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General review

The incidence and prevalence of serious fungal diseases in Tunisia

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ABSTRACT

With increasing concern about the negative health impact of fungal disease, there is a need to survey what is and is not known about the epidemiology of these infections in Tunisia. We have estimated the incidence and prevalence of the most serious fungal diseases in Tunisia for the first time. Using published literature from Tunisia, or if absent other countries, we have estimated the burden of life-threatening fungal infections and those causing significant morbidity, using deterministic modeling, based on populations at greatest risk. An estimated 250,494 (2.12% of the Tunisian population) are affected by a serious fungal disease annually. Invasive and chronic pulmonary aspergillosis are relatively common with 708 and 2090 patients affected, partly linked to the prevalence of chronic obstructive pulmonary disease (COPD). Fungal asthma (allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization) have an estimated prevalence of 38,264 (5.8% of the adult asthma population). Fungal keratitis probably affects 1,761 eyes annually, often leading to uniocular blindness. Candidaemia and *Candida* peritonitis probably affect at least 680 people annually, with a high mortality. Recurrent vulvovaginal candidiasis probably affects over 200,000 women. While fungal diseases are regularly diagnosed in Tunisia, epidemiological studies with denominators are uncommon. Some fungal diseases are poorly addressed with the current diagnostic portfolio, and surveillance is lacking. Studies on these diseases and the implementation of a national program of surveillance are required.

Introduction

Fungal infections or mycoses cause a wide range of diseases in humans, most of which have been documented in Tunisia. They vary in extent from superficial infections such as tinea capitis, onychomycosis, vulvovaginal candidiasis to disseminated and invasive infections including invasive candidiasis, invasive aspergillosis (IA), mucormycosis, *Pneumocystis jirovecii* pneumonia (PCP) and cryptococcal meningitis.

Morbidity and mortality attributed to fungal diseases are underestimated. Until recently it was thought that about 2 million people die from invasive fungal infections each year in the world; this estimate has been updated to about 3.8 million [1–3]. The incidence of invasive fungal infections has probably increased recently, particularly in immunocompromised and intensive care unit (ICU) patients, not only in Tunisia but also worldwide. However knowledge about fungal disease is lacking in many countries and diagnostic provision in much of Africa is limited [4,5]. In this paper, we summarize what is and is not known about the epidemiology of fungal disease in Tunisia, and estimate its burden.

Medical mycology as a discipline has a long history in Tunisia, even though its beginnings are poorly documented. The first laboratory to be involved in diagnosis of mycosis was that of Pasteur Institute of Tunis; followed by La Rabta Teaching Hospital, Military Hospital of Instruction of Tunis, Farhat Hached Teaching Hospital of Sousse, Fattouma Bourguiba Teaching Hospital of Monastir, Habib Bourguiba Teaching Hospital of Sfax and Charles Nicolle Teaching Hospital in Tunis. Before the implementation of the laboratory of parasitology in Charles Nicolle Hospital, the diagnosis of superficial mycoses was carried out in a small laboratory unit housed within the Department of Dermatology of the same hospital. No laboratory exclusively devoted to mycology was created and mycology was usually integrated with parasitology.

At first, the laboratory of Pasteur Institute of Tunis was managed by French medical staff, later by Prof. Mohamed Sadok Ben Rachid (1933–2004). He trained three doctors in medical mycology: Prof.

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Moncef Ben Said, Prof. Ali Ayadi and Prof. Riadh Ben Ismail and founded the laboratory at La Rabta University Hospital subsequently managed by Prof. Emna Chaker.

Initially diagnosis of mycoses was limited to superficial infections such as tinea capitis and usually was based on clinical presentation alone because of scarcity of labs and technologists. Studies of tinea capitis and dermatophytes have been carried out since 1952. Mycology has progressively developed and extended from the diagnosis of superficial to invasive fungal infections. However, diagnostic tools in Tunisia are still incomplete [5]. Molecular methods are only available in a few laboratories and usually used for research purposes and rarely for diagnosis. Because of the current global context and in the wake of the Covid-19 pandemic, fungal infections do not yet appear to be a national health priority. Thus, in this study, we aimed to provide estimates of the burden of some fungal infections using published and local data.

