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Supplement article

Burden of serious fungal infections in Belgium

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Summary

We aimed to estimate the total number of serious fungal infections occurring yearly in Belgium. The number of cryptococcal infections was retrieved from the National Reference Center for Mycosis. Populations at risk and fungal infections frequencies in these populations were used to estimate incidence or prevalence of other fungal infections. The Belgian population consists of 11.10 million people. Cryptococcal meningitis is rare. In all, 15 of the 1227 newly diagnosed HIV/AIDS cases presented with *Pneumocystis jirovecii* pneumonia. This accounts for ±14% of total PCP cases ($n = 120$). The incidence of candidaemia is estimated as 5/100 000 resulting in 555 cases and 213 deaths. A total number of 675 invasive aspergillosis cases and ≥169 deaths attributed to this infection were calculated. Chronic pulmonary aspergillosis is estimated to be prevalent in 662 cases. Allergic bronchopulmonary aspergillosis cases were estimated to be 23 119 applying a 2.5% and 15% rate in adult asthma and cystic fibrosis patients respectively. Severe asthma with fungal sensitisation cases was estimated to be 30 402. There were 174 760 women with recurrent *Candida* vaginitis assuming a 6% rate in women aged between 15 and 50. Approximately 233 000 people of the Belgian population (2.1%) are estimated to suffer from a fungal infection on a yearly basis.

Key words: fungal infections, burden, Belgium.

Introduction

Fungal infections are not notifiable in Belgium, as in most other countries. As such, population-based data are not available and thus the true burden of these infections is largely unknown. No media or political attention is given to fungal infections in Belgium, which contrasts strongly to the attention given to, e.g. Lyme disease, an infection responsible for substantial morbidity but no mortality. Very few studies were designed to determine incidence rates of fungal infections in Belgium and these studies were mainly conducted on a single institution level.[1–3] A recent candidaemia study conducted in 30 Belgian hospitals revealed large variations in incidence rates between different hospitals (0.07–1.44 per 1000 admissions and 0.11–2.03 per 10 000 patient-days).[3] An increasing incidence of mucormycosis was reported from a large tertiary care centre during the period 2000–2009.[2] Herein, we aimed to estimate the burden of serious fungal infections in Belgium using the LIFE methodology. Many other countries worldwide have undertaken the same exercise or are in the process of doing so.[4–6] This will enable us to get a view on the global burden of fungal infections and to compare the impact of these infections and the specific needs of different countries around the

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world. It is of utmost importance to provide healthcare professionals with knowledge about fungal infections, available diagnostic tools and treatment options to improve the outcome of the patients affected by these pathogens.

Methods

The methodology of the LIFE program was used (www.LIFE-worldwide.org) to estimate the burden of fungal disease in Belgium. The number of cryptococcal infections was retrieved from the National Reference Center (NRC) for Mycosis (https://nrchm.wiv-isp.be/nl/ref_centra_labo/mycosis/default.aspx). The incidence or prevalence of other fungal diseases was estimated based on populations at risk and fungal infections frequencies in these populations. The following sources were consulted to retrieve data about the at risk populations: the Civil Registration Database 2013 (http://bestat.economie.fgov.be/BeStat/) for demographic data; the registry of the Belgian AIDS Reference Centers (2012) for numbers of HIV/AIDS cases that presented with *P. jirovecii* pneumonia (PCP) as AIDS indicator disease; a retrospective study (2010–2013, non-published data) of PCP cases in UZ Leuven (1900 bed tertiary care hospital, Leuven, Belgium) for the ratio of PCP diagnosis in HIV vs. non-HIV infected patients; the Belgian tuberculosis register (2012) for the number of pulmonary tuberculosis (TB) patients; Eurotransplant (2011) for the number of solid organ transplantations; the Belgian Cancer Register for the number of patients with acute myeloid leukaemia (AML) and the European Cystic Fibrosis Society (2013) for the number of cystic fibrosis (CF) patients.

Results

Belgium is a country with a population of about 11 million people (11 099 544 million in 2013), 50.9% are woman and 17% are under the age of 18. HIV infects at least 20 000 people. The gross domestic product per person in 2013 was $46 878. The estimated burden of serious fungal infections is shown in Table 1.

Invasive fungal infections

During the period 2005–2014, the NRC for mycosis received between 3 and 12 cryptococcal isolates annually.

In 2012, 1227 HIV/AIDS patients were newly diagnosed, including 15 cases that presented with PCP as an AIDS indicator disease. A retrospective study of PCP cases diagnosed between 2010 and 2013 in UZ Leuven (Belgium), a large tertiary care centre that is one of nine Belgian AIDS Reference Centers, was conducted (unpublished data). In this cohort, the PCP ratio in HIV vs. non-HIV infected patients was 1/6.1. Based on this ratio, the total yearly number of PCP cases is estimated to be 120.

