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Updated estimation of the burden of fungal disease in Vietnam

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Abstract

Background: Anecdotally, the burden of fungal diseases in Vietnam is rapidly rising, but there has been no updated estimate on this issue since a previous report in 2015.

Objectives: In this study, we aimed at estimating the incidence and prevalence of serious fungal infections for the year 2020.

Methods: We made estimates with a previously described methodology, using reports on the incidence and prevalence of various established risk factors for fungal infections from local, regional or global sources.

Results: We estimated 2,389,661 cases of serious fungal infection occurred in Vietnam in 2020. The most common condition was recurrent vaginal candidiasis (4047/100,000 women annually). Among people living with HIV, we estimated 451 cases of cryptococcal meningitis, 1030 of pneumocystis pneumonia, 166 of histoplasmosis and 1612 of talaromycosis annually. Candidaemia incidence was estimated at 12/100,000 population each year. Owing to its high burden of tuberculosis and respiratory diseases, Vietnam had high rates of severe infections caused by *Aspergillus* species. Incidence of invasive aspergillosis is 24/100,000 population, allergic bronchopulmonary aspergillosis 78/100,000 and severe asthma with fungal sensitisation 102/100,000. Five-year period prevalence of chronic pulmonary aspergillosis is 120/100,000 population /5-year period. Mucormycosis, fungal keratitis and tinea capitis were estimated at 192, 14,431 and 201 episodes each year, respectively.

Conclusions: The number of patients with mycoses in Vietnam is likely underestimated due to a lack of local data and limited diagnostic capacity, but at least 2.5% of the population might have some form of serious fungal disease.

KEYWORDS
burden, epidemiology, fungal, incidence, prevalence, Vietnam

1 | INTRODUCTION

Serious fungal diseases cause significant morbidity and mortality worldwide. They affect more than 150 million people, with >1.6 million deaths a year.[1] Identification of high-risk patients is an important initial step to reduce fungal infection-associated mortality. The risk of serious fungal infections increases with the presence of certain underlying conditions, including HIV/AIDS, pulmonary tuberculosis (PTB), asthma, chronic obstructive pulmonary disease (COPD), leukaemia and solid organ transplantation. In addition, COVID-19 has

recently been identified as a new risk factor for invasive fungal infection because of its effect on the immune system and because treatments for COVID-19 can weaken the body's defences against fungi.[2] Fungal co-infections have been reported in COVID-19 patients, with most commonly caused by *Aspergillus*, *Candida* and *Mucormycetes*.[3-7]

Vietnam has a population of about 100 million, and large numbers of people are affected by tuberculosis, HIV infection and more recently COVID-19.[8] In the limited context of both reliable diagnostics and antifungal medications, it is a challenge for Vietnamese clinicians to confirm causative fungal pathogens and to select appropriate antifungal therapy. Therefore, there is a need to raise awareness among clinicians and community members about mycoses. In 2015, the first report on the burden of fungal diseases in Vietnam was published, but since then, no further estimates on this issue have been made.[9]

Many factors including the advancement of medicine and public health initiatives, emerging diseases and changes to vulnerable populations are likely to have altered the frequency of fungal diseases. Furthermore, access to national databases in Vietnam is improving, for example, Health Statistics Yearbook. Therefore, an updated and improved estimate of the fungal disease burden in Vietnam is timely. This will provide critical baseline information that enables government leaders to identify which programmes are working and achieving the highest returns.

2 | MATERIALS AND METHODS

The authors confirm that the ethical policies of the journal have been adhered to. No ethics approval is required since the study only used publicly available data. No individual patient data were used.

We estimated the burden of serious fungal infections in Vietnam using an updated version of the methodology previously described.[9] In brief, this approach sources publicly available data on the prevalence of risk factors and multiplies them by published data on the incidence of fungal infections related to those risk factors, to arrive at estimates of likely annual incidence and prevalence. In the absence of surveillance, this is the best method to make such estimates. By virtue of using the same methods as implemented in numerous other countries, this approach has the additional benefit of generating data that are comparable between countries. We held a series of round table discussions with Vietnamese clinicians, researchers, scientists and international collaborators to establish optimal sources of data and to identify clinicians working in relevant areas, who could potentially supplement published data with personal communications.

