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Abstract

The burden of serious fungal infection in Thailand is increasing but data regarding its incidence and prevalence are lacking. In this study we aimed to estimate the burden of serious fungal diseases in Thailand based on the size of the populations at risk and available epidemiological databases. Data derived from The Bureau of Epidemiology, Department of Disease Control, Thai Ministry of Public Health, World Health Organisation, international and local reports, and some unreported data were used. When no data existed, risk populations were used to estimate frequencies of fungal infections, using previously described methodology by LIFE. Recurrent vulvovaginal candidiasis (>4 episodes per year) is estimated to occur in 3310 per 100,000 population. Using a previously described rate that 14/10,000 admissions with fungaemia and 94% being *Candida*, we estimated 8650 patients with candidaemia. The prevalence of chronic pulmonary aspergillosis is relatively high with a total of 19,044, approximately half subsequent to pulmonary tuberculosis. Invasive aspergillosis is estimated to affect 941 patients following leukaemia therapy, transplantations, and chronic obstructive pulmonary disease, approximately 1.4/100,000. In addition, allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitisation were estimated at approximately 58.4/100,000 and 77/100,000, respectively. Given approximately 8134 new cases of AIDS annually, cryptococcal meningitis, *Pneumocystis* pneumonia, and *Talaromyces marneffei* infection are estimated at 1.9/100,000, 2.6/100,000, and 0.3/100,000, respectively. The present study indicates that about 1.93% (1,254,562) of the population is affected by serious fungal infections. Owing to the lack of data, reports, and statistics, the number of patients with mycoses in Thailand can only be estimated.

Keywords: Fungal diseases; Fungal infection; Burden; Epidemiology; Thailand

Introduction

IFDs in Thailand have become more prevalent and are a major cause of hospital death, especially in individuals with immunocompromised conditions [1, 2]. In the past, most IFDs were associated with human immunodeficiency virus (HIV) infection, including cryptococcosis and pneumocystosis [3]. Although the number of HIV-infected individuals in Thailand is still high, almost all HIV-infected patients nowadays have access to antiretroviral therapy (ART). Therefore, the rising incidence of IFDs seems to be associated with the increasing number of patients who undergo organ transplantation and stem cell transplantation, as well as those who receive immunosuppressive therapy or are critically ill. As a result, the number of patients with invasive aspergillosis and candidiasis has significantly increased [1, 4, 5]. However, specific data regarding the incidence and prevalence of IFDs are lacking, primarily due to unavailability of diagnostic tools and the lack of any surveillance systems. The aim of this study is to estimate the prevalence of serious fungal diseases in Thailand, based on the size of the populations at risk and the available epidemiological databases, and thus indicate the national burden of these conditions.

Methods

The methodology of the LIFE program (www.LIFE-worldwide.org) was used to estimate the burden of fungal diseases in Thailand with the model described previously [6]. We searched the literature related to the epidemiology of invasive fungal diseases in Thailand using PubMed and local journal databases. Where the information was not available, we calculated populations at risk for each fungal infection and used these data to estimate the burden of each fungal infection. Specific risk factors for acquirement of invasive fungal infections included HIV infection, use of

immunosuppressive drugs, haematopoietic stem cell transplantation, solid organ transplantation, chronic pulmonary diseases, and intensive care unit (ICU) admission.

Population data and data related to HIV infection were derived from the Official Statistics Registration System (http://stat.dopa.go.th; access 2014) and The Bureau of Epidemiology and Department of Disease Control of the Thai Ministry of Public Health (www.ddc.moph.go.th; access 2013), UNAIDS (www.unaids.org; access 2012), and the World Health Organisation (www.who.int). Data related to transplant recipients were derived from the Thai Transplantation Society (www.thai-transplant.org). Data gathered related to the period 2012 to 2014, depending on availability. International and local reports were used to estimate each invasive fungal disease.

Results and Discussion

Thailand is classified as an upper middle income country by the World Bank (www.worldbank.org). The gross domestic product per capita in 2013 was $5,779. During the study period, the population of Thailand was approximately 65,124,716, 18% of whom were children under 15 years of age, 41% were adult women, and 14% were women over 50 years of age. According to the UNAIDS report, the total number of HIV-infected cases was 306,336, with 8134 new cases of acquired immune deficiency syndrome (AIDS) annually. Only 76% of HIV-infected patients received ART. The total number of annual cases of tuberculosis was approximately 47,201 in both HIV-negative and HIV-positive individuals. Approximately 731,450 cases were diagnosed with chronic obstructive pulmonary disease (COPD), 51,202 of whom were admitted to hospital annually. The asthma rate in adults was 2.91 per 100,000, in about 1.5 million patients, whereas cystic fibrosis is extremely rare [7]. We estimated 911 patients with acute myeloid leukaemia (AML) based on the incidence rate of 1.5/100,000 in males and 1.3/100,000 in females [8]. According to the limited data available in 2013, about 150 patients received allogeneic haematopoietic stem cell transplantation (HSCT) [9], 465 renal transplantation, 7 lung transplantation, and 12 liver transplantation. However, the number of transplantation cases continues to increase.

