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Recent Trends in the Epidemiology of Fungal Infections

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INTRODUCTION

Historically, fungal infections were viewed as a relatively uncommon cause of clinically relevant disease compared with other bacterial and viral pathogens.[1] This trend shifted in the second half of the 20th century, as the number of immunocompromised patients susceptible to opportunistic fungal infections increased, following advancements in medical treatment and the HIV/AIDS epidemic.[1,2] Fungi previously assumed to be rare causes of infection, such as *Cryptococcus* species, emerged as substantial causes of invasive disease in hosts with impaired immunity.[3] The emergence of these opportunistic fungal infections, which caused increasing morbidity and mortality, introduced notable diagnostic and therapeutic challenges in health care and resulted in increased epidemiologic attention on fungal diseases.[4]

Over the past decade, the variety of fungi identified causing human disease and the spectrum of clinical presentations associated with these infections has increased.[5,6] With the evolution of antiretroviral therapy (ART), HIV-associated cases of cryptococcosis and other opportunistic fungal infections declined in North America, yet diseases caused by health care–associated fungal pathogens, including *Candida* species, *Aspergillus* species, and other molds, increased, to a large extent owing to substantial increases in at-risk populations.[3,6-8] Although traditionally transmission between humans was rare, with only sporadic reports of fungal outbreaks, transmission of certain fungi between patients has increasingly been reported in clinical settings, causing numerous health care–associated outbreaks.[2,9] Molds,

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DISCLOSURE

The authors have nothing to disclose.

including mucoromycetes, *Fusarium* species, *Scedosporium* species, and dimorphic fungi specific to certain geographic regions such as *Blastomyces, Coccidioides,* and *Histoplasma,* have also grown in importance.[4,6] For some, environmental changes have contributed to geographic expansion.[4,6,10] Furthermore, epidemiologic trends demonstrate dramatic increases in the incidence of resistant infections and emergence of novel multidrug-resistant fungi.[9,11] The frequency of fungal infections continues to increase; according to some global estimates, more than 300 million people are affected by serious fungal disease each year.[5] Worldwide, mortality estimates exceed 1.5 million deaths annually, with the death rate for certain invasive infections in some populations surpassing 50%.[1,5,12] In the United States, more than 75,000 hospitalizations and nearly $7.2 billion in medical care costs were attributed to fungal infections in 2017.[13]

Many health care–related, environmental, and socioeconomic factors have influenced these recent epidemiologic shifts, introducing considerable challenges to decreasing disease burden.[2,12,14] The expansion of prophylactic antifungal use has resulted in a decline in candidemia incidence within certain populations, yet such use also contributed to the growing threat of increasing resistance.[15] Advances in health care practices and medical procedures have resulted in new risk factors and an overall increase in the number of susceptible hosts.[6,14] For instance, a dramatic expansion in the use of immunosuppressive medications, chemotherapeutic regimens, and antibiotics have resulted in new and expanding patient populations at risk.[2,4,14] Advances in therapeutics that have prolonged survival in patients with previously fatal conditions have allowed more time for infection by opportunistic pathogens.[8] Furthermore, although some fungi are commensal organisms that live in the gastrointestinal tract and on the skin, the increased use of invasive medical devices and procedures (eg, catheters and hematopoietic transplantation modalities) provides additional opportunities for these fungi to reach tissues and blood and cause invasive disease.[1,6,16] Increased global travel and environmental changes also interplay to increase the intensity of interactions between humans and the environment, ultimately extending geographic disease ranges.[17-19] In recent years, major health events not typically associated with mycoses, such as seasonal influenza epidemics and the severe acute respiratory syndrome novel coronavirus pandemic, resulted in larger proportions of the population becoming critically ill and susceptible to secondary fungal infections.[20]

Early diagnosis, intervention, and appropriate antifungal treatment are the keys to decreasing the burden of fungal diseases.[4,14] Yet, despite developments in diagnostic techniques, antifungal options are still limited, and morbidity and mortality remain high, while awareness remains low.[2] Understanding, the epidemiology and emerging trends in fungal infections remains critical for prevention, diagnosis, management of care, and improvement in patient outcomes. In this review, we aim to summarize recent updates to the epidemiologic profiles of clinically significant fungal pathogens in North America (Table 1).

Candida

Candida bloodstream infection, known as candidemia, is the most common invasive *Candida* infection; at the genus level, *Candida* ranks as one of the most prevalent causes of health care–associated infections in North America.[21,22] Data from a nationally representative

US-based surveillance system indicated a decline in incidence from 2009 to 2013, which stabilized at approximately 9 cases per 100,000 population from 2013 to 2017.[16,23] This decrease occurred primarily among patients with health care exposure, specifically those with central venous catheters and, therefore, may be related to increased infection control practices in catheter care.[23] Of particular note, a large proportion of cases historically occurred in children less than 1 year of age, yet candidemia incidence among this age group sharply decreased from 2009 to 2012, likely because of increased prophylaxis and improved catheter-related care among neonates.[23,24] In the United States, neonatal incidence decreased from approximately 32 cases per 100,000 births in 2009 to less than 12 cases per 100,000 births by 2012, and has remained stable since then.[24] Despite overall declines through 2013 in the United States across all age groups, incidence remains the highest among those 65 years and older. Large racial disparities persist across all age groups (the incidence among Blacks is 2.3 times higher than among non-Blacks). All-cause hospital mortality among all persons infected remains high at approximately 25% (yet varies by age group ranging from 10% among 1- to 18-year-olds to 32% among those ≥65 years old).[16,23]