Using relevant keywords, we searched for updates on local disease and risk factor data through PubMed (https://www.ncbi.nlm.nih.gov/) with date of publication within the last 5 years; if there were no matches in the certain period of time, we would extend the search period, but no later than 2010. In the absence of local information, the best alternative source would be from other Southeast Asian countries, otherwise from international reports.

We used the national population estimates 2019 from the General Statistics Office of Vietnam (www.gso.gov.vn). HIV-related data were derived from the Vietnam Administration of HIV/AIDS Control (www.vaac.gov.vn). The WHO Global Tuberculosis Programme (https://www.who.int/teams/global-tuberculosis-programme) and the Vietnam National Tuberculosis Programme provided information on tuberculosis (TB) and pulmonary TB incidences in 2020, respectively.

In this study, we calculated the burden of HIV-related fungal diseases including cryptococcal meningitis (CM), pneumocystis pneumonia (PCP) and histoplasmosis, in the HIV population at risk for new AIDS infections and drug resistance; except talaromycosis (previously termed penicilliosis) was calculated against the at-risk population of new HIV infections and drug resistance to match the reference disease rate used. We considered new AIDS cases were newly diagnosed HIV patients having CD4 ≤ 100 cells/μl, with an assumption of patients presenting CD4 count 100–200 cells/μl as not at risk.

For candidaemia, we used a regional median rate to estimate its incidence based on hospital admissions in Vietnam.[10-15] Since the number of national inpatients in 2019 was not available, we referred to the 2018 figure recorded by Vietnam Ministry of Health (www.moh.gov.vn). Other *Candida* infections such as peritoneal candidiasis, oral candidiasis, oesophageal candidiasis and recurrent vulvovaginal candidiasis (RVVC) incidences were updated with more recent data.

In the current estimate of invasive aspergillosis (IA), besides leukaemia, organ transplant and COPD hospitalisation, we added risk factors of haematopoietic stem cell transplantation (HSCT), lung cancer and HIV/AIDS-related death into the calculation. Chronic pulmonary aspergillosis (CPA) incidence was estimated based on combination of misdiagnosed cases, CPA cases arising within 12 months of TB diagnosis or subsequent years plus 33% additional cases, for those not linked to TB (based on international reports).[16-20] The method for estimating allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitisation (SAFS) remained unchanged from 2015, except the denominator numbers for adult asthma cases were updated to reflect local reports.[8,21]

The incidence of fungal keratitis, mucormycosis and tinea capitis was estimated based on recent regional data.

3 | RESULTS

3.1 | Population and country profile

Vietnam is one of the most dynamic emerging countries in the Southeast Asia region and now classified as a lower middle-income country by the World Bank (https://www.worldbank.org). In 2019, the entire country population was 96,208,984 with 24.3% under 15 years old (n = 23,378,783). 32.9% of women were over 50 years, and there were 27,810,118 women between 15 and 54 years old.[8] Figure 1 shows the population structure of Vietnam in 2019.

According to the Vietnam Health Statistics Yearbook 2018, there were approximately 15,361,698 inpatients.[23]

Table 1 presents the estimated prevalence and incidence rates of selected serious fungal infections burden in Vietnam in 2020. We estimate 2,389,661 episodes of serious fungal infection occurred in Vietnam in 2020.

3.2 | HIV-related fungal infections

In the Vietnam Administration of HIV/AIDS Control report, the total number of people living with HIV cumulative to 2020 was 213,724 with 13,955 new HIV/AIDS cases; 73% of patients were on antiretroviral therapy or ART (n = 155,973). There were 2160 deaths, almost all in adults.[25]

According to two different reports from Vietnam, 38.6% of newly diagnosed HIV patients would have a CD4 count ≤100 cells/μl and 7.2% of patients on ART would develop drug resistance, we expected about 5387 new AIDS cases and 11,230 cases with virologic failure in 2020.[26,27] Therefore, the total population at risk used to estimate the burdens of CM, PCP and histoplasmosis was 16,617 cases.

