Editorial

Health threat caused by fungi of medical interest: where are we in 2021?

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When non-scientific people are interviewed about the most dangerous fungus in the world, most instinctively cite the—so famous—death cap amanita (*Amanita phalloides*). However, this macroscopic species related to the Basidiomycota division, largely widespread in Europe and subsequently imported to all other continents, actually causes only few dozens of deaths per year. The real threat is rather microscopic and is responsible for a heavy burden in worldwide public health. According to the GAFFI (Global Action Fund for Fungal Infection) website (https://gaffi.org/), 13,500,000 people are currently suffering from common life-threatening fungal infections and >1.6 million die annually of related complications (Fig. 1).

Fungal infection is described in both high and low resources countries, but their relative representations are variable therein [1]. In addition to the influence of numerous factors, their respective prevalence notably depends on the local climate, demographics and healthcare situation and habits, e.g., prevalence of tuberculosis and human immunodeficiency virus (HIV) infection, easy access to cancer chemotherapy, practice of transplantation, distribution of novel immunosuppressive regimens like monoclonal antibodies… [2]. For instance, tropical areas are mostly concerned by endemic infections, e.g., mycetoma in the Saharan band from Senegal to Sudan, *Penicillium marneffei* talaromycosis in Southeast Asia, or histoplasmosis in central and South America: all these entities are associated with poverty, underlying infectious diseases and certain temperatures. In contrast, Northern and Western countries are rather interested in opportunistic diseases induced by iatrogenic processes, e.g., candidiasis following solid organ transplantation or surgery, aspergillosis associated to hematopoietic stem-cell transplantation or intensive anticancer chemotherapy [1].

Nowadays, historic infections like *Pneumocystis* pneumonia or *Cryptococcus* meningitis in HIV-positive patients are becoming less incident (especially because of the advent of highly active antiretroviral therapies), as illustrated by the –14.3% decrease per year in France during the 2001–2010 period for the former [3], and the 3 to 4-fold reduction in Africa over the last decade for the latter [4]. They have been progressively replaced by other fungal diseases that have been newly emergent or just relatively more represented. For instance, numbers of candidemia and invasive aspergillosis were 89.5% and 63.6% increased in France, during the same aforementioned period [3]. Several causes linked to the medical advances can explain these findings: the diversification of the medical procedures and the arrival of new immunosuppressive drugs on the market, but also the prolongation of the overall survival of patients (so that consequently the exposure risks are proportionally increased). Currently, around 400,000 new cases of candidemia occur annually worldwide, primarily in intensive care units (ICU), but not exclusively [1]. The incidence rose up by >50% over only five years at the beginning of the 21st century in the USA [5]. Death rate for *C. glabrata* infection is approximately 55–60%, and only a little bit less for *C. albicans* ≈40%. Of note, a progressive increase in non-*albicans* species prevalence has been globally observed, although it is slight and quite variable between the continents [6, 7]. This trend could have some therapeutic consequences over time. For instance, the high overrepresentation of *C. krusei* (>10%) in the article written by Martin *et al.* [8] might lead to systematic failures when using fluconazole. Over 300,000 patients develop invasive aspergillosis yearly [1, 9]; the mortality still remains close to 30–50%, in spite of adequate antifungal therapies [3]. Recently, new *Aspergillus*-related enti-

