

DR SEYEDMOJTABA SEYEDMOUSAVI (Orcid ID : 0000-0002-6194-7447)

DR MACIT ILKIT (Orcid ID : 0000-0002-1174-4182)

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### **Estimated burden of serious human fungal diseases in Turkey**

Süleyha Hilmioglu-Polat,<sup>1</sup> Seyedmojtaba Seyedmousavi,<sup>2-4\*</sup> Macit Ilkit,<sup>5</sup> Mohammad Taghi Hedayati,<sup>3,6</sup> Ramazan Inci,<sup>1</sup> Emel Tumbay,<sup>1</sup> David W. Denning,<sup>7</sup>

<sup>1</sup> Department of Microbiology, Faculty of Medicine, University of Ege, Izmir, Turkey

<sup>2</sup> Present address: Molecular Microbiology Section, Laboratory of Clinical Infectious Diseases (LCID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, USA

<sup>3</sup> Invasive Fungi Research Center, Mazandaran University of Medical Sciences, Sari, Iran

<sup>4</sup> Center of Expertise in Microbiology, Infection Biology and Antimicrobial Pharmacology, Tehran, Iran

<sup>5</sup> Division of Mycology, Department of Microbiology, Faculty of Medicine, University of Çukurova, Adana, Turkey

<sup>6</sup> Department of Medical Mycology and Parasitology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

<sup>7</sup> The National Aspergillosis Centre, Wythenshawe Hospital, The University of Manchester, Manchester Academic Health Science Centre, Manchester M23 9LT, UK

**\*Address correspondence to:** Seyedmojtaba Seyedmousavi, PhD, FECMM.

BG 10 RM 11C106, 10 CENTER DR, 9000 Rockville Pike, Bethesda, MD 20892, United States of America. Tel: +1 (301) 402-5139. E-mail: Seyedmousavi@nih.gov

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## Abstract

The current number of fungal infections occurring each year in Turkey is unknown. We estimated the burden of serious human fungal diseases based on the population at risk, existing epidemiological data from 1920 to 2017, and modelling previously described by the LIFE program (<http://www.LIFE-worldwide.org>).

Among the population of Turkey (80.8 million in 2017), approximately 1,785,811 (2.21%) people are estimated to suffer from a serious fungal infection each year. The model used predicts high prevalences of allergic fungal rhinosinusitis episodes (312,994 cases) (392/100,000), of severe asthma with fungal sensitization (42,989 cases) (53.20 cases/100,000 adults per year), of allergic bronchopulmonary aspergillosis (32,594 cases) (40.33/100,000), of fungal keratitis (26,671 cases) (33/100,000), and of chronic pulmonary aspergillosis (5,890 cases) (7.29/100,000). The estimated annual incidence for invasive aspergillosis is lower (3,991 cases) (4.94/100,000 annually). Amongst about 22.5 million women aged 15-50 years, recurrent vulvovaginal candidiasis (RVVC) is estimated to occur in 1,350,371 (3,342/100,000) females. The burden of three superficial fungal infections was also estimated: tinea pedis (1.79 million), tinea capitis (43,900), and onychomycosis (1.73 million).

Given that the modeling estimates reported in the current study might be substantially under- or over-estimated, formal epidemiological and comprehensive surveillance studies are required to validate or modify these estimates.

## Key words

Serious fungal infection, candidiasis, invasive aspergillosis, severe asthma with fungal sensitization, recurrent *Candida* vaginitis, Turkey

## Introduction

Fungal infections are considered as a major public health concern, worldwide.<sup>1</sup> Annually, over a billion people are believed to suffer from a fungal infection, resulting in over 1.6 million deaths in patients who are immunocompromised, hospitalized with severe underlying diseases (e.g., acute myelogenous leukemia), require complex surgical procedures (e.g., for trauma), and need support in intensive care units.<sup>2</sup> In addition, chronic pulmonary aspergillosis (CPA) – a chronic progressive infection that destroys lung tissue in non-immunocompromised patients – is thought to affect about 3 million people, worldwide.<sup>2, 3</sup> CPA complicates individuals with pre-existing lung disease such as pulmonary tuberculosis (TB), non-tuberculous mycobacterial infection, asthma, allergic bronchopulmonary aspergillosis (ABPA), chronic obstructive pulmonary disease (COPD), sarcoidosis, and pneumothorax.<sup>4</sup> If untreated 50–85 % of patients with CPA will die within 5 years.<sup>5, 6</sup>

