

# Burden of serious fungal infections in Bangladesh

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**Abstract** In Bangladesh there are several published papers on superficial mycoses. Deep mycoses are also recognized as an important emerging problem. Here, we estimate the annual incidence and prevalence of serious fungal infections in Bangladesh. Demographic data were obtained from world population reports and the data on TB and HIV extracted from the online publications on tuberculosis in Bangladesh and Asia Pacific research statistical data information resources AIDS Data HUB. All the published papers on fungal infections in Bangladesh were identified through extensive search of literature. We estimated the number of affected people from populations at risk and local epidemiological data. Bangladesh has a population of ~162.6 million, 31% children and only 6% over the age of 60 years. The pulmonary TB caseload reported in 2014 was 119,520, and we estimate a prevalence of 30,178 people with chronic pulmonary aspergillosis, 80% attributable to TB. An anticipated 90,262 and 119,146 patients have allergic bronchopulmonary

aspergillosis or severe asthma with fungal sensitization. Only 8,000 people are estimated to be HIV-infected, of whom 2900 are not on ART with a CD4 count <350  $\mu$ L, *Pneumocystis* pneumonia and cryptococcal meningitis being rare. Superficial mycoses are very common with *Trichophyton rubrum* as the predominant etiological agent (80.6%). Numerous cases of mycotic keratitis have been reported from several parts of Bangladesh. *Candida* bloodstream infection was estimated based on a 5 per 100,000 rate (8100 cases) and invasive aspergillosis based primarily on leukemia and COPD rates, at 5166 cases. Histoplasmosis was documented in 16 cases mostly with disseminated disease and presumed in 21 with HIV infection. This study constitutes the first attempt to estimate the burden of several types of serious fungal infections in Bangladesh.

## Introduction

Fungal diseases are being increasingly recognized as important determinants of survival in immunocompromised patients and in other patients with chronic illnesses. Fungal infections in Bangladesh are diverse and many studies have documented their frequency. There are several published papers on dermatomycoses and other superficial mycoses such as *Candida* infections [1, 2]. In a study on 3,435 patients attending a dermatology clinic in a rural area [2], 601 (17.5%) were diagnosed with superficial fungus infections. A study of ocular infections, showed mycotic keratitis accounting for 35.9% of suppurative keratitis, often following ocular trauma [3]. Deep mycoses are also recognized as an important emerging problem as evidenced by reports of 16 cases of histoplasmosis with varying clinical manifestations [4–6]. Several other systemic mycoses have also been reported, viz. a case of blastomycosis [4], two of mucormycosis [7, 8], and one each of

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renal aspergillosis caused by *Aspergillus fumigatus* [9], pulmonary aspergilloma [10] and cryptococcal meningitis [11]. Given this substantial impact on human health, gaining a better understanding of the burden in different countries is important, for public health, health policy and research priorities.

## Materials and methods

Demographic data were obtained from a world population report [12]. Data on TB and HIV extracted from the online publications on tuberculosis in Bangladesh and Asia Pacific research statistical data information resources AIDS Data HUB [13, 14]. COPD and asthma data were extracted from publications from Bangladesh [15, 16]. From 1988 to 2012, 1000 kidney transplants were done till 2012, though the annual demand is at least 5000; and two liver transplants have been carried out successfully [17, 18]. All the published papers on fungal infections in Bangladesh were identified through extensive search of literature, using PubMed, MEDLINE, Med Facts, and different sets of key words, viz. Bangladesh, mycoses, superficial mycoses, deep mycoses, *Candida* infection, aspergillosis, mucormycosis etc. in the search engines.