A candidaemia incidence of 5/100 000 was assumed resulting in 555 yearly candidaemia cases. About 30% of these cases (n = 165) are usually diagnosed in an intensive care unit (ICU).[7] Intra-abdominal *Candida* infection is a frequent complication in surgical ICU patients. In a large multicentre study in 101 French ICUs the rate of *Candida* peritonitis was approximately 50% of ICU candidaemia cases.[8,9] Assuming a similar rate in Belgian ICUs, the number of post-surgical intra-abdominal candidiasis cases was estimated to be 83.

The number of patients suffering from invasive aspergillosis was calculated on the assumption of a 10% rate in AML patients (n = 1641), an equal number in the non-AML haematological patient population including stem cell transplant recipients[10,11]; 0.5% in renal transplant recipients (Tx) (n = 437), 4% in lung Tx (n = 106), 6% heart Tx (n = 67), 4% liver Tx (232) and 1.3% in chronic obstructive pulmonary disease (COPD) hospital admissions (n = 21 005)[12] adding up to an annual incidence of 675 cases.[13]

Chronic lung infection

In 2011, there were 1044 TB patients in Belgium. The annual incidence of chronic pulmonary aspergillosis was assumed to be 22% in TB patients with cavities (12% of all TB patients) and 2% in TB patients without cavities, resulting in a 5-year period prevalence of 132 cases.[14] Assuming that TB was the underlying diagnosis in 20% of cases,[15] we estimate a prevalence of about 662 cases, assuming a 15% annual mortality or surgical cure rate.

Allergic fungal disease

Asthma is prevalent in adults; this disease affects about 10% of adults.[16] Assuming a prevalence of allergic bronchopulmonary aspergillosis (ABPA) of 2.5% in adult asthmatics (n = 921 262) and 15% in adult CF patients (n = 581), a prevalence of ABPA 23 119 was calculated.[17]

Assuming a prevalence of severe asthma with fungal sensitisation of 3.3%, 30 402 Belgian patients are afflicted with this syndrome.[18]

Table 1 Burden of fungal diseases in Belgium according to the risk population.

Infection	Number of infections per underlying disorder per year					Total burden	Rate/ 100 000 inhabitants
	None	HIV/ AIDS	Respiratory disease	Cancer/ Tx	ICU		
Candidaemia				388	165	555	5.0
Intra-abdominal candidiasis					83	83	0.75
Recurrent *Candida* vaginitis (≥4×/year)	174 760					174 760	3149[1]
Invasive aspergillosis				402	273	675	6.08
Chronic pulmonary aspergillosis			662			662	22.7
ABPA			23 119			23 119	208.3
Severe asthma with fungal sensitisation			30 402			30 402	273.9
Cryptococcal meningitis						10	0.09
Pneumocystis pneumonia		15	105			120	1.1
Total burden estimated						233 000	2099

ABPA, allergic bronchopulmonary aspergillosis; Tx, transplant recipients.

[1]Rate of recurrent *Candida* vaginitis per 100 000 females, not per total population.

Mucosal infection

We estimated a 'discounted' rate of 6% of women aged between 18 and 50 to be suffering at least four times a year (= recurrent) from *Candida* vaginitis (= recurrent vulvovaginal candidiasis or rVVC) because the self-reported rate by Internet survey of 9%[19] is likely to be an over-estimation given the difficulty for women in precisely determining the cause of their symptoms, and to be conservative. Nonetheless our estimate of the number of Belgian women affected by affected rVVC in any 1 year is 174 760, with a much higher number affected at some time in their lifetime.

Discussion

Sending of *Cryptococcus* spp. isolates to the Belgian NRC for mycosis is not mandatory, but is usually done to confirm the identification of the isolate and for susceptibility testing. The incidence of cryptococcal meningitis is low (0.09 cases per 100 000 inhabitants) in Belgium and lower than the incidence reported for the neighbouring country France (0.2 per 100 000 inhabitants).[20] Highly effective antiretroviral treatment of HIV-infected patients may explain this low incidence rate. Very few cases occur in other immunocompromised patients in Belgium.