In contrast with the United States, Canada's estimated incidence of candidemia is less than 3 cases per 100,000, with little change over the past 15 years.[25-27] Similar to the United States, incidence is highest among those 65 years and older, followed by those less than 1 year old.[27] Few studies have examined trends in Mexico; 1 study using demographic data and population-based surveys estimated national incidence to be 5 cases per 100,000 population, with the intensive care unit (ICU) incidence 10-fold higher than the non-ICU incidence.[28] In 14 medical centers in Mexico from 2010 to 2011, *Candida* species accounted for nearly all (98%) fungal bloodstream infections among pediatric patients.[29]

The major risk factors for invasive *Candida* infections have varied little over the past decade.[16] These include the presence of indwelling catheters (mainly central venous catheters) and other medical devices, hematologic or solid organ malignancies, recent abdominal surgeries, hemodialysis, diabetes, receipt of systemic antibiotics or immunosuppressive medications including steroids, and receipt of total parenteral nutrition.[16,30] Recently, injection drug use emerged as a risk factor; it is becoming more common in the context of the opioid epidemic.[31,32] In the United States, approximately 10% of candidemia cases identified through surveillance in 2017 occurred in patients with recent injection drug use.[31] Patients with injection drug use tend to be younger, non-Hispanic Whites, and the disease is often community-associated rather than health care-associated.[31,32]

Five species account for most candidemia infections worldwide: *C albicans, C glabrata, C tropicalis, C parapsilosis,* and *C krusei.*[16,33] Worldwide, these 5 species are estimated to account for more than 90% of all infections; however, the precise distribution and rank order of *Candida* species differ by geographic area, health care unit, underlying conditions, and patient demographic characteristics.[16,33,34] Although C *albicans* remains the most common *Candida* species causing invasive infection in most clinical settings in North America, an increasing proportion of diagnoses in recent years have been attributed to non-*albicans* species, particularly *C glabrata* and *C parapsilosis.* In some settings, these species have even surpassed *C albicans*.[28,35] The increased proportion of *C parapsilosis* infections is

concerning because this species can colonize health care workers' hands, ultimately causing outbreaks.[9] In one US surveillance site, the proportion of cases caused by *C albicans* decreased from 52% (1992–1993) to 41% (2008–2011), whereas *C glabrata* cases increased from 12% to 27% over the same time period.[35] Similar trends have been documented in Canada, where in 1 multicenter study the proportion of *C albicans* cases declined from 61% to 42% and *C glabrata* cases increased from 17% to 22% from 2011 to 2016.[36]

Furthermore, non-*albicans* species often have decreased susceptibility to first-line antifungal therapies used to treat candidemia, including azoles and echinocandins.[37] Approximately 10% of *C glabrata* isolates in the United States are resistant to fluconazole.[35,38] Yet similar to species distributions, resistance patterns vary geographically and by medical institution (eg, a Canadian study found fluconazole resistance in only 1% among *C glabrata* isolates, whereas susceptibility testing from 2 Mexican tertiary care hospitals revealed fluconazole resistance to be 11% among *C glabrata* isolates).[28,36] However, multidrug resistance remains uncommon among these top 5 species.[34]

Although some *Candida* species are intrinsically resistant to certain antifungals (eg, *C lusitaniae* and amphotericin B, *C krusei* and fluconazole), of increasing concern is acquired resistance, particularly among *C glabrata* isolates.[37,39-43] These genomic and epidemiologic shifts in species and resistance patterns have been attributed to frequent prophylactic antifungal use, favoring less susceptible species.[44] These changes have introduced new challenges to patient care and management.

The recent emergence of *C auris* represents a paradigm shift in *Candida* epidemiology.[9] First described in 2009 in Japan and first reported in North America in 2016 (with the earliest reported isolate from 2013), *C auris* differs from other *Candida* species, behaving more like a bacterium than a fungus.[9,45] By late 2019, more than 1000 cases had been reported to the US Centers for Disease Control and Prevention (Fig. 1). Multidrug resistance is common in *C auris*, and unlike other *Candida* species, some isolates are resistant to all 3 major antifungal classes, presenting substantial challenges to successful treatment.[46] In the United States, approximately 90% of *C auris* isolates are resistant to fluconazole, 30% to amphotericin B, and 5% to echinocandins.[9] Furthermore, like *C glabrata,* acquired resistance in patients undergoing treatment for *C auris* infection has been documented.[9,47] Unlike most *Candida* species, *C auris* is commonly transmitted among patients in the health care environment, and outbreaks have been reported worldwide.[48,49] Further complicating the control of transmission, patients can become colonized on skin, nares, groin, or axilla and spread *C auris* in the health care environment, yet remain asymptomatic.[48,50] In 2019, the US Centers for Disease Control and Prevention classified *C auris* as an urgent threat.[51]

Most perplexing is the simultaneous emergence of *C auris* within different geographic regions of the world, with whole genome sequencing revealing 4 distinct geographic clades: South Asia, South Africa, South America, and East Asia (Fig. 2).[19,52-54] To date, *C auris* cases have been reported in dozens of countries, yet the prevalence is likely underestimated owing to limited diagnostic capacities to accurately identify the species.[55,56] Clinically, *C auris* causes invasive infection, and mortality estimates range from 30% to 60%; among recovered patients, indefinite colonization can occur.[46] Identified risk factors are similar

to those of other invasive *Candida* infections.[9,46,55] Additional risk factors specific to *C auris* include the receipt of antifungals at or near the time of diagnosis and, unlike other *Candida* infections often associated with ICU settings, patients tend to have exposure to long-term care or skilled nursing facilities.[57] The rapid emergence of *C auris* indicates the need for improved diagnostics and a broader range of treatments for multidrug-resistant fungal pathogens.[9]

