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ORIGINAL ARTICLE

WILEY mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Estimated burden of serious human fungal diseases in Turkey

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Summary

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 sensitisation (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 (5890 cases) (7.29/100 000). The estimated annual incidence for invasive aspergillosis is lower (3911 cases) (4.84/100 000 annually). Among about 22.5 million women aged 15-50 years, recurrent vulvovaginal candidiasis is estimated to occur in 1 350 371 (3342/100 000) 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 modelling estimates reported in the current study might be substantially under- or overestimated, formal epidemiological and comprehensive surveillance studies are required to validate or modify these estimates.

KEYWORDS

candidiasis, invasive aspergillosis, recurrent *Candida* vaginitis, serious fungal infection, severe asthma with fungal sensitisation, Turkey

1 | INTRODUCTION

Fungal infections are considered as a major public health concern, worldwide.[1] 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, hospitalised with severe underlying diseases (eg acute myelogenous leukaemia), require complex surgical procedures (eg for trauma) and need support in intensive care units.[2] In addition, chronic pulmonary aspergillosis (CPA)—a chronic progressive infection that destroys lung tissue in nonimmunocompromised patients—is thought to affect about 3 million people, worldwide.[2,3] CPA complicates pre-existing lung disease such as pulmonary tuberculosis (TB), nontuberculous mycobacterial infection, asthma, allergic bronchopulmonary aspergillosis (ABPA), chronic obstructive pulmonary disease (COPD), sarcoidosis and pneumothorax.[4] If untreated, 50%-85% of patients with CPA will die within 5 years.[5,6]

Knowledge of the local epidemiology of invasive and serious fungal infections, as well as risk factors for infection, is essential

for effective infection control programmes 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 socioeconomic diversity. Several studies have examined the epidemiology of fungal infections and antifungal utilisation in Turkey,[7-10] but most were local, single-centre 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%).[9] A single-centre 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.[8] Another study reported the epidemiological trends in antifungal treatment on the national level;[11] 408 patients and 505 episodes of invasive fungal infections was recorded. In this study, data were collected from 7 major hospitals (7052 beds), representing 26% of all the beds in university hospitals and 16% of all education hospitals across Turkey. However, these data are over 15 years old. In another retrospective study,[12] the cumulative incidences of invasive fungal infections in Turkish paediatric 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.[12]

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

2 | 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 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.[6,16,17] Where there were 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.[3]

The first case of *Pneumocystis* pneumonia (PCP) in Turkey was reported in 1955.[18] Since then, the majority of studies in Turkey have been directed towards evaluation of efficacy of diagnostic methods.[19] 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[20] from Eastern Europe.

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

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.[22] The burden of ABPA in adults with asthma and its correlation with CPA was considered 2.5% (range 0.72%-3.5%).[23] The prevalence of severe asthma with fungal sensitisation (SAFS) was estimated as the worst 10% of the total asthma population, of whom at least 33% have fungal sensitisation. The number of patients with COPD in the general population of Turkey was considered 4.2% in those 40 years and older,[24] of whom 19.3% had been hospitalised[25,26] and 36% reported experiencing an exacerbation of their respiratory condition.[27] COPD classification was done according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. GOLD stages I, II, III, IV refer to COPD severity of mild, moderate, severe and very severe, respectively.[28] The rate of IA in the context of hospitalised patients with COPD was estimated 13 cases per 1000 admissions as described previously by Guinea et al.[29]

Recent data also suggest that chronic rhinosinusitis affects approximately 1%-1.5%, 11% and 12.5% of the population in North India (rural), the European Union and the United States, respectively.[30,31] The proportion of allergic rhinosinusitis attributed to

fungal sensitisation appears to vary between 0.11% and 27%,[31-35] depending on the geographical regions favouring 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 leukaemia (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). Equal number of cases was considered in all other haematological patients. The risk of IA development was considered in 10% of these patients as reported previously in France[36] and Austria[37] and an equal number for all other haematological 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.[38]

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.[6]

To estimate the number of candidaemia and *Candida* peritonitis cases, the annual incidence of 5/100 000 and 1.5/100 000, respectively, was used, in the absence of any national or regional population incidence data.[39,40] 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).[41] We assumed an infection rate of 1.6 episodes/patient-year and that 2% were attributable to fungi.[42] The burden of oropharyngeal and oesophageal candidiasis was assessed using incidence data previously published in the literature.[43-45] 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.[46,47]

