

Epidemiology of fungal infections in China

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Abstract With the increasing number of immunocompromised hosts, the epidemiological characteristics of fungal infections have undergone enormous changes worldwide, including in China. In this paper, we reviewed the existing data on mycosis across China to summarize available epidemiological profiles. We found that the general incidence of superficial fungal infections in China has been stable, but the incidence of tinea capitis has decreased and the transmission route has changed. By contrast, the overall incidence of invasive fungal infections has continued to rise. The occurrence of candidemia caused by *Candida* species other than *C. albicans* and including some uncommon *Candida* species has increased recently in China. Infections caused by *Aspergillus* have also propagated in recent years, particularly with the emergence of azole-resistant *Aspergillus fumigatus*. An increasing trend of cryptococcosis has been noted in China, with *Cryptococcus neoformans* var. *grubii* ST 5 genotype isolates as the predominant pathogen. Retrospective studies have suggested that the epidemiological characteristics of *Pneumocystis* pneumonia in China may be similar to those in other developing countries. Endemic fungal infections, such as sporotrichosis in Northeastern China, must arouse research, diagnostic, and treatment vigilance. Currently, the epidemiological data on mycosis in China are variable and fragmentary. Thus, a nationwide epidemiological research on fungal infections in China is an important need for improving the country's health.

Keywords fungi; infection; epidemiology; China

Introduction

Fungi are eukaryotic organisms found throughout nature. They emerged about 1.6 million years ago and serve the important function of returning the nutrients removed by plants to the soil [1]. Historically, fungi are major pathogens of plants, rotifers, insects, and amphibians, with a relative few causing infections in humans. However, human modification of natural environments has intensified the dispersal of fungal infections [2]. Global warming

has also augmented the prevalence of fungal infections in mammals by its selection of adaptive thermo-tolerant fungal species possessing significant pathogenic potential despite their current nonpathogenicity due to being restricted by mammalian temperatures [3]. To date, approximately 400 fungal species have been reported to be pathogenic to humans, with emerging pathogenic fungal species recorded annually [4].

The patterns of fungal infections are diverse and vary worldwide depending on the fungal species, host immune status, and infection site. For example, superficial fungal infections (SFIs), such as tinea capitis, are closely related to host lifestyle and socioeconomic conditions [5–7], whereas invasive fungal infections (IFIs), such as candidemia, are closely linked to host immune status and fungal species [8]. Since the 1950s, SFIs have steadily declined in incidence globally, especially in fast-developing countries, such as

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China, because of improving sanitary conditions [6,7]. By contrast, IFIs have been recognized as an increasing major threat to human health because of the growing prevalence of immunocompromised populations in recent decades [8]. For example, the human immunodeficiency virus (HIV) epidemic in Uganda has dramatically increased the incidence of IFIs that were once considered rare, such as cryptococcosis and disseminated histoplasmosis [9–11].

China, one of the largest countries in the world, is located at the western part of the Pacific Ocean. This country is rich in diversity of geographical environments and microorganisms. As the nation with the world's largest population (1400 million people), China has also reportedly steadily increased in the number of immunocompromised hosts [12,13]. A retrospective research based on single-center autopsy data (3447 cases) in China indicated that the prevalence of IFIs has risen steadily for decades [13]. The drastic socioeconomic lifestyle transformation among Chinese people may have altered the epidemiological characteristics of fungal infections in the country. Nonetheless, epidemiological data on fungal infections in China remain scarce. In the present research, we systematically reviewed the epidemiological data on fungal infections across China to obtain the epidemiological profiles and trends of Chinese fungal infections.

Superficial fungal infections

SFIs are fungal infections limited to the outermost layers of the skin and appendages. These infections are believed to affect approximately 25% of the world's population [5,6,14]. SFIs can be classified by infection site, for example tinea corporis, tinea pedis, tinea cruris, tinea manuum, onychomycosis, tinea capitis, and tinea faciei. The chief causative agents of SFIs are dermatophytes and yeasts. Dermatophytes are a group of filamentous fungi that infect keratin-rich tissues, such as the skin. The geographic distribution of dermatophytes is variable [5,6]. Currently, *Trichophyton rubrum*, *Trichophyton interdigitale*, *Trichophyton tonsurans*, and *Microsporum canis* are the major dermatophyte species globally [15]. Meanwhile, *Malassezia* spp. and *Candida* spp. are the principal yeast pathogens that cause SFIs [5,6]. To date, the majority of epidemiological studies on SFIs in China were conducted in separate disease categories or segmental regions [7]. Consequently, the epidemiological profile of SFIs in China remains thin and fragmented. In this portion of our research, we sought to summarize the epidemiological data on SFIs in China, particularly tinea capitis and onychomycosis.

Previous studies demonstrated that the patterns of SFIs and their chief causative agents vary across the many different geographical regions of China. Tinea corporis and tinea cruris (53.4%; 1682/3152) are the most prevalent

types of SFIs in Northern China [16], whereas onychomycosis is the most prevalent in Eastern (55.2%; 5277/9566) and Southern China (28.6%; 199/697) [17,18]. Notably, tinea faciei is the most frequent SFI in Southern China among patients aged below 22 years (median age of 9 years). In Central China, tinea corporis (32.4%; 67/207) is the most prevalent type of SFI, and *T. rubrum* (50.7%; 34/67) is the predominant fungal pathogen [19]. In Northwestern and Northeastern China, tinea pedis (33.1%, 471/1422; 20.0%, 164/818, respectively) is the most prevalent type of SFI, and *T. rubrum* is again the predominant fungal pathogen [20,21]. In Southwestern China, tinea cruris (30.1%; 385/1279) is the most prevalent type of SFI, and *T. rubrum* is the predominant fungal pathogen [22].

In summary, dermatophytes, such as *T. rubrum*, remain as the most common fungal pathogens causing SFIs, especially onychomycosis, tinea pedis, and tinea cruris, in the majority of China. Similar observations were described by investigators in Brazil, America, Sweden, and France [23–26]. Tinea pedis is also the most prevalent type of SFI in Northern China, a finding compatible with previous epidemiological studies from Singapore [27].