MOLD

Aspergillus

More than 180 species make up the *Aspergillus* genus, although only a subset have been tied to human disease. *A fumigatus* has historically been responsible for most aspergillosis-related conditions, though infections are increasingly associated with non-*fumigatus* species, including *A flavus*, *A terreus*, and *A niger*.[58-60]

Aspergillosis remains a substantial risk for persons with weakened immune systems. Illness severity ranges from mild to serious, and invasive infection substantially increases the risk of death.[61] Invasive aspergillosis, although relatively rare, is the most common type of invasive mold infection and can cause severe health problems, particularly among immunocompromised populations.[62,63]

Invasive fungal disease (IFD), including invasive aspergillosis, is classified according to consensus definitions of the Mycoses Study Group (MSG) and the European Organization for Research and Treatment of Cancer (EORTC). Criteria include a strict set of host factors and clinical features comprising classic symptoms and radiologic findings.[64] The definitions reflect persons particularly at risk for invasive aspergillosis, including those with hematologic malignancies, a recent history of neutropenia, and hematopoietic transplant or solid organ transplant recipients. Similarly, patients receiving immunosuppressive therapies or high doses of corticosteroids may be more susceptible to opportunistic infection.[65]
A trend analysis is difficult because invasive aspergillosis is not a reportable disease. A combination of literature reviews and modeling have been used to assess the burden of disease in Canada and Mexico, where incidence is estimated to be 1.6 per 100,000 population and 4.6 per 100,000 population, respectively.[25,28] Validation of these estimates through formal epidemiologic studies is needed.

Hospitalization data can provide valuable insight into the epidemiology of this disease because most people with invasive aspergillosis require hospitalization. In a nationally representative database of US hospitalizations, invasive aspergillosis-associated hospitalizations increased by 57% from 2000 to 2013, and the overall rate of invasive aspergillosis-associated hospitalizations increased by 3% during the same timeframe.[66]

The increase in US hospitalizations may reflect a number of factors. The susceptible population has likely grown owing to an increase in the number of stem cell and organ transplantations in recent years, as well as the more widespread use of immunosuppressive agents.[2,67,68] Additionally, diagnostic advancements may have contributed to increased detection of invasive aspergillosis, particularly in patients who present without classic

symptoms. Despite the increased hospitalization numbers, decreases in crude mortality rates and excess attributable length of stay suggest that invasive aspergillosis outcomes have improved.[69] The increased survival of invasive aspergillosis is likely attributable in part to the development of newer azole antifungal medications, including voriconazole and posaconazole.[70]

However, azole-resistant strains of *A fumigatus* have been discovered, with serious implications for the management of aspergillosis. Azole resistance was first identified in Europe, but has since been detected worldwide.[71-73] These strains present a clear challenge to treatment and are associated with high mortality rates.[74]

Of note, the main resistance mechanism found in Europe has been detected in azole-naïve patients and not in those who have undergone long-term azole therapy, where other mutations were detected.[75] This finding has led researchers to suspect an environmental source, and reports have confirmed that resistance may develop as a result of exposure to azole fungicides used for agricultural purposes.[75,76] This finding is of particular concern given the widespread use of azoles as crop pesticides.[71,77,78]

The epidemiologic characteristics of recently described patients coinfected with aspergillus and influenza are distinct from the classic MSG/EORTC criteria, which may lead physicians to forgo testing for these infections. A substantial proportion of patients with influenza-associated pulmonary aspergillosis (IAPA) may be immunocompetent or may not present with classic IFD host factors.[79,80] Clinical and radiologic findings are not necessarily indicative of IFD; lesions on a computed tomography scan with halo signs are typically absent in ICU patients. A consensus case definition has been proposed to account for IAPA's epidemiologic differences from the MSG/EORTC classifications.[80] IAPA is associated with severe outcomes among critically ill patients in the ICU.[79,81,82] Results from a multicenter study in the Netherlands and Belgium showed that the 90-day mortality rate among ICU patients with IAPA (51%) was nearly double that of ICU patients with influenza without invasive aspergillosis (28%).[79] It is suggested that physicians consider IAPA in selected ICU patients with influenza, especially those with ventilator-associated pneumonia, yet physician awareness of IAPA remains low, particularly in the United States.[83,84]

The advent of the severe acute respiratory syndrome novel coronavirus, that causes the coronavirus disease 2019 (COVID-19), has posed a similar challenge. Critically ill patients with COVID-19 present with clinical characteristics comparable with patients with severe influenza and are likewise susceptible to secondary infection.[85] Early reports of COVID-19–associated pulmonary aspergillosis (CAPA) show that patients do not generally meet MSG/EORTC criteria, prompting the need for specific diagnostic and screening criteria to classify cases of CAPA.[85]

Evidence to date suggests that critically ill IAPA and CAPA patient symptoms may be notably different from classic IFD features. However, much remains to be learned about these emerging infections.[80,85,86]

Non–Aspergillus Molds

Recent reports show a potential increase in non-*Aspergillus* invasive mold infections (NAIMIs) among patients with hematologic malignancies and transplant recipients.[87-89] These molds, such as mucoromycetes, *Fusarium*, and *Scedosporium spp.*, are rare but extremely hazardous to the health of those infected. Mucormycosis is typically the most common NAIMI, followed by fusariosis and scedosporiosis; prominence has been shown to vary geographically.[90-92]

These infections are characterized by high mortality rates, resistance to multiple antifungal drugs, and dissemination to multiple organs. Analyses showed the proportion of HSCT patients who contracted a NAIMI was 1% or less, but the alarming 1-year survival rate ranged from 6% to 22%.[62,93] These findings are consistent with previous reports, suggesting that problems associated with disease management and treatment have persisted.[94]

The increased in NAIMIs could be a result of expanded immunosuppressive therapy use and anti-*Aspergillus* prophylaxis,[95] or it could stem from the increase in susceptible patients. Additional NAIMI risk factors such as neutropenia, extended corticosteroid use, and diabetes align with established risk factors for all fungal infections,[96,97] although variations across pathogens have been reported.[97]

The early detection of NAIMIs is essential to determine the optimal clinical course and most appropriate antifungal therapy. A nonspecific clinical presentation and limited diagnostics present challenges to diagnosis, although advancements in the identification of mold pathogens through molecular techniques is promising.[80,89,98] The infection may not become evident until later stages of disease when illness is more severe.[88] Although host factors such as immune system recovery or progression of underlying conditions play a substantial role in patient prognosis, continued advancements in diagnostics and therapeutic approaches will be important to increase survival from these deadly diseases.