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

3 | 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 as follows: 66 cases of

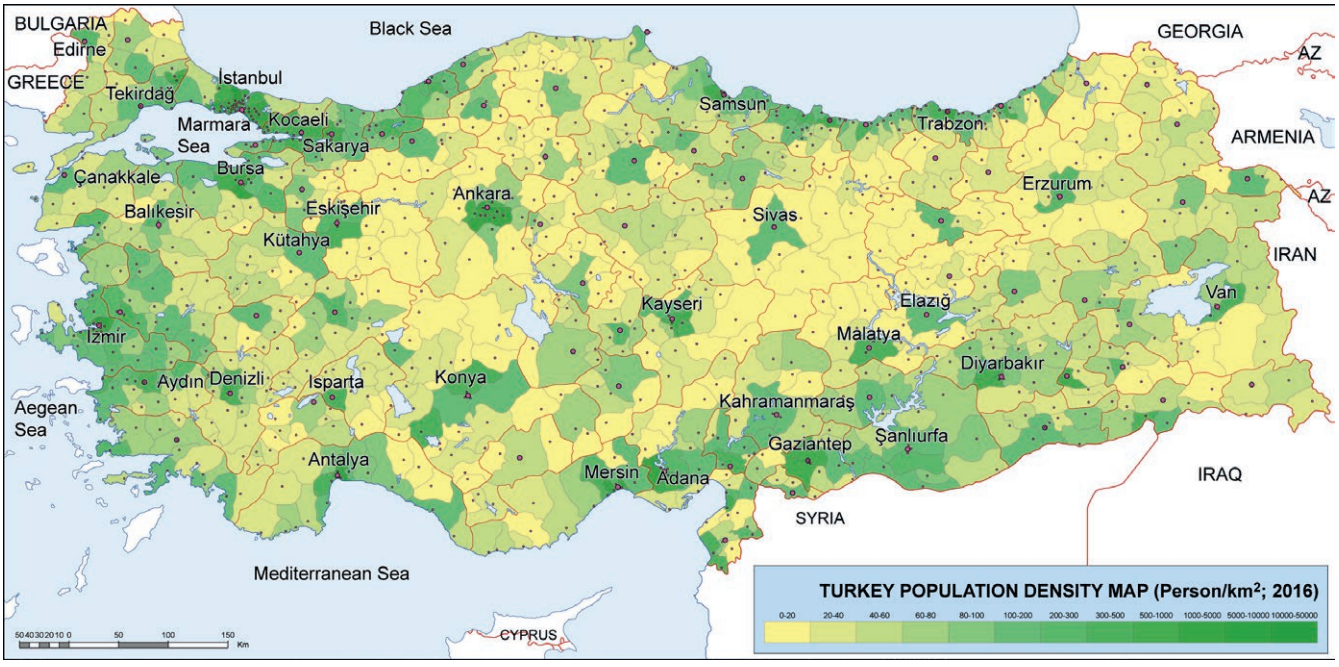

FIGURE 1 Turkey population density map and localisation of cities with active organ transplant programmes

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	66	23	14	6	16	4
Pneumocystis pneumonia	101	36	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 - other	30	10		7	10	3
Allergic bronchopulmonary aspergillosis	39	26		12		1
Fungal rhinosinusitis	293	164		3	124	2
Candidaemia	3847			600	1930	1701 + 640
Candida peritonitis	67	66			1	
Oral candidiasis	540	252	54	54	125	55
Oesophageal candidiasis	120	52	2	1	65	
Recurrent *Candida* vaginitis (>4 times/y)	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	7892	7804				
Onychomycosis	13 319	12 864				
Disseminated infections by melanised fungi	6	6				
Malassezia infections	488	488				
Scedosporium infections	18	18				
Histoplasmosis	6	4			2	

cryptococcal meningitis, 101 cases of PCP, 605 cases of IA, 244 cases of CPA following TB, 39 cases of ABPA, 293 cases of fungal rhinosinusitis, 3847 cases of candidaemia, 67 cases of *Candida* peritonitis, 540 cases of oral candidiasis, 120 cases of oesophageal candidiasis, 525 cases of RVVC, 416 cases of mucormycosis, 18 cases of *Scedosporium* infections, 18 cases of disseminated fusariosis, 8 cases of sporotrichosis, 6 cases of histoplasmosis and 6 cases of disseminated infections by melanised fungi. In addition, 37 933 cases of tinea pedis, 13 319 cases of onychomycosis, 7 892 cases of tinea capitis, 488 cases associated with *Malassezia* infections and 95 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 Table S1.