The burden of fungal infections in Thailand is shown in Table 1, stratified by specific risk groups. Recurrent vulvovaginal candidiasis (RVVC) was defined as having at least four specific episodes of vulvovaginal candidiasis occur in one year or at least three episodes unrelated to antibiotic therapy within one year [10, 11]. Given that data related to RVVC are not available in Thailand, we estimated according to previous studies that RVVC occurs in approximately 6% of adult women 15–50 years old [12]. Therefore, the prevalence of RVVC was about 1655/100,000,

giving a total burden of 1,077,721 each year. However this number may be underestimated, because many women with RVVC do not seek medical advice, preferring to take over-the-counter drugs.

Candidaemia can occur in neutropenic and non-neutropenic hosts. Approximately 10% of the total population, about 6.5 million people, are admitted to hospital each year. For non-neutropenic patients, using a previously reported rate in a Thai publication that 14 out of 10,000 admissions had fungaemia and 94% were *Candida* spp., we estimated 8561 non-neutropenic patients with candidaemia annually [13]. Our local data revealed that about 4.5% of neutropenic patients had candidaemia, producing an estimate of 89 cases per year. These data made up a total burden of 8650 candidaemia cases per year. We estimated that approximately 20% of HIV-infected individuals who received ART and 5% of HIV-infected individuals who did not receive ART would have oesophageal candidiasis, producing a burden of oesophageal candidiasis of 45,396 cases [14, 15]. We were unable to estimate oropharyngeal and oesophageal candidiasis in patients with other immunocompromised conditions because of the lack of data.

Data from The Department of Disease Control, Ministry of Public Health of Thailand reported that the number of new AIDS cases in 2013 amounted to 8134. We estimated that 21% of these presented with *Pneumocystis* pneumonia (PCP) [16]. Therefore, the total burden of PCP was 1708 cases (2.6 per 100,000) annually. However, for PCP in steroid users or transplant recipients we were not able to estimate its incidence due to unavailability of local data.

Thailand is an endemic for *Talaromyces marneffei* but the disease is prevalent in the northern part of Thailand, and *Histoplasma capsulatum* is found sporadically throughout the country. Histoplasmosis and *T. marneffei* infection were estimated to occur in about 0.39% and 2.26% of new AIDS cases, respectively. Therefore, the total burden of histoplasmosis and *T.*

marneffei infection was 184 and 32 cases per year, respectively. However, these dimorphic fungal infections also occur in non-HIV-infected patients but this requires active surveillance to capture.

Among 306,336 AIDS cases, 232,816 were on ART (76% coverage of those with a CD_4 T-lymphocyte count <350 cells/mm^3); therefore, 73,520 individuals were not on treatment. If 25% of these patients have a CD_4 T-lymphocyte count <100 cells/mm^3, 18,380 patients are at risk for fungal infection. From seroprevalence studies in Thailand [17, 18], we estimated that cryptococcosis occurred in about 13% of HIV-infected individuals who had a CD_4 T-lymphocyte count <100 cells/mm^3. Therefore, the incidence of cryptococcosis cases was 2389 annually, assuming that all those on ART are not at risk and there is no risk for those with a CD_4 T-lymphocyte count between 100 and 200 cells/mm^3. The number in HIV-infected patients has decreased from the last decade because of the improved access to ART.

A previous study reported approximately 15 cryptococcal meningitis cases in non-HIV patients per 100 HIV-infected patients with cryptococcal meningitis [19]. Therefore, the burden of cryptococcal meningitis was calculated to be 4.2/100,000, including an estimated 108 cases in non-immunocompromised people (Table 1).

