

Estimating the Burden of Fungal Diseases in Israel

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ABSTRACT: Fungal diseases affect a large proportion of the population, ranging in severity from mild superficial infections to life-threatening invasive diseases. Estimates of disease burden are needed to inform public health policies. We estimated the incidence of fungal diseases in Israel based on published surveillance data and risk-based calculations using previously established models. Deaths associated with fungal diseases were estimated from local surveillance data (candidemia) and published reports (invasive aspergillosis). Candidemia was estimated in 649 persons/year and invasive aspergillosis in 254 persons/year; the associated mortality was 2.75 and 0.96 per 100,000 population/year, respectively. Recurrent *Candida* vulvovaginitis occurs in 130,440 women annually. National incidence rates of cryptococcosis, pneumocystis pneumonia and mucormycosis could not be reliably estimated. Single-center data-derived estimates yielded 24, 26 and 20 cases/year, respectively. Allergic bronchopulmonary aspergillosis, asthma with fungal sensitization and allergic fungal sinusitis affect 8297 (range 2323–11,615), 14,372 (14,372–17,965) and 39,922 (15,969–183,643) persons, respectively. In Israel, candidemia and invasive aspergillosis rank high among infection-related causes of mortality. Allergic fungal diseases cause chronic or recurrent symptoms in a large population and may contribute to asthma-related hospitalization and death. These general estimates should serve as a primer for future efforts to study fungal epidemiology.

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KEY WORDS: fungal disease, invasive aspergillosis, candidiasis, allergic bronchopulmonary aspergillosis, epidemiology

Fungal pathogens are among the most frequent causes of infectious diseases in humans [1]. Fungal diseases range in severity from mild superficial infections that affect a large proportion of the otherwise healthy population to life-threatening invasive diseases limited mostly to vulnerable immunosuppressed patients [1]. The most frequent fungal diseases, such as infections of the integument and mucosal surfaces, tend to be chronic or relapsing in nature,

Fungal diseases are a significant cause of morbidity and mortality in Israel

whereas invasive fungal diseases (IFDs) are progressive and often cause death or disability unless promptly recognized and treated [1]. Yet despite the significant impact of fungi on human health, precise estimates of fungal disease rates are generally lacking. *Coccidioidomycosis* is the only IFD for which reporting is mandated by the United States Centers for Disease Control (CDC), and no IFD reporting is required by health authorities in the UK, Australia or Israel [e1-4]. Moreover, the detection of IFD is often limited by lack of sufficiently sensitive diagnostic modalities. Country-specific incidence rates are needed to inform public health decisions and to allocate funds for infection control and drug-development efforts. Hence, the current lack of data is an impediment to the design and implementation of effective control strategies.

Population- or hospital-based surveillance studies provide important information on the incidence and characteristics of fungal diseases in specific regions [2,3]. However, when epidemiological data are unavailable, incidence can be extrapolated from the prevalence of predisposing illnesses, such as AIDS, leukemia, and solid organ and stem cell transplantation [e5]. Although imperfect, such estimates may provide a frame of reference for future studies.

In Israel, several groups of vulnerable patient populations are at risk of serious fungal diseases. Immunocompromised patients, such as those with malignant neoplasms treated with chemotherapy, recipients of stem cell and solid organ transplantation, and patients living with human immunodeficiency virus (HIV) are at risk of invasive mold infections and cryptococcosis [2]. Complex medical and surgical patients receiving intensive care are the highest risk population for invasive candidiasis [3]. Most such patients in Israel are cared for in tertiary-level medical centers, implying that the incidence of IFD may be biased to certain high volume hospitals [3]. Patients with chronic respiratory illness, including cystic fibrosis, chronic obstructive pulmonary disease (COPD) and cavitary tuberculosis are an increasingly recognized risk group for *Aspergillus* spp. infection [4-6]. Finally, a significant proportion of patients with severe asthma are sensitized to airborne fungi which may play a role as exogenous drivers of respiratory disease [4]. Here, we used epidemiological data to estimate the incidence rates of fungal diseases in Israel.