Knowledge of the local epidemiology of invasive and serious fungal infections, as well as risk factors for infection, is essential for effective infection control programs and guiding effective treatment approaches. There are currently no epidemiological data on nation-wide burden of fungal infections in Turkey, a country located at the crossroads between Eastern Europe and Western Asia with prominent geographical and socio-economic diversity. Several studies have examined the epidemiology of fungal infections and antifungal utilization in Turkey,<sup>7-10</sup> but most were local, single-center, or regional and focused on individual infections in specific populations. For instance, the epidemiology of candidiasis was evaluated retrospectively at the Hacettepe University Hospital in Ankara between January 2001 and December 2010. Among 381 candidaemia episodes, 58.3% were due to *C. albicans*, followed by *C. parapsilosis* (15.2%), *C. tropicalis* (13.4%) and *C. glabrata* (6.8%).<sup>9</sup> A single-center study between October 2012 and December 2013 at Ege University in İzmir showed that incidence of proven and probable invasive fungal infections (IFIs) was 6.7% in those with haematological disease. Prophylaxis and antifungal therapy were given only in 30.5% and 23.6% of 522 chemotherapy episodes, respectively.<sup>8</sup> Another study reported the epidemiological trends in

antifungal treatment on the national level;<sup>11</sup> 408 patients and 505 episodes of invasive fungal infections was recorded. In this study, data were collected from 7 major hospitals (7,052 beds), representing 26% of all the beds in University hospitals and 16% of all education hospitals across Turkey.<sup>7, 11</sup> However, these data are over 15 years old. In another retrospective study,<sup>12</sup> the cumulative incidences of invasive fungal infections in Turkish pediatric allogeneic hematopoietic stem cell transplant (HSCT) recipients receiving fluconazole prophylaxis, were 2.7%, 5.0%, and 6.5% at 30, 100, and 180 days post-transplantation, respectively. Among 408 patients, 77 (18.9%) died within 180 days after HSCT, and fungal infections accounted for 1.5% of these cases (6/408) (IFI-related mortality). The overall mortality (case fatality) rate for all types of IFI was 27% (7/26) at 180 days.<sup>12</sup>

Given that Turkey's unique geographical situation has been responsible for the epidemiology of various infectious diseases occurring throughout the country,<sup>13-15</sup> here we sought to provide an estimate of the national burden of serious fungal infections in Turkey, using a modeling approach previously applied to over 50 countries.

## Materials and Methods

A systematic literature review for incidence and prevalence of fungal diseases was conducted in both local and international research databases including PubMed website and Google Scholar to identify fungal infections frequencies and specific populations at risk in Turkey from 1920 to 2017. We used the search terms "Turkey", "fungal infections", "cryptococcosis", "pneumocystis", "*Aspergillus*", "invasive aspergillosis", "chronic pulmonary aspergillosis", "allergic bronchopulmonary aspergillosis", "fungal rhinosinusitis", "*Candida*", "candidemia", "candidiasis", "recurrent *Candida* vaginitis", "mucormycosis", "fusariosis", "sporotrichosis", "histoplasmosis", "mycotic keratitis", "tinea", "onychomycosis", "*Malassezia*", "melanized fungi", and "*Scedosporium*". The search was

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supplemented by consultation of the bibliographies of the articles retrieved. No language restrictions were applied to the search. The burden of serious fungal diseases was then estimated, using literature review and methodology previously described by the LIFE program.<sup>6, 16, 17</sup> Where there was no data, we used proportion of specific risk groups and fungal infection frequencies in each population to estimate national incidence or prevalence, depending on the condition.

Demographic data were obtained from the state-run Turkish Statistical Institute (TurkStat) (<http://www.turkstat.gov.tr>). Data on the HIV/AIDS population were derived from the 2011 report issued by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO) (<http://www.who.int/en>).

Estimates of tuberculosis (TB) incidence and mortality were taken from the 2017 report issued by WHO (<http://www.who.int/en>). The incidence and 5-year period prevalence of chronic pulmonary aspergillosis (CPA) following TB was estimated assuming a 22% cavitation rate following therapy in TB, using a previously reported model by Denning et al.<sup>3</sup>

The first case of *Pneumocystis* pneumonia (PCP) in Turkey was reported in 1955.<sup>18</sup> Since then, the majority of studies in Turkey have been directed towards evaluation of efficacy of diagnostic methods.<sup>19</sup> The prevalence of PCP in AIDS patients was assessed assuming that 5.5% of new AIDS cases present this infection, according to the report of Serraino et al from Eastern Europe.<sup>20</sup>

The first isolation of *Cryptococcus* from Turkey was reported in 1959 from a patient with intestinal infection.<sup>21</sup> In the current study, the rates of cryptococcal meningitis was estimated at 0.6 per 100,000 based on the published data in HIV patients.<sup>6</sup>

