

Burden of serious fungal infections in Spain

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Abstract

Introduction: Spain has an estimated population of 47 million people. We have estimated the number of serious fungal infections to define the burden in Spain. **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. HIV/AIDS, tuberculosis, transplant and cystic fibrosis cases (2010) were obtained from the relevant registries. COPD cases from Miratvilles et al. Thorax 2009; 64: 863-8, PCP cases from Calderón et al. Clin Microbiol Infect 2004; 10: 673-6 and candidaemia cases from M. Puig et al. Abstract O110. Clin Microbiol Infect 2012; 18 (s3): 1-113. **Results:** 40.5% of the 47 M population are adults, 21% women and 14% children below 14 years. 22% of population are >60 years old. Estimates are: 822,094 Spanish women get recurrent vaginal thrush. Of the 5351 cases of TB in 2010, most in HIV negative people, it is estimated that 342 new cases of chronic pulmonary aspergillosis (CPA) occurred and that the 5-year period prevalence is 1,079 cases (assuming 15% annual mortality). As total CPA cases as COPD etc., are more frequent, 4,318 total CPA cases are estimated. Estimates of asthma prevalence in adults are between 5-8% and assuming 2.5% of asthmatics have ABPA, 59,210 patients with ABPA are likely and 93,044 with SAFS. Of the 150,000 estimated HIV positive patients, 15 (1%) of 1,500 new AIDS cases each year develop cryptococcal meningitis. Annual incidence of Pneumocystis pneumonia is 3.4 cases/100,000 consistent with 1,598 cases (87% in HIV+ patients). In HIV infection, oral candidiasis is estimated to occur at least once in 90% of those with low CD4 counts (33,750 cases), and oesophageal candidiasis in 20%. The rate of candidemia in Spain is 10.7/100,000 inhabitants consistent with 5,029 cases. There is one case of candida peritonitis for every 2 ICU patients with candidaemia. Invasive aspergillosis in immunocompromised patients is estimated at 1,346 patients annually including 874 cases in critical care, many with COPD. For mucormycosis, the general rate of 2/1,000,000 suggests nearly 100 cases annually. For histoplasmosis, incidence can be estimated in 10 new cases per year. **Conclusion** Using local data and literature estimates of the incidence or prevalence of fungal infections, almost 1 M (2.12%) people in Spain suffer from a fungal infection each year. These figures are dominated by recurrent vaginitis. Substantial uncertainty surrounds these estimates except for candidaemia and PCP figures where recent population-based surveillance studies exist. Therefore, epidemiological studies are urgently required to validate or modify these estimates.

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

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 Voss et al. (1). Number of women between 14 and 55 years was obtained from National Statistics Institute. A 5% rate was assumed to have recurrent vaginal candidiasis (4 or more episodes per year). The number of HIV/AIDS patients from epidemiologic surveillance of AIDS in Spain (2). Proportion of diagnosed cases on ARVs, number of cases diagnosed not receiving ARVs, annual new AIDS cases (at risk of OIs), proportion of AIDS patients presenting with Pneumocystis pneumonia (PCP), proportion of AIDS patients presenting with cryptococcal meningitis and AIDS-related deaths in 2010 were obtained from Caro-Murillo et al (3). Number of tuberculosis cases from the National Registry (4). Using the approach taken in Denning et al (5) the 5-year point prevalence of chronic pulmonary aspergillosis (CPA) following tuberculosis, assuming a 12% cavitation rate following therapy. It was assumed that tuberculosis (TB) was the underlying diagnosis of CPA in 25% of cases. The number of people with chronic obstructive pulmonary disease (COPD) was ascertained nationally (6) and a regional estimate of the number of admissions with COPD obtained from Andalucía (7), recently confirmed by the OECD statistics (8). Asthma rates in adults were obtained from multiple sources and a mean of 7% of the adult population was used for estimates. The risk of allergic bronchopulmonary aspergillosis (ABPA) was estimated at 2.5% based on 5 previous studies (9). The rate of SAFS was estimated as the worst 10% of the total asthma population of whom at least 33% have fungal sensitisation (10). Cystic fibrosis numbers were obtained from the European registry of ECFS and Spanish Scientific Society of Cystic Fibrosis. Incidence and prevalence of haematological diseases were taken from Globocan 2008 (<http://globocan.iarc.fr>) and Spanish Registry of Leukaemia and Lymphomas (11). Percentages of invasive aspergillosis (IA) in this population were taken from a study performed in Italy in 2004 (12). Italy is a neighbour Mediterranean country and the haematological diseases figures are similar in 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 (13). The number of transplants was obtained from the Spanish National Organization for Transplantation (<http://www.ont.es/infesp/Paginas/Memorias.aspx>). PCP cases were derived from Calderón et al. (14). Candidaemia cases were estimated from a population-based surveillance study recently performed in Spain (15) It was assumed that 33% of all candidaemias occurred in ICU, and the annual number of cases of Candida peritonitis and ratio to candidaemia was assumed to the same as in France (16). The number of critical care beds in Spain in 2010 was obtained from Intensive care units (17). For mucormycosis, it was used 0.43 cases/1 million of inhabitants (18). The annual incidence of histoplasmosis was calculated after reviewing the records of the Mycology Reference Laboratory for the last five years. Most of the cases happening in Spain are diagnosed or confirmed in this laboratory (19).