ENDEMIC MYCOSES

Geographically restricted fungal diseases, commonly referred to as endemic, namely, blastomycosis, coccidioidomycosis, and histoplasmosis, present a growing public health concern. Preventing exposure to the causative fungi may be difficult in areas where they are prevalent in the environment. Infection can result in serious illness or death, particularly among immunocompromised populations. However, public and physician awareness of these diseases remains low.[99] Surveillance and diagnostic challenges limit the known epidemiology of these mycoses.

Blastomycosis, coccidioidomycosis, histoplasmosis, and other dimorphic fungi are often collectively referred to as endemic mycoses, although the term “endemic” may be misrepresentative. These diseases have historically been associated with specific geographic regions.[100,101] However, infections and outbreaks acquired outside of traditional locations indicate that geographic distribution is wider than previously recognized.[102] Within the classic regions, there are areas of hyperendemicity and hypoendemicity as well as seasonal trends that are not fully captured by the classification of endemic versus nonendemic.[103]

Estimates of case counts and incidence are likely subject to under-reporting and misdiagnosis, masking the true burden of disease. These fungal infections are often clinically indistinguishable from other respiratory illnesses such as community-acquired pneumonia.[104] Nonspecific symptoms such as cough, fever, and shortness of breath may lead persons with mild cases not to seek care. Many cases may go undetected by surveillance efforts as blastomycosis, coccidioidomycosis, and histoplasmosis are each only reportable in a subset of US states (5, 26 plus the District of Columbia, and 12, respectively).[105] Only coccidioidomycosis is nationally notifiable in the United States.

An innovative approach toward understanding the current distribution is multidisciplinary modeling of environmental characteristics. These models leverage environmental data to detect areas with risk of exposure based on the suitability of the surrounding conditions for the causative fungi.[10] Such techniques are important to appreciate the expanding geographic range of regional fungal diseases and tailor public health efforts accordingly. However, more robust and widespread surveillance for these diseases is needed to better understand their changing geographic distribution and epidemiologic trends.

Blastomyces

Rates of blastomycosis seem to be stable, although the rarity of the disease complicates assessment. In US states where it is reportable, the annual incidence rates have been consistent at approximately 1 to 2 cases per 100,000 population,[106,107] and evidence from Canada indicates a similar rate of 0.62 per 100,000 population.[108] Wisconsin classically has the highest rate of any state, ranging from 10 to 40 cases per 100,000 persons in some counties.[101]

Blastomyces primarily lives in regions surrounding the Ohio and Mississippi River valleys, the Great Lakes, the Saint Lawrence River, and southern Canada. Although the disease is relatively uncommon, it covers a wide geographic area, as shown in Fig. 3. Several US states with comparatively high rates of blastomycosis-associated hospitalizations, including Illinois, Kentucky, and Tennessee, do not mandate reporting.[109] Recent cases have been reported in areas not known to be endemic for blastomycosis.[110] It is unclear whether environmental factors such as fluctuations in temperature or precipitation may have contributed to this spread as the ecology of *Blastomyces* is not well-understood.[111]

Anyone can contract blastomycosis in areas where the fungus lives; hospitalization and death are more likely among individuals with immunocompromised status or other underlying medical conditions.[102,109] Outdoor activities such as boating, fishing, and hiking may put people at greater risk of infection.[110] The disease is more prevalent among older populations, although finding this could be a factor of weakening immune systems.[112] Historically, the higher proportion of blastomycosis-related morbidity and mortality among males was thought to be a consequence of occupational differences or varied recreational activities.[113] However, it is possible that the discrepancy is due to hormonal distinctions between the sexes, as suggested for other fungal diseases.[114,115]

Coccidioides

The number of coccidioidomycosis cases reported to the US Centers for Disease Control and Prevention has increased consistently in recent years. This increase follows a downward trend from 2011 (22,634 cases) to 2014 (8232 cases), after which the total number of cases increased each year, reaching 15,611 in 2018.[116] Arizona and California account for more than 95% of the reported cases. The incidence in California more than tripled from 6.0 per 100,000 population in 2014 to 18.8 per 100,000 population in 2018.[117] In recent years, the total number of cases reported in California surpassed those reported in Arizona.[116] Arizona's incidence also increased from 2014 (84.4 per 100,000 population) to 2018 (105.7 per 100,000 population), although it remained well below the 2011 peak (255.8 per 100,000 population).[118]

Reasons for the decrease and subsequent increase in reported cases are likely multifaceted. The year-to-year changes may have been influenced by environmental or climate changes, increases to the susceptible population based on travel or new residence in endemic areas, revised reporting and testing practices, or changes in land use.[119-121]

The presence of *Coccidioides* in the southwestern United States as well as parts of Mexico and Central and South America is well-established. Recently reported cases beyond these traditional areas indicate a northward expansion of the geographic range (see Fig. 3), stretching to Northern California, Utah, and Washington.[103,122-124] In Washington, whole genome sequencing determined that infection was locally acquired rather than a result of travel.[125,126]

Histoplasma

Evaluating the true burden of histoplasmosis is a continuing challenge, though the disease is likely more common than currently appreciated. In 2016, the US Council of State and Territorial Epidemiologists approved a standardized surveillance case definition for histoplasmosis. Previously, US states in which the disease was reportable used varying definitions, limiting the ability to make comparisons across states or evaluate overall trends in incidence using public health surveillance data.