## Results and discussion

### Fungal infections affecting those without underlying disorders

Bangladesh has a population of ~162.6 million as of May 4, 2016 based on latest UN estimates, 31% children and only 6% over the age of 60 years [12]. The GDP per capita in 2015 was 972.88 USD. Superficial mycoses are very common in Bangladesh, the vast majority occurring in normal immunocompetent people of all ages, in urban as well as in rural areas. In a study of superficial mycoses [1], out of 320 clinically suspected cases 105 (32.8%) were found to be positive for fungi by direct microscopy, and 97 (30.3%) were culture positive, tinea unguium being most common followed by tinea corporis. *T. rubrum* was the most common etiological agent (80.6%), followed by *T. mentagrophytes* (8.2%) and *Epidermophyton floccosum* (5.2%) [1]. In another study, out of 3435 patients with skin ailments in rural areas, 601 (17.5%) proved to be of fungal etiology [2]; tinea corporis was the most frequent infection (22.6%) followed by tinea capitis (10.3%), tinea pedis (9.8%), and tinea cruris (8.3%), while in children, the most frequent clinical types were oral thrush (13.96%), pityriasis versicolor (12.5%) and tinea capitis (11.85%).

Among superficial *Candida* infections, oral thrush is the most common with a prevalence rate of 11.5–14% [1, 2],

followed by intertrigo (6.49%) and chronic paronychia (3.49%) [19]. A study of infections of skin and soft tissue reported 0.3% of skin and soft tissue sepsis due to *Candida* [20]. Regarding genital infections in women vulvovaginal candidiasis (VVC) occurred in 49% of 350 women including those on oral contraceptives; the incidence was significantly higher in contraceptive users (56.7%) than that in non-users (31.1%) ( $p < 0.001$ ) [21]. Also the women using oral pills had a much higher prevalence of *Candida* vaginal infection (64.9%) than those using injectables (12%) or an IUCD (21.1%) ( $p < 0.001$ ) [21]. No studies have addressed recurrent VVC in Bangladesh, but using European and US data we estimate that 2,622,627 women are affected (Table 1).

Though there are no population denominators to establish the prevalence of all superficial fungus infections across the country, it is evident from the aforesaid data that superficial mycoses including those attributable to dermatophytes, pityriasis versicolor and *Candida* infections of the skin are very common in Bangladesh. The vast majority of these infections occur in normal immunocompetent people of all ages, in urban as well as in rural areas, thus constituting a major public health problem. Community-based surveys with laboratory support are desirable to correctly estimate the burden of these infections.

### Chronic and allergic pulmonary conditions

Based on a large UK study from the late 1960s, we have estimated the annual incidence and five-year period prevalence of chronic pulmonary aspergillosis (CPA) after pulmonary TB [22]. The pulmonary TB caseload reported in 2014 was 159,391 patients [13]. A 25% mortality of pulmonary TB (51/100,000) leaves 119,520 alive, of whom an estimated 7,649 subsequently develop CPA. Assuming an annual mortality of 15%, an estimated prevalence of 24,111 people have CPA including many with an aspergilloma. If we assume that TB accounts for 80% of the CPA cases, then overall CPA prevalence will be 30,138 (69/100,000) (Table 1) [22]. There is only one reported case of pulmonary aspergilloma in a 70-year-old man with past history of tuberculosis [10], diagnosed radiologically and confirmed by fine needle aspiration cytology.

A study using the GOLD criteria recorded a COPD rate of 11.4% in a population of 900 aged  $\geq 35$  including 481 smokers, and identified smoking and low socio-economic status as risk factors of COPD [15]. Also ~20–25% of the population suffers from different types of allergic disorders; the prevalence of asthma is 3.23% in adults and 7.4% in children, the overall prevalence being 5.2% with a prevalence of 3.23% in adults and 7.4% in children, and the total number of asthmatics being estimated to be 8.4 million people [16]. Asthma is also very common in rural children and is an important cause of morbidity [23].