Tinea capitis

Tinea capitis, an infection of scalp hair follicles and the surrounding skin caused mainly by dermatophyte fungi [28], is the most common SFI among children of school age, especially in developing countries [7]. From the 1950s through the 1960s, hyperendemic favus, generally a severe form of tinea capitis, was dominant in some provinces of China, such as Hubei, Jiangsu, and Jiangxi [7]. For example, in 1965, the prevalence of favus in Jiangxi reached 3410 per 100 000 [29]. However, after a prevention and treatment project for tinea capitis was initiated successfully in the 1960s, the incidence of favus decreased significantly, down from 1160 per 100 000 in the 1970s to below 1 per 100 000 in the 2000s [7,30–32]. Over time, the prevalence of tinea capitis gradually resurged in some regions of China. For example, in Shanghai, the number of tinea capitis cases increased from 25 cases in 1993 to 105 cases in 2001 [32]. These changes in incidence were probably related to the changing lifestyles of the population. Although finding a nationwide epidemiologic study on tinea capitis in China is difficult, a recent review suggested that anthropophilic fungi overwhelmed the zoophiles across vast regions of China before 1985 and that the dominant species nationwide was *T. schoenleinii* despite the variability of endemic species across different geographic regions [7]. Notably, the predominant etiology switched from *T. schoenleinii* to *T. violaceum* in Europe during 1963–1993, whereas the zoophile *M. canis* increased dramatically since 2000 [33]. Similarly, a shift of etiological agents from anthroponoses to zoonoses also

occurred in contemporary China. Pets became the most likely sources of tinea capitis in modern society, replacing the earlier human-to-human transmission mode [7]. The details are provided in Fig. 1.

Onychomycosis

Onychomycosis is a chronic fungal infection involving the nails, nail bed, nail plate, and matrix. This infection is responsible for almost 50% of all nail diseases [34]. In 2015, Wang *et al.* reported that the dominant form of onychomycosis in China is distal lateral subungual onychomycosis (DLSO: 54%; 531/978), followed by total dystrophy (TD: 24%; 237/978), superficial white onychomycosis (SWO: 16%; 155/978), and proximal subungual onychomycosis (PSO: 6%; 55/978) [35]. The details are provided in Fig. 2. The global prevalence of onychomycosis was estimated to be 5.5% [36], but no accurate data exist about the incidence rate of onychomycosis in China. Onychomycosis can be caused by dermatophytes, non-dermatophyte molds, or yeasts. In China, the pathogenic fungi that cause onychomycosis were found to be most commonly composed of dermatophytes (84.0%; 672/800), followed by yeasts (11.4%; 91/800) and non-dermatophyte molds (4.6%; 37/800) [35]. These observations are consistent with those of some previous reports [6,34,37]. Among the dermatophyte species, *T. rubrum* was dominant (80.9%; 647/800) [35]. These observations are compatible with previous epidemiological studies from China and other countries, such as India and Italy [34,37–40], but different from the findings

in Greece, Iran, and Brazil, where yeasts were the predominant agents of onychomycosis [41–43]. These differences may be attributed to the geography, regional climate, or population migration, among other factors, in the regions studied [38]. *C. glabrata* was the most frequently found pathogenic yeasts (16.8%; 135/805) in Guangdong Province [44]. Increasing reports of onychomycosis in China have also implicated a new yeast pathogen as a causative agent. For example, our team reported the first case of onychomycosis caused by *Rhodotorula minuta* in an immunocompetent girl in 2013 [45]. A nationwide epidemiology survey on onychomycosis in China is needed in the future.

Invasive fungal infections

Invasive fungal infections (IFIs) are opportunistic fungal pathogens that infect deep solid organs and/or the bloodstream mainly in immunocompromised patients, such as those with prolonged neutropenia or cancer [8,46]. IFIs are caused primarily by *Candida* spp., *Aspergillus* spp., *Cryptococcus* spp., and others, all of which are distributed universally in the environment [8,47–49]. In general, the epidemiological profile of IFIs is characterized by geographical and temporal variability, with different incidence rates and new emergence incidents revealed over the past 20 years [50]. Notably, two separate single-center autopsy studies conducted in the 2000s showed that the incidence of IFIs increased steadily over time [51,52]. Until recently, the epidemiology of IFIs in China was

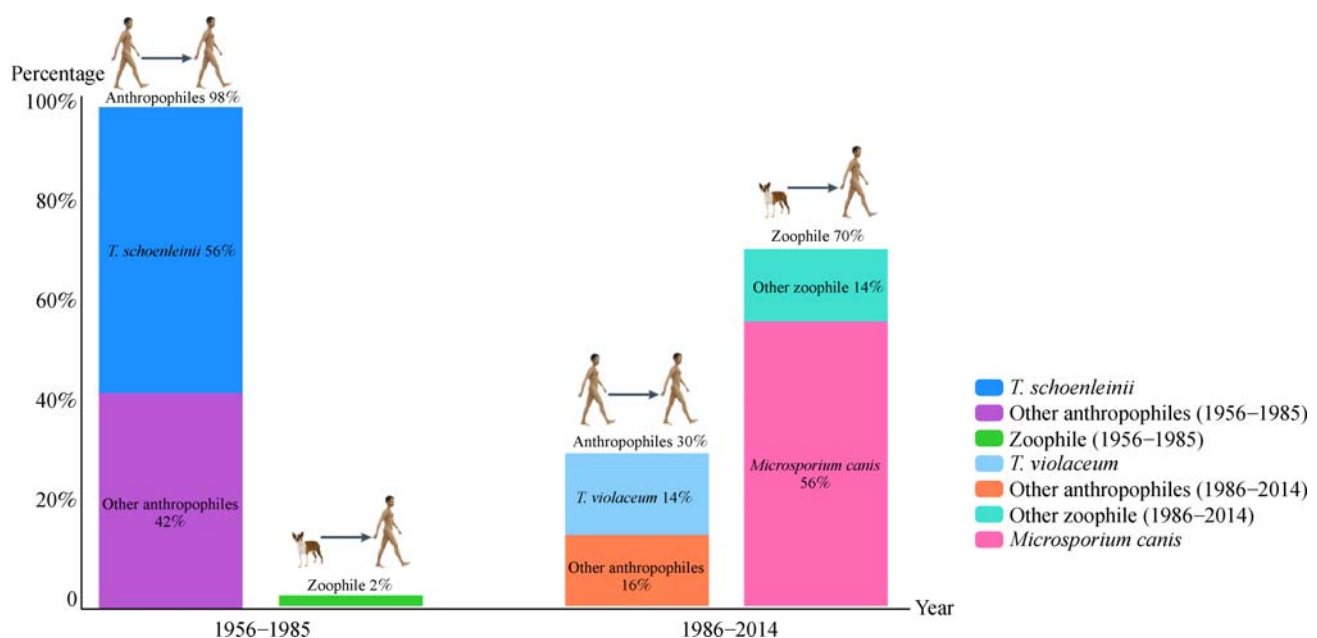


Fig. 1 Dynamic change of fungal etiology of tinea capitis in China.