DATA SOURCES

Demographic data were obtained from the Israeli Central Bureau of Statistics [e6]. Prevalence rates of chronic illnesses predisposing for fungal diseases were extracted from national surveys available from the Israeli Ministry of Health [e7-8], the World Health Organization (WHO) [e9], the joint United Nations program on HIV and AIDS (UNAIDS) [e10] and the Organisation for Economic Co-operation and Development (OECD) [e11]. We performed an extensive review of the literature and extracted epidemiological surveys of fungal disease incidence rates. Where no national-level data were available, we reviewed published case series and single-center datasets. Fungal disease estimates were generated according to previously proposed principles [e5]. Generally, disease estimates were conservative as they assumed the lowest incidence rates reported in the literature and focused only on well-defined risk populations. For allergic fungal diseases, such as asthma with fungal sensitization and allergic bronchopulmonary aspergillosis, we estimated prevalence rates (number of persons living with fungal disease per 100,000 population), whereas for acute fungal diseases, such as candidemia and invasive pulmonary aspergillosis, incidence rates were calculated (number of new cases per population at risk per year).

CANDIDA INFECTION

Candida spp. are the fourth most common cause of nosocomial bloodstream infection [7]. The incidence rate of candidemia in Israel was obtained from a nationwide surveillance study performed from 2005 through 2007. The current incidence of candidemia was estimated from this incidence rate adjusted to the number of acute-care hospital days in 2012 [e6].

Esophageal candidiasis among persons infected with HIV occurs yearly in about 20% of patients not receiving antiretroviral treatment (ART) and 0.5% of patients receiving ART [8,9]. There are no reliable data about ART coverage in Israel. Specifically, data are lacking for displaced immigrants from Africa, who often lack sufficient access to HIV testing and care. A rough estimate of 80% ART coverage was made for the purpose of these estimates. Recurrent vulvovaginal candidosis, defined as four or more episodes a year, was estimated based on an incidence of 5–8% among adult females [10].

ASPERGILLUS INFECTIONS

- Invasive aspergillosis (IA) is the most frequent IFD in immunocompromised patients [11,12]. Moreover, IA is an emerging problem in patients with chronic pulmonary diseases [13]. Since no surveillance studies have been conducted in Israel, the following annual incidence rates were used [2, e5]: 10% of patients with acute leukemia, 10% of stem cell trans-

plants, 0.5% of renal transplants, 4% of lung transplants, 6% of heart transplants, and 4% of liver transplants. For IA complicating COPD, we used mean incidence rates described by Guinea et al. (3.6 cases/1000 hospital admissions) [13].

- Chronic pulmonary aspergillosis (CPA) is a complication of a variety of infectious and inflammatory lung diseases, most importantly pulmonary tuberculosis. We used a previously described model to estimate the annual incidence of CPA in survivors of pulmonary tuberculosis [5]. The incidence of CPA in patients with allergic bronchopulmonary aspergillosis (ABPA) was calculated assuming an annual incidence of 10% [6].

CRYPTOCOCCOSIS AND PNEUMOCYSTIS PNEUMONIA

Cryptococcal meningitis is the most frequent fungal disease of the central nervous system (CNS). AIDS is the best defined risk factor, but other immunosuppressed patients, such as recipients of solid organ or hematopoietic stem cell transplantation are also at risk [14]. The published incidence in patients with AIDS ranges from 0.04% to 2% [15]. To arrive at general estimates, we searched the 2012 and 2013 records of the Clinical Microbiology Laboratory of the Tel Aviv Medical Center, which serves a population of 1.3 million and provides regular care to 1400 HIV-infected patients, 83% of whom receive antiretroviral therapy. Single-center incidence rates and HIV to non-HIV ratios were extrapolated to the general Israeli population with ~6500 HIV-infected persons [16].

MUCORMYCOSIS

Mucormycosis is a rare and often fatal fungal disease affecting patients with uncontrolled diabetes mellitus as well as immunocompromised patients [17]. Several single-center reports were published, suggesting that tertiary medical centers provide care for 1 to 4 patients a year [18,19].