**Table 1** Estimated cases per year (incidence and prevalence) of more frequent serious fungal diseases

Infection	Subpopulation						Total burden	Rate/100,000
	None	HIV	Respiratory	Cancer/Tx/Imm <sup>a</sup>	ICU			
Oesophageal candidiasis		835				835	0.5	
Recurrent candida vaginitis	2,622,627					2,622,627	3238 <sup>a</sup>	
Candidemia				5670	2430	8100	5	
Allergic bronchopulmonary aspergillosis			90,262			90,262	56	
Severe asthma with fungal sensitisation			119,146			119,146	74	
Chronic pulmonary aspergillosis			20,720			20,720	48	
Invasive aspergillosis				972	4194	5166	3.2	
<i>P. jirovecii</i> pneumonia		58				58	0.04	
Cryptococcal meningitis		15				15	0.01	
Allergic fungal rhinosinusitis	178,200					178,200		

<sup>a</sup> Female population only

Assuming that 2.5% of adults with asthma have allergic bronchopulmonary aspergillosis (ABPA), 90,262 are then estimated to have ABPA (Table 1). This may be a substantial underestimate as ABPA appears to be much more common in India than in North America or Europe [24]. Likewise if 10% of the adult asthmatics have severe asthma, and 33% or 50% are sensitized to fungi, then we would anticipate 119,146 (Table 1) or 180,525 patients with severe asthma with fungal sensitization (SAFS). There is probably some overlap between these groups as some ABPA patients have severe asthma, even if treatment with corticosteroids is discounted in determining the severity of their asthma.

Another noteworthy publication is the report of eight cases of non-invasive fungal maxillary sinusitis, the diagnosis being based on histopathology without identification of the infecting fungi [25]. One study on estimate of allergic fungal rhinosinusitis (FRS) in rural India [26] found a population prevalence of 0.11% of chronic FRS with allergic FRS in 41 (56.1%), chronic granulomatous FRS in 13 (17.8%), eosinophilic FRS in 11 (15.0%), fungal ball in 7 (9.5%) and chronic invasive FRS in one (1.3%). If the Indian figure is applied to the Bangladesh population, then an estimated 178,200 people have chronic FRS (110/100,000) (Table 1). In view of our above-mentioned estimates, it is evident that CPA, ABPA and fungal rhinosinusitis constitute a serious burden of mycoses in Bangladesh.

### Invasive mycoses

The rate of candidaemia varies substantially by country, and using a conservative 5 per 100,000 rate, we estimate 8100 cases in Bangladesh each year (Table 1). These estimates are likely to be too low and additional data are required to model these numbers more accurately. Among other serious fungal infections, invasive aspergillosis (IA) is barely recognized in

Bangladesh. Among the estimated 34.5 million adults over the age of 40, there are an estimated 2,481,444 patients with COPD (7.2%) [15]. Assuming that 13% of these patients are admitted to hospital each year and that 1.3% develop IA, then based on data from Trinidad and Tobago [27], 4194 cases of IA would be seen in this population annually (Table 1). In view of the aforesaid data, invasive candidaemia and aspergillosis constitute a serious burden in Bangladesh.

The prevalence of HIV is low in Bangladesh, an estimated 9600 infected people, of whom 8117 are not on ART with a CD4 count <350  $\mu$ L as recorded in 2014 [14]. HIV infects about 0.1% TB patients [14]. Among adults hospitalized with HIV infection over 3 years in hospital in Dhaka in Bangladesh [28], six developed presumptive cryptococcal meningitis, 23 *Pneumocystis* pneumonia (PCP), and 21 presumptive disseminated histoplasmosis. In another study of 24 hospitalized children with HIV, four (17%) developed PCP [29]. We estimate that in patients with AIDS, 58 develop PCP each year and 15 cryptococcal meningitis (Table 1), based on these data from Shahrin and colleagues [29]. One case of post-renal transplant cryptococcal meningitis has also been reported from Bangladesh [11].