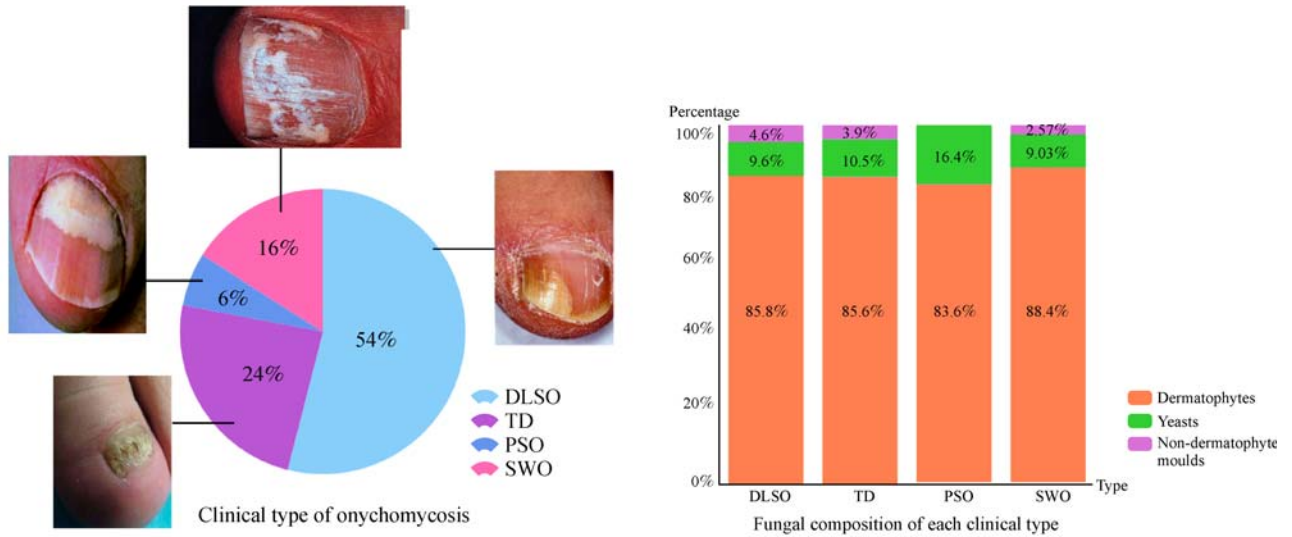


Fig. 2 Clinical type and fungal etiology of onychomycosis in China.

poorly understood because of insufficient and inaccurate data. Epidemiological studies on IFIs were reported mainly in numerous, separate case studies, and most of these studies were written in Chinese [53,54]. Consequently, information about the epidemiology of IFIs in China remains limited. In the following sections, we summarize the epidemiological data of IFIs in China with focus on the five main IFIs caused by *Candida*, *Aspergillus*, *Cryptococcus*, *Mucorales*, and *Pneumocystis* species.

Invasive candidiasis (IC)

Candida species are important nosocomial yeast pathogens that cause IC, including candidemia. These pathogens may be disseminated to internal organs [8,55,56]. The mortality rates can reach 35%–80% among immunocompromised

and other seriously ill patients [57–60], a finding that is similar to the mortality rates reported by several studies (36.6%–60%) of IC in China [56,61–64]. Risk factors for IC include the extensive use of invasive procedures and devices, broad-spectrum antimicrobial agents, advanced life support, and aggressive chemotherapy [62,65]. Improved detection may also have raised the reported number of cases. The risk factors for Chinese patients infected with IC [56] are similar to the factors found by studies of patients from Spain and Canada [66,67], except for some unique risk factors. One such factor was IC caused by *Candida albicans* commonly found in patients with subclavian vein catheters or peritoneal drainage tubes [61]. The details are provided in Fig. 3.

For the past two decades, the incidence of candidemia doubled and currently ranks as the fourth and sixth most

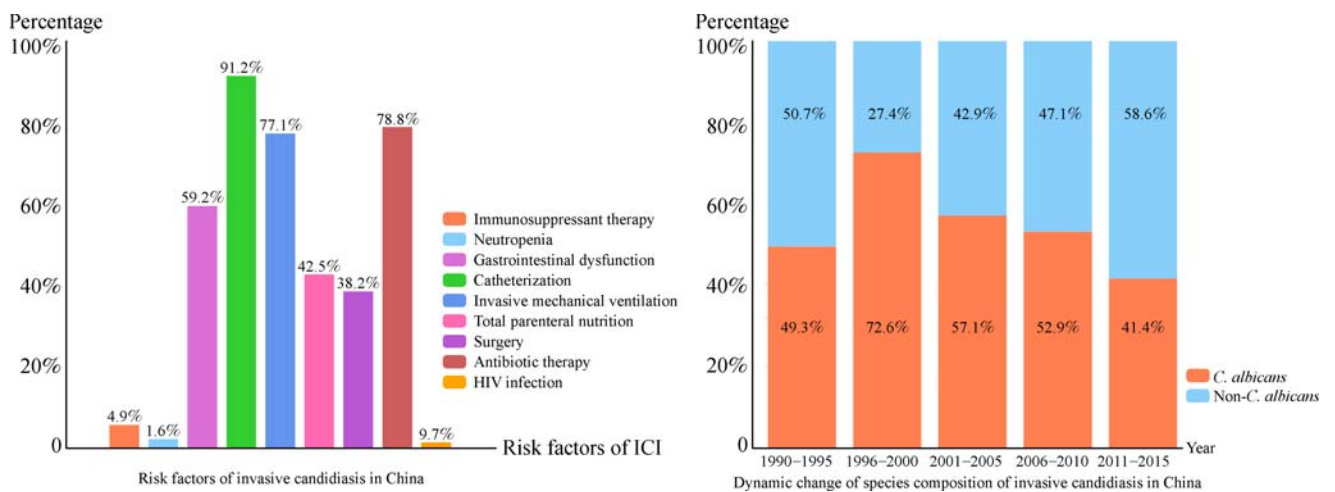


Fig. 3 Risk factors and dynamic change of species composition in invasive candidiasis in China.

