

The burden of fungal disease in Denmark

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Summary

The aim of this study is to calculate the burden of fungal disease in Denmark. We identified all published epidemiology papers reporting fungal infection rates in Denmark. Where no data existed, we used numbers of specific populations at risk and fungal infection frequencies in those populations to estimate national incidence or prevalence. Approximately, one in six Danes will suffer from a fungal infection each year, most of which are skin or mucosal diseases causing disability but no deaths. Good data exist on candidaemia where a national voluntary reporting system is in place and have shown a high rate (9.6 per 100 000 inhabitants) compared other European countries. We present estimates of invasive aspergillosis and chronic pulmonary aspergillosis with rates of 4.4 per 100 000 and 3.1 per 100 000 inhabitants, respectively. Further studies are needed in order to better ascertain high-burden fungal infections such as recurrent vulvovaginal candidiasis (~1350 cases in 100 000 women) as well as allergic bronchopulmonary aspergillosis (~131 cases in 100 000 inhabitants) and severe asthma with fungal sensitisation (cases in 100 000 inhabitants). In conclusion, more than 93 000 Danes or about 2% of Denmark's population will have a non-trivial fungal infection during 1 year, which underscores the magnitude of the fungal burden.

Key words: Aspergillosis, candidiasis, Denmark, fungal, global, HIV.

Introduction

Invasive fungal disease (IFD) and other serious fungal diseases are thought to be increasing worldwide as well as in Denmark due to a number of factors including an increasing elderly population, increased survival time from lethal diseases and increase in prevalence and treatments causing immunosuppression. However, increased reporting and more

advanced diagnostic techniques may also be part of the explanation.

In Denmark, the epidemiology of fungal infections is largely unknown except for candidaemias, where a voluntary active surveillance programme has been in place since 2003, and covering the entire country from 2006.^{1,2} However, our knowledge of the epidemiology of most fungal infections is limited because there is no formal systematic or mandatory surveillance of fungal diseases.

Recently, global estimates of fungal infections of the skin, invasive fungal infections and chronic pulmonary aspergillosis following pulmonary tuberculosis, sarcoidosis and allergic bronchopulmonary aspergillosis complicating asthma have been made.³⁻⁶ Furthermore, national estimates from Spain and Nigeria have recently been published.^{7,8}

Invasive fungal infections are serious and associated with high morbidity and mortality if not diagnosed and treated promptly. Therefore, in order to provide

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health authorities with better data we have attempted to quantify the burden of IFD and other serious fungal diseases in Denmark with an estimated population of 5.6 million (2013). No estimate of the burden of fungal disease has been calculated previously in Denmark.

Materials and methods

We searched the PubMed database for published epidemiology papers reporting fungal infection rates from Denmark using the search words fungal, disease, infection, superficial, invasive, and Denmark from 1990 onwards. Where no data existed, we used specific populations at risk and fungal infection frequencies in those populations to estimate national incidence or prevalence, depending on the condition. From Statistics Denmark (<http://www.dst.dk/>), 2013 population statistics were derived.

We obtained the prevalence of skin fungal diseases from the studies of Vos *et al.* and Saunte *et al.* [3,9] and incidence of fungal keratitis from the study of Nielsen *et al.* [10]

The number of women between 15 and 50 years was obtained from the Statistics Denmark (<http://www.dst.dk/>). A 6% rate of recurrent vulvovaginal candidiasis (RVVC) was used and was defined as at least four episodes per year.¹¹

In 2013, the number of persons who lived with HIV in Denmark was 5065¹² and 40 new AIDS cases were reported in 2012 (EPI-NYT, week 44, 2013). National data from 2010 show that 83% of Danish HIV patients are on ART.¹³

We obtained the number of pulmonary tuberculosis (TB) cases from the Statens Serum Institut (EPI-NYT, week 4, 2014). Using the approach as described previously,⁴ a 5-year point prevalence of chronic pulmonary aspergillosis (CPA) following pulmonary TB was estimated, assuming a 12% cavitation rate following therapy.⁴ We assumed that pulmonary TB was the underlying diagnosis of CPA in 16% of all CPA cases in Denmark.¹⁴

The number of persons with acute admission with chronic obstructive pulmonary disease (COPD) was obtained from Danish Registry for COPD National Annual Report 2011 (Dansk Register for Kronisk Obstruktiv Lungesygdom, National Årsrapport 2011).

