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A GLOBAL CALL FOR TALAROMYCOSIS TO BE RECOGNISED AS A NEGLECTED TROPICAL DISEASE

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Abstract

Talaromycosis (penicilliosis) is an invasive mycosis endemic in tropical and subtropical Asia. Talaromycosis primarily affects individuals with advanced HIV disease and other immunocompromised conditions and disproportionally affects people in low and middle-income countries, particularly agricultural workers in rural areas during their most economically-productive years. Approximately 17,300 talaromycosis cases and 4,900 deaths occur annually. Talaromycosis is highly associated with the tropical monsoon season, where 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 a mortality of up to one in three diagnosed cases, talaromycosis has received little attention and investment from regional and global funders, policy-makers, researchers, and industry. Diagnostic and treatment modalities remain extremely limited. This paper is a global call for talaromycosis to be recognised as a Neglected Tropical Disease to alleviate its impact on vulnerable populations.

Introduction

In 2005, the World Health Organization (WHO) established a list of Neglected Tropical Diseases (NTDs). The list included a diverse group of largely chronic, parasitic, tropical infections that disproportionately impact people living in poverty.[1] Fungal diseases were not included on the NTD list until 2016 when the WHO expanded the list to include mycetoma, chromoblastomycosis, and an undefined category of ‘other deep mycoses’. In January 2021 the WHO released the 2021–2030 road map for NTDs, a visionary framework that emphasises impact measurement, cross-cutting programming, and country-driven policy.[2] The 2021–2030 NTD road map has, for the first time, named paracoccidioidomycosis and sporotrichosis among the ‘deep mycoses’. The editors of *PLOS Neglected Tropical Diseases (PLOS NTD)* have also increasingly recognised neglected fungal diseases, adding histoplasmosis and cryptococcosis ‘on the cusp’ of the *PLOS NTD* list in 2020.[3]

Talaromycosis is an invasive fungal infection with a high mortality, killing up to one in three diagnosed individuals.[4,5] As with other NTDs, talaromycosis disproportionally affects people living in poverty in the tropical and subtropical zones of Asia. It is not currently recognised as an NTD despite being quintessentially so. Talaromycosis satisfies all NTD criteria identified by the WHO, *PLOS NTD*, and the 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 multi-level neglect is the main barrier to reducing its significant morbidity and mortality. This paper 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 an NTD by the WHO, *PLOS NTD*, 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* (Tm) that is endemic in the tropical and subtropical regions of Asia (Appendix Figure 1). Tm 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 Tm 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, Myanmar), East Asia (southern China, Hong Kong, Taiwan), and north-eastern 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% to 19·6%, depending on the geographic region and country (Appendix Table 1).[7] A total of 288,000 cases have been reported in 33 countries to the end of 2018, with an estimated 17,300 cases (95% confidence interval [CI]: 9,900 – 23,700) and 4,900 deaths (95% CI: 2,500 – 7,300) 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 apparently healthy individuals can develop talaromycosis, albeit rarely.[9] Disease can be localised to the upper or lower respiratory tract,[10–12] bones, joints, and intestinal tract, or disseminated to multiple organ systems.[13] Advanced HIV disease (defined by the WHO as a CD4 cell count <200 cells/m^3) 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] Talaromycosis is not limited to people living with HIV. It is increasingly diagnosed in people with other immunosuppressing conditions, including the primary immunodeficiency condition due to interferon-gamma autoantibodies, auto-immune diseases, malignancy, and solid organ and bone marrow transplantations.[13,14] Non-HIV-infected individuals are less likely to have

skin lesions (44% vs. 71%)[5,14] and positive blood cultures (47% vs. 77%).[15] As a result, diagnosis is delayed (180 days vs. 45 days),[16] and mortality is higher (29% vs. 21%) compared to HIV-infected individuals.[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 Figure 2a),[18] alveolar consolidation, cavitary lung disease, solitary or multiple nodules, mediastinal lymphadenopathy, and pleural effusion (Appendix Figure 2b–c).[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 may be a more common cause of pneumonia in endemic areas than currently recognised.

Talaromycosis is a tropical infectious disease trapped in a cycle of poverty, stigma, and neglect

The WHO has four criteria for inclusion on the NTD list (Appendix Table 2). Talaromycosis fulfils all four criteria as detailed below.

