

An estimate of the burden of serious fungal diseases in Greece

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Abstract Data on the epidemiology of serious fungal infections in Greece are scarce. Our aim was to calculate the burden of serious fungal diseases in Greece. A thorough literature search for papers reporting epidemiological data on serious fungal diseases in Greece was performed. Where no Greek data existed, we used a structured set of assumptions to estimate fungal disease burden, based on specific high-risk populations. Of the 10.8 million population, 85.5 % are adults and 27 % are over 60 years of age. The annual fungal disease estimates are as follows: 142,337 Greek women get recurrent vaginal thrush (2,632 cases/100,000 females); there are 889 cases of esophageal candidiasis (8.2 cases/100,000); annual incidence of *Pneumocystis* pneumonia is 112 cases; chronic pulmonary aspergillosis prevalence is 386 cases; there are 20,843 patients with allergic bronchopulmonary aspergillosis and 27,744 with severe asthma with fungal sensitization; candidaemia incidence is 541 cases (5.0/100,000); there are 81 cases of *Candida* peritonitis; invasive aspergillosis occurs in 1,125 patients. According to our calculations, 194,067 individuals (1.79 cases/100,000) in Greece suffer from serious

fungal diseases each year. This is the first attempt to determine the burden of fungal diseases in Greece, and provides a crude estimate on its impact on public health.

Fungal diseases · Burden · Epidemiology · Greece

Introduction

Fungal infections constitute a growing global problem that is difficult to calculate in terms of prevalence and mortality, while their impact on public health and economy, especially in resource-deprived countries, is largely unknown [1]. With the exception of the frequent mild cutaneous and mucosal fungal infections, most are serious, associated with high morbidity and mortality, since they are notoriously difficult to diagnose, and lethal if not treated promptly [2].

Epidemiological data on fungal infections are scarce, due to the lack of surveillance systems and population-based epidemiological studies, and vary by locality and medical practice. Under-reporting is common, because superficial fungal infections are diagnosed and treated by general practitioners, while the majority of invasive fungal infections run undiagnosed, due to the lack of effective diagnostic modalities. Recently, researchers have published global estimates of cutaneous fungal infections, invasive fungal infections, chronic pulmonary aspergillosis following pulmonary tuberculosis and sarcoidosis, and allergic bronchopulmonary aspergillosis complicating asthma [1–5]; however, these data are crude estimates that need validation in multiple epidemiology studies.

The aim of this study was to calculate for the first time the burden of fungal infections in Greece, a country with an estimated population of 10.8 million, as part of a multi-national project that attempts to collect estimates from several countries worldwide, in order to provide a global assessment of

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fungal infection. Estimates of the incidence and prevalence of serious fungal diseases are essential in order to raise awareness and design proper public health interventions to prevent them, given the limited modalities for their diagnosis and treatment.

Methods

We used a template provided by the Leading International Fungal Education- LIFE program [www.LIFE-worldwide.org] that included demographic data and specific disease-related information, as described previously [6–8]. We performed a thorough literature search for papers reporting epidemiological data on serious fungal infections in Greece, by using the Medline, Google Scholar, and Scopus online databases. After an initial series of reports was reviewed, individual references listed in each publication were again reviewed for ascertainment of additional epidemiological studies. For fungal diseases where no Greek data existed, we used a structured set of assumptions to estimate their burden, based on specific populations with risk factors for fungal infection, such as immunosuppression, chronic disease, intensive care unit (ICU) admission, and surgical procedures. The template we used involved extrapolated estimates of fungal infection from published data across many countries.

Population statistics were derived from the Hellenic Statistical Authority (ELSTAT) and the latest (2011) population census (<http://www.statistics.gr/portal/page/portal/ESYE/PAGE-census2011>). The number of adult women (age > 14 years) and pre-menopausal women aged between 14 and 55 years was obtained from the same source.

Data on HIV/acquired immune deficiency syndrome (AIDS) (2014) were obtained from the Hellenic Centre for Disease Control and Prevention (KELPNO) (<http://www.keelpno.gr>); the same source was used to calculate the proportion of HIV-infected patients receiving antiretroviral therapy (ARV), and the proportion with AIDS. The annual number of new AIDS cases and the proportion of AIDS patients presenting with *Pneumocystis jirovecii* pneumonia (PCP) or with cryptococcal meningitis was obtained from KELPNO.

Transplantation data (2012) were received from the Hellenic Transplant Organization (<http://www.eom.gr>). Tuberculosis (TB) data (2012) were derived from the World Health Organization (www.who.int/tb/publications/global_report/en); data on chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), asthma, and abdominal surgeries from the relevant scientific Greek Societies; and data on the number of critical care beds and hospital admissions from the Greek Ministry of Health (<http://www.moh.gov.gr>).

