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Estimated burden of fungal infections in Sweden

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Summary

The aim of this study was to estimate the annual burden of fungal infections in Sweden using data mainly from 2016. Data on specific populations were obtained from Swedish national data registries. Annual incidence and prevalence of fungal disease was calculated based on epidemiological studies. Data on infections due to *Cryptococcus* sp., Mucorales, *Histoplasma capsulatum*, *Coccidioides immitis* and *Pneumocystis jirovecii* were retrieved from Karolinska University Laboratory and covers only 25% of Swedish population. In 2016, the population of Sweden was 9 995 153 (49.8% female). The overall burden of fungal infections was 1 713 385 (17 142/100 000). Superficial fungal infections affect 1 429 307 people (1429/100 000) based on Global Burden of Disease 14.3% prevalence. Total serious fungal infection burden was 284 174 (2843/100 000) in 2016. Recurrent *Candida* vulvovaginitis is common; assuming a 6% prevalence in women. Prevalence of allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitisation were estimated to be 20 095 and 26 387, respectively. Similarly, chronic pulmonary aspergillosis was estimated to affect 490 patients after tuberculosis, sarcoidosis and other conditions. Candidemia incidence was estimated to be 500 in 2016 (4.7/100 000) and invasive aspergillosis 295 (3.0/100 000). In Stockholm area, Mucorales were reported in three patients in 2015, while *Cryptococcus* spp. were reported in two patients. In 2016, there were 297 patients PCR positive for *P jirovecii*. The present study shows that the overall burden of fungal infections in Sweden is high and affects 17% of the population. The morbidity, mortality and the healthcare-related costs due to fungal infections warrant further studies.

KEYWORDS
epidemiology, fungal infections

1 | INTRODUCTION

The number of serious fungal infections is increasing worldwide due to the rising size of the population at risk. Fungi primarily infect immunocompromised patients, such as those undergoing chemotherapy or infected with human immunodeficiency virus (HIV), and those acquired in hospitals. However, fungal infections in healthy individuals are also increasing.[1] Over 300 million people suffer from serious fungal-related disease, and the annual mortality due to fungal infections is estimated to be over 1.6 million. Although, *Candida*, *Aspergillus*, *Pneumocystis* and *Cryptococcus* spp. are the most common cause of the serious fungal infections in Europe, there has been an increase in the incidence of infections caused by other filamentous fungi such as mucormycosis.[2]

Superficial infections of the nails and skin are the most common fungal diseases in humans and affect ~25% of the general population worldwide.[3] These infections are caused primarily by dermatophytes. The clinical appearance and the causative fungi and species

of superficial fungal infections vary with geographic region, socioeconomic conditions and habits.[3] Mucosal infections of the oral and genital tracts are also common, especially vulvovaginal candidiasis. In fact, 50% to 75% of women in their childbearing years suffer from at least one episode of vulvovaginitis, and 5% to 8% of these have recurrent Candida vulvovaginitis, that is at least four episodes annually.[4] In countries with limited healthcare services and high frequency of HIV/AIDS, oral thrush and oesophageal fungal infections are very common.[5] Oral infections are also common in babies and denture wearers, in individuals with diabetes and in people who use inhaled steroids for asthma.[5]

Global warming is inducing rapid movement of fungal pathogens and may increase the prevalence of fungal disease in human, as fungi adapt to survive in warmer temperatures.[6] Knowledge of the local epidemiology of invasive fungal infections is essential for effective infection control programs and antifungal stewardship.[7] The epidemiology of fungal infections in Sweden is largely unknown, except for candidemia.[8] The aim of this study was to estimate the annual burden of fungal infections in Sweden using data mainly from 2016.

2 | MATERIALS AND METHODS

Systematic literature reviews were done. We searched PubMed database for published epidemiological studies reporting fungal infection in Sweden. We used search terms 'fungal', 'infections', 'diseases', 'invasive', 'superficial', and 'Sweden.' Where no data existed, we used portion of specific population at risk for fungal infections to estimate national incidence. From Statistics, Sweden (http://www.scb.se) population statistics 2016 were derived. In Sweden, there were 6983 patients with HIV in 2016. National data show that 90% of HIV-diagnosed patients are on antiretroviral (ART) therapy.