US histoplasmosis-associated hospitalizations nearly doubled from 0.9 per 100,000 persons (2604 hospitalizations) in 2001 to 1.7 per 100,000 persons (5175 hospitalizations) in 2012.[11] Considerable increases observed across certain patient populations suggest the emergence of new high-risk groups, specifically transplant recipients and patients whose conditions warrant treatment with biologic agents.[127] These increases correspond with the proliferation of new biologic treatments and the increase in solid organ and hematopoietic stem cell transplants. Notably, the proportion of histoplasmosis-associated hospitalizations among HIV/AIDS patients decreased, which can likely be attributed to the availability of ART.[127]

In the United States, *Histoplasma* generally lives in the central and eastern states, especially in areas surrounding the Ohio and Mississippi River valleys (see Fig. 3). Surveillance data and outbreak investigations suggest that the occurrence of histoplasmosis extends well beyond the already broadly defined historical region.[11,106] A geographic suitability

model suggests that preferred soil environments for *Histoplasma* have extended to the upper Missouri River basin, possibly owing to environmental changes.[108]

CRYPTOCOCCUS

Cryptococcosis is an opportunistic infection that typically presents as meningitis or meningoencephalitis and emerged as a predominant cause of disease during the HIV/AIDS epidemic in the 1980s.[128,129] With the increase in immunocompromised susceptible hosts, cases of cryptococcosis increased dramatically worldwide throughout the early years of the epidemic.[129,130] The incidence of cryptococcosis has decreased since the implementation of ART and other improvements to the early detection and treatment of HIV/AIDS.[129] Most cryptococcosis cases are due to 2 species complexes: *C neoformans*, which comprises the vast majority of isolated species, and *C gattii*.[131] We continue to learn about the ecological and environmental niches of *Cryptococcus*, but *C gattii* has been mainly associated with certain trees and soil debris and may be more limited in distribution. *C neoformans* is cosmopolitan and can be associated with soil contaminated by bird, particularly pigeon, excrements.[12,132,133]

Recent data show approximately 15% of AIDS-related deaths are attributed to cryptococcal meningitis.[134] Worldwide cryptococcal meningitis estimates exceed 220,000 cases annually, with most geographically concentrated in sub-Saharan Africa.[134,135] North America experienced the most dramatic decreases in HIV-associated cryptococcosis incidence in recent decades.[129] Advanced modeling methods estimate 3700 people are cryptococcal antigenemia positive in the region; the annual burden of cryptococcal meningitis and cryptococcal meningitis-related deaths are estimated at 3000 and 700 cases, respectively.[134]

In the United States, cryptococcosis incidence decreased by approximately 90% in the 1990s among people living with HIV, and a recent study using sera collected from 1986 to 2012 estimates that approximately 3% of individuals living with advanced HIV with CD4 counts of less than 100 cells/μL are cryptococcal antigen positive.[130,136,137] Estimated incidence of cryptococcal meningitis ranges from 2 to 7 cases per 1000 person years among individuals living with HIV in the United States, with mortality ranging from 12% to 25%.[130,138] The US cryptococcal infection burden is estimated to be between 2500 and 5000 cases.[134] In Mexico, cryptococcal infection annual burden is estimated to be less than 1000 cases. In Canada, the burden is estimated to be less than 500 cases.[134]

Although ART has contributed to overall decreases in disease burden, ART initiation may not directly correlate with decreased infection rates; additional factors including continuous care and high ART adherence also contribute to preventing infection.[139,140] Recent studies have also identified individuals with subclinical meningitis, meaning that *Cryptococcus* species is present in the central nervous system yet the patient remains asymptomatic, shifting the understanding of the burden of disease.[128]

The fungus also infects persons with impaired immunity owing to non-HIV conditions, including those with lymphoproliferative disorders, sarcoidosis, malignancies, and diabetes; those who have received immunosuppressive therapies or solid organ transplants; and

those with no identified underlying immunodeficiencies.[141,142] In a recent US-based retrospective analysis, only 36% of patients with cryptococcosis were HIV positive, with the remainder including solid organ transplant recipients (28%) or other non-HIV/nontransplant patients.[138] Cryptococcosis ranked as the third most common invasive fungal infection among solid organ transplant recipients in a review of transplant infections in the United States.[143] Approximately 25% to 54% of transplant patients who develop cryptococcosis have pulmonary disease.[144] The cumulative lifetime risk of disease among solid organ transplant recipients ranges from 1% to 2%.[129]

As the rate of disease among people living with HIV in North America has decreased, the rate among those living without HIV has not, resulting in an increased proportion of non–HIV-associated cases.[129] HIV-negative patients tend to be older and have lower rates of meningitis, although other forms of disseminated disease are still common.[129,138] Furthermore, although immunodeficiencies remain a significant risk factor, approximately 20% of non-HIV patients who develop *Cryptococcus* disease have no known immune impairments.[142] Notably, non-HIV/nontransplant patients experience poorer clinical outcomes compared with both HIV-positive and solid organ transplant patients, with higher rates of morbidity and mortality (46% mortality in nonimmunosuppressed vs 19% among those immunosuppressed and 15% among HIV-positive patients), potentially related to delayed detection and an overly reactive immune response among immunocompetent individuals.[129,145]