common nosocomial bloodstream infection in American and European studies, respectively [68,69]. Notably, the incidence of IC in intensive care units was 0.32% (32 per 1000 admissions) in a multicenter prospective observational study in China from November 2009 to April 2011. This rate was consistent with the global incidence rates of 0.03%–0.5% in hospital-based studies [59].

Although *C. albicans* remains the most common etiological agent worldwide, *Candida* species other than *C. albicans* have been encountered more often than previously reported [8,64,70–76]. In some countries, these species account for increased number of episodes of IC, including candidemia, relative to *C. albicans* [50,56,77–79]. In China, *C. albicans* (40.1%; 156/389) also remains the most common causative agent of IC in recent decades, followed by *C. parapsilosis* (21.3%; 83/389), *C. tropicalis* (17.2%; 67/389), *C. glabrata* (12.9%; 50/389), *C. krusei* (2%; 1/389), and others (8.2%; 32/389) [56,61,78,80,81]. These findings differ slightly from the results based on data of ARTEMIS DISK Global Antifungal Surveillance Program, associated with China from 1997 to 2007, which showed that *C. tropicalis* was the second most common *Candida* species found in IC patients within the Asia-Pacific regions, including China's Taiwan [71,82,83]. Moreover, *C. parapsilosis* was the most common *Candida* isolates from blood in China (33.2%; 107/322) [78].

Significant geographical differences exist in the distribution of *Candida* species involved in IC worldwide. Similarly, variations are present in the distribution among different geographic regions in China [62,84–89]. In general, *C. albicans* is the strain most commonly isolated from candidemia in China, particularly in Southern China, but *C. tropicalis* (28.6%; 38/133) is the most common cause of candidemia in Nanjing [62,84–89].

Recently, uncommon *Candida* species, such as *C. guilliermondii*, *C. rugosa*, *C. quercitrusa*, and *C. auris*, have emerged worldwide, including in China [90–93]. For example, *C. guilliermondii* has been recently reported to cause candidemia in Taipei, Shanghai, and Nanjing and has been proven to be more resistant to both fluconazole (FLU) and voriconazole (VRC) in the Asia-Pacific region than in other regions [62,71,94,95]. More recently, *C. auris* emerged globally as a nosocomial pathogen, which is the multidrug-resistant yeast that exhibits resistance to FLU and shows a markedly variable susceptibility to other azoles, including amphotericin B (AMB) and echinocandins [93,96–98]. To date, IC caused by *C. auris* remains unreported in China, but this new yeast pathogen has been found recently in India and Oman and hence must still be monitored by mycologists [99,100].

In China, the majority of studies on the antifungal susceptibility patterns of *Candida* spp.-associated IC were defined partially in specific regions and/or particular

populations [80,86,101–103]. Consequently, results reflecting the distribution and the associated antifungal susceptibility patterns of *Candida* species frequently differed among these studies. Because many non-*albicans* *Candida* spp. are resistant or mildly susceptible to antifungal agents [90–92], the timely and continuous determination of the antifungal susceptibility patterns of these yeasts is required. In the multicenter nationwide China Hospital Invasive Fungal Surveillance Net (CHIF-NET) study, most (> 94%) of the isolates of *C. albicans*, *C. tropicalis*, and *C. parapsilosis* were susceptible to FLU and VRC, although such susceptibility varied with the species [78]. Again, this result was consistent with those of other studies, such as the ARTEMIS DISK Global Antifungal Surveillance Program [56,66,72,87,104]. Notably, 12.2% of the *C. glabrata* isolates were FLU resistant, and 17.8% exhibited a non-wild-type susceptibility to VRC [78].

The China Survey of Candidiasis reported a widespread resistance to itraconazole (ITC) [56]. Only 0.6% *C. albicans* showed susceptibility to ITC, and 96.0% of *C. glabrata* were ITC resistant. No resistance to caspofungin (CFG) was identified in any *Candida* strain isolated from China [56]. Regarding ketoconazole (KTC), the resistance rate was particularly high in *Candida* spp. (61.9%), and almost all isolates were resistant to KTC [62]. AMB and 5-flucytosine (5-FC) remained close to 100% effective against common *Candida* spp. in China, except for *C. krusei* and *C. guilliermondii* (which were only 20% and 71.4% susceptible to 5-FC, respectively) [72,85]. Notably, the resistance to FLU and VRC of *Candida* species other than *C. albicans* in elderly patients was approximately double that of younger patients (30.6% vs. 15.1% and 8.3% vs. 3.8%, respectively). However, the distribution of *Candida* species did not differ between the elderly and younger patients in China [86].

In conclusion, *C. albicans* remains the most common causative agent of IC in China, whereas the number of cases of IC caused by other *Candida* species has increased in the last decade. *C. parapsilosis* is the most common pathogen causing candidemia, but with geographical variation in China. FLU and VRC demonstrated good activity against *C. albicans*, *C. parapsilosis*, and *C. tropicalis* but not against *C. glabrata*. Cross-resistance to both azoles was noted in *C. glabrata* and in uncommon *Candida* strains, such as *C. auris*. Continued surveillance of IC in China is warranted. Details are shown in Fig. 3.

