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Supplement article

Burden of serious fungal infections in Nepal

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Summary

There are few reports of serious fungal infections in Nepal though the pathogenic and allergenic fungi including *Aspergillus* species are common in the atmosphere. Herein, we estimate the burden of serious fungal infections in Nepal. All published papers reporting fungal infection rates from Nepal were identified. When few data existed, we used specific populations at risk and fungal infection frequencies in those populations to estimate national incidence or prevalence. Of the 27.3 M population, about 1.87% was estimated to suffer from serious fungal infections annually. We estimated the incidence of fungal keratitis at 73 per 100 000 annually. Chronic obstructive pulmonary disease is common with 215 765 cases, contributing to 1119 cases of invasive aspergillosis annually. Of 381 822 adult asthma cases, we estimated 9546 patients (range 2673–13 364) develop allergic bronchopulmonary aspergillosis and 12 600 have severe asthma with fungal sensitisation. Based on 26 219 cases of pulmonary tuberculosis, the annual incidence of new chronic pulmonary aspergillosis (CPA) cases was estimated at 1678 with a 5 year period prevalence of 5289, 80% of CPA cases. Of 22 994 HIV patients with CD4 counts <350 not on antiretrovirals, *Pneumocystis* pneumonia was estimated at 990 cases annually. Cases of oral and oesophageal candidiasis in HIV/AIDS patients were estimated at 10 347 and 2950, respectively. There is a significant burden of serious fungal infections in Nepal. Epidemiological studies are necessary to validate these estimates.

Key words: Fungal infections, *Aspergillus*, IA, ABPA, SAFS, CPA.

Introduction

The epidemiology of fungal infections is poorly documented in many countries and regions. Few diagnostic mycology laboratories provide a comprehensive service, and even fewer conduct any form of surveillance or epidemiology studies. Yet these infections are increasingly being associated with many different clinical conditions especially in immunocompromised patients[1–4] and those with fungal allergy.[5]

Global estimates of cutaneous fungal infections, invasive fungal infections, chronic pulmonary aspergillosis (CPA) after pulmonary tuberculosis (PTB), and sarcoidosis and allergic bronchopulmonary aspergillosis (ABPA) complicating asthma have recently been published.[6–10] Recently, there have been estimates of burden of ABPA (and severe asthma with fungal sensitisation, SAFS) complicating asthma and CPA as a sequel to PTB in India.[11]

In Nepal, about 45 percent of the total population is infected with tuberculosis (TB), of which 60 percent are adult. Every year, 45 000 people develop active TB, and 20 580 have infectious pulmonary disease.[12] As of 2012, national estimates indicate that approximately 48 600 adults and children are infected with

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the HIV virus in Nepal. The estimated prevalence of HIV in the adult population is 0.28 percent.[12,13] In this context, estimates of the burden of serious fungal infections have a role in public health for diagnosis and treatment of fungal diseases in Nepal. Fungal keratitis has also been a particular problem in Nepal.[14–18]

In this article, we estimate the burden of serious fungal infections including ABPA and SAFS complicating asthma, and CPA complicating PTB in Nepal. Such an estimate of fungal burden has not previously been attempted in this country.

Materials and methods

All published papers reporting fungal infection rates from Nepal were identified using Google search and Pubmed website. The publications on the prevalence of fungal infections, which were reported from the laboratory diagnosed cases in the different hospitals of the country, were selected for the estimation. We used the population estimates, annual morbidity data of infections nationally and the asthma rate from the annual report of the Department of Health Services (DoHS), 2012/2013, for estimating populations at risk.[12] Where there was no data, we used specific risk populations and fungal infection frequencies in each population to estimate national incidence or prevalence, depending on the condition.

The number of women probably suffering from recurrent vulvovaginal candidiasis (rVVC) was estimated by assuming that rVVC affects 6% of adult women aged between 14 and 55 years and 'recurrent' defined as at least four episodes per year.[19] The number of reported cases of HIV in Nepal was taken from epidemiological surveillance of National Centre for AIDS and STD control.[20] The proportion of AIDS patients presenting with *Pneumocystis* pneumonia (PCP) was estimated assuming that 16.7% of new AIDS cases in children present with this infection[21] and 22.4% of adults.[22] This was calculated by assuming that 50% of those with CD4 counts <350 are susceptible and that 50% of these patients present with AIDS in any given year. The rate of cryptococcal meningitis was estimated at 0.6 per 100 000 based on the published data.[23–25] In HIV infection, oral candidiasis was assumed to occur at least once in 90% of those without antiretrovirals (ARVs) and CD4 counts <200, and oesophageal candidiasis in 20% of patients without ARVs and CD4 counts <200 and 5% of patients on ARVs.[26–28]