Cryptococcal meningitis infection occurred in both HIV and non-HIV groups at a ratio of 4:1.[28] In the HIV population, 3.1% were found to be positive for cryptococcal antigenaemia (CrAg), and 70% of CrAg-positive cases would develop cryptococcal diseases.[26,29] Based on these reported figures, we estimated approximately 451 cases of CM (0.5/100,000 annually), with 361 in the HIV group and 90 in the non-HIV group. PCP was expected to affect 1030 cases (1.1/100,000) and disseminated histoplasmosis 166 cases (0.2/100,000).[30,31]

Talaromycosis was assumed to occur in the HIV population at risk for new infection and drug resistance (n = 25,185); we predicted 1612 cases (1.7/100,000).[32]

Oral candidiasis occurred in 37.7% of HIV-infected patients, whereas oesophageal candidiasis affected 20% of HIV patients not on ART and 5% of those on ART.[33,34] As a result, oral candidiasis and oesophageal candidiasis were estimated in 83.7/100,000 and 20.1/100,000 population, respectively. Due to a lack of information, we were unable to estimate incidences in other non-HIV populations, such as those with cancer, neonates and taking steroid inhalers.

3.3 | Fungal infections in patients with respiratory diseases

Vietnam is a high TB burden country, with 172,000 cases occurring annually in the population.[35] Of which, 137,600 cases were PTB, including 4480 having HIV positive and 133,120 having HIV negative [personal communication with the Vietnam National TB Programme]. According to a study from Vietnam, COPD admissions to hospital per year were 574,162.[36] More men smoke cigarettes than women in Vietnam, but smoke exposure is common (passive smoking). Asthma was found to affect 4.1% of adults (n = 2,986,321), whereas cystic fibrosis is rare.[22]

Among PTB survivors, we estimated approximately 17,702 cases of CPA occurred each year. The CPA 5-year prevalence was about 77,502 cases after taking into account the annual expected deaths among those survivors over the course of 5 years. The total prevalence of CPA was anticipated to be 115,675 cases by adding the 33% of cases that are unrelated to TB.[16-20]

Allergic bronchopulmonary aspergillosis was first described in Vietnam in 2016.[37] Using international data, indicating that typically around 2.5% of adult asthmatics have ABPA, we estimated 74,658 cases per year.[22,38,39] Assuming that fungal sensitisation occurs in 33% of the worst 10% adult asthmatics, SAFS was anticipated to affect 98,549 cases annually (102.4/100,000).[22,40]

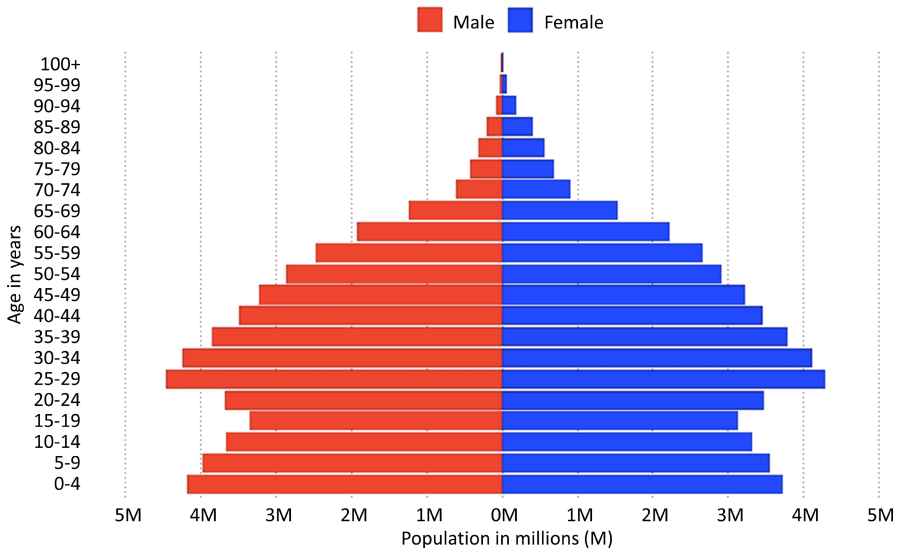

FIGURE 1 Population structure by age and gender in Vietnam, 2019 (data source: https://population.un.org/wpp/Download/Standard/CSV/)[24]

TABLE 1 Estimation of total case numbers, prevalence and incidence rates of selected serious fungal infections in Vietnam, 2020.