Methods

Key population denominators and populations at risk for different fungal diseases are described in Table 1. Population data were taken from the Central Intelligence Agency (CIA) world fact book [6]. Human Immunodeficiency Virus (HIV) prevalence and (Acquired Immunodeficiency Syndrome (AIDS) deaths were taken from the 2021 UNAIDS report [7]. We assumed that HIV-infected people (PLHIV) not taking antiretroviral therapy (ART) have a fall in CD4 count to <200/uL over 7 years and that in those persons living with HIV (PLHIV) taking ART, they are non-compliant or have viral resistance in 11%. Pulmonary tuberculosis (TB) annual incidence was taken from the World Health Organization (WHO) Global Tuberculosis Report 2020, and we derived the pulmonary TB survivors [8]. Asthma prevalence in adults was taken from a cross-sectional survey of 4470 interviewees in Tunis in 2009–2010 [9]. The prevalence of chronic obstructive pulmonary disease (COPD) prevalence was taken from the BOLD study reported by Daldoul et al. with 11.3% patients admitted to hospital each year [10]. Lung cancer annual incidence was taken from Global Cancer Observatory [11] and acute myeloid leukaemia (AML) from the WHO expert committee on middle income countries[12]. Between June 1986 and December 2015, there had been 1686 kidney transplants performed in Tunisia [13]. According to National Center for the Promotion of Organ Transplantation CNPTO, 132 kidney transplants were performed in 2010 and 125 in 2013. Heart, liver, and pancreas transplantation are also practiced in Tunisia but less frequently than kidney transplantation [14,15]. In 2012, 45 allogeneic hematopoietic stem cell transplants were done [16].

To derive fungal disease estimates, published articles were retrieved from PubMed/Medline searches in English and French. The keywords searched were: Tunisia, fungal infection, fungal disease, HIV/AIDS, tuberculosis, chronic pulmonary, *Cryptococcus, Candida*, candidiasis, *Aspergillus*, aspergillosis, mucormycosis, *Pneumocystis*, tinea capitis, keratitis, otitis, mycetoma, onychomycosis. We also drew on recently published reviews which collated the global cases of mycetoma and chromoblastomycosis.[18,19] If data on a particular fungal infection was not available for Tunisia, we considered data from neighboring countries preferably or data from countries outside North Africa. The assumptions used to estimate fungal diseases incidence and prevalence are shown in Table 2.

We used unpublished laboratory data from Sousse to estimate tinea capitis from 2009 to 2018 (10 years inclusive), assuming patients only came from this area.

Table 1
Population and underlying disease demographics in Tunisia used for our estimations.

Data	Number	Comments	Reference
Population	11,818,000	2020	[6]
Proportion children 0–14	2,718,140	25% of the population	[6]
HIV/infection	5400	Prevalence of HIV/AIDS, 2021	[7]
Pulmonary tuberculosis	1505	Annual incidence 2020	[17]
Asthma in adults	659,740	6.9% prevalence	[9]
COPD patients	827,260	7.8% of those >40 years of age	[10]
Lung cancer	2927	2020	[11]
Acute leukaemia	449	3.8/100,000 incidence	[11,12]
Renal transplantation	125		[13,15]
Allogeneic HCST	45		[16]

Results

Tunisia is located in Northern Africa and encompasses 163,610 square kilometers with a population of 11,818 million people in 2020. Children between 0 and 14 years old represent 25% of the population (2,718,140) (Table 1). The sex ratio male/female is 0.95 for people aged 25–54. In 2021, the gross domestic product per capita was 10,720 USD, placing Tunisia as an upper middle income country [47].

In Tunisia, several single-center studies addressing fungal infections are published every year and usually limited to one-off studies. Data on fungal infections have not been standardized and some fungal diseases such as chronic and allergic mycoses are very poorly documented. The individual and total burden estimation of fungal diseases and the rate per 100,000 inhabitants of each fungal disease is given in Table 3. Overall 251,219 people (2.13% of the population) are estimated to suffer from a serious fungal disease in any one year.

Chronic and allergic pulmonary aspergillosis

The incidence of tuberculosis in Tunisia increased by 2.86% between 2019 and 2020, from 35 to 36 cases/100,000 population in 2020. According to WHO, there were 1505 new cases of pulmonary tuberculosis in 2020 and 136 deaths (0.22 %) [17]. The incidence of CPA co-infection with TB is probably 40 cases annually and another 36 cases are probably mistaken for TB. At the end of anti-tuberculous therapy (4–12 months after TB diagnosis), we estimate another 140 patients having CPA, an annual incidence figure of 216 patients most of whom are probably classified as TB currently. Of these, we would expect 15 deaths, given a 20% 12 month mortality. Another 20 patients would be expected to present with CPA annually in the years after cure of TB, most with residual cavitations. Given the mortality in year one and in subsequent years (7.5%), we anticipate a prevalence of ~1045 patients linked to TB.

