusion

Fungal infections are more prevalent than previously appreciated, partly because of missed diagnosis, partly because of new risk factors and partly because of the emergence of new and muti-drug resistant pathogens. Fungal allergic disease and exposure in water-damaged buildings is also relatively common. The last decade delivered great progress on commercialized, simple and inexpensive diagnostic tests which can transform lives blighted by chronic ill health. Routine use of these diagnostics will reduce unnecessary anti-bacterial therapy and contribute to AMR control. Restriction of use of azole fungicides in agriculture should minimise repetitive emergence of resistant *Aspergillus*, which is important as azole antifungals increasingly become established for fungal asthma and prophylaxis. New antifungals with

Table. Diagnostics recognized as essential by the World Health Organization, in addition to direct microscopy, histopathology and fungal culture

Test	Major usage	Recommended turnaround time
Cryptococcal antigen[53]	HIV/AIDS, transplant recipients	1 day or less
Aspergillus antigen[30]	Critical care, bronchoscopy, immunocompromised	2 days or less
Histoplasma antigen[55]	HIV/AIDS, transplant recipients	2 days or less
Pneumocystis PCR[73]	HIV/AIDS, transplant recipients, immunocompromised	2 days or less
Aspergillus IgG antibody[30]	Respiratory patients, especially smear or GenXpert negative suspected TB patients	7 days or less

alternative modes of action are in clinical development, but their importance to human health should be heeded before these chemistries are contemplated for agricultural fungicides.

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