Burden of serious fungal infections in Spain

J. L. Rodriguez-Tudela1, A. Alastruey-Izquierdo1,2, S. Gago1, M. Cuenca-Estrella1,2, C. León1, J. M. Miro4, A. Nuñez Boluda5, I. Ruiz Camps6, A. Sole7 and D. W. Denning8 The University of Manchester in association with the LIFE program at http://www.LIFE-worldwide.org

1) National Center for Microbiology, Madrid, Spain, 2) Spanish Network for the Research in Infectious Diseases (REIPI RD12/0015), Instituto de Salud Carlos III, Madrid, Spain, 3) Intensive Care Unit – Valme University Hospital, University of Seville, Seville, Spain, 4) Infectious Diseases Department, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain, 5) Department of Respiratory Medicine, 12 October University Hospital, Madrid, Spain, 6) Infectious Diseases Department Vall d’Hebron University Hospital, Barcelona, Spain, 7) Cystic Fibrosis and Lung Transplant Unit, La Fe University Hospital, Valencia, Spain and 8) The National Aspergillosis Centre, University Hospital of South Manchester and The University of Manchester, Manchester, UK

Abstract

Estimates of the incidence and prevalence of serious fungal infections, based on epidemiological data, are essential in order to inform public health priorities given the lack of resources dedicated to the diagnosis and treatment of these serious fungal diseases. However, epidemiology of these infections is largely unknown, except for candidaemia and cryptococcosis. The aim of this work is to calculate the burden of serious fungal infections in Spain. All published epidemiology papers reporting fungal infection rates from Spain were identified. 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. Around 8.1 million people suffer a fungal infection every year. Most of them are skin or mucosal infections causing no deaths. Candidaemia is more common than in other European countries and has risen by 1.88-fold in frequency in the last decade (8.1 cases × 100 000). Good estimates of invasive aspergillosis (2.75 cases × 100 000) and mucormycosis (0.04 × 100 000) are available. Fungal infections with a high mortality such as invasive aspergillosis, candidaemia, Pneumocystis pneumonia and mucormycosis are not numerous in Spain, but they affect those with severe underlying diseases and are therefore linked to poor outcomes. Additional studies are required, especially for high burden diseases such as recurrent thrush in women (~9000 cases × 100 000 women), allergic bronchopulmonary aspergillosis (126 cases × 100 000) and severe asthma with fungal sensitisation (198 cases × 100 000).

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Keywords: ABPA, aspergillosis, burden, candidiasis, cryptococcosis, fungal infections, histoplasmosis, mucormycosis, Pneumocystis pneumonia, SAFS

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Introduction

Epidemiology of fungal infections is largely unknown except for candidaemia and cryptococcosis where some population-based surveillance studies have been published [1,2]. Global estimates of cutaneous fungal infections, invasive fungal infections, chronic pulmonary aspergillosis after pulmonary tuberculosis, and sarcoidosis and allergic bronchopulmonary aspergillosis complicating asthma have recently been published [3–7]. Apart from the mildest cutaneous and mucosal fungal infections, most are serious, causing a high mortality and morbidity that increase if they are not suspected, diagnosed and treated as quickly as possible. Estimates of the incidence and prevalence of serious
fungal infections, based on epidemiological data, are essential in order to inform public health priorities given limited resources to diagnose and treat these diseases.

The aim of this work is to calculate the burden of serious fungal infections in Spain, a country with an estimated population of 47 million. Such an estimate of fungal burden has not previously been attempted in this country.

**Material and methods**

All published epidemiology papers reporting fungal infection rates from Spain were identified. 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.

2010 population statistics were derived from the Statistics National Institute (http://www.ine.es/).

Prevalence of skin fungal diseases was obtained from Vos et al. [3].

The number of women aged between 14 and 55 years was obtained from the National Statistics Institute (http://www.ine.es). A 9% rate of recurrent vulvovaginal candidiasis was used and ‘recurrent’ defined as at least four episodes per year [8].

The number of HIV/AIDS patients in Spain was taken from epidemiologic surveillance of AIDS [9,10]. The proportion of HIV-infected patients receiving antiretroviral therapy (ART) was estimated from the PISCIS cohort [11,12]. The annual new AIDS cases, the proportion of AIDS patients presenting with Pneumocystis pneumonia (PCP) or with cryptococcal meningitis and AIDS-related deaths in 2010 were obtained from the CoRIS cohort [13].