In Tunisia, there is a paucity of population-based data on chronic obstructive pulmonary disease (COPD) prevalence. According to Daldoul et *al.;* the prevalence of COPD was 7.8% of those aged over 40 years (over 334,300 people) [10]. Given the many other respiratory disorders linked to CPA of which COPD is the most common), we estimate a 5 year period prevalence of 2090 CPA cases (17.8/100,000) (Table 3).

Asthma is common in Tunisia. Its prevalence documented in a cross-sectional study in Tunis in 2010 was 6.9% in adults (15 years old and over) and 5.7% in children [9]. The estimated global rate of ABPA among asthmatic adult patients is 2.5%, partly based on data from Saudi Arabia [23]. Thus, we estimated that there are 659,740 asthmatic adults in Tunisia of whom 16,493 are estimated to have ABPA (140/100,000) (Table 3). Cystic fibrosis is barely recognized in Tunisia. Severe asthma with fungal sensitization (SAFS) occurs at a prevalence of 3.3% in the asthma population according to previous estimates. The prevalence estimate of SAFS in asthmatic adults is 21,771 (184/100,000) (Table 3). There is likely some overlap between

Table 2
Fungal disease incidence or prevalence assumptions and sources. .

Fungal Infection	Underline condition	Assumptions	Reference
Chronic pulmonary aspergillosis post TB	Respiratory disease	20% of unconfirmed PTB cases, 10% of PTB patients as they complete therapy, 6.5% annually of PTB survivors with a cavity and 0.2% without and a 20% year 1 and 10% year 2–5 mortality.	[20,21]
Chronic pulmonary aspergillosis - all	Respiratory diseases	50% of CPA cases related to TB	[22]
Allergic bronchopulmonary aspergillosis (ABPA)	Respiratory diseases	2.5% of adult asthmatics	[3,23,24]
Severe asthma with fungal sensitisation (SAFS)	Respiratory diseases	33% of 10% adult asthmatics with severe asthma	[3,25]
Cryptococcal meningitis	HIV/AIDS	2.9% in HIV/AIDS patients with CD4 < 200/ul In Tunisia 6/22 (27.3%) occurred in non-HIV patients.	[26–29]
Candidaemia	Cancer Surgery Critical care	5/100,000 33% in ICU	[1,30,31]
Candida peritonitis	Critical care, major surgeries	50% cases of candidaemia in ICU	[1,32]
Oesophageal candidiasis	HIV/AIDS	20% of new HIV/AIDS patients and 5.0% of those on ARVs	[33,34]
Recurrent *Candida* vaginitis (≥4x/year)		6% females aged 15–49	[35,36]
Invasive aspergillosis	HIV/AIDS respiratory diseases, cancer	15% of AML develop IA and an equal number of non-AML hematological conditions. 2.6% of lung cancer patients and 1.3% COPD annual admissions and 1% of renal transplant recipients	[37–42]
Mucormycosis		0.2/100,000	[43]
Pneumocystis pneumonia	HIV/AIDS	33% of newly presenting patients with AIDS	[44]
Tinea capitis		Sousse data 14.9/100,000	Unpublished
Fungal keratitis		14/100,000	[45,46]

ABPA and SAFS, but overall, about 5.8% of the adult asthma population, and many of the worst affected probably have fungal asthma, amenable to antifungal therapy.

Invasive fungal diseases in non-HIV patients

Invasive fungal infections are most common in cancer, transplant, severe COPD, poorly controlled diabetes, renal failure and in those requiring intensive care (including premature infants) or major surgery. According to Ben Ayed et *al*., 12,189 new cases of cancer and 7339 related deaths were reported in 2012 in Tunisia; and the top three cancers in Tunisia are lung (463.6/100,000 population), prostate (128/100,000 population) and colorectum (117.5/100,000 population) in males and breast (241/100,000 population), colorectum (111.7/100,000 population), and ovary cancer (86.5/100,000 population) in females [48]. According to Globocan, there were 19,446 new cases of which 2927 were cases of lung cancer and 11,855 deaths caused by cancer in Tunisia in 2020 [11]. Leukaemia (all forms) was estimated at 617 by Globocan, but we have assumed that 449 of these are AML patients based on WHO general estimates, possibly a slight over-estimation. The National Center for Stem Cell Transplantation is the only facility in Tunisia performing HSCT and each year, 40 to 50 allogeneic HSCT are performed, giving a total of 789 from 1998 to 2018. The main indications are leukemia (48%) and aplastic anemia (36%). A total of 60 to 70 autologous HSCT are performed yearly for a total of 1713 during the same period; 70% are for multiple myeloma and nearly 30% for lymphomas. It was reported that 20% of these patients had an history of aspergillosis [49].