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Results

Country profile: Spain is a country with an estimated population of 47 millions of people. Of them, 40.5% are adults, 21% women and 14% children are under the age of 14 (<http://www.ine.es/>). Table 1 shows the total burden of fungal infections, the number of infections classified according the main risk factors as well as the rate for 100,000 inhabitants.

Skin fungal infections: The most prevalent fungal infection in Spain. According to the global prevalence of 14,3% estimated by Voss et al (1), 6,721,000 Spanish inhabitants would have a skin fungal infection. The Global Burden of Disease estimates (1) placed cutaneous fungal infections as the 4th most common health problem with about 1,000 million affected. In 2010, skin fungal diseases produce a mean of 2,303,000 years live with disability (YLDs) or 33 YLDs x 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 is also very prevalent in Spain. 660,688 Spanish women (between 14 and 55 years) get recurrent vaginal thrush every year. This means an annual incidence of 5,000 cases x 100,000 women. In HIV infection, oral candidiasis is estimated to occur at least once in 90% of those with low CD4 counts (33,750 cases), and oesophageal candidiasis in 20%. Therefore, 67,500 cases of oral candidiasis and 11,250 of oesophageal candidiasis are expected annually.

Respiratory Infections: In table 2 the number of IA in allogeneic and solid organ transplanted patients is shown. Table 3 shows the incidence, prevalence, and the number of IA cases. In 2010, at least 247 cases were estimated. Therefore, in transplanted and haematological diseases patients a total of 408 cases of IA are expected annually. 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 (7). Among the causes of CPA are COPD, sarcoidosis, ABPA, prior pneumothorax, rheumatoid arthritis, TBC and non-tuberculous mycobacterial infection. TBC is an infrequent cause of CPA. In 2010, there were 5,351 cases of TBC in Spain most in HIV negative people, thus, 1,338 cases of chronic pulmonary aspergillosis related with TBC were expected. As it is estimated that 342 new cases of CPA occurred, the 5-year period prevalence is 1,079 cases (assuming 15% annual mortality). Taking in consideration the other more frequent causes of CPA cases such as COPD, sarcoidosis, ABPA, prior pneumothorax, rheumatoid arthritis and non-tuberculous mycobacterial infection (20), a total of 4,318 total CPA cases are estimated. Estimates of asthma prevalence in adults are between 5-8% and assuming 2.5% of asthmatics have ABPA, 59,210 patients with ABPA are likely and 93,044 with SAFS. Annual incidence of Pneumocystis pneumonia is 3.4 cases/100,000 (14) consistent with 1,598 cases. Most of the case (87%) occurred in HIV+ patients.

Candidemia: The rate of annual candidemia in Spain is 10.7/100,000 inhabitants consistent with 5,029 cases (15). Previous study performed in Barcelona (21) showed a rate of 4,3 cases/100,000 inhabitants. This means that the incidence has doubled in approximately 10 years.