Allergic fungal diseases affect a large segment of the population, while invasive candidiasis and invasive aspergillosis account for the greatest number of fungus-related deaths

ALLERGIC FUNGAL DISEASES

- **Allergic bronchopulmonary aspergillosis (ABPA).** ABPA is a complication of bronchial asthma and cystic fibrosis (CF) and is an important precursor of CPA. We estimated the prevalence of ABPA using a previously described model [6], based on the prevalence of asthma and CF in the Israeli population. We restricted the asthma prevalence calculation to adults because ABPA is uncommon in children without CF. The prevalence of asthma was included in a national health survey conducted in 2004, in which 286,100 of the adult population (≥ 21 years) reported having been diagnosed with asthma at any time. Given a 16% population growth from 2004 to 2012, this translates into 331,876 adults with asthma in 2012 (6.5% of the adult population). These rates are

somewhat lower than the 9.0% prevalence cited in the global initiative for asthma (GINA) report [20], which is not surprising since the latter is weighted towards children. The median rate of ABPA reported in the literature is 2.5% of all asthma cases [6,21]. The prevalence of CF in Israel as reported by the European Cystic Fibrosis Patient Registry was 6.99/100,000 in 2008; 6.6% of these patients developed ABPA [22].

- **Severe asthma with fungal sensitization (SAFS).** Accumulating evidence points to an important role of fungi as exogenous drivers of asthma, particularly in the segment of the asthmatic population with poorly controlled disease [4]. SAFS refers to patients with severe asthma and evidence of fungal sensitization who do not meet diagnostic criteria for ABPA [23]. In the GINA report, Israel stood out among Middle Eastern countries as having high rates of severe asthma: one in five asthmatic children visits the emergency room annually, and one in 10 children is hospitalized in the same period due to severe asthma [20]. Similarly, Israel ranks high among OECD countries in annual asthma hospital admission rates of adults (68.4/100,000 among persons aged ≥ 15 years) [24]. Thus, using a conservative estimate, 10% of patients with asthma have severe disease, and 20–25% of them meet the criteria for SAFS [21,23].

Prospective surveillance is needed to provide ongoing assessment of fungal disease epidemiology

- **Allergic fungal rhinosinusitis (AFRS).** Allergic rhinosinusitis is a common condition affecting between 5% and 40% of the adult and pediatric population, with wide variability between geographic regions [25]. Most patients become symptomatic before age 18 years. A population prevalence study in which the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was administered to Israeli schoolchildren aged 13–14 years revealed that 41.6% had ever had allergic rhinitis symptoms, and 9.4% were currently symptomatic [26]. The proportion of allergic rhinosinusitis attributed to fungal sensitization appears to vary according to distance from the equator, favoring hot and humid climates. For example, in the U.S., incidence was highest in southern states, accounting for 10–23% of all endoscopic sinus procedures [27]. In Brazil, 62 of 890 patients (6.9%) who underwent sinus endoscopy for chronic rhinosinusitis were found to have AFRS [28]. *Aspergillus* spp. and dematiaceous molds are implicated most frequently [28]. Based on geoclimatic characteristics, high incidence rates of AFRS may be predicted in Israel. However, published data are limited to single-center case series [29,30]. For the purpose of our estimates, we assumed a conservative proportion of 5% of allergic rhinosinusitis.

DISEASE ESTIMATES

Israel's population at the end of 2012 was 7,984,500; 50.4% were female, median age was 29 years (34% ≤ 18 years, 10%

≥ 65 years). Prevalence data of co-morbid conditions predisposing for fungal infections are detailed in Tables 1 and 2.

CANDIDA BLOODSTREAM INFECTION

A hospital-based nationwide surveillance study of candidemia was performed from 2005 through 2007 in 18 medical centers, accounting for 75% of the acute care beds in Israel [3]. This survey revealed an annual candidemia incidence rate of 5.5/100,000 population/year, 11/100,000 in-patient days/year, with a crude in-hospital mortality rate of 49%. Incidence rates varied significantly between medical centers: 11.9/100,000 patient days versus 7.3/100,000 patient days for high and low volume hospitals, respectively [3]. Applying these incidence rates to 2012 hospitalization data yields 649 cases of candidemia and 318 deaths [Table 1].

Based on the prevalence of HIV infection alone, we estimate the incidence of esophageal candidiasis at 286 cases/year [Table 1]. As this figure does not reflect the non-HIV risk groups such as patients treated for malignant neoplasms, organ transplant recipients and patients treated with corticosteroids, the true number may be two to three times greater. Recurrent vulvovaginal candidosis (≥ 4 episodes/year) was conservatively estimated to occur in 130,440 women/year [Table 1].