Owing to a relatively high incidence of pulmonary tuberculosis (TB) in Thailand (about 47,201 cases annually), the estimated prevalence of chronic pulmonary aspergillosis (CPA) is relatively high. We estimated that approximately 22% of pulmonary TB cases have cavitary lesions and 22% of cavitary TB cases have CPA, whereas 2% of non-cavitary TB patients have CPA [20]. Therefore, using the LIFE program, we estimated over 3000 new CPA cases annually and a 5 year prevalence of 9,522 cases after pulmonary tuberculosis. Given a high rate of COPD, numerous non-tuberculous mycobacterial infections and moderately large number of asthmatic

patients, we estimated that tuberculosis comprises 50% of the total of CPA cases in Thailand. Therefore we estimate the total to be about 19,044 CPA cases a year, approximately half following TB.

Invasive aspergillosis (IA) is estimated to affect 941 patients following leukaemia therapy, transplantation, and COPD, for a rate of ~1.4/100,000. We estimated these figures from our local data estimation, assuming that IA occurred in approximately 13.5% of leukaemia patients, 3% of kidney transplant patients and 4% of lung and liver transplant patients [21, 22]. Furthermore, IA was estimated to occur in 1.3% of COPD, which was less than reported from Western countries [21].

Allergic bronchopulmonary aspergillosis (ABPA) is an uncommon, but significant complication of asthma, almost always occurring in adulthood. Various studies put the prevalence at about 2.5% of patients, including one from China [23]. We therefore estimated that about 38,000 are affected, or 58.4/100,000 [24]. Severe asthma with fungal sensitisation (SAFS) also responds to antifungal therapy and was estimated to occur in 33% of severe asthma, which was about 10% of all asthma cases. Therefore, the burden of SAFS is thought to be about 50,000 adults (77/100,000). There is probably some overlap or duplication between ABPA and SAFS as sensitisation to *A. fumigatus* is universal in ABPA, common in SAFS, and many ABPA patients have severe asthma, depending on the definition used.

In addition, owing to the lack of epidemiological data we could only assume a total of about 130 cases of mucormycosis annually in Thailand. This rate is based on a simple and conservative 2 per million estimate which is likely to be an underestimate. In one hospital, for example, 11 patients were diagnosed and treated over five years at in Khon Kaen, a city with a population of about 370,000 [25]. Numerous other reports attest to mucormycosis occurring in

multiple locations in Thailand. This low estimate is in contrast to higher rates in India, where diabetes is now very common, with a rate of 14/100,000.

For fungal keratitis, we calculated from the available data in Thailand that infectious keratitis occurs in about 1 per 1000 of population and 15% of infectious keratitis were caused by fungi [26]. The burden of fungal keratitis was therefore 15/100,000. This contrasts with rates in other SE Asian countries substantially higher than this, notably Myanmar (710/100,000) [27] and Nepal (73/100,000) [28].

For tinea capitis, local data revealed about 16 cases per year at the National Children's Hospital (with a total of 350,000 outpatient cases per year), so we estimated a burden of about 5 in 100,000 children. In a total paediatric population of 1,172,245, the total number of tinea capitis cases was 59 per year. In fact, this number is probably an underestimate because the data we used to calculate this number are limited.

In conclusion, the present study indicates that approximately 1.93% (1,254,562) of the population in Thailand is affected by serious fungal infections. Owing to the lack of data, reports, and statistics, the number of patients with mycoses in Thailand can only be estimated.

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254 **Table 1** Burden of fungal infections in Thailand

Infection	No. of infections per underlying disorder per year					Total burden	Rate/100,000
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU/Non-neutropenics		
Oesophageal candidiasis	–	45,396	–	–	–	45,396	69.7
Candidaemia	–	–	–	89	8,561	8,650	13.3
Recurrent vaginal candidiasis (≥4×/year)	1,077,721	–	–	–	–	1,077,721	1654.9
ABPA	–	–	38,009	–	–	38,009	58.4
SAFS	–	–	50,172			50,172	77.0
Chronic pulmonary aspergillosis	–	–	19,044	–	–	19,044	29.2
Invasive aspergillosis	–	–	–	276	666	941	1.4
Mucormycosis	–	–		130		130	0.2
Cryptococcal meningitis	108	2,389	–	251	–	2,747	4.2
Pneumocystis pneumonia	–	1,708	–	–	–	1,708	2.6
Histoplasmosis	–	32	–	–	–	32	0
Talaromyces marneffei infection	–	184	–	–	–	184	0.3
Fungal keratitis	9,765	–	–	–	–	9,769	15.0
Tinea capitis	59	–	–	–	–	59	0.1
Total burden estimated						**1,254,562**	

ABPA: allergic bronchopulmonary aspergillosis; AIDS: acquired immune deficiency syndrome; HIV: human immunodeficiency virus; ICU: intensive care unit; SAFS: severe asthma with fungal sensitisation