A global call for talaromycosis to be recognised as a neglected tropical disease

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Talaromycosis (penicilliosis) is an invasive mycosis that is endemic in tropical and subtropical Asia. Talaromycosis primarily affects individuals with advanced HIV disease and other immunosuppressive conditions, and the disease disproportionally affects people in low-income and middle-income countries, particularly agricultural workers in rural areas during their most economically productive years. Approximately 17 300 talaromycosis cases and 4900 associated deaths occur annually. Talaromycosis is highly associated with the tropical monsoon season, when flooding and cyclones can exacerbate the poverty-inducing potential of the disease. Talaromycosis can present as localised or disseminated disease, the latter causing cutaneous lesions that are disfiguring and stigmatising. Despite up to a third of diagnosed cases resulting in death, talaromycosis has received little attention and investment from regional and global funders, policy makers, researchers, and industry. Diagnostic and treatment modalities remain extremely insufficient, however control of talaromycosis is feasible with known public health strategies. This Viewpoint is a global call for talaromycosis to be recognised as a neglected tropical disease to alleviate its impact on susceptible populations.

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Introduction

In 2005, WHO established a list of neglected tropical diseases. The list included a diverse group of largely chronic, parasitic, tropical infections that disproportionately affect people living in poverty.[1] Fungal diseases were not included on the neglected tropical disease list until 2016, when WHO expanded the list to include mycetoma, chromoblastomycosis, and an undefined category of other deep mycoses. In January, 2021, WHO released their 2021–30 road map for neglected tropical diseases, a visionary framework that emphasises impact measurement, cross-cutting programming, and country-driven policy.[2] WHO's 2021–30 neglected tropical disease road map has, for the first time, named paracoccidioidomycosis and sporotrichosis among the deep mycoses. The editors of *PLOS Neglected Tropical Diseases* have also increasingly recognised neglected fungal diseases, adding histoplasmosis and cryptococcosis to the "on the cusp" section of the *PLOS Neglected Tropical Diseases* list in 2020.[3]

Talaromycosis is an invasive fungal infection with a high case-fatality rate, killing up to a third of diagnosed individuals.[4,5] As with other neglected tropical diseases, talaromycosis disproportionally affects people living in poverty in the tropical and subtropical zones of Asia. It is not currently recognised as a neglected tropical disease despite being quintessentially so. Talaromycosis satisfies all neglected tropical disease criteria identified by WHO, *PLOS Neglected Tropical Diseases*, and the US Food and Drug Administration (FDA), and warrants recognition by these global entities. Talaromycosis has been neglected by local, regional, and international clinicians, researchers, funders, and public health organisations; this multilevel neglect is the main barrier to reducing its substantial morbidity and mortality. This Viewpoint brings together physicians and scientists working in talaromycosis endemic areas, policy makers, and fungal experts to elevate the profile of this neglected mycosis. We present a global viewpoint on why talaromycosis should be considered a neglected tropical disease by WHO, *PLOS Neglected Tropical Diseases*, and the Tropical Disease Priority Review Voucher Programme of the FDA.

Talaromycosis is a tropical infectious disease with high morbidity and mortality

Talaromycosis (formerly penicilliosis) is caused by the thermally dimorphic fungus *Talaromyces marneffei* that is endemic in the tropical and subtropical regions of Asia (appendix p 2). *T marneffei* has a reservoir in wild bamboo rats living in the highlands of endemic regions and in the soil associated with the bamboo rats. Human infection is presumed to occur via inhalation of *T marneffei* spores from the environment.[6] The HIV pandemic has led to a rapid rise in global incidence, particularly in the hyperendemic areas of southeast Asia (Thailand, Vietnam, and Myanmar), east Asia (southern China, Hong Kong, Taiwan), and northeastern India.[6] Although prevalence in the general population is unknown, talaromycosis has a pooled prevalence of 3·6% among people living with HIV, ranging between 0·1% and 19·6%, depending on the geographical region and country (appendix p 5).[7] 288 000 cases have been reported in 33 countries to the end of 2018, with an estimated 17 300 cases (95% CI 9900–23 700) and 4900 deaths (2500–7300) a year.[8] The highest reported incidence of talaromycosis is in China, Thailand, and Vietnam, where it is the third most common opportunistic infection and a leading cause of HIV-associated death, surpassing tuberculosis and cryptococcal meningitis.[4,5]

