Burden of serious fungal infections in Spain

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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).

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

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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 (ARV) 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/webfm/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.leucemiaylinfoma.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/infesp/Paginas/Memorias.aspx). 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/UCI.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 20 s, but continues to beyond menopause in a few women [8]. This translates into an annual incidence of ~9000 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-81c4fd333152.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 the main risk factors

	Number of infections per underlying disorder per year						
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU	Total burden	Rate /100 K
Fungal skin diseases	6 721 000	–	–	–	–	6 721 000	14 300
Oral candidiasis	–	55 440	–	–	–	55 440	117.96
Oesophageal candidiasis	–	16 240	–	–	–	16 240	34.55
Candidaemia	–	–	–	–	1336	3807[a]	8.1
Candida peritonitis	–	–	–	–	668	668	1.42
Recurrent vaginal candidiasis (4×/year or more)	1 189 238	–	–	–	–	1 189 238	9000
Allergic bronchopulmonary aspergillosis	–	–	59 210	–	–	59 210	126
Severe asthma with fungal sensitization	–	–	93 044	–	–	93 044	198
Chronic pulmonary aspergillosis	–	–	4318	–	–	4318	9.19
Invasive aspergillosis	–	–	–	419	874	1293	2.75
Mucormycosis	20	–	–	–	–	20	0.04
Cryptococcal meningitis	–	12	–	–	–	12	0.03
Pneumocystis pneumonia	–	97	–	208	–	305	3.40
Histoplasmosis	–	10	–	–	–	10	0.02
Total burden estimated	7 910 258	67 212	156 572	627	2878	8 144 605	

ICU, intensive care unit.
[a]Rate of annual candidaemia in Spain according to a recent study [29] is 8.1 per 100 000 inhabitants, consistent with 3807 cases.

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

Underlying disease	Number of cases in 2010	Number of IA
Allogeneic HSCT	866	87
Renal transplant	2225	22
Lung transplant	235	9
Heart transplant	243	15
Liver transplant	971	39
Total	4540	172

HSCT, haematopoietic stem cell transplantation; IA, invasive aspergillosis.

(Table 3). In 2010, at least 247 cases were estimated (Table 3). Therefore, in transplanted and haematological disease patients, a total of 419 cases of IA are expected annually.

Finally, in critical care, 874 cases were calculated, most with COPD. It was assumed that 1.3% of COPD cases admitted to a hospital have or develop IA, based on a prospective study from Madrid [18]. Other conditions associated with IA in this setting, such as severe hepatic or autoimmune disease, have been ignored for these estimates, although a recent study from Hangzhou documented a 5% IA rate in acute-on-chronic hepatic failure [40].

Among the causes of CPA are COPD, sarcoidosis, ABPA, prior pneumothorax, rheumatoid arthritis, PTB and non-tuberculous mycobacterial infection. PTB is an infrequent cause of CPA in Europe. In 2010, there were 5351 cases of PTB in Spain, most in HIV-negative people; 342 new cases of CPA are expected annually, with a 5-year period prevalence of 1079 cases (assuming 15% annual mortality or surgical resection). Taking into consideration the other more frequent causes of CPA cases, such as COPD, sarcoidosis, ABPA, prior pneumothorax, rheumatoid arthritis and nontuberculous mycobacterial infection [15], a total of 4318 total CPA cases are estimated, assuming that PTB patients account for only 25% of CPA cases (Table 1).

Estimates of asthma prevalence in adults are between 5% and 8%, and assuming that 2.5% of asthmatics have ABPA, 59 210 adults with ABPA are likely, and 93 044 with SAFS (Table 1). 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 3. Burden of invasive aspergillosis in patients with haematological diseases

Haematological disease	Incidence × 100 000[a]	5 year prevalence × 100 000[a]	Cases in 2010	% of IA[b]	Annual cases of IA
Leukaemia	10.6	22.5	4982		
Acute myeloid leukaemia + MDS	4.44	9.43	2088	7.11	148
Acute lymphoblastic leukaemia	1.14	2.43	538	3.87	21
Chronic myeloid leukaemia	0.67	1.42	314	2.07	6
Chronic lymphatic leukaemia	3.63	7.7	1704	0.36	6
Other acute leukaemias[c]	0.21	0.45	100	?	–
Unclassified[c]	0.51	1.08	239	?	–
Multiple myeloma	6.47	15.31	3041	0.27	8
Hodgkin lymphoma	2.50	8	1175	0.31	4
Non-Hodgkin lymphoma	14.30	38	6721	0.81	54
Total			15 919		247

IA, invasive aspergillosis; MDS, myelodysplastic syndrome.
[a]Globocan 2008 (http://globocan.iarc.fr).
[b]Pagano *et al.* [26].
[c]Other 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

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The other authors declare no conflicts of interest.

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