ASPERGILLUS SPP. INFECTION

- **Chronic pulmonary aspergillosis.** Pulmonary tuberculosis was reported in 396 individuals in 2012 [35]. The rate of post-treatment cavitation ranges from 20% to 50% [5]. Using a 22% cavitation rate, 13 new CPA cases complicating pulmonary tuberculosis were projected annually (range 11–31 cases) [Table 1] with a 5 year period prevalence of 42 cases (range 42–99) assuming an annual attrition rate of 15% due to death or surgical resection [5]. If pulmonary tuberculosis comprises ~20% of all CPA cases, as it does in the UK [37], then the total CPA prevalence is estimated to be around 200 cases.

CRYPTOCOCCAL MENINGITIS AND PNEUMOCYSTIS PNEUMONIA

There is a glaring lack of data on the epidemiology of *Cryptococcus neoformans* and *Pneumocystis jirovecii* infection in Israel. Moreover, estimating incidence is particularly difficult given the wide variation in incidence rates within defined risk groups [15] and the lack of data on antiretroviral therapy coverage in Israel. A search of the Tel Aviv Medical Center Microbiology Laboratory database revealed four cases of *C. neoformans* infection a year in HIV-infected patients and two cases a year in non-HIV patients in 2012 and 2013, corresponding with a 0.25% annual incidence rate for the HIV patient population served by this center. Applied to the national HIV population, these rates translate to 16 cases among HIV-infected patients and 8 among non-HIV patients [Table 1]. Similarly, three cases of

Table 1. Estimated annual incidence of serious fungal diseases in Israel

Fungal disease	Predisposing condition	Population at risk	Incidence rate	Total new cases in 2012 (range)	Level of data	Ref
Candidemia	Prolonged hospitalization	5,899,156*	11/100,000	649	NREG	[3]
<i>Candida</i> esophagitis	HIV/AIDS	6500			RFBC	[16,31]
	On ART	5200	0.5%	26		
	Not on ART	1300	20%	260		
Recurrent <i>Candida</i> vulvovaginitis**	Adult female	2,608,800	5%	130,440	RFBC	[10]
Invasive aspergillosis	SOT				RFBC	[32, e8]
	Heart	14	4.8%	1		
	Lung	38	4.1%	1–2		
	Liver	50	0.8%	0–1		
	Kidney	171	0.3%	0–1		
AML	776	10%	78	RFBC	[e7]	
Non-AML hematological cancer	1468		78	RFBC	[2]	
	SCT				RFBC	[2, e7, e19]
	Allogeneic	373	8.1%	30		
	Autologous	285	0.9%	3		
Admission for COPD	18,683†	3.6/1000 admissions	65 (65–243)	RFBC	[13,24]	
Chronic pulmonary aspergillosis	New pulmonary TB	393		10 (9–19)	RFBC	[5,35]
	Cavitary TB	86	12%	3 (2–12)		
	Non-cavitary TB	307	1%	5 year prevalence: 42 (42-99)		
Cryptococcal meningitis	HIV/AIDS	6500	0.25%	16	SSD	[16,31]
	SOT, SCT, cancer			8	SSD	50% of HIV/AIDS-associated cases
<i>Pneumocystis jirovecii</i> pneumonia	HIV/AIDS	6500	0.2%	13	SSD	[16]
	SOT, SCT, cancer			13	SSD	
Mucormycosis				20 (8–30)	SSD	[18,19]

Israeli population in 2012 = 7,984,500; Tel Aviv district in 2011 = 1,295,000

*Hospital days in 2011

**Four or more episodes of *Candida* vulvovaginitis per year [10]

†According to 234 admission per 100,000 population [24]

NREG = national registry, RFBC = risk-factor based calculation, SSD = single-center data, ART = antiretroviral therapy, TB = tuberculosis, SOT = solid organ transplantation, SCT = stem cell transplantation, AML = acute myeloid leukemia