The total annual incidence of pulmonary tuberculosis (TB) was obtained from the WHO global tuberculosis reports (https://www.who.int/tb/country/data/profiles). The total annual incidence of all tuberculosis and pulmonary tuberculosis was 7.3 and 4.9 in 100 000 individuals in 2016. Data on chronic obstructive pulmonary disease (COPD) were derived from previously published studies from Sweden.[9,10] The number of patients with COPD in general population of Sweden in 2016 was between 400 000 and 700 000 individuals. The prevalence of asthma was estimated according to the Health Survey published by To et al a mean of 8% of adult population.[11] The prevalence of allergic bronchopulmonary aspergillosis (ABPA) was estimated using a rate of 2.5% of adult patients with asthma based on data from Denning et al.[12] The incidence of 5 years prevalence of chronic pulmonary aspergillosis (CPA) following TB was estimated, assuming 22% are left with cavitation following therapy for TB and 22% of these develop CPA and 2% of the remainder.[13] We assumed that pulmonary TB was the underlying diagnosis of CPA in 20% of all CPA cases.[14]

Data on incidence and prevalence of haematological malignancies were obtained from NORDCAN.[15,16] The prevalence of new cases of acute myeloid leukaemia (AML) was estimated as 3.5 per 100 0000 inhabitants. Equal number of cases was considered in all other haematological patients as in AML. The risk of invasive aspergillosis (IA) was estimated at 10% in AML patients and an equivalent number in all other leukaemia and lymphoma patients.[17,18] The number of transplants was obtained from the scandiatransplant database (http://www.scandiatransplant.org). The incidence of IA in transplanted patients was evaluated according to prior estimates: renal, lung, heart and liver transplant annual incidence was set at 0.5%, 4%, 6% and 4%, respectively.

Candidemia data were derived from the latest data from national epidemiological fungemia surveillance programme. The incidence of candidemia is 4.7/100 000 individuals in Sweden.[8] The number of cases with intra-abdominal candidiasis (*Candida* peritonitis), usually a postsurgical complication was also seen only in intensive care unit at a rate of 50% of the candidemia cases based on previous study.[19] Data on *Cryptococcus* meningitis were retrieved from all laboratories in Sweden.[20] Infections due to Mucorales and *P jirovecii* were retrieved from Karolinska University Laboratory and cover only 25% of Swedish population. *Histoplasma capsulatum* and *Coccidioides immitis* infections are diagnosed for the whole population at Karolinska University Laboratory.

It is estimated that approximately 80%-90% of HIV-infected patients develop oropharyngeal candidiasis at some time during the progression of the disease.[21] The incidence of oesophageal candidiasis is estimated to occur in around 20% of HIV-infected patients without ART and 5% of those receiving ART. Recurrent vulvovaginal candidiasis (RVVC) was defined as at least four episodes per year. A rate of 5%-9% of adult women have RVVC according to a study by Denning et al.[22] The prevalence of fungal keratitis was estimated to be 14.3% of population according to the data from Vos et al.[23]

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as the research in this article related to microorganisms.

3 | RESULTS

In 2016, Sweden had a total population of 9 995 153 inhabitants, of which 49.8% were women and 21.8% were children (0-14 years). In total, 33% of the women were over 60 years old. The standard of living in Sweden is high with a gross domestic product per capita of 53 165 USD in 2017.

The present study shows that the overall burden of fungal infections in Sweden is 1 713 410 (17 142/100 000 inhabitants) and affects 17% of the population. Given the availability of the rates of several major diseases and with the help of literature where we did not have Swedish data, we present the estimated annual burden and total cases of fungal infection in Sweden in Table 1.

Not surprisingly, the most common fungal infections in Sweden are superficial infections, affecting 1 429 307 individuals annually. Among the superficial infections, recurrent vulvovaginal candidiasis (RVVC) affect 235 484 women annually (Table 1).

TABLE 1 Estimated annual burden and total cases of fungal infection in Sweden

Disease	Number of infections per underlying condition per years						
	None	HIV/Aids	Respiratory	Cancer/ Immuncom-promised	Critical care	Total burden	Rate per 100 000
Superficial							
Dermatophyte infections	1 429 307					1 429 307	1429
Oral		311				311	3
Oesophageal candidiasis		56				56	1
Recurrent volvuvaginal candidiasis (RVVC)	235 484					235 484	4712
Tinea capitis	135					135	1
Fungal keratitis	5					5	0.05
Invasive							
Candidemia		1		30	97	471	4.7
Candida peritonitis					50		0.50
Histoplasmosis	3					1	0.01
Cryptococcal meningitis	2	1				7	
Pneumocystis	281 (only Karolinska data)	16				297	3
Invasive aspergillosis			108	98	89	295	3.0
Respiratory (Prevalence)							
Chronic pulmonary aspergillosis—post TB			99			99	1.0
Chronic pulmonary aspergillosis—all			494			494	4.9
Allergic bronchopulmonary aspergillosis (ABPA)			20 095			20 095	201
Severe asthma with fungal sensitisation (SAFS)			26 387			26 387	264