To date, no adult asthma epidemiology studies have been recorded for Turkey. Due to lack of local data, the estimate of asthma prevalence in adults in Turkey was obtained from the 2003 World Health Survey published by To et al.<sup>22</sup> The burden of ABPA in adults with asthma and its correlation with CPA was considered 2.5% (range 0.72%–3.5%).<sup>23</sup> The prevalence of severe asthma with fungal

sensitization (SAFS) was estimated as the worst 10% of the total asthma population, of whom at least 33% have fungal sensitization. The number of patients with COPD in the general population of Turkey was considered 4.2 % in those 40 years and older,<sup>24</sup> of whom 19.3% had been hospitalized,<sup>25</sup> <sup>26</sup> and 36% reported experiencing an exacerbation of their respiratory condition.<sup>27</sup> COPD classification was done according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. GOLD stage I, II, III, IV refer to COPD severity of mild, moderate, severe and very severe respectively.<sup>28</sup> The rate of IA in the context of hospitalized patients with COPD was estimated 13 cases per 1000 admissions as described previously by Guinea et al.<sup>29</sup>

Recent data also suggests that chronic rhinosinusitis affects approximately 1–1.5%, 11% and 12.5% of the population in North India (rural), the European Union and the US, respectively.<sup>30, 31</sup> The proportion of allergic rhinosinusitis attributed to fungal sensitization appears to vary between 0.11 to 27%,<sup>31-35</sup> depending on the geographic regions favoring hot and humid climates and diagnostic methods used. To estimate the prevalence of allergic fungal rhinosinusitis (AFRS), we assumed that a conservative proportion of 5% of chronic rhinosinusitis in Turkey are AFRS.

The prevalence of new cases of acute myeloid leukemia (AML) was estimated 2.8 per 100,000 men and women per year according to estimates reported by GLOBOCAN database of International Agency for Research on Cancer ([http://globocan.iarc.fr/Pages/fact\\_sheets\\_population.aspx](http://globocan.iarc.fr/Pages/fact_sheets_population.aspx)). Equal number of cases were considered in all other haematological patients. The risk of IA development was considered in 10% of these patients as reported previously in France,<sup>36</sup> and Austria,<sup>37</sup> and an equal number for all other hematological malignancies and lymphomas. We also used the GLOBOCAN database to determine the number of lung cancer cases each year (n=24,489) and assumed that 2.6% developed IA.<sup>38</sup>

The information about all transplantation procedures performed in 2017 was obtained from the international registry of organ transplantation (<http://www.irodat.org>). Among patients who underwent HSCT and solid organ transplantation (SOT), the incidence of IA and mucormycosis was evaluated according to previous LIFE database recommendations.<sup>6</sup>

To estimate the number of candidemia and *Candida* peritonitis cases, the annual incidence of 5/100,000 and 1.5/100,000 respectively were used, in the absence of any national or regional population incidence data.<sup>39, 40</sup> In Turkey, the number of patients on renal replacement therapy in 2008 was 756 per million, and 10% were receiving chronic ambulatory peritoneal dialysis (CAPD) (n=6109).<sup>41</sup> We assumed an infection rate of 1.6 episodes/patient-year and that 2% were attributable to fungi.<sup>42</sup> The burden of oropharyngeal and oesophageal candidiasis was assessed using incidence data previously published in the literature.<sup>43-45</sup> The number of women probably suffering from recurrent vulvovaginal candidiasis (RVVC) was estimated by assuming that RVVC affects 6% of adult women aged between 15 and 50 years.<sup>46, 47</sup>

The prevalence of presenting corneal diseases and infectious keratitis was considered 0.8% and 0.148% of general population as previously reported.<sup>48</sup> The incidence of fungal keratitis was then estimated by using data obtained from documented studies in Turkey.<sup>49</sup> The estimates for cases of onychomycosis (2.8%) and tinea pedis (2.9%) in the general adult population of Turkey was derived from the study published previously.<sup>50</sup> The number of patients with tinea capitis was considered 0.23% amongst children population.<sup>51</sup> The incidence of uncommon and emerging fungal diseases such as mucormycosis, *Scedosporium* infections, sporotrichosis, and disseminated infections by melanized fungi was estimated from the number of reported cases per year nationally.

## Results and discussion

In 2017, the population of Turkey was estimated at 80,810,525 inhabitants, of which 86.4% were adults and 23.6% were children 0–14 age group. The female population (40,243,641 persons) constituted 49.8%. The elderly population (65 years and over) was 8.5%. The gross domestic product of Turkey per person in 2016 was USD 10,788. Turkey population density map is shown in figure 1.