Table 2. Estimated prevalence of allergic fungal diseases in Israel

Fungal disease	Predisposing condition	Population at risk	Prevalence rate	No. of persons with disease in 2012	Data type	Source
Allergic bronchopulmonary aspergillosis (ABPA)	Asthma in adults	331,876	2.5% (0.7–3.5)	8297 (2323–11,615)	RFBC	[6,22]
	Cystic fibrosis	559*	6.6%	37	NREG	
Severe asthma with fungal sensitization (SAFS)	Severe asthma	71,860	20% (20–25)	14,372 (14,372–17,965)	RFBC	[4,23]
Allergic fungal rhinosinusitis	Allergic rhinosinusitis	798,450**	5% (2–23)	39,922 (15,969–183,643)	RFBC	[25,27,28]

*Cystic fibrosis 6.99/100,000 population according to 2008 data

**Allergic sinusitis prevalence in 10% of general population [25]

NREG = national registry, RFBC = risk factor-based calculation

pneumocystis pneumonia were observed at the Tel Aviv Medical Center in HIV-infected patients in 2012 (annual incidence rate 0.18%). Three additional cases were diagnosed in non-HIV-infected persons, all of whom had cancer and were treated with corticosteroids. Applied to the general population, these incidence rates translate into 13 cases among HIV-infected patients and 13 cases among non-HIV patients annually [Table 1].

MUCORMYCOSIS

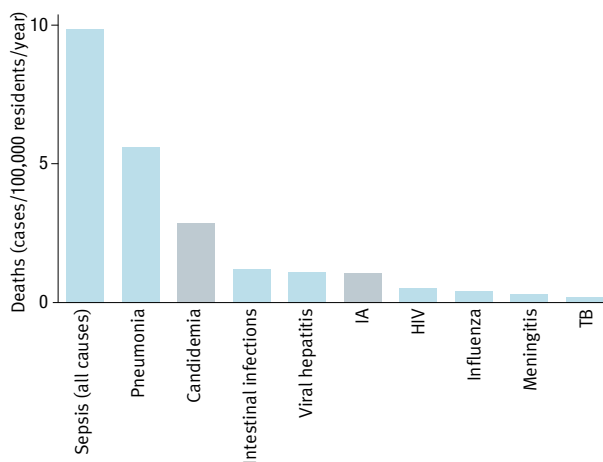
Researchers from two tertiary hospitals reported on their experience treating patients with mucormycosis. In one report, 19 patients received care over a 5 year period [18]. In a report

from another hospital, 6 patients were treated over 5 years (2005–2010) [19]. Seasonality has been suggested, with most cases occurring in the summer months [18]. Assuming 80% of mucormycosis cases are treated in tertiary medical centers, these figures can be extrapolated to a national incidence of ~20 cases a year (range 8–30) [Table 1].

ALLERGIC FUNGAL DISEASES

ABPA was reported in 2.5% (range 0.7%–3.5%) of adults with asthma [6]. In addition, the reported incidence in persons with CF in Israel is 6.6% [22]. These data allowed us to estimate that 8334 persons in Israel (range 2323–11,615) suffer from ABPA.

Figure 1. Comparison of deaths related to candidemia, invasive aspergillosis and chronic pulmonary aspergillosis, as estimated in this study, and other infection-related deaths in Israel



IA = invasive aspergillosis, HIV = human immunodeficiency virus. Source: [e12]

Fungal sensitization has been reported in 20–33% of persons with severe asthma [23], indicating that 14,372 persons (range 14,372–17,965) had SAFS in 2012, using the lower estimate to minimize double counting of ABPA cases. Based on the prevalence of allergic rhinosinusitis [27] we estimated that allergic fungal rhinosinusitis affects 39,922 persons in Israel (range 15,969–183,643) [Table 2].

DEATHS ATTRIBUTABLE TO FUNGAL DISEASES

We estimated deaths associated with the two most frequent serious fungal diseases in Israel, candidemia and IA. The crude in-hospital mortality rate for patients with candidemia in a national study was 52.6% [3], or 2.75 deaths/100,000 population [Figure 1]. By comparison, sepsis of all causes (including candidemia) was associated with 9.8 deaths/100,000 population [e12]. Using currently accepted treatment regimens, IA has been consistently associated with a 12 week mortality rate of 30–45% [2] [e13–15]. Applied to the IA estimate, the projected mortality rate for IA in the Israeli population is 0.96/100,000 (range 0.96–2.4/100,000), and the number of estimated deaths in 2012 is 76 [Figure 1].