Results and discussion

The population of Greece is 10,816,286 inhabitants, of whom 53 % are women, 14.5 % are children under 16, and 27 % are older than 60; 40.3 % of women are over 50, and 27.4 % are over 60 years. The number of annual abdominal surgeries is approximately 55,000. Approximately 80,000 patients with COPD are admitted to Greek hospitals annually, for a rate of 1.4 admissions per 100 persons >40 years old. In Greece, there are annually approximately 324 patients with a new diagnosis of acute myeloid leukemia (AML), while the incidence of all leukemias is 66/100,000 population [9]. With regard to transplantations in 2012, there were 153 allogeneic hematopoietic stem-cell transplantations (HSCT), and 171 renal, 18 heart and 47 liver transplantation procedures done. Nationally, the number of critical care beds is 542. The estimates of serious, non-superficial, fungal infections and other fungi-related medical conditions in Greece are displayed in Table 1, giving absolute numbers and rates per 100,000 population (Table 1).

Vulvovaginal candidiasis (VVC) is very common among women worldwide. Multiple recurrences cause considerable distress to patient and physician alike. If four or more acute episodes occur in a 12-month period, the woman is considered to have recurrent VVC (RVVC). We included rVVC in the severe fungal infections because it compromises the quality of women's life, as it is associated with increased depression and anxiety [10]. The estimated incidence of RVVC in adult women ranges between 5 % and 9 % per year in different countries [11–13]. An internet-based survey in five European countries and the USA found an incidence rate of 9 % [14]. The only relevant study from Greece [15] found that among 4,743 women with signs and symptoms of vaginal infection attending the outpatient clinic of the Obstetrics and Gynaecology Department of a large tertiary care hospital, the rate of RVVC was 8.5 %. However, these data cannot be extrapolated to the general population, because this is a selective population of symptomatic women attending a referral clinic, probably after failure of over-the-counter medicines or medicines prescribed by their family physician. Moreover, >85 % of that study population were pre-menopausal, while according to the latest census 40 % of the women in Greece are older than 50 years. Therefore, we took a conservative approach and adjusted to the lower rate reported in the literature, 5 % of adult (>14 years) pre-menopausal women. By using this assumption, we estimated that 142,337 Greek women get recurrent vaginal thrush per year, or 2,632 cases per 100,000 females.

The cumulative number of reported HIV infections (including AIDS cases) in Greece by 31/12/2014 was 14,434, and the cumulative number of deaths was 1,862. Thus, on January 1, 2015, in Greece there were 12,575 persons living with HIV in Greece, 1,732 of whom were not receiving ARV. In most populations, it is assumed that 90 % of patients with HIV

Table 1 Burden of fungal diseases in Greece according to major risk factors

Disease	Number of infections per underlying disorder per year					Rate/ 100,000	Total burden
	None	HIV/AIDS	Respiratory	Cancer/ chemotherapy	ICU		
Oesophageal candidiasis	–	889	–	–	–	8.2	889
Candidaemia	–	–	–	379	162	5.0	541
<i>Candida</i> peritonitis	–	–	–	–	81	0.8	81
Recurrent vaginal candidiasis (4x/year +)	142,337	–	–	–	–	2,632 ^a	142,337
Allergic bronchopulmonary aspergillosis	–	–	20,843	–	–	193	20,843
Severe asthma with fungal sensitization	–	–	27,744	–	–	256.5	27,744
Chronic pulmonary aspergillosis	–	–	386	–	–	3.66	386
Invasive aspergillosis	–	–	–	85	1,040	10.4	1,125
Mucormycosis	–	–	–	7 ^b	–	0.06	7
Cryptococcal meningitis	–	2	–	–	–	0.02	2
<i>Pneumocystis</i> pneumonia	–	28	–	84	–	1	112
Total burden estimated	142,337	919	48,973	555	1283	1.79	194,067

^a Rate of recurrent candida vaginitis is per 100,000 females. ^b also diabetes mellitus, major trauma, and other immunodeficiencies. ICU: intensive care unit

who are not being treated with ARV will develop oral candidiasis and also that 20 % of patients with HIV not taking ARV and 5 % of those taking ARV develop oesophageal candidiasis [16, 17]. By adopting these assumptions, we estimated that there are 1,559 cases of oral candidiasis and 889 cases of esophageal candidiasis in Greece. However, these numbers are an underestimate, as oropharyngeal and oesophageal candidiasis occur in multiple other patients, such as immunocompromised patients after chemotherapy, but an estimate is not possible.