Similar to other fungi, antifungal resistance remains a challenge. There are no breakpoints for *Cryptococcus*, so the burden of resistance is relatively unknown and additional studies are needed. In a recent systematic review that included nearly 5000 isolates of *Cryptococcus* species, the majority being *C neoformans*, across 29 studies (1988–2017), the average prevalence with elevated fluconazole minimum inhibitory concentration values was found to be 10.6% among incident isolates.[135,146]

Cryptococcus gattii Species Complex

In contrast with *C neoformans*, historically *C gattii* was limited to the tropical and subtropical regions of South America, Asia, Australia, and parts of Africa.[12,131,133,147] Yet in 1999, *C gattii*'s known geographic distribution expanded when the species caused an unprecedented outbreak on Vancouver Island in British Columbia, Canada.[132] An increasing number of cases have since been reported on mainland Canada and the US Pacific Northwest, with many of those infected lacking any immunocompromising condition.[12,141] In the Vancouver Island outbreak, only 40% of cases had any immunocompromising disorder.[142] Recently, sporadic cases of *C gattii* have also been reported in the Southeastern United States, and in Mexico *C gattii* comprises 12% to 20% of all cryptococcal isolates.[132,148,149] Genetically, the *C gattii* species complex is divided into 5 different species: *C gattii sensu stricto, C deuterogattii*, *C bacillisporus, C tetragattii*, and *C decagattii.* All species have been detected in Mexico, yet most isolates in Canada and the northwestern US region belong to *C deuterogattii*.[150] Nonetheless, environmental distributions have not been fully characterized owing to limited environmental sampling.[150]

OTHER FUNGAL INFECTIONS

Pneumocystis jirovecii

Pneumocystis pneumonia (PCP) is an infection that affects persons with weakened immune systems. Although uncommon before the HIV/AIDS epidemic in the 1980s,[151] PCP quickly became one of the leading AIDS-defining illnesses.[152] The introduction of ART and treatment with trimethoprim and sulfamethoxazole corresponded with a considerable decrease in PCP among people living with HIV/AIDS.[153-155] However, PCP remains an important cause of morbidity and mortality worldwide.

A study of HIV-infected patients in the United States and Canada found PCP to be the most common opportunistic infection, despite a decrease in incidence from 0.92 cases per 100 person-years to 0.39 cases per 100 person-years from 2000 to 2010.[156] Among persons living with HIV/AIDS, the risk of PCP persists for those who do not receive or do not respond to ART.

Populations at risk for PCP have shifted toward HIV-uninfected immunocompromised groups owing to immunosuppressive regimens that weaken the immune system. Risk factors include stem cell transplants or solid organ transplants, cancer, chronic lung disease, and autoimmune diseases.[112,157,158] The clinical presentation can vary by HIV status, and HIV-uninfected persons with PCP may experience a greater diagnostic delays and increased risk of mortality compared with HIV-infected counterparts.[113] The changing epidemiology of PCP as a result of therapeutic developments highlights the continued threat of the disease.

Sporothrix

Sporotrichosis, typically associated with contact with plant matter including sphagnum moss, rose bushes, and hay, is rare in North America.[159,160] *Sporothrix schenckii* has been found worldwide, with most US cases occurring in southern coastal regions and river valleys.[159] Using a large commercial health insurance database, US sporotrichosis incidence was estimated to be 2 cases per 1 million people from 2012 to 2018; the incidence was highest in Oklahoma, Michigan, Kansas, and Kentucky.[161] *S schenckii* outbreaks in the United States have been associated with forestry, gardening, and exposure to farms.[159,160,162]

In Mexico, where the incidence peaks during the cold and dry seasons, *S schenckii* is the most prevalent species. In some areas, the incidence reaches 25 cases per 1000 population, suggesting high endemicity within some regions.[162] In the state of Puebla, Mexico, 53% of residents were reactive to sporotrichin on intradermal skin tests.[160] Differences by age and sex are typically related to occupational exposures.[163]

The species *S brasiliensis* recently emerged in South America and is associated with zoonotic transmission, spreading via animal scratches and bites.[159] Brazil is currently experiencing an unprecedented outbreak of *S brasiliensis* with more than 4500 human cases reported; sporadic cases and smaller outbreaks have been reported in Argentina and other South American countries.[159] Although *S brasiliensis* has not been reported in North

America, there is concern the species could spread through the movement of infected animals.

DISCUSSION

The epidemiology of fungal diseases is constantly evolving. Environmental changes, medical advancements, emerging species, and diagnostic and therapeutic developments have all contributed to meaningful shifts in the geographic distribution, population risk, pathogen virulence, and disease progression in recent years. Increasingly widespread use of immunosuppressive agents among patients with underlying conditions has contributed to increasing opportunistic infections and emerging pathogenic fungi.[1-3] Although *Candida* and *Aspergillus* spp. remain the most common causes of IFD, the increase in regional fungal diseases and NAIMIs is of concern. Even within the *Candida* and *Aspergillus* genera, changes in the distribution of disease reflect the growing prevalence of non-*C albicans* and non-*A fumigatus* species.[28,35,58]

Large-scale health events such as seasonal influenza epidemics and the COVID-19 pandemic merge ongoing with new public health challenges in the context of fungal disease. Recent resurgence of *C auris* in health care facilities where its spread had previously been controlled highlights the importance of infection control measures. The emergence of IAPA and CAPA stress the need for standardized case definitions and IFD testing to detect secondary infection.[86,164]

It is critical to consider that documented updates regarding fungal diseases only paint part of the picture. To advance the field of mycotic epidemiology, more robust surveillance is needed to monitor long-term trends and identify the emergence of new infections. Because most fungal diseases are not nationally notifiable, this lack of surveillance often leads to underestimation of disease burden. As a result of generally nonspecific symptoms associated with fungal infections, patients may not seek care or physicians may not test appropriately, leading to underdiagnosis or delayed diagnosis.