1) 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 and middle income countries (LMIC) (Appendix Figure 1), with most countries falling into the lower middle income category.[21] Many people in Tm hyperendemic regions live in poor, rural areas. For example, 63% of the Vietnamese population and 67% of southern China's Guangxi province live rurally.[22,23] Although the soil-burrowing bamboo rats are the enzootic reservoir of Tm, 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.[6,24,25] Farmers have a 70% to 90% greater odds of developing talaromycosis than non-farmers,[24,25] and residence in or any travel of more than three days duration to highland communities is associated with a three-fold greater odds of disease.[25] Talaromycosis disproportionally affects rural communities and agricultural workers due to prolonged exposure to soil in the endemic regions.[24] 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 USD $1,300, approximately one-year salary for an average farmer in Vietnam), exacerbates the poverty inducing potential of talaromycosis.

Talaromycosis is characterised by disfiguring cutaneous lesions that predominate on the face and extremities (Appendix Figure 3). They are a feature of disseminated infection which prompts hospital admission and epitomise the visually stigmatising nature of the disease. The pathogen, *Talaromyces marneffei*, and the disease, talaromycosis, are difficult to pronounce, further hampering efforts to bring the disease on to 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 recent estimate of the global burden of talaromycosis, the incidence is projected to increase by 35% by 2025.[8] This 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.[26] Despite improved access to antiretroviral therapy across Asia, talaromycosis mortality remains unchanged,[4] suggesting diagnostic delay and access to HIV services remain significant barriers to survival.

2) 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 Figure 1). The tropical ecosystems in Southeast Asia are among the most vulnerable 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.[27] Talaromycosis is highly associated with the tropical monsoon weather with disease incidence increasing by 30% to 73% during the rainy months in Thailand, Vietnam, and southern China.[5,28] This remarkable seasonality is driven by high humidity,[29] which likely promotes infection through poor air quality and expansion of the fungal reservoir in the environment. The monsoon season brings intense, prolonged rainfall and floods, and the warmer oceans feed tropical cyclones which threaten agriculture production and food supply. These climate factors exacerbate the impact of talaromycosis on the rural poor and are likely to increase with global warming.[30]

3) Research support for talaromycosis has been insufficient to determine optimum diagnosis and treatment

Diagnosis.—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 based on typical microscopic findings on a skin smear, skin lesions are absent in 30% to 60% of patients.[15,28] Talaromycosis mortality doubles from 24% to 50% when the diagnosis is delayed and reaches 100% when the diagnosis is missed.[31] Non-culture diagnostic approaches are urgently needed to disrupt the cycle of delayed 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 (EIAs) are currently in development. The mAb-4D1 EIA and its immunochromatographic platform developed in Thailand show high sensitivity and specificity in small studies.[32,33] The mAb-Mp1p EIA developed in Hong Kong has been studied more extensively and was shown to be superior to blood culture in sensitivity (86% versus 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.[34] The Mp1p EIA is currently being evaluated in a multi-centre prospective study as a rapid diagnostic and screening tool for talaromycosis (ClinicalTrials.gov: NCT04033120). A commercial version of the Mp1p EIA was approved for clinical use in China in October 2019, and a Mp1p point-of-care lateral flow antigen (LFA) test is being developed through industry-public partnership with support from the National Institute of Health in the U.S. The WHO 2021–2030 NTD road

map has identified diagnostics as one of four priority areas, and established a Diagnostics Technical Advisory Group (DTAG) 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 NTD list. DTAG coordination 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.

Treatment.—Amphotericin B and itraconazole have been the mainstay of treatment for talaromycosis. In 2017, a multi-centre randomised controlled trial found induction therapy with amphotericin B achieved more rapid fungal clearance in blood and reduced six-month mortality from 21% to 11% compared to itraconazole.[35] 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, LMICs in Asia are still using the deoxycholate amphotericin B formulations that have not been used in high income countries (HICs) for two decades. The less toxic liposomal amphotericin B formulation (AmBisome™) is still not available in most of Asia despite coming off patent protection in the U.S. in 2016.[36] Therapeutic options for patient in LMICs who cannot tolerate amphotericin B are largely absent. The role of newer triazole compounds that are widely available in developed countries (voriconazole, posaconazole, isavuconazole) 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,[37] is also more efficacious for talaromycosis. No controlled studies have been conducted for treatment of non-HIV-infected people, and the duration of consolidation/maintenance antifungal therapy is unknown. For an infectious disease that has an on-treatment mortality of 30%, research to improve treatment is imperative. This will require substantial investment from both the global scientific community and industry. Inclusion on the NTD 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 HICs. This can be achieved collectively through the Drugs for Neglected Diseases initiative and the WHO Model Lists of Essential Medicines.[38]

4) 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.[39] However, this blanket approach to disease prevention has not been widely adopted due to concerns of 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,[40] is highly cost effective,[41] and is being implemented in HIV programmes across the world.[42,43] A similar diagnostic-driven approach is likely to be an effective strategy to control talaromycosis, as Tm antigenaemia has been shown to precede development of culture-confirmed talaromycosis by up to 16 weeks,[44,45] and antigenaemia is associated with 12-month mortality.[46] The Tm LFA 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.