In 2014, 107 new AIDS cases were diagnosed in Greece, and in 28 (26.2 %) cases the presenting diagnosis was PCP. The calculated burden of PCP in Greece based only in patients with HIV infection is an underestimation because there are no data on the incidence of PCP on other high-risk populations, such as patients receiving corticosteroids or other immunosuppressive therapy for autoimmune or neoplastic diseases or transplant recipients. Indeed, in a recent retrospective, single-centre study, 62 adult HIV-negative patients with PCP were hospitalized at the University Hospital of Heraklion, Crete, Greece during a 10-year period (2004–2013) [18]. A recent study in Belgium [19] found that HIV accounts for only 14 % of all PCP cases. Based on clinical experience, we preferred to use for our calculations data from Ireland, a country with similar socioeconomic status, reporting that HIV infection accounts for 25 % of PCP infections [20]. By adopting this assumption, we calculated that 84 additional cases of PCP occur annually in non-HIV infected patients with other underlying diseases, making a total of 112 cases of PCP annually, corresponding to 1/100,000 population.

There are case reports from Greece describing HIV-infected patients with cryptococcal meningitis [21–23], but

no epidemiological data exist. Therefore, by using the LIFE template, we calculated that two (2 %) of 107 new AIDS cases each year develop cryptococcal meningitis. However, this may again be a slight underestimation, as there are Greek reports of cryptococcal meningitis in non-HIV infected patients [24, 25].

There were 557 cases of TB notified in 2012 in Greece, 45 with AIDS. It is expected that an average of 12 % of patients with pulmonary (PTB) will have residual cavitory lung lesions [26]. It is assumed that 22 % of patients with lung cavities, and 2 % of those without cavities, following TB will develop chronic pulmonary aspergillosis (CPA) [4]. Following these assumptions, it is estimated that 25 new cases of CPA have occurred and that the 5-year period prevalence is 77 cases (assuming 15 % annual death and/or surgical excision rate). Patients with PTB are only 25 % of the total annual number of CPA cases due to other conditions such as COPD, sarcoidosis, allergic bronchopulmonary aspergillosis (ABPA), prior pneumothorax, rheumatoid arthritis, and non-tuberculous mycobacterial infection [26]. Therefore, by using the national PTB figures, a total of 386 CPA cases from any cause are estimated, or a rate of 3.66/100.000 populations.

In a population-based, multiregional, cross-sectional descriptive study conducted in 2004, the overall prevalence of COPD among 888 randomly identified adult Greeks, aged >35 years with a smoking history of >100 cigarettes per lifetime was 8.4 % [27]. In another study conducted in 2005, among 6,112 subjects aged 21–80 years, from three regions of northern Greece, the prevalence of COPD was 5.6 % [28]. According to a more recent nation-wide, cross-sectional, community-based survey of asthma conducted by the Hellenic Thoracic Society, the prevalence of physician -

diagnosed asthma in adults was 9 %, in accordance with similar international studies [29]; therefore, adults living with asthma in Greece are estimated to be 832,313. Adults suffering from CF are estimated to be 195, according to the Hellenic Cystic Fibrosis Association (<http://www.cysticfibrosis.gr>). ABPA figures were determined by assuming rates of 2.5 % among adult asthmatics and 17.7 % among adult CF patients [3, 30, 31]. According to these assumptions, the number of patients with ABPA in Greece is 20,843 (20,808 with asthma and 35 with CF), accounting for a rate of 193/100,000 population. For severe asthma with fungal sensitisation (SAFS) the assumption is that among asthmatics with most severe disease (10 % of adult asthma patients), one-third will be sensitised to fungi and amenable to antifungal therapy [32]. Similar data have been reported from Greece; a positive skin reaction to fungal spores was observed in 421 (32 %) of the 1311 asthmatics, in Thessaloniki between 1990–2001 [33]. Positive skin reaction to *Alternaria* species was observed in 177 patients (13.5 %), to *Cladosporium* in 98 (7.4 %), to *Aspergillus* in 65 (5 %), to *Fusarium* in 45 (3.4 %) and to *Rhizopus* in 36 (2.7 %) patients. Therefore, it is likely to have 27,744 Greek patients with SAFS (256.5 cases per 100,000). There is probably some duplication between ABPA and SAFS because all ABPA patients are sensitised to *Aspergillus*, and some have severe asthma. Moreover, SAFS patients may be sensitised to other fungi, as well.

With regard to candidaemia, there are two studies from Greece assessing its frequency in specific populations. In the first prospective study, there were 24 cases of candidemia among 1,627 admitted patients in a 25-bed, medical–surgical ICU over a 2-year period (2000–2002) [34]. In a similar ICU study, there were 33 cases among 855 patients [35]. In another population-based, prospective, multicentre study of patients ≥ 18 years admitted to haematology and/or haematopoietic stem cell transplantation units of nine tertiary care Greek hospitals from January 2009 through to February 2012, candidaemia was detected in 40 of 27,864 patients with haematological malignancies, vs 967 of 1,158,018 non-haematology patients. The incidence was 1.4 cases/1000 admissions vs 0.83/1000 admissions respectively [36]. There are no Greek studies of candidaemia in the general population, but the above-mentioned figures allow us to assume that the rate of candidaemia in Greece is similar to that reported in other countries (5.0/100,000 population); therefore, we calculated 541 cases of candidemia — 379 in immunocompromised patients and 162 in ICU and surgery patients. By making the assumption that the rate of candida peritonitis is half the rate of candidemia among patients with abdominal surgery [37], we have estimated 81 cases of post-surgical *Candida* peritonitis.