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 summarises the burden of different fungal diseases and their incidence or prevalence per 100 000 inhabitants as estimated from our study.

3.1 | 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 4000 and 7000 with approximately 56% (45%-72%) of patients receiving antiretroviral therapy (ARV). In the current study, 66 cases of cryptococcal meningitis, and 101 cases of PCP,[52] were diagnosed over an 18-year period (1998-2016). Taking undiagnosed HIV/AIDS infections into account and based on the incidence rate published previously,[6,20] 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.

TABLE 2 The estimated burden of serious fungal infections in Turkey

Fungal diseases	Rate/100 000	Total burden
Cryptococcal meningitis	0.13	106
Pneumocystis pneumonia	0.79	635
Invasive aspergillosis	4.84	3911
Chronic pulmonary aspergillosis	7.29	5890
Allergic bronchopulmonary aspergillosis	40.33	32 594
Severe asthma with fungal sensitisation	53.20	42 989
Allergic fungal rhinosinusitis	392	312 994
Candidaemia	4.76	3847
Candida peritonitis	0.80	649
Oral candidiasis	5.61	4536
Oesophageal candidiasis	0.76	618
Recurrent *Candida* vaginitis (>4 times/y)	3342	1 350 371
Fungal keratitis	33.00	26 671
Total:	3886	1 785 811

3.2 | Invasive aspergillosis (IA)

In our study, a total of 3911 cases (4.84/100 000 annually) of IA were estimated to occur in Turkey, mainly in cancer/immunocompromised patients followed by patients with severe COPD and those hospitalised in ICU.

IA is a common complication in severely immunocompromised patients with haematological malignancies, such as bone marrow transplantation recipients or patients under extensive chemotherapy for haematological 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 some other haematological patients develop IA.[36,37] Patients with solid tumours also are at risk for IA because they may develop neutropenia as a result of chemotherapy and radiotherapy.[38] The estimated number of IA in the lung cancer population of Turkey is about 637 cases (2.6%). In 2017, a total of 4906 SOTs were performed in the Turkey including 3342 kidney (2649 living + 693 deceased), 1446 liver (1087 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.[26] Of note, patients with severe COPD who are receiving broad-spectrum antibiotics and corticosteroids are one of the main risk groups to develop IA.[29,53] We estimated that around 2782 COPD patients develop IA annually in Turkey, assuming 13 cases per 1000 hospitalised COPD.[29] The number of patients admitted to hospital with COPD in Turkey is estimated 214 005 cases per year among Turkey's general population ≥40 years old.[24] 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 ≥18 years old was 4.5%.[54]

3.3 | Noninvasive pulmonary aspergillosis

Individuals with chronic respiratory disease are susceptible to airborne fungal infections including ABPA,[23] SAFS[55] and CPA.[3] 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.[3] Post-TB cavitation acts as a predisposing factor for the colonisation of *Aspergillus* spp., largely owing to the development of empty residual lung cavities.[3] Given that numerous other conditions are associated with CPA, including pneumothorax, sarcoidosis, asthma and nontuberculous mycobacterial infections,[6] we estimate that TB contributes 33% of the cases and the overall prevalence of CPA is 5890 (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%,[23] 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* and other fungal sensitization prevalence of 33%.[56] Atopic adults with rhinitis or asthma of all severities tested in Ankara for sensitisation to *Alternaria* spp. and *Cladosporium* spp. by skin prick test were positive in 11.9% and 8.1% of cases, respectively; *Aspergillus fumigatus* was not tested.[57] This frequency is similar to other European countries.[58] Older data are indicative of a high rate of sensitisation to *A. fumigatus*—26% in one series of asthmatic (73%) and allergic rhinitis patients.[58]

3.4 | Allergic fungal rhinosinusitis (AFRS)

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

3.5 | Invasive candidiasis

Invasive candidiasis is the main invasive fungal infection that affects worldwide more than 700 000 people each year,[2] with various clinical presentations from intra-abdominal infections to deep-seated infections and candidaemia. The disease is particularly diagnosed in intensive care units.[39] The total incidence of candidaemia for Turkey is 3847 cases/year (4.76/100 000), of which 1701 occurred in critical care settings and 1930 in cancer/immunosuppressed patients. The incidence of candidaemia was in agreement with a general conservative rate of 5 per 100 000 population, as described previously.[39] Candidaemia is only one manifestation of invasive candidiasis, as blood cultures are often (~50 %) falsely negative.