Most individuals diagnosed with talaromycosis are immunocompromised, but healthy individuals can develop talaromycosis, albeit rarely.[9] Disease can be

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See Online for appendix

localised to the upper or lower respiratory tract,[10–12] bones, joints, and intestinal tract, or disseminated across multiple organ systems.[13] Advanced HIV disease (defined by WHO as a CD4 cell count <200 cells/μL) is a major risk factor for talaromycosis. Patients with advanced HIV disease commonly present with disseminated disease involving the lungs, liver, spleen, gastrointestinal tract, blood stream, skin, and bone marrow.[4,5,13] Although talaromycosis predominantly affects people living with HIV, it is increasingly diagnosed in people with other immunosuppressing conditions, including the primary immunodeficiency condition due to interferon-γ autoantibodies, autoimmune diseases, malignancy, and solid organ and bone marrow transplantations.[13,14] Individuals without HIV are less likely to have skin lesions (44% *vs* 71%)[5,14] and positive blood cultures (47% *vs* 77%) than are those with HIV.[15] As a result, diagnosis is delayed (180 days *vs* 45 days),[16] and mortality is higher (29% *vs* 21%) compared with individuals with HIV.[15] Similar to some other endemic mycoses, primary pulmonary talaromycosis has been described in apparently healthy individuals.[9,17] The diverse manifestations of primary pulmonary infections include tracheal and endobronchial lesions that can cause airway collapse (appendix p 3),[18] alveolar consolidation, cavitary lung disease, solitary or multiple nodules, mediastinal lymphadenopathy, and pleural effusion (appendix p 3).[19] Individuals with underlying structural lung disease, such as chronic obstructive pulmonary disease, lung malignancy, and cavitation associated with tuberculosis or sarcoidosis, are at risk for pulmonary infection.[9,17,20] These cases suggest that talaromycosis could be a more common cause of pneumonia in endemic areas than currently recognised.

Talaromycosis is a tropical infectious disease perpetuated by a cycle of poverty, stigma, and neglect

WHO has four criteria for inclusion on the neglected tropical disease list (appendix p 6).[21] Talaromycosis fulfils all four criteria as detailed below.

Talaromycosis causes stigma, morbidity, and mortality among impoverished people

Several predisposing factors of talaromycosis are inextricably linked with poverty. The endemic region of talaromycosis consists almost entirely of low-income and lower-middle-income countries (appendix p 2), with most countries falling into the lower-middle-income category.[22] Many people in *T marneffei* hyperendemic regions live in poor, rural areas. For example, 63% of the Vietnamese population and 67% of southern China's Guangxi province live rurally.[23,24] Although the soil-burrowing bamboo rats are the enzootic reservoir of *T marneffei*, human infection is neither linked to bamboo rat exposure nor consumption. Rather, infection is linked to occupational exposure to crops or livestock, and travel to highland farming areas.[6,25,26] Farmers have a 70–90% greater risk of developing talaromycosis than non-farmers,[25,26] and residents in highland communities and travellers to highland communities have three-fold greater odds of disease compared with non-highland residents and those not travelling to highland communities.[26] Talaromycosis disproportionally affects rural communities and agricultural workers due to long-term exposure to soil in the endemic regions.[25] The disease predominantly affects young people during their peak years of economic productivity,[4,5,13] burdening the families of primary wage earners in rural communities. These factors, combined with the high cost of treatment (average US$1300, approximately the 1-year salary for an average farmer in Vietnam), exacerbate the poverty inducing potential of talaromycosis.

Talaromycosis is characterised by disfiguring cutaneous lesions that predominate on the face and extremities (appendix p 4). They are a feature of disseminated infection, which prompts hospital admission, and epitomise the visually stigmatising nature of the disease. The pathogen, *T marneffei*, and the disease, talaromycosis, are difficult to pronounce, further hampering efforts to bring the disease onto national health agendas in endemic countries. Although talaromycosis has been associated with HIV, it has not benefited from the overall decline in HIV incidence in Asia nor from funding through HIV programmes. In a 2020 estimate of the global burden of talaromycosis, the incidence was projected to increase by 35% by 2025.[8] This projection is driven by the persistent or rising incidence of advanced HIV disease among people newly diagnosed with HIV in Indonesia, Thailand, Vietnam, the Philippines, and China.[27] Despite improved access to antiretroviral therapy across Asia, talaromycosis mortality remains unchanged,[4] suggesting that diagnostic delay and access to HIV services remain substantial barriers to survival.