Contrary to the Nordic countries, population-based data on the incidence of candidaemia are not available for Belgium. A yearly number of 555 was found, assuming an incidence rate of 5 per 100 000. In a recent prospective Belgian candidaemia trial (TANSIR trial), 341 cases were retrieved from 29 hospitals during a 1-year period.[3] It seems plausible to assume that about two thirds of all Belgian candidaemia cases were retrieved by this study. The annual incidence of fungaemia in the UZ Leuven ranged between 1.30 and 1.68 episodes per 10 000 patient-days during the period 2001–2005 (on a total of 2 680 932 patient-days), with a decreasing trend observed over the 5-year study period.[1] However in 2013, the incidence of candidaemia in this hospital was 2.03 per 10 000 patient-days. These data are most consistent with an increasing incidence in Belgium, which is particularly worrisome because of the high morbidity and mortality[7,21] of this infection. An active hospital-based surveillance program of episodes of candidaemia in 24 tertiary care hospitals in the Paris area, France, between October 2002 and September 2010 revealed a significant increased incidence in the overall population and ICU. Even more worrisome, in this study the day-30 and early (<day 8) death rates increased over time in ICU despite the availability of new antifungals

(echinocandin drugs) and the progressive implementation of recent candidaemia treatment guidelines.[20] Applying the same mortality rates (38.8% within 8 days of infection in ICU vs. 15.1% outside ICU and 56.9% within 30 days of infection in ICU vs. 30.7% outside ICU), we calculated that in Belgium each year 123 and 213 patients die within 8 and 30 days, respectively, following their diagnosis of a *Candida* bloodstream infection.

Based on the estimated rate of IA in at risk populations and reliable data about the size of these risk groups, 48% of calculated IA cases had a haematological malignancy as underlying disease. In a recent Belgian surveillance study of azole resistance in patients with *Aspergillus* disease, only 25% of total number of IA cases were haematology patients.[22] However, culture of *Aspergillus* species from a clinical sample was the entry criterion in this study, and culture is known to be an insensitive marker of IA.[23] The diagnosis of IA in haematology patients is more often made in an early phase, based on galactomannan positivity. It is likely that the group of haematology patients is underrepresented in a surveillance study based on culture. In IA patients without haematological malignancy, COPD is the most common underlying condition in Belgium,[24] and carries a high mortality, partly because of late diagnosis or no ante-mortem diagnosis. The mortality rate of IA differs according to the underlying disease. Based on surveillance studies conducted in different patient populations, a minimum mortality rate of 25% seems to be a good lower estimate for case fatality in the global population suffering from this disease.[20,25,26] For Belgium this implies at least 169 deaths yearly that can be attributed to IA.

Striking differences in rates of serious fungal infections between Belgium and other countries can be recorded: e.g. in comparison with Nigeria the incidence of cryptococcal meningitis (37.4 vs. 0.09/100 000 inhabitants) and PCP (48.2 vs. 1.08/100 000 inhabitants) is much lower in Belgium, whereas it is the opposite (higher rate in Belgium) for ABPA (208.3 vs. 60.5/100 000 inhabitants). The incidence of IA (6.08 vs. 2.75/100 000 inhabitants) and chronic pulmonary aspergillosis (22.7 vs. 9.19/100 000 inhabitants) seems to be higher in Belgium compared to Spain.

Recurrent *Candida* vaginitis is by far the most common fungal disease for which the burden was estimated, with 174 760 woman affected by this mucosal infection. About 75% of women have at least one vaginal yeast infection at some point in their lives. Treatment of women suffering from recurrent vaginitis is far more difficult than treatment of women with a single *Candida* vaginitis episode and often needs daily maintenance treatment for 6 months or longer to keep these women symptom free. A recent cross-sectional online survey in five European countries revealed that 68% of 620 women with recurrent *Candida* vaginitis reported depression/anxiety problems during acute episode despite antifungal therapy, and 54% outside episodes, compared to <20% in general population. The average index score for health status derived from the questionnaire was comparable in women with recurrent *Candida* vaginitis to other diseases such as asthma or COPD and worse than diseases such as headache/migraine.[27]

The total burden of fungal infections is certainly higher than the number calculated here as for instance skin, hair or nail infections and fungal keratitis infections were not taken into account due to the lack of reliable estimates.

In conclusion, this report is a first attempt to estimate this burden of fungal disease in Belgium. However, improved diagnostic testing and reporting is needed to further validate these data. The total number of patients with invasive fungal infections is much lower than the number of patients with mucosal fungal infections or allergic fungal syndromes, but the burden of these invasive infections is particularly high because of their poor outcome and high costs due to prolonged hospital stay and treatment with very expensive and potentially toxic antifungal drugs.

Conflict of Interest

KL has received research grants, travel support and lecture honoraria from Gilead, MSD and Pfizer. She is also member of the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis guideline group. JM received personal fees and non-financial support from Basilea; grants, personal fees and non-financial support from Astellas Pharma, MSD, Gilead Sciences and Pfizer. He is also member of the European Society for Clinical Microbiology and Infectious Diseases Aspergillosis guideline group. EVE 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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