The number of pulmonary tuberculosis (PTB) cases was obtained from the National Registry [14]. Using the approach taken in Denning et al. [4], the 5-year point prevalence of chronic pulmonary aspergillosis (CPA) following PTB was estimated, assuming a 12% cavitation rate following therapy [4]. Further, it was assumed that PTB was the underlying diagnosis of CPA in 25% of cases (slightly higher than that of Smith & Denning [15], but lower than in France [16]).

The number of people with chronic obstructive pulmonary disease (COPD) was ascertained nationally [17] and a regional estimate of the number of admissions with COPD obtained from Andalusia [18], recently confirmed by the Organisation for Economic Co-operation and Development statistics [19].

Asthma rates in adults (children were not included for risk estimation) were obtained from multiple sources [20–24] and a mean of 7% of the adult population was used for estimates. The risk of allergic bronchopulmonary aspergillosis (ABPA) complicating asthma was estimated at 2.5% based on five previous studies [6]. The rate of severe asthma with fungal sensitisation (SAFS) was estimated as the worst 10% of the total asthma population, of whom at least 33% have fungal sensitisation [25].

Cystic fibrosis numbers were obtained from the European registry of the European Cystic Fibrosis Society and the Spanish Scientific Society of Cystic Fibrosis (https://www.ecfs.eu/files/webfiles/File/ecfs_registry/ECFSPR_Report0809_v32012.pdf).

Incidence and prevalence of haematological diseases were taken from Globocan 2008 (http://globocan.iarc.fr) and the Spanish Registry of Leukaemia and Lymphomas (http://www.anl.es/leucaemialinfoma.com/resources/files/f9412075-9481-479b-a8ef-81c4fd333152.pdf). Percentages of invasive aspergillosis (IA) in this population were taken from a study performed in Italy in 2004 [26]. Italy is a neighbouring Mediterranean country, and the haematological diseases figures are similar in the Globocan database (http://globocan.iarc.fr).

The rate of IA in critical care was assumed to be all attributable to COPD, and the Madrid-based study showed that 1.3% of COPD admissions developed IA in the final year, based on culture with support from serum (but not respiratory) galactomannan in a few patients [27].

The number of transplants was obtained from the Spanish National Organization for Transplantation (http://www.ont.es/). The incidence of invasive aspergillosis in solid organ-transplanted patients was taken from different studies [28–31]. PCP cases in non-AIDS patients were derived from Calderón et al. as a population estimate was provided, 3.4 cases per 100 000 [32]. Cases in AIDS patients were calculated using data obtained in the CoRIS study [13].

Candidaemia cases were estimated from a population-based surveillance study recently performed in Spain [33]. The number of critical care beds in Spain in 2010 was obtained from the intensive care units registry (http://www.msssi.gob.es/organizacion/sns/planCalidadSNS/docs/UCL.pdf); 35.1% of candidaemia cases were among patients admitted to the intensive care unit (ICU) [33]. The annual number of cases of Candida peritonitis following surgery and ratio to candidaemia was assumed to be the same as in France, as there are no data from Spain, and as it is a neighbouring country we expect the number to be similar to that in Spain [34]. Candida peritonitis complicating chronic ambulatory peritoneal dialysis was not estimated.

For mucormycosis, we used a rate of 0.43 cases per 1 million inhabitants, as previously documented [35].

The annual incidence of histoplasmosis was calculated after reviewing the records of the Mycology Reference Laboratory for the last 5 years. Most of the cases identified in Spain are diagnosed or confirmed in this laboratory [36].
Results and discussion

Country profile
Spain is a country with an estimated population of 47 million people; 49.4% are men and 15% are children <14 years old (http://www.ine.es/). The estimated number of HIV-infected patients ranged between 130,000 and 150,000 people (number set to 140,000 for calculation purposes) [10]. The number of HIV-infected patients without ARVs was estimated according to Ambrosioni et al. [12] as 44% of the total HIV population (61,600 people). Table 1 shows the total burden of fungal infections, the number of infections classified according to the main risk factors, as well as the rate for 100,000 inhabitants.