The number of PTB cases was obtained from the annual report of DoHS[12]. Using the approach taken in Denning *et al.*[7], the incidence and 5-year period prevalence of CPA following PTB in Nepal was estimated, assuming a 22% cavitation rate following therapy in PTB.[7] Asthma rates in adults (children were not included for risk estimation) were obtained from national morbidity data.[12] The prevalence of ABPA in adults with asthma was estimated at 2.5% (0.7–3.5%) using a scoping review methodology.[9] The prevalence of SAFS was estimated as the worst 10% of the total asthma population, of whom at least 33% have fungal sensitisation.[29]

The number of people with chronic obstructive pulmonary disease (COPD) was estimated nationally.[12] The rate of invasive aspergillosis (IA) attributable to COPD patients assumes that 3.9% of COPD admissions developed IA.[30] Additionally, IA was estimated in haematological malignancy by assuming that 10% of acute myeloid leukaemia patients (rate 3 per 100 000 population) develop IA and that an equal number of cases are found in all other haematological patients, as in France and Austria.[31,32] The annual incidence of infection due to *Aspergillus* species was calculated after reviewing the published paper reporting a population-based surveillance study in Nepal.[2]

We estimated the incidence of microbial keratitis from the number of reported cases of keratitis per year nationally[12] and fungal keratitis was estimated by using data obtained from different studies which documented the incidence of fungal keratitis in Nepal.[14–17] Allergic fungal rhinosinusitis was estimated according to reported cases.[3] The estimate for cases of fungal otomycosis and onychomycosis was done according to the data extracted from published papers.[2,33,34] For mucormycosis, we used a rate of 0.2 per 100 000 as previously documented.[35]

Results

Nepal is a mountainous country on the south side of the Himalaya mountain range, with 3915 Village Development Committees (VDCs) that are rural areas and 58 Municipalities that are urban areas. Geographically, the country is divided into three East-West ecological zones: the Northern Range – Mountain, the Mid Range – Hill and the Southern Range – Terai (flat land). The altitude ranges from 70 to 8848 m and the climate varies from tropical to arctic depending upon altitude. The gross domestic product in 2013 was $694 per person. The population of Nepal was estimated at 27.3 M of which 2.8 M are children (under 5 years) and 7.38 M are women aged between 15 and 49 years in 2014. 22.6 M Nepali live in rural

Table 1 Estimated burden of serious fungal diseases in Nepal.

Infection	No of infections per underlying disorders per year				Total burden	Rate/100K
	None	HIV/AIDS	Respiratory	Immunocompromised		
Oral candidiasis	–	10 347	–	–	10 347	37.9
Oesophageal candidiasis	–	2950	–	–	2950	10.8
Cryptococcal meningitis	–	109	–	55	164	0.6
Pneumocystis pneumonia	–	990	–	–	990	3.6
Recurrent vulvovaginal candidiasis (4× year^{-1})	443 237	–	–	–	443 237	2908[1]
Aspergillus infection[2]	847	–	–	–	847	3.1
Invasive aspergillosis	–	–	936	183	1119	4
ABPA	–	–	9546	–	9546	35
SAFS	–	–	12 600	–	12 600	46.1
CPA	–	–	6611	–	6611	24.2
Fungal keratitis	19 938	–	–	–	19 938	73
Allergic fungal rhinosinusitis	628	–	–	–	628	2.3
Fungal otomycosis	1010	–	–	–	1010	3.7
Fungal onychomycosis	819	–	–	–	819	3
Mucormycosis	–	–	–	55	55	0.2
Total burden estimated	466 479	14 396	29 693	293	510 861	

ABPA, Allergic bronchopulmonary aspergillosis; SAFS, Severe asthma with fungal sensitisation; CPA, Chronic pulmonary aspergillosis.

[1]rate for all females.

[2]Infection of nails, ears, eyes, respiratory tract and skin.

areas of the country. As of July 2013 a total of 22 994 cases of HIV had been reported to the National Centre for AIDS and STD Control (NCASC). There are an estimated 48 600 HIV infected patients in Nepal and those requiring ARVs were estimated (using CD4 count <350) at 25 589 (adults: 23 402, children: 2187) in 2012.[12,36] Table 1 shows the total burden of fungal infections, the number of infections classified according to the main risk factors, as well as the rate for 100 000 inhabitants annually.

We estimate that 443 237 Nepalese women between 15 and 49 years of age probably suffer from rVVC, i.e. at least four episodes annually. This translates into an annual incidence of 2908 cases per 100 000 females.