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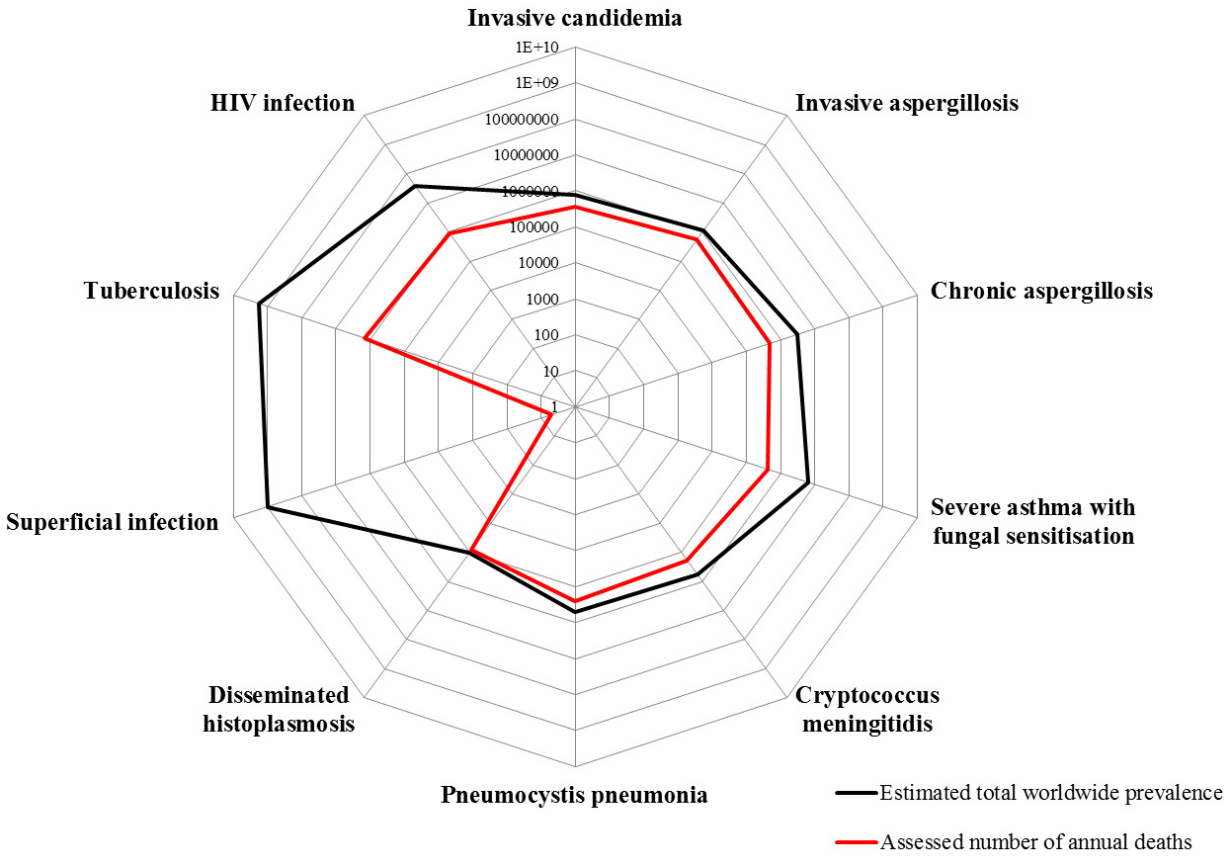

Fig. 1. Summarizing representation of the relative burden for the most common fungal infections (according to the data of the GAFFI website (https://gaffi.org/). For each one, the global current prevalence and the annual related deaths are showed by the means of a radar graph, and compared to those caused by tuberculosis and human immunodeficiency virus (HIV) infection, according to a logarithmic scale.

ties have emerged in patients hospitalized in ICU because of severe underlying virus pneumonia, like influenza or COVID-19 (Coronavirus disease 2019) infection, thus leading to IAPA (influenza-associated pulmonary aspergillosis) or CAPA (COVID-19-associated pulmonary aspergillosis). Respective occurrence rates in such contexts were estimated at 12–28% [10] and 14–20% [11], but the lack of standard definitions in ICU precludes a reliable incidence picture in non-classical populations at risk. Besides, mucormycosis was reported with an incidence elevating from 0.7/million in 1997 (40 cases) to 1.2 in 2006 (72 cases), at a national scale in France [12]. The role of previous exposure to antifungal drugs lacking activity against Mucorales species (e.g., prophylaxis based on voriconazole during hematologic malignancies or bone marrow transplantation) has been raised to explain this trend in patients at risk, but does not seem exclusive. The recent COVID-19 pandemic reminded the importance of the local prevalence of diabetes in the occurrence of mucormycosis (in addition to the aforementioned conditions conventionally related to the viral infection: intubation, corticosteroid treatment, ICU stay) [13]. Most case reports and series were published in India, where a recent survey found 11.8% inhabitants affected by such endocrine pathology [14].