Skin fungal infections
These are the most prevalent fungal infections in Spain. Using the global prevalence of 14.3% estimated by Vos et al. [3], 6,721,000 Spanish inhabitants would have a skin fungal infection (Table 1). Recently, the Global Burden of Disease estimates [3] placed cutaneous fungal infections as the fourth most common health problem (after dental caries and headaches), with about 1 billion affected worldwide. In 2010, skin fungal diseases were estimated to lead to a mean of 2,303,000 years lived with disability (YLDs) or 33 YLDs per 100,000 inhabitants, a significant number when compared with many other infectious diseases already included in the Health Programs of International Agencies.

Mucosal infections
Recurrent vaginal thrush, defined as at least four episodes every year, is also very prevalent in Spain. As many as 1,189,238 Spanish women between 14 and 55 years of age get recurrent vaginal thrush every year (Table 1). The rate of recurrent thrush is slightly higher in those in their 20s, but continues to beyond menopause in a few women [8]. This translates into an annual incidence of ~9,000 cases per 100,000 women (Table 1).

In HIV infection, oral candidiasis is estimated to occur at least once in 90% of those without ARVs, and oesophageal candidiasis in 20% of patients without ARVs and 5% of patients on ARVs [37–39]. Therefore, 55,440 cases of oral candidiasis and 16,240 of oesophageal candidiasis are expected annually (Table 1). The number of oral or oesophageal candidiasis related with cancer or transplanted patients are unknown in Spain. There are no official records and we have found no published studies about incidence or prevalence in this setting.

Respiratory infections
In Table 2 the number of IA in allogeneic (haematopoietic stem cell transplantation) and solid organ-transplanted patients is shown. One hundred seventy-two cases of IA were estimated in allogeneic and solid organ-transplanted patients. We assumed that IA (proven and probable) occurred in 10% of haematopoietic stem cell transplantation, 6% of heart, 4% of lung and liver, and 1% of kidney-transplanted patients [31]. Much higher rates of colonisation and tracheobronchitis are found in lung transplant recipients, but we have discounted these to focus on IA only. Infrequent transplantation procedures, such as small bowel and pancreas, have also been ignored in these estimates.

Haematological diseases are another important risk factor for IA. In 2010, there were a total of 15,919 leukaemias, lymphomas, and multiple myeloma cases in Spain (http://www.leucemiaylinfoma.com/resources/files/f9412075-9481-479b-a8ef-81c4fd33152.pdf). Table 3 shows the incidence, prevalence, and the number of IA cases. The highest incidence of IA was among acute myeloid leukaemia patients, where 148 cases were estimated. IA in other haematological conditions is limited, and for some of them the incidence is unknown.

Table 1. Burden of fungal diseases in Spain according to the main risk factors

<table>
<thead>
<tr>
<th>Number of infections per underlying disorder per year</th>
<th>None</th>
<th>HIV/AIDS</th>
<th>Respiratory</th>
<th>Cancer/Tx</th>
<th>ICU</th>
<th>Total burden</th>
<th>Rate/100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal skin diseases</td>
<td>6,721,000</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6,721,000</td>
<td>14,300</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>–</td>
<td>55,440</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>55,440</td>
<td>117.96</td>
</tr>
<tr>
<td>Oesophageal candidiasis</td>
<td>–</td>
<td>16,240</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>16,240</td>
<td>34.55</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1336</td>
<td>0.02</td>
</tr>
<tr>
<td>Candida peritonitis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>668</td>
<td>0.02</td>
</tr>
<tr>
<td>Recurrent vaginal candidiasis (4+/year or more)</td>
<td>1,189,238</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1,189,238</td>
<td>9000</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>–</td>
<td>59,210</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>59,210</td>
<td>126</td>
</tr>
<tr>
<td>Severe asthma with fungal sensitisation</td>
<td>–</td>
<td>93,044</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>93,044</td>
<td>198</td>
</tr>
<tr>
<td>Chronic pulmonary aspergillosis</td>
<td>–</td>
<td>4318</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4318</td>
<td>9.19</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>–</td>
<td>–</td>
<td>419</td>
<td>674</td>
<td>874</td>
<td>1293</td>
<td>2.75</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>20</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>20</td>
<td>0.04</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>–</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>12</td>
<td>0.03</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>–</td>
<td>97</td>
<td>208</td>
<td>–</td>
<td>–</td>
<td>305</td>
<td>3.40</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>–</td>
<td>10</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>0.02</td>
</tr>
<tr>
<td>Total burden estimated</td>
<td>7,910,258</td>
<td>67,212</td>
<td>156,572</td>
<td>627</td>
<td>2878</td>
<td>8,144,605</td>
<td></td>
</tr>
</tbody>
</table>