Talaromycosis primarily occurs in tropical or subtropical regions of Asia

The endemicity of talaromycosis includes most countries in the tropical and subtropical zones of Asia (appendix p 2). The tropical ecosystems in southeast Asia are among the most susceptible areas in the world to climate change due to a large low-income population, an economy dependent on natural resources and agriculture, and the threat of climate-related disasters including floods and typhoons.[28] Talaromycosis is highly associated with the tropical monsoon weather, with disease incidence increasing by 30–73% during the rainy months in Thailand, Vietnam, and southern China.[5,29] This remarkable seasonality is driven by high humidity,[30] which probably promotes infection through poor air quality and expansion of the fungal reservoir in the environment. The monsoon season brings intense, persistent rainfall and floods, and the warmer oceans feed tropical cyclones that threaten agriculture production and food supply. These climate factors exacerbate

the impact of talaromycosis on people living in low-income households in rural areas and are likely to increase with global warming.[31]

Research support for talaromycosis has been insufficient to determine the optimal diagnostic and treatment approaches

Current culture-based diagnosis is slow and insensitive. Blood culture takes up to 14 days for identification, only detects disease in its advanced stage, and misses up to 50% of infections.[4,5,15] Although a presumptive diagnosis can be made on the basis of typical microscopic findings on a skin smear, skin lesions are absent in 30–60% of patients.[15,29] Talaromycosis mortality doubles from 24% to 50% when the diagnosis is delayed and reaches 100% when the diagnosis is missed.[32] Non-culture diagnostic approaches are urgently needed to disrupt the cycle of delayed diagnosis or misdiagnosis, disseminated disease, and high mortality.

There are few translational scientists and companies working on developing novel diagnostics for talaromycosis. Two promising monoclonal antibody (mAb)-based antigen detection enzyme immunoassays are currently in development. The mAb-4D1 enzyme immunoassay and its immunochromatographic platform developed in Thailand show high sensitivity and specificity in small studies.[33,34] The mAb-Mp1p enzyme immunoassay developed in Hong Kong has been studied more extensively than the mAb-4D1 and was shown to be superior to blood culture in sensitivity (86% *vs* 73%) and had a specificity of 98%. Sensitivity was higher in urine than in plasma and was the highest when testing plasma and urine in combination.[35] The Mp1p enzyme immunoassay is being evaluated in a multicentre prospective study as a rapid diagnostic and screening tool for talaromycosis (NCT04033120). A commercial version of the Mp1p enzyme immunoassay was approved for clinical use in China in October, 2019, and a Mp1p point-of-care lateral flow antigen test is being developed through industry–public partnership with support from the National Institutes of Health in the USA. The WHO 2021–30 neglected tropical disease road map has identified diagnostics as one of four priority areas, and established a Diagnostics Technical Advisory Group to centralise diagnostic advances and drive progress within the field in a coordinated manner.[2] Talaromycosis stands to benefit from this initiative if included on the neglected tropical disease list. Coordination by the Diagnostics Technical Advisory Group can advance non-culture diagnostics for talaromycosis and has the best chance of saving lives, by effectively facilitating industry and research partnership to rapidly validate and commercialise these antigen detection assays for clinical use.

