

Burden of fungal disease in Ireland

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Our objective was to estimate the burden of fungal disease on the island of Ireland, as part of a coordinated project estimating the global burden. Published epidemiology data describing fungal infection in Ireland were identified. Population and underlying disease data were collected for 2010 and a structured set of assumptions were applied to estimate burden of fungal disease based on immunosuppression, chronic disease, and other demographic information indicating predisposition to fungal infection. From Ireland's population of 6.4 million, we estimate 117 000 patients develop significant fungal disease each year. By far the most common fungal disease is recurrent *Candida* vaginitis, with an estimated 95 000 episodes annually (3000 per 100 000 women). Other fungal diseases which may be less well recognized are severe asthma with fungal sensitization and allergic bronchopulmonary aspergillosis, with estimated episodes per year of 11 700 and 9000, respectively (182 and 140 per 100 000 population, respectively). The model also estimates 450 episodes of invasive aspergillosis, 200 of chronic pulmonary aspergillosis, 600 of oesophageal candidiasis and 450 of candidaemia per year (7, 3, 9 and 6 episodes per 100 000 population, respectively). This is, we believe, the first attempt to estimate the burden of fungal disease in our population and provides a basis for estimating its impact on human health and resource use.

Received 2 October 2014

Accepted 31 December 2014

INTRODUCTION

Fungal infections are a growing global problem that is difficult to quantify in terms of population affected, mortality, resources used and opportunities for prevention. There is little understanding of the true impact of fungal infections on patients and healthcare systems since often superficial infections are diagnosed at a general practice level, there is little routine fungal specific surveillance and diagnosing invasive fungal infections is notoriously difficult. Currently available data on fungal infections worldwide are crude estimates that have not been standardized. We present data from Northern Ireland (NI) and the Republic of Ireland (ROI), as part of a multi-country project that attempts to compile estimates from several countries worldwide to form a better overall picture of the current state of fungal infection globally.

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AML, acute myeloid leukaemia; ARV, anti-retroviral drug; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CP, *Candida* peritonitis; CPA, chronic pulmonary aspergillosis; IA, invasive aspergillosis; HIV, human immunodeficiency virus; NI, Northern Ireland; PCP, pneumocystis pneumonia; PTB, pulmonary tuberculosis; ROI, Republic of Ireland; SAFS, severe asthma with fungal sensitization.

METHODS

For the purpose of creating a comparable dataset for each country, a template was provided to all participants that included demographic data, and specific disease-related information was gathered. Relevant published epidemiology describing fungal infection in Ireland was identified by literature search. Where there was no available dataset specific to Ireland, worldwide data were used to derive estimates of fungal infection based on a variety of factors; these included human immunodeficiency virus (HIV) status, acute and chronic lung disease, immune status, number of critical care beds and abdominal surgeries. The template used across the countries involved extrapolated estimates of fungal infection from published data. Standardized assumptions, which allow directly observed incidence of fungal infection to be used in conjunction with surrogate markers, enabled an estimate of the total national burden to be derived. Population data were obtained from the Northern Ireland Research and Statistics Agency and the Central Statistic Office of Ireland; patients were stratified by age and gender.

The estimated incidence of recurrent *Candida* vaginitis in adult women ranges between 5 and 9% per year; however, in regions such as Ireland, where a large percentage of women are over 50, this may be an overestimate (Sobel, 2007; Foxman *et al.*, 2013). Therefore, taking an extremely conservative approach, we have applied a downward adjustment (to 80%) to the lower point of this range and use an estimated rate of 4%.

HIV/AIDS data for ROI were obtained from the World Health Organization 'People living with HIV' report (WHO, 2009) and from the Health Service in Ireland 2011 HIV report (Health Service in

Ireland, 2011). NI data were gathered from the NI Public Health Agency HIV and STI surveillance report 2011 (Public Health Agency, 2011) and an audit of HIV attendances at the regional centre. In most populations, it is assumed that 90 % of patients with HIV who are not being treated with anti-retroviral drugs (ARVs) will develop oral candidiasis and it is assumed that 20 % of patients with HIV not taking ARVs and 5 % of those taking ARVs develop oesophageal candidiasis (Matee *et al.*, 2000; Smith & Orholm, 1990; Buchacz *et al.*, 2010). Pneumocystis pneumonia (PCP) is usually considered to be associated primarily with HIV and it is inferred that 25 % of patients with AIDS develop PCP; however, in NI a recent published study suggests that only 25 % of the PCP infections seen in this population are in patients with HIV as a risk factor (Coyle *et al.*, 2012).