Invasive aspergillosis

Invasive aspergillosis (IA) is a serious opportunistic infection that mainly affects immunocompromised patients, with an extremely high mortality rate ranging between 40% and 90% [105,106]. Inevitably, people inhale

Aspergillus spores or conidia daily; these particles can induce the occurrence of the following four main types of IA: invasive pulmonary aspergillosis (IPA), chronic necrotizing aspergillosis (CNA), allergic bronchopulmonary aspergillosis (ABPA), and aspergilloma [107]. Approximately 60 000 IA cases per year occurred in Europe, whereas more than 160 000 IA patients per year were estimated to have occurred in China, suggesting a heavy burden [108].

In China, the most dominant pattern of aspergillosis is IPA (approximately 15%), followed by ABPA (approximately 4%), CNA (approximately 3%), and aspergilloma (approximately 1%) [107]. IPA is the most severe type of pulmonary aspergillosis, with a high mortality in immunocompromised individuals (39%–100%), especially in patients with malignant hematological disorders, such as neutropenia, or who have undergone hematopoietic stem cell transplantation (HSCT) [109–111]. The mortality rate of IPA in China is similar to the rates found in various countries of Europe, including Italy [50,112].

Previous studies revealed that the overall IA infection rate in China ranged from 0.29%–14% depending on different underlying diseases or conditions [13,110,111,113]. Overall, this rate is similar to the rates exhibited in other countries, such as Italy (0.2%; 13/5561), and in Europe (6.9%; 127/1850) [50,112]. In addition, the lung (71.9%; 1047/1457) is the most frequent site of aspergillosis infection in China [53], followed by sinus infection (18.7%; 273/1457), eye infection (5.0%; 72/1457), and others (4.4%; 64/1457), all of which is consistent with reports from other nations [106,114]. However, the proportion of lung infections in China was lower than noted in an international, multicenter observational study in which lung infections accounted for 94% of the cases [114].

Currently, more than 30 *Aspergillus* species have been implicated in IA, the most common are the following: *A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus*, and *A. nidulans* [115]. In China, *A. fumigatus* was the most commonly isolated *Aspergillus* species (59.3%; 153/258), followed by *A. flavus* (27.5%; 71/258), *A. niger* (5.8%; 15/258), *A. terreus* (2%; 5/258), *A. sydowii* (2%; 5/258), and others (3.4%; 9/258) [53]. These preponderance levels are higher than those found by an Italian study, where *A. fumigatus* accounted for 41.7% (5/12) [50], but lower than those in an international, multicenter observational study and a European study, where *A. fumigatus* accounted for 92.2% (519/563) and 96.1% (98/102), respectively [112,114].

The occurrence of IA caused by *Aspergillus* species other than *A. fumigatus* has increased in China recently [53]. For example, Li *et al.* reported an elevated number of IA cases caused by *A. niger* and *A. tubingensis*, the main black *Aspergillus* species present in clinical and environmental samples in China [116]. Wang *et al.* also found that for patients with HBV-related liver failure, the number of

IPA occurrences caused by *A. flavus* (37.9%; 25/66 cases) was greater than that attributed to *A. fumigatus* (27.3%; 18/66 cases) [117].

Since 1997, azole-resistant *A. fumigatus* has been widely identified in clinical isolates from all over the world [118]. Currently, most *A. fumigatus* azole-resistant strains have been associated with mutations of *cyp51A*, followed by TR34/L98H and TR46/Y121F/T289A mutations [118]. In 2011, the ARTEMIS DISK Global Antifungal Surveillance Program first reported that the TR34/L98H mutation can be found in *A. fumigatus* isolates collected in China [115]. Subsequently, Liu *et al.* found that the TR34/L98H mutation (or isolates containing the S297T/F495I mutation) remains the predominant mutation in China and is fairly common in Europe and some other Asian countries [118,119]. Studies in China found that mutations in *A. fumigatus* isolates were the TR34/L98H/S297T/F495I mutation, TR34/L98H mutation, G432A, M220I mutation, and TR46/Y121F/T289A mutation [115,118,120,121]. At present, azole-resistant *A. fumigatus* has spread mainly across Southeastern and Northern China [108]. Until recently, no infection caused by *A. fumigatus* in China has developed the TR/L98H mutation under pressure of triazole therapy, which has proposed that the increase in frequency of this particular mutation in clinical isolates from the Netherlands is driven by the use of azole compounds as fungicides in agricultural practice [115].

In summary, the incidence of IA in China has increased over the past 20 years, with new emerging *Aspergillus* species and azole-resistant *A. fumigatus*. The lung is the most frequent site of IA in China. Molecular methods are essential for the identification of uncommon *Aspergillus* pathogens, such as azole-resistant *Aspergillus* species, in China. Further nationwide surveillance of IA is needed in China.

Cryptococcosis

Cryptococcosis is a life-threatening infection afflicting both immunosuppressed and immunocompetent individuals, which is caused primarily by two sibling basidiomycetous yeasts, *Cryptococcus neoformans* and *Cryptococcus gattii* [122]. In general, *C. neoformans* and *C. gattii* have been further subdivided into several genotypes, such as VN I – VN IV genotypes in *C. neoformans* and VG I – VG IV genotypes in *C. gattii* [12,123,124]. Recent phylogenetic tools have improved our understanding of molecular epidemiological cryptococcosis. In 2009, multilocus sequence typing (MLST) was recommended by the International Society of Human and Animal Mycoses as the preferred method for typing cryptococcal strains [125]. According to research based on the MLST analysis of 305 Chinese clinical *C. neoformans* isolates, sequence type 5 (ST 5) was the predominant sequence type (89.2%) in *C.*

neoformans isolates, followed by ST 31 (6.2%) [126]. The predominance of ST 5 genotype in Chinese clinical *C. neoformans* isolates was also reported by Dou *et al.* (94.9%; 75/79) and Wu *et al.* (82.9%; 34/41) [127]. Actually, ST 5 is the major sequence type in *C. neoformans* isolates from East Asian countries where cryptococcal data were available, including China, Japan, and South Korea [128–130]. However, in Thailand, ST 4 and ST 6 were found to be the major MLST types, whereas ST 93 was dominant in India and Indonesia [128,131]. Recent MLST analysis has indicated that the evolutionary origin of *C. neoformans* var. *grubii* in Thailand is in Africa [131]. The *C. neoformans* var. *grubii* in China was of the same low molecular diversity as the *C. neoformans* var. *grubii* in Thailand. Thus, the *C. neoformans* var. *grubii* in China may have the same evolutionary origin followed by a global expansion and is potentially vector transmitted by avian migration.