The documented episodes of opportunistic fungal infections from 1920 to 2017 (Table 1) were: 60 cases of cryptococcal meningitis, 100 cases of PCP, 605 cases of IA, 244 cases of CPA following TB, 39 cases of ABPA, 293 cases of fungal rhinosinusitis, 3,847 cases of candidemia, 67 cases of *Candida* peritonitis, 540 cases of oral candidiasis, 120 cases of oesophageal candidiasis, 525 cases of RVVC, 416 cases of mucormycosis, 17 cases of *Scedosporium* infections, 18 cases of disseminated fusariosis, 8 cases of sporotrichosis, 6 cases of histoplasmosis, and 6 cases of disseminated infections by melanized fungi. In addition, 36,387 cases of tinea pedis, 12,864 cases of onychomycosis, 7,804 cases of tinea capitis, 488 cases associated with *Malassezia* infections, and 94 cases of fungal keratitis were recorded. A summary of extracted data from bibliographical information based on population at risk is detailed in Table 1. Complete list of documents from 1920 to 2017 used in this study is presented in Supplementary Table 1.

Using local data and available national and international literature estimates of the incidence or prevalence of fungal infections, approximately 1,785,811 (2.21%) people in Turkey are estimated to suffer from a fungal infection in Turkey each year. Table 2 summarizes the burden of different fungal diseases and their incidence or prevalence per 100,000 inhabitants as estimated from our study.

- Cryptococcal meningitis and PCP

Cryptococcal meningitis and PCP are among the most severe opportunistic infections occurring in HIV/AIDS populations. According to the UNAIDS 2012 report, people living with HIV/AIDS in Turkey ranged between 4,000–7,000 with approximately 56% (45–72%) of patients receiving antiretroviral

therapy (ARV). In the current study, 60 cases of cryptococcal meningitis, and 100 cases of PCP<sup>52</sup>, were diagnosed over a 18-year period (1998 to 2016). Taking undiagnosed HIV/AIDS infections into account and based on the incidence rate published previously,<sup>6, 20</sup> one might expect that, yearly as many as 106 and 635 cases of cryptococcal meningitis and PCP, respectively, occur in HIV/AIDS patients across Turkey, each year.

- Invasive aspergillosis (IA)

In our study, a total of 3,991 cases (4.94/100,000 annually) of IA were estimated to occur in Turkey, mainly in cancer/immunocompromised patients followed by patients with severe COPD and those hospitalized in ICU.

IA is a common complication in severely immunocompromised patients with hematologic malignancies, such as bone marrow transplantation recipients or patients under extensive chemotherapy for hematologic malignancies. According to the GLOBOCAN database the prevalence of AML was considered 2.8/100,000 indicating that 453 cases are susceptible to IA annually, assuming that 10% of AML and all other hematological patients develop IA.<sup>36, 37</sup> Patients with solid tumors also are at risk for IA because they may develop neutropenia as a result of chemotherapy and radiotherapy.<sup>38</sup> The estimated number of IA in the lung cancer population of Turkey is about 637 cases (2.6%). In 2017, a total of 4,906 SOTs were performed in the Turkey including 3,342 kidney (2,649 living + 693 deceased), 1,446 liver (1,087 living + 359 deceased), 76 heart (all deceased), and 42 lung (all deceased) transplants, corresponding to an estimated 12-month cumulative incidence of 81 cases of IA.

In middle income countries such as Turkey, many IA cases have also been reported in hosts with no apparent immune defect or underlying diseases. In addition, COPD is a progressive pulmonary disease, which may have a profound impact on general health status and quality of life.<sup>26</sup> Of note, patients with severe COPD who are receiving broad-spectrum antibiotics and corticosteroids are one

of the main risk groups to develop IA.<sup>29,53</sup> We estimated that around 2,782 COPD patients develop IA annually in Turkey, assuming 13 cases per 1000 hospitalized COPD.<sup>29</sup> The number of patients with COPD in Turkey is estimated 21,4005 cases per year amongst Turkey's general population  $\geq 40$  years old.<sup>24</sup> Our overall estimation agreed with a local study in the urban and rural areas of the Elazig Region of Turkey, in which the prevalence of COPD at  $\geq 18$  years old was 4.5%.<sup>54</sup>

- Non-invasive pulmonary aspergillosis

Individuals with chronic respiratory disease are susceptible to airborne fungal infections including ABPA<sup>23</sup>, SAFS<sup>55</sup>, and CPA.<sup>3</sup> Extrapolating from WHO pulmonary tuberculosis 2015 annual incidence data (n = 14,000), the prevalence of CPA following tuberculosis was estimated at 1956 cases based on the assumption that 22% of the patients with lung cavities and 2% of patients without cavities generally develop CPA.<sup>3</sup> Post-TB cavitation acts as a predisposing factor for the colonisation of *Aspergillus* spp., largely owing to the development of empty residual lung cavities.<sup>3</sup> Given that numerous other conditions are associated with CPA, including pneumothorax, sarcoidosis, asthma, and non-tuberculous mycobacterial infections,<sup>6</sup> we estimate that TB contributes 33% of the cases and the overall prevalence of CPA is 5867 (7.3/100,000).