ICU, intensive care unit.
*pRate of annual candidaemia in Spain according to a recent study [29] is 8.1 per 100,000 inhabitants, consistent with 3807 cases.
Children were not taken into account for these estimates because both ABPA and SAFS appear to be very rare in childhood. No estimate of prevalence exists, and therefore, applying the adult rates will greatly overestimate the total rates.

The annual incidence of *Pneumocystis* pneumonia according to Calderón et al. [32] is 3.4 cases per 100 000, consistent with 1598 cases annually in Spain. Most of the cases (87%) occurred in HIV-positive patients (Table 1). The CoRIS [13] cohort, a more recent study dealing only with HIV patients, showed that only 97 cases of PCP are expected in this population. One reason for the different number of cases of PCP presented in the two studies analysed [13,32] might be the time passed between them (1998–1999 vs. 2004), highlighting the need to perform epidemiologic surveillance in order to allocate the right budget to control every disease. Because of the lack of data for other non-HIV populations at risk, we have used Calderón’s rate to calculate PCP’s incidence [32].

### Candidaemia

A population-based survey performed in Barcelona in 2002–2003 [41] showed a rate of 4.3 candidaemia cases per 100 000 inhabitants. However, a more recent study [33] performed in 2010–2011 in five areas of Spain reported an annual candidaemia rate of 8.1 per 100 000 inhabitants. This means that the incidence has almost doubled in approximately 10 years. This rate is similar to the one found in Denmark (8.6 cases per 100 000 inhabitants) [1], but higher than other European countries such as Norway or Finland (3–5 cases per 100 000 inhabitants) [42,43]. In the United States, comparable rates were found in some states (6–8 cases per 100 000), while others showed higher rates, with up to 20 cases per 100 000 inhabitants [44]. As 35.1% of all candidaemias occurred in an ICU, 1336 cases are expected annually in Spain (Table 1).

There is one case of candida peritonitis for every two ICU patients with candidaemia [34], so we estimated 668 cases, most postoperative.

### TABLE 2. Burden of invasive aspergillosis in allogeneic transplanted patients and solid organ transplanted populations

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>Number of cases in 2010</th>
<th>Number of IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic HSCT</td>
<td>866</td>
<td>87</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>2225</td>
<td>22</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>235</td>
<td>9</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>243</td>
<td>15</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>971</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>4540</td>
<td>172</td>
</tr>
</tbody>
</table>

### TABLE 3. Burden of invasive aspergillosis in patients with haematological diseases

<table>
<thead>
<tr>
<th>Haematological disease</th>
<th>Incidence × 100 000</th>
<th>5-year prevalence × 100 000</th>
<th>Cases in 2010</th>
<th>% of IA</th>
<th>Annual cases of IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia</td>
<td>10.6</td>
<td>22.5</td>
<td>4982</td>
<td>7.11</td>
<td>148</td>
</tr>
<tr>
<td>Acute myeloid leukaemia + MDS</td>
<td>4.44</td>
<td>9.43</td>
<td>2088</td>
<td>3.07</td>
<td>63</td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia</td>
<td>1.14</td>
<td>2.43</td>
<td>538</td>
<td>0.87</td>
<td>13</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia</td>
<td>0.67</td>
<td>1.42</td>
<td>314</td>
<td>0.47</td>
<td>8</td>
</tr>
<tr>
<td>Chronic lymphatic leukaemia</td>
<td>3.63</td>
<td>7.7</td>
<td>1704</td>
<td>2.6</td>
<td>55</td>
</tr>
<tr>
<td>Other acute leukaemiasa</td>
<td>0.21</td>
<td>0.45</td>
<td>100</td>
<td>0.27</td>
<td>5</td>
</tr>
<tr>
<td>Unclassifiedb</td>
<td>0.51</td>
<td>1.08</td>
<td>239</td>
<td>0.27</td>
<td>–</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>6.47</td>
<td>15.31</td>
<td>3041</td>
<td>0.27</td>
<td>84</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>2.50</td>
<td>8</td>
<td>1175</td>
<td>0.31</td>
<td>34</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>14.30</td>
<td>38</td>
<td>6721</td>
<td>0.81</td>
<td>167</td>
</tr>
<tr>
<td>Total</td>
<td>15 919</td>
<td>247</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IA, invasive aspergillosis; MDS, myelodysplastic syndrome.