Regarding histoplasmosis, skin testing surveys of histoplasmin sensitivity in Bangladesh (when it was called East Pakistan) in 1962 [30] and in 1971 [31] reported positive skin reactions in 12–23% in the different population groups tested. The staff and students of an agricultural farm area including dairy and poultry farms had significantly higher rates of skin reactivity to histoplasmin than nurses, students, workers in a jute mill, and workers in a paper mill; 23.2% of the reactors had pulmonary calcifications, consistent with resolved acute histoplasmosis [30]. Sixteen autochthonous cases of histoplasmosis, all males aged from 20–65 years with varying clinical manifestations some of them mimicking tuberculosis, have been reported from Bangladesh during the period

1982–2013 [4–6]. This provides enough evidence of endemicity of histoplasmosis in the country. Most of Bangladesh lies in the Indo-Gangetic plain as does the entire state of West Bengal in India. In India, the majority of the cases of histoplasmosis have been reported from West Bengal and other north-eastern parts of the country [32]. *Histoplasma capsulatum* has been recovered from soil of the Gangetic plains [32]. Considering the similarity of geo-climatic conditions, it is likely that many more cases of histoplasmosis occur in Bangladesh than are currently documented. Endemicity of histoplasmosis in Bangladesh should be further evaluated by histoplasmin skin testing of population groups in different locales.

Two cases of mucormycosis have been described in Bangladesh. One of these was a fatal case of rhino-cerebral involvement by *Mucor* sp. in an immunocompetent 42-year-old mechanic [8]. The other case of rhino-orbital and cerebral involvement in a 25-year-old diabetic with osteomyelitis [9] was diagnosed histopathologically. In addition to these, in a study of 13 cases of acute fungal rhinosinusitis [33], eight were due to unspecified mucoraceous fungi and five to *Aspergillus* sp diagnosed histopathologically. The underlying disease was diabetes in most of them.

### Fungal keratitis

Mycotic keratitis appears to be very common in Bangladesh, as evidenced by the report of numerous cases of mycotic corneal ulcers reported from several parts of the country constituting 25–84% of suppurative keratitis. The total annual incidence of mycotic keratitis in three of the studies [3, 34, 35] was 140 cases (32.9%) out of 425 corneal ulcers examined. The predominant fungal agents in these studies were *Aspergillus* and *Fusarium*; in most of the studies *Aspergillus* species were identified as *A. fumigatus*, *A. flavus*, *A. ochraceous*, and *A. niger*, and *Fusarium* as *F. solani* [3, 34, 35]. *Lasiodiplodia theobromae* was the causal agent in four cases in one of these studies [35].

The present study is the first attempt to estimate the burden of different serious fungal infections in Bangladesh. Superficial mycoses including those attributable to dermatophytes are very common in urban and rural areas of Bangladesh constituting a major health problem [2, 3]. Community-based surveys with laboratory based support should be carried out in representative population groups to estimate the real burden of superficial mycoses. It is also apparent that blastomycosis, and opportunistic fungal infections like mucormycosis, aspergillosis, and cryptococcosis are present in this country, though the cases known so far are very few [5, 8–11]. One would expect cases of mycetoma, chromoblastomycosis and fusariosis but there are no reports from Bangladesh. A greater awareness and easy access to laboratory diagnostic facilities at several centers is likely to detect many more cases of opportunistic fungal infections.

Life-threatening invasive infections and deaths rates are likely to increase, especially invasive aspergillosis as more transplantation is undertaken and more aggressive cancer chemotherapy is given. We have not been able to estimate the number of patients with cryptococcal meningitis who do not have HIV infection, as there is no risk denominator. Our estimates emphasize the public health importance of mycotic keratitis. Community-based investigation of mycotic etiology in corneal ulcers in representative areas of Bangladesh would give a correct estimate of the burden of mycotic keratitis and its impact on blindness in the country.

### Conclusion

It is hoped that the present analysis will create greater awareness of the burden of fungal infections on public health and promote effective diagnosis and therapy. It is suggested that international collaboration can help to enhance diagnosis and elucidate the epidemiology of several deep mycoses. More work on mycotic keratitis is needed; cases of mycetoma and chromoblastomycosis are likely to occur. The number of known cases of histoplasmosis represents only the tip of probably much higher occurrence. Establishment of more adequately equipped medical mycology laboratories in Bangladesh would greatly enhance the correct and timely diagnosis of serious mycotic fungal infections and their rational therapy.

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