ABPA and SAFS are the most common fungal infections among asthmatics with a notably high prevalence rate. The proportion of ABPA among asthma patients was estimated at 2.5%<sup>23</sup>, leading to a calculated national prevalence of 32,594 cases per year. SAFS burden was derived from asthma prevalence and estimated at 42,989 cases, assuming a severe asthma prevalence of 10% of all cases of asthma and an *Aspergillus* sensitization prevalence of 33%.<sup>56</sup> Atopic adults with rhinitis or asthma of all severities tested in Ankara for sensitization to *Alternaria* spp. and *Cladosporium* spp. by skin pick test were positive in 11.9% and 8.1% of cases respectively; *Aspergillus fumigatus* was not tested.<sup>57</sup> This frequency is similar to other European countries.<sup>58</sup> Older data is indicative of a high rate of sensitisation to *A. fumigatus* – 26% in one series of asthmatic (73%) and allergic rhinitis patients.<sup>58</sup>

- Allergic fungal rhinosinusitis (AFRS)

AFRS is a unique variety of chronic polypoid rhinosinusitis mainly in atopic individuals, characterized by presence of eosinophilic mucin and fungal hyphae in paranasal sinuses without invasion into surrounding mucosa.<sup>59</sup> The fungi causing AFRS have a great diversity and regional variation, and the incidence of AFRS has been reported worldwide.<sup>30</sup> Histopathologic analysis of Turkish patients who underwent endoscopic sphenoidotomy revealed that fungal infection is a common cause of (14.1%) sphenoid sinus lesion.<sup>60</sup> Based on geo-climatic characteristics of Turkey,<sup>13-15</sup> high incidence rates of AFRS are predicted. However, published data are limited to microbiological analysis and single-center case series.<sup>61-63</sup> Assuming 5% population prevalence for allergic rhinosinusitis, we estimated that AFRS affects 312,994 adults (392/100,000) in Turkey annually (Table 2).

- Invasive candidiasis

Invasive candidiasis is the main invasive fungal infection that affects worldwide more than 700,000 people each year<sup>2</sup>, with various clinical presentations from intra-abdominal infections to deep-seated infections and candidemia. The disease is particularly diagnosed in intensive care units.<sup>39</sup> The total incidence of candidemia for Turkey is 3,847 cases/year (4.76/100,000), of which 1,701 occurred in critical care settings and 1,930 in cancer/immunosuppressed patients. The incidence of candidemia was in agreement with a general conservative rate of 5 per 100,000 population, as described previously.<sup>39</sup>

*Candida* peritonitis is still a severe disease with a mortality rate of at least 38%, as high as for candidemia, most commonly affecting those following complex abdominal surgery or pancreatitis.<sup>64</sup>

<sup>65</sup> In our literature review, *Candida* peritonitis (intra-abdominal candidiasis), was only reported in 67 cases. However, using our population-based estimation model, by making the assumption that deep-seated *Candida* infections such as peritonitis are accompanied by positive blood cultures in 50% of candidemia cases,<sup>40</sup> 387 cases are estimated to occur in Turkey annually as post-surgical

*Candida* peritonitis. Among CAPD patients, we estimate 195 cases (3.2% annually in the CAPD population). This is more than the experience of 4 CAPD centers in Northwest Turkey (15 cases over 10 years in 795 patients; 0.2%)<sup>66</sup>, but may be conservative as most studies have found fungal peritonitis makes up 6–10% of infection episodes.

- Mucosal candidiasis

Vulvovaginal candidiasis (VVC) is the second most common cause of vaginitis after bacterial vaginosis, and it is diagnosed in up to 40% of women with vaginal complaints in the primary care setting.<sup>67</sup> The presence of *Candida* in the vagina in the absence of immunosuppression or damaged mucosa is usually not associated with any signs of disease, which is referred as ‘asymptomatic colonization’. VVC, however, is defined as signs and symptoms of inflammation in the presence of *Candida* spp. and in the absence of other infectious etiologies.<sup>46</sup> Among problematic superficial mycoses, RVVC should be considered the most common fungal infection in Turkey. RVVC is defined as at least four episodes per year (>4x/year).<sup>46, 47</sup> The Turkish prevalence of RVVC per year was calculated by applying 6% to the adult women’s population (between 15 and 50 years old) (n = 22,506,176), yielding an estimated 1,350,371 cases present. Of note, RVVC is very common among women worldwide and reported to affect 5 to 9% of women of reproductive age.<sup>46, 47</sup> The gold standard mycological methods used for diagnosis include microscopic examination, fungal culture, and antigen tests.<sup>46, 47</sup>