Amphotericin B and itraconazole have been the mainstay of treatment for talaromycosis. In 2017, a multicentre randomised controlled trial found induction therapy with amphotericin B achieved more rapid fungal clearance in blood and reduced 6 month mortality from 21% to 11% compared with itraconazole.[36] Despite this large mortality benefit, many patients in Vietnam, where the trial was conducted, and in other countries in Asia, still struggle to gain access to amphotericin B due to its high cost and difficulties with procurement and distribution. Even where there is access, low-income and lower-middle-income countries in Asia are still using the deoxycholate amphotericin B formulations that have not been used in high-income countries for two decades. The less toxic liposomal amphotericin B formulation (AmBisome) is still not available in most of Asia despite patent protection expiring in the USA in 2016.[37] Therapeutic options for patients in low-income and lower-middle-income countries who cannot tolerate amphotericin B are largely absent. The role of more recently developed triazole compounds that are widely available in high-income countries (voriconazole, posaconazole, and isavuconazole [rINN, isavuconazonium]) and the role of novel antifungal compounds in development in the treatment of talaromycosis have never been systematically studied in animals or in humans. It is also unknown whether combination therapy with amphotericin B plus flucytosine, shown to be more efficacious than amphotericin B alone for treatment of cryptococcosis,[38] is also more efficacious for talaromycosis. Further, the duration of consolidation and the maintenance of antifungal therapy for patients without HIV is unknown. For an infectious disease that has an on-treatment mortality of 30%, research to improve treatment is imperative. This research will require substantial investment from both the global scientific community and industry. Inclusion on the neglected tropical disease list would raise the profile of talaromycosis globally and would increase access to less toxic formulations of amphotericin B and newer antifungal drugs used routinely in high-income countries. This progress can be achieved collectively through the Drugs for Neglected Diseases initiative and the WHO Model Lists of Essential Medicines.[39]

Control of talaromycosis is feasible with known public health strategies

Primary prophylaxis with itraconazole has been shown to reduce the incidence of talaromycosis and other invasive fungal infections in patients with advanced HIV disease.[40] However, this blanket approach to disease prevention has not been widely adopted due to concerns about toxicity, drug–drug interactions, drug resistance, and cost. In cryptococcosis, a more targeted approach of antigen screening and pre-emptive fluconazole therapy prevents cryptococcal meningitis, reduces mortality,[41] is highly cost-effective,[42] and is being implemented in HIV programmes across the world.[43,44] A similar diagnostic-driven approach is most likely to be an effective strategy to control talaromycosis, as *T marneffei* antigenaemia has been shown to precede development of culture-confirmed

talaromycosis by up to 16 weeks,[45,46] and antigenaemia is associated with 12-month mortality.[47] The *T marneffei* lateral flow antigen assays in development would allow for testing at the point of care in the community and enable a screen and treat strategy to reduce disease burden at a population level.

Although antigen screening is an effective approach in patients with advanced HIV disease, pathogen-based detection is still limited by delayed clinical presentation. Host-based diagnostics, such as an antibody test or interferon-γ release assay would enable identification of latent infections in people undergoing immunosuppressive therapy, chemotherapy, and organ transplantations, and would allow for pre-emptive therapy to interrupt disease development. Host-based assays would permit new knowledge of disease exposure, latent infection, and population burden. Seroprevalence data could advance our understanding of pathogen ecology and the environmental reservoir of *T marneffei*. This understanding could inform strategies that control *T marneffei* at its source and could delineate geographical risk regions to effectively guide resource allocation for diagnosis, treatment, and prevention strategies.

The WHO 2021–30 neglected tropical disease road map is focused on integration of neglected tropical disease prevention and control strategies within national health-care systems with the support of domestic financing.[2] Currently there is no provision for talaromycosis funding within national health-care policies in the endemic regions. Sustainable national health resource allocation for talaromycosis will not occur without an endorsement from global health entities. Talaromycosis and other neglected mycoses stand to greatly benefit from being included on the neglected tropical disease road map focusing on health system strengthening and national cross-cutting approaches to tackle the root causes of poverty and access to care for rural populations.[48]

Conclusions

Talaromycosis meets all criteria to be included in the WHO neglected tropical disease list and shares many features of other infectious diseases associated with poverty currently recognised by WHO, *PLOS Neglected Tropical Diseases,* and the FDA. The substantial challenges in diagnosis and treatment of talaromycosis represent enormous opportunities to make an impact on the disease at both the individual and population level. Recognition of talaromycosis as a neglected tropical disease by global public health organisations, funders, and other stakeholders will show the commitment and provide the necessary impetus to improve the control and prevention of this deadly infectious disease.

Contributors

SN and TL conceptualised and wrote the first manuscript draft of the Viewpoint. All authors contributed to the content of the manuscript and read and approved the final manuscript.

Declaration of interests

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