Cystic fibrosis (CF) figures were derived from data supplied by the CF trust (NI) and CF registry (ROI). Chronic obstructive pulmonary disease (COPD) information from ROI was taken from the Organization for Economic Co-operation and Development library and asthma rates were obtained from the Asthma Society of Ireland. There are insufficient direct data for NI for COPD and asthma numbers, so these data were extrapolated using population figures from the ROI dataset. Pulmonary tuberculosis (PTB) data for ROI were obtained from the World Health Organization and NI information was obtained directly from the NI Public Health Agency with supporting HIV audit data. It is assumed that 22 % of patients with lung cavities, and 2 % of those without cavities, following PTB will develop chronic pulmonary aspergillosis (CPA) (Denning *et al.*, 2011). Further, it is assumed that there is an annual death and/or surgical excision rate of 15 %. Patients with PTB are expected to represent ~25 % of the total number of CPA cases annually (Smith & Denning, 2011) and so the total prevalence of CPA from any cause is estimated using the national PTB figures (Denning *et al.*, 2011).

ROI transplant data were obtained from the 2011 Council of Europe report on organ transplant and NI data from the organ donation registry, supported by direct figures from the regional Haematology Transplant Co-ordinator to capture the stem cell transplants performed. The numbers of acute myeloid leukaemia (AML) patients per year were obtained from local cancer registries. It is assumed that non-AML haematological conditions in total represent the same population incidence of invasive aspergillosis (IA) as AML patients; in each group there is an incidence of approximately 10 % (Lortholary *et al.*, 2011). Further, it is assumed that the incidence of IA in allogeneic haematopoietic stem cell transplants is 8 % (Lortholary *et al.*, 2011). IA is also associated with solid organ transplantation, although the reported incidence varies by both dataset and anatomical site. The Transplant-Associated Infection Surveillance Network data suggest an IA 1 year cumulative incidence of 0.5 % of renal, 2.0 % of heart, 0.9 % of liver and 9.1 % of lung transplants (Pappas *et al.*, 2010). Given the size of this dataset, it provides most precise disease rates and we have adopted these.

Allergic bronchopulmonary aspergillosis (ABPA) figures were determined by assuming rates of 17.7 % among adult CF patients and 2.5 % among adult asthmatics; fungal sensitization is assumed to occur in 14.6 % of adult CF patients (Denning *et al.*, 2013; Baxter *et al.*, 2013). For severe asthma with fungal sensitization (SAFS) the assumption is that, among asthmatics with most severe disease (10 % of adult asthma patients), a third will be affected (Denning *et al.*, 2006).

For candidaemia, data for NI were obtained from the DHSSPSNI Statistics and Research records office voluntary laboratory reporting programme and these were used to infer the ROI incidence. The national figure for level 3 critical care beds was obtained from the critical care census (Prospectus, 2009). These figures were used to estimate the incidence of *Candida* peritonitis and the assumption is that there is one case of *Candida* peritonitis for every two cases of

candidaemia in critical care units (Montravers *et al.*, 2011; Brown *et al.*, 2012; Zilberberg *et al.*, 2008).

RESULTS AND DISCUSSION

Ireland has a population of 6 399 152, of which 22 % are children under 16, and 8 % are women over 60 years old. The estimates of most serious, non-cutaneous, fungal infection in Ireland are displayed in Table 1, giving absolute numbers and rate per 100 000 population.

Ireland has approximately 7374 people living with HIV. There are relatively few AIDS-related opportunistic infections seen in this population as the uptake of ARV therapy is high. We estimate that in Ireland there are 1394 cases of oral candidiasis and 601 cases of oesophageal candidiasis. Of people with AIDS, it is assumed that 25 % have PCP (Zilberberg *et al.*, 2008) and, since HIV infection accounts for 25 % of PCP cases in NI (assumed to be similar in ROI), this gives a rate of 0.8 per 100 000 population (Coyle *et al.*, 2012). The estimates for oral and oesophageal candidiasis rely on the presumption that HIV patients not receiving ARVs are at higher risk of opportunistic infections than those who are receiving treatment. This may overestimate the numbers affected by these conditions in countries like Ireland, where patients may not be receiving ARVs because their clinical condition does not warrant ARV treatment, as opposed to due to drug unavailability. By contrast, we have not estimated infection as a result of inhaled steroid use, which may reduce the number of patients captured (perhaps notable in a population with high asthma, chronic lung disease and systemic steroid use), nor other predisposing conditions such as head and neck radiotherapy or denture use. Such limitations are implicit in use of a template across countries with varying health needs, practice and resources.

There were 245 people diagnosed with PTB in Ireland in 2010 and it is assumed that 90 % survived. Using previously described assumptions, the annual CPA incidence is estimated to be 14 patients, with a 5 year period prevalence of 45 people with CPA following PTB (Denning *et al.*, 2011). Assuming these patients represent a quarter of CPA cases in a year, it is inferred that there is an approximate prevalence of 180 cases of CPA in Ireland.