While antigen screening is an effective approach in patients with advanced HIV disease, pathogen-based detection is still limited by delayed clinical presentatio.. Host-based diagnostics such as an antibody test or interferon-gamma 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 Tm. This understanding could inform strategies that control Tm at its source and could delineate geographic risk regions to effectively guide resource allocation for diagnosis, treatment, and prevention strategies.

The WHO 2021–2030 NTD road map is focused on integration of NTD prevention and control strategies within national healthcare systems with the support of domestic financing.[2] Currently there is no provision for talaromycosis funding within national healthcare 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 NTD 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.[47]

Conclusions

Talaromycosis meets all criteria to be included in the WHO NTD list and shares many features of other infectious diseases associated with poverty currently recognised by the WHO, *PLOS NTD*, and the FDA. The significant 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 an NTD by global public health organisations, funders, and other stakeholders will demonstrate the commitment and provide the necessary impetus to improve the control and prevention of this deadly infectious disease.

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Declaration of Interests

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Appendix

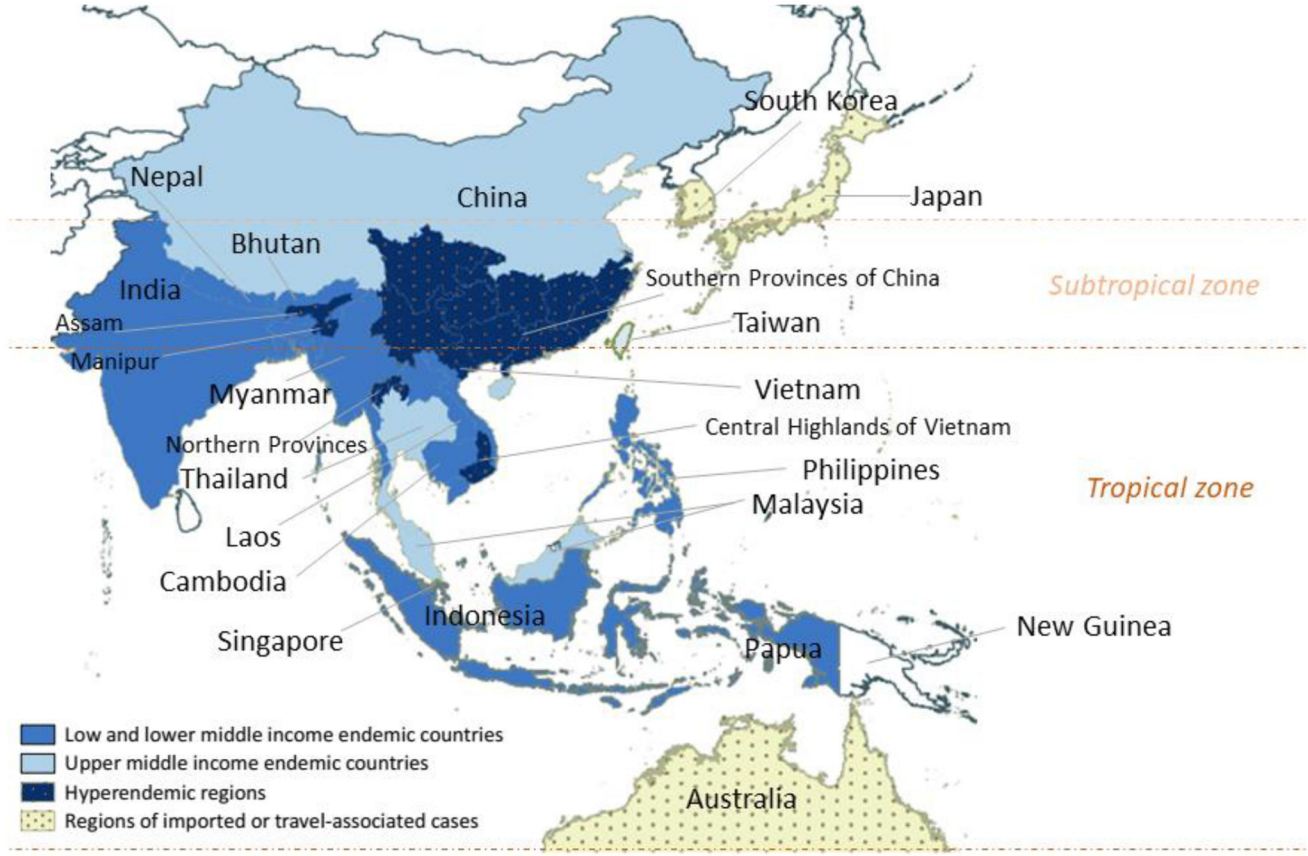

FIGURE 1:
Geographic distribution of talaromycosis according to income status and climate zones