Diversification of the panel of the underlying chronic diseases, as well as the increasing absolute number of concerned patients, also plays a major role in the global burden of fungal infections. Thus, it is thought that at least 3,000,000 subjects are affected by chronic aspergillosis among those with debilitated terrain, like chronic obstructive pulmonary disease [COPD], alcoholic cirrhosis, sarcoidosis, or corticosteroid treatments [15]. More specifically, its prevalence was evaluated at about 1.2 million cases in the context of ancient tuberculosis [16]. Case fatality rate approaches 15–40%. All over the world, more than 23,500,000 individuals are currently concerned by allergic fungal diseases, whatever the pathophysiology, like severe asthma with fungal sensitization (SAFS) in 5–20% asthmatics [17] and allergic bronchopulmonary aspergillosis (ABPA) in 15% adults with cystic fibrosis (teenagers and kids are usually less affected) [18].

In tropical countries, the actual burden of endemic fungal diseases is tough to assess, primarily because the access to efficient diagnostics still lacks in rural areas. Incidence rate of histoplasmosis is likely ~100,000 cases per year [19], and the cumulated prevalence close to 50 million over time, although the infection remains most often asymptomatic [1]. According to a recent study, the number

of deaths related to histoplasmosis in Latin America was estimated at range of 671 to 9394 during one unique year, so that they were somewhat equivalent to the 5062 deceases related to tuberculosis meantime [20]. Like chromoblastomycosis (in all, 7740 cases have been reported worldwide, but this fungal entity is mostly present in Madagascar with prevalence up to 14/100,000 inhabitants, and in Brazil) [21], mycetoma have been recently listed among the neglected tropical diseases by the World Health Organization (WHO). In the world, almost 20,000 cases of mycetoma have been reported in the literature in more than 100 countries. Notably, mycetoma is now described far outside the tropics, including for example Italy, China, Australia and USA [22]. Sporotrichosis is mainly found in central and South America: a new epidemic wave has spread from Rio de Janeiro to the North through cat transmission [23]. Only in China, talaromycosis is supposed to concern 20% HIV-positive subjects geographically exposed, resulting in 0.35 cases per 100,000 inhabitants, whereas its worldwide incidence is supposed to be close to 10,000 new cases per year [24]. Coccidioidomycosis due to *Coccidioides immitis* is largely underestimated: the actual incidence is likely closer to 140,000–150,000 cases per year, most occurring asymptomatically in America [1]. In California, 7466 workers were contaminated in 2017 subsequently to digging agricultural works and creation of embankments in the ground [25].

Finally, we can also cite the burden represented by superficial fungal infection, like *tinea corporis*, *capitis*, *pedis* or *unguium* that altogether probably count for a prevalence of one billion persons [26]. All people categories can be concerned, but *tinea pedis*, or athlete's foot, is more common in young sportsmen (-women), while *tinea unguigum*, or onychomycosis, is increasingly more prevalent in elderly, up to 50% individuals $>$70 years old [27]. Recurrent vulvovaginal candidiasis affects 138 million women per year [28].

In conclusion in the light of all the aforementioned rates (although they are probably significantly underestimated), one could legitimately acknowledge that mycologists and specialists of infectious diseases still have a lot of efforts to provide in order to better diagnose and treat the fungal diseases. The direct costs related to the care for managing fungal infections were estimated at $\geq$7 billion US$ per year in the United States, i.e., 0.22% of total health expenses [29]. Recent outbreaks of *Candida auris* infection/colonization inside healthcare facilities are obvious examples of the emergence risk of new species that are highly resistant to conventional antifungals [30–32], with up to 90% strains not susceptible to fluconazole, and around 10% to amphotericin B [33]. Focusing only in the USA, 948 cases of proven or probable *C. auris* infection have been notified so far to the Center for Diseases Control (CDC) in Atlanta.

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5. Conflict of interest

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