The candidaemia rate is approximately 6.3 per 100 000 population, which gives a total of 403 cases of candidaemia per year (Public Health Agency, 2011). Of these, there are more *Candida* bloodstream infections in males than females, with this being particularly marked at extremes of age. In fact, all patients with candidaemia in the <14 age group in NI in 2011 were male; this figure includes neonates. Over 50 % of bloodstream infections were caused by *Candida albicans*, ~25 % by *Candida glabrata*, ~10 % by *Candida parapsilosis*, ~5 % by *Candida tropicalis* and the remainder by other *Candida* species. The candidaemia rate varies year on year between 5.5 and 7.38 per 100 000 population (HPA Northern Ireland, 2011). These rates are

Table 1. Burden of serious fungal infection in Ireland

Infection	No. of infections per underlying disorder per year					Total burden	Rate per 10 ⁵
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU		
Oesophageal candidiasis		601				601	9.4
Candidaemia				275	128	403	6.3
CP					64	64	1
Recurrent <i>Candida</i> vaginitis (≥ 4 year ⁻¹)	94 974					94 974	2968*
ABPA			8 960			8 960	140
SAFS			11 675			11 675	182.4
IA				46	399	445	7
Mucormycosis	13					13	0.2
Cryptococcal meningitis		3				3	0
PCP		13		37		50	0.8
CPA			196			196	3.1
Total burden estimated	94 987	617	20 831	358	591	117 384	

*Note rate of recurrent *Candida* vaginitis is per 100 000 females, not per total population.

specific for NI, but are expected to be mirrored in ROI and broadly represent the island of Ireland.

There are 257 level 3 critical care beds in use for both the adult and paediatric populations in Ireland. Of all cases of candidaemia reported each year, 128 occur in critical care. In addition to bloodstream infection, 64 cases of *Candida* peritonitis are estimated to occur per year. This has been derived from the number of candidaemias in critical care patients but does not include other potential sources of *Candida* peritonitis, like peritoneal dialysis. About half of patients globally with end-stage renal failure have continuous ambulatory peritoneal dialysis, and although infection rates vary it is estimated that 0.05 episodes per patient per year of peritoneal-dialysis-related infections are caused by *Candida* (Montravers *et al.*, 2011). Although globally this may be another underestimated infection meriting further investigation, in Ireland we lack primary data to corroborate this, and it may be an overestimate.

There are approximately three patients diagnosed with AML per 100 000 population per year in Ireland. In 2010 there were a total of 192 patients with AML. These figures, along with transplant data, give an estimate of 50 cases of IA in patients with significant immunosuppression outwith critical care. In the critical care setting there were a further 399 estimated cases of IA, assumed to arise as a result of COPD, since 1.3 % of patients admitted to hospital with COPD are estimated to have IA (López-Campos Bodineau *et al.*, 2002; Guinea *et al.*, 2010). These assumptions do not account for corticosteroids prescribed for other conditions, and a risk of underestimation is acknowledged.

Adult asthma rates were used to estimate the incidence of both SAFS and, with additional CF data, ABPA. There will be some overlap in the patients at risk in these groups, which may lead to overestimation of the incidence of infection. In Ireland it is estimated that 11 675 patients will

develop SAFS and 8960 will have ABPA each year. The majority of patients estimated to develop these conditions are those with asthma. ABPA occurs in a higher proportion of patients with CF than with asthma and Ireland has a notably high prevalence of CF. Of 1073 patients with CF in ROI in 2011, 559 were aged 18 or older (Cystic Fibrosis Registry of Ireland, 2011). This compares to 210 adults and 188 children with CF in NI in 2011 (UK Cystic Fibrosis Registry, 2011). Of the 559 adults in ROI, we estimate that 99 currently have ABPA – which would extrapolate to a total of approximately 136 adults with CF-related ABPA in all of Ireland (Mastella *et al.*, 2000). Twenty-one adults were diagnosed with CF-related ABPA in ROI during 2011 (which would extrapolate to a total of approximately 30 new ABPA diagnoses among adults in all of Ireland).

Some countries have high rates of histoplasmosis, coccidioidomycosis, tinea capitis and fungal keratitis, but there are few resources available in the literature to give an acceptable estimate of these for the Irish population. Since these conditions are not routinely reported, neither was there accessible resource for direct calculation of these numbers in Ireland.

Most fungal infections are unreported and therefore are impossible to count in absolute numbers where possible direct measurements have been made, such as candidaemia and pneumocystis. To have an impression of the overall fungal burden in Ireland, it is necessary to make assumptions about the population from known datasets and published literature. Implicit in such an approach is uncertainty and the data derived from population-based assumptions should, by necessity, be regarded as approximations. Based on these, almost 2 % of Ireland's population will experience significant fungal disease each year. Since most of our results are extrapolated from surrogate markers of fungal infection, this model requires

validation; however, it provides a starting point for developing a standardized means of estimating the burden of disease across populations and drawing comparisons between Ireland and other countries.

The data presented estimate an unexpectedly high burden of recurrent *Candida* vaginitis, SAFS and ABPA. As more data become available on the potential impact fungal infection has on the population, both in Ireland and globally, perhaps a focus of resources in this area will allow for direct measurement of these infections and therefore a more accurate representation of their impact on global health. With the evolution of fungal diagnostic tools it should be possible to have more accurate measurements of the burden of IA and CPA in the future, which could possibly demonstrate that these data represent an under-estimation in these conditions.

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