Starting in 1986 at Charles Nicolle Hospital, there were 132 renal transplants in 2010 and 90 in 2016 (CNPTO). Tunisia has an advanced kidney transplantation program in 7 units including 20% from deceased kidney donors [13,14]. Rarely a liver transplant will be done. In a retrospective study in Sfax, Trabelsi et al. reported 11 cases (3.4%) of invasive fungal infections (IFI) among 324 transplant patients in the study period between 1995 and 2012. Those IFI included four cases of PCP, two cases each of invasive candidiasis, IA and cryptococcosis and one case of mucormycosis.

In a retrospective study in the Sousse Region in 2011, Saghrouni et *al*. found an average of 24 candidaemia episodes per year from 1995 to 2009 with an incidence 12.2/1000 admissions in neonatology and

Table 3
Incidence and prevalence of serious fungal diseases in Tunisia.

Infection		Number of infections per underlying disorders per year					Rate/ 100K	Total burden (%)
	Incidence or prevalence	None	HIV/AIDS	Respiratory	Cancer/ transplant	ICU		
Chronic pulmonary aspergillosis	P	–	–	2090	–	–	17.7	2090
ABPA	P	–	–	16,493	–	–	140	16,493
SAFS	P	–	–	21,771	–	–	184	21,771
Oesophageal candidiasis	I	–	272	–	–	–	2.3	272
Cryptococcal meningitis	I		36	–	10	–	0.4	46
Pneumocystis pneumonia	I	–	144	–	?	–	1.22	144
Invasive aspergillosis	I	–	–	76	140	491	6.0	708
Mucormycosis	I	–	–	–	23	–	0.2	23
Candidaemia	I	–	–	–	414	177	5	591
Candida peritonitis	I	–	–	–	–	89	0.8	88
Recurrent vaginal candidiasis (>4 times/year)	P	204,400	–	–	–	–	3459*	204,400
Tinea capitis	P	1761					14.9	1761
Fungal keratitis	I	1655	–	–	–	–	14	1655
Total burden estimated		207,835	884	40,431	587	757		250,494

ICU = intensive care unit; ABPA = Allergic bronchopulmonary aspergillosis; SAFS = Severe asthma with fungal sensitization;.
* = females only.

4.6/1000 admission in ICU [30]. As there are 270 ICU beds in Tunisia and the median length of stay is 6 days, we estimate about 16,425 ICU admissions annually. This computes to 75 cases of candidaemia annually in ICU. We have assumed that 5/100,000 are affected in all patient groups, an annual incidence of 591 cases, of which 177 (33%) occur in ICU (Table 3), probably indicating significant underdiagnosis [31]. *Candida albicans* is still reported as the most frequent species [30]. Non *albicans* species are increasingly reported mainly: *Candida tropicalis, Candida krusei* and *Candida glabrata.*

Assuming that there are half as many patients with *Candida* peritonitis as those with candidemia in ICU, we estimate that the annual incidence of *Candida* peritonitis is 89 [1]. In a retrospective study in the region of Sousse, from 2006 to 2016, 186 peritonitis episodes in peritoneal dialysis patients were recorded of which five were attributed to *Candida* spp. (5.8%) [50]. Ajimi et al. reported 12 fungal peritonitis cases in a 32 years retrospective study in the years 1983 to 2015 in peritoneal dialysis patients in Tunis. Two were caused by *Candida albicans* [51,52]. There are probably about 90 cases of *Candida* peritonitis annually.