The rates of asthma in adults were obtained from the study of Von Bülow *et al.* [15] and a mean of 6.4% of the adult population was used for estimates. The risk of allergic bronchopulmonary aspergillosis (ABPA) was estimated at 2.5% based on Dennin

et al.'s study [6], although this figure may be an over-estimation as no national data of ABPA in asthmatics exist. The rate of severe asthma with fungal sensitisation was estimated as the worst 8.3% of the total asthma population, of which at least 33% have fungal sensitisation.¹⁶ We obtained data on cystic fibrosis (CF) numbers from Armstead *et al.* [17]

We obtained data on incidence and prevalence of haematological malignancies from NORDCAN.^{18,19} Percentages of invasive aspergillosis (IA) in this population were taken from a previous European study.²⁰ The number of transplants was obtained from the Scandiatransplant website (http://www.scandiatransplant.org/data/-sctp_figures_2012_4Q.pdf) and the 2011 Annual Report from the Acute Leukemia Group (<http://leukemia.hematology.dk/index.php/om-alg/arsrappor/128-3/file>).

Non-haematological IA in the intensive care unit (ICU) was all assumed to be attributable to COPD, and based on a previous European study we assumed that 1.3% of COPD admissions developed IA.²¹

Candidaemia data were based on the most current data from the national epidemiological fungaemia surveillance programme.² The number of cases of intra-abdominal candidiasis, usually post-surgical, was assumed to be one for every two ICU cases of candidaemia²² (*Candida* peritonitis complicating chronic ambulatory peritoneal dialysis was not estimated).

Results

Country profile

Denmark has an estimated population of 5.6 million people (excluding the Faeroe Islands and Greenland); 17% are children under 15; and 27% of women are over 60. The standard of living is high with a gross domestic product of \$59 831 per person in 2013. The total burden of fungal infections, the numbers of infections according to the main risk groups, as well as the rate for 100 000 inhabitants are shown in Table 1.

Superficial fungal infections

Assuming a rate of RVVC of 6% in women aged between 15 and 50 years of age, 75 812 women suffer from this condition, giving an annual rate of approximately 2700 cases per 100 000 women.

Based upon stable national rates of tinea capitis reported in 1993 and 2003,⁹ there are 185 cases of this infection each year.⁹ Of all dermatophyte-positive samples in 2003, 60% represent onychomycosis, 25%

Table 1 Burden of fungal disease in Denmark according to the main underlying conditions.

Disease	Number of infections per underlying condition per year						Total burden	Rate/100 K
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU			
Superficial fungal diseases								
Skin fungal infection	800 800						800 800	14 300
Oral candidiasis		775					775	13.8
Oesophageal candidiasis		382					382	6.8
Recurrent vaginal candidiasis	75 812						75 812	1354
Tinea capitis	185						185	3.3
Fungal keratitis	3						3	0.05
Invasive/systemic/deep								
Candidaemia	84			174	269		527	9.4
Candida peritonitis					176		176	3.1
Mucormycosis				1			1	0.02
Cryptococcal meningitis		2					2	0.04
<i>Pneumocystis jirovecii</i> pneumonia		15	67				82	1.5
Invasive aspergillosis				38	256		294	5.3
Chronic pulmonary aspergillosis			270				270	4.8
Allergic disease								
Allergic bronchopulmonary aspergillosis			7328				7328	131
Severe asthma with fungal sensitisation			7793				7793	139
Total	876 884	1174	15 458	213	701		894 430	

ICU, intensive care unit, Tx transplant recipient.

tinea pedis, 11% other skin and finally 4% tinea capitis. Taking Saunte *et al.* data to the population level will give 4625 annual dermatophyte infections, which is somewhat in contrast to the global prevalence of 14.3% by Vos *et al.* [3]. Using this figure will result in up to 800 800 Danes suffering from a fungal skin infection. We estimate three cases of fungal keratitis based on Nielsen *et al.* [10].