An increased awareness at both the patient and physician levels is needed to avoid delays in diagnosis and proper treatment.[99,113,165] Given the expanding geographic boundaries of regional fungal diseases and the potential for travel-related infections, it is important that physicians outside of the traditional endemic areas are familiar with these mycoses and do not discount them solely on the basis of location.

Continued improvements in laboratory diagnostics are also essential for early diagnosis and appropriate treatment. Advancements in molecular techniques and lateral flow assays show progress toward testing ease and efficiency.[166,167] Additionally, the use of whole genome sequencing is valuable to understand disease exposure, transmission, and overall genetic composition.

SUMMARY

The epidemiology of fungal infections is complex and multifaceted. Limitations with surveillance, diagnostics, and overall awareness demonstrate the interdisciplinary challenges

facing current efforts to curtail the burden of disease. As the field continues to evolve, it will be necessary to effectively address these shortcomings to decrease morbidity and mortality from infection.

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KEY POINTS

- Environmental changes, medical advancements, and diagnostic developments have all contributed to meaningful shifts in at-risk populations, geographic distribution, and fungal disease progression in recent years.
- Although *Candida* and *Aspergillus* spp. remain the most common causes of invasive fungal disease, the increase in regional fungal diseases and non-*Aspergillus* invasive mold infections is of concern.
- Early intervention and appropriate treatment are key to reducing disease burden.
- Yet, despite developments in diagnostic techniques, there are limited antifungal options, mortality remains high, and awareness remains low.
- Large-scale health events such as seasonal influenza epidemics and the coronavirus disease 2019 pandemic have introduced new public health challenges in the control of fungal disease.

CLINICS CARE POINTS

- Physicians may not consider fungal diseases in the differential diagnosis owing to low awareness and nonspecific clinical presentation.
- Adherence to infection control practices is important to the prevention of health care–associated infection and likely contributed to a recent decrease in the incidence of candidemia in the United States.
- Diagnosis of fungal disease is further complicated by patients who present with atypical host characteristics. Resulting misdiagnosis and diagnostic delays may lead to unnecessary antibiotic use and increased morbidity and mortality.
- Large-scale health events such as seasonal influenza epidemics and the COVID-19 pandemic may lead to an increase in the proportions of the population susceptible to secondary fungal infection.

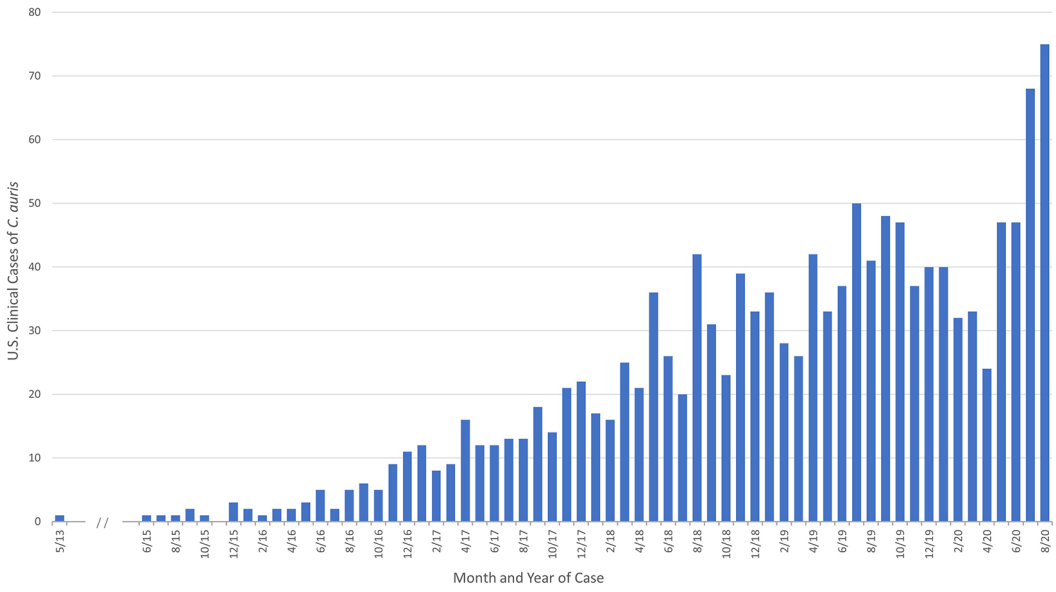

Fig. 1.

Reported U.S. Clinical Cases of *C auris* from 2013 to 2020. *C auris* began spreading in the United States in 2015; the earliest reported US cases were identified through a retrospective review. (*From* Centers for Disease Control and Prevention [CDC] unpublished data.)