Of 22 994 HIV patients with CD4 counts <350 not on ARVs in July 2013, approximately 2100 were children, and PCP was estimated at 990 (3.6 per 100 000), of which 115 cases are in children. We estimated 164 cases of cryptococcal meningitis annually in HIV/AIDS and immunocompromised patients. Cases of oral and oesophageal candidiasis in HIV/AIDS patients were estimated at 10 347 and 2950 respectively.

Based on 26 219 cases of PTB, the annual incidence of new CPA cases was estimated at 1678 with a 5 year period prevalence of 5289 cases (assuming 15% annual mortality or surgical resection). A total of 6611 total CPA cases were estimated, assuming that PTB patients account for 80% of CPA cases in Nepal. Of 381 822 adult asthma cases, we estimated 9546 patients (range 2673–13 364) develop ABPA and 12 600 have SAFS. COPD is common with 215 765 cases, contributing to an estimated total of 1119 cases of IA of which 183 cases are in immunocompromised patients and 936 due to respiratory disorders, mostly COPD.

Fungal otomycosis and onychomycosis were estimated at 1010 and 819, respectively, almost certainly underestimates. Fungal infections including infection of the nails, ears, eyes, respiratory tract and skin due to *Aspergillus* species was estimated at 3.1 per 100 000 usually *Aspergillus flavus* followed by *A. niger* and *A. fumigatus* with a total of 847 cases annually. We estimated the incidence of microbial keratitis at 188 per 100 000 annually of which 19 938 cases of fungal keratitis were estimated annually (73 per 100 000). Allergic fungal rhinosinusitis was estimated at 2.3 per 100 000 according to 628 documented cases probably a significant underestimate. The annual incidence of mucormycosis was estimated at 55 cases.

Discussion

The epidemiology and burden of serious fungal infections in Nepal is not known. Our estimate indicated that about 1.87% of the Nepalese population suffers from a serious fungal infection annually and the most

serious fungal infections occur in HIV/AIDS and immunocompromised patients. Due to the geographical challenges in remote and hilly regions of Nepal, it is difficult to provide a good quality healthcare service in various parts of the country for the treatment of complex infectious diseases. Apart from the public awareness in infectious diseases and its treatment, hospital hygiene and sanitation could play an important role in prevention and control of serious fungal infections in Nepal.

It is estimated that worldwide deaths attributed to fungal infections (>1 500 000)[37] are as high as those of tuberculosis (1 500 000)[38] and higher than malaria which has fallen lately (584 000 with an uncertainty range of 367 000 to 755 000),[39] two priority diseases on the global health agenda. Fungal infections with a high mortality, such as IA, candidaemia, PCP and mucormycosis, are not numerous, as exemplified in Spain,[1] but they affect those with severe underlying diseases and are therefore linked to poor outcomes.[8] The prevalence of HIV is rising rapidly in Nepal and effective control measures for HIV/AIDS as well as for TB is more important now than ever before.[12] In this context, serious fungal infections will have a significant impact on public health with a high mortality in Nepal.

Fungal keratitis is the most prevalent fungal infection in Nepal with the annual incidence of 73 per 100 000, slightly under 50% of all microbial keratitis (188 per 100 000) annually. During 1992/1993, the annual incidence of microbial keratitis was documented as 799 per 100 000.[40] Microbial and especially fungal keratitis are reported to follow minor ocular trauma or corneal injury sustained during agricultural work by farmers or in domestic activities in women in most cases.[14,15,18,40] The frequency of fungal keratitis was greater in men than in women.[14–17] Trauma with vegetative matter such as rice stalks, thorns, tree branches and leaves and paddy grain and animal products like the tails of cows and cow dung leads to a higher risk of fungal keratitis.[14,15,17] The etiological pattern of microbial keratitis varies significantly from country to country or even region to region within the same country depending upon the different occupations, climatic conditions etc.[15,16,18] The poor outcome of fungal keratitis is due to extensive corneal damage, delay or inability to access medical services, unavailability of antimicrobials and cost of treatment linked to the poor socioeconomic status of most patients.[15,17,40]

Chronic and allergic rhinosinusitis is very common in Nepal usually caused by airborne fungi.[3] While there were 628 recorded cases, this is likely to be a small fraction of the total, and so we believe our estimate of 2.3 per 100 000 to be a significant underestimate. Chronic and allergic fungal rhinosinusitis are also common in India.[41–44] The only population estimate of allergic fungal rhinosinusitis comes from Israel, and that was estimated to affect 39 922 persons (range, 15 969–183 643), 500 per 100 000.[45]

The study of opportunistic infection among HIV seropositive cases in Nepal showed that about 4% of the HIV seropositive patients had polymicrobial infections, which included oral candidiasis plus PTB in 2%.[24] In our study, the cases of oral candidiasis and oesophageal candidiasis were expected annually at 10 347 and 2950, respectively, in HIV patients, based on high frequency in those with low CD4 cell counts, over the course a year. There are no official data or published studies on the number of oral or oesophageal candidiasis related to cancer transplantation or other patient groups in Nepal. As we have not estimated oral and oesophageal candidiasis in any other patient group, our estimates will certainly be significant underestimates of the total burden of these infections.