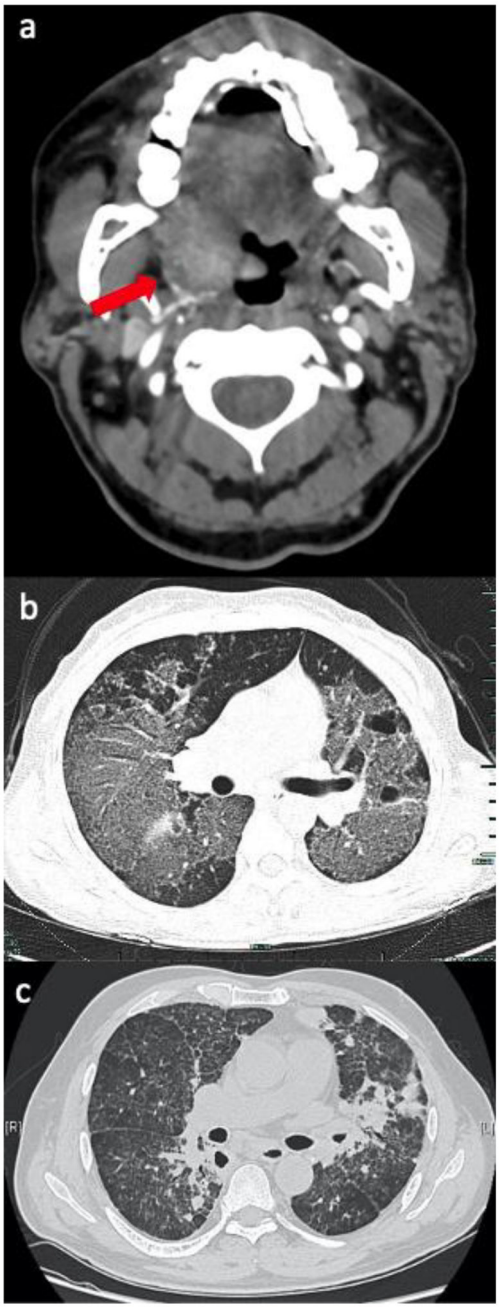

FIGURE 2.

Upper and lower respiratory tract manifestations of talaromycosis.

a) Computed tomography (CT) Angiogram of the neck demonstrating an ill-defined mass along the right lateral aspect of the hypopharynx involving the base of the tongue, right lingual tonsil, and right vallecula extending along the right palatine tonsil and into the pharyngeal space, in a 63 year-old man with HIV,[1] b) Axial CT Chest demonstrating multiple disseminated ground glass opacities and bullae in a 34 year old immunocompromised female with a *STAT3* mutation,[2] c) Chest CT with interstitial

infiltrates and nodules in a 57-year-old non-HIV-infected man with a history of prolonged steroid use.[3]