OVERVIEW

Due to the increasingly successful care provided to patients with cancer, patients with immunodeficiency, and recipients of solid organ and stem cell transplants, the frequency of invasive fungal diseases and their impact on human health have risen sharply in the last three decades [1]. Moreover, life-threatening fungal diseases have been identified in patients not belonging to classic risk groups. Recent prominent examples include IA in patients with chronic lung disease [13], mucormycosis in tor-

nado victims [e16], and a large-scale nosocomial outbreak of mold infections resulting from injection of contaminated methylprednisolone [e17]. Thus, accurate detection and continuous surveillance of fungal diseases should be on the agenda of any national agency for disease control. Our goal in this paper has been to crudely estimate the burden of serious fungal diseases in Israel, and to identify high priority areas for future research.

Quantitatively, superficial dermal and mucosal infections and allergic diseases that originate from or are triggered by fungal sensitization constitute the bulk of fungal-related diseases. In particular, our estimates of ABPA, SAFS and allergic fungal rhinosinusitis suggest a potentially significant proportion of patients with these conditions that are undiagnosed and therefore receive suboptimal care. The chronic and relapsing nature of reactive airway diseases and the potential for serious exacerbations leading to hospitalization and death underscore the importance of addressing this gap.

The incidence of invasive fungal diseases, such as *Candida* bloodstream infections and invasive aspergillosis is much lower. However, the high death rates associated with these infections position them as significant causes of mortality. Compared with other infection-related causes of death in Israel, candidemia ranks third after sepsis of all causes and pneumonia [Figure 1]. [e12]. IA is broadly comparable as a cause of mortality to viral hepatitis and gastrointestinal infections, ranking higher than influenza, HIV and meningitis [Figure 1]. Our estimates may in fact have under-appreciated the true burden of fungal-associated mortality, because sepsis from all causes does not differentiate between fungal and bacterial sepsis. Similarly, some of the HIV-associated mortality is caused by fungal opportunistic infections, such as pneumocystis pneumonia and cryptococcosis.

Cryptococcosis, mucormycosis, histoplasmosis and other opportunistic fungal diseases are uncommon in Israel. Nevertheless, treatment of such patients often requires the involvement of multidisciplinary medical teams and the devotion of many personnel hours and hospital resources. As an example, the treatment of a single patient with rhinocerebral mucormycosis is an endeavor that requires coordination among clinical teams (surgery, ophthalmology, otolaryngology, intensive care, infectious diseases) and supporting services (radiology, microbiology, pathology, clinical pharmacology) [38,39]. These organisms are best described as low incidence–high consequence pathogens. Appropriate management depends to a large degree on preparedness and designation of key partners in the multidisciplinary response to such events [39].

Our analysis highlights three main aspects of fungal diseases that require national attention: epidemiology, diagnostics and treatment. First, we need better data on the epidemiology of fungal diseases in Israel. Establishing a national reporting system and a microbiology laboratory network should facilitate dynamic surveillance and the formation of a fungal disease registry. Second, accurate and timely diagnosis of fungal dis-

eases is hampered by the lack of clinician awareness and the limited availability of state-of-the-art fungal diagnostics in most hospitals. These barriers can be overcome by educating physicians and utilizing capable reference laboratories. Third, the availability of some antifungal drugs is limited due to the small size of the Israeli market. Liposomal amphotericin B, the only lipid amphotericin B formulation marketed in Israel, has been subject to intermittent shortages in local hospitals. Flucytosine, an essential component in the treatment of cryptococcal disease [e18], is unavailable in hospital pharmacies. A small amount of flucytosine (intravenous formulation only) can be obtained from the Ministry of Health emergency stockpiles. Therapeutic drug monitoring is currently available only for voriconazole. Availability of sensitive assays for drug level monitoring of anti-fungal triazoles and flucytosine is highly desirable in order to optimize therapy and avoid toxicity.

Summary

Fungal diseases are a significant cause of morbidity and infection-related mortality in Israel. Ongoing surveillance, universal access to fungal diagnostics, and improved availability of anti-fungal drugs are immediate priorities. Public health resources should be directed towards this growing threat, which will undoubtedly become more significant in the future.

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