Good estimates of PCP, IA complicating COPD, rVVC and mucormycosis have also been determined in Spain and Nigeria,[1,46] although in some cases the data are old and some discrepancies in the number of cases between studies were found.[1] Here, the annual incidence of PCP was estimated at 990 cases annually with reference to number of HIV-positive patients. Because of the lack of data for other non-HIV populations at risk, we have used rate according to HIV infection. Estimated cases of cryptococcal meningitis in HIV/AIDS and immunocompromised patients were 0.6 per 100 000. The incidence of rVVC, at least four episodes annually, was estimated at 443 237 assuming that rVVC affects 6% of adult women aged between 15 and 49 years. Vulvovaginal candidiasis prevalence rates ranges between 21 and 35% in Nigeria.[46]

There is a significant burden of chronic pulmonary disorders due to *Aspergillus* (ABPA, SAFS and CPA) in India. The prevalence of ABPA complicating asthma is believed to 2.5% globally, however, the occurrence is reported to be higher (5–20%) in India.[11] We also estimated a high prevalence of ABPA, SAFS and CPA in Nepal that at 9546, 12 600 and 6611 patients, respectively. Children were not taken into account for these estimates because both ABPA and SAFS appear to be rare in childhood, although Singh *et al.*[47] described an association between ABPA and poorly controlled asthma in children. As no estimate of

prevalence of either ABPA or SAFS in children exists, applying the adult rates to the whole population may greatly overestimate the total rates. There is also likely to be some overlap between SAFS and ABPA cases because 40% of patients with *Aspergillus* sensitisation develop ABPA, and many patients with ABPA have severe asthma.[11] Globally there are >350 000 asthma deaths, most in adults, and many of these will be in those with SAFS.[6] All CPA assumptions used in this analysis are based on pulmonary cavitation rates after TB (assessed on chest radiography) being about 22%.[7] Among the causes of CPA are COPD, sarcoidosis, ABPA, prior pneumothorax, rheumatoid arthritis, PTB and non-tuberculous mycobacterial infection. PTB is an infrequent cause of CPA in Europe.[48] Additional studies are required in Nepal, especially for high burden diseases such as ABPA, SAFS and CPA to precisely define the national burden of this debilitating disease.[6,11] Early recognition and treatment with antifungal azoles has the potential to reduce the morbidity and mortality associated with these conditions.[11]

The rate of IA was estimated according to the number of patients with COPD and haematological malignancy. Other conditions associated with IA such as severe hepatic or autoimmune disease, have been ignored for these estimates, although a recent study from Hangzhou documented a 5% IA rate in acute-on-chronic hepatic failure.[49] The prevalence of pathogenic and allergenic species of *Aspergillus* in Nepal has indicated the increased risk of IA for residents.[50] We estimated 1119 cases of IA of which 183 cases are in immunocompromised patients and 936 due to respiratory disorders. Additionally, fungal infections including the infection of nails, ears, eyes, respiratory tract and skin due to *Aspergillus* species was estimated at 3.1 per 100 000 annually (*Aspergillus flavus* followed by *A. niger* and *A. fumigatus*).

In the present study, mucormycosis were estimated at 0.2 per 100 000 per year. A prevalence of mucormycosis cases at 0.14 per 100 000 was reported in India.[51] There is no data published on histoplasmosis cases.

The limitations of our estimates are the few number of studies performed in the country for some infections and frequencies of some hospital based data of fungal infections in regional population that may not be representative of the overall population of the country. Also, our estimation of serious fungal infections is based mostly on the frequency of fungal infections in patients at risk.

In conclusion, a significant burden of serious fungal infections exists in Nepal that has a high morbidity and mortality rate. Early diagnosis of fungal infections and treatment with antifungal agents will aid in management of these diseases. This study provides preliminary data to determine the public health impact of fungal diseases in Nepal and further epidemiological studies are required to validate these estimates.

Conflict of interest

USK declares no conflict of interest. DWD holds Founder shares in F2G Ltd a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, NorthWest Lung Centre Charity, Medical Research Council, Astellas and the Fungal Infection Trust. He acts as a consultant to T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology and Pulmicort. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups. He is also President of the Global Action Fund for Fungal Infections.

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