IA is consistently the most common fungal infection in leukaemia and haematopoietic allogeneic stem cell transplant (HSCT) patients, as well as COPD patients. IA accounts for 30 to 50% of invasive mycoses and is currently the most frequent invasive mycosis, followed by candidemia in hematology [53]. IA is a relatively rare complication in solid organ transplant recipients but with deleterious consequences. Its incidence remains below 10 % [54]. Increasing recognition of IA in both intensive care patients (including influenza and Covid-19) and also COPD patients has probably significantly increased case numbers in recent years. We estimated the number of IA cases annually at 76 cases in lung cancer, 140 cases in leukaemia and transplant recipients and 491 in ICU and COPD patients, an annual total of 708 (6.0/100,000).

The estimated annual incidence of mucormycosis primarily in those with poorly controlled diabetes or malignancy (occasionally trauma and intravenous drug use) is 23. The first tunisian case of rhinocerebral mucormycosis was reported by Ben Said et *al.* in 1994 [55]. Later, additional new cases were repeatedly reported [56–63]. In the region of Sousse, we counted 29 cases from 1992 to 2022, most of them the rhinocerebral form.

HIV-related opportunistic infections

In 2021 UNAIDS estimated that there were 5400 persons living with HIV in Tunisia with 1600 on ART (30%) [7]. CD4 cells count and viral load are evaluated once every 12 months for patients who are stable on ART. We estimate that the population of patients at risk of a serious opportunistic infection is 960 (lower than the UNAIDS estimate of 25% of PLVIH had CD4 <200). Fewer than 500 people are reported dying of AIDS annually, probably fewer than 200. Cryptococcosis, PCP and mucosal candidiasis are the fungal diseases most commonly associated with AIDS.

Considering a 20% attack rate of oesophageal candidiasis in HIV patients with CD4 cell count <200, and a 5% rate in those on ART, we estimated the annual incidence of 272 (2.3/100,000 population). Many more cases are very likely in other at risk patient groups. Assuming an incidence of 33%, we estimate 144 cases (1.22/100,000) of PCP in HIV patients, and probably at least double that number in other immunocompromised patients.

There are no epidemiological data about cryptococcosis in Tunisia but many studies have reported numerous cases. We estimated an incidence of 46 cases of cryptococcal meningitis, 36 of them in HIV-infected patients. We collected cases from published and local data and we counted 135 cases of documented cryptococcal meningitis from 1991 to 2019 in different centres of the country. In a study carried out in La Rabta Hospital in Tunis, between 1995 and 2006, 22 cases of cryptococcal meningitis were diagnosed among 350 specimens of CSF examined. Sixteen patients were HIV positive whereas 6 patients carried other immunosuppressive conditions [64]. Therefore, we estimate an additional 10 cases nationally in other patient groups (0.4/100,000 overall).

Serious superficial and subcutaneous fungal infections

Vulvovaginal candidiasis (VVC) is relatively common in Tunisia [65]. In a Tunisian study in 2010, 1415 vaginal swabs were collected over a period of 1 year (between 2006 and 2007), *C. albicans* was isolated most frequently (81.2%) followed by *C. glabrata* (12.2%) [66]. In 2017, Mtibaa et *al.* performed 2160 vaginal swabs over 2 years (January 2014-December 2015) at the Laboratory of Parasitology and Mycology of La Rabta Hospital in Tunis. *C. albicans* was isolated most frequently (76.6%) followed by *C. glabrata* (17.2%). Cultures were most frequently positive in 25–34 years old age group. The prevalence of VVC in this study was 32.9%. No studies of recurrent VVC have been done in Tunisia. We estimated a total of 204,400 cases of RVVC at an incidence of 3459/100,000 female population.

Tinea capitis is a common disorder and represents the commonest mycosis in childhood globally. Low standard of living and health education, overcrowding, poor hygiene, close personal and animal contact are favorable factors of tinea capitis. In the 10 year period to 2018 we analysed data from, 1100 cases were positively diagnosed, 110 per year in a population of 737,000. This equates to a population prevalence of 14.9/100,000 and therefore for the country (assuming the rates are similar elsewhere) of 1761 cases. This estimation underestimates the real prevalence since the diagnosis is not only performed in our hospital but also in private laboratories. Several studies on tinea capitis and dermatophytes have been carried out since the early 1950s in Tunisia [67]. Tinea due to *Trichophyton violaceum* and *T. schoenleini* was the most frequent at that time. Since the 1980s, the prevalence of tinea capitis due to *Microsporum canis* and the suppurative presentation of tinea capitis (kerion) have steadily increased while favus has dramatically decreased and nearly disappeared [68]. Infection with *T. violaceum* has decreased in frequency from 64.7% in 1950 to 31.7% in 2014 in the study of Kallel et al. in Tunis. *M. canis* was reported for the first time in Tunisia in 1950 in two children originally from Europe. Since then it has increased progressively to exceed *T. violaceum* in some Tunisian studies such as that of Dridi et al. in Charles Nicolle Hospital of Tunis. The two last cases of favus were observed in Sousse in 2009 and 2014, and Kallel et al. reported one case in Tunis between 2005 and 2014 [69–71].