In a single center study between January 2004 and June 2005 in Turkey, among 569 women with symptoms of vulvovaginitis, 240 (42.2%) were positive for *Candida* spp., of which 106 (44.2%) were *C. albicans* and 134 (55.8%) were non-*albicans* spp. The age group 26-30 years old had the highest frequency of *Candida* spp. (23.7%). *Candida* spp. were isolated from 44.2% of contraceptive method users, and 37.9% of non-contraceptive users (p>0.05). The isolation rate of *C. albicans* was higher among oral-contraceptive users (57.5%) than IUCD users (38.5%), coitus interruptus (48.5%) and condom users (42.8%).<sup>67</sup> In another study, the use of antibiotics, intrauterine devices (IUDs), perineal

laceration, short anovaginal distance (< 3 cm), and genital epilation were predisposing factors for RVVC. Moreover, few studies are available on superficial fungal infections of the male genitalia in Turkey.<sup>68</sup> In a recent study, Iskit et al.<sup>69</sup> noted a significantly higher prevalence of yeasts, both *Candida* spp. and *Malassezia* spp., in samples from the prepuce and glans penis of uncircumcised (62.5%) compared to circumcised (37.5%) boys in Turkey ( $P < 0.01$ ). Aridogan et al. also highlighted the potential medical benefits of circumcision as a significant factor decreasing the colonisation rate of *Candida* and *Malassezia* yeasts.<sup>70</sup>

In HIV patients, oral candidiasis is a frequent condition occurring at least once in 90% in those with low CD4 cell counts.<sup>43, 44</sup> Using this assumption, HIV infection is responsible for 4050 cases, and other risk groups such as head and neck cancer, inhaled corticosteroids contribute more cases. So at least 4,536 cases of oral candidiasis are annually expected, but these numbers will be an underestimate, as oropharyngeal candidiasis occurs in multiple other patients, such as immunocompromised patients after chemotherapy.

Oesophageal candidiasis is another AIDS-defining illness affecting nearly 20% of patients without ARV and 5% of patients on ARV.<sup>45</sup> Thus, at least 618 cases of oesophageal candidiasis (0,76/100,000) are expected to occur annually in Turkey. Usually, two or more episodes of oral candidiasis occur each year in these subjects.

- Mucormycosis

Mucormycosis is a life-threatening infection responsible for increasing morbidity and mortality in patients who are immunocompromised because of diabetic ketoacidosis, neutropenia, organ transplantation, and/or increased serum levels of available iron. Based on the observations made from literature reviewed in this study (Table 1), most of the infections occurred in patients with hematological malignancy (223 cases), and diabetic ketoacidosis (214 cases).

- Uncommon and emerging fungal diseases

In the context of the increasing patient population with immunosuppression and the expanding use of antifungal agents against common fungal pathogens such as *Candida* and *Aspergillus*, the number of patients with invasive fungal diseases due to emerging and uncommon fungal pathogens is increasing, worldwide.<sup>71</sup> However, according to our estimates, invasive scedosporiosis, fusariosis, sporotrichosis, and disseminated infections by melanized fungi are rare fungal infection in Turkey (Table 1). In addition, there are a limited number of histoplasmosis cases reported from Turkey,<sup>72, 73</sup> given that infected patients are mostly asymptomatic. Of note, the first case of histoplasmosis was reported in Turkey in 1946 by Saglam.<sup>74</sup>

Moreover, a recent study in Turkey found that 14.2% of the iatrogenically immunosuppressed patients without HIV had pulmonary microsporidiosis<sup>75</sup>, which suggests that *Microsporidia* spp. should be taken into account in the differential diagnosis of pulmonary infections in immunosuppressed patients. *Microsporidia* are highly specialized obligate intracellular organisms that are recently reclassified with the fungi.<sup>76</sup> Of the 14 species of *Microsporidia* currently known to infect humans, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common causes of human infections and are associated with diarrhea and systemic disease.