Infection	Burden	Cases incidence/ prevalence per 100 k population	Estimation method	References
Cryptococcal meningitis	451	0.5	3.1% of both newly diagnosed AIDS and HIV drug resistance are CrAg-positive; 70% of positive cases develop into CM	26,28,29
Pneumocystis pneumonia	1030	1.1	6.2% cases of both newly diagnosed AIDS and HIV drug resistance	30
Histoplasmosis	166	0.2	1% cases of both newly diagnosed AIDS and HIV drug resistance	31
Talaromycosis	1612	1.7	6.4% cases of newly diagnosed HIV/AIDS and HIV drug resistance	32
Oral candidiasis	80,574	83.7	37.7% of total HIV patients	32
Oesophageal candidiasis	19,349	20.1	20% of HIV patients not on ARTs and 5% of those taking ARTs	33
Chronic pulmonary aspergillosis (CPA)	115,675	120.2	Combination of misdiagnosed cases, CPA cases arising within 12 months of TB diagnosis and subsequently; plus 33% additional cases, not linked to TB	16-20
Allergic bronchopulmonary aspergillosis (ABPA)	74,658	77.6	2.5% of adult asthmatics	38,39
Severe asthma with fungal sensitisation (SAFS)	98,549	102.4	33% of the most severe adult asthmatics	40
Invasive aspergillosis (IA)	23,470	24.4	10% AML; 10% non-AML haematological malignancy; 10% allogeneic HSCT; 1% renal transplants; 6% lung transplants; 6% heart transplants; 4% liver transplants; 2.6% lung cancer; 3.9% COPD hospitalisation; 4% AIDS-related death	1,42,43,44,45,46,47
Candidaemia	11,291	11.7	0.74/1000 hospital admissions; 23.1% of cases occurred in the ICUs	10,11,12,13,14,15,49
Candida peritonitis	1305	1.4	50% of candidaemia cases in ICU	50
Recurrent vaginal candidiasis >4/times/ year	1,946,708	4047	7% of women 15–54 years old	51
Mucormycosis	192	0.20	2 cases per 1000,000 population	52
Fungal keratitis	14,431	15	15 cases per 100,000 population	52
Tinea capitis	201	0.21	0.86 per 100,000 children <15 years old	53
Total estimated cases	2,389,661			

Abbreviations: AIDS, acquired immune deficiency syndrome; AML, acute myeloid leukaemia; ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease; CM, cryptococcal meningitis; CPA, chronic pulmonary aspergillosis; CrAg, cryptococcal antigenaemia; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; TB, tuberculosis.

4 | FUNGAL INFECTIONS ASSOCIATED WITH HAEMATOLOGICAL AND TRANSPLANTATION RISK FACTORS

The incidence of acute myeloid leukaemia (AML) was approximately 1.54 per 100,000 population.[40] Over a 15-year period (2006–2020), there were an estimated 1127 cases of HSCT and 58.74% were allogeneic HSCTs—approximately 44 cases per year. From 2013 to 2021, 553 kidneys, 5 hearts, 1 lung and 35 livers were transplanted annually, but with no national registry. These HSCTs and solid organ transplantation figures were collected from the 20 major national hospitals [personal communication Dr. Nguyen Thi Bich Ngoc, Respiratory dept, National Lung Hospital in Hanoi]. Vietnam had 26,262 new cases (14.4% of all cancers) of lung cancer diagnosed in 2020, with men affected three times as commonly as women.[41]

We estimated that IA might occur in 10% of AML patients, 10% of patients with non-AML haematological malignancies, 10% of allogenic HSCT transplants, 1% of renal transplants, 6% of lung transplants, 6% of heart transplants, 4% of liver transplants and 2.6% lung cancer patients. IA was also anticipated to be present in 4% of AIDS-related deaths and 3.9% of COPD hospitalisations.[1,43,44,45,46,47,48] Overall, IA was expected to occur in 991 immunocompromised and transplant patients, 22,392 COPD hospitalisations and 86

AIDS-related deaths. The total annual incidence of IA was 23,470 cases (24.4/100,000).