In addition, skin and nail infections (onychomycosis) remain very common in the Tunisian population. Onychomycosis accounts for up to 50% of nail diseases in our country. National data on incidence and prevalence of this fungal infection are not available but numerous regional studies were published. Dhib et al. reported in a 22 years retrospective study from 1986 to 2007 in the region of Sousse, that 325 cases were reported annually (ranging between 53 cases in 1986 and 986 cases in 2007) [72]. Dermatophytes, mainly represented by *T. rubrum* and to a lesser extent by *T. mentagrophytes*, predominates in foot onychomycosis, and tinea cutis; whereas *C. albicans* predominates in hand onychomycosis. Malassezia skin infections are frequent and are mostly caused by *Malassezia globosa* followed by *M. sympodialis* [73]. We have not attempted to quantify the prevalence of these conditions.

Mycetomas are rare in Tunisia. The first case was published by Vincent H. in 1894. Most cases were of *Actinomycetes* origin; those caused by fungi are uncommon [74,75]. Seven cases of chromoblastomycosis have been reported from Tunisia but no sporotrichosis [76–82].

There are 3 series of fungal keratitis published from Tunisia [83–85]. The first study was carried out in the region of Tunis between 1998 and 2008. Anane et al. reported 19 cases of fungal keratitis. Direct examination and culture were positive in 77% and 100% of

cases respectively. *C. albicans, Aspergillus spp*. and *Fusarium spp*. were the most frequent fungi isolated. The evolution was favourable in six (31.6%) cases. In the region of Sfax, Cheikhrouhou et al. reported 60 cases between 1995 and 2012. Direct examinations of scraping material were positive in all cases and cultures isolated fungi in 93% of cases, most of them were *F. solani* and *Aspergillus* spp.; after therapy, 71% of cases had persistent corneal opacities and 13% of patients lost the eyeball. Zbiba et al. reported 30 cases in the region of Cap Bon diagnosed between 2010 and 2015. *Fusarium* spp. and *Aspergillus* spp. were the most isolated fungi from the 18 positive cultures. At follow up, final visual acuity was less than 20/200 in 16 eyes (53.3%) with corneal perforation in 16.7%. We counted 38 cases of fungal keratitis from 236 cases of corneal abscesses in the Department of Ophthalmology in the region of Sousse during the period between 2016 and 2021 (unpublished data). Direct examination was positive in 58% and culture was positive in 82% of cases with *Aspergillus* spp. and *Fusarium* spp. the most frequent pathogens isolated (19 cases). Corneal perforation occurred in seven cases, endophthalmitis in three and fungal graft recurrence in three cases. The major risk factor mentioned in these different studies was ocular trauma with vegetal matter. These studies do not provide a denominator, so we have used that provided from a population-based ophthalmology service in Egypt (14/100,000) [45]. A likely annual incidence for fungal keratitis in Tunisia is 1655 cases.

Malignant external otitis or necrotizing external otitis (NEO) is frequently bacterial in origin, but recently, many cases due to fungal pathogens have been reported worldwide and in Tunisia. We identified six series reporting 109 cases of NEO in Tunisia [86–89]. In Sousse, we counted 35 cases between 2015 and 2021. NEO occurs mainly in older patients with diabetes mellitus, some with immunosuppression. *Aspergillus* spp. and *Candida* spp. are the most frequent fungi incriminated. NEO can lead to numerous complications such as nerve palsy, vascular thrombosis and in some cases to septic shock.