Candida peritonitis is still a severe disease with a mortality rate of at least 38%, as high as for candidaemia, most commonly affecting those following complex abdominal surgery or pancreatitis.[64,65] 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 candidaemia cases,[40] 387 cases are estimated to occur in Turkey annually as postsurgical *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 centres in north-west Turkey (15 cases over 10 years in 795 patients; 0.2%),[66] but may be conservative as most studies have found fungal peritonitis makes up 6%-10% of infection episodes.

3.6 | 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.[67] 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 colonisation." VVC, however, is defined as signs and symptoms of inflammation in the presence of *Candida* spp. and in the absence of other infectious aetiologies.[46] 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 (>4 times/y).[46,47] 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.[46,47] The gold standard mycological methods used for diagnosis include microscopic examination, fungal culture and antigen tests.[46,47]

In a single-centre 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 noncontraceptive 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%).[67] 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.[68] Iskit et al[69] noted a significantly higher prevalence of yeast, 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 ($P < 0.01$). Arıdogan et al[70] also highlighted the potential medical benefits of circumcision as a significant factor decreasing the colonisation rate of *Candida* and *Malassezia* yeast.

In HIV patients, oral candidiasis is a frequent condition occurring at least once in 90% in those with low CD4 cell counts.[43,44] Using this assumption, HIV infection is responsible for 4050 cases, and other risk groups, such as head and neck cancer and inhaled corticosteroids contribute more cases. So at least 4536 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.[45] 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.

3.7 | 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 haematological malignancy (223 cases) and diabetic ketoacidosis (214 cases).

3.8 | 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.[71] However, according to our estimates, invasive scedosporiosis, fusariosis, sporotrichosis and disseminated infections by melanised fungi are rare fungal infections in Turkey (Table 1). In addition, there are a limited number of histoplasmosis cases reported from Turkey,[72,73] given that infected patients are mostly asymptomatic. Of note, the first case of histoplasmosis was reported in Turkey in 1946 by Saglam.[74]

Moreover, a recent study in Turkey found that 14.2% of the iatrogenically immunosuppressed patients without HIV had pulmonary microsporidiosis,[75] which suggests that *Microsporidia* spp. should be taken into account in the differential diagnosis of pulmonary infections in immunosuppressed patients. *Microsporidia* are highly specialised obligate intracellular organisms that are recently reclassified with the fungi.[76] 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 diarrhoea and systemic disease.

3.9 | Fungal keratitis

Fungal keratitis is a challenging condition in ophthalmological practice in developing countries, including Turkey.[77] 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 depend 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[49] reviewed the medical records of microbial keratitis clinically diagnosed at the Izmir Ataturk Training and Research Hospital from 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. (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),[16] Malaysia (1.3/100 000)[78] and Egypt (14/100 000)[79] and less than Pakistan (44/100 000)[80] and Nepal (73/100 000).[81]

3.10 | 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".[82,83] The study of Celal Muhtar in the dermatophyte arena was continued by Talad,[84] and Englaender,[85] who described the first cases of favus and onychomycosis in Turkey, respectively.

Tinea capitis is one of the most common causes of paediatric 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.[86] 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.

TABLE 3 The estimated annual incidence of superficial fungal infections in Turkey

Fungal diseases	Rate/100 000	Total burden
Tinea pedis	2215	1 790 438
Tinea capitis	54	43 864
Onychomycosis	2139	1 728 699
Total	4409	3 563 000

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, 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%.[87] 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 centre 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 in 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).[87] In another study evaluating 1222 samples of nail scrapings from 1146 patients, nondermatophytic fungi were responsible for approximately 50% of onychomycoses cases attending the dermatology outpatient clinic of a university hospital in Izmir, Turkey.[88] Dermatophytes were detected in 175 (48%), yeasts in 150 (41%), moulds in 33 (9%) and mixed (two different fungi) in 8 (2%) patients. The agents of mould 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).[88]

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%).[89] 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*.[90]

4 | 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 modelling estimates reported in the current study are substantially more than the documented cases, suggesting a "diagnostic gap" for fungal infections. 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 are lacking. Nonculture-based diagnostic testing is somewhat patchy in Turkey. Molecular tests are not routinely available, and galactomannan antigen testing is only performed at 38 centres 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.

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CONFLICT OF INTEREST

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