bPagano et al. [26].

cOther acute leukaemias include: acute biphenotypic, T granular cells, mast cell, NK cells.
Other fungal infections

Of the 130,000–150,000 estimated HIV-positive patients, 12 (0.8%) of 1500 new AIDS cases each year develop cryptococcal meningitis [13]. Other cases of cryptococcal meningitis occur, but we have no reliable means to estimate this. For mucormycosis, a Spanish study found an incidence rate of 0.04 cases per 100,000 inhabitants that suggests 20 cases every year [35]. However, in France, a neighbouring country, the incidence recently found was 0.12 cases per 100,000 inhabitants. For histoplasmosis, incidence can be estimated in 10 new cases per year [36].

Conclusions

The epidemiology and burden of most fungal infections in Spain is well documented for many infections. Candidaemia is more common than in other European countries and has risen by almost twofold in frequency in the last decade. Good estimates of PCP, invasive aspergillosis complicating COPD, recurrent vulvovaginal candidiasis and mucormycosis have also been determined in Spain, although in some cases the data are old and some discrepancies in the number of cases between studies were found. Clearly, additional studies are required, especially for high burden diseases such as APBA and SAFS. Globally there are 350,000 asthma deaths, most in adults, and many of these will be in those with SAFS [3]. The underlying disease profile of sequentially diagnosed chronic pulmonary aspergillosis and annual mortality would be helpful in determining the national burden of this debilitating disease.

Apart from cutaneous fungal infections and Pneumocystis pneumonia, most fungal infections are not transmitted from person to person. Most are acquired from the environment or, in the case of Candida, from endogenous (gut) flora. Most pathogenic fungi are therefore unavoidable. No vaccines are available.

As no fungal infection is considered notifiable, the current records rely on epidemiologic studies performed in one or more institutions. However, for many fungal diseases, the rates have been calculated based on the frequency of fungal infections in patients at risk. In addition, there is no information about YLDs for fungal disease that is usually not fatal, a crucial parameter in the promotion and monitoring of health.

Around 8.1 million people suffer a fungal infection in Spain every year. Most of them are skin or mucosal infections causing no deaths. However, the number of YLDs of skin fungal infections is a matter of concern. Fungal infections with a high mortality, such as IA, candidaemia, PCP and mucormycosis, are not numerous in Spain (6718 annual cases), but they affect those with severe underlying diseases and are therefore linked to poor outcomes.

LIFE (www.LIFE-worldwide.org) has launched an initiative in many countries to calculate the burden of fungal diseases following a similar approach. We will obtain some preliminary data in order to ascertain the public health importance of fungal diseases in many of these countries. This will facilitate the undertaking of better epidemiologic studies, which will inform public health priorities. Currently, inadequate resources are applied to most fungal infections and so could be considered “neglected diseases,” although they are not currently designated as such.

As a matter of concern, it is estimated that worldwide deaths attributed to fungal infections (＞1 350 000) [5] are as high as those of tuberculosis (1 400 000) and malaria (1 240 000) [45], two priority diseases on the global health agenda.

Transparency declaration


C.L. received research grants and/or educational grants and/or speaker’s honoraria and/or consultant’s honoraria from (in alphabetic order): Astellas, Merck and Pfizer.

J.M.M. has received consulting honoraria and/or research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Cubist, Novartis, Glaxo Smith Kline, Gilead Sciences, Pfizer, Roche, Theravance and ViiV.

D.W.D. holds founder shares in F2G Ltd, a University of Manchester spin-out company, and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, The European Union and AstraZeneca. He acts as a consultant to Trinity group, T2 Biosystems, and GSK, as well as other companies over the last 5 years, including Pfizer, Schering Plough (now Merck), Astellas and Gilead. In the last 3 years, he has been paid for talks on behalf of Gilead Sciences, Merck Sharp and Dohme, Pfizer, Astellas Pharma and Schering Plough.

The other authors declare no conflicts of interest.

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