In China, cryptococcosis caused by *C. gattii* has been reportedly increasing mostly in patients living in subtropical and tropical regions [132,133]. VG I genotype strains were predominant in Chinese *C. gattii* isolates, whereas the VG IIb genotype strain has been reported in recent studies [134]. The *C. gattii* isolates from China may be distantly related to the highly virulent strain (VG IIa genotype) that caused the outbreaks of cryptococcal infection in western North America. In 2010, the VG IIa genotype strain was reported to have caused infections in Japan, which is adjacent to China [135]. This observation suggests that the VG IIa genotype strain has spread already to the Asia Pacific as a result of international travel and commerce and animal migration. Xue *et al.* [132] stated that if a greater number of laboratories undertook MLST analysis, more cases of *C. gattii* would be diagnosed.

Although an accurate incidence rate of cryptococcosis in China is unavailable, the number of reported cryptococcosis cases in China has increased gradually over the past two decades [12]. A recent survey of invasive yeast infections has indicated that cryptococcosis has become the second most common invasive yeast infection (7.7%) in China [78]. Moreover, meningitis is the most frequent meningoencephalitis in cryptococcosis in China. According to the latest literature review of cryptococcosis in Chinese mainland (1985–2010), central nervous system (CNS) infections occurred in 83.4% (7315/8769) of cryptococcosis patients [136]. A high CNS prevalence involving cryptococcosis was also reported in China's Taiwan (58.9%) and Hong Kong (67.4%) [137,138]. Cryptococcosis is an opportunistic fungal infection because it occurs mainly in immunocompromised populations, such as patients with AIDS, organ transplant recipients, and patients with autoimmune diseases. Notably, a significantly high proportion of cryptococcosis cases have been reported in immunocompetent individuals in China [139–141], which might be the result of a predisposition in the ethnic Chinese population [142].

However, in accordance with a recent meta-analysis of cryptococcosis in China based on 8769 cases in 1032 reports, only 17% of the cases were without identifiable underlying diseases [136]. Therefore, a large-scale epidemiological study is necessary for further understanding of cryptococcosis in China.

Research on environmental *Cryptococcus* strains has been relatively lacking in China. Existing research is either limited in geographic area [143] or lacking the application of the latest molecular typing techniques [144]. Soil enriched with pigeon excreta, decaying wood, and tree detritus such as *Eucalyptus* species and *Laurus* species are ecological niches for *C. neoformans* and *C. gattii*, respectively [144]. Our research group has already isolated *C. gattii* from eucalyptus trees in Yunnan Province (unpublished data). Further high-density sampling of the environmental strain of *Cryptococcus* is needed.

Until today, our understanding on the epidemiological features of *Cryptococcus* and cryptococcosis in China was mainly based on single-center retrospective studies, which cannot reflect the overall prevalence and fungal burden of cryptococcosis in China. The large numbers of reported cryptococcosis in immunocompetent patients but low numbers in immunocompromised hosts in China warrant re-evaluation. Thus, an effective nationwide surveillance of cryptococcosis in China is necessary.

Mucormycosis

Mucormycosis (previously called zygomycosis) is an opportunistic infection caused by fungi belonging to the order Mucorales and the family Mucoraceae [145,146]. *Rhizopus*, *Mucor*, and *Lichtheimia* (formerly *Absidia*) are the most common genera that cause mucormycosis [147]. With the augmented size of immunocompromised populations, the prevalence of mucormycosis has also increased annually.

In places such as California and Spain, the annual incidence of mucormycosis was 0.43–1.7 cases per 1 million individuals [148–150]. By contrast, the morbidity in China is unclear. A review conducted in 2016 found that the prevalence of diabetes combined with mucormycosis increased in Chinese mainland from 10 cases before 2000 to 28 cases in 2010–2016 [151]. Several researchers reported that the overall mortality rate was 29.4% (126/428)–40.8% (40/98) [151–153], which is similar to the rate reported by non-Chinese sources. For example, the rate for Europe ranged from 23.5% (125/531) to 54.3% (504/929) [145,154,155]. The most frequent pathogen of mucormycosis in China is *Mucor* spp. (54.3%; 19/35), followed by *Rhizopus* spp. (28.6%; 10/35) [152]. These statistics vary from the findings in Europe, where *Rhizopus* spp. accounted for 33.7% (58/172), *Mucor* spp. accounted for 19.2% (33/172), and *Lichtheimia* spp. accounted for 18.6% (32/172) [145].

According to one report external to China [147], the variability of susceptibility to AMB, along with resistance to most other conventional antifungal agents, leads to high mortality. Currently, no large sample studies in China conducted the antifungal susceptibility testing of *Mucorales*.

Because mucormycosis is an opportunistic infectious disease, patients with underlying diseases are more likely to be infected than healthy individuals [151]. Internationally, mucormycosis is most common in patients with malignant tumors, diabetes, or organ transplants [154]. However, in China, this disease is more common in patients with diabetes, HIV infection, and viral hepatitis and in individuals who are long-term steroid or immunosuppressant users [152]. The close connection of mucormycosis with diabetes is worth noting because China has seen a rising burden of diabetes (92.4 million adults above the age of 20 years) [156].

In China, mucormycosis has occurred mainly on the coast and in humid areas [152]. The most common sites of infection are pulmonary (36.5%; 27/74), followed by rhinocerebral (32.4%; 24/74), skin (10.8%; 8/74), intracranial (6.8%; 5/74), and others (13.5%; 10/74) [151]. This finding is similar to the observations in Europe [145] but differs from the results of an international review that reported the sinus area as the most common site (39%; 359/929) [154].

To date, epidemiological data for this type of mucormycosis are scant in China. Most reports about mucormycosis lack evidence of molecular biological diagnosis. Additional effort should be exerted to identify species by molecular biology, and antifungal susceptibility testing is needed. Mucormycosis and diabetes are closely related; thus, attention must be focused on preventing and controlling diabetes.