The data on respiratory fungal infections are calculated based on previously published epidemiological studies.[12,24,25] Of adult Swedes with asthma (800 000 people), we estimated a prevalence of ABPA of 20 095 and severe asthma with fungal sensitisation (SAFS) of 26 387 (Table 1). There is likely some overlap between these patients as the most common mould to be sensitised to is *Aspergillus fumigatus* and many patients with ABPA are defined as having severe asthma. There is no direct estimate of ABPA prevalence from Sweden, but a recent paper shows on phenotype of severe asthma to be linked to *A fumigatus* sensitisation and at a frequency of 10%-17% in severe asthmatics, depending on the definition of severe asthma (3.6% to 6.1%).[26] This estimate would put the SAFS prevalence at 2480 to 8296, substantially lower than our estimate, but still a significant problem.

Aspergillus spp. can lead to ABPA, *Aspergillus* sensitisation and *Aspergillus* bronchitis, in cystic fibrosis (CF). The burden of aspergillosis and ABPA cases in adult CF patients wasstudies in 30 countries reporting CF, by Armstead et al.[27] The proportions of ABPA were 17.7%, Aspergillus sensitisation 14.6% and Aspergillus bronchitis 30% in adult CF patients.

Similarly, chronic pulmonary aspergillosis (CPA) was estimated to follow 31/490 (6.3%) in patients with tuberculosis in 2016, each year with a prevalence of 99 cases (Table 1). Sweden has the highest prevalence of sarcoidosis in the world (64/100 000; ~6400 patients) and a recent large French cohort study found 2.6% with CPA, which translates in Sweden to 166 patients.[25] There are no reports of CPA in sarcoidosis from Sweden. CPA also complicates COPD, pneumothorax, non-tuberculous mycobacterial infection, asthma, rheumatoid arthritis and other pulmonary conditions, so our overall estimate of 494 cases (4.9/100 000) is probably an underestimate (Table 1).

In contrast, the data on *Pneumocystis jirovecii* are based on our clinical data at Karolinska University Hospital. In 2016, there were 297 patients PCR positive for *P jirovecii* and of these, only 16 (5.4%) were thought to be from patients with HIV (Table 1).

Lung exposure to *Aspergillus* spores, that are found worldwide in environment, may lead to colonisation and finally IA. IA affects mainly patients with cancer/immunocompromised patients, including those with haematological malignancy, lung cancer but also influenza patients in intensive care unit (ICU). In our study, a total number of 287 episodes of IA was estimated to occur in Sweden. We assumed that 10% of patients with haematopoietic stem cell transplantation, 1% with renal, 20% of lung, 6% of heart and 4% of patients with liver transplantation are at risk for IA (Table 2). This is

TABLE 2 Estimated burden of invasive aspergillosis (IA)

Type of transplantation	Number of cases	Rate of IA	Number of IA
Allogeneic HSCT[a] per year	350	10	35
AML[b] patients per year	350	10	35
Renal Tx[c] per year	425	1	4
Lung Tx per year	62	20	12
Heart Tx per year	64	6	4
Liver Tx per year	199	4	8
Lung cancer	4135	2.6	108
Severe chronic obstructive pulmonary disease	6810	1.3	89
Total			295

[a]Allogenic haematopoietic stem cell transplantation.
[b]Acute myeloid leukaemia.
[c]Transplantation.

likely an underestimate because other patients with leukaemia, lymphoma and other immunosuppressed patients are not allowed for.

The number of patients with HIV in Sweden is 6983. Oral candidiasis is a frequent condition occurring at least in 90% of HIV-infected patients with low CD4 cells. It is estimated that 90% of HIV-infected patients without ARV, develop oral candidiasis. Oesophageal candidiasis is another AIDS-related illness affecting nearly 20% of AIDS patients with ARV and 0.5% without ARV. Thus, at least 56 cases of oesophageal candidiasis are expected to occur in Sweden annually (Table 1).

Recently, we reported that the incidence of candidemia in Sweden has slightly increased to 4.7/100 000 population/y in 2015-2016 (Table 1). The three most common *Candida* spp. isolated from blood cultures were *Candida albicans* (54.7%), *Candida glabrata* (19.7%) and species in the *Candida parapsilosis* complex (9.4%).

The prevalence of fungal keratitis was high, and almost one of seven Swedish inhabitants suffers from infection (Table 1). The prevalence of skin fungal infections was estimated to be 14.3% of population according to the data from Vos et al.[23] Retrospective analysis of skin, hair and nails scrapings in the mycology laboratory at Karolinska University Hospital, in Stockholm (Swedish capital) showed that onychomycosis had the highest prevalence of 14.1%, followed by tinea pedis (4.4%). *Trichophyton rubrum* and *T mentagrophytes* were the most predominant pathogens.[28]

Mucormycosis was reported in 3 patients in 2015, while cryptococcosis were reported in two patients. *Histoplasma capsulatum* and *Coccidioides immitis* were each diagnosed as the cause of infection in one patient in 2016. The data on *Cryptococcus* sp., Mucorales, *H capsulatum*, *C immitis* and *P jirovecii* were obtained from our own laboratory which serves as the reference laboratory for clinical mycology in Sweden.