Respiratory infections

The estimated number of IA in allogeneic haematopoietic stem cell transplantation (HSCT) and solid organ transplantation is shown in Table 2. We assumed that IA (proven and probable) occurred in 10% of HSCT, 6% of heart and lung, 4% liver and in 1% of kidney-transplanted patients based on the data described previously,^{23,24} giving a total of 12 annual cases of IA. Higher rates of *Aspergillus* colonisation and tracheobronchitis are expected in lung transplant recipients but have not been taken into account in this study, although a study from Denmark showed a 25% *Aspergillus* colonisation rate among lung transplant recipients and was associated with a significantly increased 5-year mortality rate.²⁴ We have also excluded infrequent transplantation procedures such as small bowel and pancreas in these estimates.

In 2012, there were a total of 2152 leukaemias, lymphomas and multiple myelomas in Denmark. We estimated a total number of 27 cases of IA (Table 3) among patients with haematological malignancies based on percentages of IA in this population from Italy.²⁰ The highest incidence was among patients with acute myeloid leukaemia where 13 cases were estimated.

Finally, we estimated 256 cases of IA in the ICU setting based on the assumption that 1.3% of admitted COPD cases develop IA.²⁵ Other underlying conditions giving increased risk of IA such as severe liver failure or autoimmune diseases were ignored in the calculations.

Globally PTB is the main cause of CPA,^{4,14} but other underlying conditions associated with CPA are COPD, sarcoidosis, ABPA, prior pneumothorax, rheumatoid arthritis and non-tuberculous mycobacterioses, all probably more important in the developed world.¹⁴ In 2012, there were 311 cases of pulmonary TB in Denmark. Using the approach described by Denning *et al.* [4] and based on these figures, we estimate 14 new cases of CPA annually and a 5-year period prevalence of 43. Assuming that pulmonary TB only account for 16% of CPA cases, we estimate a prevalence of 270 CPA cases.

With an adult asthma prevalence of 6.4%,¹⁵ there are 291 548 adults with asthma in Denmark. Using

Table 2 Estimated burden of invasive aspergillosis in transplant populations.

Transplant type	Number of cases	IA occurrence (%)	Number of IA
Allogeneic haematopoietic stem cell transplantation ¹	41	10	4
Renal	214	1	2
Lung	30	6	2
Heart	26	6	2
Liver	48	4	2
Total	368		12

DATA: scandiatransplant_tx_figures_2013, except ¹Average 2009, 2010 and 2011, Annual Report 2011, Acute Leukemia Group, 2012.

the assumption that 2.5% of asthmatics have ABPA, we estimate 7289 cases of ABPA. Adding 39 cases of ABPA among 259 adult CF patients this gives a total of 7328 APBA cases. Adding to this we estimate a total of 7793 cases of SAFS in Denmark. It is likely that there is some overlap between ABPA and SAFS, as some ABPA patients have severe asthma as defined by high-dose inhaled corticosteroid requirements, but not oral steroid courses for ABPA exacerbations. Children were excluded in these calculations.

According to Thorsteinson *et al.* [26], the proportion of AIDS patients presenting with *Pneumocystis pneumonia* (PCP) as AIDS defining illness is 123 out of 331 patients during 1997–2009. Applying this to 2012 data with 40 new AIDS cases gives 14 PCP cases among AIDS patients.

No national data exist for PCP in the non-HIV population, but a study at the national hospital (Rigshospitalet) in Denmark found 50 cases among non-HIV patients during 2002–2004, giving a rate of 16.7 annual cases. Assuming that Rigshospitalet takes care of one fourth of at-risk patients the annual national rate would be 67 cases.

Invasive candidiasis

A remarkable high annual rate of candidaemia (11 per 100 000 inhabitants) was reported from Denmark using semi-national data from the years 2003–2004.¹ This rate has remained stable in 2011 with 527 cases (10.6 annual cases per 100 000 inhabitants).² It is comparable to rates in Spain (8.1 per 100 000),²⁷ but substantially higher than in Northern European countries such as Norway and Finland (3–5 cases per 100 000), although not as high as in Baltimore reporting more than 20 cases per 100 000 inhabitants.²⁸ More than half of the candidaemia cases occurred in the ICU.²⁹ We assumed, based on prospective French data, that *Candida* peritonitis adds 50% to the number of candidaemia cases in the ICU setting giving 176 cases of intra-abdominal peritonitis³⁰ (Table 1).