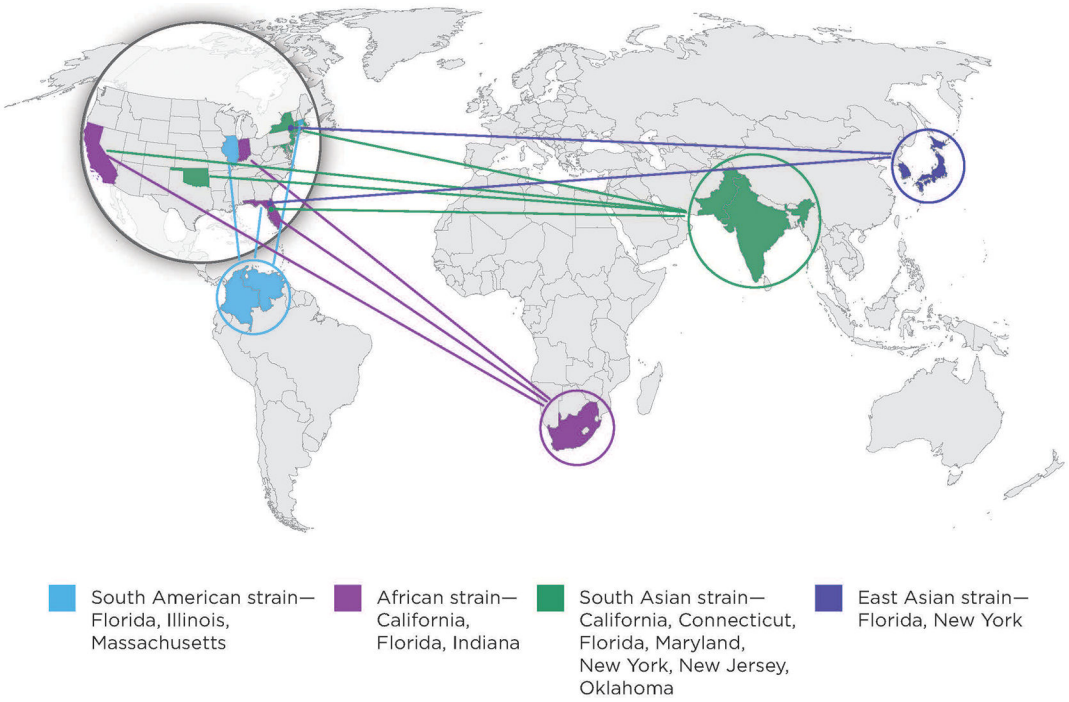

Fig. 2.

Geographic representation of the 4 major *C auris* clades identified in the United States through 2019. Shading of certain countries is used to represent the geographic regions that the specific *C auris* clades are associated with, and does not represent direct introduction from these countries to the United States. (*From* Centers for Disease Control and Prevention [CDC]. Antibiotic Resistance Threats in the United States. 2019. Available at: http://www.cdc.gov/drugresistance/Biggest-Threats.html. Accessed February 23, 2021.)

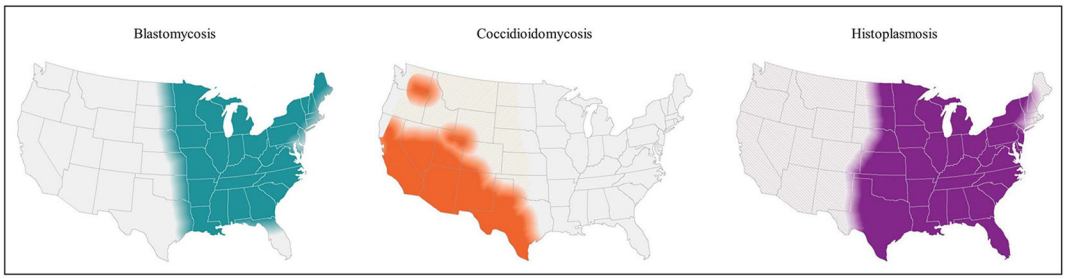

Fig. 3.

Geographic distribution of blastomycosis, coccidioidomycosis and histoplasmosis in the United States. (*From* Centers for Disease Control and Prevention [CDC]. More information about the estimated areas with blastomycosis, coccidioidomycosis (Valley fever), and histoplasmosis in the United States. 2020. Available at: https://www.cdc.gov/fungal/pdf/more-information-about-fungal-maps-508.pdf. Accessed February 23, 2021.)

Table 1

Summary of top trends in the epidemiology of clinically significant fungal pathogens in North America

Fungal Pathogen	Top Epidemiologic Trends
Candida	Injection drug use has emerged as a risk factor and is becoming more common in the context of the opioid epidemic. Although *C albicans* remains the leading cause of invasive candidiasis, a growing proportion of diagnoses have been attributed *C glabrata* and *C parapsilosis*. *C auris*, a multidrug-resistant organism shown to cause outbreaks in clinical settings, has rapidly emerged since first identified in 2009.
Mold (*Aspergillus* and non-*Aspergillus*)	Influenza-associated pulmonary aspergillosis and coronavirus disease 2019–associated pulmonary aspergillosis are emerging coinfections. Azole-resistant strains of *A fumigatus* are increasing in prevalence. Reports point to a potential increase in non-*Aspergillus* invasive mold infections among patients with hematologic malignancies and transplant recipients.
Blastomyces	The US annual incidence remains consistent at 1–2 cases per 100,000 population. Recent cases have been reported in areas not known to be endemic.
Coccidioides	US cases have increased in recent years, reaching >15,000 in 2018. Recently reported cases beyond the traditional geographic areas indicate a northward expansion into Northern California, Utah, and Washington.
Histoplasma	Evidence suggests that the occurrence of histoplasmosis may extend beyond the already broadly defined historical region. Histoplasmosis-associated hospitalizations nearly doubled from 2001 to 2012.
Cryptococcus	As the rate of disease among people living with HIV has decreased, the rate among those living without HIV has not. Approximately 20% of non-HIV patients who develop *Cryptococcus* disease have no known immune impairments. Understanding of *C gattii's* geographic distribution expanded during an outbreak in Canada and a recent uptick in cases in the US Pacific Northwest.
Pneumocystis jirovecii	Among people living with HIV in the United States and Canada, *Pneumocystis* pneumonia is the most common opportunistic infection. Populations at risk have shifted toward HIV-uninfected immunocompromised groups owing to immunosuppressive regimens that weaken the immune system.
Sporothrix	The US incidence is estimated to be 2 cases per 1 million people, with the highest incidence in southern and south-central states. *S brasiliensis* recently emerged in South America and is associated with zoonotic transmission, spreading via animal scratches and bites.