Discussion

Tertiary care is delivered by 24 university hospitals in Tunisia, secondary care by 33 regional hospitals, and primary care by 109 local hospitals and 2172 primary health centres. Regional hospitals are only found in cities which do not have a university hospital. Mycology has progressively developed and extended from the diagnosis of superficial to invasive fungal infections in Tunisia. There are seven mycology laboratories in the country, four in Tunis, two by the coast in Sousse and Monastir and one in the south in Sfax. None has a BSL-3 laboratory. Diagnostic tools in teaching hospitals include microscopic examination, culture, detection of antigens of *Candida, Aspergillus* and *Cryptoccoccus neoformans*, detection of antibodies against *Aspergillus* and *Candida* but still scarce; molecular methods such as PCR for *P. jirovecii* are only available in some laboratories and usually for research only [5]. Mycoses are underdiagnosed because of the absence of systematic screening, limited awareness among many physicians and low performance of many diagnostic tools all conspiring to delay diagnosis.

The overall burden of fungal diseases in Tunisia remains poorly documented. Our estimates here find approximately 2.12% of Tunisians suffer from fungal infections yearly. Our study indicates that the total burden of serious fungal infections is 250,494 cases annually comparable to other North Africa countries. The basis of the estimates has recently been set out in a global summary paper, for severe fungal diseases [3]. The most frequent infections we found were RVVC, ABPA, SAFS and CPA. Opportunistic fungal infections occur in immunocompromised patients. There are many published data attesting to many mycoses in Tunisia, but denominators are lacking for many.

Cryptococcosis is uncommon; it is fifth among opportunistic infections (3.47 to 6%), its incidence among non-HIV-patients is 4.5%; however, it remains serious, associated with high mortality (62.5 to 83.3%). It currently affects 2 to 30% of HIV-infected patients [32]. Cryptococcal meningitis is the most common clinical presentation of cryptococcosis. It is a frequently fatal opportunistic infection and occurs mainly in PLVIH with CD4 <200/mm3. In Sub-Saharan Africa, Asia and the Pacific region, the prevalence of cryptococcal meningitis is up to 6–7%, of the population at risk for cryptococcosis [27]. Globally, death from cryptococcal meningitis is 19% in PLVIH, the highest incidence in sub-Saharan Africa [27]. An increasing number of cryptococcosis has been reported in non-HIV infected immunocompromised patients such as solid organ transplant recipients and haematologic malignancies, but also in patients with no immunosuppressive conditions [90].

As in most African countries, PCP is a common and serious opportunistic infection among AIDS patients (8.6 to 21%) but has also been reported in other immunocompromising conditions (hematological malignancy, transplant recipients and immunosuppressive therapy). We have used an estimate of 33% to estimate PCP incidence in HIV [44]. A lower estimate of 12% was found in women with PLHIV early in the epidemic, probably based on microscopy[28]. The largest study published by Kaouech et al. 2009 reported 15 cases between 2005 and 2007 in La Rabta Hospital of Tunis [29]. Underlying conditions were AIDS in 11 cases and post-hepatitis C cirrhosis, congenital immunodeficiency, leukemia and lymphoma in the other cases. In another series of patients in Sfax, Jarboui et al. reported 14 cases of PCP of which 11 were HIV positive from 2005 to 2007 [91].

IA is consistently the most common fungal infection in haemato-oncological HSCT patients. Its incidence ranges between 7.5 and 15% among patients suffering from hematological malignant diseases and given immunosuppressive treatment [92]. Incidence reported by Gheith et al. in the region of Sousse (center of Tunisia) was 7.5% [93] and that reported by Hadrich et al. in Sfax (South of Tunisia) was 15 % [41]. According to available data on the local IA epidemiology, the leading causative agent of IA is *A. flavus* followed by *A. niger. A. fumigatus* is uncommon in Tunisia [41,93]. *A. flavus* is also a common agent responsible for fungal sinusitis, keratitis, otitis and onychomycosis in our region (data not published). The estimate of COPD is based on the prevalence of COPD in Tunisia, and how many of these people are admitted to hospital with an exacerbation. We have used a prevalence figure 7.8% of those aged over 40 years, but others have put the prevalence at 9.1% [37], so our estimate may be conservative. The death rate of IA remains high despite therapeutic progress made over the last two decades [53].

Although IA is a rare complication in solid organ transplant (SOT) recipients, it has significant implications on graft and patient survival. Diagnosis of IA in SOT recipients requires a high degree of awareness, especially as serum galactomannan does not provide the same sensitivity and specificity observed in the neutropenic population. IA treatment relies primarily on mold-active triazoles, but potential interactions with immunosuppressants and other concomitant therapies need special attention. There is a need for well-orchestrated efforts to study IA diagnosis and management in SOT recipients and to develop comprehensive guidelines for this population in Tunisia and North Africa.