4 | DISCUSSION

Sweden has a developed healthcare system with broad coverage, and most services are free for citizens. Carefully implemented immunisation programmes and relatively high economic resources have led to a decrease in morbidity and mortality rates due to bacterial infections. However, the overall fungal burden in Sweden has not been studied. The present study is part of a global study initiated by Leading International Fungal Education (http://www.life-worldwide.org). The overall objective of the initiative was to calculate the fungal burden in individual countries to ascertain the public health importance of fungal infections and the need to improve diagnostics and treatment. The present study shows that the overall burden of fungal infections in Sweden is 1 713 350 and affects 17% of the population.

Despite the significantly high numbers of patients presented here, the fungal infections draw very limited attention in media and politics. More interestingly, the resources allocated for research in clinical mycology are limited compared with other areas in medicine. The underlying reason for this relative ignorance is not known, but could in part relate to a lack of public health mycology as a sub-discipline.[29] A major reason is the limited availability of epidemiological data for fungal infections. Despite the high mortality rates and healthcare-related costs due to candidemia, the disease is still not considered as a notifiable disease in Sweden and therefore not regarded as mandatory contact tracing, dangerous to public health and dangerous to society.

Compared with the common bacterial and viral infections, the description of fungal burden at country level is challenging. To estimate the rates of diseases, it is important to have a meticulous documentation system for the underlying conditions that are related to fungal infections. Sweden has in general a very effective surveillance system for major common diseases with some exceptions as fungal infections as mentioned above.

The most common fungal infections in Sweden are superficial infections and RVVC. RVVC is related to high morbidity and affects the life-quality of the patients dramatically. In high-income countries, the economic burden from lost productivity could be up to US$14·39 billion annually.[22] A recent systemic review by Denning et al[22] shows that RVVC affects about 138 million women annually (range 103-172 million), with a global annual prevalence of 3871 per 100 000 women worldwide.

Pneumocystis jirovecii pneumonia was previously associated with HIV infection. In this study, only 5.4% of *P jirovecii* was associated with HIV infection. The changing epidemiology of *Pneumocystis* pneumonia may depend on improved treatment possibilities in patients with HIV as well as better diagnostic tools in detection of the fungi.

Approximately 40 million individuals are infected with HIV worldwide, and the number of cases in Sweden is 6983. In HIV-infected patients, mucocutaneous candidiasis is the first sign of HIV infection.[30] Oral candidiasis is caused mainly by *C albicans*, a part of healthy individuals' oral microbiota.

The incidence of candidemia has been regularly analysed in Sweden. In a previous study, we reported the incidence of candidaemia as 4.2/100 000 inhabitants in 2005-2006.[31] We reported recently an increased incidence.[8,20] The incidence of candidemia has been increasing worldwide. Our studies show that the incidence in Sweden is low, and there is no significant increase in numbers of patients with candidemia. The underlying reason for this finding is unclear. However, similar results were reported in a recent study from Norway.[32]

The present study has the following limitations. The data obtained on several fungal infections including superficial infections and RVVC are based on previously published epidemiological data from other countries.[23] There is an obvious risk that the estimates valid for another country might not be precise for Sweden because of the socioeconomic and geographical differences. However, we believe that the present estimates are important and will hopefully lead to well-designed epidemiological studies for these diseases in Sweden. Our study has also several strengths. The data obtained for the majority of invasive infections such as candidemia were obtained from a recent study from our group covering all microbiology laboratories in Sweden. Similarly, one of the major underlying diseases for fungal infections, HIV/AIDS, is a notifiable disease in our country and there is reliable detailed data available for the estimation of fungal burden in these patients.

In conclusion, fungal infections are very common in Sweden and affect 17% of the population. The significant morbidity, mortality and healthcare-related costs due to fungal infections deserve detailed epidemiological data. We hope that the present study will bring light to further studies in the field in Sweden.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest with regard to designing, collecting material, analysing or writing the paper.

AUTHOR CONTRIBUTIONS

David W. Denning conceived and designed the study; Volkan Özenci, Lena Klingspor, Måns Ullberg, Erja Chryssantou, Nahid Kondori and David W. Denning contributed materials; Volkan Özenci and Nahid Kondori analysed the data; Volkan Özenci, Nahid Kondori and David W. Denning wrote the paper.

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