Other fungal infections

We estimate two new cases of cryptococcal meningitis each year based on the 1.4 annual cases reported during 1997–2008 in Copenhagen Region, where two hospitals take care of more than two thirds of HIV-

Table 3 Burden of invasive aspergillosis in patients with haematological disease.

Disease	Incidence of the haematological disease/100 000 ¹	Cases in 2012 (based on av. 2008–2012) ²	Prevalence of IA (%)	Annual cases of IA
Leukaemia				
Acute myeloid leukaemia	3.3	183	7.07	13
Acute lymphoblastic leukaemia	1.2	65	3.75	2
Chronic myeloid leukaemia	1.2	67	2.35	2
Chronic lymphatic leukaemia	4.9	274	0.45	1
Other leukaemias	1.1	64	–	–
Unclassified	0.1	6	–	–
Multiple myeloma	5.6	314	0.25	1
Hodgkin lymphoma	2.4	133	0.36	–
Non-Hodgkin lymphoma	18.7	1046	0.78	8
Total		2152		27

IA, invasive aspergillosis.

¹Data from Engholm *et al.* [18]

²Pagano *et al.* [20].

infected persons in Denmark.³¹ Other non-central nervous system cryptococcal infections probably at similar rates are also estimated, but we have excluded these calculations.

Most mucormycoses are observed among transplant recipients or patients with haematological malignancy. One case was identified in 2011 giving a rate of 0.02 per 100 000 that is similar to reports from Spain³² but lower than in France which reported a rate of 0.12 per 100 000.

For endemic fungal infections very few cases are estimated. The national reference laboratory at Statens Serum Institut that receives samples for this infection is reporting 1–2 cases every 5 years.

Discussion

Almost one in six inhabitants in Denmark suffers from a fungal infection every year. Approximately 90% of these are skin or superficial infections not associated with increased death rates. Superficial fungal infections of the skin and mucosa are the most frequent fungal infections and primarily involve dermatophytes, *Candida* and *Malassezia* species. A large number of infections will probably not be brought to the attention of the doctor and others are treated based solely on clinical diagnosis without submitting samples for mycological diagnosis. This may explain the huge gap between Vos *et al.* estimate and Saunte *et al.* data. Although Saunte *et al.* data-based estimate of around 4600 dermatophyte cases, does not include infections caused by *Candida*, *Malassezia* and non-Dermatophyte filamentous fungi and although the sensitivity for nail infection is probably 50%, there is a long way from to the 800 800 figure in Vos *et al.* data-based estimate. Geographical differences and free access to healthcare may explain some of these discrepancies.

Most infections can be treated with topical treatments, but oesophageal candidiasis, RVVC and tinea capitis and onychomycosis require systemic therapy. Moreover many women prefer (and receive) systemic fluconazole rather than topical azoles for uncomplicated vaginitis. On the other hand, these infections can be a serious debilitating factor in the individual. Global Burden of Disease estimates has placed skin fungal infections as the fourth most common health problem with one billion affected globally and has been estimated to lead to a mean of 2.3 million years lived with disability (YLD) or 33 YLDs per 100 000 inhabitants.³

More than 1000 individuals will suffer from a serious invasive fungal infection such as candidaemia, IA

and PCP every year in Denmark. Although not frequent infections, they are associated with poor outcomes and high costs due to prolonged stay in hospital and the expense of consolidation oral antifungal treatment after discharge.³³

Both chronic and allergic pulmonary aspergillosis and SAFS are also relatively common with population rates of 18.3, 130 and 139 per 100 000. As long-term conditions which can benefit from antifungal therapy, additional studies on the prevalence of these conditions are warranted.