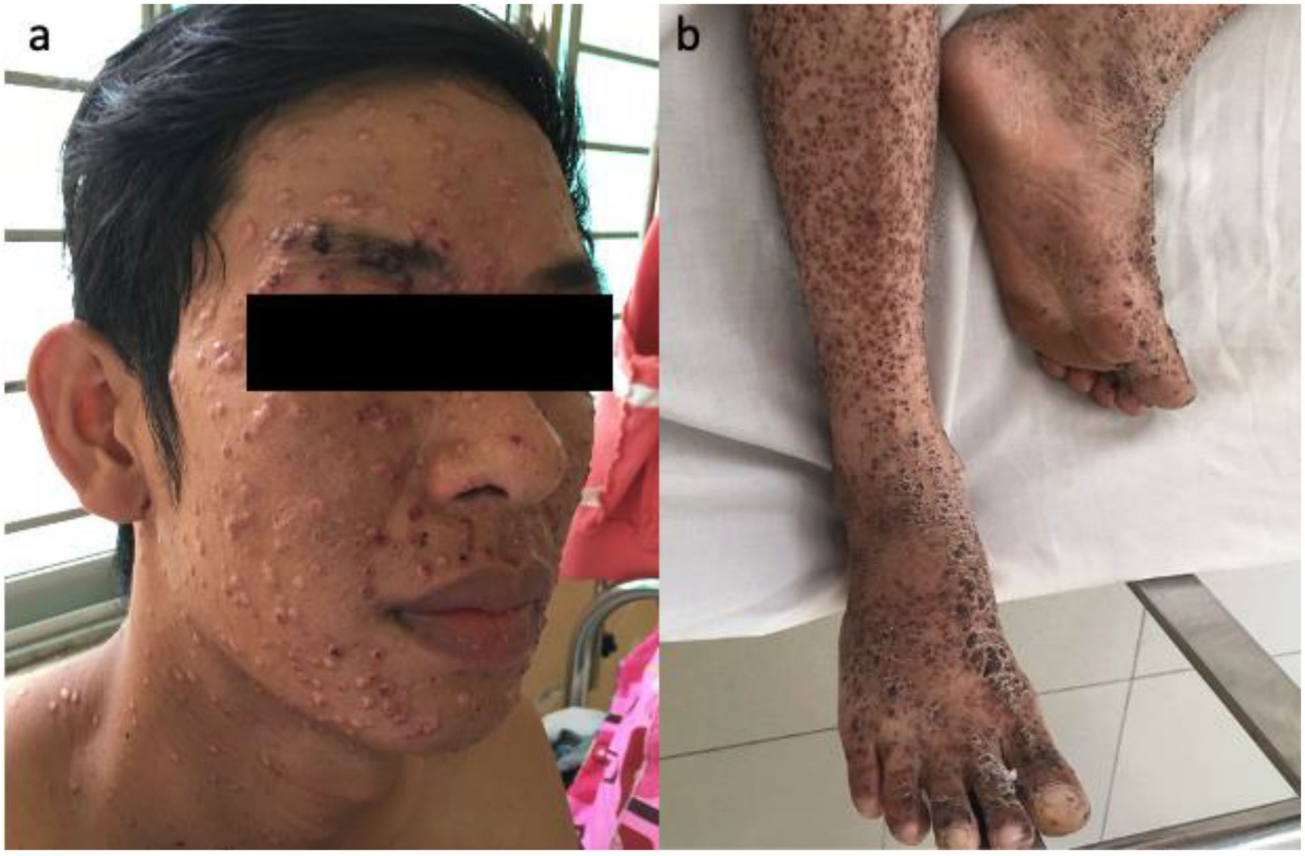

FIGURE 3:

Disfiguring skin lesions in talaromycosis.

a) Typical disfiguring central-umbilicated skin lesions on the face of a patient with advanced HIV and disseminated talaromycosis in Vietnam, b) Talaromycosis cutaneous lesions in the lower extremities in another patient with HIV in Vietnam.

Table 1:

Talaromycosis prevalence and mortality among people living with HIV/AIDS in endemic countries

	Prevalence	**Mortality**
China	16.1%[4] 3.3% (95% CI 1.8–5.8)[5] 16%[6]	17.5%[4] 14%[6]
Vietnam	6.4% (95% CI 4.4–9.5)[5] 0.23/100,000 population[7] 4.4% (range, 3.4% - 5.4%)[8] 4.9%[9]	6.3% (range, 5%−8.3%)[8] 33.3%[9] 12.6%[10]
Thailand	3.9% (95% CI 1.8–8.3)[5]	20.7% (HIV)[5]
Malaysia	2.1% (95% CI 0.7 – 6.6)[5]	4.8%, case report data [11,12]

	Prevalence	Mortality
Taiwan	1.1% (95%CI: 0.5–2.8)[5] 0.6%[13]	50%, case report data[14]
India	3.2% (95% CI 0.3–32.6)[5] 77 reported cases, most in Manipur state[15]	6.5%[15]

Table 2.

WHO criteria for classifying a condition as a neglected tropical disease (NTD)[16]

Disease conditions that

1	disproportionately affect populations living in poverty; and cause important morbidity and mortality – including stigma and discrimination - in such populations, justifying a global response
2	primarily affect populations living in tropical and sub-tropical areas
3	are immediately amenable to broad control, elimination or eradication by applying one or more of the five public health strategies adopted by the Department for Control of NTDs, **and/or**
4	are relatively neglected by research – i.e., resource allocation is not commensurate with the magnitude of the problem - when it comes to developing new diagnostics, medicines and other control tools

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