- Fungal keratitis

Fungal keratitis is a challenging condition in ophthalmological practice in developing countries, including Turkey.<sup>77</sup> Ocular trauma, particularly trauma contaminated by vegetative material, is reported as the most common predisposing risk factor. The epidemiological pattern and the spectrum of causative pathogens responsible for microbial keratitis vary substantially and depends on geographical location, with differences from country to country, and even from region to region within the same country. In a retrospective study, Yilmaz et al.<sup>49</sup> reviewed the medical records of microbial keratitis clinically diagnosed at the Izmir Ataturk Training and Research Hospital from

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January 1990 to December 2005. Microbial keratitis was diagnosed in 620 patients (250 women and 370 men). Pathogens from cultures were identified in 225 eyes (36.2%), of which 22.3% (50 cases) were fungi. *Fusarium* spp. (25 cases; 11%) were the most prevalent fungal species, followed by *Candida* spp. culture (15 cases; 6.6%) and *Aspergillus* spp. (10 cases; 4.4%). Based on the assumption that 22.3% of microbial keratitis are due to fungi, we estimated the incidence of fungal keratitis in Turkey at 33 per 100,000 population annually, which suggests fungal keratitis is a particular problem in Turkey. This estimate is more than expected number of cases in Italy (0.94/100,000)<sup>16</sup>, Malaysia (1.3/100,000)<sup>78</sup> and Egypt (14/100,000)<sup>79</sup>, and less than Pakistan (44/100,000)<sup>80</sup> and Nepal (73/100,000)<sup>81</sup>.

- Superficial mycoses

It is generally considered that dermatophytic infections are the most common types of human fungal infections, worldwide. Using local data and available national and international literature, there were many documented cases of superficial mycoses including dermatophytic infections in Turkey (Table 1). The estimated annual incidence of superficial fungal infections in Turkey is shown in Table 3.

Historically, the chronic hyperkeratotic (moccasin) tinea pedis also known as “two feet-one hand syndrome” was reported for the first time in 1892 by an Ottoman dermatologist “Celal Muhtar”.<sup>82, 83</sup> The study of Celal Muhtar in the dermatophyte arena was continued by Talad<sup>84</sup>, and Englaender,<sup>85</sup> who described the first cases of favus and onychomycosis in Turkey, respectively.

Tinea capitis is one of the most common causes of pediatric dermatophyte infections of the scalp, with a propensity for attacking the hair shafts and follicles. Tinea capitis predominantly affects preadolescent children, accounting for up to 92.5% of all cases of dermatophytosis in children younger than 10 years.<sup>86</sup> In addition, the prevalence of asymptomatic scalp carriage (ASC) generally

correlates well with the incidence of symptomatic infections regionally. Data from Çukurova region in Turkey revealed that the prevalence of ASC is 0.1% in preliminary school children.

Notably, tinea pedis, commonly known as Athlete's foot, is particularly common in the developed world, whereas tinea capitis is relatively more prevalent in developing countries. Tinea pedis, is a dermatophytic infection of the feet, can involve the interdigital web spaces or the sides of the feet and may be a chronic or recurring condition. Tinea pedis and onychomycosis seems to be a major problem among the adult Muslim male population (50 years and older) in Turkey, with a prevalence rate of 29.5%.<sup>87</sup> The exposure of these specific populations to sweating, trauma, occlusive footwear, and communal areas predisposes these groups to an increased incidence of tinea pedis. An epidemiological survey among 461 subjects regularly attending mosques in the city center of Adana Province showed that 136 (29.5%) had tinea pedis, 23 (5%) had tinea unguium and 21 (4.5%) had both infections simultaneously, resulting a total of 180 (39%) cases of dermatomycoses. The mycological results were as follows: *Trichophyton rubrum* (n=69), *T. interdigitale* (n=32), *C. albicans* (n=2), and direct microscopy-positive only (n=77).<sup>87</sup> In another study evaluating 1,222 samples of nail scrapings from 1,146 patients, non-dermatophytic fungi were responsible for approximately 50% of onychomycoses cases attending the dermatology outpatient clinic of a university hospital in Izmir, Turkey.<sup>88</sup> Dermatophytes were detected in 175 (48%), yeasts in 150 (41%), molds in 33 (9%), and mixed (two different fungi) in 8 (2%) patients. The agents of mold onychomycosis in order of frequency, were *A. niger* (n=7), *Acremonium* spp. (n=6), *Fusarium* spp. (n=6), *Ulocladium* spp. (n=4), *sterile mycelia* (n=2), *Alternaria* sp. (n=1), *A. flavus* (n=1), *A. fumigatus* (n=1), *A. terreus* (n=1), *Cladosporium* sp. (n=1), *Paecilomyces* spp. (n=1), *Scopulariopsis* sp. (n=1) and *Trichoderma* sp. (n=1).<sup>88</sup>