5 | OTHER FUNGAL INFECTIONS

Using a regional median incidence of 0.74/1000 hospital admissions, we estimated approximately 11,291 cases of candidaemia in Vietnam.[10-15] Assuming that 23.1% of episodes occurred in intensive care unit (ICU) and half of those might develop *Candida* peritonitis, we therefore calculated approximately 1305 cases of *Candida* peritonitis.[49,50]

Based on 7% of the female population 15–54 years of age being affected, we found RVVC was the most prevalent fungal infection, with an annual case rate of 4047 per 100,000.[51]

According to some regional studies, mucormycosis and fungal keratitis were expected to occur in 2/1000,000 and 15/100,000 of the population, respectively.[52,53] Tinea capitis, instead, affected only children at a rate of 0.86/100,000.[54] We estimated that there were 192 cases of mucormycosis, 14,431 of fungal keratitis and 201 of tinea capitis in 2020.

Very few cases of mycetoma and chromoblastomycosis are described in Vietnam and none of sporotrichosis.[55,56]

6 | DISCUSSION

We estimated that 2,389,661 people were affected by serious mycoses in Vietnam in 2020, approximately 2.48% of the population. This infection rate is comparable to those reported previously in Indonesia (2.89%), Thailand (1.93%), Malaysia (1.93%) and the Philippines (1.9%).[31,53,54,57] Compared with 2015 estimates, the total number of infections has risen by 1.57% in 2020; yet, the incidences of aspergillosis, candidaemia and HIV-related fungal diseases have significantly increased, driven by changes in the at-risk populations.[9] In Vietnam, the high prevalence of TB and HIV/AIDS remains key risk factors for the most serious mycoses, and opportunistic fungal infections remain a topic of public concern.

There were some updates and modifications in the 2020 methodology calculation of the fungal disease burden (Table 2). For HIV-associated fungal diseases, in 2015 the incidences were estimated

TABLE 2 Difference in estimation method of fungal diseases in Vietnam between 2015 and 2020 studies

Fungal infection	Estimation method	
	2015 study	2020 study
Cryptococcal meningitis Pneumocystis pneumonia	Population at risk for newly diagnosed AIDS	Population at risk for both newly diagnosed AIDS and HIV drug resistance
Talaromycosis	Population at risk for newly diagnosed AIDS	Population at risk for both newly diagnosed HIV/AIDS and HIV drug resistance
Histoplasmosis Oral candidiasis	-	Added in this study
Chronic pulmonary aspergillosis	Population at risk: survivors of pulmonary tuberculosis with and without cavities	Refined method for estimating population at risk among survivors of pulmonary tuberculosis
Invasive aspergillosis	Population at risk for leukaemia, organ transplant and COPD hospitalisation	At-risk population similar to that in 2015 study with some changes: • Increased rate for renal transplant patient from 0.5% to 1% • Adding patients with HSCT, lung cancer patients and AIDS deaths into the at-risk population
Candidaemia	Calculation was based on the occurrence rate in ICU and non-ICU population (global rate)	Calculation was based on the occurrence rate in hospital admission population (Asian rate)

Abbreviations: AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HSCT, haematopoietic stem cell transplantation; ICU, intensive care unit; PTB, pulmonary tuberculosis.

based on new HIV/AIDS cases only, but in this study, we included an additional HIV group of drug resistance with a consideration that drug-resistant patients would also be at higher risk of invasive fungal infections. The proportion of IA in the renal transplant group increased from 0.5% to 1%, and new risk factors of HSCT, lung cancer and HIV/AIDS were added in the 2020 calculation of IA incidence.[43,45,46,48] The burden of candidaemia was estimated based on a regional median incidence of 0.74/1000 hospital admissions, instead of using a global reference rate of 5/100,000 population as before.[9-15] These changes make the current estimate much more realistic and reflective of the situation in Vietnam, suggesting an increasing burden of most serious fungal diseases over time.