There are several limitations in this study and there is a high degree of uncertainty around the total estimate. First, there are diagnostic limitations. Most superficial fungal infections are diagnosed clinically without supportive microbiological data. Moreover, the conventional diagnosis of invasive *Candida* infections with blood culture is insensitive, probably missing more than 50% of infections.²² Invasive mould infections are also difficult to diagnose and very few infections are proven, most being diagnosed on clinical, imaging and surrogate microbiological markers of infection.³⁴ We have previously estimated 50–60 annual cases of IA based on *Aspergillus* spp. culture positive respiratory samples (sputum, tracheal secretion, endolaryngeal aspiration and BAL).³⁵ The estimated almost 300 cases of IA in the present study may be an overestimation in light of the wide implementation of mould prophylactic strategies, especially in the haematological setting, and also the number of patients in ICU receiving empirical antifungal therapy with anti-*Aspergillus* activity. However, estimates based on culture will inevitably be low because the culture positivity rate for invasive (and chronic) pulmonary aspergillosis is <30%.

Second, although a national voluntary surveillance system on candidaemia exists²⁹ and the epidemiology of candidaemia is well elucidated,^{1,2,29} there is no systematic national surveillance of other fungal infections and there is only a limited number of studies published describing the epidemiology of other types of invasive candidiasis probably due to the difficulty diagnosing these infections. Very few endemic fungal infections, such as histoplasmosis and coccidioidomycoses, are diagnosed each year and most at the Mycology laboratory at Statens Serum Institut. However, no comprehensive national seroprevalence study of these infections in returned Danish travellers have been performed. Furthermore, incidence rates do vary, even from other European countries, so country-specific estimates are necessary. The institution of widespread molecular detection of candidaemia will probably

increase the number of cases detected. Finally, there are methodological limitations of calculating the burden. This is mainly due to the fact that the rates have been based on frequencies of at-risk populations. We will need to combine methods (pragmatic and surveillance-based), take into account any new published information on specific incidence rates and consider using alternative data sources such as the Hospital Information Systems to make more precise estimates. However, an accurate estimate of total burden will ultimately rely on improved diagnostic testing and laboratory reporting a wide range of incidence estimates for one of the largest high-risk population, such as patients in ICU.

To the best of our knowledge, this is the first attempt at a comprehensive estimation of burden of fungal disease in Denmark which align with the high and increasing use of anti-fungals (1 450 000 defined daily doses/year).² Further studies are clearly needed especially focusing on improving the diagnosis of invasive fungal infections, better surveillance of invasive mould infections and allergic aspergillosis. Different epidemiological approaches will be needed, given that some conditions such as ABPA and SAFS are long term, others are short term and often fatal, such as PCP and IA, and others recurrent, such as RVVC and mucosal candidiasis in AIDS.

Finally, fungal infections may be considered a neglected disease and inadequate resources are applied to most fungal infections. Furthermore, patients with fungal infections are distributed among a huge variety of medical fields and often involve patients where the main focus is on the underlying disease, thus rendering the fungal infection less notified. This is an obstacle for development of the field and for attracting attention and funding to this under prioritised area. It has been estimated that worldwide deaths due to fungal infections (>1.350 000)³⁶ are as high as those of tuberculosis (1.400 000) and even higher than those for malaria (627 000).³⁷ This study is part of a global study initiated by LIFE (www.LIFE-worldwide.org) which has launched an initiative to calculate the fungal burden in many countries in order to ascertain the public health importance of fungal diseases and with hope of better informing the health authorities and facilitate improved epidemiologic studies.

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Data have previously been presented in part at the 24th ECCMID Congress in Barcelona, Spain, May 2014.

Conflicts of interest

KLM has received grant support from Pfizer, has been paid for talks on behalf of MSD and has received travel grants from Pfizer, MSD and Schering Plough. 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, North-West 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. MCA has received grant support from Astellas Pharma, Gilead Sciences, Merck Sharp and Dohme (MSD), Pfizer and T2 Biosystems. She has been a consultant at the advisory board for Gilead Sciences, MSD, Pfizer, Pcovery and Schering Plough. She has been paid for talks on behalf of Gilead Sciences, MSD, Pfizer, Astellas Pharma and Schering Plough. No financial support was received for the present study.

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