With regard to invasive aspergillosis (IA), two studies have shown that its incidence is similar among all non-AML haematological conditions combined and AML patients [38, 39]. In a Greek prospective, single-centre study the incidence of IA

was 3.2 cases per 100 patients admitted with hematological malignancies [40], similar to that found in two other European countries [38, 39]. Therefore, we used for our calculations assumptions based on these studies. In AML, the incidence of IA is approximately 10 %, and in allogeneic HSCT is 8 % [38, 39]. IA is also associated with solid organ transplantation; we assumed that IA occurred in 6 % of heart-, 4 % of lung- and liver-, and 1 % of kidney-transplanted patients [41]. Our calculations, by using these assumptions, give an estimate of 85 cases of IA in non-ICU immunosuppressed patients. We also have estimated a further 1,040 cases of IA, mainly due to COPD as the underlying diagnosis, since according to studies from Spain 1.3 % of patients admitted to hospital with COPD are estimated to have IA [42, 43]. This approach is rather conservative, as a recent retrospective study from China showed that 3.6 % of COPD patients had IA [44]. We have placed COPD patients in the ICU category, although some will not be transferred to ICU. The unexpectedly high estimate of IA cases reflects the under-diagnosis of this dreadful disease among COPD patients, and underlines the need for increased awareness among respiratory medicine physicians. The disease should be actively sought and treated.

For mucormycosis, according to a multicentre, nationwide and ongoing study [45], 71 confirmed cases have been registered from January 2005 to December 2014, giving an annual incidence of 7 cases. Most of these infections occurred in patients with haematological malignancies (44 %); 17 % occurred in patients with diabetes mellitus, and 24 % in immunocompetent individuals complicating severe trauma. The crude mortality was 55 %. There are 51 additional non-registered cases published since 1984, with a stable rate of seven cases per year since 1999.

According to our estimates, 194,067 people (1.79 cases/100,000) in Greece suffer from serious fungal infections each year. Our study has limitations, as there are no population-based, epidemiological studies in Greece on the incidence of fungal infections. The total burden of fungal infections is certainly higher than the number calculated here, because frequent fungal infections, such as skin, hair, or nail infections and fungal keratitis, were not taken into account due to the lack of reliable estimates. The limited existing data originate from specific high-risk populations, while ‘under-reporting’ is considered significant when registries exist.

Another factor that could potentially affect the interpretation of our calculations is the Greek climate and geographical diversity, as a great variety of climate subtypes are encountered in several regions of Greece [Hellenic National Meteorological Service, <http://www.hnms.gr>]. This is due to the influence of topography (great mountain chains along the central part of the country) on the air masses coming from the moisture sources of the central Mediterranean Sea. Thus, the weather in Greece varies from the dry climate of Athens’ greater area and of Eastern Greece to the wet climate of

Northern and Western Greece. Accordingly, we could expect higher incidence of severe mycoses in regions with a wet climate, but unfortunately such epidemiological data are lacking.

Finally, the currently evolving financial crisis might have an effect on our estimates of the burden of fungal diseases in Greece. The drastic curtailing of government spending has significantly affected public hospitals that cope with understaffing, deficits, and shortage of drugs and basic medical supplies [46]. In a recent audit conducted in 2014 among 141 physicians prescribing antifungal agents in 26 hospitals, only a minority of physicians reported availability of the serum galactomanan test, of timely CT scans, of bronchoalveolar lavage, and of isolation rooms with HEPA filters for leukemic patients [Sipsas N et al., unpublished data]. These shortages might result in increased incidence and underdiagnosis of IFIs, and delayed treatment initiation among high-risk patients. The lack of funds for health promotion policies inhibits disease prevention and health promotion educational initiatives. Moreover, increasing poverty might affect hygiene conditions and access to the healthcare system [46]. All these factors allow the prediction of an increase in the incidence of severe fungal infections in the future.

In conclusion, this is the first attempt to depict the burden of fungal diseases in Greece and the presented data estimate an unexpectedly high burden of recurrent *Candida* vaginitis, SAFS, and ABPA. This study, along with similar studies in other counties, under the auspices of LIFE, will raise awareness of the impact of fungal infections on public health and facilitate effective interventions.

Compliance with ethical standards

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Conflict of Interest The authors declare that they have no conflict of interest related to this research.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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