Pneumocystis pneumonia

Pneumocystis pneumonia (PCP) is a potentially fatal pulmonary infection that occurs in immunocompromised individuals, especially in AIDS patients with a low CD4 cell count (below 200/mm³) [157,158]. PCP in humans is only caused by *Pneumocystis jirovecii*, which has recently been reclassified as fungal species [159–163]. Given the widespread use of PCP prophylaxis and highly active antiretroviral therapy, the incidence of PCP has declined significantly in developed countries [164].

However, PCP remains a common opportunistic infection in HIV-infected patients in developing countries, including China [165–167]. The earliest HIV/AIDS-associated PCP case in China was reported in 1985 [167]. From 1985 to 2009, the number of PCP patients afflicted by HIV/AIDS increased dramatically in China, apparently 70.2% (1646/2344) of which were identified along with HIV infection [167]. PCP also affects other

immunocompromised patients [168]. In China, the prevalence of *P. jirovecii* colonization in patients with chronic pulmonary diseases is apparently 63.3% (62/98), which is higher than previous reports in North Lebanon (17.3%; 4/23) and Iran (7.9%; 7/89) [169]. However, the incidence of PCP in China is rare among HIV-positive and HIV-negative hosts because all performed epidemiological studies on PCP in China were retrospective studies [170].

The mortality of PCP is diverse among different studies in the world, including China. A retrospective study in Beijing showed that mortality (15.2% vs. 12.4%) did not significantly differ between the PCP cases of HIV-positive and HIV-negative populations [171], which differ from studies in Beijing. Moreover, the mortality of non-HIV-PCP (30%–60%) in other countries, such as Japan, is higher than that of HIV-PCP (11.3%–20%) [157,172–174]. The difference in mortality may be associated with the different genetic backgrounds of *P. jirovecii* and anti-PCP treatment strategy.

Although trimethoprim (TMP)–sulfamethoxazole (SMX) remains the first-line agent for PCP [170], mutations in the dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) genes of *P. jirovecii* with resistance to TMP and SMX, respectively, have progressively emerged [170]. Currently, the prevalence of *P. jirovecii* DHPS and DHFR mutations in HIV-positive patients in China remains low, which is similar to that in other developing countries [175]. Approximately 60% of *P. jirovecii* isolates harbor nucleotide mutations in the DHFR gene in China. The majority (> 90%) of these mutations were synonymous, similar to the data reported in Japan and Thailand [175–177]. Meanwhile, the prevalence of *P. jirovecii* DHPS mutations in China was 12.0% (3/25) [175], which is similar to those reported from other developing countries, such as South Africa (3.8%; 2/53) [178], but lower than those determined from developed countries, such as the United States (40%; 58/145) [179].

In summary, the epidemiological data on PCP are limited in China to date, although the above-mentioned retrospective studies suggested that the epidemiological characteristics of PCP in China are similar to those in other developing countries. A prospective epidemiological survey focused on PCP in China is needed.

Endemic fungal infections

Sporotrichosis

Sporotrichosis is a subcutaneous mycosis caused by several *Sporothrix* species, namely, *S. brasiliensis*, *S. globosa*, *S. mexicana*, and *S. luriei*, besides the classical species *S. schenckii* [180]. Sporotrichosis is globally distributed, but *Sporothrix* species have shown high degrees of endemicity [180]. Given the data in existing

literature, the most endemic regions are China (3299 cases), South Africa (3154 cases), and Brazil (5814 cases) [181]. In China, since sporotrichosis was first found in 1916 [182], the disease has existed nationwide but has been observed mainly in Northeastern China, including Jilin Province, Heilongjiang Province, and Liaoning Province [180,183]. *S. globosa* exhibits a global distribution with nearly identical genotypes, and this species is the only pathogenic *Sporothrix* species that has been reported to date in China [180,183–186]. Such pattern is similar to those found in India and Spain [181].

Although the transmission mode of sporotrichosis remains unclear, trauma may be strongly implicated. Contact with decaying plant material was frequently noted in *S. globosa* and *S. schenckii*, whereas *S. brasiliensis* was significantly associated with transmission by cats [181]. Relative immune impairment and underlying metabolic diseases are important risk factors for sporotrichosis [180].

Sporotrichosis presents as the following three main clinical types: lymphocutaneous, fixed cutaneous, and multifocal or disseminated cutaneous sporotrichosis [187]. Globally, the most common clinical form is lymphocutaneous sporotrichosis, but in China, the fixed cutaneous form is prevalent, followed by the lymphocutaneous form [180,181,187,188]. Classically, sporotrichosis occurs in temperate and subtropical climates of relatively high humidity. By contrast, the climate is relatively cold in the hyperendemic area of Northeastern China, where *S. globosa* is prevalent [181].

As the number of immunocompromised patients rises, the epidemiological monitoring of sporotrichosis is increasingly needed, and research is necessary to indicate whether *S. schenckii* or other *Sporothrix* species exist in China. Additional protective measures should be undertaken to avoid infection during agricultural activities.

Penicilliosis

Penicilliosis is a deep fungal infection caused mainly by the dimorphic fungus *Talaromyces marneffeii* (formerly known as *Penicillium marneffeii*), a species endemic to Southeast Asia, including some districts in China (e.g., Guangdong, Guangxi, Yunnan, Fujian, Yunnan, and Hong Kong) [189–191]. The organism was discovered in 1956 in bamboo rats [192], and the first natural human case of infection was reported in 1973 [193]. In China, the first case of *T. marneffeii* infection was noted in 1984 [194]. After the 1990s, with the prevalence of AIDS in Southeast Asia, the number of patients with *T. marneffeii* infection increased rapidly in this area, including Chinese mainland [195,196]. More than 87% of the number of reported *T. marneffeii* infections was noted with HIV infection in China [196], and nearly 16% of the patients with AIDS were

infected with *T. marneffeii* in Guangxi [197]. To date, more than 600 cases of *T. marneffeii* infection have been identified in China, with 82% of the cases reported in Guangxi and Guangdong [196,198]. The mortality of *T. marneffeii* infection is higher in patients without antifungal therapy (50.6%; 45/89) than in patients with antifungal therapy (24.3%; 138/569) [196]. Cao *et al.* confirmed that the *T. marneffeii* isolates from humans are similar to those from infected bamboo rats, and in some cases, the isolates are identical, which parallel the data from Thailand and India [197,199,200]. Although the potential sources of infection are rodent species, particularly bamboo rats, the transmission route of *T. marneffeii* to humans remains a mystery [197]. In recent years, *T. marneffeii* infection has increasingly impacted immunocompromised patients in Southern China, especially individuals with HIV/AIDS [196]. Additional studies should be conducted to determine the transmission route of *T. marneffeii*, and raised attention should be paid to immunocompromised patients, especially those in endemic areas.