Other fungal infections: Of the 150,000 estimated HIV positive patients, 15 (1%) of 1,500 new AIDS cases each year develop cryptococcal meningitis (3). For mucormycosis, a Spanish study found an incidence rate of 0.04 cases/100,000 inhabitants that suggests 20 cases every year (18). For histoplasmosis, incidence can be estimated in 10 new cases per year (19).

	Number of infections per underlying disorder per year					Total burden	Rate /100K
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU		
Fungal skin diseases	6,721,000	-	-	-	-	6,721,000	14,300
Oral candidiasis	-	67,500	?	?	-	67,500	143
Oesophageal candidiasis	-	18,750	-	?	-	18,750	39,89
Candidaemia	-	-	-	1,886	3,143	5,029	10,70
Candida peritonitis	-	-	-	-	588	588	1,25
Recurrent vaginal candidiasis (4x/year or more)	660,688	-	-	-	-	660,688	1,406
Allergic bronchopulmonary aspergillosis	-	-	59,210	-	-	59,210	126
Sever asthma with fungal sensitization	-	-	93,044	-	-	93,044	198
Chronic pulmonary aspergillosis	-	-	4,318	-	-	4,318	9,18
Invasive aspergillosis	-	-	-	408	874	1,282	2,73
Mucormycosis	20	-	-	-	-	20	0,04
Cryptococcal meningitis	-	15	-	-	-	15	0,03
Pneumocystis pneumonia	-	1,390	-	208	-	1,598	3,40
Histoplasmosis	?	10	-	?	-	10	0,02
Fungal keratitis	?	-	-	-	-	-	-
Total burden estimated	7,381,708	87,665	156,572	2,502	4,605	7,633,052	16,240

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

Underlying disease	Number of cases in 2010	Number of IA
Allogeneic HSCT	866	87
Renal Transplant	2225	11
Lung Transplant	235	9
Heart Transplant	243	15
Liver Transplant	971	39
Total	4,540	161

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

Haematological disease	Incidence x 100,000 ¹	5 year prevalence x 100,000 ¹	Cases in 2010	% of IA ²	Annual cases of IA
Leukaemia	10.6	22.5	4,982		
Acute Myeloid Leukaemia + MDS	4.44	9.43	2,088	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 Laeukemias ³	0.21	0.45	100	?	--
Unclassified ⁴	0.51	1.08	239	?	--
Multiple Myeloma	6.47	15.31	3,041	0.27	8
Hodking lymphoma	2.50	8	1,175	0.31	4
Non-Hodking lymphoma	14.30	38	6,721	0.81	54
Total			15,919		

Table 3. Burden of invasive aspergillosis in patients with haematological diseases
¹ Globocan 2008; ² Pagano et al (12); ³ Other Acute Laeukemias include: acute biphenotypic, T granular cells, Mast cell, NK cells

Conclusions

- Epidemiology of fungal infections in Spain is uncertain with an exception, candidemia where two population-based studies have been performed in the last decade.
- 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 are therefore unavoidable. No vaccines are available.
- As none fungal infection is considered modifiable the current records rely on epidemiologic studies performed for different institutions but in many cases, the rates have been calculated based on the frequency of fungal infections in patients at risk. In addition, there is no information about YLDs that fungal infection causes a crucial parameter in the promotion and monitoring of health.
- Around 7,6 million of people suffer a fungal infection 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 consideration.
- Fungal infections with a high mortality as IA or candidemia are not numerous in Spain (6311 annual cases) but they affect a population with severe underlying diseases that worsen the outcome of the patient.
- LIFE (www.LIFE-worldwide.org) has launched an initiative in many countries in order 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 countries what facilitates the performance of better epidemiologic studies that allow allocate the right resources for this group of infections that are not even considered as "neglected diseases".
- We have estimated that worldwide deaths attributed to fungal infections (1,350,000) are as high as those produce by tuberculosis (1,400,000) and malaria (1,240,000) (20), two priority diseases in the global health agenda.