High levels of air pollution and smoking habits increase the risk and the severity of respiratory diseases like asthma, COPD, lung cancer and tuberculosis, which will lead to increased *Aspergillus* infections due to expanded susceptible populations.[58-61] A high proportion of our estimated *Aspergillus* cases are related to COPD—we note that there is considerable debate on diagnostic criteria for invasive aspergillosis in this patient group and further work is needed to narrow the range of incidence rates. Although we used a moderate rate from a large Chinese study, an overestimate is possible.[44] Rates of other fungal infections, such as RVCC, fungal keratitis and tinea capitis, are likely to be underestimated because infected patients often feel embarrassed and refuse to get medical care, which makes it difficult for the healthcare system to evaluate local fungal burden.

All these estimates indicate a growing threat of serious mycoses to the Vietnamese population. Early diagnosis and timely treatment of fungal infections are essential for improving clinical outcomes; however, this is still a big challenge in Vietnam because of limited diagnostic capacity, drug unavailability and unaffordable medication costs. In addition, empiric therapy is frequently favoured by physicians, increasing the risk of inappropriate drug use. Reports from Greece and Thailand showed that hospitals have been overusing antifungals at worrisome rates of 25% and 74%, respectively.[61,62] Abuse of antifungal drugs in either clinical or agricultural settings is major contributors to the development of drug-resistant fungal pathogens, which may complicate treatment outcome. Our environmental studies conducted in Vietnam have identified an unprecedented rate of azole-resistant *Aspergillus fumigatus*, which raises concerns for underappreciated threat of antifungal-resistant infections in clinical practice.[63,64]

The 2015 burden of fungal disease estimates for Vietnam attracted the interest and attention of the Vietnamese community and the government, and the first official set of guidelines on diagnosis and treatment of invasive fungal infections in clinical practice was released in 2021 by the Vietnamese Ministry of Health.[66] It is important that policies guidelines are informed by regularly updated data.

Our report has some limitations. First, reports on fungal diseases are limited to only a few regions of the country and updated sporadically. We had to use the latest regional or global epidemiological data for most of our estimations since national epidemiological data were lacking; only the estimates of CM, PCP, and talaromycosis were based on local rates. Second, not all CrAg-positive patients would develop CM, the burden of CM calculated using CrAg prevalence might be overestimated. Finally, our analyses of CM, PCP, and histoplasmosis were restricted to those with very advanced disease (CD4 count < 100 cells/μl) and did not extend to those with CD4 count 100–200 cells/μl.

In conclusion, our study provides an updated and improved estimate of the burden of serious fungal infections in Vietnam. Reducing the populations at risk, improving diagnostic capacity and updating national epidemiological data are essential steps towards mitigating this significant burden of disease.

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CONFLICT OF INTEREST

Dr Denning and family hold founder shares in F2G Ltd, a University of Manchester spin-out antifungal discovery company and share options in TFF Pharma. He acts or has recently acted as a consultant to Pulmatrix, Pulmocide, Biosergen, TFF Pharmaceuticals, Pfizer, Omega, Novacyt and Cipla. He sat on the DSMB for a SARS CoV2 vaccine trial. In the last 3 years, he has been paid for talks on behalf of Hikma, Gilead, BioRad, Basilea, Mylan and Pfizer. He is a longstanding member of the Infectious Disease Society of America Aspergillosis Guidelines group and the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines group and recently joined the One World Guideline for Aspergillosis. Dr Justin Beardsley is supported by an NHMRC Australia Fellowship and has received Honoraria from Gilead Life Sciences for hosting meetings. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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