The yeast of the genus *Malassezia* was also identified in 44 patients with pityriasis versicolor: *M. globosa* was the predominant pathogen (47.7%), followed by *M. furfur* (15.9%), and *M. sloffiae* (15.9%).<sup>89</sup> In another study in Turkey, 49 out of 264 (18.5%) folliculitis patients were diagnosed

(using cytological examinations with May-Grünwald-Giemsa stain) with *Malassezia* folliculitis (MF). PCR sequencing of the rDNA internal transcribed spacer region showed that *M. globosa* was the most common agent, followed by *M. sympodialis*, *M. restricta*, and *M. furfur*.<sup>90</sup>

### **Conclusion**

Overall, our study reports a first picture of the frequency and epidemiological estimation of serious and invasive fungal infections in Turkey. As a limitation, the modeling estimates reported in the current study are substantially more than the documented cases, suggesting a 'diagnostic gap' for fungal infections among public health agencies. While Turkey has a good network of professional mycologists in diagnostic laboratories and there are many publications originating from the country, the public health aspects of fungal disease is lacking. Non-culture based diagnostic testing is somewhat patchy in Turkey. Molecular tests are not routinely available, and galactomannan antigen testing is only performed at 38 centers across country (24 University clinics and 14 state Hospitals). Antifungal availability is good, although voriconazole (a WHO Essential Medicine) is expensive and topical natamycin is not available. Additional prospective and comprehensive surveillance, and formal epidemiological studies are warranted to validate these measures towards management of fungal diseases.

### **Potential conflict of interest**

The authors declare no conflict of interests related to this publication.

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### Table legends

**Table 1:** Documented episodes of fungal infections in Turkey from 1920 to 2017.

**Table 2.** The estimated burden of serious fungal infections in Turkey.

**Table 3:** The estimated annual incidence of superficial fungal infections in Turkey.

### Figure legends

**Figure 1.** Turkey population density map and localization of cities with active organ transplant programs.

**Table 1:** Documented episodes of fungal infections in Turkey from 1920 to 2017.

	Totals	No / other underlying disease	HIV/AIDS	Respiratory disease	Cancer + immunocompromised	Critical care + surgery
Cryptococcal meningitis	60	23	14	6	13	4
<i>Pneumocystis pneumonia</i>	100	35	15	3	38	9
Invasive aspergillosis	605	11	2	35	531	16+10
Chronic pulmonary aspergillosis post TB	244	234	1		8	1
Chronic pulmonary aspergillosis - all	30	10		7	10	3
Allergic bronchopulmonary aspergillosis	39	26		12		1
Fungal rhinosinusitis	293	164		3	124	2
Candidemia	3,847			600	1,930	1,701+640
<i>Candida peritonitis</i>	67	66			1	
Oral candidiasis	540	252	54	54	125	55
Oesophageal candidiasis	120	52	2	1	65	
Recurrent <i>Candida</i> vaginitis (>4x/year)	525	525				
Mucormycosis	416	120	2	29	223	42
Invasive fusariosis	18				17	
Sporotrichosis	8	8				
Fungal keratitis	95	95				
Tinea pedis	37,933	36,387				
Tinea capitis	7,892	7,804				
Onychomycosis	13,319	12,864				
Disseminated infections by melanized fungi	6	6				

<i>Malassezia</i> infections	488	488				
<i>Scedosporium</i> infections	18	18				
Histoplasmosis	6	4			2	

**Table2.** The estimated burden of serious fungal infections in Turkey.

Fungal Diseases	Rate/100,000	Total Burden
<b>Cryptococcal meningitis</b>	0.13	106
<i>Pneumocystis</i> pneumonia	0.79	635
Invasive aspergillosis	4.84	3,911
Chronic pulmonary aspergillosis	7.29	5,890
Allergic bronchopulmonary aspergillosis	40.33	32,594
Severe asthma with fungal sensitization	53.20	42,989
Allergic fungal rhinosinusitis	392	312,994
Candidaemia	4.76	3,847
<i>Candida</i> peritonitis	0.80	649
Oral candidiasis	5.61	4,536
Oesophageal candidiasis	0.76	618
Recurrent <i>Candida</i> vaginitis (>4x/year)	3,342	1,350,371
Fungal keratitis	33.00	26,671
<b>Total:</b>	<b>3,886</b>	<b>1,785,811</b>

**Table 3:** The estimated annual incidence of superficial fungal infections in Turkey.

Fungal Diseases	Rate/100,000	Total Burden
<b>Tinea pedis</b>	2,215	1,790,438
<b>Tinea capitis</b>	54	43,864
<b>Onychomycosis</b>	2,139	1,728,699
<b>Total:</b>	<b>4,409</b>	<b>3,563,000</b>