Histoplasmosis

Histoplasmosis, caused by the soil-based dimorphic fungus *Histoplasma capsulatum*, is a common endemic mycosis in midwestern United States and in Central America [201]. However, sporadic cases of autochthonous histoplasmosis have been encountered in China, a region traditionally considered non-endemic for *H. capsulatum* [202]. The first case of histoplasmosis in China was reported in 1958 in an individual returning from the USA [203]. Since 1990, 300 cases of histoplasmosis have been reported in China, of which only 17 cases were potentially imported cases [204]. The majority of these cases (75.0%; 225/300) occurred in nine provinces and regions traversed by the Yangtze River. Among these regions, Yunnan Province accounted for more than 27.7% (83/300) of the reported cases of histoplasmosis [204]. Pan *et al.* found that Chinese *H. capsulatum* isolates may have originated from Australia or other continents, such as North America [202].

Underlying diseases associated with histoplasmosis include HIV infection (22.0%; 38/173), diabetes mellitus (10.4%; 18/173), and liver diseases (7.5%; 13/173). Diabetes and malignancy are common in patients with pulmonary infection, but HIV-infected patients are prone to systemic dissemination. This information suggests that the clinical spectrum of histoplasmosis depends on the underlying host immune status [204]. Although histoplasmosis may prefer infecting individuals with underlying illness, research demonstrated that 49.1% (85/173) of patients lack an identifiable underlying disease [204].

At the time of our research, the epidemiology and ecology of *H. capsulatum* in China were unknown. As

Table 1 Recent reports of fungal infections caused by rare fungal species in China

Case	Date	Species	Infective sites	Prognosis	Reference
1	2004	<i>Arthrographis kalrae</i>	Eye and sinuses	Blindness	[207]
2	2007	<i>Prototheca wickerhamii</i>	Brain	Cured	[208]
3	2010	<i>Coniosporium epidermidis</i>	Toes	Cured	[210]
4	2011	<i>Exophiala asiatica</i>	Brain	Died	[209]
5	2012	<i>Filobasidium uniguttulatum</i>	Brain	Cured	[211]
6	2013	<i>Pichia fabianii</i>	Blood	Cured	[212]
7	2013	<i>Trichophyton tonsurans</i>	Face	Cured	[213]
8	2013	<i>Penicillium capsulatum</i>	Lung	Cured	[214]
9	2013	<i>Rhinocladiella basitona</i>	Face	Cured	[215]
10	2014	<i>Rhodotorula minuta</i>	Nail	Cured	[45]
11	2014	<i>Phialemonium curvatum</i>	Brain	Cured	[216]
12	2015	<i>Veronea botryosa</i>	Cutaneous	Cured	[217]
13	2016	<i>Bipolaris oryzae</i>	Corneal	Cured	[218]
14	2017	<i>Chrysosporium keratinophilum</i>	Subcutaneous	Cured	[219]

international travel becomes increasingly accessible, *H. capsulatum* may progressively spread globally from China or other endemic countries. A further detailed epidemiologic investigation of *H. capsulatum* is worthwhile.

Coccidioidomycosis

Coccidioidomycosis (CM) is a deep mycotic infection endemic to the Americas [205]. Although China is not a known endemic area for CM, the number of case reports of CM has risen [206]. Since 1958 when the first case was reported, 30 CM cases, of which 27 cases were from Southern China, have been recorded in China. Risk factors for infection include residence in or travel to a CM-endemic region, occupations with high exposure risk, immunocompromising conditions, or other underlying diseases [206]. However, the majority of Chinese patients (80.0%; 24/30) presented with no history of exposure to CM-endemic areas [206]. Since CM has been reported rarely in China, the possible local sources of CM in such region or in other countries remain uncertain.

Rare fungal infections

With the development of molecular diagnosis approaches, the number of case reports on fungal infections caused by rare fungal species has been increasing in China since 2000 [45,207–219]. For example, Pan *et al.* reported a case of meningitis caused by azole- and FLU-resistant *Filobasidium uniguttulatum* in 2012 [211]. Chen *et al.* also published the first case of a fungus ball (*Penicillium capsulatum*) in the left lung of a patient with type 2 diabetes [214]. Fungal infections caused by newly reported species should be monitored in China in the future. The details are provided in Table 1.

Conclusions

We systematically reviewed the epidemiological data of fungal infections across China to understand the related epidemiological profiles and trends. Our analysis demonstrated that the overall incidence of SFIs in China was stable. The overall incidence of IFIs in China continued to increase in both immunocompromised and immunocompetent individuals, with rising numbers caused by *Candida* species besides *C. albicans*, azole-resistant *A. fumigatus*, and *Cryptococcus* species. Moreover, epidemiological studies on mucormycosis and *Pneumocystis* are scarce in China. As regards the endemic fungal infections in China, sporotrichosis, penicilliosis, and histoplasmosis showed obvious regional distribution characteristics with raised number of cases. In addition, the occurrence of fungal infections caused by rare fungal species has augmented in China during the last decade. Considering these findings, we conclude that a nationwide epidemiological research focused on fungal infections in China is direly needed.

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Compliance with ethics guidelines

Min Chen, Yuan Xu, Nan Hong, Yali Yang, Wenzhi Lei, Lin Du, Jingjun Zhao, Xia Lei, Lin Xiong, Langqi Cai, Hui Xu, Weihua Pan, and Wanqing Liao declare no conflict of interest. This manuscript does not involve a research protocol requiring approval from a relevant institutional review board or ethics committee.

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