CPA is the most severe long-term sequelae of PTB [21,22]. The number of deaths from CPA in the world is estimated to be at least 340,000 annually.[3] We have estimated a prevalence of 2090 cases of CPA in Tunisia most of them occurring in patients with TB or COPD (17.7/100,000) which is higher than that in Algeria (2.2/100,000) and less than estimated in Morocco (52.8/100,000) [94,95].

The number of cases of candidemia seems to be underestimated for many reasons such as the lack of specimens submitted to the laboratory compared to the number of patients at risk of IC, the use of empiric antifungal therapy in suspected cases reducing the already low sensitivity of blood culture [30]. We used the same incidence estimated in Morocco and in Algeria (5/100,000). A three-fold higher rate was reported in Qatar (15.4/100,000 population), 6.8/100,000 in

Kuwait, and 6.1 in Iran assuming that we underestimated the reality of candidemia episodes in Tunisia. *C. albicans* remains the most frequent causative agent, but the emergence of *non-albicans* species needs to be pointed out. *Candida tropicalis* is the most frequent species cultured, followed by *C. albicans, C. glabrata* and *C. parapsilosis* [96].

With an estimated annual incidence of 23 cases, a national survey of mucormycosis would be valuable as the disease may be more common than documented to date. Mortality of mucormycosis remains high [97], partly because of the delay in diagnosis as cultures are often negative as are biomarkers such as B-d-glucan and *Aspergillus* antigen. Rapid institution of effective medical treatment and resection surgery are required for survival.

VVC is a common health problem in Tunisia. We estimated a 6% rate of recurrent VVC in premenopausal women giving about 204,400 cases each year. Prevalence of VVC varies by countries and types of population: it was 6.3% in China, 20.5% in India, 26% in Morocco, 28.2% in Iran [65,98,99]. In Africa, point prevalence of VVC varies between 36% and 43% [100,101].

Tinea capitis continues to be frequent in Tunisia [67]. The prevalence and incidence of this infection is difficult since diagnosis is performed in hospitals but also in private laboratories. The distribution of dermatophytes as the causative agent of tinea capitis has changed in recent decades in many countries including Tunisia. *T. violaceum* is the most isolated species but there has been a gradual decline in its incidence recently and *M. canis* has increased. *M. canis* has become the main causative agent in most parts of Europe and the Middle-East [100]. Findings from different studies in Tunisia suggest that the distribution of different species of dermatophytes causing tinea capitis seems to show a north/south gradient.

Fungal keratitis is a potentially devastating ocular infection. Prognosis remains poor despite the improvement of diagnosis and treatment in our country. Misdiagnosis is attributed to difficulties of sampling and the disparity of mycological results depending on quality of sampling and experience of the laboratory. *Fusarium sp*., *Aspergillus sp*., and in some cases *C. albicans* are the most frequent fungi recorded. Data are still scarce because of the retrospective nature of studies carried out in our country.

NEO is an aggressive and potentially fatal infection often caused by fungi, but still neglected. In Tunisia, many more cases have recently been recognized. Early recognition, diagnosis and anti-fungal therapy are mandatory to decrease the complications and death.

Many limitations should be considered in our study. Estimations based on frequencies of diseases in other countries should be interpreted with caution. Many diseases are diagnosed and treated in private healthcare facilities such as tinea capitis, so not captured in our laboratory records and studies as most carried out in university public hospitals. There is lack of national studies tackling many fungal diseases and some data are not updated. Further epidemiological studies are needed to validate and improve these estimations.

Conclusion

Invasive fungal infections have become a more common health problem in Tunisia. Both their incidence and frequency of diagnosis has steadily increased over the last decades. This can be attributed to the improvement of specialized laboratories, the availability of a higher number of technologists involved in the diagnosis of mycoses; together with a better knowledge of these diseases, increasing numbers of patients with risk factors and the development of new diagnostic tools. On the other hand, there is no active surveillance or control program of fungal infections in Tunisia. Some fungal infections are transmissible (notably dermatophyte and *Pneumocystis*) or hospital acquired (especially invasive candidiasis), so must be controlled and limited to avoid poor clinical outcomes. An estimation of the accurate burden of invasive mycoses in Tunisia is crucial to encourage public health authorities developing appropriate surveillance of fungal diseases and setting policy priorities. Early reliable diagnosis and treatment of invasive fungal infections will improve patient outcome.

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